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Normal Anatomy

The breast or mammary gland is covered by skin and subcutaneous tissue and rests on the pectoralis muscle, from which it is separated by a fascial layer. The morphofunctional unit of the breast is a complex branching structure that is topographically arranged into lobes and which is made up of two major components: the *terminal duct–lobular unit (TDLU)* and the *large duct system*.¹ The TDLU is formed by the *lobule*, which in turn is made up of acini, and the *terminal ductule* and represents the secretory portion of the gland. It connects with the *subsegmental duct*, which in turn leads to the *segmental duct*, and this to the *collecting (lactiferous) duct*, which empties

into the nipple. A fusiform dilation located beneath the nipple between the collecting and segmental ducts is known as the *lactiferous sinus* (Fig. 36.1).

The TDLU is recognized by its distinctly lobular architecture, the presence of a mantle of specialized, myxoid-appearing hormone-responsive connective tissue, and the absence of elastic fibers. The development of the breast is dependent on the close interaction of these specialized epithelial and mesenchymal tissues.² The large ducts have less specialized stroma and are enveloped by a continuous and well-developed layer of elastic tissue. The entire ductal–lobular system of the breast is lined by a specialized *inner epithelial cell layer* with secretory and absorptive functions (often simply called epithelium)

Abstract

Breast pathology encompasses a wide range of benign, atypical, and malignant lesions. This chapter reviews both neoplastic and non-neoplastic lesions of the breast with discussion of differential diagnoses and appropriate adjunctive studies. Consideration is given to challenges that may be encountered with particular specimen types, such as core needle biopsies. Risk factors and molecular alterations are discussed as they pertain to the entities described.

Keywords

Breast,
carcinoma,
benign breast disease,
fibroepithelial lesions,
papillary lesions,
adenosis,
nipple lesions

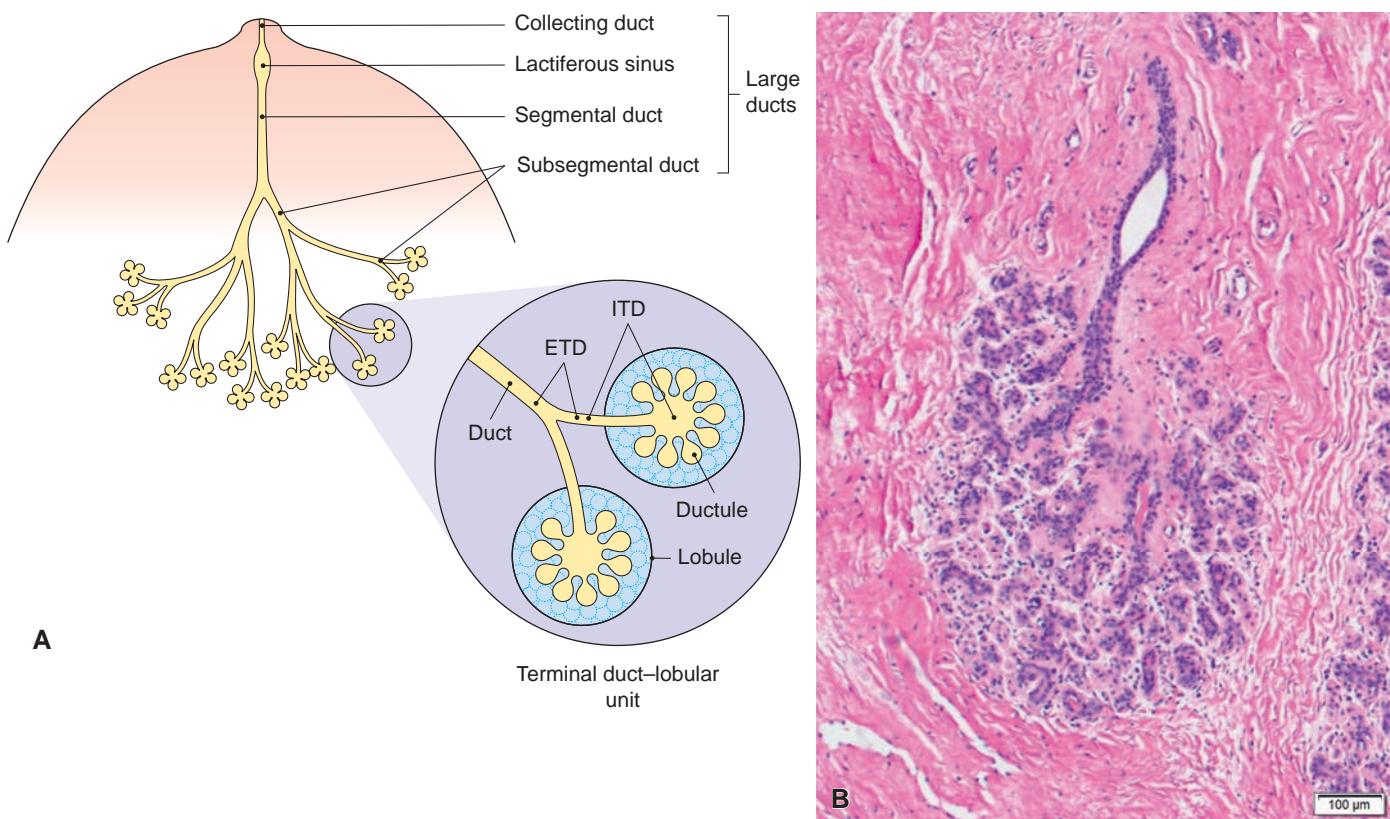


Figure 36.1 Terminal Duct-Lobular Unit. **A**, Diagrammatic representation of this structure. **B**, Photomicrograph of this unit as seen in a normal adult female. *ETD*, Extra-lobular terminal duct; *ITD*, intralobular terminal duct.

and is surrounded by an outer *myoepithelial cell layer*. These two cell types have distinctive immunohistochemical features. The most reliable markers for the epithelial cells are the various cytokeratins (see later), epithelial membrane antigen (EMA), mammaglobin (Fig. 36.2A), GCDFP-15, and GATA3. Myoepithelial cells react with high-molecular-weight (HMW) cytokeratins, smooth muscle actin (SMA), calponin, smooth muscle myosin heavy chain (see Fig. 36.2B), maspin, and caldesmon (the latter only in the ductal portion). They also show nuclear reactivity for p63 (a member of the TP53 gene family) and p75 neurotrophin receptor (p75NTR).

EMA reacts strongly with the apical region of active secretory cells but may be faint or negative in other epithelial cells. Pankeratin antibodies react with both epithelial and myoepithelial cells. Cytokeratins (CK) 8, 18, and 19 react with the epithelial cells throughout the TDLU but not with the myoepithelial cells, whereas the converse is true for CK14. Other immunohistochemical features of mammary epithelial cells are discussed in the section on invasive carcinoma. A sparse population of endocrine cells has been demonstrated in the normal breast with the use of chromogranin stain.³

It has been proposed that the two basic cell lineages of the breast—epithelial and myoepithelial—derive from a common cell that displays the phenotypic features of a committed stem cell (progenitor cell). This cell expresses CK5 in the absence of CK8, 18, and 19 and SMA. These progenitor cells are postulated to differentiate through an intermediary cell type that is CK5+ and either CK8/18+ or SMA+.^{4,5}

The entire glandular system rests on a continuous basement membrane. This can be demonstrated with reticulin stains or with immunohistochemical reactions for laminin or type IV collagen.

The nipple has a very characteristic microscopic appearance. In addition to the large collecting ducts, which open onto the surface

through five to nine orifices arranged as a central and a peripheral group,⁶ it contains numerous sebaceous glands that open independently of hair follicles, and a dense fibrous stroma in which erectile smooth muscle tissue is embedded. *Montgomery tubercles* are areolar protuberances, usually between 10 and 20 in number, which become prominent during pregnancy; microscopically, they are formed by the association of a collecting (lactiferous) duct with sebaceous glands. The epidermis of the nipple and areola resembles that of the skin elsewhere, except for an increase in melanin content in the basal layer and the occasional presence of clear cells known as *Toker cells*, which can be mistaken for the cells of Paget disease.^{7,8} The irregular corrugated appearance of the lactiferous sinus should not be confused with a pathologic condition. In approximately 15% of individuals, normal breast lobules are present in the nipple region.⁹

Breast tissue responds to hormonal and other influences throughout life, and, as a result, it may display a wide range of “normal” appearances: the immature and largely resting breast before puberty; the developed breast of reproductive life, which exhibits changes depending on the point in the menstrual cycle¹⁰; the actively secreting breast of lactation (Fig. 36.3); and the involuted postmenopausal breast. In the resting breast, cellular proliferation is largely confined to epithelial cells¹¹; during pregnancy and lactation, all cell types show a high level of proliferative activity.¹² Nodularity and leakage of milk into the stroma can occur; exaggerated expressions of these phenomena have been designated *lactating adenoma* and *milk granuloma*, respectively.^{13,14}

Mild, transient changes may be seen with initiation of contraceptive therapy. Microscopically, the only definite mammary change that can be ascribed to the medication is the development of true acini resembling those seen in the lactating breast.¹⁵

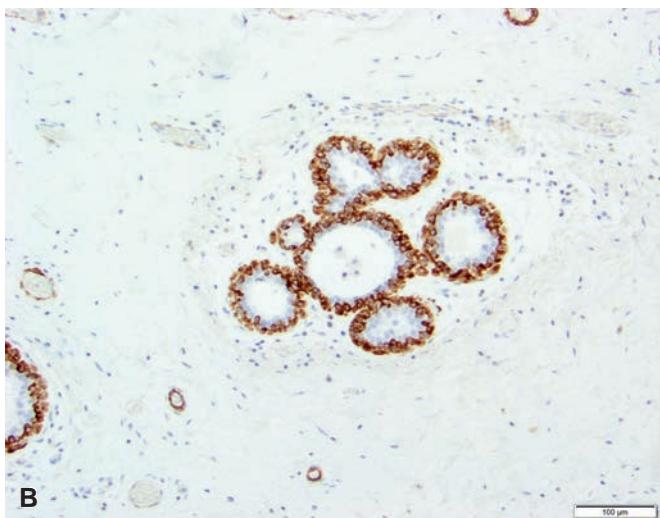
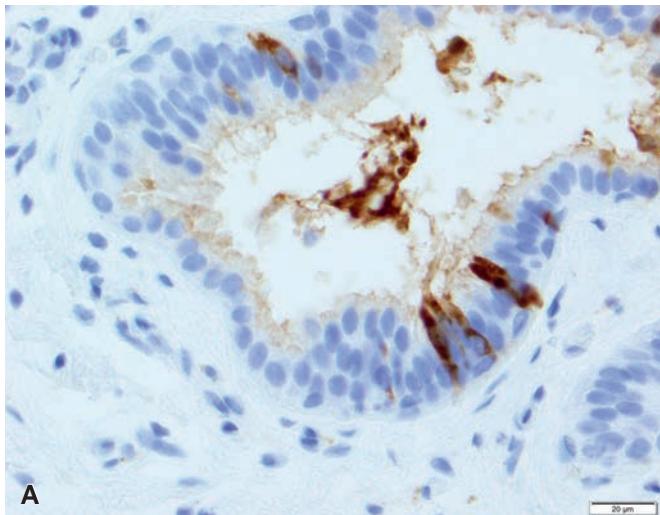


Figure 36.2 Immunohistochemical Markers of Mammary Lobule. **A**, Mammaglobin, showing positivity in scattered secretory epithelial cells and material in the glandular lumen. **B**, Smooth muscle myosin heavy chain, showing positivity in the outer myoepithelial cell component. Smooth muscle cells present in adjacent vessel walls serve as internal controls.

The process of normal *postmenopausal involution* is most apparent in the TDLU and involves both epithelium and specialized stroma (Fig. 36.4); it may acquire a microcystic quality. Deposits of elastic tissue around the ducts (*elastosis*) have been reported in nearly half of all women over 50 years of age.¹⁶

There are two morphologic curiosities of the breast worth knowing about, not because of their clinical significance, but because they can simulate other conditions of greater consequence. One is the *pregnancy-like change* seen in one or several lobules in the absence of pregnancy or hormonal manipulation.^{17,18} The cells have abundant vacuolated cytoplasm, the nuclei are large and sometimes apically located (giving the lesion an appearance that resembles the Arias-Stella reaction), and the lumina are dilated (Fig. 36.5). Pregnancy-like change may be seen in association with *cystic hypersecretory hyperplasia (CHH)*, though the exact relationship of these two lesions is unknown at present.¹⁹ The other process is *clear cell change* of the ductal or lobular epithelium, in which the cytoplasm acquires a finely granular, finely vacuolated, or totally clear appearance (Fig. 36.6).^{17,20} The mechanism of these two changes is unknown.

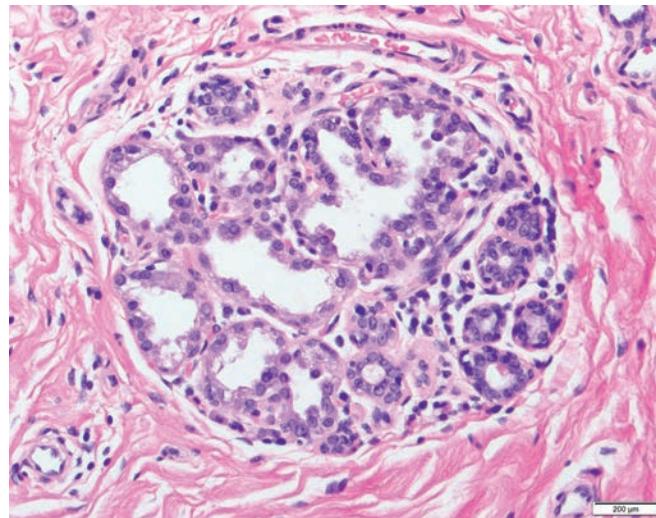


Figure 36.3 Lactational or Secretory Changes in Mammary Lobule. Some of the acini of this lobule demonstrate cytoplasmic vacuolization and protrusion as well as nuclear enlargement in keeping with lactation or secretory change.

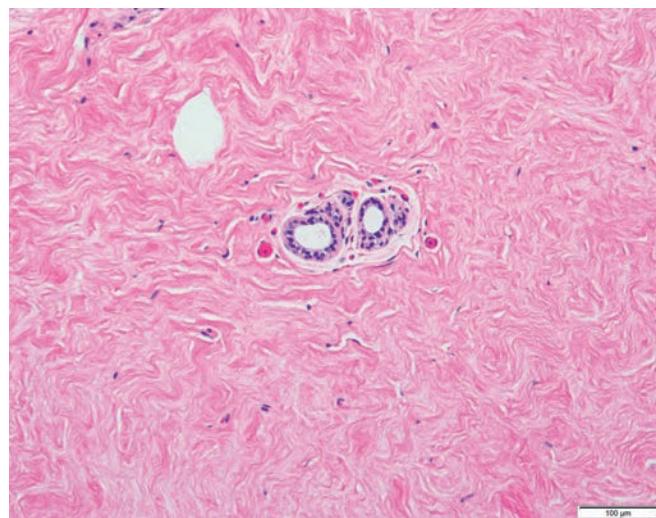


Figure 36.4 Postmenopausal Breast Tissue. The TDLU undergoes involution leaving few atrophic acini.

The main importance of the division of the mammary gland unit into two major portions (ducts and lobules) resides in its relation to diseases of this organ. As Wellings et al.²¹ convincingly showed and Azzopardi²² strongly emphasized, the site of origin of benign breast disease, and most carcinomas (including those of so-called ductal type) is the TDLU and not the large duct system. The latter is instead the primary site of most single solitary papillomas and of duct ectasia.

Ectopia

The mammary gland is not a sharply demarcated organ; as a result, isolated mammary lobules can sometimes be seen outside the standard anatomic confines of the breast parenchyma, such as in the nipple or axilla.^{9,23} The latter may explain the occurrence of some seemingly primary breast carcinomas in the axilla. Ectopic breast tissue has also been reported within axillary lymph nodes^{24,25} and along the

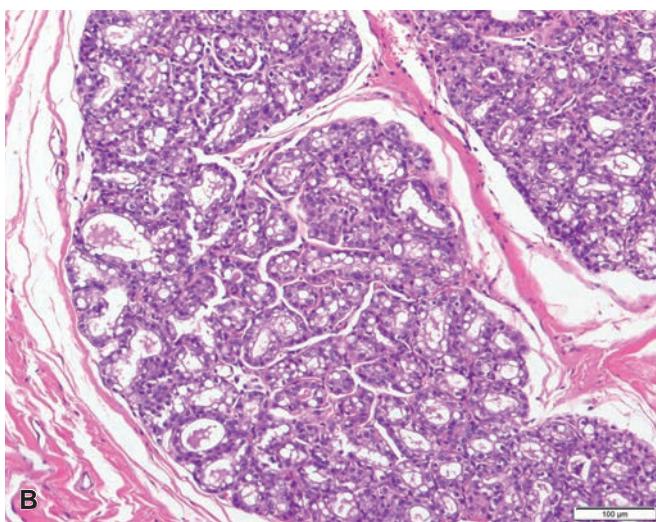
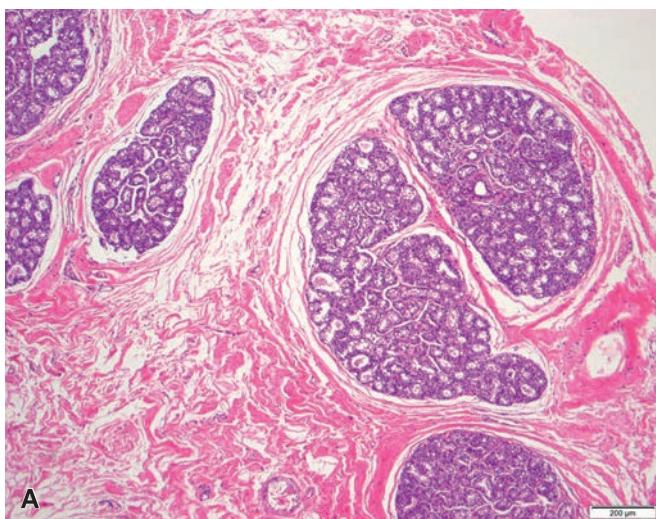


Figure 36.5 Pregnancy-Like Change in Mammary Lobule. **A**, Low-power view. **B**, Higher-power view.

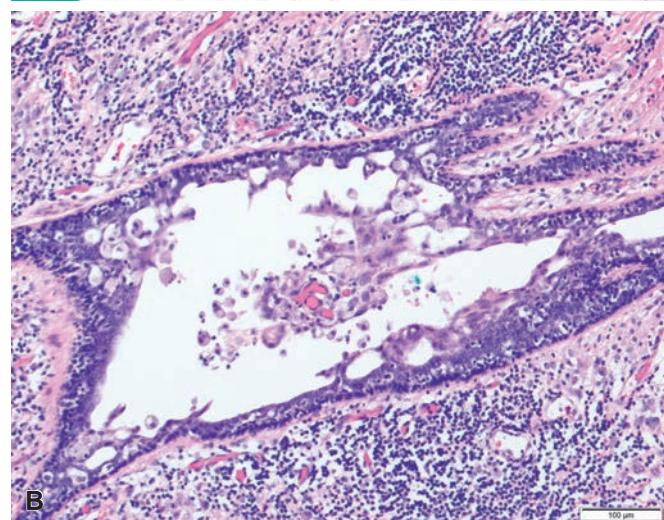


Figure 36.7 Gross and Microscopic Appearance of Mammary Duct Ectasia. **A**, Some of the dilated ducts contain a thick dark material. **B**, Inflammatory stage of duct ectasia in which there is dilation of a large duct, with accumulation of lipid-rich detritus in the lumen and a florid inflammatory reaction rich in macrophages and plasma cells.

“milk line” that runs from the axilla to the inguinal region, the most common sites being the chest wall and the vulva.²⁶

Ectopic breast parenchyma is subject to changes similar to those of the orthotopic organ, including lactational changes, benign neoplasms, and carcinomas.^{26,27} There is considerable overlap between ectopic breast tissue and breast-like metaplasias of sweat glands, a fact that renders precise histogenetic identification of some of these lesions almost impossible.²⁸

Inflammatory and Related Lesions

Mammary Duct Ectasia

Mammary duct ectasia has also been referred to as periductal mastitis and mastitis obliterans (Fig. 36.7).²⁹ Most cases are seen in premenopausal women and may represent a localized response to stagnant secretions. While the pathogenesis remains unknown, some studies have shown an association with smoking.³⁰ As beautifully described and illustrated in the classic article by Haagensen,³¹ the disease may produce retraction or inversion of the nipple and thus clinically and radiologically may simulate invasive carcinoma.

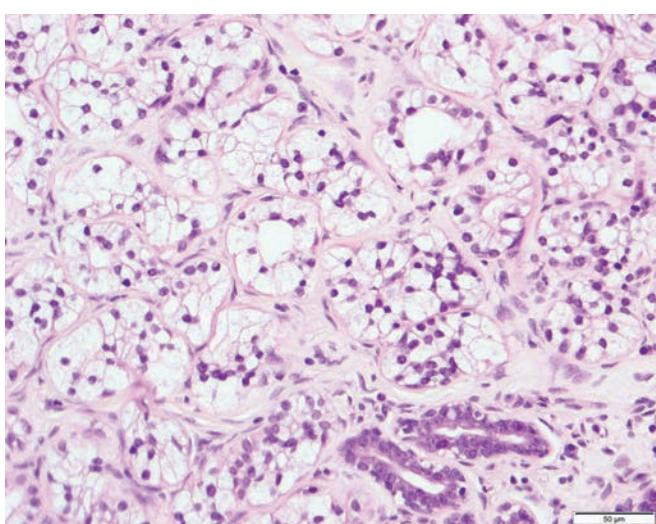


Figure 36.6 Clear cell change.

Calcification is common, producing tubular, annular, and linear shadowing on mammographic examination. Nipple discharge is present in 20% of cases. Microscopically, there is dilation of large ducts, with accumulation of lipid-rich detritus in the lumen and fibrous thickening of the wall, which contains an increased amount of elastic fibers. There is usually no accompanying epithelial hyperplasia or apocrine metaplasia. If the luminal material escapes from the duct, a florid inflammatory reaction rich in macrophages and plasma cells may ensue. In advanced stages, fibrous obliteration of the ducts can occur. Some authors have suggested that the inflammatory stage ("periductal mastitis") and the later fibrotic stage ("duct ectasia") represent two different disease processes, given the younger age and greater association with smoking in the former.^{30,32}

Fat Necrosis

A process with the microscopic features of fat necrosis (i.e., foamy macrophages infiltrating partially necrotic adipose tissue) can be seen in the breast under two disparate circumstances. One is as a secondary and relatively minor event in mammary duct ectasia and—to lesser extent—with large cyst formation. In these cases, rupture of the dilated duct or cystic structures leads to extravasation of luminal contents, some degree of tissue necrosis, and a secondary inflammatory reaction in which foamy macrophages can be numerous. In particularly florid examples of this phenomenon, the term *xanthogranulomatous mastitis* has been used.³³ Parenthetically, small collections of foamy cells are seen not infrequently within duct lumina or in cohesive masses along duct walls; their immunohistochemical profile is that of histiocytes rather than epithelial cells.³⁴

The other circumstance, which perhaps is the one that deserves to be called fat necrosis, is the traumatic (either accidental or surgical) type. This usually involves the superficial subcutaneous tissue rather than the breast parenchyma itself in accidental trauma (Fig. 36.8). A history of trauma, usually 1 to 2 weeks before diagnosis, can be elicited in about half the cases. The process can simulate carcinoma clinically because of skin retraction (Fig. 36.9), and also on imaging studies.³⁵ In long-standing cases, the nodule is harder and more fibrotic and has an orange-brown color because of the deposition of hemoglobin-derived pigments. The microscopic diagnosis is usually straightforward on core needle or excisional biopsy.

Cases of mammary fat necrosis have also been reported following radiation therapy for breast carcinoma³⁶ and as a local manifestation

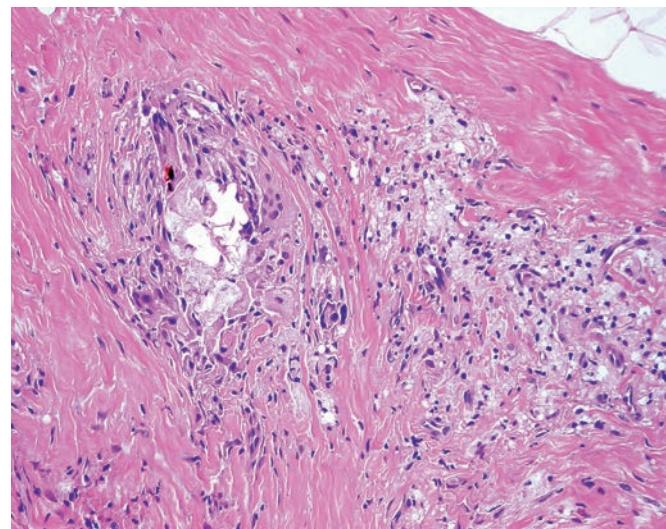


Figure 36.8 Post-traumatic fat necrosis involving breast.

of Weber-Christian disease. Exceptionally, the fat necrosis acquires the morphologic features of the so-called membranous type, which is of variably sized cystic spaces with eosinophilic membranes, particularly in postradiation therapy cases.³⁷

Lymphocytic Mastopathy

Lymphocytic mastopathy is an unusual breast lesion of probable immune-mediated pathogenesis consisting microscopically of dense perilobular, and perivascular lymphocytic infiltrates associated with lobular atrophy and keloid-like fibrosis (Fig. 36.10).^{41,42} The lymphocytes are mainly of the B-cell type. Often, the lymphocytic infiltrate is accompanied by stromal epithelioid myofibroblasts that can lead to a mistaken diagnosis of invasive carcinoma, granular cell tumor, or Rosai-Dorfman disease.^{43,44} Lymphocytic mastopathy can result clinically in a palpable mass; cases can be seen in association with diabetes (hence the synonym *diabetic mastopathy*)⁴⁵⁻⁴⁷ but may also occur in the absence of this disease or in the presence of other



Figure 36.9 Retraction of skin in a patient with fat necrosis (arrow), as seen in a photograph taken from a well-seasoned paper. (From Lee BJ, Adair F. Traumatic fat necrosis of the female breast and its differentiation from carcinoma. *Ann Surg*. 1924;80:670-691.)

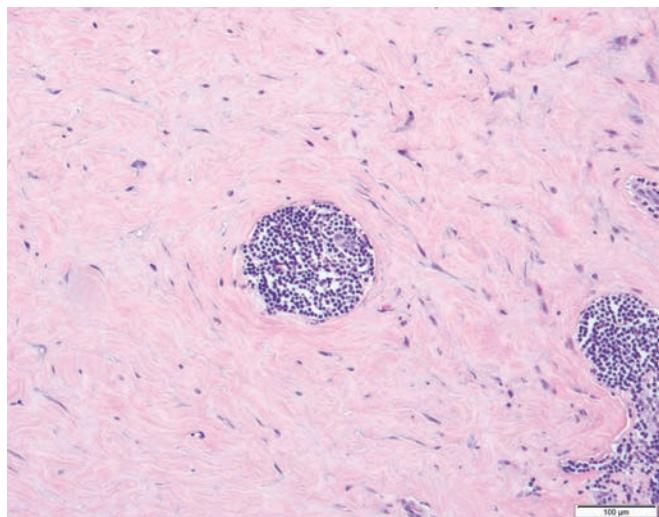


Figure 36.10 Lymphocytic Mastopathy. This process is characterized by periductal and perivascular lymphocytic infiltrates, fibrosis, and epithelioid myofibroblasts present in the stroma.

autoimmune diseases.⁴⁸ There is no increased risk for malignancy associated with a diagnosis of lymphocytic mastopathy though coexistent carcinoma has been reported.⁴⁹

Core needle biopsy specimens of lymphocytic mastopathy may go underrecognized due to the subtle stromal changes and a tendency to overlook benign inflammatory cells. In an apparently nondiagnostic core needle biopsy of a targeted mass, the constellation of perilobular and perivascular lymphocytic infiltrates, keloidal collagen and epithelioid myofibroblasts should be examined for, before rendering a diagnosis of normal or unremarkable breast tissue.

Idiopathic granulomatous mastitis

Idiopathic granulomatous mastitis is a term applied to a granulomatous inflammatory process of the breast characterized by the presence of non-necrotizing granulomas confined to breast lobules, in which no microorganisms are identified. The suggestion has been made that the disease may be immunologically mediated and, therefore, analogous to granulomatous thyroiditis or granulomatous orchitis.^{50,51} It can simulate malignancy clinically and on imaging studies.⁵² Microscopically, lobulocentric granulomatous inflammation is present, usually with admixed neutrophils. It has been postulated that some cases of granulomatous mastitis may belong to the family of IgG4-related diseases^{53,54} or be cases of cystic neutrophilic granulomatous mastitis (CNGM) (see next). Idiopathic granulomatous mastitis is a diagnosis of exclusion.

Cystic Neutrophilic Granulomatous Mastitis

CNGM is a relatively newly recognized entity that presents as mastitis in parous or lactating women.⁵⁵⁻⁵⁸ It has also been described in nulliparous women with hyperprolactinemia.⁵⁹ Patients are often febrile and have a leukocytosis. Nipple inversion or retraction is common and fistulas can occur.

Histologically, this lesion is characterized by lobulocentric granulomas that often contain neutrophils or areas of microabscess formation similar to that described for idiopathic granulomatous mastitis. The feature distinguishing CNGM from idiopathic granulomatous mastitis is the presence of empty "cystic" spaces consistent with dissolved lipid (Fig. 36.11). These spaces are surrounded by neutrophils; giant cells may also be present. With careful searching, faint rod-like structures may be identified within some of these "cystic" spaces. The bacteria are more easily identified on a Gram stain as gram-positive rods morphologically consistent with *Corynebacteria*. Microbiologic identification has shown that the lipophilic bacteria *Corynebacterium kroppenstedtii* is the species most commonly present.^{55,56,58} It is hypothesized that women who have been unable to breastfeed from one breast (due to nipple inversion, for example) may have stasis of lipid-rich milk secretions predisposing to the development of CNGM in that breast. It is possible that some (if not all) cases of idiopathic granulomatous mastitis represent CNGM in which the bacteria have not been recognized/identified. Note that these organisms are difficult to grow in the laboratory, requiring special culture media and prolonged incubation times. Treatment often includes antibiotic therapy (though to date this likely has not been specific to *Corynebacterium* spp.), excision and sometimes steroids. As this is an underrecognized entity, the most appropriate therapeutic algorithm has not yet been established.^{55,56,60,61}

Other Inflammatory Diseases

Abscess of the breast usually results from rupture of mammary ducts, occurring most often during lactation but also independently of it.³⁸ It may be located deep within the parenchyma or in the

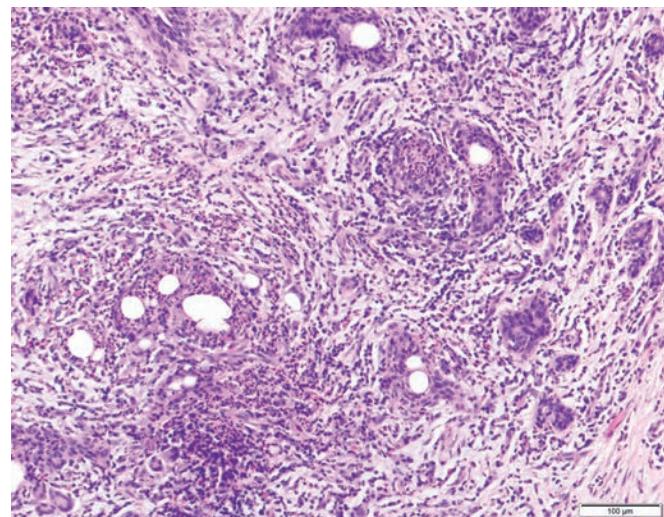


Figure 36.11 Cystic Neutrophilic Granulomatous Mastitis. In this field note the presence of "cystic" spaces cuffed by neutrophils and a background of lymphocytes, histiocytes, and giant cells (bottom left of field).

periareolar region.³⁹ Microscopically, a central cavity filled with neutrophils and secretion is surrounded by mixed inflammatory cells and, eventually, fibrosis, with obliteration of the lobular pattern. Clinically, a localized abscess may simulate carcinoma. Periareolar abscess associated with squamous metaplasia of lactiferous ducts (SMOLD) is referred to as such or as *Zuska disease* (see later).^{39,40}

Tuberculosis of the breast may be secondary either to bloodstream dissemination or direct extension from an adjacent tuberculous process.⁶² Grossly, multiple sinuses and areas of caseous necrosis occur. Microscopically, typical necrotizing granulomas are identified in most cases. The lesion may be mistaken clinically for advanced breast carcinoma. Regional nodes are often involved; occasionally, these tuberculous nodes are in an intramammary location.⁶³

Actinomycosis, coccidiomycosis, and histoplasmosis of the breast can cause necrotizing granulomatous masses and multiple sinus tracts.^{64,65}

Sarcoidosis can begin in the breast and remain localized in this organ for long periods.^{66,67} Alternatively, breast involvement may be seen as a component of systemic disease.⁶⁸ The morphologic features are the same as those described for sarcoidosis elsewhere in the body.

Foreign body reaction to the polyvinyl plastic or silicone used for mammoplasty in the past or that is occasionally injected directly into the breast by unorthodox practitioners sometimes resulted in tumorlike masses and sinus tracts (Fig. 36.12) (see later for discussion of malignancy associated with implants).⁶⁹

Breast infarct can complicate a large variety of conditions, including intraductal papilloma, fibroadenoma, phyllodes tumor, hyperplastic lobules during pregnancy, syphilis, and granulomatosis with polyangiitis.^{70,71} It also has been reported in association with anticoagulant therapy, postpartum abscess, thrombophlebitis migrans disseminata, and mitral stenosis with heart failure.⁷²

Mondor disease is the eponymous term given to a peculiar thrombophlebitis involving the breast and contiguous thoracoabdominal wall.⁷³ The condition, which may simulate clinically a malignant neoplasm, often has a sudden onset and appears as a firm, slightly nodular cord beneath the skin. Ecchymosis may or may not be present. Microscopically, the process is one of phlebitis with thrombosis. With time, the thrombus recanalizes completely. The condition is self-limited and practically never recurs. It may be related to mechanical injury, as suggested by the fact that in 8 of

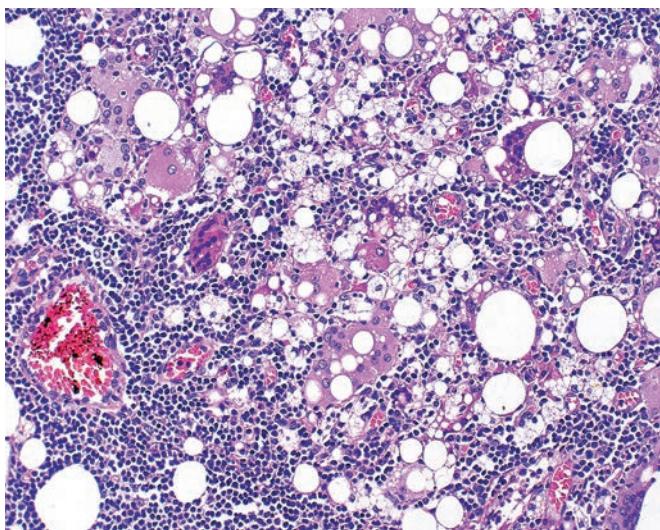


Figure 36.12 **Florid Granulomatous Reaction to Silicone.** Foamy macrophages, foreign body-type multinucleated giant cells, and lymphocytes are present.

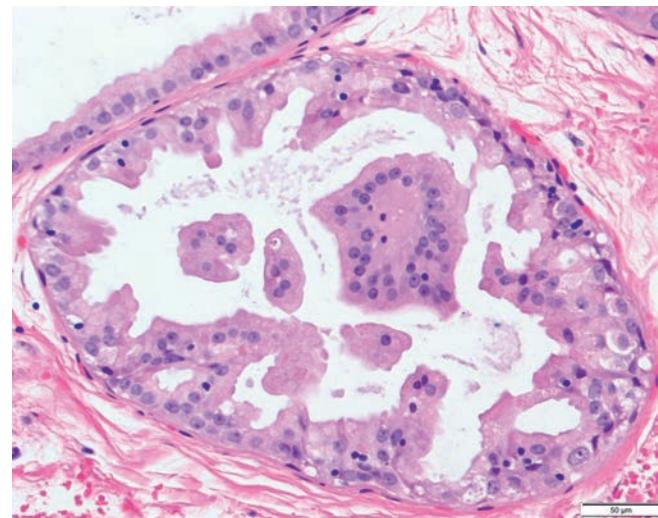


Figure 36.13 **Apocrine Metaplasia.** The cells have abundant granular eosinophilic cytoplasm, often with an apical "apocrine snout." The nuclei are round, of medium size and have prominent nucleoli.

the 15 cases reported by Herrmann⁷⁴ the disease appeared a few months after radical mastectomy. A few cases have been found to be associated with untreated breast carcinoma.⁷⁵

Rheumatoid nodules, periarteritis nodosa, lupus profundus, and granulomatosis with polyangiitis (Wegener granulomatosis) may present as single or multiple breast masses.^{70,76-82}

Benign Breast Disease

Benign breast disease is the term used to describe collectively an interrelated group of proliferative disorders of the breast parenchyma, many of which are not true neoplasms but, rather, hormone-induced hyperplastic processes.⁸³

Intraductal Proliferative Lesions and Nonproliferative Changes

Fibrocystic change was the term introduced by the College of American Pathologists (CAP) for the collective description of nonproliferative and proliferative changes of the breast.⁸⁴ It was the term preferred over "fibrocystic disease," and was to be followed by specification of the component lesions in the body of the pathology report or in the diagnosis, but neither of these terms is widely used in reports today, rather the component lesions are listed a priori. Benign breast lesions form an extremely important group because of their high frequency, the ability of some of the lesions to simulate the clinical, radiographic, gross, and microscopic appearance of carcinoma, and the relationship of some of the lesions to carcinoma.⁸⁵

Nonproliferative and intraductal proliferative lesions are most frequently seen, at least at the clinical level, between the ages of 25 and 45 years. Proliferative lesions of the breast are more common in Anglo-Saxon than in Latin American, Native American, or Japanese women.⁸⁶ The real incidence is difficult to estimate because the diagnosis depends a great deal on definitions used by the individual clinician, radiologist, or pathologist.⁸⁷ The cumulative incidence of biopsy-proven benign breast disease is approximately 9% among women below the age of 65 years, which compares with a rate of between 50% and 60% from autopsy series.^{87,88} Hormones play a role in the development of proliferative lesions of the breast, but the exact pathogenesis remains obscure.⁸⁹ There is no definitive evidence

that administration of oral contraceptives increases the degree of epithelial proliferation.⁹⁰ Epidemiologic evidence suggests a modest relationship between alcohol consumption and the development of benign breast disease and ultimately to subsequent breast cancer risk, with an inverse relationship being found for coffee consumers.^{91,92}

It is important to realize that nonproliferative and proliferative breast lesions primarily affect the TDLU, although epithelial hyperplasia can also extend to larger ducts. The basic morphologic changes are the following:

Nonproliferative Changes

1. **Cysts.** These can be microscopic or grossly visible and sometimes reach large proportions. They usually contain a cloudy yellow or clear fluid. Some of these cysts have a bluish cast ("blue dome cysts" of Bloodgood). Occasionally, numerous small thin-walled cysts are seen in the breast parenchyma surrounding a large cyst. Microscopically, the epithelial lining of most cysts, especially the larger ones, is flattened or absent, the cyst having only a thick fibrous wall. Frequently cysts rupture and elicit an inflammatory response in the stroma, with abundant foamy macrophages and cholesterol clefts. Azzopardi has observed that cysts—no matter how large—arise from the TDLU rather than from ducts.²²
2. **Apocrine metaplasia.** This is a very common change. It is most often seen in dilated and cystic structures, but it may appear in normal-sized lobules as well. The individual cells have abundant granular eosinophilic cytoplasm, often with supranuclear vacuoles and yellow-brown pigment, some of which contains iron. The apical portion of the cytoplasm shows the typical "apocrine snout." The nucleus is round and medium sized, and the nucleolus can be very prominent (Fig. 36.13). Periodic acid-Schiff (PAS) stain shows a crescent of coarse glycolipid granules on the luminal side. Immunohistochemical stain for GCDFP-15 shows strong cytoplasmic reactivity, and there is strong nuclear reactivity for androgen receptor.⁹³ Clusters of apocrine cysts may be detected on imaging studies as a "mass lesion" or as an area of calcifications, prompting core needle biopsy. Typically the calcifications take the form of calcium oxalate crystals, which may be overlooked on routine histologic examination. Viewing the cysts through polarized light will reveal the translucent crystals.

3. **Fibrosis.** "Fibrosis" is often present, but its degree varies markedly and thus deciding when it is pathologic can be a challenge. It is probably most often seen as an event secondary to cyst rupture, and it may proceed to hyalinization. The terms *fibrous disease* of the breast and *fibrous mastopathy* have been used by some authors to designate a breast condition in which the main change seems to be a more or less localized stromal fibrosis; however, it is not clear that this represents a distinct clinicopathologic entity, and since it is difficult to determine an individual woman's degree of "fibrosis," particularly on a core needle biopsy, use of the term is discouraged.
4. **Calcification.** Chemically, calcification may be composed of calcium phosphate or calcium oxalate. On mammography, calcium oxalate is amorphous, of low-to-medium density and is nearly always associated with benign disease. The crystals can be easily missed on routine sections; they are better seen with polarized lenses (because of their birefringent quality). As mentioned previously, calcium oxalate is frequently associated with apocrine cysts, and searching for the crystals with that knowledge in mind can be fruitful. Calcium phosphate is of medium-to-high density on imaging studies and is readily detectable on hematoxylin-eosin (H&E) stained sections.
5. **Chronic inflammation.** This is another common but secondary feature present in benign breast biopsies. It is usually related to cyst rupture, with release of secretion into the stroma. Lymphocytes, plasma cells, and foamy histiocytes are the predominant elements. Cysts with associated intense chronic inflammation should not be confused with mammary duct ectasia.

Intraductal Proliferative Lesions

Usual Ductal Hyperplasia

Usual ductal hyperplasia (UDH) is the preferred term of the WHO Working Group. The degree of proliferation may be commented upon if desired: *mild* (when made up of three or four epithelial cells in thickness) or *moderate to florid* (when more pronounced). In florid UDH, the entire lumen is filled by the epithelial proliferation. The features most helpful in recognizing the benign nature of the proliferation are the following:

1. Nuclei that are oval (rather than round, except when cut transversely), normochromatic (rather than hyperchromatic), with nuclear grooves, and with slight overlap; small, single, indistinct nucleoli; occasional intranuclear inclusions; scant or no mitotic activity (Fig. 36.14).
2. Cytoplasm that is eosinophilic rather than pale and homogeneous.
3. Indistinct cytoplasmic borders, so that the nuclei seem to lie in a syncytial mass rather than within sharply outlined cell membranes.
4. Streaming effect, induced by the oval cells being vaguely arranged in parallel bundles (Fig. 36.15).
5. "Tufts" and "mounds" projecting into the lumen.
6. Presence of peripheral elongated clefts, bound on one side by a single layer of basally located cells and on the other by a solid intraluminal formation; sometimes this cleft spans almost the entirety of the circumference, with the retracted solid ball of epithelial cells hanging from the wall like the vascular tuft of a renal glomerulus. The intercellular lumina of UDH tend to be irregular in size, shape (elongated rather than round), and location (predominating at the periphery) rather than regular in all three parameters as seen in the cribriform pattern of ductal carcinoma in situ (DCIS). Notably, there is an absence of cellular polarization around the clefts.
7. Presence of irregularly shaped bridges connecting opposite portions of the wall. The cells in these bridges have oval nuclei arranged parallel to the long axis of the bridge. Their appearance is very different from that seen in the rigid trabecular bars and Roman bridges of low nuclear grade DCIS.
8. Complete or incomplete apocrine metaplasia.
9. Presence of a peripheral layer of myoepithelial cells, with clear or eosinophilic cytoplasm, or elongated and smooth muscle-like ("myoid").
10. Presence of foamy macrophages, both in the lumen and intimately admixed with the proliferating epithelial cells.⁹⁴
11. Occasional intraluminal or stromal calcifications.
12. Absence of necrosis (though see below).

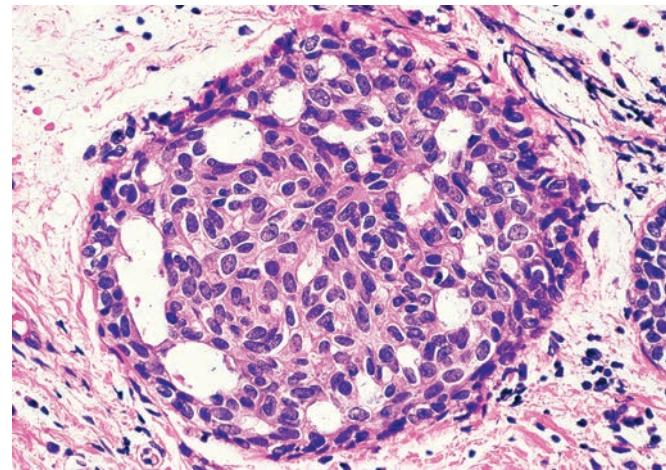


Figure 36.14 Usual Ductal Hyperplasia. In this proliferation note the presence of oval nuclei that are normochromatic, with slight overlap giving the cells a streaming appearance. The clefts are preferentially located at the periphery of the duct and there is a lack polarization of cells around the spaces.

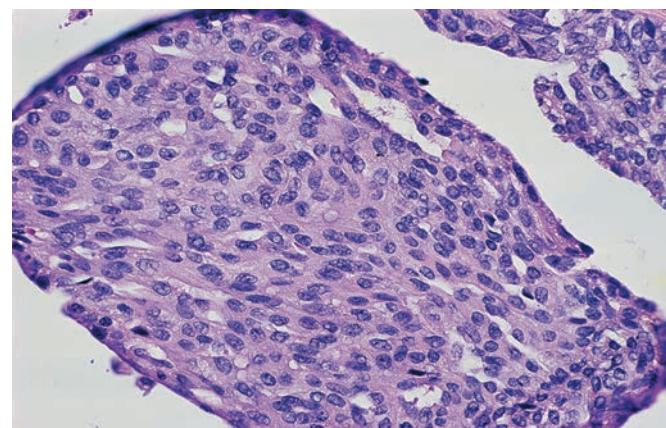


Figure 36.15 Usual Ductal Hyperplasia. Note the oval shape of the nuclei and the parallel arrangement, resulting in a "streaming" effect.

As important as these features are, none of them is diagnostic by itself. They need to be weighed against each other, sometimes modified depending on the nature of the case, and occasionally ignored altogether. For instance, focal necrosis may be found in UDH, particularly in the setting of UDH in a nipple adenoma. Furthermore, proliferative benign breast disease and carcinoma can coexist, which means that an area may be diagnostic of DCIS even

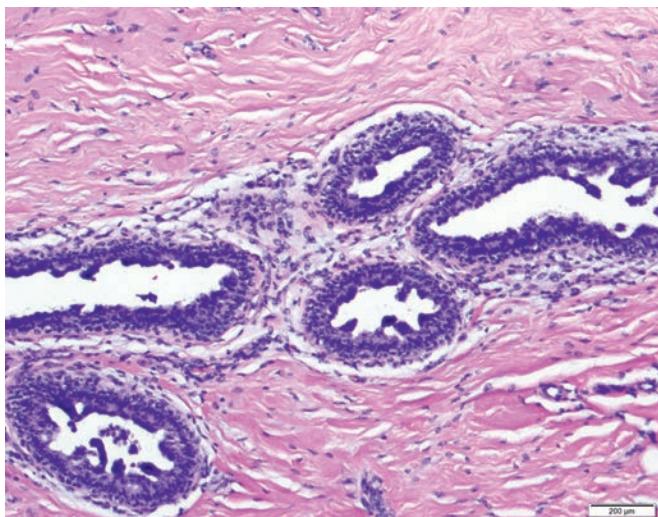


Figure 36.16 Gynecomastoid Hyperplasia. A form of UDH characterized by micropapillary tufting of the lining epithelium; the micropapillae have broader bases and narrow pinched tips. The nuclei are also smaller and more hyperchromatic at the tips than at the bases of the micropapillae.

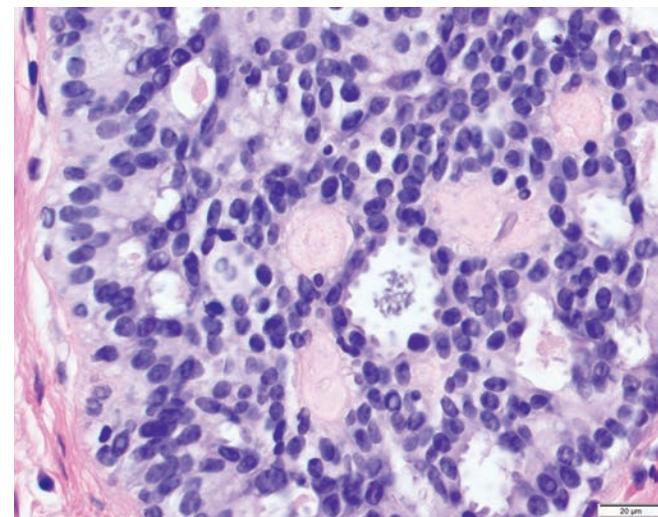


Figure 36.17 Collagenous Spherulosis. The round spaces contain eosinophilic or sometimes basophilic collagen-rich spherules composed of basement membrane material. Note the more spindled nuclei of the myoepithelial cells surrounding the spaces containing the eosinophilic basement membrane material.

if the immediately surrounding glands show features indicative of benign disease.

Immunohistochemically, UDH is characterized by a heterogeneous or "mosaic" pattern of immunoreactivity for HMW cytokeratin antibodies, in particular for CK 5/6 (which is preferred over 34 β E12).⁹⁵ This is of importance in the differential diagnosis with atypical ductal hyperplasia (ADH) and low and intermediate nuclear grade DCIS, which lack reactivity for HMW cytokeratins. The combination of CK 5/6 with estrogen receptor (ER), which also shows a heterogeneous pattern of staining in UDH whereas strong, diffuse nuclear staining is seen in ADH and DCIS, can be particularly helpful in this differential diagnosis.

Other benign intraductal proliferations, or variants of UDH, of note include the following:

Gynecomastoid hyperplasia is a form of UDH of the female breast that resembles gynecomastia of the male breast and is characterized by micropapillary tufting of the lining epithelium. The micropapillae have broad bases and narrow pinched tips with nuclei that are larger at the base than at the tip of the micropapillae (Fig. 36.16).

The special variant of ductal hyperplasia known as *juvenile papillomatosis* or "Swiss cheese" disease is discussed later in this chapter.

Collagenous spherulosis is characterized by the presence of intraluminal eosinophilic but sometimes basophilic, collagen-rich spherules that arise within spaces surrounded by myoepithelial cells (Fig. 36.17).⁹⁶ Ultrastructurally, the spherules show a variable composition of basement membrane material, banded collagen, and mineral deposition.⁹⁷ This curious entity can be confused with adenoid cystic carcinoma, signet ring carcinoma, and cribriform pattern DCIS. It should be noted that collagenous spherulosis can be seen in association with intraductal papilloma, sclerosing adenosis and lobular carcinoma in situ (LCIS).⁹⁸ The latter can be a particular pitfall in the distinction with cribriform pattern DCIS due to the monomorphic appearance of the LCIS cells in combination with the cribriform appearance of collagenous spherulosis (Fig. 36.18).⁹⁹

Cystic hypersecretory hyperplasia is characterized by the presence of cystically dilated ducts containing a bright pink colloid-like material lined by cells that have relatively abundant vacuolated or secretory cytoplasm (Fig. 36.19A); this lesion needs to be distinguished from

cystic hypersecretory carcinoma, not always an easy task.¹⁰⁰ CHH can become atypical (CHH with atypia or DCIS), which is recognized by an increase in architectural and nuclear atypia (see Fig. 36.19B).¹⁰¹

Having discussed benign *ductal* proliferations, specifically UDH, it should be noted that the term *lobular* hyperplasia should never be used unless qualified as atypical lobular hyperplasia (ALH) (see next).

Atypical Ductal Hyperplasia and Atypical Lobular Hyperplasia

As already mentioned, there is a wide range in the degree of epithelial proliferation in benign breast disease. It has been demonstrated that there is a correlation between proliferative breast disease and the risk of development of invasive carcinoma.^{102–105} Dupont and Page¹⁰³ proposed the terms *ADH* and *ALH* for proliferative lesions in which some but not all of the features of DCIS or LCIS, respectively, are present. Using these criteria in a retrospective study of women with benign breast disease, they diagnosed atypical hyperplasia (ADH and/or ALH) in 3.6% of the cases and demonstrated that these patients had a relative risk for the subsequent development of invasive breast carcinoma that was 4 to 5 times that of the general population (i.e. about half of that of DCIS or LCIS). Largely on the basis of that study, the recommended grouping of patients with benign breast disease (previously "fibrocystic change") is into the following three categories¹⁰⁶:

1. No or mild UDH (**nonproliferative changes**): no increased risk for subsequent invasive carcinoma.
2. Moderate or florid UDH (**proliferative disease without atypia**): 1.5–2 times the risk.
3. ADH or ALH (**atypical hyperplasia**): 4–5 times the risk.

For completeness and comparison purposes, Page¹⁰⁷ added to this list the following category:

4. DCIS or LCIS: 8–10 times the risk.

The Page-Dupont studies represent an extremely important contribution to the study of benign breast disease vis-à-vis breast carcinoma, as well as the standardization of nomenclature and criteria in the diagnosis of benign breast disease, which in turn have had a

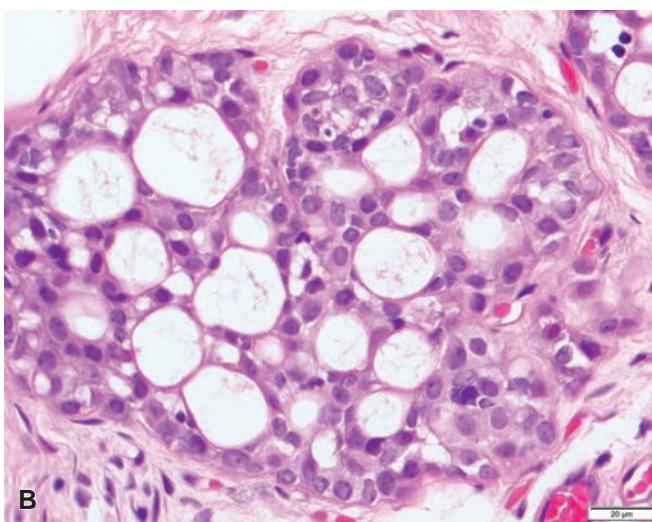
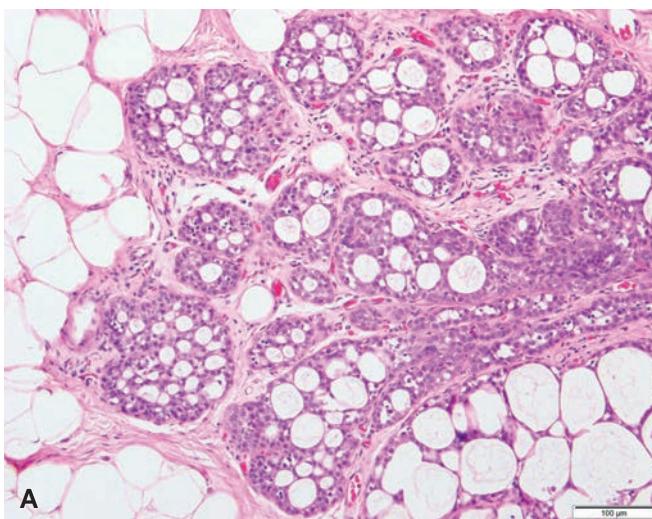


Figure 36.18 Lobular Carcinoma In Situ Involving Collagenous Spherulosis. The monomorphic appearance of the LCIS cells in combination with the cribriform appearance of the collagenous spherulosis can be a mimic for ductal carcinoma in situ at low power (A). At high power (B), the cytologic atypia and cellular dyshesion of the LCIS is better appreciated. Again, note the presence of myoepithelial cells surrounding the spaces containing the eosinophilic basement membrane material.

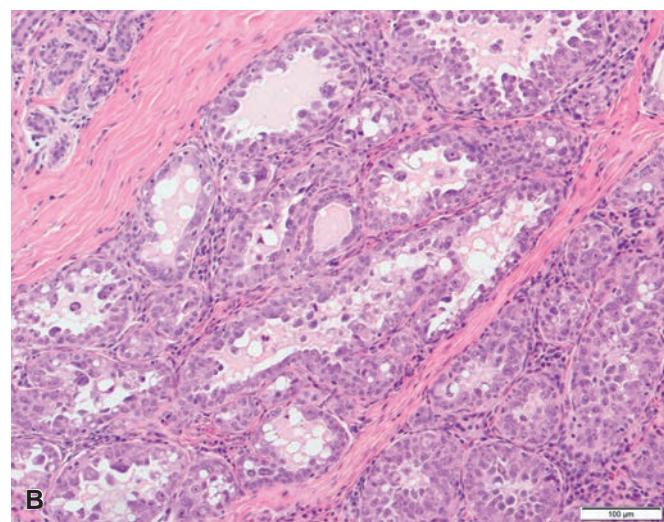
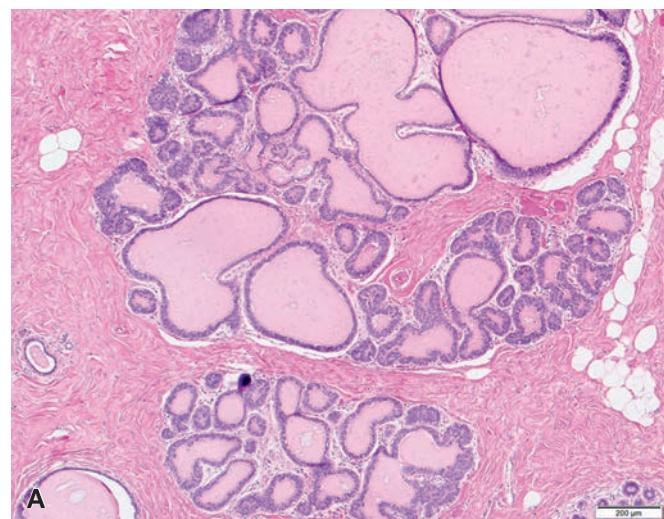


Figure 36.19 A and B, Cystic hypersecretory hyperplasia (CHH) is characterized by the presence of cystically dilated spaces containing a bright pink colloid-like material lined by cells that have relatively abundant vacuolated or secretory cytoplasm (A). The lesion can demonstrate areas of architectural and cytologic atypia (B), in this case sufficient for a diagnosis of ductal carcinoma in situ.

great impact on patients, clinicians, and pathologists. The currently accepted definition of ADH is that of a lesion with cytologic and architectural features indistinguishable from those of low-grade DCIS, that is, monomorphic cells with ovoid to rounded nuclei and the formation of micropapillae, tufts, fronds, bridges, solid, and/or cribriform patterns within the involved space (Figs. 36.20–36.22), but either (1) intimately admixed with UDH or (2) showing only partial involvement of the TDLU. Quantitative requirements have been proposed for when there is complete involvement of the space(s) involved (namely to be ≤ 2 mm or to be present in fewer than two adjacent spaces; the corollary being that a diagnosis of low-grade DCIS would be rendered if these same cells involved two or more spaces or measured >2 mm); the most recent WHO Working Group did not recommend one size/extent approach over another.¹⁰⁸

ALH is defined as a monomorphic proliferation of atypical epithelial cells with round nuclei and indistinct nucleoli. The cells are dyshesive and often have intracytoplasmic lumina (Figs. 36.23 and 36.24). ALH is said to be present when less than 50% of the

TDLU is expanded by the atypical proliferation, with LCIS being defined as greater than 50% of the TDLU expanded by the atypical proliferation. Pagetoid extension along the ducts may also be seen in ALH.

There are no special techniques (e.g., morphometry, DNA ploidy studies, immunohistochemical stains, or genetic molecular tests) that are able to separate ADH and ALH from low nuclear grade DCIS and LCIS, respectively.^{109,110}

Columnar Cell Lesions and Flat Epithelial Atypia

A further variation on the theme of mammary ductal hyperplasia, the identification of which has increased through screening mammography because of the association with microcalcifications, is the group of lesions collectively referred to as columnar cell lesions. The lesions that make up this group are columnar cell change, columnar cell hyperplasia, and flat epithelial atypia (FEA), which is the terminology preferred by the WHO Working Group.¹¹¹

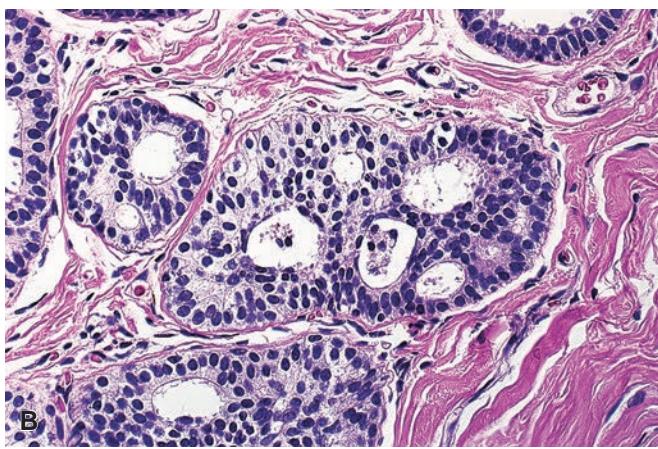


Figure 36.20 **A** and **B**, Atypical ductal hyperplasia. Proliferative ductal lesion with monomorphic cells and cribriform architectural pattern diagnosed as atypical ductal hyperplasia on account of these cytoarchitectural features and small lesion size.

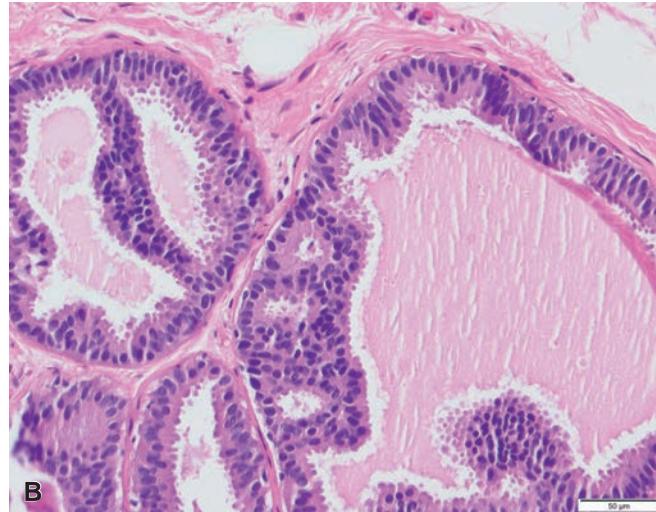
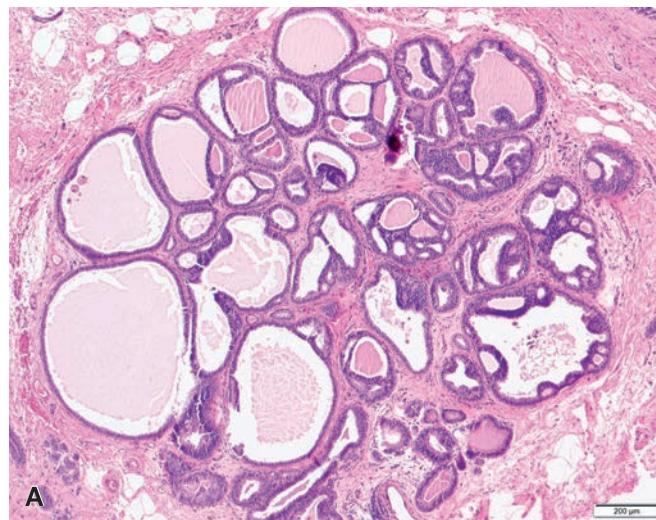


Figure 36.22 Atypical Ductal Hyperplasia. **A**, A TDLU with a predominantly cribriform proliferation of monomorphic epithelial cells; some rigid bridges and bars are also present. **B**, At high power note the low-grade nuclear atypia and the polarization around the cribriform spaces.

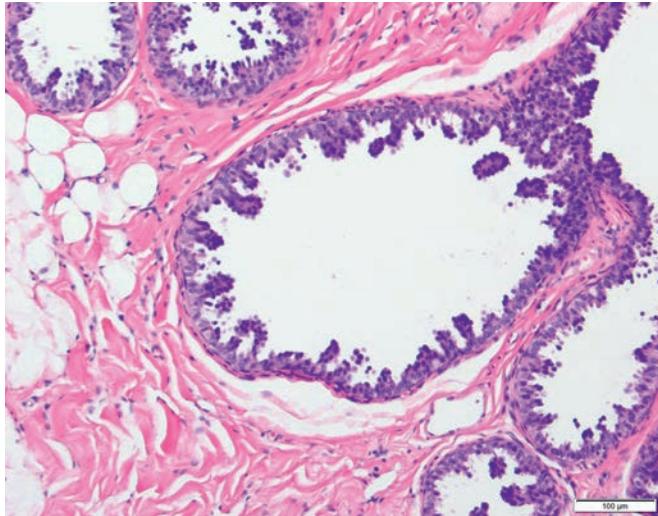


Figure 36.21 Atypical Ductal Hyperplasia. This micropapillary proliferation demonstrates bulbous micropapillations with enlarged atypical nuclei present both at the base and the tip of the micropapillations.

Unfortunately, the literature is awash with other names for these lesions. For example, early terms for FEA included low-grade (monomorphic) clinging carcinoma, atypical cystic lobules, atypical columnar change, columnar cell hyperplasia and columnar cell change with atypia.

FEA is characterized by a single or stratified layer of columnar to cuboidal cells with low nuclear grade cytologic atypia and loss of polarization with respect to the basement membrane. There is variable dilatation of the acini of the affected TDLUs, with smooth, rather than irregular, contours (Figs. 36.25 and 36.26). Apical snouts can be prominent. The lumens of the acini contain granular secretions and/or calcifications.¹¹² It may seem paradoxical that a lesion can be flat and columnar at the same time; the explanation is that "flat" refers to the "architectural" appearance of the involved acini, whereas "columnar" refers to the shape of the lining epithelial cells.

In contrast to FEA, *columnar cell change* and *columnar cell hyperplasia* refer to these same architecturally "flat" lesions but without the cytologic atypia. It is these two lesions in which the lining epithelial cells are most recognizably columnar with elongated nuclei oriented perpendicular to the basement membrane, whereas in FEA the lining epithelial cells tend to have a more cuboidal appearance. In columnar

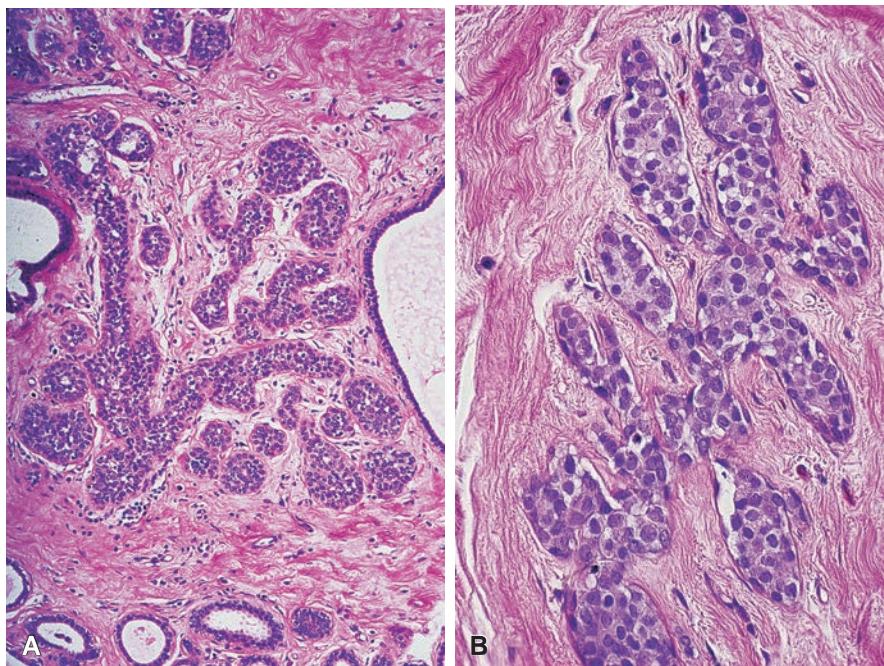


Figure 36.23 Atypical Lobular Hyperplasia. **A**, There is expansion of the lobules by a monomorphic proliferation of atypical epithelial cells with round nuclei and indistinct nucleoli. **B**, The cells are dyshesive and often have intracytoplasmic lumina, which can be appreciated at higher power.

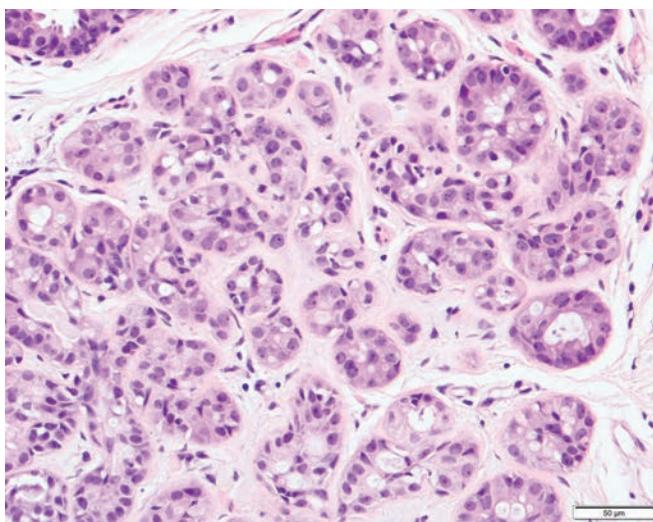


Figure 36.24 Atypical Lobular Hyperplasia. There is expansion of the lobules by a monomorphic proliferation of atypical epithelial cells with enlarged nuclei and small nucleoli. The cells are dyshesive and many have intracytoplasmic vacuoles.

cell hyperplasia, there is stratification of the lining epithelial cells with some tufting but no true micropapillations. Other features of these lesions include variably dilated acini with irregular acinar contours, prominent apical snouts, luminal secretions, and calcifications (Figs. 36.27 and 36.28).¹¹¹ ER is strongly positive, CK5/6 is negative, and there is an increased expression of MIB-1 in all columnar cell lesions.¹¹³

The biologic significance of FEA is still being elucidated, but it is generally thought to be the earliest step in the low-grade breast neoplasia pathway (perhaps the precursor to ADH),¹¹⁴ with a subsequent breast cancer risk similar to proliferative lesions without

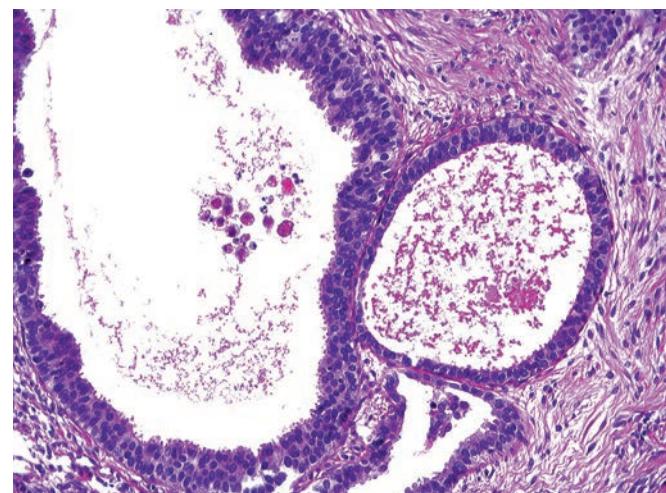


Figure 36.25 Flat Epithelial Atypia. The spaces are dilated and lined by a stratified layer of cuboidal cells with low-grade cytologic atypia.

atypia (i.e., 1.5- to 2-fold risk), though it may be that there is no increase in risk over and above that of any associated proliferative lesion present.^{115–117} In several studies, columnar cell lesions have been found to be frequently associated with low-grade DCIS, LCIS, and pure and/or mixed forms of tubular carcinoma.^{118–121}

Nomenclature of Proliferative Ductal and Lobular Lesions

While the nomenclature first suggested by Page et al. and endorsed by the CAP is the preferred term of the WHO Working Group,¹²² other terminology has been suggested, such as mammary intraepithelial neoplasia (MIN) of either ductal or lobular type, followed

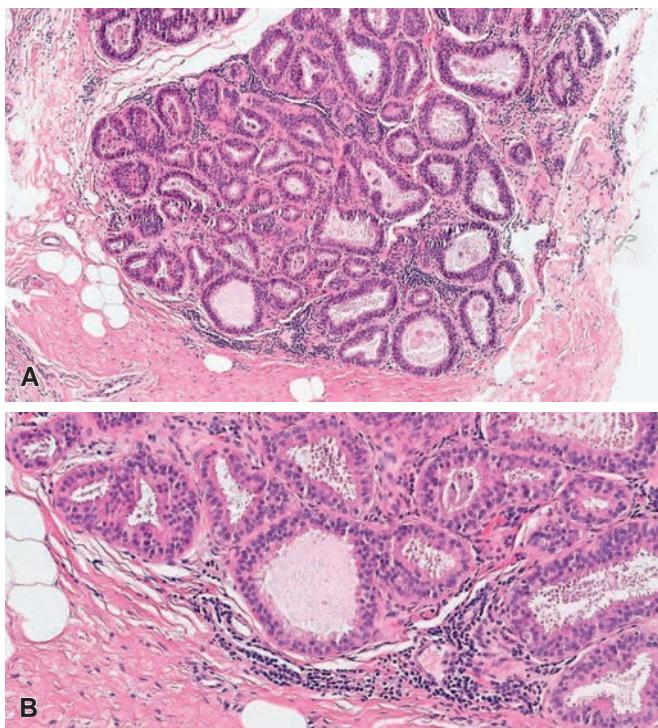


Figure 36.26 Flat Epithelial Atypia. **A**, The acini of the terminal duct lobular unit are variably dilated and the spaces lined by a stratified layer of monomorphic cuboidal cells. **B**, At higher power the low-grade cytologic atypia is appreciated as well as the apical snouts and secretions.

by a grading system¹²³ in accordance with the trend at many other sites, such as cervix (CIN), prostate (PIN), and gastrointestinal tract. Tavassoli and her group have further developed this nomenclature, according to the scheme shown in Table 36.1.^{124–126}

The proposal has some merit; in point of fact, many of the arguments that have been raised against its adoption apply to other organ sites just as well, yet they have not prevented a terminology change taking place in those sites. There is one issue, however, that deserves comment. The ductal intraepithelial neoplasia (DIN) numerical terminology implies a continuum of changes, which may or may not exist. The alternative view, masterfully articulated by Azzopardi²² and currently supported by many experts, is that proliferative breast disease can be divided into distinct categories: the “usual” hyperplasia category and the intraductal carcinoma category, which may be further subdivided into a low-grade and a high-grade pathway.¹²⁷ In this scheme, ADH and likely FEA are the nonobligate precursors to low nuclear grade DCIS. Given this, linking these conditions (i.e., low- and high-grade DCIS) in a grading system that presupposes a nosologic unity might be misleading. In practice, the MIN schema has not been widely adopted in the United States, and this terminology was not included in the 2012 edition of the WHO publication on Tumors of the Breast.¹²⁸

Relationship With Carcinoma and Management

A relationship between benign breast disease and breast carcinoma has been suggested over the years on the basis of the following evidence:

1. The observation that breast tissue excised for carcinoma usually also exhibits changes of benign breast disease¹²⁹ and that there is a greater degree of epithelial proliferation than is found in a population without carcinoma.¹³⁰

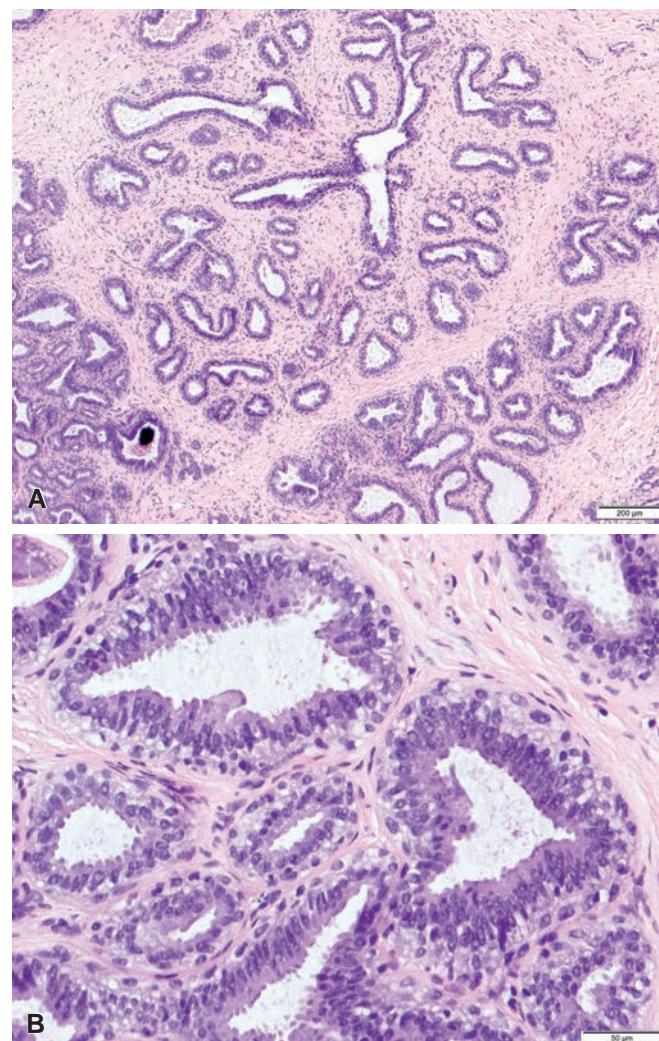
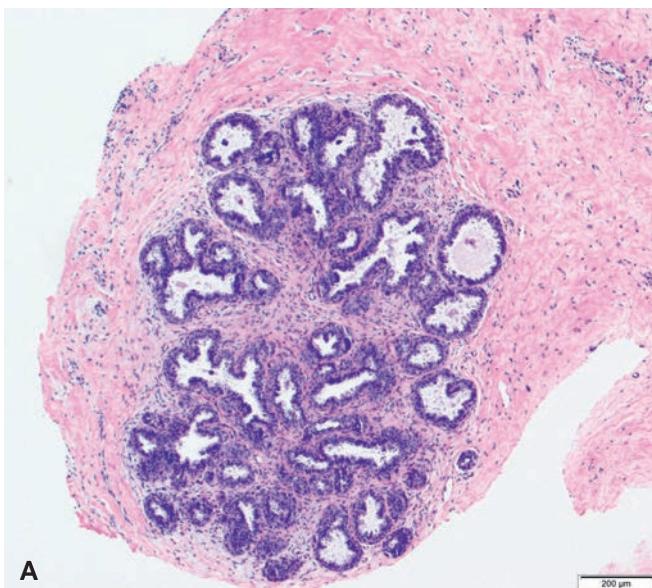


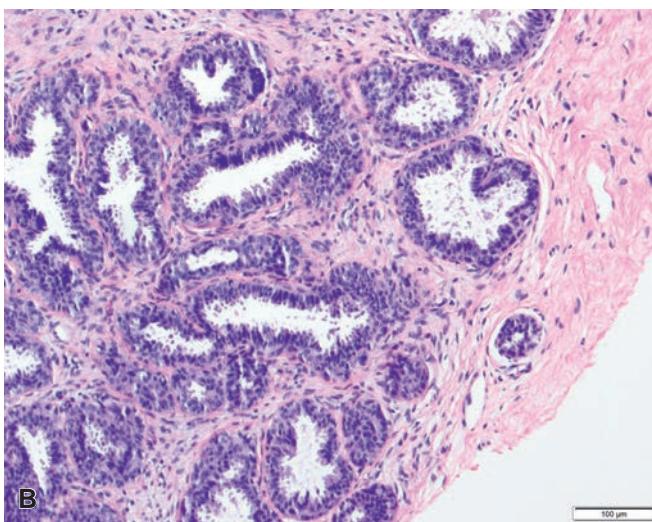
Figure 36.27 Columnar Cell Change. **A**, The acini of the terminal duct lobular unit are variably dilated and the spaces lined by a layer of columnar epithelial cells; a calcification is present in the lower left of the field. **B**, At higher power the columnar cells are seen to be arrayed perpendicular to the basement membrane; apical snouts are present.

2. The fact that retrospectively studied breast biopsies in patients who subsequently developed invasive carcinoma often show proliferative disease without atypia or atypical hyperplasia rather than nonproliferative changes.^{131,132}
3. The parallelism in incidence of breast carcinoma and benign proliferative breast lesions in various populations,¹³³ including the fact that kindreds susceptible to breast carcinoma also inherit a predisposition to proliferative breast disease.¹³⁴
4. The presence of molecular alterations in atypical hyperplasias that parallel those of breast carcinoma.^{114,135–138}
5. The observation that patients with benign breast disease are found to develop invasive carcinoma at a higher rate than a control population.^{139–141} Parenthetically, the breast carcinomas that develop in patients with a previous diagnosis of benign breast disease do not differ depending on the histologic category of the latter.¹⁴²

A quantitative leap was made once it was demonstrated that it is not benign breast disease per se but rather the presence and type of epithelial proliferation that determines the risk for subsequent carcinoma and that this risk seems to range from one to five times



A



B

Figure 36.28 Columnar Cell Hyperplasia. **A**, The acini of the terminal duct lobular unit are variably dilated and the spaces lined by a layer of columnar epithelial cells with some multilayering and tufting; calcifications are present in some acini (upper part of field). **B**, At higher power the columnar nature of the cells is appreciated as well as the apical snouts.

that of the control population, as indicated in the section on atypical hyperplasia.^{107,143} This fact, which has been confirmed in independent studies,^{139,140} indicates that evaluation of epithelial hyperplasia is an important gauge in deciding on the best approach to ongoing management for these patients. Naturally, several other factors need to be taken into consideration, such as the length of time since the diagnosis of atypical hyperplasia was made and the type of atypical hyperplasia (ADH vs. ALH).^{144–147} In general, a conservative approach to benign breast disease is amply justified.¹⁴⁸

Fibroepithelial Lesions

Fibroadenoma

Fibroadenoma is a very common benign neoplasm typically occurring in patients between the ages of 20 and 35 years. It increases in size during pregnancy and tends to regress with age. It is usually single,



Figure 36.29 Gross Appearance of a Fibroadenoma. The lesion is sharply circumscribed and has a bulging cut surface with slit-like spaces. (Photograph courtesy of Dr. M. DiStasio).

Table 36.1 Alternate nomenclature of proliferative ductal and lobular lesions

TRADITIONAL TERMINOLOGY	MIN TERMINOLOGY
Usual ductal hyperplasia	(No DIN equivalent)
Flat epithelial atypia	DIN1A
Atypical ductal hyperplasia	DIN1B
DCIS low nuclear grade	DIN1C
DCIS intermediate nuclear grade	DIN2
DCIS high nuclear grade	DIN3
Lesions in the ALH/lobular CIS spectrum	LIN 1, 2, and 3
Proliferative epithelial lesions not easily placed into either a ductal or a lobular category	MIN

ALH, Atypical lobular hyperplasia; CIS, carcinoma in situ; DCIS, ductal carcinoma in situ; DIN, ductal intraepithelial neoplasia; LIN, lobular intraepithelial neoplasia; MIN, mammary intraepithelial neoplasia.

but in 20% of cases there are multiple lesions in the same breast or bilaterally.

Grossly, the typical fibroadenoma is a sharply demarcated, firm mass, usually no more than 3 cm in diameter. The cut surface is solid, grayish white, and bulging, with a whorled pattern and slit-like spaces (Fig. 36.29). Necrosis is absent.

Microscopically, fibroadenomas vary in appearance from case to case, depending on the relative amounts of glandular and fibrous tissue and the configuration of the former (Fig. 36.30). They are labeled *intracanalicular* when the connective tissue invaginates into the glandular spaces so that it appears to be within them, and *pericanalicular* when the regular round or oval configuration of the glands is preserved. Often, both growth patterns are seen in the same lesion and the distinction has no clinical connotations. The glands are composed of cuboidal or low columnar cells with round, regular nuclei resting on a myoepithelial cell layer. The stroma is usually made up of loose connective tissue rich in acid mucopolysaccharides, but it may be partially or completely composed of a dense

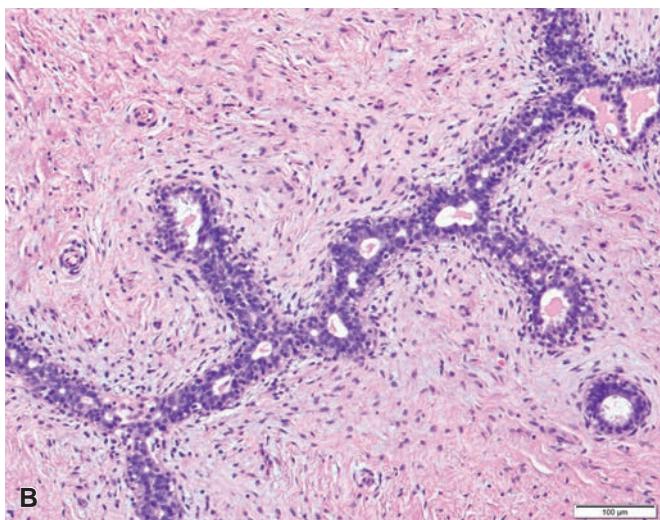
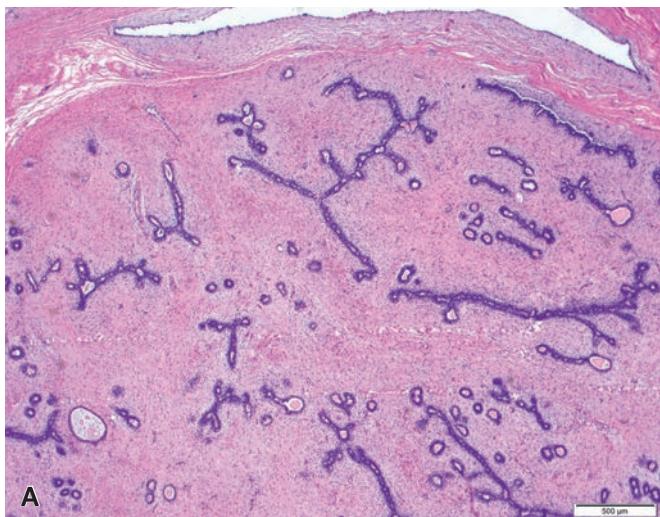


Figure 36.30 Microscopic Appearance of Fibroadenoma. **A**, Low-power image showing the circumscribed border, mixed glandular and stromal growth. **B**, On higher power, the bland nature of the stromal spindle cells is appreciated as well as the presence of mild epithelial hyperplasia.

fibrous-type stroma. The spindle cells are predominantly CD34-positive fibroblasts.¹⁴⁹ Elastic tissue is absent, in keeping with the presumed TDLU origin of the lesion. The cellularity of the stroma varies from case to case, but in any unduly hypercellular lesion the alternative diagnosis of phyllodes tumor should be considered (see later).

Morphologic variations in fibroadenoma are plentiful, some of greater significance than others:

1. Hyalinization, calcification, and/or ossification of the stroma. These changes are more commonly seen in older patients and can be appreciated radiographically.
2. Presence in the stroma of multinucleated giant cells of reactive nature, similar to those seen in polypoid lesions of nasal cavity and other sites.^{150,151}
3. Presence in the stroma of mature adipose tissue, smooth muscle, or metaplastic cartilage.¹⁵² Some of the lesions described as hamartoma or choristoma of the breast probably belong to this category.¹⁵³
4. Prominent myxoid changes. Most of these fibroadenomas are not otherwise different from the others. However, whenever

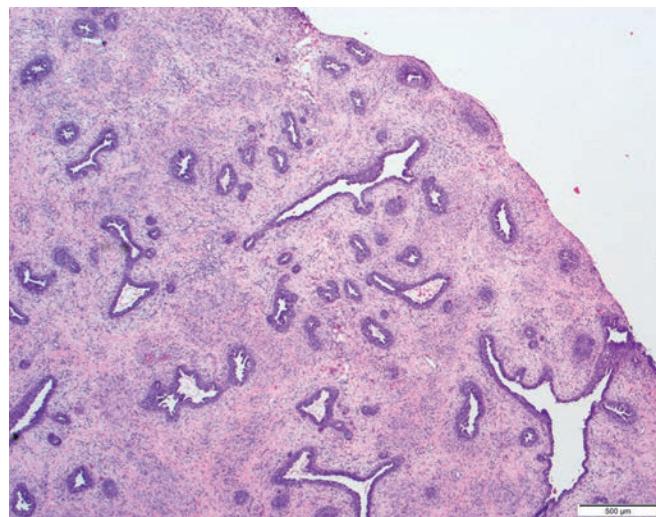


Figure 36.31 Juvenile Fibroadenoma. In this particular lesion the pericanalicular growth pattern predominates; florid hyperplasia is often seen as part of the epithelial component.

multiple, highly myxoid fibroadenomas are found, the possibility that they are a component of Carney complex, which also includes endocrine hyperactivity, cardiac myxoma, cutaneous hyperpigmentation, and other abnormalities should be investigated. Parenthetically, other breast abnormalities that can be seen in this syndrome are myxoma and ductal adenoma with tubular features.¹⁵⁴

5. Hypercellular stroma. On occasion, fibroadenomas will have an increase in stromal cellularity raising the differential diagnostic consideration of *cellular fibroadenoma* versus benign phyllodes tumor.
6. Hemorrhagic infarct. Fibroadenomas with this complication show a bulging, red appearance grossly that can be quite perplexing. This complication is more likely to occur during pregnancy.
7. Ill-defined edge blending with the surrounding breast parenchyma. This appearance is usually referred to as *fibroadenomatous change*.
8. Sclerosing adenosis. This occurs in less than 10% of cases.²² Fibroadenomas with cysts larger than 3 mm, sclerosing adenosis, calcifications, or papillary apocrine change are referred to as "complex fibroadenomas."¹⁵⁵
9. Squamous metaplasia. This is a rare finding; its presence in abundance should suggest the alternative possibility of phyllodes tumor.
10. Lactational changes. These are manifested by an increase in the amount of cytoplasm in the epithelial cells, which appear vacuolated, and by dilation of the glandular lumina by secretion.²⁶ It has been suggested that lactation adenomas in actuality represent this phenomenon rather than a distinct entity.
11. Young patients, large tumor size, and hypercellularity. There is a reasonably distinct type of fibroadenoma that tends to occur in adolescents (often in African-Americans and sometimes involving both breasts), reach a large size (over 10 cm), and show hypercellularity of glands and/or stroma.¹⁵⁶ A plethora of names exists to designate these lesions, depending on which feature predominates or which has impressed the writer the most. There are age-related terms, such as *juvenile fibroadenoma*,^{157,158} size-related terms, such as *giant* or *massive* fibroadenoma; and cellularity-related terms, such as *cellular fibroadenoma*.¹⁵⁸ In juvenile fibroadenoma the cellularity is mainly florid UDH and a pericanalicular growth pattern predominates (Fig. 36.31).¹⁵⁷ What

matters most is to recognize the lesion as a fibroadenoma and not to confuse it with virginal hypertrophy or, more importantly, phyllodes tumor. The epithelial hypercellularity can be dismissed as clinically inconsequential (unless it has the cytoarchitectural features of DCIS). Stromal hypercellularity and stromal cell atypia should be evaluated more carefully in terms of degree; it is good to remember, however, that it is rare for phyllodes tumors to occur in young patients (although they certainly can).

Fibroadenomas removed from patients taking oral contraceptives occasionally demonstrate formation of acini.¹⁵⁹

Fibroadenomas express progesterone receptor (PR) almost universally and ER in approximately a quarter of cases.¹⁶⁰ Interestingly, the stromal cells of fibroadenomas express ER beta rather than ER alpha, this expression being related to the expression of smooth muscle markers.¹⁶¹

Cytogenetically, approximately 20% of fibroadenomas have been found to have clonal chromosome aberrations.¹⁶² A lineage-restricted analysis has shown that these clonal aberrations are present in the stromal component, suggesting that fibroadenoma is a benign neoplasm of the specialized stroma of the breast with an accompanying epithelial component.¹⁶³ A recent large-scale epidemiologic study has confirmed that fibroadenoma represents a low, long-term risk for the development of breast carcinoma (1.5–2-fold; i.e., similar to proliferative lesions without atypia) and that there is no further increase in risk in women with complex fibroadenomas¹⁶⁴ nor is the risk further increased if the fibroadenoma contains foci of atypical hyperplasia.¹⁶⁵

Malignant Changes

Malignant changes in fibroadenomas are found in only 0.1% of cases.^{166,167} The malignant change usually involves the epithelial component, and the large majority are *in situ* lesions (Fig. 36.32).¹⁶⁸ In some cases the malignant tumor is entirely within the confines of the fibroadenoma, but in others it involves the surrounding breast parenchyma as well. The latter may simply represent extension into the fibroadenoma by a carcinoma originating elsewhere in the breast.¹⁶⁸

Phyllodes Tumor

Phyllodes tumor is the term for the biphasic neoplasm originally named cystosarcoma phyllodes by Johannes Müller in 1838, a term that is to be avoided because of its malignant connotations. Phyllodes

tumor occurs in middle-aged and older women. Very few patients are younger than 25 years of age, which is in striking contrast with the age distribution of fibroadenoma. However, phyllodes tumor can certainly occur in young adults and even in adolescents,¹⁶⁹ and, therefore, the diagnosis cannot be excluded on the basis of age. Of note, in Asian populations the average age is 41 years.¹⁷⁰ The interesting observation has been made that phyllodes tumors are more common in Hispanics than in other ethnic groups and that this risk is higher among Hispanics born in Latin America than those born in the United States.¹⁷¹

Grossly, the typical phyllodes tumor is round, relatively well circumscribed, and firm. The nipple may be flattened, but the overlying skin is almost never attached. The cut surface is solid and gray-white and shows the cleft-like spaces that give the tumor its name (Fig. 36.33A). Areas of necrosis, cystic degeneration, and hemorrhage may be present (see Fig. 36.33B). Rarely, the entire tumor undergoes hemorrhagic infarction. Many phyllodes tumors are large, and some reach huge dimensions, but others measure less than 5 cm in diameter. It follows, then, that the diagnosis of phyllodes tumor can be neither made nor ruled out by size alone. A lesion with the microscopic appearance of fibroadenoma should still be diagnosed as such, after appropriate sampling, even if large.

Microscopically, the two key features of phyllodes tumor are stromal hypercellularity and the presence of benign glandular elements as an integral component of the neoplasm (Fig. 36.34). It is the amount and appearance of the stromal component that determine whether a breast neoplasm should be called a fibroadenoma or a phyllodes tumor and, in the latter instance, what the chances are of the tumor behaving clinically in an aggressive fashion. Three histologic categories of phyllodes tumor have been defined, although there is considerable overlap in the features such that a sharp distinction between benign and borderline and to lesser extent between borderline and malignant forms of phyllodes tumor is not always possible.¹⁷² Furthermore, at the benign end of the spectrum it can be difficult to reliably distinguish cellular fibroadenoma from benign phyllodes tumor.

Tumors with the configuration of fibroadenomas but with a hypercellular stroma and some imbalance of the gland to stroma ratio are on the “benign” end of the spectrum; the stromal component has a fibroblastic appearance with little or mild stromal cell atypia and few mitoses (<5 per 10 high-power fields). Malignant phyllodes tumors have a high degree of stromal cellularity, marked stromal cell nuclear atypia, numerous mitoses (≥10 per 10 high-power fields), and a greater imbalance in the distribution of glands in the stroma. An important diagnostic criterion of malignancy is overgrowth of the glands by the malignant stroma such that low-power views (4× microscopic field) of the tumor show stroma only, without epithelial elements (“stromal overgrowth”).¹⁷² The neoplastic stromal component may be monomorphic or highly pleomorphic, and its appearance is most often reminiscent of fibrosarcoma, but liposarcomatous differentiation (Fig. 36.35) may also be seen; heterologous elements such as metaplastic cartilage, bone, or, exceptionally, skeletal muscle may be encountered. Phyllodes tumors with heterologous stromal elements are more aggressive. Tumor necrosis is also associated with poor prognosis.¹⁷³ It goes without saying that borderline tumors have features intermediate between benign and malignant phyllodes tumors with moderately cellular stroma, mild to moderate stromal cell atypia, 5–9 mitoses per 10 high-power fields and no (or very focal) stromal overgrowth. The border of the tumor is another feature used to help categorize phyllodes tumors: benign phyllodes tumor has a well-defined border, and malignant phyllodes tumor has an infiltrative or permeative tumor border. Borderline phyllodes tumor usually has a well-defined border, but it may be focally permeative. The epithelial component, although not neoplastic, can have a



Figure 36.32 Fibroadenoma with focal involvement by low-grade ductal carcinoma *in situ*.

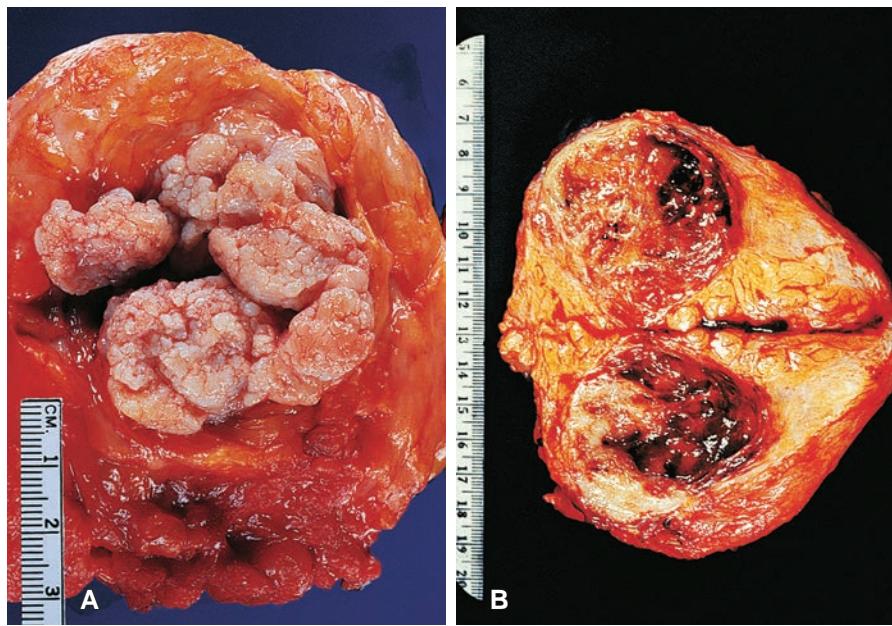


Figure 36.33 Gross Appearance of Phyllodes Tumor. The tumor shown in **(A)** exhibits the typical appearance of the cut surface. The tumor illustrated in **(B)** has undergone extensive infarction.

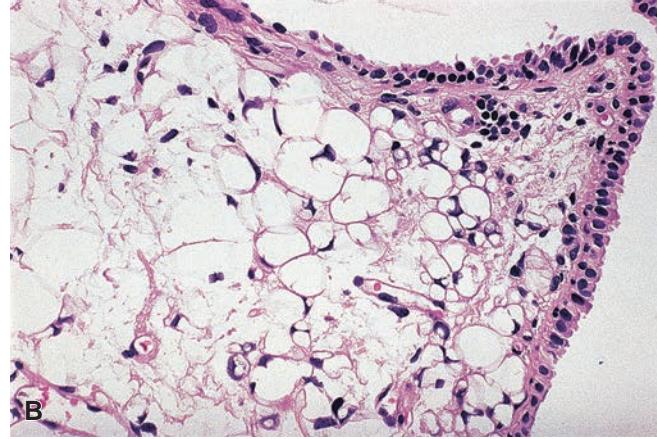
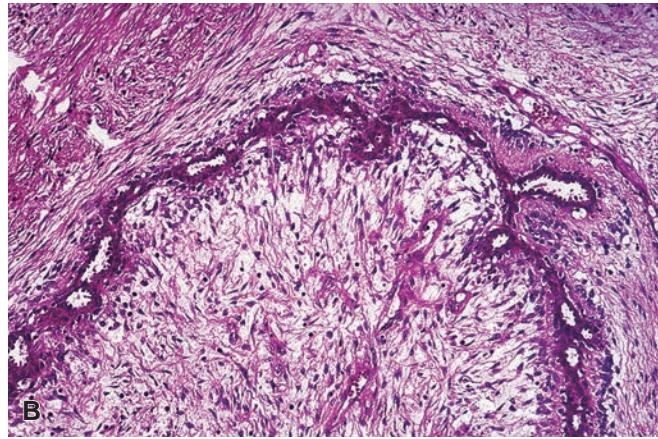
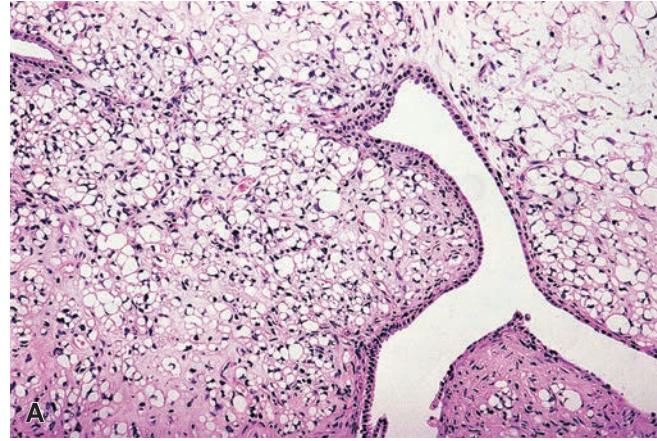


Figure 36.34 **A** and **B**, Two views of benign phyllodes tumor, showing cleft-like spaces and condensation of stromal cells under the epithelium.

Figure 36.35 **A** and **B**, Malignant phyllodes tumor with liposarcomatous differentiation of the neoplastic stromal component.

markedly proliferative appearance, as it sometimes does in fibroadenoma, a finding of no clinical significance. On rare occasions, the features of carcinoma *in situ* of either ductal or lobular type may be present.^{174–176}

Immunohistochemically, there is frequent expression of CD34 and bcl2, similar to other stromal tumors of the breast and in contrast to spindle cell metaplastic carcinomas, a feature of significance in the differential diagnosis.^{161,177} Of note, recent reports have demonstrated staining with both p63 and cytokeratin in the stromal cells of phyllodes tumors,^{178,179} albeit focal and weak in the majority of cases, a finding that may be problematic when working up a core needle biopsy of an apparently pure spindle cell lesion. Whenever the diagnosis of a spindle cell metaplastic carcinoma is being considered on a core needle biopsy, bear in mind that such specimens may represent sampling of the stromal component of a malignant phyllodes tumor. CD117 is expressed in about a third of all phyllodes tumors and over half of malignant ones.¹⁸⁰ ER beta and PR are expressed in the stromal cells of nearly all cases.¹⁶⁰ There is overexpression of p53 in a variable number of histologically malignant and borderline cases but very rarely in those with bland microscopic features; however, there is insufficient discrimination for this marker to prove clinically useful.

Fibroepithelial lesions have been shown to harbor *MED12* mutations with slightly greater prevalence in phyllodes tumor compared with fibroadenoma (62.5% vs. 59%).¹⁸¹ Phyllodes tumors on the malignant end of the spectrum have a higher complexity of alterations, with recent array-based comparative genomic hybridization (CGH) data demonstrating interstitial deletion of 9p21 involving the *CDKN2A* locus.^{182,183}

The behavior of benign phyllodes tumors is characterized by a potential for local recurrence but an extreme rarity of distant metastases.¹⁷² If an enucleation has been performed under the clinical impression of fibroadenoma, the patient can be safely followed for the possibility of recurrence. If the latter develops or if this type of phyllodes tumor is recognized at the time of initial surgery, local excision with a wide margin of normal tissue is the treatment of choice.¹⁸⁴ Recurrent phyllodes tumor may still be managed with wide local excision.

The cytologically malignant tumors have the potential for metastasis, with the incidence of metastases ranging from 3% to 12% in various series, though local recurrence is still the more common event. Axillary lymph node metastases are exceptional. The most common sites of distant involvement are lung and bone.^{185,186} The metastases are of the stromal component, although entrapment of normal structures in the lung may simulate a biphasic composition.

Wide local excision with an adequate margin of normal breast tissue is sufficient therapy for most cytologically malignant phyllodes tumors,¹⁸⁴ but if there is any question of invasion of the fascia, the tumor should be removed together with the underlying muscle. There is no need for removal of the axillary nodes, except for the exceptional instances in which they are clinically involved.

If both the benign epithelial component and the stromal component are sampled, the diagnosis of phyllodes tumor is generally straightforward (tumor grading notwithstanding). The main differential diagnosis of malignant phyllodes tumors is with spindle cell metaplastic carcinoma (as discussed previously) and far less likely with other types of sarcoma (again largely depending on the presence or absence of a non-neoplastic epithelial component). Benign phyllodes tumors need to be distinguished mainly from cellular fibroadenomas, both of which will have increased stromal cellularity, but the latter is more likely to have a pericanalicular growth pattern and will have an even balance in the gland distribution within the stroma. It should be acknowledged that in some instances this may not be possible at a practical level or justified at a conceptual

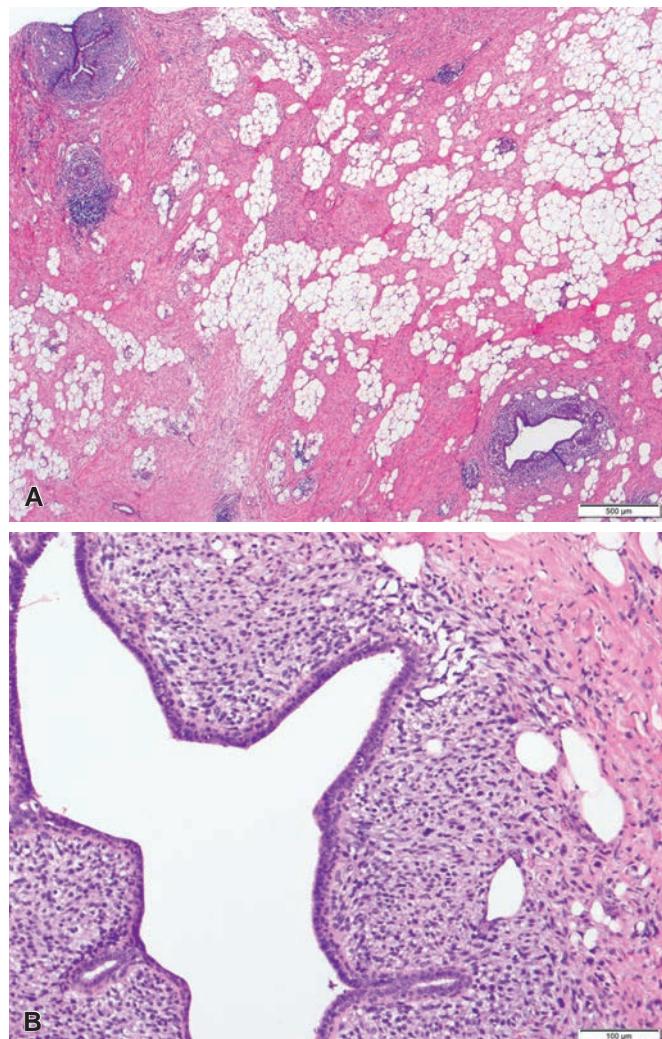


Figure 36.36 Periductal Stromal Tumor. **A**, This fibroepithelial tumor lacks the circumscription of fibroadenoma or phyllodes tumor and instead is seen as dispersed nodules. **B**, Higher power view reveals the hypercellular stroma surrounding a benign epithelial element.

level, in which case the term “benign fibroepithelial neoplasm” has been proposed by the WHO.¹⁷²

The neoplasm described as *periductal stromal tumor*¹⁸⁷ contains epithelial structures like those of fibroepithelial lesions, but the stromal component lacks the phyllodes architecture and tumor circumscription and instead is seen as dispersed nodules (Fig. 36.36). Stromal cell cytologic atypia and mitoses may be present.

Adenosis and Sclerosing Lesions

Adenosis

The term adenosis can be applied to any hyperplastic process that primarily involves the glandular component of the breast; it should, therefore, be used with a qualifier in order to acquire a specific clinicopathologic connotation.

Blunt Duct Adenosis

This is a term that has been applied variably in the literature and as such its use is no longer recommended. The WHO Classification

of Tumors of the Breast refers to this term as a synonym of columnar cell change.¹²²

Sclerosing Adenosis

Sclerosing adenosis is the best known form of adenosis because of its relative frequency and the potential for misdiagnosis as carcinoma. Most often, sclerosing adenosis is an incidental microscopic finding; however, in some instances it may present as an image-detected breast mass or as mammographically detected microcalcifications. The gross appearance can be of a small mass with a disk-like, somewhat multinodular configuration that cuts with increased resistance. In some cases, the overall gross appearance may be quite reminiscent of invasive carcinoma.

Microscopically, the most important diagnostic feature of the lesion is its architecture, as seen at low magnification. Sclerosing adenosis retains a rounded, lobulocentric configuration and is more cellular centrally than peripherally (Figs. 36.37 and 36.38). The elongated and compressed proliferating tubules are lined by epithelial cells and have a peripheral myoepithelial cell layer. The myoepithelial component predominates in some lesions and may even acquire spindle-shaped "myoid" features. Atypia in the form of cribriform areas, nuclear pleomorphism, and necrosis is absent. The stroma is dense and may show foci of elastosis, although not as commonly as in radial scar or invasive carcinoma. Microcalcifications may be present.

The involvement of myoepithelial cells in the process can be demonstrated with various immunohistochemical stains (see Figs. 36.37C and 36.38C) (smooth muscle myosin heavy chain, calponin, p63, or, less commonly now, actin), and the presence of basement membrane around the tubules with stains for laminin or type IV collagen, although the latter are not commonly used in clinical practice.

Morphologic variations of sclerosing adenosis that further complicate interpretation are the florid changes that may accompany pregnancy, the presence of apocrine metaplasia (which is accompanied by nuclear and nucleolar enlargement), the occasional occurrence of perineural invasion (Fig. 36.39),¹⁸⁸ and permeation of the walls of veins.¹⁸⁹

The risk of subsequent invasive carcinoma in patients with sclerosing adenosis is the same as for proliferative disease without atypia.¹⁹⁰

On occasion, foci of sclerosing adenosis may be secondarily involved by LCIS or even DCIS (Fig. 36.40).¹⁹¹ In these cases, the distortion already present because of the sclerosing adenosis may result in a mistaken diagnosis of invasive carcinoma. The low-power impression is critical to arriving at the correct diagnosis; foci of sclerosing adenosis (with or without CIS) have dilated ductules peripherally and narrow ones centrally, whereas invasive lobular carcinoma has no overall organization.¹⁹² Immunohistochemical evaluation demonstrating the presence of myoepithelial cells can be of assistance in recognizing the underlying benign lesion.

Nodular adenosis and **adenosis tumor** refer to sclerosing adenosis lesions that form a palpable or mammographic mass. The proliferating glands are better circumscribed forming a more discrete mass than in sclerosing adenosis.

Microglandular Adenosis

Microglandular adenosis is a rare form of adenosis in which small, uniform glands with open lumina containing eosinophilic secretions are distributed in a haphazard fashion within the fibrous tissue or fat (Fig. 36.41).^{193–195} The glands are composed of a single layer of small, uniform cuboidal cells with vacuolated or granular cytoplasm, lacking apocrine-type "snouts." In contrast to other forms of adenosis,

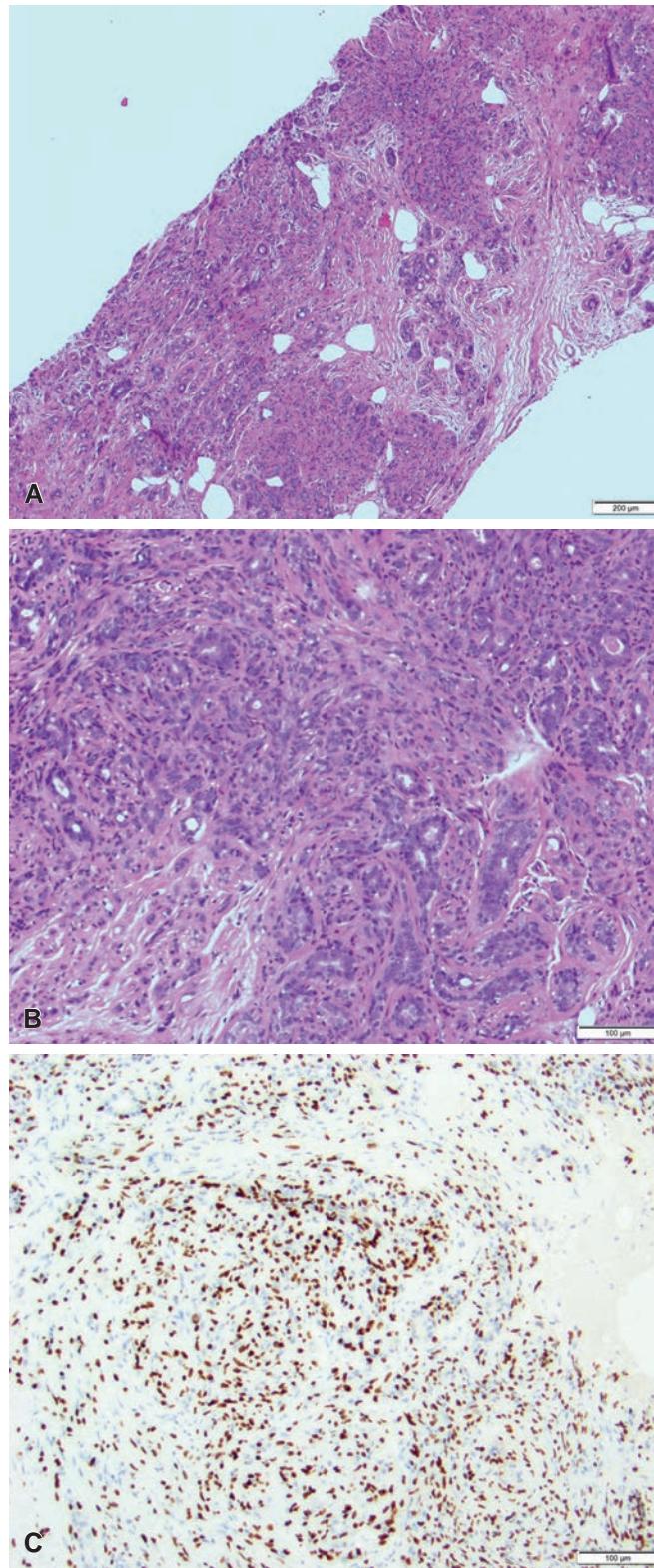


Figure 36.37 Sclerosing Adenosis. **A**, Low-power view. The lobular configuration of the small glandular proliferation is readily apparent even on this core needle biopsy specimen. **B**, Medium-power view. Note the spindle shape of the myoepithelial cells present. **C**, Immunohistochemical stain for p63 showing strong immunoreactivity in the myoepithelial cell component.

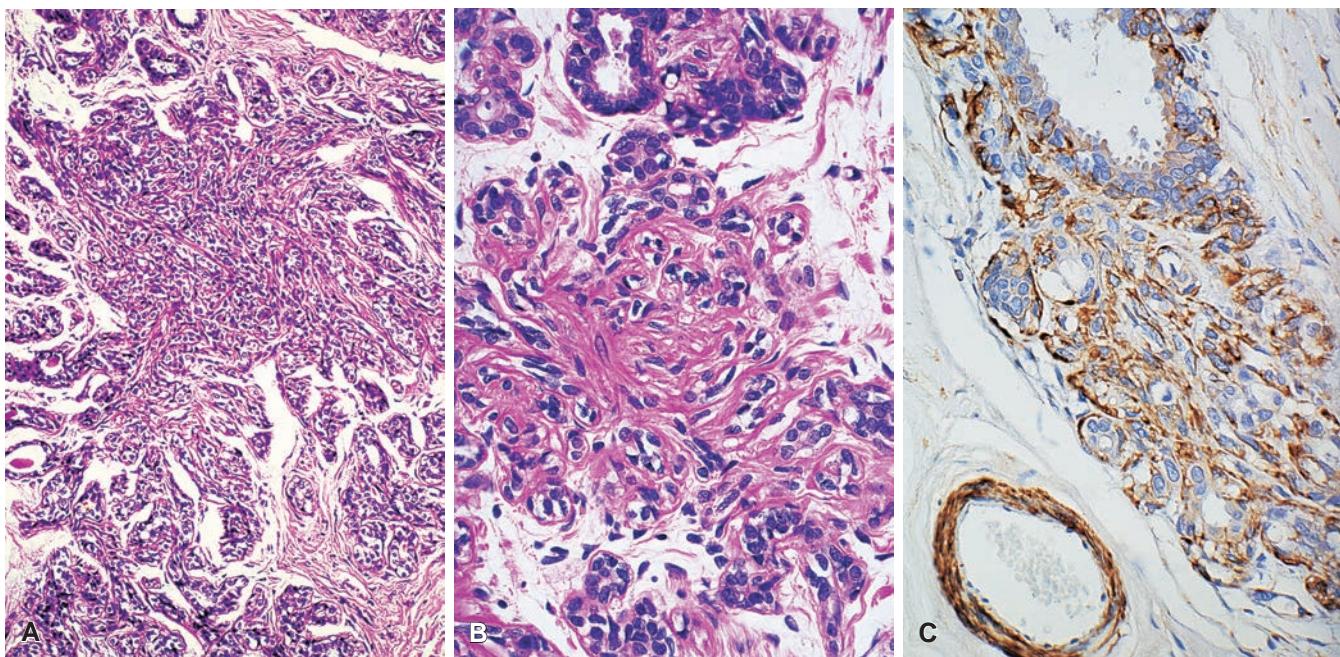


Figure 36.38 Sclerosing Adenosis. **A**, Low-power view. The lobular configuration of the lesion is obvious. **B**, Medium-power view of the myoepithelial cells in the center of the TDLU. **C**, Actin immunostain showing strong reactivity in the myoepithelial cell component.

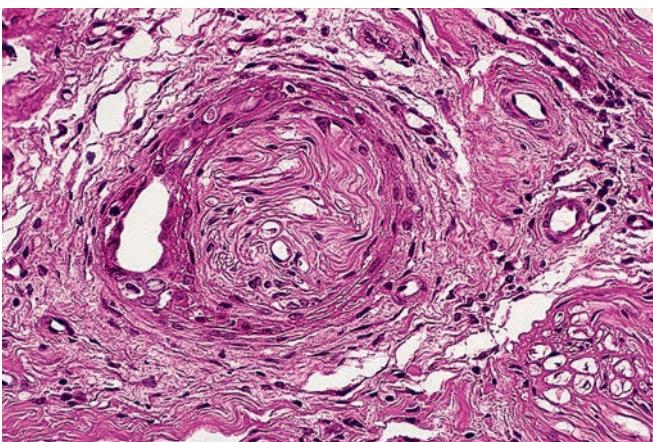


Figure 36.39 Benign "perineural invasion" in a breast lesion that had elsewhere the typical features of sclerosing adenosis.

the myoepithelial layer is absent.^{193,196} However, there is a basement membrane that can be appreciated immunohistochemically and ultrastructurally.¹⁹⁵ The stroma may be hyalinized but is not cellular or elastotic. Microglandular adenosis is ER, PR, and HER2 negative and strongly and diffusely positive for S-100 protein. The main differential diagnosis of this lesion is with tubular carcinoma, which also lacks a myoepithelial cell layer but is uniformly ER positive.¹⁹³

Atypical microglandular adenosis should be diagnosed when the glands begin to coalesce, forming small nests either solid or cribriform in architecture, often with cytologic atypia (Fig. 36.42). Luminal secretions are less prominent in atypical microglandular adenosis.

It is unclear whether microglandular adenosis is a benign process or whether it may be a precursor lesion¹⁹⁷; enough cases have been reported in continuity with carcinoma to suggest that the lesion may evolve into malignancy in some patients.¹⁹⁷⁻¹⁹⁹ Interestingly, a high percentage of these carcinomas in one series have been of the adenoid cystic type.¹⁹⁸ Actually, this frequently occurring spatial

relationship with an easily recognizable carcinoma, and the fact that microglandular adenosis is the only "benign" epithelial breast lesion devoid of myoepithelial cells, makes one wonder whether it represents an indolent form of invasive ductal carcinoma. Indeed recurrent losses of chromosome 5q and gains of 8q as well as mutations in TP53 have been reported in microglandular adenosis, particularly in cases with coexistent atypical microglandular adenosis and invasive carcinoma, specifically triple negative breast carcinomas.²⁰⁰⁻²⁰² Given the uncertainty about the role of microglandular adenosis as a precursor lesion, the need for excision to clear margins is controversial; diagnosis on a core needle biopsy should prompt an excision.

Apocrine Adenosis

Apocrine adenosis is a form of adenosis in which the glands are larger, the lining epithelium is apocrine in nature, and myoepithelial cells are present (Fig. 36.43).^{203,204} Occasionally nuclear atypia and nucleolar prominence are noted; when at least threefold variation in nuclear and nucleolar size is seen, *atypical apocrine adenosis* is said to be present. The subsequent breast cancer risk associated with apocrine adenosis and atypical apocrine adenosis is uncertain.^{205,206}

Tubular Adenosis

Tubular adenosis is an unusual form of adenosis, which is characterized by elongated, tubular, and branching glands arranged in a somewhat haphazard pattern. A myoepithelial cell layer is present, which is of value in distinguishing this lesion from invasive carcinoma, of which it can be a mimic (Fig. 36.44).²⁰⁷

Radial Scar and Complex Sclerosing Lesions

This is a group of breast lesions characterized by a generally small size, stellate shape, and a central fibroelastic core, with variable degree of epithelial proliferation and distortion.^{208,209} They have been variously designated as radial scar, complex sclerosing lesion,

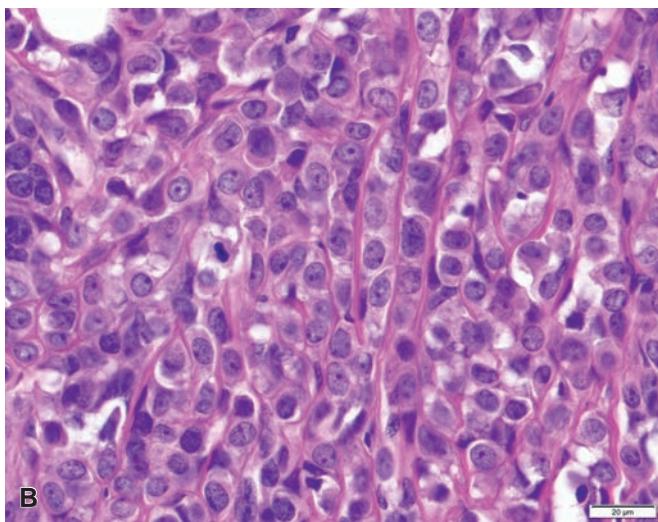
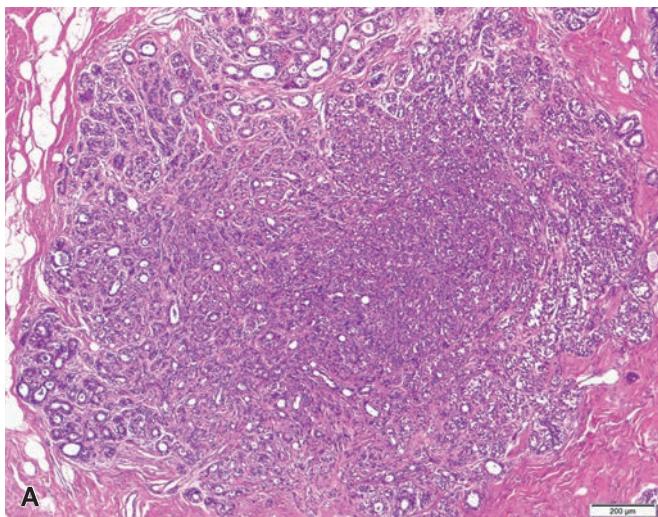


Figure 36.40 Sclerosing Adenosis With Lobular Carcinoma In Situ. **A**, Note the absence of infiltrative features at the border of the proliferation on low power. **B**, High power confirming the presence of LCIS in adenosis.

and infiltrating epitheliosis.²¹⁰ On mammography and gross examination, the irregular, stellate shape confers a resemblance to invasive ductal carcinoma (Fig. 36.45). Microscopically, the connective tissue center is densely fibrotic or fibroelastotic (Fig. 36.46). Basophilic elastic tissue may be seen in the walls of obliterated ducts and the stroma, sometimes in abundance. Embedded within the stroma are small ducts and glands that appear disorganized due to the distortion caused by the fibrosis, but which are still composed of both epithelial and myoepithelial cells; at the periphery of the “radial spokes” are larger duct-like structures that may be dilated and/or may exhibit UDH.

The terms radial scar and complex sclerosing lesion are used somewhat interchangeably, with some authors making the distinction on size (<1 cm for the former vs. >1 cm for the latter) and others making the distinction based on the degree to which the lesion is organized around a central scar. The most important aspect of radial scars/complex sclerosing lesions is the differential diagnosis with invasive ductal carcinoma, a problem that may be compounded if the radial scar is involved by DCIS or LCIS (Fig. 36.47). The diagnostic criteria for the identification of carcinoma should be the same whether a central scar is present or not. They include the cytoarchitectural criteria as seen in H&E-stained sections, as well as evaluation for

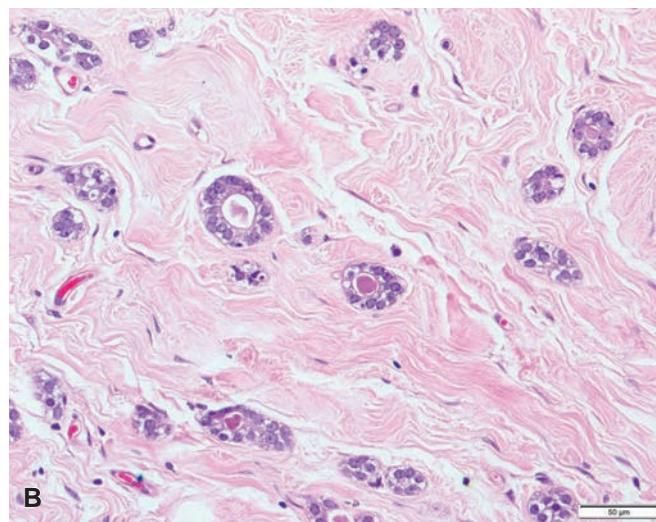
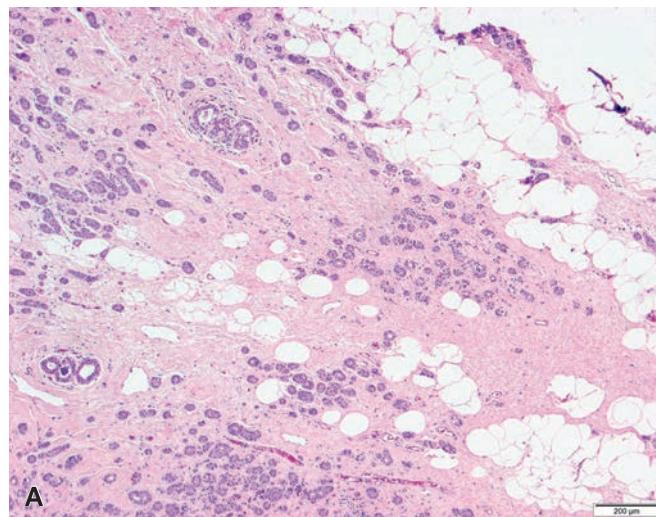


Figure 36.41 Microglandular Adenosis. **A**, Low-power appearance, showing haphazardly scattered small round glands. **B**, On high power, the glands are open and contain bright eosinophilic luminal secretion. There is no myoepithelial cell layer.

the presence of a myoepithelial cell layer, using immunohistochemistry if necessary. Note that reduction in staining has been reported with some myoepithelial cell markers in this setting, thus a panel of immunohistochemical stains is recommended.²¹¹

There is no evidence to suggest radial scars are a direct precursor lesion to invasive breast carcinoma; any risk associated with this lesion is related to the presence of proliferative disease within the lesion.²⁰⁸ Studies have demonstrated that women with radial scars have a risk for breast cancer that is almost twice that of women without radial scars, regardless of the histologic type of benign breast disease present^{212,213}; however others contend that there is no increase in breast cancer risk above and beyond that conferred by the histologic type of benign breast disease present in the background breast tissue.^{214,215} The management of mammographically detected radial scar is usually core needle biopsy with follow-up conservative excision to exclude a worse lesion, though with greater sampling by large gauge and vacuum-assisted core biopsy needles, excision may not be necessary in every case.²¹⁶

Tubular adenoma presents in young adults as a solitary, well-circumscribed, firm, tan-yellow mass composed microscopically of closely packed uniform small tubules lined by a single layer of epithelial cells and an attenuated layer of myoepithelial cells; the

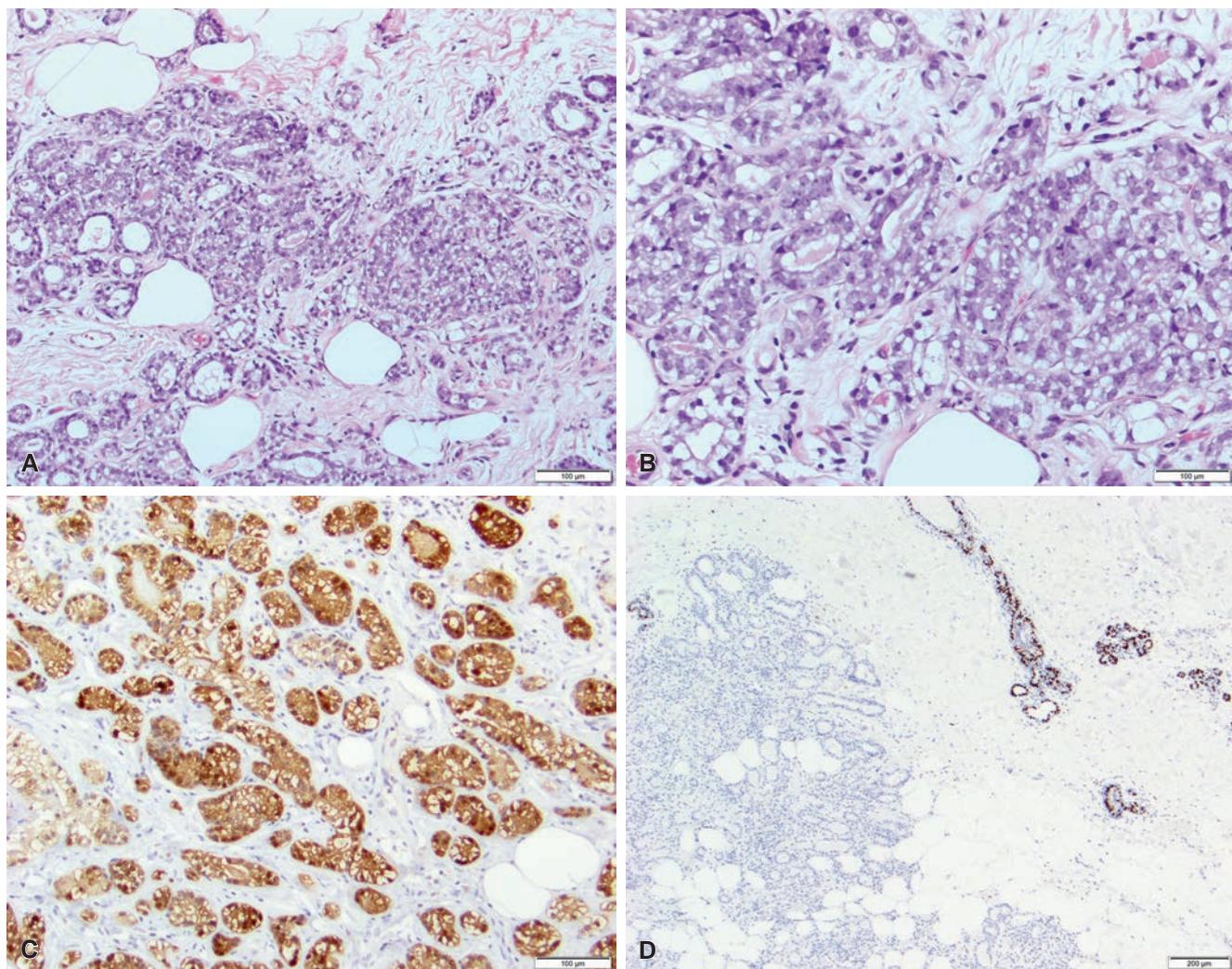


Figure 36.42 Atypical Microglandular Adenosis. **A**, Intermediate-power appearance, showing haphazardly arranged small round glands peripherally, with solid nests centrally. **B**, On high power, the cytologic atypia is appreciated; some luminal secretions are retained (top right of field). **C**, An S-100 protein immunostain is strongly positive. **D**, Estrogen receptor immunostain is negative in microglandular adenosis with good internal control in an adjacent normal duct.

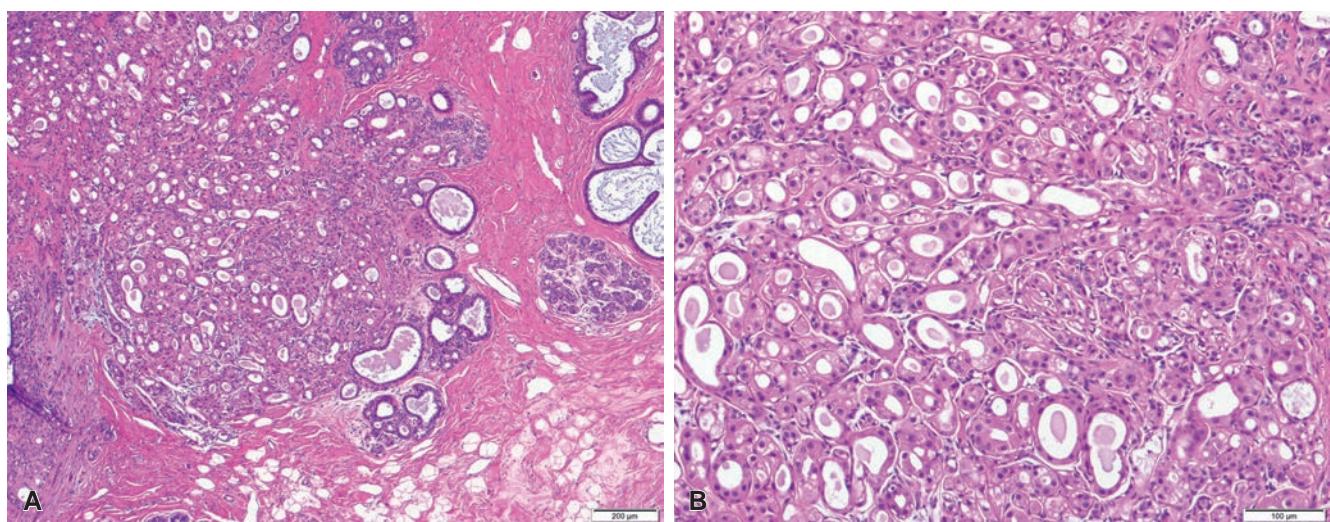


Figure 36.43 Apocrine Adenosis. **A**, This low-power image shows the lobulo-centric architecture of adenosis; apocrine features are present. **B**, At higher power, the apocrine cells can be evaluated. The nuclei are round with large nucleoli, but there is no significant nuclear enlargement or variability.

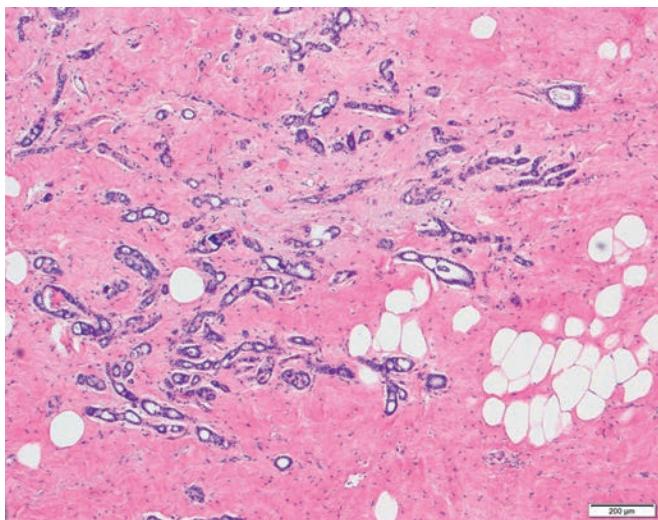


Figure 36.44 **Tubular Adenosis.** This low-power image shows the characteristic elongated, tubular, and branching glands of tubular adenosis arranged in a somewhat haphazard pattern.



Figure 36.45 Gross appearance of radial scar.

stroma is sparse. It is not clear whether this is a separate entity or a pattern of fibroadenoma.²¹⁷

Lactating adenoma presents as a solitary or multiple freely mobile breast masses during pregnancy or the puerperium. The lesion is more likely a localized focus of hyperplasia in the lactating breast, which may also develop in ectopic locations such as the axilla, chest wall, or vulva.^{26,217} Grossly, the lesion is well circumscribed and lobulated. The cut surface is gray or tan, in contrast to the white color of fibroadenoma (Fig. 36.48). Areas of infarction may be seen. Microscopically, hyperplastic lobules are present lined by actively secreting cuboidal cells (Fig. 36.49). This lesion may be confused with the proliferative and secretory changes brought on by pregnancy

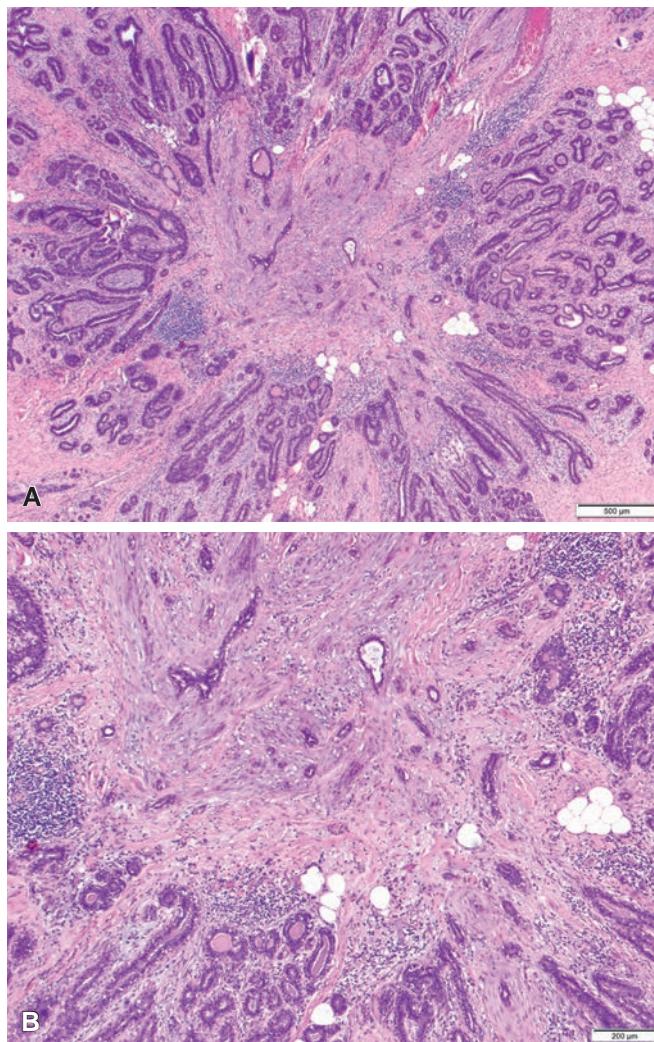


Figure 36.46 **Radial Scar.** **A**, Typical stellate shape of radial scar as seen on low power. **B**, Benign ductular structures are entrapped in the central fibroelastic stroma.

in a preexisting fibroadenoma, a distinction that is likely of no clinical consequence.²⁶

Papillary Lesions

Intraductal Papilloma

Intraductal papilloma of the breast occurs most commonly between the ages of 30 and 50 years. It can arise in large or small ducts; consequently, it can be identified grossly as a polypoid intraductal mass or be found only on microscopic examination. Intraductal papilloma can give rise to bloody nipple discharge and may be palpable in the subareolar location, but its diameter rarely exceeds 3 cm. The lesion is soft and friable and may have areas of hemorrhage. The duct that contains the papilloma may be dilated (Fig. 36.50). Approximately 90% of cases are solitary. Multiple papillomas are seen in slightly younger patients, arise in smaller, more peripherally located ducts, are usually not associated with nipple discharge, and are bilateral in one-quarter of cases.

Microscopically, papillomas are complex, cellular, and often intricately arborescent (Fig. 36.51A). Features favoring benignity in a papillary breast lesion are a hyalinized stroma in broad papillary

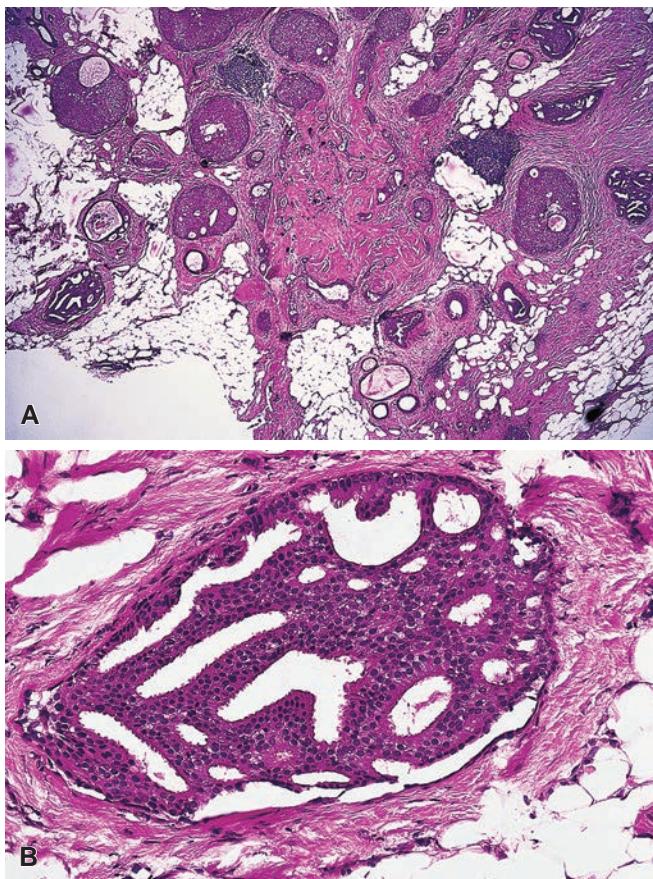


Figure 36.47 **A** and **B**, Radial scar with associated low-grade ductal carcinoma in situ.

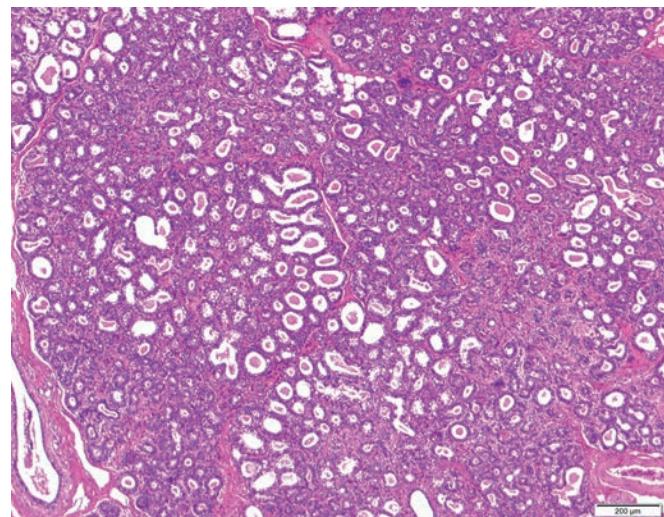


Figure 36.49 So-called Lactating Adenoma. The hyperplastic lobules show secretory change.

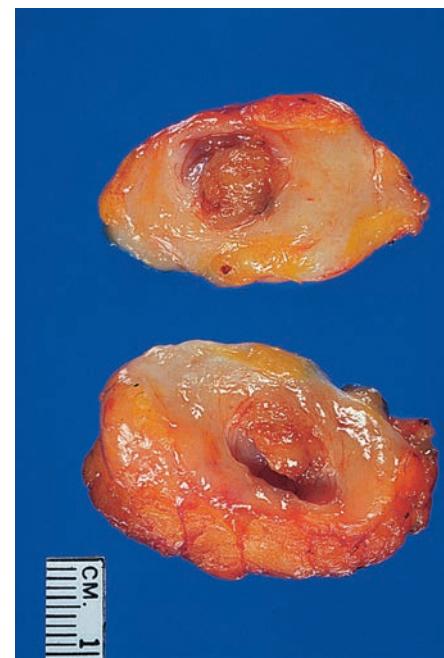


Figure 36.50 Gross Appearance of an Intraductal Papilloma. A polypoid mass is seen protruding within the lumen of a markedly dilated duct.

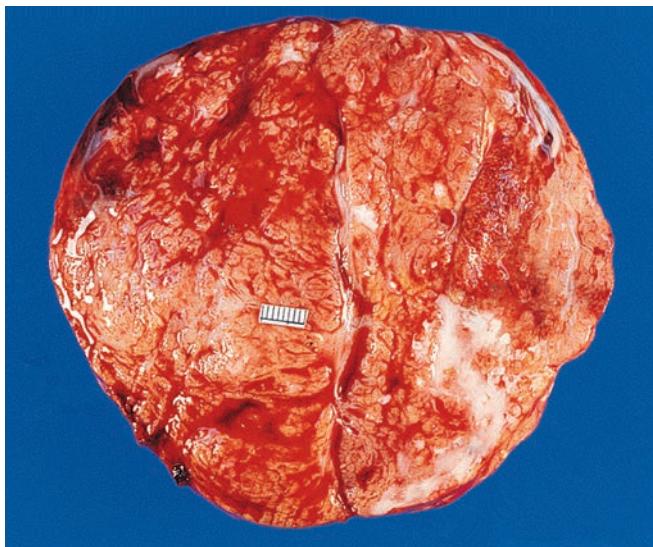


Figure 36.48 Gross Appearance of a Lactating Adenoma. The mass has a distinct lobular configuration, yellowish color, and marked vascularization.

fibrovascular cores, the presence of two cell types (epithelial and myoepithelial) (see Fig. 36.51B), normochromic often oval epithelial cell nuclei, scanty mitotic activity, the presence of foci of apocrine metaplasia, and lack of a cribriform pattern.²¹⁸ Necrosis is nearly always absent (but see later). The presence of a myoepithelial cell

component can be highlighted with various immunostains, such as p63, calponin, and smooth muscle myosin heavy chain. Clonal analysis has shown that intraductal papilloma is a clonal lesion, a finding that supports its neoplastic nature.²¹⁹

Morphologic variations sometimes encountered in intraductal papilloma include:

1. Partial or total hemorrhagic infarct. This change, which is probably caused by interruption of the blood supply, is entirely different from the tumor necrosis seen in carcinoma, and is most commonly seen following a fine-needle aspiration (FNA) or core needle biopsy procedure.
2. Necrosis. Necrosis has been described in papillomas involved by florid UDH; its presence should not lead to a misdiagnosis of DCIS.²²⁰ The necrosis is most often focal in nature.

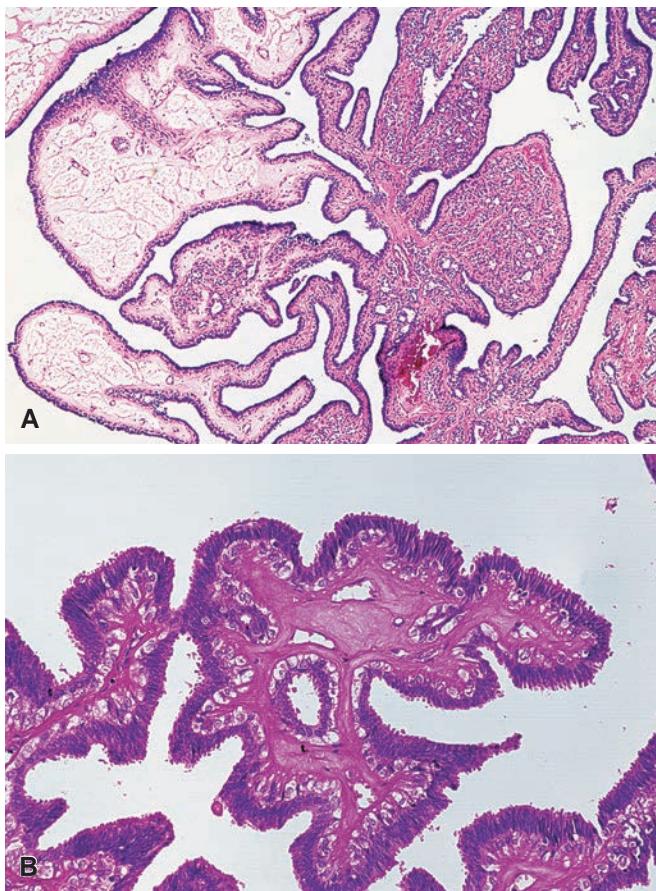


Figure 36.51 Intraductal Papilloma. **A**, Low-power appearance showing complex arborizing architecture. **B**, High-power view showing dual cell composition, with a well-defined row of myoepithelial cells.

3. Squamous metaplasia. This change is probably secondary to focal necrosis and is uncommon.
4. Entrapped glands within or adjacent to the papilloma. This is the most problematic change in terms of possible overinterpretation. It is the result of sclerosis (perhaps sometimes secondary to infarction), which leads to marked distortion of the glandular component and sometimes to the presence of isolated tubules embedded in dense fibrous tissue. When pronounced throughout the lesion, use of the diagnosis "sclerosed papilloma" is appropriate (Fig. 36.52). Preservation of the two-cell layer, as well as accompanying hemosiderin deposits and cholesterol clefts, are supportive diagnostic features. Immunohistochemical stains for myoepithelial cells, such as p63 or smooth muscle myosin heavy chain, are often helpful in cases where the two-cell layer is difficult to appreciate on H&E stained sections.
5. Superimposed florid UDH. In cases in which distinction between usual (florid) ductal hyperplasia and carcinoma *in situ* is problematic, the combination of ER and HMW cytokeratin stains (e.g., CK5/6) can be very useful. The former will demonstrate a heterogeneous pattern of staining with both ER and CK5/6; atypical ductal proliferations and DCIS will show strong, diffuse staining with ER and an absence of staining with CK5/6.
6. **Ductal adenoma.** This lesion lacks the arborescent papillary quality of the typical papilloma, but its intraductal location with a dense fibrotic capsule and the distorted epithelial proliferation composed of two cell types (as confirmed immunohistochemically) embedded in a sclerotic stroma suggest that these lesions likely represent highly sclerotic variants of intraductal papilloma.^{221,222} Ductal

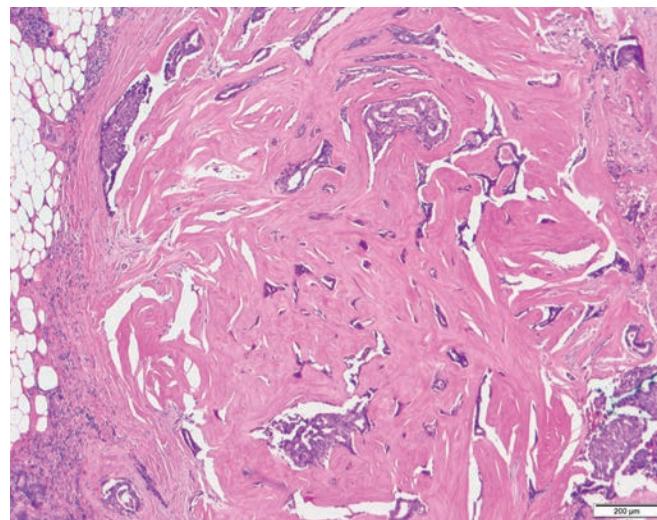


Figure 36.52 Sclerosed papilloma of breast showing entrainment of epithelial structures by fibrotic stroma, resulting in a pseudo-invasive appearance.

adenoma with tubular features can be seen as a component of Carney syndrome.²²³

7. Sebaceous metaplasia. This is an exceptionally rare but well-documented event.²²⁴
8. **ADH and DCIS** arising in an intraductal papilloma. The cytologic criteria for the recognition of these alterations are no different from those employed when a papilloma is not present (see later).^{225,226} The absence of myoepithelial cells in the areas of atypia may be confirmed with immunohistochemical stains (e.g. p63, SMMHC); of greater utility is the combined use of ER and CK5/6 (see previous discussion for use of these immunostains in the differential diagnosis with UDH). The recommendation of the WHO Classification of Tumors of the Breast Working Group is that foci of low nuclear grade atypia measuring less than 3 mm in extent arising in a papilloma be classified as intraductal papilloma with ADH; those with ≥ 3 mm of atypia merit a diagnosis of DCIS involving an intraductal papilloma (Fig. 36.53).¹²²
9. Post-biopsy or FNA with benign epithelial displacement/implantation. Excision specimens of benign intraductal papilloma that have had a prior needling procedure can have small irregular nests and single epithelial cells with degenerative features distributed haphazardly within the biopsy site, which can be a mimic for invasive carcinoma. (Fig. 36.54).²²⁷

Solitary intraductal papilloma is a benign lesion that is curable by local excision. Management following core biopsy is evolving; however, most patients are still referred for surgical consultation. The subsequent breast cancer risk is similar to that of other proliferative lesions without atypia (1.5–2 fold).^{228,229} Multiple papillomas have been found to be associated with a higher risk.^{229–231} Some authors have reported that papillomas with foci of atypical hyperplasia ("atypical papillomas") are associated with a substantially increased risk for carcinoma largely restricted to the anatomic region of the original papilloma,²³² whereas others report that the risk is the same as when the atypical hyperplasia is unrelated to a papilloma and furthermore that the risk is conferred equally on both breasts.²²⁹

Papillary Ductal Carcinoma *In Situ*

A lesion considered to be distinct from papilloma with DCIS, as explained later, is papillary DCIS.²³³ In contrast to the dual population of epithelial and myoepithelial cells seen in intraductal papilloma,

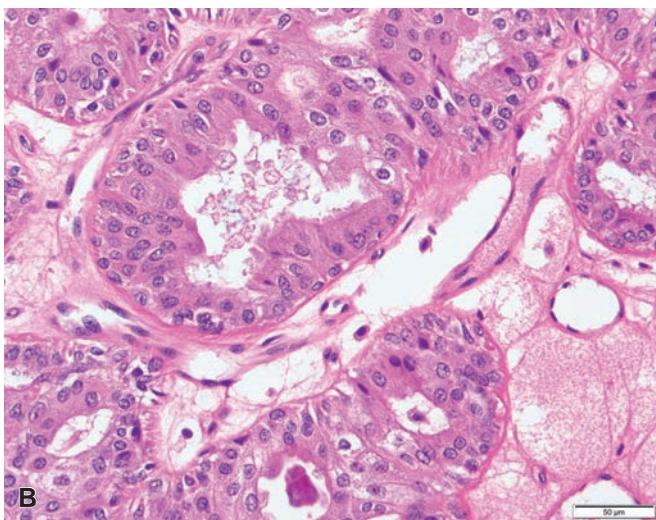
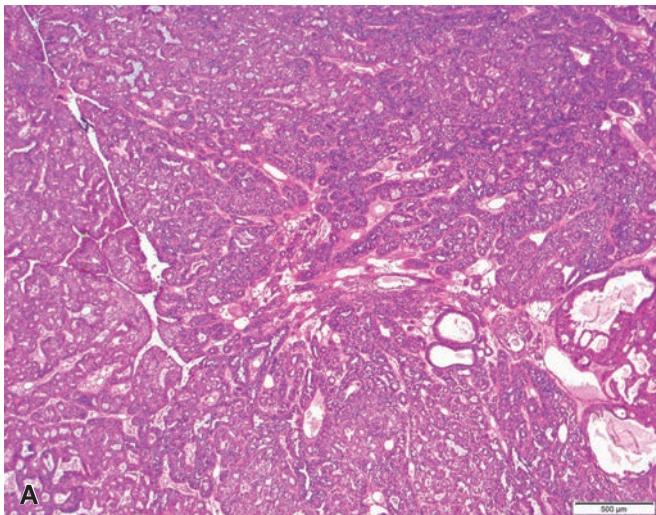


Figure 36.53 Intraductal Papilloma Involved by Ductal Carcinoma In Situ. **A**, Low-power appearance showing complex arborizing architecture with fibrovascular cores (particularly prominent in the *lower left* of field) and epithelial proliferation. **B**, High-power view showing monomorphic epithelial cells with areas of cribriforming; note the presence of scattered myoepithelial cells juxtaposed to the fibrovascular cores.

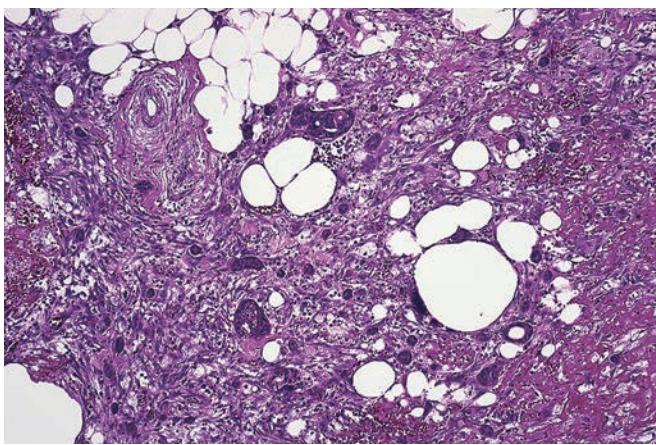


Figure 36.54 Displaced epithelium following core needle biopsy of a benign intraductal papilloma. The presence of nests and single squamoid-appearing cells embedded in a reactive stroma are characteristic of displaced epithelium.

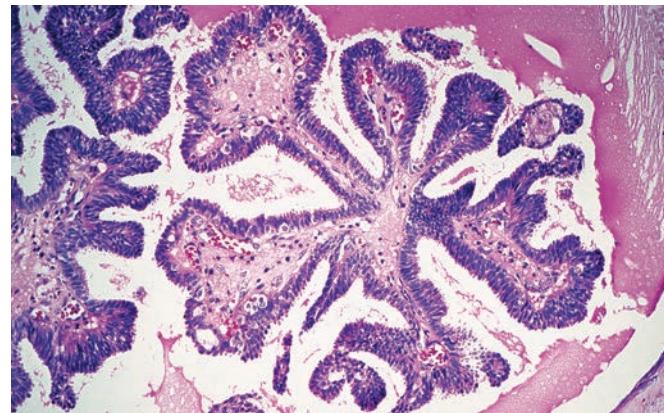


Figure 36.55 Papillary Ductal Carcinoma In Situ. The arborizing nature of this tumor and the prominent fibrovascular core in this example are not too different from those of a benign papilloma. The absence of a myoepithelial cell layer along the fibrovascular core along with the nuclear atypia clinch the diagnosis.

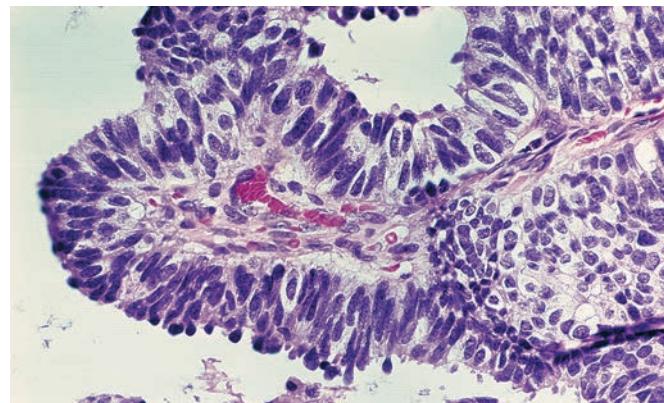


Figure 36.56 High-Power View of Papillary Ductal Carcinoma In Situ. Note the multi layering of cells, loss of nuclear polarity, marked hyperchromasia, and lack of a myoepithelial cell layer along the fibrovascular cores.

Papillary DCIS is characterized by a single, uniform population of atypical epithelial cells, usually of low or intermediate nuclear grade (Figs. 36.55 and 36.56). The cells are arranged perpendicular to the delicate fibrovascular cores that typify papillary carcinomas (see following sections).²¹⁸ Notably, there are no myoepithelial cells lining the fibrovascular cores, supporting the premise that the papillae arise *de novo* as part of the neoplastic process,²³³ whereas in DCIS involving a papilloma, the identification of a myoepithelial cell layer along the fibrovascular cores indicates the presence of an underlying benign papilloma. A myoepithelial cell layer is present at the periphery of spaces involved by papillary DCIS, consistent with the *in situ* nature of the disease. Helpful clues to the diagnosis of papillary DCIS are the presence of other patterns of DCIS in adjacent ducts and the absence of apocrine metaplasia within the papillary proliferation. A potential diagnostic trap is the occasional presence of scattered large pale eosinophilic cells, known as globoid cells, concentrated along the basal layer, which can be mistaken for myoepithelial cells (Fig. 36.57).²¹⁸

Encapsulated Papillary Carcinoma

Encapsulated papillary carcinoma is a well-circumscribed papillary tumor surrounded by a thick fibrous capsule (Fig. 36.58). This tumor

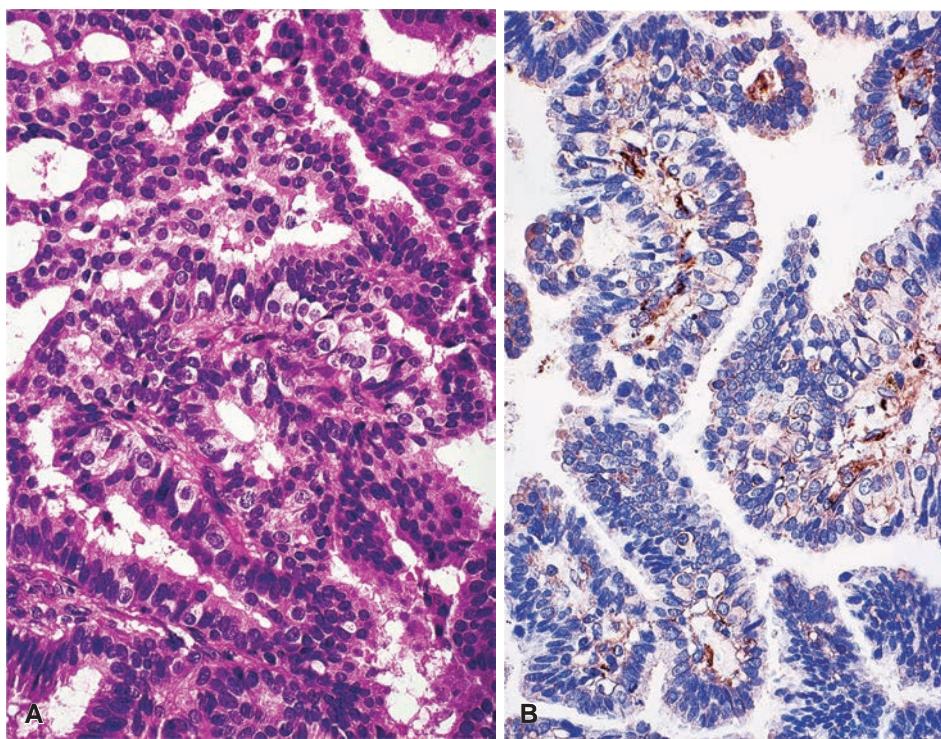


Figure 36.58 **A** and **B**, Papillary ductal carcinoma in situ with “globoid” cells. These cells, which are immunoreactive for GCDFP-15 and cytokeratin, should not be confused with myoepithelial cells. **B**, The globoid cells are negative for myoepithelial cell markers, as is demonstrated with this smooth muscle actin immunostain.



Figure 36.59 Encapsulated Papillary Carcinoma of the Breast. The papillary configuration of the tumor is grossly evident.

arises in older women, is centrally located, and often presents as a breast mass with or without bloody nipple discharge. On microscopic examination, the tumor gives the appearance of arising within a duct or “cyst” and had traditionally been considered to be an *in situ* or “intracystic” lesion. The fibrovascular cores are delicate and are surmounted by a monotonous proliferation of atypical epithelial cells that may, in addition to the papillary pattern, have areas of solid or cribriform architecture (Fig. 36.59). As with papillary DCIS, there is an absence of myoepithelial cells along the fibrovascular cores, but in contradistinction to the aforementioned DCIS, there is also an absence of myoepithelial cells at the periphery of most encapsulated papillary carcinomas,^{234–236} raising the possibility that these tumors may be low-grade invasive carcinomas rather than *in*

situ lesions.^{237,238} Further evidence of the potential invasive nature of encapsulated papillary carcinoma is the rare occurrence of axillary lymph node metastases, even in the absence of conventional invasive carcinoma.²³⁹ It is important to evaluate for areas of unequivocal conventional invasive carcinoma, as this will influence how the patient is staged and treated. This can be more challenging than might be imagined as the majority of patients have undergone a core needle biopsy procedure with the consequent displacement of epithelial nests into the biopsy site and fibrous capsule. Therefore, it is prudent to restrict diagnosis of associated invasive carcinoma to foci clearly away from the biopsy site. As far as tumor staging, it is the recommendation of the WHO Working Group that encapsulated papillary carcinomas be staged and managed as *in situ* lesions (Tis); any associated microinvasive or invasive carcinoma should be reported and staged according to the size of the largest focus of conventional invasive carcinoma.²³⁷ Encapsulated papillary carcinomas are typically ER and PR positive and HER2 negative. The vast majority of encapsulated papillary carcinomas have low- or intermediate-grade nuclei and behave in an indolent manner; however, there are rare cases of encapsulated papillary carcinoma that have high-grade nuclei and a brisk mitotic rate.²⁴⁰ Recent data indicate that these particular tumors, which represent approximately 3% of encapsulated papillary carcinomas, behave in a more aggressive manner and as such should be staged and managed as conventional invasive carcinoma of similar size.²⁴⁰

Solid Papillary Carcinoma

Solid papillary carcinoma presents in older women, often as an image-detected breast mass. Microscopically the tumor is composed of multiple, solid nests of neoplastic epithelial cells, within which is a fine fibrovascular network conferring the papillary architecture (Fig. 36.60). The epithelial cells may be spindled and have a streaming

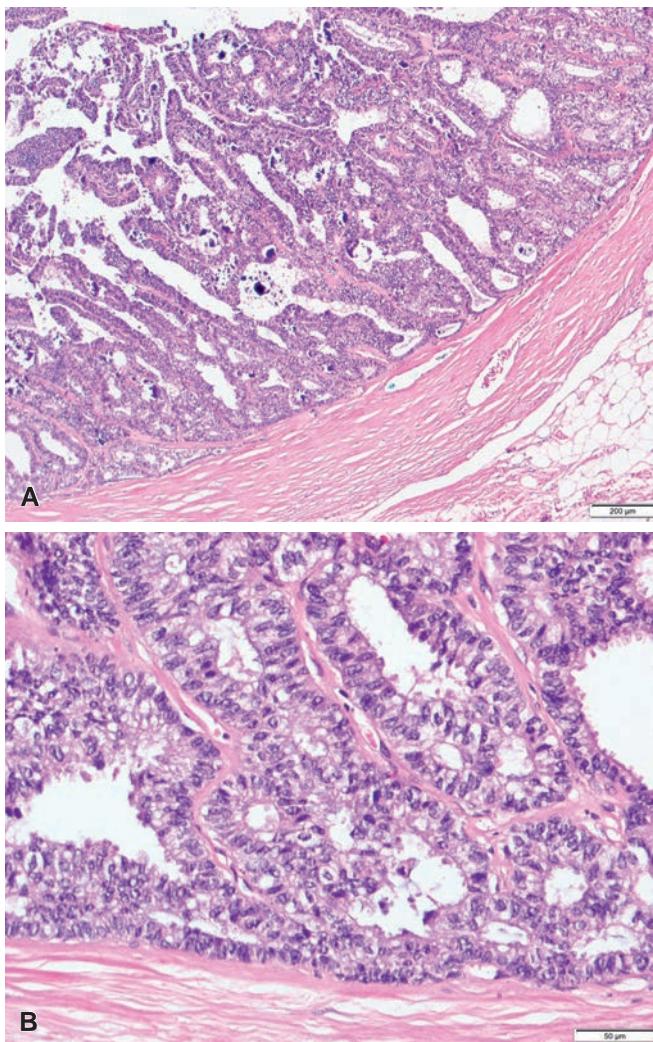


Figure 36.59 Encapsulated Papillary Carcinoma. **A**, Low-power view showing the fibrous capsule surrounding an encapsulated papillary carcinoma. At this power, the papillary architecture is apparent. **B**, At higher power the monotonous neoplastic epithelial cell population is better appreciated; in addition, note the cribriform architecture, the absence of myoepithelial cells at the periphery of the EPC (lower left of field), and the absence of myoepithelial cells running along the fibrovascular cores.

appearance mimicking usual ductal hyperplasia. They may also have granular eosinophilic cytoplasm and fine nuclear chromatin consistent with endocrine differentiation. Mucin production is commonly seen in solid papillary carcinoma. As with papillary DCIS and encapsulated papillary carcinoma, there is an absence of myoepithelial cells within the neoplastic nodules. Studies have reported an absence of myoepithelial cells at the periphery of at least some cases of solid papillary carcinoma.²⁴¹ Thus, like encapsulated papillary carcinoma, this tumor may be an indolent, invasive carcinoma rather than an *in situ* lesion.²⁴² The WHO Working Group provides recommendations to aid in categorization of solid papillary carcinoma as *in situ* or invasive disease.²⁴²

Tumors with rounded nests and a complete or partial myoepithelial cell layer should be classified as DCIS, solid papillary pattern. Tumors composed of nests with irregular borders and a geographic, jigsaw growth pattern and an absent myoepithelial cell layer may be considered invasive disease.²⁴²

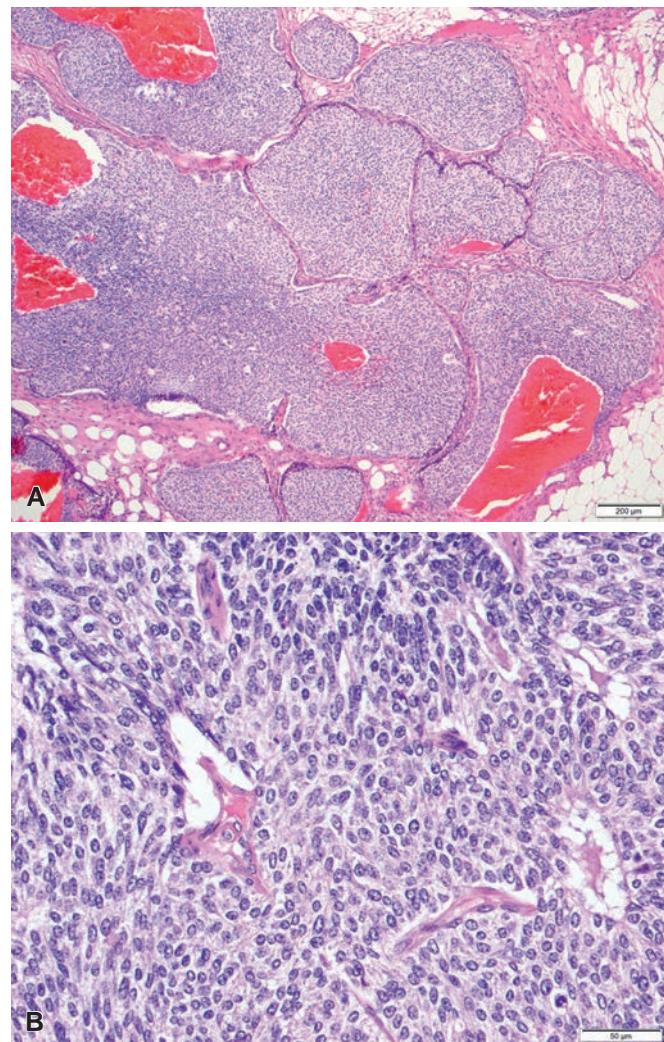


Figure 36.60 Solid Papillary Carcinoma. **A**, Low-power view showing multiple solid nests of neoplastic epithelial cells. **B**, High-power view reveals the fibrovascular network not readily appreciated at low power. The cells have a streaming appearance in areas but are monotonous with cytologic atypia.

Tumors in which some but not all nests lack a myoepithelial cell layer are more difficult to classify. The recommendation is that if there is uncertainty about invasion, the lesion should be reported as *in situ* carcinoma for staging and management purposes.

The major differential diagnostic consideration is with UDH. Recognition of the fine fibrovascular network is the first step to separating these two entities. Other features favoring solid papillary carcinoma over UDH include a very monotonous appearance to the epithelial cells, cellular polarization around the fibrovascular cores, mucin production, and mitotic activity. In problematic cases, the combination of ER and CK5/6 can aid in diagnosis. ER is strongly and diffusely positive and CK5/6 is negative in solid papillary carcinoma.²⁴³

Solid Papillary Carcinoma With Reverse Polarity

Solid papillary carcinoma with reverse polarity (SPCRP) is a relatively recently described entity that is characterized by, as the name implies, solid papillary nests of bland columnar epithelial cells in which

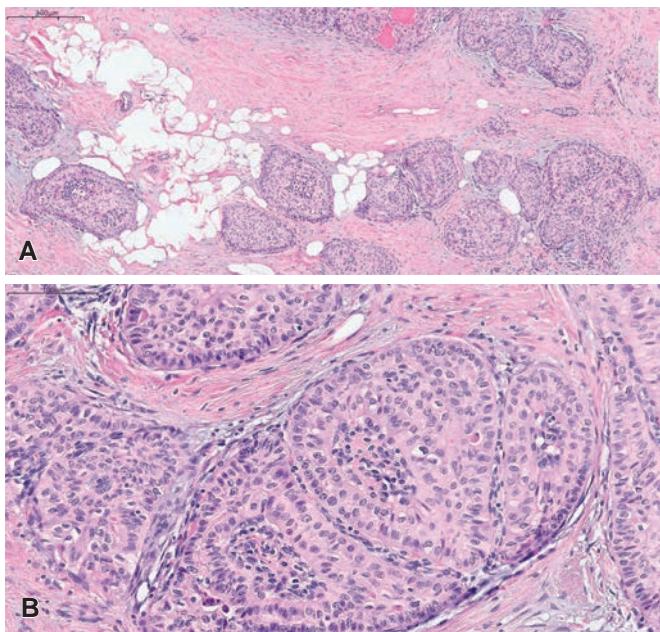


Figure 36.61 Solid Papillary Carcinoma with Reverse Polarity. **A**, Low-power view showing solid papillary nests of neoplastic epithelial cells infiltrating through the breast parenchyma. **B**, Higher-power demonstrating the fibrovascular core and the characteristic reverse polarization of the tumor cells.

nuclei of low or intermediate grade are apically rather than basally located (“reverse polarity”). Foamy histiocytes are often present in the papillary cores.^{243a} The tumor cell nests infiltrate through the breast parenchyma and adipose tissue in a haphazard pattern, and lack a surrounding myoepithelial cell layer (Fig. 36.61). The morphology of these tumors is so striking, that once encountered, subsequent cases are readily recognized. The tumor cells are typically ER, PR and HER2 negative (though ER and/or PR positivity is reported); interestingly both low and high molecular weight cytokeratins are expressed by the epithelial cells.^{243a} Earlier reports describing a “breast tumor resembling tall cell variant of papillary thyroid carcinoma”^{243b,243c} bear some similarities to SPCRP, but because SPCRPs express breast markers (GCDFP-15, mammaglobin) and lack expression of thyroid markers (TTF-1 and thyroglobulin) this term better describes the lesions. Molecular analysis of these tumors has demonstrated recurrent *IDH2* as well as *PIK3CA* and *PIK3R1* mutations.^{243a,243d} While little clinical follow-up is available for these rare tumors, they appear to behave in an indolent manner.

Invasive Papillary Carcinoma

Invasive papillary carcinoma is a very rare entity.²⁴⁴ Papillary DCIS, encapsulated papillary carcinoma, and/or solid papillary carcinoma with associated invasive ductal or mucinous carcinoma should be categorized as such and not as invasive papillary carcinoma. Metastasis to the breast, such as from the ovary or lung, should be considered in cases of apparent invasive papillary carcinoma before rendering a diagnosis of primary papillary carcinoma of the breast.

Nipple Lesions

Nipple Adenoma

Nipple adenoma, also known as florid papillomatosis of the nipple ducts and erosive adenomatosis, is a benign proliferation of glands

embedded in a fibrotic stroma (Fig. 36.62). It usually occurs in the fourth or fifth decade, is nearly always unilateral, and is often accompanied by serous or bloody discharge from the nipple. Clinically, the nipple may appear eroded, and the disease may be confused with Paget disease.

Microscopically, the most common pattern seen is of marked papillomatous changes, often associated with distortion induced by the dense stroma present. The latter is referred to by Rosen and Caicco²⁴⁵ as the sclerosing papillomatosis pattern, the other patterns being papillomatosis (without sclerosis) and adenosis (the least common of the three). The features used to identify this lesion as benign are to a large extent analogous to those seen in intraductal papilloma and UDH. They include the presence of a dual population of epithelial and myoepithelial cells (confirmed if needed by immunohistochemical evaluation), an oval nuclear shape, lack of atypia, “streaming,” the formation of peripheral clefts, and the absence of a cribriform pattern. Features of which to be aware in this lesion relate to the close interaction of the glandular epithelium of the mammary ducts with the squamous epithelium from the epidermis (Fig. 36.62), resulting in formation of adenosquamous nests that may be overinterpreted. Otherwise typical nipple adenomas can exhibit small foci of necrosis in the center of the proliferating ducts (Fig. 36.63).²⁴⁵

A note of warning is in order; just because an intraductal papillary lesion is located in or close to the nipple, it does not necessarily mean that it is a nipple adenoma and, therefore, benign. Papillary DCIS and invasive ductal carcinomas can also occur in this location, some occasionally even arising within a nipple adenoma.^{245,246}

The treatment of uncomplicated nipple adenoma is local excision.^{245,247}

Squamous Metaplasia of Lactiferous Ducts

SMOLD presents clinically as recurrent abscess with or without fistula formation.²⁴⁸ As the name implies, the lesion is characterized by extension of the squamous epithelium of the nipple further than the usual 1–2 mm down the lactiferous ducts. The resulting accumulation of keratinaceous debris leads to duct rupture with consequent inflammatory response (Fig. 36.64). Patients are often managed with incision and drainage on the presumption of mastitis with abscess formation. By the time tissue samples reach the pathology department, the inflammatory response is often quite severe and specimens are sent piecemeal, making recognition of the underlying squamous metaplasia of the lactiferous ducts difficult. The diagnosis should be considered in this clinicopathologic scenario so that the patient may be directed to appropriate management, namely wide excision of the involved duct often with a wedge resection of the nipple to facilitate eradication of the process.

Paget Disease

Paget disease is the name given to a crusted lesion of the nipple caused by breast carcinoma in the nipple epithelium, as originally described by Sir James Paget in 1874. It is accompanied in nearly all instances (>95%) by an underlying breast carcinoma, typically high-grade DCIS, with or without associated stromal invasion. In this regard, the presence of Paget disease is a secondary, albeit dramatic, feature of the tumor. The management and prognosis depend largely on the *in situ* versus invasive nature of the underlying carcinoma, and on the presence or absence of axillary lymph node involvement, rather than on the presence or appearance of the intraepidermal component in the nipple.

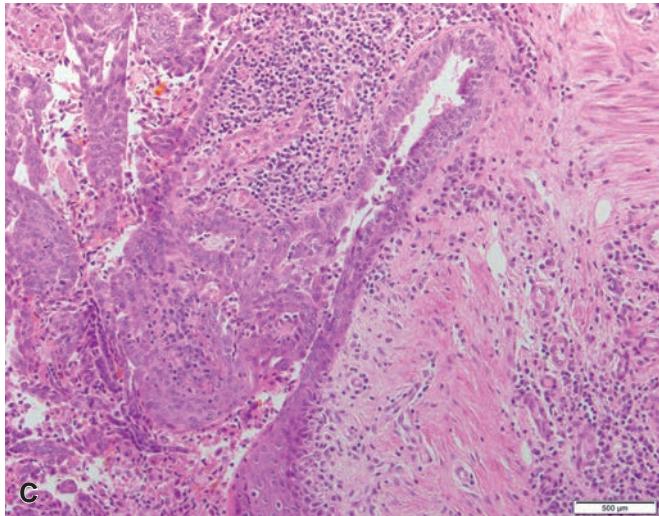
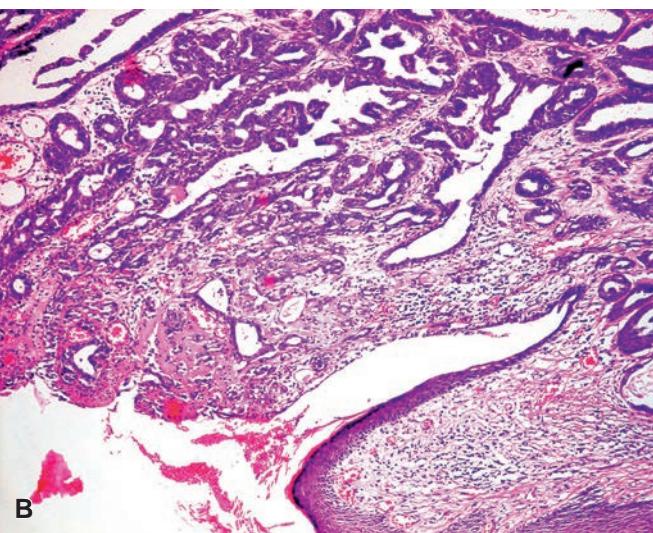
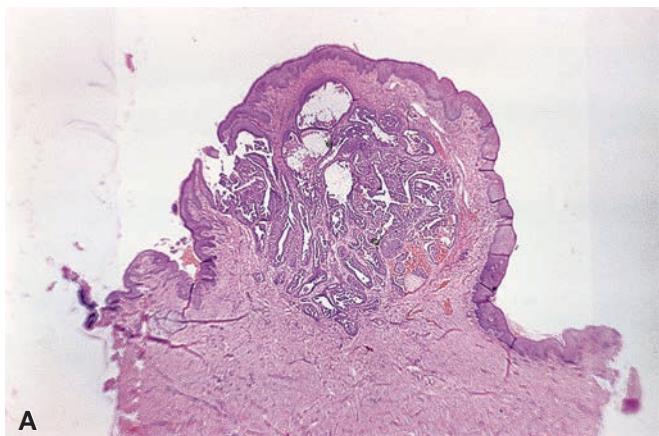


Figure 36.62 **A**, Typical polypoid shape of nipple adenoma, as seen in a whole mount section. **B**, The complex architectural arrangement can lead to overdiagnosis. **C**, The continuity with the squamous epithelium of the skin is a characteristic feature of this entity.

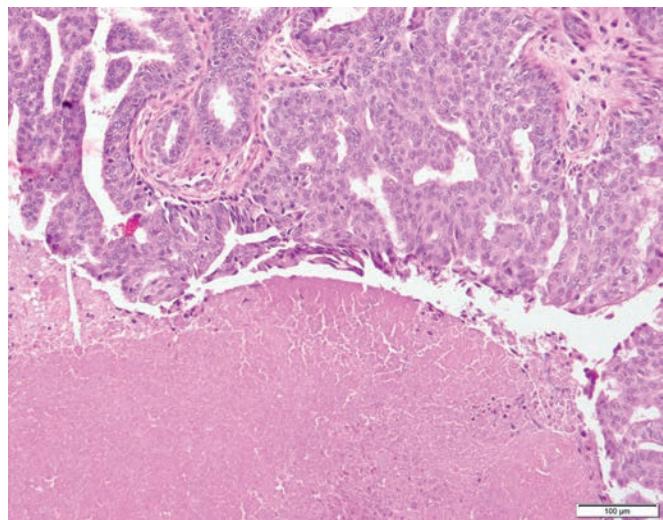


Figure 36.63 **Nipple Adenoma.** High-power view showing usual ductal hyperplasia and necrosis present in a nipple adenoma.

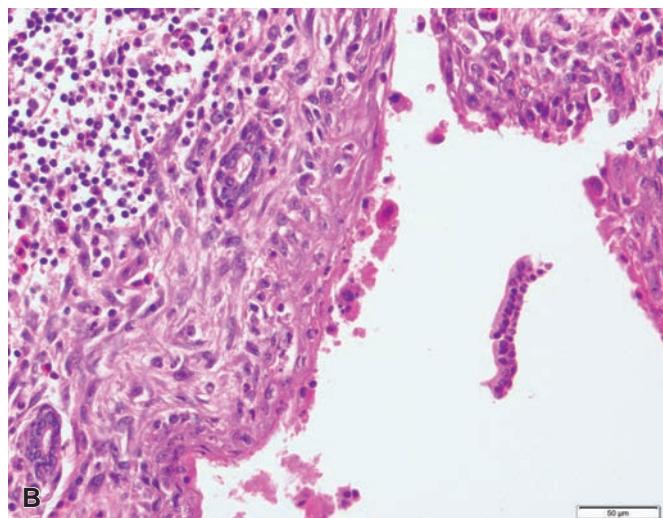
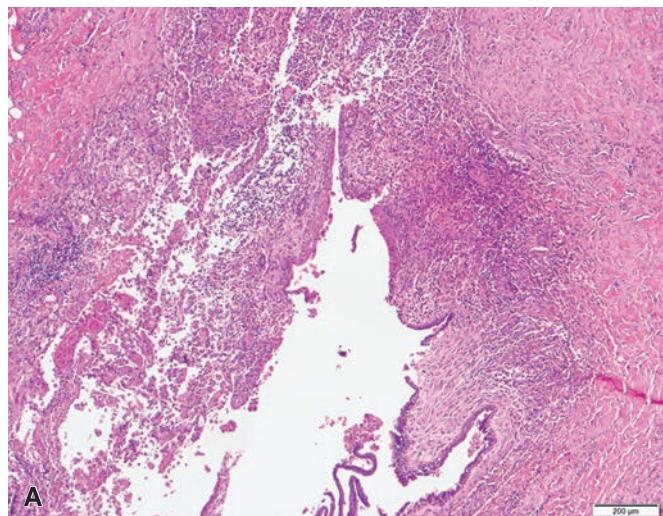


Figure 36.64 **Squamous Metaplasia of Lactiferous Ducts.** **A**, Low-power view of a dilated nipple duct partially lined by squamous epithelium, with surrounding inflammation. **B**, High-power view of the squamous epithelial lining.



Figure 36.65 Eczematous hyperemic and eroded clinical appearance of Paget disease. (Courtesy of Dr RA Cooke, Brisbane, Australia. From Cooke RA, Stewart B. *Colour Atlas of Anatomical Pathology*. Edinburgh: Churchill Livingstone; 2004.)

Clinically, these weeping, eczematous lesions are centered on the nipple (Fig. 36.65). Later the areola and surrounding skin may become involved over an area of a few centimeters. Microscopically, large clear cells with highly atypical nuclei are seen within the epidermis, usually concentrated along the basal layer but also spreading up through the epidermal layers (pagetoid growth pattern) (Fig. 36.66). The cells can be isolated or present in clusters, and sometimes they form small glandular structures.²⁴⁹ Occasionally, intracytoplasmic melanin granules are present, a feature that may result in a mistaken diagnosis of malignant melanoma.²⁵⁰

The underlying breast carcinoma is practically always of high-grade ductal type and is composed of cells similar to those present within the epidermis. Mucin stains are usually positive. Immunohistochemically, Paget cells show reactivity for EMA, polyclonal CEA, low-molecular-weight cytokeratin (including CK7), HER2 and, in some cases, GCDFP-15 (Fig. 36.67). In general, they are negative for HMW cytokeratins and S-100 protein. ER may be positive or negative.

The main differential diagnostic considerations are Bowen disease, malignant melanoma, and Toker cells. Immunohistochemical stains are often necessary to help differentiate these entities in the absence of a readily identifiable breast carcinoma or in a small biopsy of the nipple (Table 36.2).

It is thought that Paget cells in the nipple epidermis have migrated there from a carcinoma present in deeper ductal structures. The similarities in immunohistochemical profile between Paget cells and any underlying high-grade carcinoma present (such as HER2 positivity, ER negativity) support this hypothesis. On the other hand, the existence of rare cases of Paget disease without underlying ductal carcinoma have led to the suggestion that in some cases the cell of origin is the Toker cell or keratinocytes at the squamocolumnar junction.^{251,252} In this regard, the observation made by Toker⁸ about the presence of clear cells in nipples without clinical evidence of Paget disease and without microscopic evidence of breast carcinoma is of great interest. These cells have some immunohistochemical similarities with Paget cells (positivity for CK7 and EMA, and negativity for p63)^{7,253} and may exhibit mild nuclear atypia, suggesting the possibility of a dysplastic or "pre-Paget" change.^{254,255} From a practical standpoint, Toker cells are distinguished from the cells of Paget disease because of the lack of clinical changes, the absence of cytologic features of malignancy (Fig. 36.68), and some histochemical and

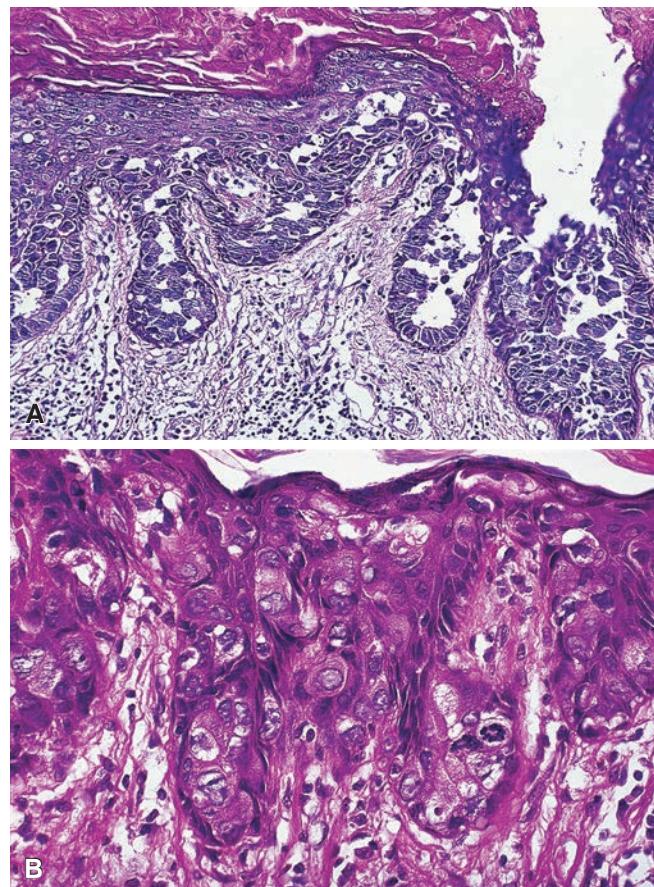


Figure 36.66 **A** and **B**, Low- and high-power views of Paget disease. **A**, The cleft-like separation between the tumor cells and the overlying squamous epithelium is characteristic. **B**, At high power, striking cytologic atypia in the tumor cells is readily apparent.

immunohistochemical differences, such as negativity for mucin and GCDFP-15.

Carcinoma

General Features

Age

The large majority of breast cancers are detected during the postmenopausal years. However, breast cancer can develop at any age, from childhood to old age.

Incidence

Breast carcinoma is the most common malignant tumor and the second most common cause of carcinoma death in women, with more than 1.7 million cases occurring worldwide annually.²⁵⁶ In the United States, approximately 230,000 new cases are diagnosed annually and approximately 40,000 patients die from the disease each year.²⁵⁷ The incidence is high in North America and northern Europe (92 new cases per 100,000 women/year), intermediate in southern European and Latin American countries, and low in most Asian and African countries (but rising rapidly in recent years in some of these countries). In the United States, there has been a sharp increase in the detection of breast carcinoma, largely due

to the widespread use of mammography.²⁵⁸ Most of these cases have been early stage, measuring less than 2 cm in diameter and/or DCIS.²⁵⁹ Initially, this increase in the number of smaller tumors did not translate into an improved survival rate. As a matter of fact, the mortality rate for breast carcinoma changed very little

from the 1930s to the early 1990s.²⁵⁹ However, in some regions of the world (North America, Western Europe, and Australia) breast cancer mortality is now declining, which has been attributed to the combined effects of earlier diagnosis and improved therapy.^{260,261}

The incidence of clinically occult carcinoma can be inferred to a degree from examination of reduction mammoplasty specimens. In a study of 2498 cases, Desouki et al. found invasive carcinoma and DCIS to be extraordinarily rarely present (0.2%); by comparison, atypical proliferative lesions were identified in 4.3% of cases; the most common lesion being lobular neoplasia (2.2%).²⁶²

Risk Factors

Several risk factors for the development of breast carcinoma have been established, whereas many others remain questionable. It has been hypothesized that the common denominator for most of these factors is strong and/or prolonged estrogen stimulation operating on a genetically susceptible background.

1. *Country of birth.* This has already been touched upon above.
2. *Family history.* Women who have a first-degree relative with breast carcinoma have a risk 2 or 3 times that of the general population, a risk further increased if the relative was affected at an early age and/or had bilateral disease.²⁶³ The aspects related to discovery

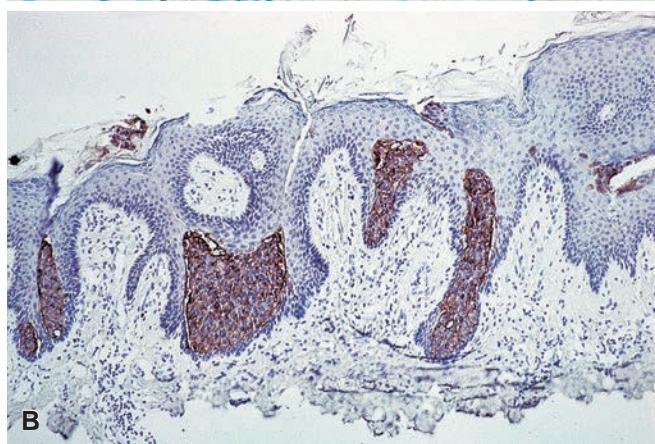
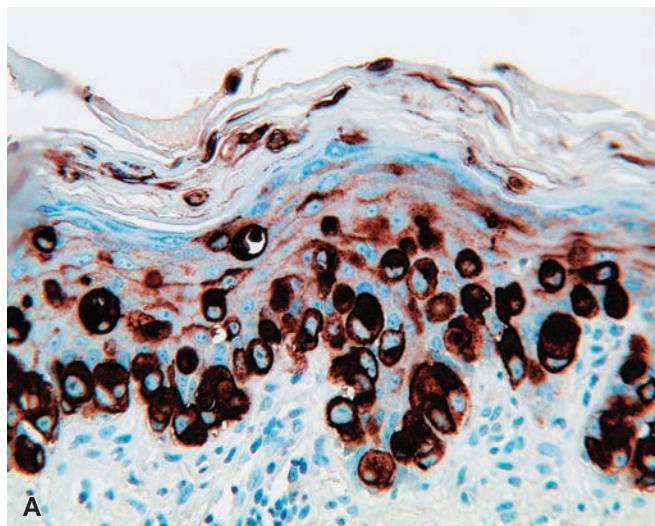


Figure 36.67 Immunohistochemical demonstration of malignant intraepidermal cells in Paget disease. **A**, EMA immunostain. **B**, HER2 immunostain.

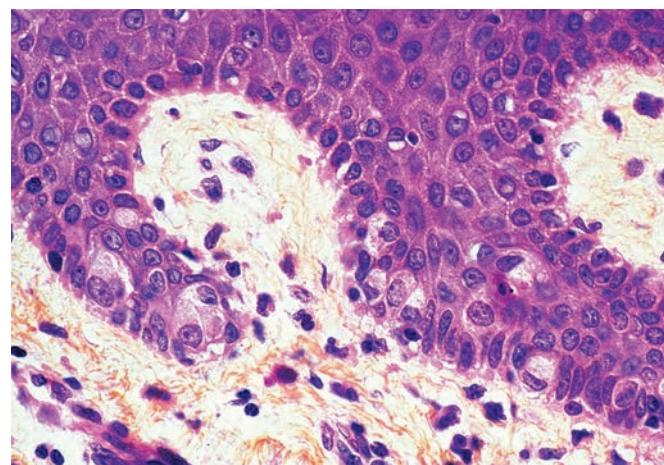


Figure 36.68 Biopsy of nipple showing scattered clear cells without nuclear atypia in the basal layer ("Toker cells").

Table 36.2 Differential histochemical and immunohistochemical staining patterns of epidermal lesions of the nipple (reported as proportion of cases expressing marker)

PAGET DISEASE	MALIGNANT MELANOMA	SQUAMOUS CELL CARCINOMA IN SITU	TOKER CELLS
Mucin	High	Negative	Negative
Cytokeratin 7	Positive	Low	Positive
HER2	High	Negative	Negative
ER/PR	Low	Negative	High
GCDFP	Moderate	Negative	Low
S100	Low	Positive	Negative
HMB45	Negative	Positive	Negative

Key: Positive >90% of cases, high 60%–90% of cases, moderate 40%–60% of cases, low 10%–30% of cases, negative <10% of cases express the marker. From Dillon D, Lester S. Lesions of the nipple. In: Collins LC ed. *Current Concepts in Breast Pathology*. Philadelphia PA: Saunders; 2009:391–412.

- of the genes responsible for predisposition to breast carcinoma are discussed in the next section.
3. *Menstrual and reproductive history.* Increased risk is correlated with early menarche, nulliparity, late age at first birth, and late menopause.²⁶⁴ Breast carcinoma is rare in women who have undergone bilateral oophorectomy; risk-reducing salpingo-oophorectomy before 35 years of age reduces the risk by about one half.^{265,266} Younger age at first pregnancy is associated with a lower lifetime risk of breast cancer. Note though, that there is a dual effect associated with pregnancy: an early transient increase in breast cancer risk followed by a prolonged protective effect.²⁶⁷ A reduction in the risk of breast carcinoma among parous women who have breastfed for at least 4 months has been documented.²⁶⁸ Breast carcinoma risk is increased in postmenopausal women with a hyperandrogenic plasma hormone profile.^{269,270}
 4. *Intraductal proliferative lesions.* The relationship between intraductal proliferative lesions without atypia and breast carcinoma has been discussed in earlier sections.
 5. *Exogenous estrogens.* The influence of exogenous hormones on breast cancer risk is complex and varies with duration of therapy and combination of agents used. In brief, the risk appears greater with longer duration of use/current use and with use of estrogen combined with progestins compared with use of estrogen alone.²⁶⁴
 6. *Contraceptive agents.* The various epidemiologic studies that have been conducted have shown no increased risk, or at most a very low increase among young long-term users.²⁷¹
 7. *Ionizing radiation.* An increased risk of breast carcinoma has been documented with exposure to ionizing radiation, particularly if this exposure occurred at the time of breast development, such as in young women receiving mantle irradiation for Hodgkin disease or atomic bomb survivors who were younger than 10 years of age at exposure.²⁷²⁻²⁷⁴
 8. *Breast augmentation.* Breast implants do not result in an increase in breast cancer risk. Re-analysis of a previously published linkage study that had reported an elevated risk has shown that the incidence of breast carcinoma in that cohort was neither higher nor lower than that among the general population (see later section for discussion of other malignancies related to breast implants).^{275,276}
 9. *Others.* A peculiar association between breast carcinoma and meningioma has been repeatedly noted, with the even more peculiar observation that sometimes the breast carcinoma is found to metastasize to the meningioma. However, a recent study evaluating over 12,000 patients with breast cancer found no increased risk of meningioma, with a 10-year cumulative incidence of just 0.37%.²⁷⁷

Genetic Predisposition

Approximately 5%–10% of all breast cancers are familial.^{278,279} An epochal event in the study of breast carcinoma was the discovery of two high-penetrance susceptibility genes which, when affected by germline mutations, are associated with a high lifetime risk for development of breast cancer, as well as some other cancers, in particular ovarian cancer.²⁷⁸ Originally, mutations in these genes were thought to be responsible for a high proportion of familial breast carcinomas, but they are now found to be responsible for only about 16% of them.²⁷⁹⁻²⁸¹ These are *BRCA1*, located on chromosome 17q21, and *BRCA2*, located on chromosome 13q12.3 (Table 36.3).²⁸²⁻²⁸⁴ Mutations of these genes are present in approximately 2% of the Ashkenazi Jewish population; it has been estimated that the risk for breast carcinoma among carriers is up to 70%–80% by

the age of 70 years.²⁸⁵⁻²⁸⁷ The finding of a positive test for the mutation can lead to an agonizing decision on the part of the affected individual, the main choices being close follow-up or bilateral prophylactic mastectomy.²⁸⁸

The *BRCA1*-encoded protein has many functions, including repair of DNA damage through homologous recombination, cell cycle checkpoint control, ubiquitylation, chromatin remodeling, and DNA decatenation.²⁷⁹ The protein encoded by *BRCA2* is involved in DNA repair, cytokinesis, and meiosis.²⁷⁹ That is, both *BRCA1* and *BRCA2* are essential for accurate repair of DNA double-strand breaks through homologous recombination.²⁷⁹ Loss of such function in the associated cancers has been exploited to develop novel therapies—for example, poly-adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors which block repair of DNA damage via alternate pathways in tumor cells deficient in DNA repair through homologous recombination—a process that has been referred to as “synthetic lethality”.^{289,290}

Analysis of breast carcinomas developing in carriers of *BRCA1* mutations has shown a higher percentage of tumors with the basal-like gene expression profile (see later discussion) and that tend to be high grade, mitotically very active, with a syncytial growth pattern, pushing margins, confluent necrosis, negativity for hormone receptors and HER2 (“triple negative”), and associated with *TP53* mutation.^{279,291-293} On the other hand, *BRCA2*-associated cancers are a heterogeneous group without specific morphology or phenotype and are commonly positive for hormone receptors.^{291,293}

In addition to *BRCA1* and *BRCA2*, several other genes (e.g., *CHEK2*, *CDH1*, *RAD50*, and *PALB2*) confer a low to moderate increased risk for the development of breast cancer.²⁹⁴ Hereditary breast cancer can also occur in the setting of multiple cancer syndromes,²⁷⁹ such as Lynch syndrome (e.g., *MLH1*), Li-Fraumeni syndrome (*TP53*), ataxia-telangiectasia syndrome (*ATM*), and Cowden syndrome (*PTEN*), as summarized in Table 36.3.^{279,295}

Location

The location of breast carcinoma is usually indicated in relation to the breast quadrants. Approximately 33% are in the upper outer quadrant, 9% in the upper inner quadrant, 6% in the lower outer quadrant, 5% in the lower inner quadrant, 7% in the central region (within 1 cm of the areola), and 40% occur in overlapping quadrants (or location not specified).²⁹⁶ Several studies have also documented the peculiar fact that breast carcinoma is slightly more frequent in the left breast than in the right (“laterality ratio”). In one recent series, the excess for the left side varied by age, quadrant, and place of birth.²⁹⁶ Preliminary studies in mouse models indicate that there may be baseline differences in gene expression that are left-right independently regulated during pubertal development, which may play a role in this observation.²⁹⁷

Multicentricity and Multifocality

Multicentricity, defined as the presence of carcinoma in a breast quadrant other than the one containing the dominant mass, was described as early as 1920 and later reported by others.^{298,299} Multifocality is defined as the presence of additional foci of carcinoma in the same quadrant as the index carcinoma. Among a contemporary population of 1495 patients with invasive carcinoma, 82.3% of tumors were unifocal, 11.3% were multifocal, and 6.4% were multicentric. Multicentricity was more common in lobular than in ductal carcinomas; patients were more likely to be younger with larger tumors, to have lymphovascular space invasion and positive lymph nodes. Multifocality was more commonly seen with invasive ductal carcinomas that had an extensive intraductal component and were

Table 36.3 Summary of the syndromes associated with hereditary breast cancer

SYNDROME (OMIM)	GENE INVOLVED AND CYTOBAND	CLINICAL FEATURES
Hereditary breast cancer and ovarian cancer syndrome (113705)	<i>BRCA1</i> (17q21)	Breast cancer, high risk (50%–80%) Ovarian cancer, high risk (40%–50%)
Hereditary breast cancer and ovarian cancer syndrome (600185)	<i>BRCA2</i> (13q12.3)	Breast cancer, high risk (50%–70%) Ovarian cancer, intermediate risk (10%) Prostate cancer Pancreatic cancer Melanoma
CHEK2 mutations (Li–Fraumeni 2 syndrome?)	<i>CHEK2</i> (22q 12.1)	Breast cancer, intermediate risk (~twofold) Sarcomas Brain tumors
Other FANC genes (114480, 610355, 607139, 600901, 605882)	<i>PALB2/FANCN</i> (16p12) <i>FANCA</i> (16q24.3) <i>FANCE</i> (6p22–p21) <i>BRIP1/FANCJ</i> (17q22)	<i>PALB2/FANCN</i> and <i>BRIP1/FANCJ</i> : moderate risk of breast cancer development Other FANC genes: low risk of breast cancer development
Familial linitis plastica type gastric cancer and lobular breast carcinoma syndrome (192090)	<i>CDH1</i> (16q22.1)	Gastric cancer Lobular breast cancer
Louis–Bar syndrome (208900)	<i>ATM</i> (11q22.3)	Lymphoma Cerebellar ataxia Immune deficiency Glioma Medulloblastoma Breast cancer
Li–Fraumeni syndrome (151623)	<i>TP53</i> (17p13.1)	High penetrance for breast cancers at young age Risk of soft tissue sarcomas and osteosarcomas, brain tumors, leukemia, and adrenocortical carcinoma
Cowden syndrome (158350)	<i>PTEN</i> (10q23.31)	Increased risk of developing neoplasms (breast cancer, thyroid carcinoma, endometrial carcinoma and others) Hamartomatous polyps of the gastrointestinal tract Mucocutaneous lesions
Bannayan–Riley–Ruvalcaba syndrome (153480)	<i>PTEN</i> (10q23.31)	Breast cancer Meningioma Follicular cell tumors of the thyroid
Peutz–Jeghers syndrome (175200)	<i>STK11</i> (19p13.3)	Melanocytic macules of the lips, buccal mucosa, and digits Multiple gastrointestinal hamartomatous polyps Increased risk of various neoplasms (breast, testis, pancreas, and cervix)
Lynch cancer family syndrome II (114400)	<i>MSH2</i> (2p22–p21), <i>MSH3</i> (5q11–q12), <i>MSH6</i> (2p16), <i>MLH1</i> (3p21.3), <i>PMS1</i> (2q31–q33), <i>PMS2</i> (7p22)	Increased risk of endometrial carcinoma and colorectal carcinoma High risk of multiple primary malignant neoplasms, including breast, ovarian, gastrointestinal, and genitourinary carcinomas, sarcomas, glioblastoma, and leukemia

FANC, Fanconi anemia.From Tan DSP, Marchio C, Reis-Filho JS. Hereditary breast cancer: from molecular pathology to tailored therapies. *J Clin Pathol*. 2008;61:1073–1082.

ER, PR, and HER2 positive.²⁹⁹ Not surprisingly, a higher incidence of multicentricity and multifocality is reported in patients undergoing preoperative MRI and mastectomy.²⁹⁹ Theoretically, multiple breast carcinomas can result from either intramammary spread of a single lesion or from independent events.³⁰⁰ Clonal studies suggest that both mechanisms play a role.^{301,302} If aggregate diameters are used, unifocal and multifocal carcinomas are similar with respect to the frequency of regional lymph node involvement,³⁰³ but other studies have shown that the single largest tumor diameter, as is recommended by the AJCC TNM staging system, even in patients with multiple tumor foci, is an accurate method for staging patients.^{299,304}

Bilaterality

The chance that a patient with invasive breast carcinoma will develop a carcinoma in the contralateral breast is estimated to be about 1% per year and is even higher if there is a family history of breast carcinoma and in cases of invasive lobular carcinoma.³⁰⁵ The use of adjuvant estrogen blockade with or without chemotherapy significantly decreases the risk of metachronous contralateral breast carcinoma.^{305,306} Annual screening mammography is the current surveillance practice for these patients, unless the lifetime risk is greater than 20%–25%, in which case adjunctive screening with MRI is recommended.³⁰⁷

Synchronous bilateral invasive breast carcinomas are being detected more frequently because of the use of MRI in the work-up of patients with a confirmed diagnosis of breast cancer, ostensibly for surgical planning purposes. An unfortunate corollary of this practice is the rising number of contralateral mastectomies being performed in patients found to have benign or atypical (nonmalignant) pathology on core needle biopsies of areas of radiologic concern in the contralateral breast.^{308,309} No significant difference in overall survival has been reported for patients with bilateral breast carcinoma when appropriately matched to women with unilateral breast cancer.³¹⁰

Diagnosis

Clinical Examination

Clinical examination is the time-honored method for the detection and evaluation of breast disease. It remains an extremely useful and practical technique, whether carried out by the physician or by the patient herself. However, both its sensitivity and discriminatory power are limited. Today, the majority of breast cancers are detected through imaging studies, with only 10% of the tumors being detected solely by palpation.³¹¹ The clinical impression is incorrect in approximately 15% of the cases thought to be benign and approximately 10% of those thought to be malignant. The clinical evaluation of axillary lymph nodes is also fraught with error; determination of lymph node status requires microscopic examination.³¹²

Mammography

The widespread use of screening mammography has led to an increase in the detection of breast cancers at an earlier stage and of smaller size, primarily based on the presence of microcalcifications, non-palpable masses, or architectural distortion.³¹³ The incidence of calcification in breast carcinoma is approximately 50%–60%, and the incidence in benign breast disease is 20%.³¹⁴ There are also important qualitative differences in the appearance of the microcalcifications, with pleomorphic or heterogeneous calcifications that are fine, linear, branching, or casting (conforming to the pattern of a duct) being more frequently predictive of malignant disease on

histology. In a study of 2545 women enrolled in a breast screening program found to have microcalcifications alone on imaging, 47.9% were subsequently shown to be associated with malignancy (31.8% DCIS and 16.1% invasive carcinoma, mostly with associated DCIS) and 52.1% of cases were associated with nonmalignant lesions.³¹⁵ In the United States, mammographic findings are universally reported using the Breast Imaging Reporting and Data System (BI-RADS), which allows the radiologist to convey the degree of suspicion, with 1 being negative and 5 being highly suspicious for malignancy.³¹⁶ The majority of core biopsy samples will be from patients with BI-RADS category 4 lesions. This category is very broad, with the likelihood of cancer being diagnosed on biopsy ranging from 2% to 94%. Consequently, subcategories were created to better convey the level of concern: BI-RADS 4A (2%–9% chance of malignancy), 4B (10%–49% chance of malignancy), and 4C (50%–94% chance of malignancy).

It should be kept in mind that a negative mammogram does not rule out the possibility of the presence of carcinoma, since approximately 15% of palpable tumors are not detectable with this technique.³¹⁷ Ultrasound may be the better modality for palpable masses. The proper management of breast lesions detected by mammography requires close cooperation between radiologist, surgeon, and pathologist. Mammographically detected nonpalpable lesions usually require preoperative wire localization, if excision is necessary, to guide the surgeon to the suspicious area within the breast. Today, most patients have undergone a core needle biopsy procedure prior to excision with placement of a radio-opaque clip, and it is this clip, along with tissue landmarks, that is used to guide wire-localization by the radiologist. Once the appropriate area is excised, the margins should be marked by the surgeon with sutures (typically superior and lateral margins, short and long sutures, respectively by convention) and an x-ray study of the specimen performed to confirm removal of the target area and biopsy clip. If no lesion/calcification or clip is seen, the surgeon should obtain additional tissue, if feasible. If the abnormal area is present in the specimen, the specimen should be inked with six different colored inks according to the orientation given by the surgeon and the specimen sliced and processed in the pathology laboratory. As mentioned above, the vast majority of patients have undergone a core needle biopsy procedure prior to definitive surgery; therefore the pathologic diagnosis from that earlier procedure can be used to guide tissue processing. The highest yield is obtained from histologic examination of the areas with radiographic calcification and fibrous parenchyma.³¹⁸

X-ray studies can be taken of the paraffin blocks to document the fact that the microcalcifications seen in the mammogram have been embedded (Fig. 36.69). An important source of discrepancy between mammographic targeting of calcifications and microscopic findings are calcium oxalate crystals, which can be easily identified radiographically but may be missed on histologic examination.³¹⁹ Every attempt should be made to identify, in the microscopic sections, the imaging target regarded by the radiologist as "suspicious" for carcinoma.

Breast ultrasonography is a valuable examination tool, particularly for determining whether a mass lesion is cystic or solid, and whether it is circumscribed and "wider than tall," which are features of benignity, or conversely whether it is hypoechoic with irregular borders, "taller than wide" and has posterior shadowing, which are features favoring a malignant diagnosis.³²⁰

MRI is unlikely to replace mammography as the imaging modality of choice, although contrast-enhanced techniques have rendered it more informative and potentially more useful. It is more sensitive but has lower specificity, resulting in greater numbers of false-positive call backs and unnecessary biopsies. There is greater application for

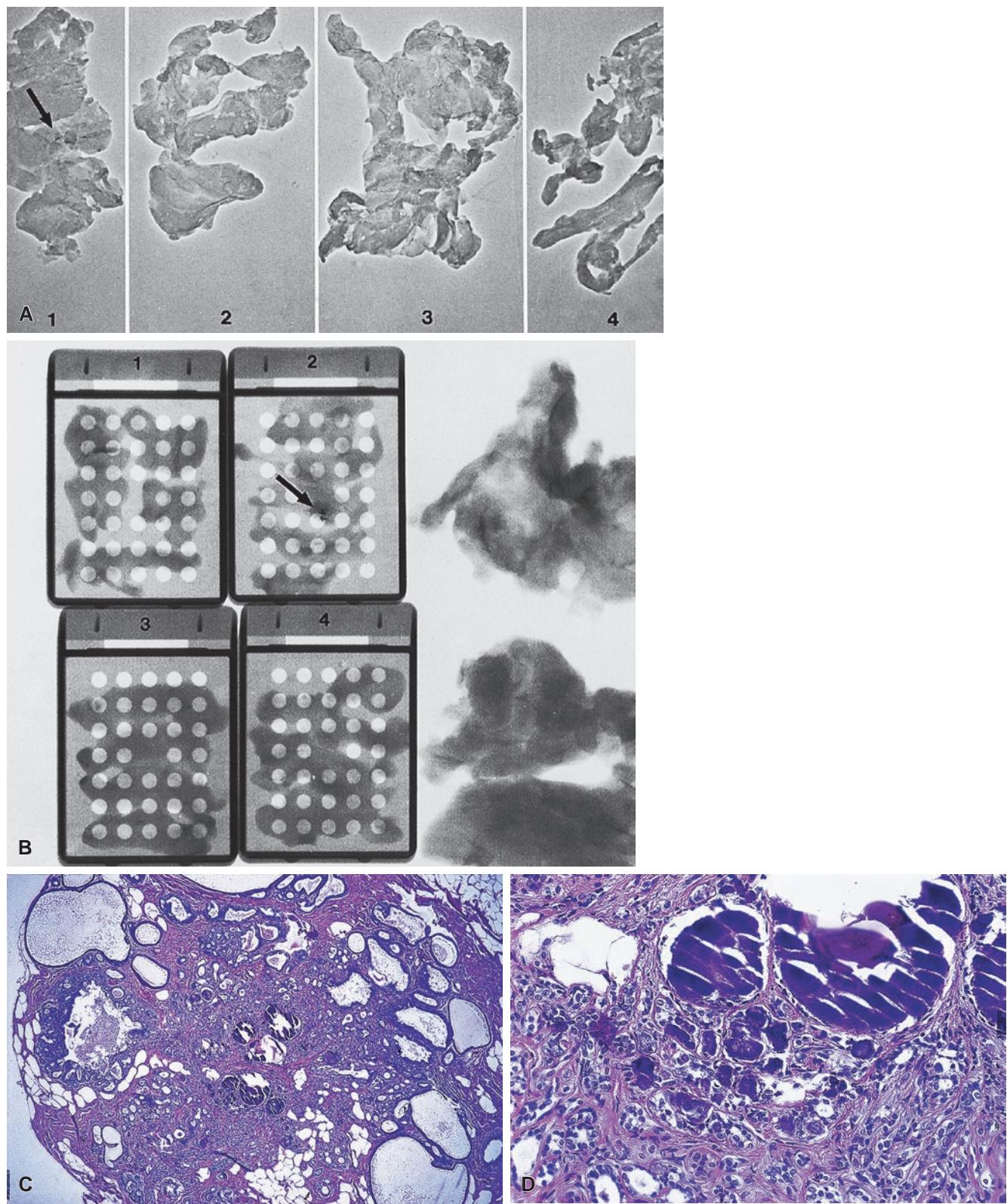


Figure 36.69 Demonstration of the Use of Specimen Radiography. A mammographically detected breast lesion was excised. **A**, The specimen was sliced into four portions and a radiograph taken. A pattern of calcification identical to that seen in original mammogram was detected in slice 1 (arrow). **B**, The portion corresponding to this area of calcification was further divided into four fragments, and all four were embedded in paraffin. A radiograph of the cassettes shows that the suspicious area is in cassette 2 (arrow). The remainder of the slice (two fragments at right) shows no calcification. **C** and **D**, Low- and high-power views of the corresponding microscopic specimen demonstrating the microcalcifications.

use of MRI in patients at high risk (>20% lifetime risk) for the development of breast cancer.³²¹

Where adopted for screening purposes, the National Cancer Institute has traditionally recommended mammography be done on an annual basis from the age of 40 years onwards. Great controversy has recently arisen following the revised recommendations from the US Preventive Services Task Force, which calls for mammograms to be done biennially from the ages of 50 to 74, with the decision to begin screening at 40 years being an individual one depending on a woman's risk factors.³²²

Cytology

The two methods that have been used to obtain cytologic material from breast lesions are collection of nipple discharge (often directly onto a glass slide) and aspiration of a palpable lesion using a fine needle.

Nipple secretion cytology is of limited use, whether for the diagnosis of a clinically or mammographically detectable breast lesion or for screening purposes. Some carcinomas may be found, but the ability to provide a definitive interpretation from these often bloody, degenerated specimens is limited, rendering this technique of only marginal value. The situation with FNA is different, as shown in the pioneer attempts at Memorial Sloan Kettering Cancer Center in the 1930s. In experienced hands the technique is highly reliable (Fig. 36.70).^{323,324} The average sensitivity is approximately 87%, the specificity close to 100%, the predictive value of a positive diagnosis nearly 100%, and the predictive value of a negative diagnosis between 60% and 90%.^{323,325} Most benign lesions misinterpreted cytologically as possibly malignant are usually fibroadenomas or intraductal papillomas with marked epithelial proliferation.³²⁶ At the malignant end of the spectrum however, it is not possible to distinguish between *in situ* and invasive carcinoma on FNA cytology,³²⁷ for these reasons core needle biopsy has largely superseded FNA cytology as the diagnostic procedure of choice in the United States. There remains a role in the evaluation of clinically positive axillary lymph nodes, particularly in the neoadjuvant setting to document lymph node metastasis prior to initiation of chemotherapy.

Core Needle Biopsy

In recent years, core needle biopsy (image-guided and with or without vacuum assistance) has become the gold standard for the diagnosis of image-detected nonpalpable and palpable breast lesions. Core needle biopsy is favored over FNA for the preoperative diagnosis of breast carcinoma. As mentioned previously, core needle biopsy allows for evaluation of both cytologic *and* architectural features, thereby permitting definitive diagnosis of invasive carcinoma when present. Conversely a benign lesion, such as fibroadenoma, can be readily recognized, and core needle biopsy allows for easier sampling and identification of microcalcifications. Furthermore, it reduces the number of inadequate samples and does not require cytopathology expertise. In order to obtain maximum information from the procedure, the pathologist should be provided with complete a clinical history, including radiographic signs and the site of the biopsies. In cases with microcalcifications, the core biopsy specimens should be x-rayed and the cores with calcifications submitted separately from those without, in the event additional levels are needed.³²⁸ The use of site-marking devices at the time of the core biopsy is helpful for the radiologist, to guide placement of a localization wire should an excision be required, and in determining whether the subsequent surgical specimen includes the radiographically abnormal area.

Per American Society of Clinical Oncology (ASCO)/ College of American Pathologists (CAP) published guidelines, breast specimens should be fixed for a minimum of 6 hours and a maximum of 72 hours to permit accurate biomarker testing, should that be required³²⁹; a minimum of three levels should be obtained initially on all core needle biopsy specimens, with additional levels and immunostains performed when necessary.³³⁰ A definitive diagnosis on the basis of a core biopsy and triage for patient management is possible in the majority of cases.³³¹ However, there are some diagnoses that are not malignant that have warranted surgical excision because of the frequency with which a worse lesion has been found upon excision of the area of concern (i.e., the "upgrade" or "underestimation" rate). Unfortunately, many of these recommendations for excision were based on data from small studies, often with radiologic-pathologic discordance and selection bias with regard to which patients underwent excision. Newer studies have taken care to address the imaging findings, ensure radiologic-pathologic correlation, and provide data on upgrade rates for incidental cases of atypia.²¹⁶ The following is a standard management algorithm:

1. All cases showing DCIS or invasive carcinoma should undergo excision.
2. Cases showing ADH or atypical ductal proliferations with features bordering on DCIS should undergo excision.²¹⁶
3. The management of LCIS and ALH is evolving. In the past, most authors recommended surgical excision,^{332,333} but more recent studies, in which there is good radiologic-pathologic correlation and the lobular neoplasia is determined to be incidental to the targeted lesion, are recommending observation over excision (if the targeted lesion is benign and does not itself require excision), with the exception of cases of nonclassical or pleomorphic LCIS.^{334,335}
4. Columnar cell lesions without atypia (i.e., columnar cell change and columnar cell hyperplasia) do not require excision. The management of FEA identified on core needle biopsy remains controversial. The WHO recommendation is for radiologic-pathologic correlation with consideration of excision in patients in whom there are residual calcifications on a post-biopsy mammogram or for whom there is radiologic-pathologic discordance.¹¹²
5. In most cases, papillomas can be distinguished from papillary carcinomas on core needle biopsies.³³⁶ A diagnosis of papillary carcinoma or papilloma with atypia warrants excisional biopsy, whereas a diagnosis of papilloma may be managed with clinical follow-up if imaging findings are concordant, though many centers still excise radiologically targeted papillomas.²¹⁶
6. The presence of stromal pools of mucin associated with mucocele-like lesion had been an indication for surgical excision because of the concern for undersampled mucinous carcinoma, but in patients in whom there is no atypia and no imaging findings of concern, observation may be acceptable.²¹⁶

Complications of the core needle biopsy procedure include hemorrhage, reactive spindle cell nodules, and epidermal inclusion cysts.^{337,338} A different type of complication, also seen in connection with the FNA procedure but more likely with the core biopsy technique, is the mechanical displacement of epithelial cells into the stroma or even inside vessel lumina (see Fig. 36.54).^{339,340} This phenomenon is more common with both benign and malignant papillary lesions, presumably because of their greater friability.³⁴¹ It is doubtful whether this finding is of any clinical significance. The greater importance lies in recognition of this phenomenon as a procedural artifact and not as a focus of invasive carcinoma for which it may be mistaken. The displaced epithelial cells may appear as small nests or single cells with atypical, "squamous," or degenerated features. Identification of

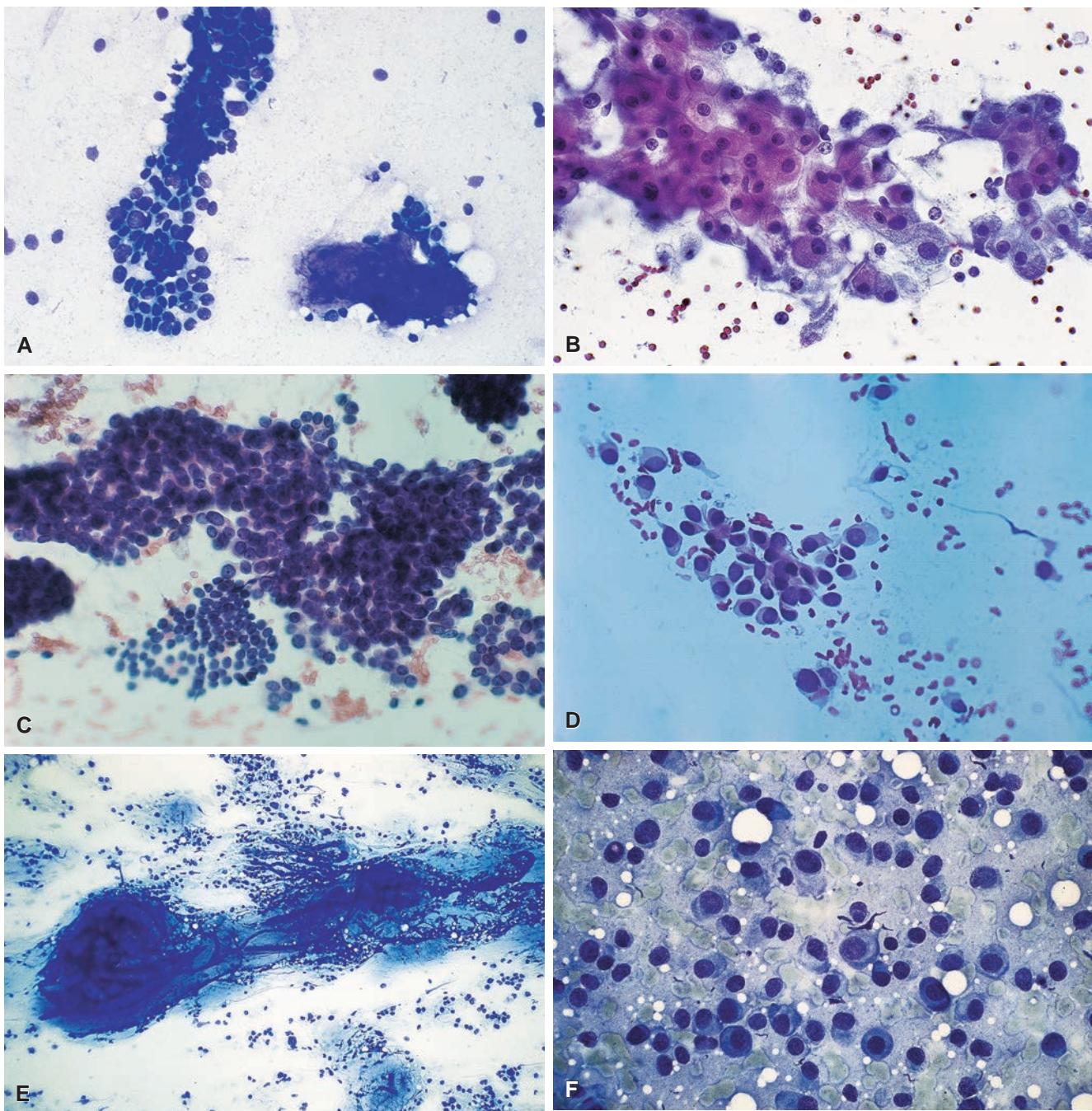


Figure 36.70 Cytologic features of various types of breast lesion as seen in FNA specimens: **(A)** fibro-adenoma; **(B)** apocrine metaplasia; **(C)** and **(D)** invasive ductal carcinoma; **(E)** mucinous carcinoma; **(F)** invasive lobular carcinoma.

biopsy site changes such as granulation tissue and hemosiderin-laden macrophages will help prevent an erroneous diagnosis. Note that myoepithelial cells are often absent, as such IHC is not helpful.

Frozen Section

Intraoperative evaluation by frozen section has limited applicability in current practice. Some centers perform intraoperative evaluation of the specimen margins with a view to immediate reexcision of involved margins. These can be technically challenging specimens to freeze because they are often composed entirely of adipose tissue,

and they can be challenging to interpret, resulting in well-documented false-positive and false-negative rates.³⁴²

A few centers still perform intraoperative frozen section evaluation of sentinel lymph nodes. The need for this is largely obsolete³⁴³ given the results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 randomized clinical trial demonstrating an absence of clinical benefit for completion axillary dissection even in patients with 1–3 positive sentinel lymph nodes.³⁴⁴ On occasion, request is made for frozen section in the setting of mastectomy, where completion dissection may be performed if the sentinel lymph node is positive.

Histologic Types

Two key determinations to make in the morphologic study of breast carcinoma are: (1) whether the tumor is confined to the ductolobular system (carcinoma *in situ*) or has invaded the stroma (invasive carcinoma), and (2) whether it is of ductal or lobular type. The first criterion, the prognostic significance of which far outweighs that of the second, is self-explanatory, but it may be appropriate to elaborate on the second. The term "ductal carcinoma" may be taken to imply that the tumor is either arising from or involving a duct, and an analogous assumption could be made about lobular carcinoma in relation to the lobule. The evidence obtained from the classic study of Wellings et al.²¹ and several others indicates instead that both tumor types (and, for that matter, most benign proliferative breast diseases) arise from the same segment of the mammary gland, that is, the TDLU. As far as location is concerned, it is certainly true that many ductal carcinomas *in situ* preferentially involve structures with the appearance of ducts and that most lobular carcinomas *in situ* preferentially involve lobules. However, numerous exceptions in both directions exist. It has been hypothesized that these cases represent—respectively—ductal carcinomas *in situ* with secondary extension into lobules ("lobular cancerization"—an obsolete term), or lobular carcinomas *in situ* with secondary extension into ducts.³⁴⁵

Be that as it may, it should be made clear that it is the type of tumor as defined by cytoarchitectural features that establishes its placement into one of these two diagnostic categories rather than its precise location within the breast. Therefore, it may be more accurate and less confusing to refer to these tumors as *ductal type* and *lobular type*, respectively. For the sake of brevity and tradition however, the conventional nomenclature of ductal and lobular will be used in this chapter.

Carcinoma *In Situ*

Ductal Carcinoma *In Situ*

DCIS is defined by the presence of neoplastic epithelial cells confined to the ductolobular system. Many architectural variants of DCIS exist, such as papillary, solid, cribriform, and micropapillary; in addition, there is nuclear variability ranging from low- to high-grade types. DCIS is believed to originate in the TDLU (although often extending into larger ducts) and had been historically divided into high-grade comedocarcinoma (characterized by large pleomorphic cells associated with necrosis) and a low-grade solid/cribriform/micropapillary group (composed of smaller uniform cells unassociated with necrosis). Contemporary classification schemes divide DCIS into a three-grade system largely on the basis of *nuclear pleomorphism* with or without the inclusion of *comedo necrosis*. These criteria apply irrespective of the architectural pattern. They may also apply independently of the presence or absence of necrosis, depending on the classification scheme employed.³⁴⁶⁻³⁴⁸ Unfortunately, there is still no international consensus on a classification scheme for DCIS, but if nuclear grade, the presence or absence of comedo necrosis, architectural pattern, and some estimate of size is reported, any of the myriad classification schemes can be used to categorize a given DCIS lesion.^{349,350}

Nowadays, the vast majority of DCIS is detected through screening mammography as clustered microcalcifications. Linear, branching calcifications raise the most concern for DCIS, but other patterns exist and are indeterminate with regard to the degree of certainty with which they can be distinguished from benign lesions associated with microcalcifications on radiologic studies. When sufficient concern exists, a core needle biopsy is performed to allow for pathologic diagnosis.

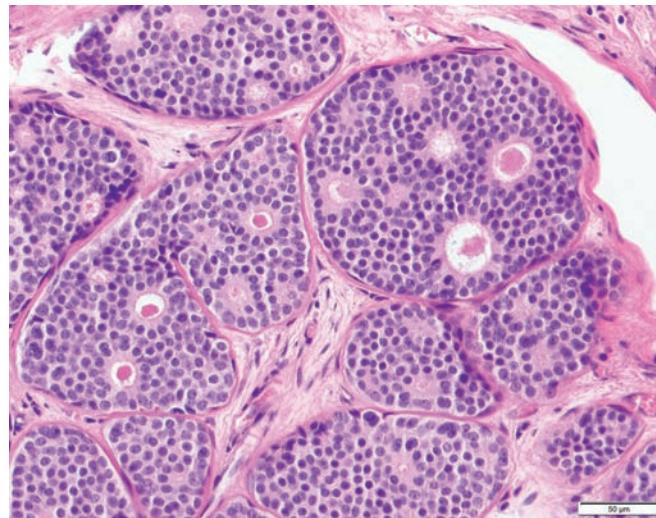


Figure 36.71 Ductal carcinoma *in situ*, low nuclear grade, cribriform pattern.

A small minority of DCIS lesions present as a palpable mass or with nipple discharge. It has been shown that DCIS occurring in younger women is more often symptomatic, more extensive, and more often accompanied by involvement of lobules than DCIS in older women.³⁵¹

Low Nuclear Grade Ductal Carcinoma *In Situ*

Low nuclear grade DCIS is characterized by a neoplastic proliferation of monomorphic epithelial cells growing in solid, cribriform, papillary, or micropapillary patterns (Fig. 36.71). Microacini and/or areas of cellular polarization may be apparent in the solid pattern; a feature that aids in the distinction from LCIS. The cells have round, regular nuclei with even chromatin and inconspicuous nucleoli. Mitoses are rare. Punctate or even comedo necrosis may be seen but is unusual. Microcalcifications are often present.

Intermediate Nuclear Grade Ductal Carcinoma *In Situ*

Intermediate nuclear grade DCIS is characterized by cells with slightly more nuclear variability than low nuclear grade DCIS. The cells are larger and less evenly spaced within the involved TDLU. Polarization is still observed, though is less pronounced (Fig. 36.72). Calcification, mitoses, and necrosis may be present.

High Nuclear Grade Ductal Carcinoma *In Situ*

High nuclear grade DCIS is characterized by a neoplastic proliferation of highly atypical epithelial cells with large pleomorphic nuclei, coarse clumped chromatin, and prominent nucleoli. The proliferation may be solid, cribriform, or micropapillary in architectural pattern, but the cells are poorly organized and polarization is not usually evident (Fig. 36.73). Mitoses are abundant, and necrosis is a common, though not a required, feature. Comedo necrosis is said to be present when approximately half of the involved space has abundant necrotic material and is surrounded by DCIS cells. A less common pattern of high nuclear grade DCIS is the clinging pattern, in which a single layer of highly atypical cells lines the involved space (see later).

DCIS is not usually detectable on gross examination, with the possible exception of large areas of high-grade DCIS with comedo necrosis that induce a desmoplastic stroma. In this scenario, a mass may be palpable and on cut surface clusters of thick-walled ducts may be seen. When these ducts are compressed, plugs of necrotic



Figure 36.72 Ductal carcinoma in situ, intermediate nuclear grade, cribriform pattern with necrosis. There is greater nuclear variability compared with that seen in low-grade DCIS.

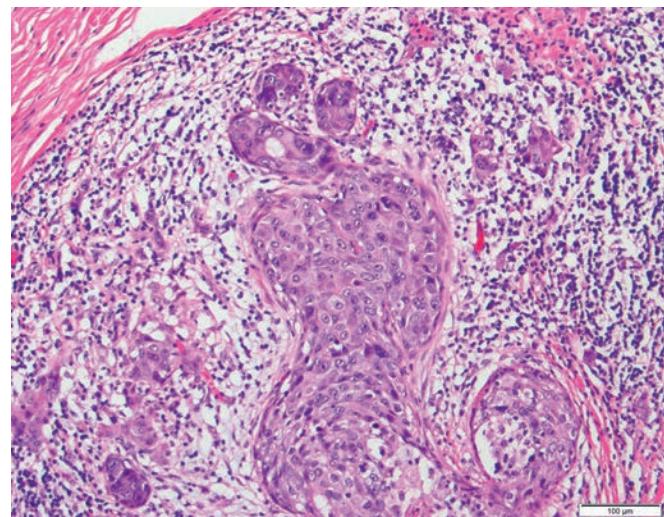


Figure 36.74 Microinvasive carcinoma associated with high-grade ductal carcinoma in situ. Notice the clusters and single highly atypical epithelial cells present in the stroma surrounding the high-grade DCIS. A dense lymphocytic infiltrate is often present.

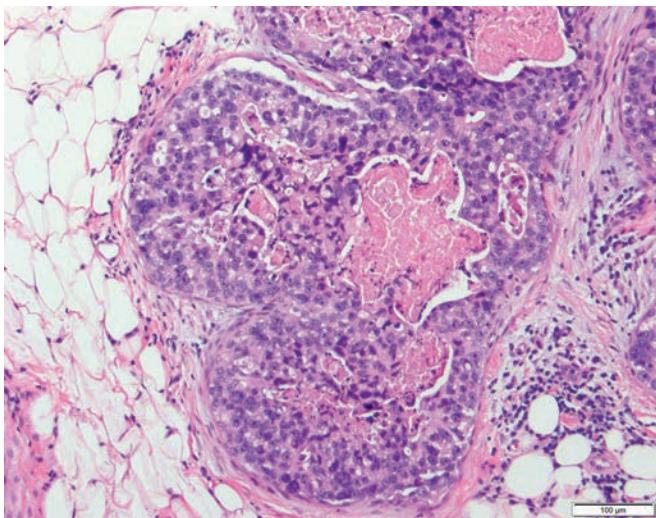


Figure 36.73 Ductal carcinoma in situ, high nuclear grade, solid pattern with necrosis.

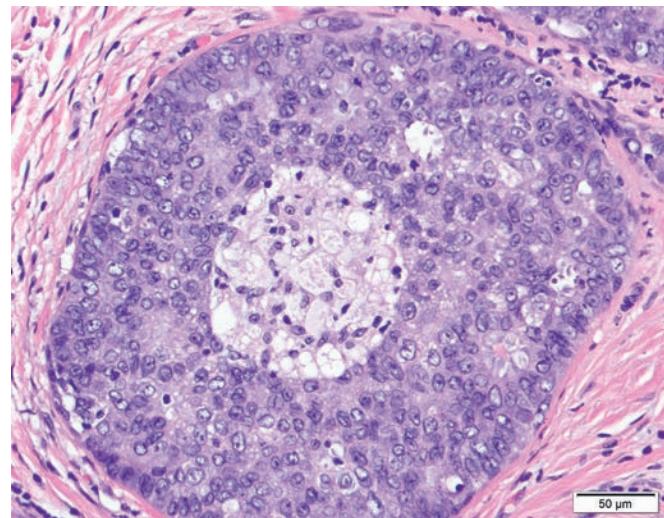


Figure 36.75 Ductal Carcinoma In Situ, Intermediate Nuclear Grade. Note how even in the absence of well-formed cribriform spaces, the cells are arranged in rosettes or microacinar structures.

tumor extrude from them, reminiscent of comedones, hence the historic appellation “comedocarcinoma.”

Once the diagnosis of DCIS has been established, two additional important determinations need to be made. The first is the extent of the lesion, which in some cases may be very extensive and even reach the nipple, resulting in Paget disease. The other is to search for areas of definite stromal invasion and, if these are present, to report the size of the largest focus of invasion. Even if no definite invasion is detected in the sections examined, the possibility always exists, especially with extensive high nuclear grade DCIS, that a minute focus of invasion is present somewhere in the specimen (Fig. 36.74).³⁵² This accounts for the observation that up to 15% of patients have tumor cells present in the axillary lymph nodes (especially with cytokeratin immunohistochemical examination) in the absence of an identifiable invasive component in the breast.^{353–355}

Architectural Patterns of Ductal Carcinoma In Situ

In the *solid* form of DCIS, the acini of the TDLU are filled by a proliferation of medium-sized cells, which are larger than those of LCIS, often with low-grade monomorphic nuclei, though any nuclear grade may be seen. Azzopardi²² pointed out the sharp cell edges (as opposed to a “syncytial” quality) and the pallor of the cytoplasm (as opposed to prominent eosinophilia) often exhibited by these cells compared with the cells of UDH. Even in the absence of true lumen formation, the cells in solid pattern DCIS attempt to polarize, creating a rosette or microacinar pattern within the solid proliferation (Fig. 36.75). It is this feature that is most helpful in distinguishing low nuclear grade, solid pattern DCIS from LCIS.

In the *cribriform* pattern, round regular spaces are formed within the involved acini of the TDLU (see Figs. 36.71 and 36.72); in DCIS

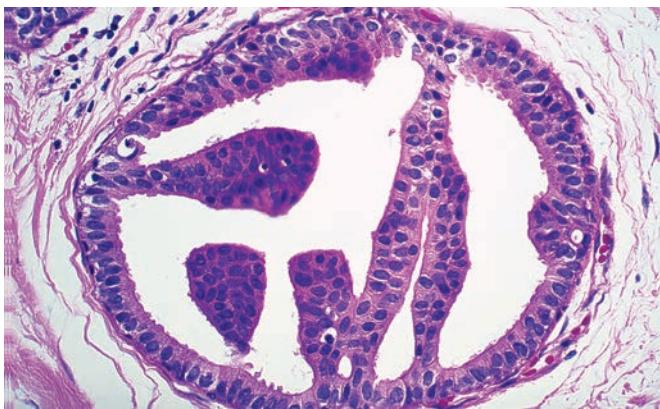


Figure 36.76 Trabecular Bars in Atypical Ductal Hyperplasia. Note the perpendicular arrangement of the nuclei in relation to the long axis of the bars.

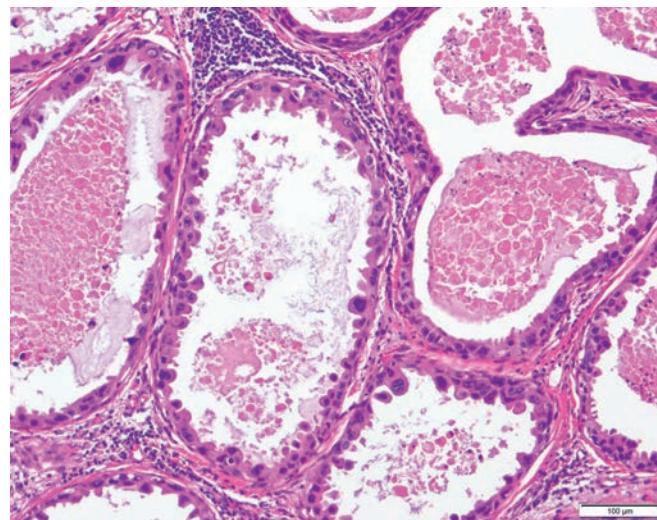


Figure 36.78 Ductal Carcinoma In Situ, Clinging Pattern. One or two layers of highly atypical cells line dilated glandular structures containing necrosis.

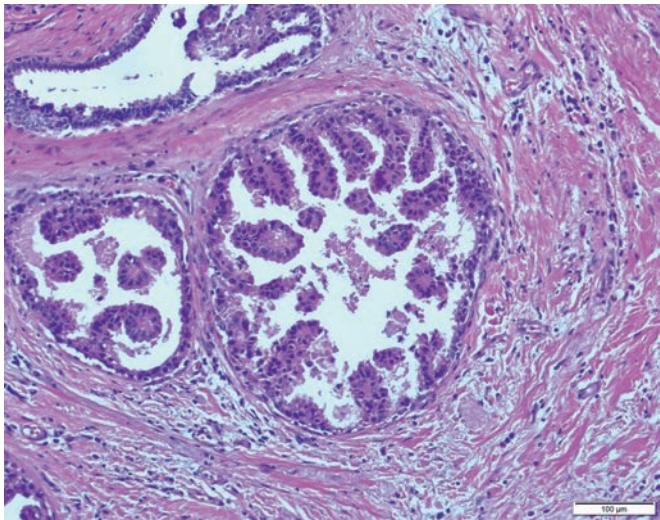


Figure 36.77 Ductal carcinoma in situ, micropapillary pattern.

the spaces are more regular in terms of distribution, size, and shape, as opposed to UDH in which the spaces are irregular and slit-like (see Figs. 36.36 and 36.37). Cribriform DCIS is often seen in association with two formations of similar pathogenesis, designated by Azzopardi²² as trabecular bars and Roman bridges, respectively. Trabecular bars are rigid rows of cells with their long axes arranged more or less perpendicular (or at least not parallel) to the long axis of the bar, features that are more readily appreciated in examples of ADH (Fig. 36.76). Roman bridges are curvilinear trabecular bars connecting two portions of the epithelial lining. Collagenous spherulosis and adenoid cystic carcinoma can be mimics for the cribriform pattern of DCIS.

The *micropapillary* pattern shows epithelial micropapillations projecting into the ductular lumen; these lack connective tissue support and often show a bulbous expansion at the tip (Fig. 36.77). This variant is more likely than others to involve multiple quadrants of the breast.³⁵⁶

Papillary DCIS is another architectural pattern characterized by papillary projections with fibrovascular cores (see previous discussion).

Clinging pattern DCIS shows one or two layers of neoplastic epithelial cells lining a space often with an empty lumen, though necrosis may be seen.^{22,357} The lining cells are large, highly atypical,

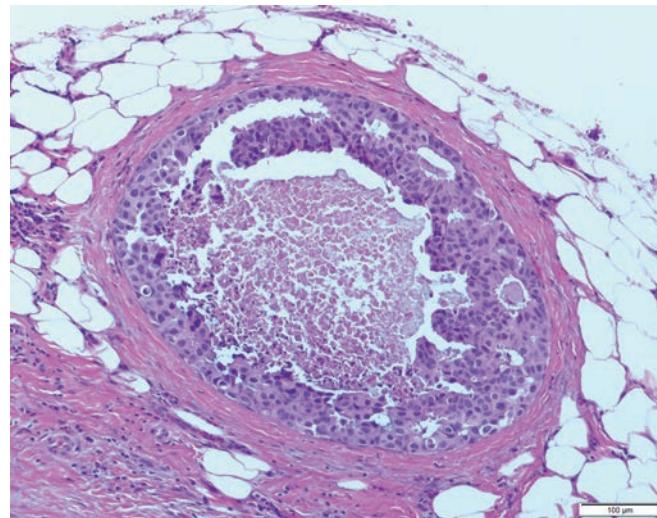


Figure 36.79 Ductal carcinoma in situ, with comedo necrosis.

and associated with apoptosis (Fig. 36.78). In the United States the term *clinging carcinoma* is restricted to the aforementioned high nuclear grade lesion. In Europe, reference is made to a pattern of DCIS referred to as *clinging carcinoma of the monomorphic type*,²² but this lesion is now classified as FEA.

Comedo DCIS really refers to a pattern of necrosis, rather than an architectural pattern of DCIS, in which the involved space is lined by several layers of neoplastic epithelial cells with approximately half the space involved by necrosis (Fig. 36.79).

There are occasions when the acini or lobules involved by DCIS remain small, a phenomenon formerly known as *lobular cancerization*; nowadays the term “*lobular involvement*” or “*involvement of lobules*” by DCIS is preferred. (Fig. 36.80). Available evidence suggests that this phenomenon represents instead a variation in the growth pattern of DCIS in which the structure involved is still easily recognizable as belonging to a lobule.³⁴⁵

Rare additional morphologic variations of DCIS include cases with *signet ring cells* (see Fig. 36.62),³⁵⁸ with *apocrine cytology* (Fig. 36.81),³⁵⁹ with *squamous features*,³⁶⁰ and with evidence of (neuro)

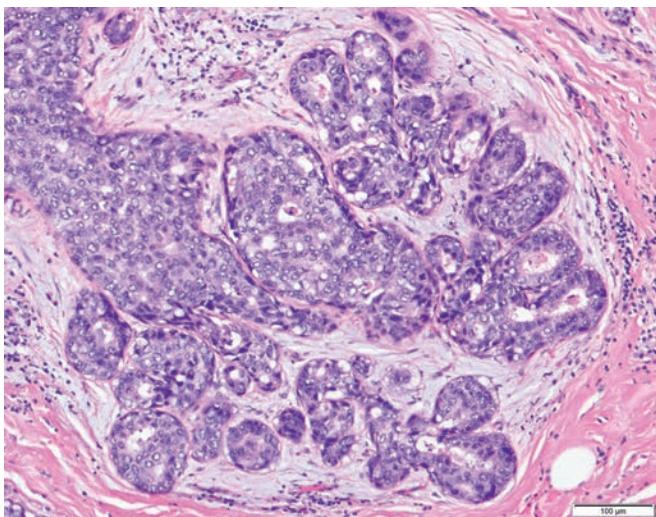


Figure 36.80 Ductal Carcinoma In Situ Involving Lobules. The terminal duct lobular unit is markedly expanded and composed of relatively large DCIS cells.

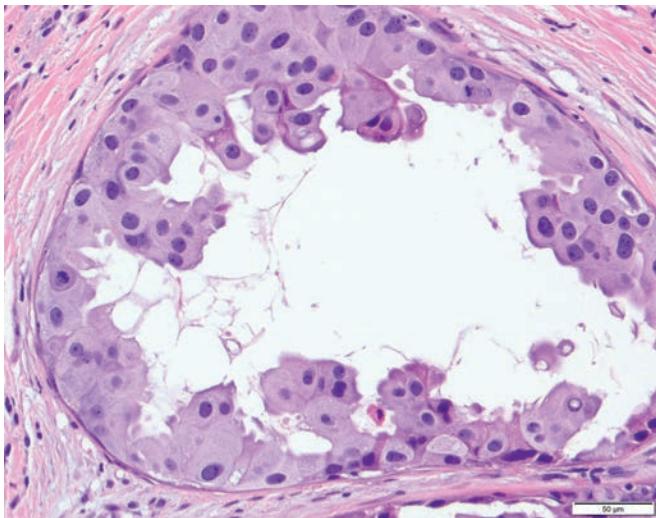


Figure 36.81 Ductal carcinoma in situ with apocrine features.

endocrine differentiation (Fig. 36.82).³⁶¹ The latter tumor, known as (neuro)endocrine DCIS (E-DCIS), is often seen in association with solid papillary carcinoma.³⁶² Sometimes these tumors are accompanied by an invasive component, which is also of neuroendocrine type. This tumor is probably closely related to the lesion that has been described as *spindle cell DCIS*.³⁶³

The two major differential diagnostic considerations of DCIS are LCIS (with low nuclear grade DCIS) and UDH (with intermediate nuclear grade DCIS), both of which can be separated on morphologic grounds supplemented by immunohistochemistry where needed.

Solid pattern, low nuclear grade DCIS is composed of cells that are cohesive and attempt to polarize (microacinar or rosette formation). In contrast, LCIS cells are dyshesive, often have intracytoplasmic vacuoles, and lack polarization. Immunostains for E-cadherin, β -catenin, and p120 catenin will show a strong membranous pattern of staining in DCIS. In general, LCIS cells have an absence of staining with E-cadherin and β -catenin and show a cytoplasmic pattern of staining with p120 catenin (but see discussion under LCIS for aberrant expression patterns).

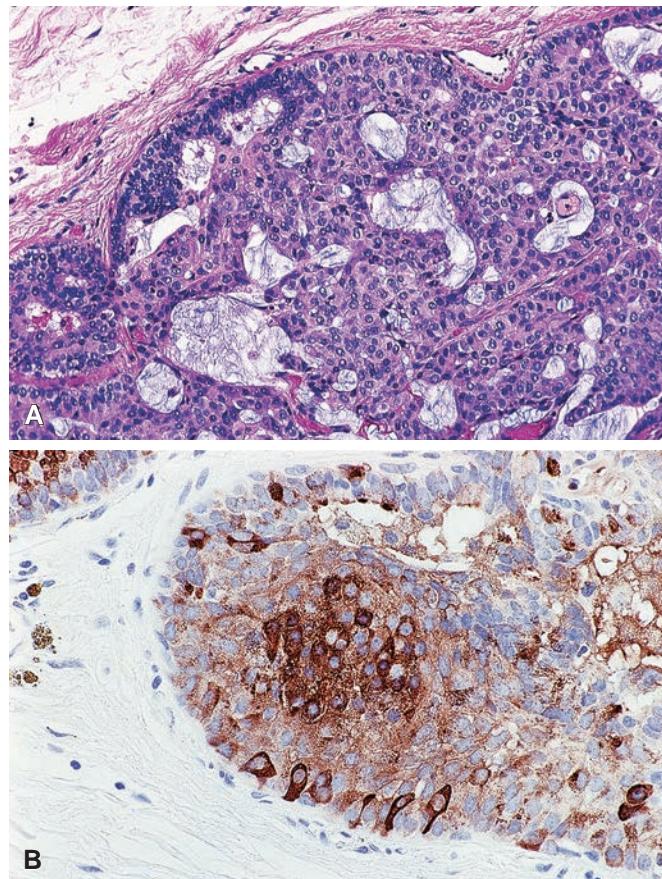


Figure 36.82 Ductal Carcinoma In Situ With Endocrine Features. **A**, Hematoxylin–eosin stain. **B**, Chromogranin immunostain.

Intermediate nuclear grade DCIS can be separated from UDH by recognizing the monotony of the atypical cells, even if showing a streaming pattern mimicking UDH. Some areas of polarization may be apparent even in intermediate nuclear grade DCIS. The cells of UDH are more variable in size, shape, and quality of chromatin. Immunohistochemically, DCIS will show an absence of staining with CK5/6 and strong, diffuse staining with ER, whereas UDH will have a heterogeneous pattern of expression with both markers.

Molecular genetic analyses in DCIS and ADH indicate that there is a low-grade pathway of neoplasia in which loss of 16q is identified in lesions as early in the progression pathway as FEA. These same genetic aberrations are present in ADH and low-grade DCIS, as well as in the lobular neoplasia pathway, suggesting that lobular lesions and low-grade ductal lesions are closely related.¹¹⁸ High-grade DCIS has a different and greater set of molecular genetic alterations, which includes 17q loss, compared with low-grade lesions.³⁶⁴ Needless to say intermediate-grade lesions are heterogeneous with regard to their molecular genetic alterations.³⁶⁵

Evolution

The implication of the diagnosis of DCIS is that, if left untreated, the lesion may progress to an invasive carcinoma of similar morphologic features. Evidence that DCIS is a nonobligate precursor lesion is as follows:

1. The transformation to an invasive phenotype does not occur in all cases, at least during the normal life span of an individual.³⁶⁶
2. When such a transformation occurs, the process usually evolves over a period of years if not decades.³⁶⁶

3. There is a substantial difference in the frequency with which this phenomenon occurs depending on the type of DCIS, with more rapid progression occurring in high nuclear grade DCIS and a more protracted course with low and intermediate nuclear grade DCIS.³⁶⁷⁻³⁷⁰
4. There is a relationship between the grade (and to some extent, microscopic type) of DCIS and the concurrent invasive component; however, numerous exceptions occur.³⁷¹
5. The molecular alterations present in DCIS are more similar to invasive carcinomas of the same grade than they are to DCIS of a differing grade (e.g., low nuclear grade DCIS has a gene expression pattern more similar to low-grade invasive carcinoma than it does to high nuclear grade DCIS and vice versa).³⁷²

Not all invasive breast carcinomas go through the sequence just described; some have a very short intraductal stage and become invasive before being detectable by any imaging modality. It is this very fact that takes some of the value away from screening techniques such as mammography, which are much more likely to detect slow-growing carcinomas with a prolonged *in situ* stage. The goal of treatment is complete eradication of DCIS, through local (breast-conserving) surgery with or without irradiation, followed by anti-estrogen therapy in those with ER-positive DCIS.^{373,374} There are some patients for whom mastectomy is indicated because of the extent of DCIS.

Lobular Carcinoma In Situ

LCIS has no distinguishing features on gross examination and is usually found incidentally in breast biopsies or excisions performed for other reasons. On occasion the term “lobular neoplasia” is used, particularly when referring to both ALH and LCIS. LCIS is multicentric in 60%–80% of cases and bilateral in approximately 30%–40%.³⁷⁵

Microscopically, the lobules are distended and completely filled by relatively uniform, round, small-to-medium-sized neoplastic epithelial cells with round and normochromic or only mildly hyperchromatic nuclei.³⁷⁶ In the typical case, there is a lack of cohesiveness among the tumor cells; intracytoplasmic vacuoles may be seen; and pleomorphism, mitotic activity, and necrosis are minimal or absent (Figs. 36.83 and 36.84).³⁷⁵ LCIS cells may form a continuous row beneath the ductal epithelium, a pattern referred to as *pagetoid* (Fig. 36.85). Any of the following minor morphologic variations can occur, singly or in combination: moderate nuclear pleomorphism, larger nuclear size, appreciable mitotic activity, scattered signet ring cells (relatively common), apocrine changes (exceptional), and focal

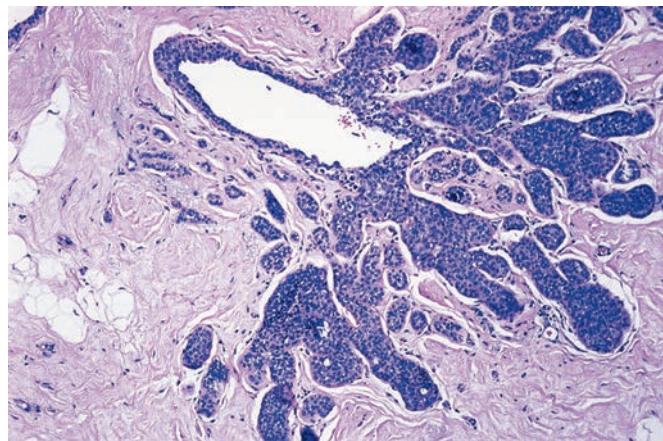


Figure 36.83 Typical pattern of involvement of terminal duct-lobular unit by lobular carcinoma in situ.

necrosis.³⁷⁷ When the tumor cells are of medium-to-large size, with more marked nuclear pleomorphism, often prominent nucleoli, and moderate-to-abundant cytoplasm, the lesion is referred to as *pleomorphic LCIS* (Fig. 36.86).³⁷⁸ Another variant form of LCIS is *florid LCIS with comedo necrosis* (Fig. 36.87), in which the involved TDLU is greatly expanded by a proliferation of LCIS cells, usually with classical cytologic features but accompanied by comedo necrosis and calcifications.³⁷⁹

LCIS can also involve fibroepithelial lesions (Fig. 36.88), sclerosing adenosis (see Fig. 36.40), a pattern that can be a mimic for invasive lobular carcinoma, or collagenous spherulosis (Fig. 36.89 and see Fig. 36.18), a pattern that can be a mimic for cribriform DCIS. The diagnosis of LCIS should be made only in those cases in which the cellular proliferation has resulted in the formation of solid nests that have expanded the lobules by greater than 50%, whereas the designation of ALH is to be given to those lesions in which the expansion of the lobules is of a lesser degree. LCIS also needs to be distinguished from solid pattern DCIS.

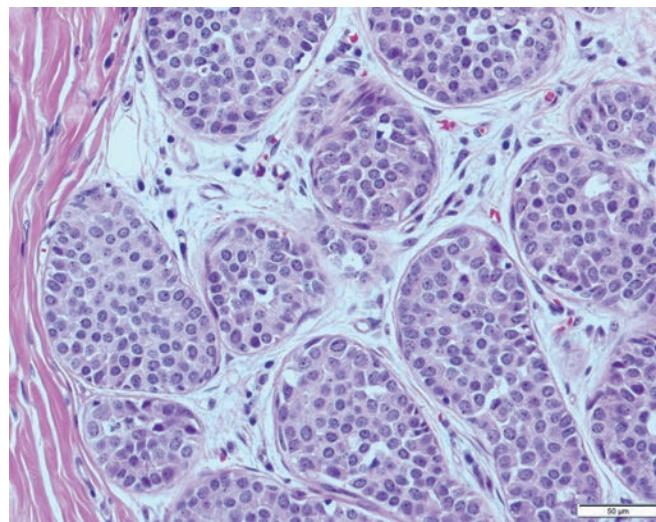


Figure 36.84 Marked expansion of a lobular unit by lobular carcinoma in situ.

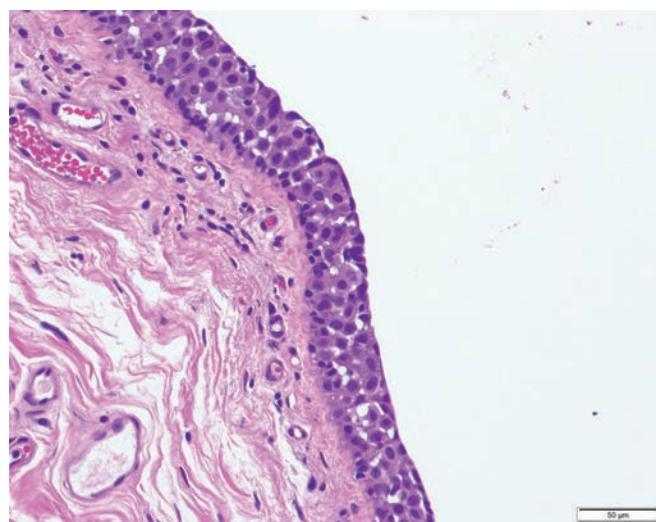


Figure 36.85 Pagetoid Involvement of Duct by Lobular Carcinoma In Situ. Note the presence of a monomorphic population of dyshesive cells underlying the attenuated layer of native ductal epithelium.

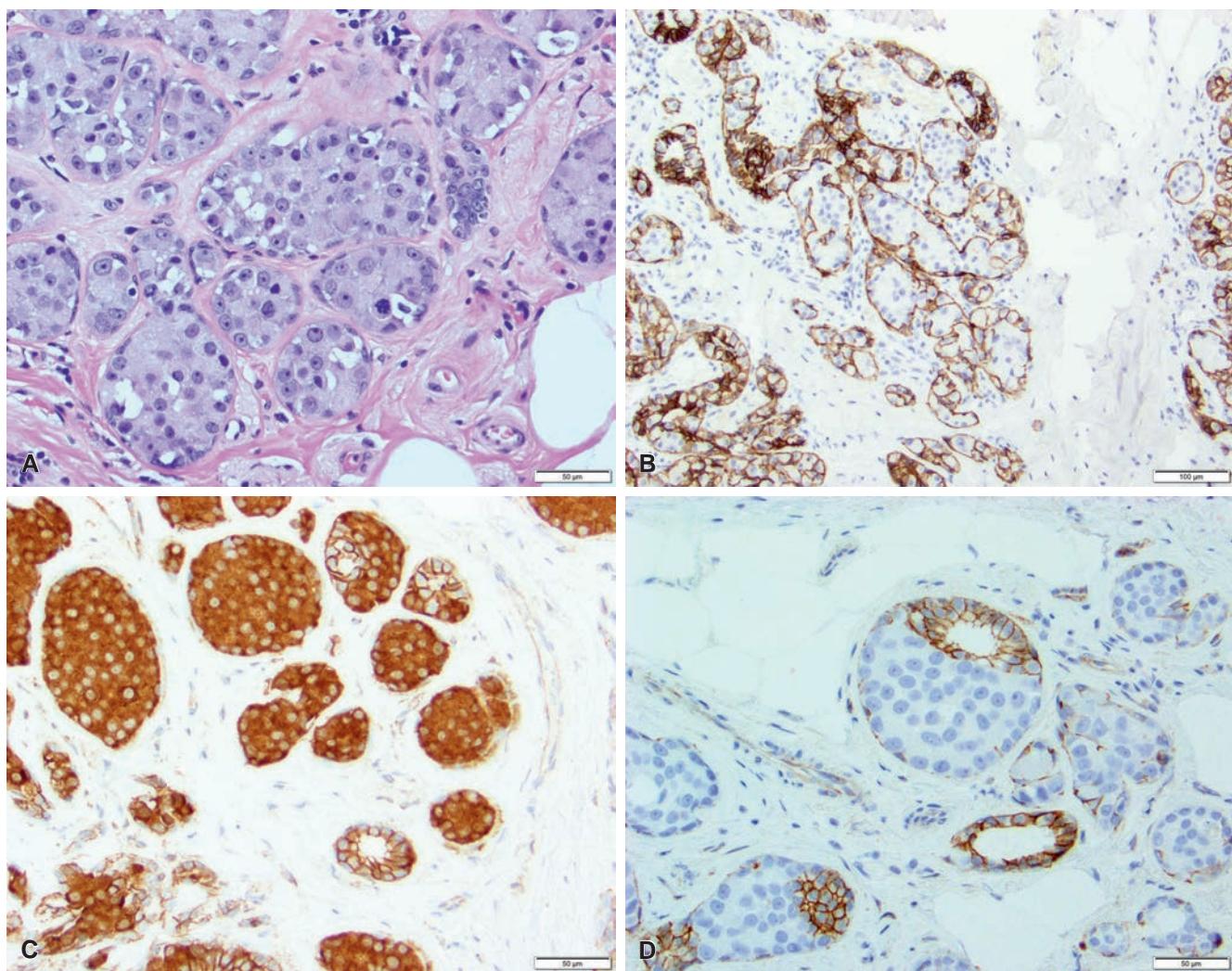


Figure 36.86 **Pleomorphic Lobular Carcinoma In Situ.** **A**, A lobule involved by pleomorphic LCIS. The cells are large with abundant eosinophilic cytoplasm and have pleomorphic nuclei with prominent nucleoli. **B**, E-cadherin immunostain. There is absence of staining in the LCIS cells. Myoepithelial cells and adjacent normal ductal epithelium show a membranous staining pattern. **C**, p120 catenin immunostain. There is cytoplasmic staining in the LCIS cells. Myoepithelial cells and adjacent normal ductal epithelium show a membranous staining pattern. **D**, β -Catenin immunostain. Like E-cadherin, there is absence of staining in the LCIS cells with myoepithelial cells and adjacent normal ductal epithelium showing a membranous staining pattern.

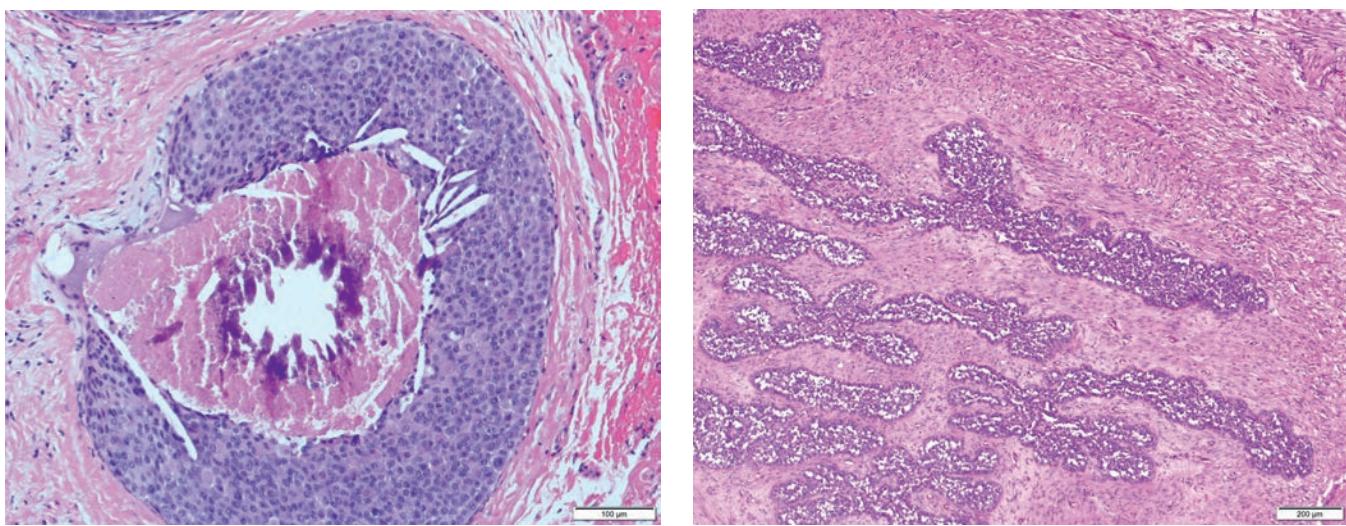


Figure 36.87 **Lobular Carcinoma In Situ With Comedo Necrosis.** The space is expanded by a monotonous proliferation of dyshesive epithelial cells (most pronounced in the lower right of the field); there is an absence of polarization of the cells. Comedo necrosis and calcifications are present in the center of the space.

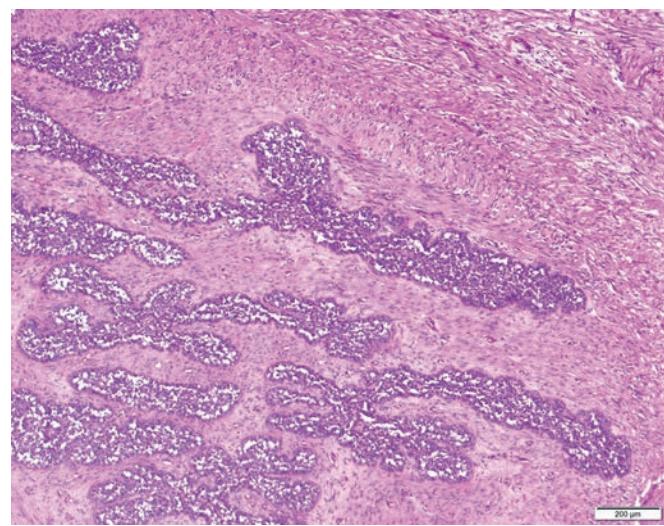


Figure 36.88 **Lobular Carcinoma In Situ Involving a Benign Phyllodes Tumor.** The ducts are expanded by a monotonous proliferation of dyshesive LCIS cells.

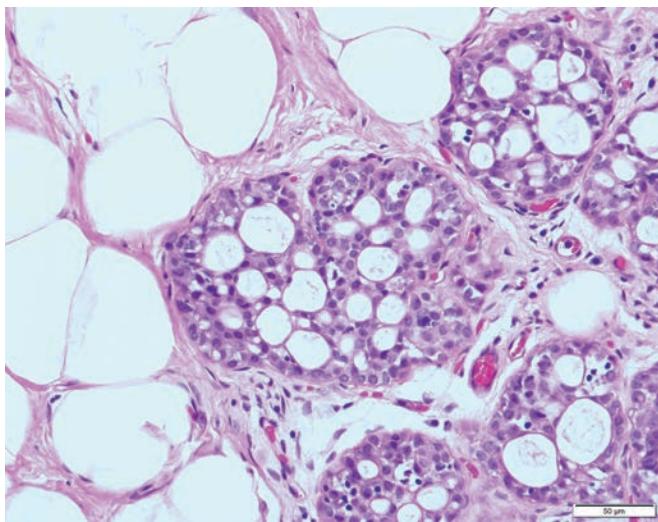


Figure 36.89 Lobular Carcinoma In Situ Involving Collagenous Spherulosis. The cribriform pattern conferred by this process can be a mimic for ductal carcinoma in situ.

From the point of view of the differential diagnosis with DCIS, morphologic features favoring a diagnosis of LCIS are cellular dyshesion, the presence of intracytoplasmic vacuoles, and an absence of polarization around the periphery of the involved space or of any attempt at microacinar formation; pagetoid involvement of ducts is also more characteristic of LCIS. Important immunohistochemical features of LCIS are an absence of expression with E-cadherin (see Fig. 36.86B and D) and β -catenin, and cytoplasmic positivity for p120 catenin (see Fig. 36.86C). By contrast, DCIS is consistently positive for all three markers, with a membranous pattern of expression.^{380,381} As might be expected, some cases of LCIS show hybrid immunohistochemical features, manifested as aberrant, weak expression with E-cadherin; helpfully, p120 catenin tends to maintain the characteristic cytoplasmic staining pattern in lesions with a lobular phenotype.³⁸¹ The molecular correlate for loss of E-cadherin expression in LCIS is alteration of the *CDH1* gene; it is speculated that aberrant expression may be a function of the type of inactivation present.^{382–384}

Evolution

One of the most controversial aspects of breast pathology is the nature of LCIS, specifically in regard to the probability of development of invasive carcinoma following a biopsy diagnosis of LCIS without additional therapy. Although the figures obtained in the various reported series^{385–389} are not exactly superimposable, it is reasonable to conclude from them that: (1) approximately 20%–30% of patients will develop invasive carcinoma, a risk about 8–10 times higher than for a control population; (2) the risk seems greater in well-developed LCIS than in ALH; (3) the risk is about the same regardless of the amount of LCIS; (4) this increased risk applies to both breasts, although it is slightly greater on the side of the biopsy; (5) the invasive carcinoma may be of either lobular or ductal type, though there is a preponderance of invasive lobular carcinoma; and (6) if a patient with a biopsy diagnosis of LCIS is examined periodically, the chances of death from breast carcinoma are minimal. There are very limited data on the subsequent breast cancer risk associated with the nonclassical or variant forms of LCIS.

Most investigators agree that careful lifelong follow-up appears to be a safe and rational option for patients with LCIS.^{387,390,391} Greater risk reduction is achieved with ER blockade with selective ER modulators (SERMs; such as with tamoxifen) or an aromatase

inhibitor (e.g., anastrozole).^{392,393} While an uncommon strategy today, the performance of simple mastectomy may be considered in the presence of a strong family history of carcinoma or if prolonged follow-up evaluation cannot be ensured, though given the bilateral nature of the risk conferred by LCIS, bilateral mastectomy would be the more appropriate surgical management.

Invasive Carcinoma

Tumors included in this category are all those in which stromal invasion is detectable, whether an *in situ* component is identifiable or not, and regardless of the relative proportion of the two components; in other words, it also includes “microinvasive carcinoma.” Like *in situ* lesions, most invasive tumors can be divided into two major categories—ductal type and lobular type—acknowledging the existence of mixed forms. It should be mentioned that the type of invasive carcinoma ought to be determined from its own appearance, rather than deduced from the type of *in situ* component present, if any, since the two do not always correspond.

The classification of invasive breast carcinoma has evolved over a long period of time and, as a result, has had incorporated into it a wide range of criteria, such as cell type (as in apocrine carcinoma), type and amount of secretion (as in mucinous carcinoma), architectural features (as in papillary carcinoma), and pattern of spread (as in inflammatory carcinoma, which strictly speaking is a clinical and not a pathologic definition).

Microinvasive Breast Carcinoma

Once the concept of “microinvasive carcinoma” was entrenched in the gynecologic literature, it was only natural that it would be proposed at other sites, including the breast. Alas, its application at this site was not as straightforward, one of the reasons being that the mammary epithelium is not separated from the stroma by a sharp, straight line as it is in the cervix.³⁹⁴ Be that as it may, microinvasive carcinoma is defined as any breast carcinoma showing stromal invasion not exceeding 1 mm in extent.³⁹⁵ The term is applicable to both ductal and lobular lesions, but the former is more frequent. There may be a single focus of microinvasion or multifocal microinvasion may be identified. The mean number of foci reported is two.³⁹⁶ Features of DCIS associated with microinvasion include greater extent, high nuclear grade, solid pattern, comedo necrosis, and periductal lymphoid infiltrates (see Fig. 36.74).³⁹³ Note though that microinvasion may be seen with other grades and patterns of DCIS and with LCIS. Immunohistochemical evaluation with myoepithelial cell markers, in combination with cytokeratin if possible to highlight the microinvasive epithelial component, may be needed to confirm the diagnosis.^{395,397} Patients with microinvasive carcinoma are at risk for nodal metastases,³⁹⁸ but their survival rate is better than for patients with T1 invasive carcinoma,³⁹⁹ and the extent of microinvasive carcinoma does not appear to be correlated with likelihood of lymph node metastases.^{400,401}

Invasive Ductal Carcinoma

This lesion represents the prototypic expression of breast carcinoma and is the tumor type usually implied when the terms “breast carcinoma” or “breast cancer” are used without further qualification. The size, shape, and tumor border are highly variable. Grossly, the typical case is firm and poorly circumscribed, cuts with a resistant gritty sensation, and shows a yellowish-gray cut surface, with trabeculae radiating through the surrounding parenchyma into the fat, resulting in the notorious stellate or crab-like configuration, from which the word “cancer” originated (Fig. 36.90). Areas of necrosis,



Figure 36.90 Typical Gross Appearance of Invasive Ductal Carcinoma. Note the irregular (crab-like) shape of the tumor, white fibrous appearance, and chalky streaks.

hemorrhage, and cystic degeneration are unusual but may be present, particularly in larger neoplasms. The tumor may invade the overlying skin or the underlying fascia and pectoralis muscle. Tumors that are particularly hard because of the large amounts of desmoplastic stroma were traditionally referred to as “scirrhouss carcinomas.” It is common for these neoplasms to exhibit “chalky streaks” on the cut surface, a feature caused by duct elastosis.⁴⁰² When this occurs, the appearance of the lesion has an uncanny resemblance to an unripe pear, further accentuated by the consistency felt while cutting it.

Microscopically, the variations are also legion. The tumor can grow in diffuse sheets, well-defined nests, cords, or as individual cells. Glandular/tubular differentiation may be well developed (Fig. 36.91), barely detectable, or altogether absent. The tumor cells vary in size and shape, the nuclei are large with varying degrees of pleomorphism, and nucleoli may be prominent. Mitotic figures vary from infrequent to more numerous. Areas of necrosis are unusual but may be identified in some cases. The amount of stroma ranges from none to abundant, and its appearance from densely fibrotic to cellular (“desmoplastic”). In cases with abundant stroma, it may be difficult to identify the tumor cells. Areas of “elastosis” may be present, which can involve the wall of the ducts and the vessels (mainly veins).⁴⁰² Calcification has been reported in approximately 60% of cases, either as coarse or fine deposits or, rarely, as psammoma bodies; most often the calcifications are identified within the associated *in situ* component.^{315,403} A mononuclear inflammatory infiltrate of variable intensity may be present at the interface between tumor and stroma. Granulomatous inflammation is rarely seen.

Definite invasion of the perineural spaces, lymphatic vessels, and blood vessels was reported by Fisher et al.⁴⁰³ in 28%, 33%, and 5% of cases, respectively. Lymphatic vessel invasion may be difficult to distinguish from artifactual tissue retraction. Features used to document the presence of lymphatic tumor emboli are the following: (1) the occurrence of the area in question outside the margin of the carcinoma, (2) the fact that the tumor emboli do not conform exactly to the space in which they lie, (3) the presence of an endothelial cell lining, and (4) the presence of blood vessels in the immediate vicinity.⁴⁰⁴ If doubts persist, a stain with D2-40 or other endothelial cell markers might prove helpful (Fig. 36.92). Note that D2-40 crossreacts with myoepithelial cells;⁴⁰⁵ thus it is prudent to include a myoepithelial cell marker in the panel also. These reactions can be carried out in the H&E-stained preparations after removing the coverslip and decolorizing the slide, if necessary.⁴⁰⁶

The term “extensive intraductal carcinoma” (EIC) applies to tumors in which the intraductal component comprises 25% or more of the

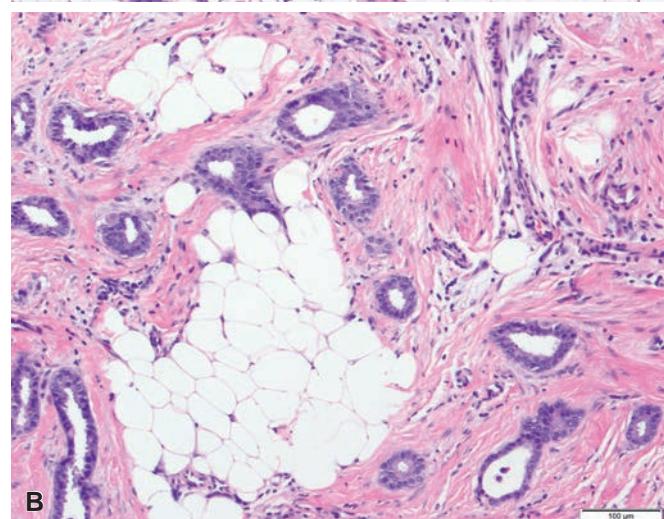
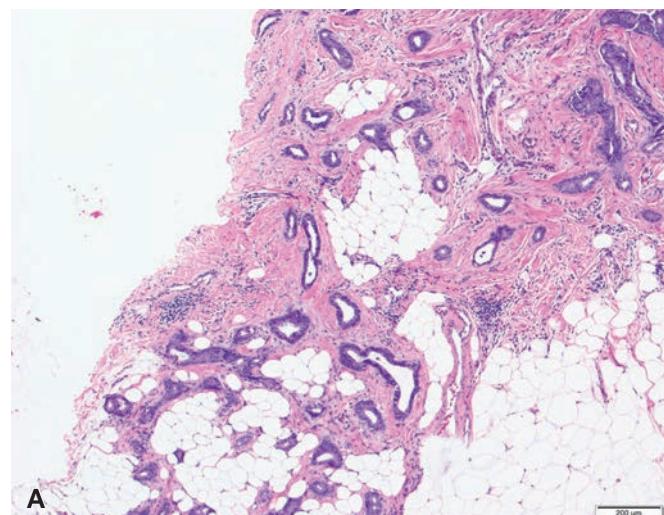


Figure 36.91 Prototypical Invasive Ductal Carcinoma. **A**, Irregularly shaped glands infiltrate through the stroma in a haphazard pattern. **B**, There is cytologic atypia present and myoepithelial cell are absent.

area encompassed by the infiltrating tumor and is also present in the surrounding breast tissue.⁴⁰⁷ The identification of EIC was of importance in predicting the likelihood of residual carcinoma in women undergoing reexcision; however, in contemporary practice, where greater attention is given to margin evaluation, this pathologic feature has become less critical.

Immunohistochemically, breast carcinoma cells show reactivity for low-molecular-weight cytokeratins (particularly types 8, 18, and 19) and EMA.⁴⁰⁸ Some tumors (particularly high-grade tumors with a solid growth pattern and those with foci of squamous metaplasia) are also immunoreactive for HMW cytokeratin (CK5/6).⁴⁰⁹ Three useful breast-related markers are mammaglobin, GCDFP-15, and GATA3. Each has varying degrees of sensitivity and specificity that can be improved by using them in combination where determination of breast origin is needed.⁴¹⁰⁻⁴¹²

Breast carcinomas can be immunoreactive for S-100 protein, the proportion ranging from 10% to 45% in the various reported series.^{413,414} This is a fact to remember in the differential diagnosis of metastatic tumors to axillary nodes, lest a breast carcinoma be mislabeled as metastatic melanoma. Even more treacherous is the fact that some breast carcinomas may show positivity for HMB-45.⁴¹⁵

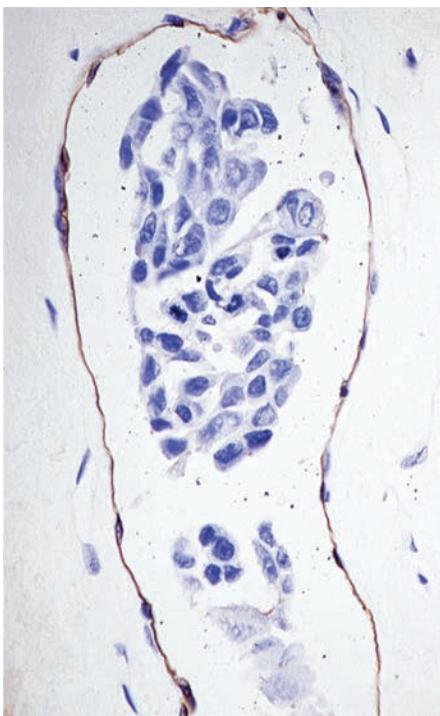


Figure 36.92 Vascular invasion by breast carcinoma demonstrated by positivity of endothelial cells for *Ulex europaeus* lectin I.

TTF-1 positivity has also been documented, a point to be remembered in the evaluation of core needle biopsies of a lung mass in a patient with a history of breast carcinoma.⁴¹⁶ While not often used in clinical practice, increased expression of the bone matrix proteins osteonectin and osteopontin has been documented, with the added suggestion that this may play a role in the bone homing of breast carcinoma metastases.^{417,418} The basement membrane components laminin and collagen IV show a discontinuous linear pattern or are altogether absent, in contrast to the continuous pattern exhibited in intraductal lesions.^{419,420} Smooth muscle myosin heavy chain, calponin, p63, and other myoepithelial cell markers are negative in invasive carcinomas, confirming the absence of myoepithelial cells around the tumor nests.

Ultrastructurally, breast carcinoma cells exhibit, in greater or lesser degree, features of glandular differentiation such as microvilli and terminal bars on their luminal side.⁴²¹ A particularly characteristic feature, although not as specific for breast carcinoma as originally suggested, is the presence of intracytoplasmic lumina bordered by microvilli.^{422,423} These formations, when sufficiently large, appear as “bulls eyes” at the light microscopic level and are different from the formations seen in signet ring cells, which are intracytoplasmic vacuoles. The desmoplastic stroma accompanying breast carcinomas is formed by cells having the ultrastructural features of fibroblasts and myofibroblasts.⁴²⁴

Invasive Lobular Carcinoma

Classic type. In its most typical form, invasive lobular carcinoma is characterized by the presence of small and relatively uniform tumor cells growing in single file and in a targetoid fashion around ducts (Figs. 36.93–36.95). Gland formation is not a feature of invasive lobular carcinoma. The stroma is usually abundant, of dense fibrous type, with areas of periductal and perivenous elastosis. Rarely, a lymphocytic infiltrate may be present.

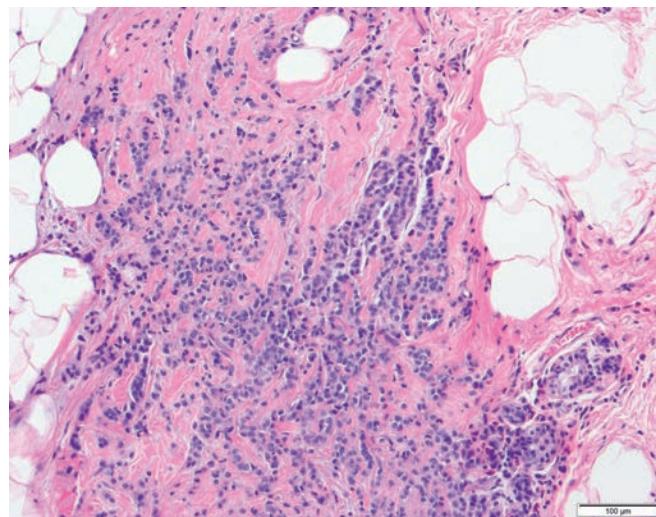


Figure 36.93 Invasive Lobular Carcinoma. The tumor cells are small and uniform with round nuclei and grow in single file fashion.

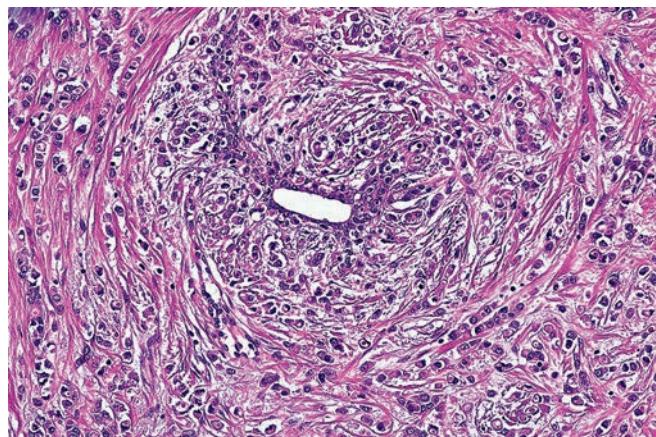


Figure 36.94 Typical target-like growth of tumor cells around an uninvolved duct in invasive lobular carcinoma.

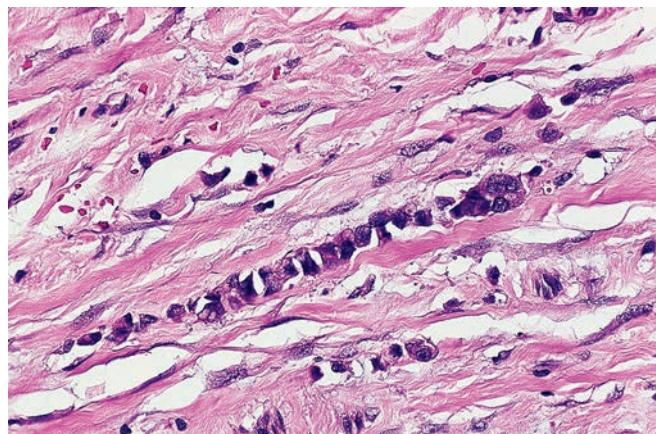


Figure 36.95 Single file pattern of growth of invasive lobular carcinoma.

The immunohistochemical features of invasive lobular carcinoma are analogous to those described for its *in situ* counterpart. This includes the presence of low-molecular-weight cytokeratins, an absence of E-cadherin expression, and a cytoplasmic staining pattern with p120 catenin.³⁸⁰ While loss of E-cadherin expression is the hallmark of lobular carcinoma, positive immunostaining for E-cadherin does not preclude this diagnosis when the morphologic features are compatible. As a matter of fact, up to 16% of cases of invasive lobular carcinomas show immunoreactivity for E-cadherin, but these cases typically exhibit abnormal expression of one or more of the catenin complex members, most commonly diffuse cytoplasmic expression of p120 catenin.^{382,426} That said, the diagnosis of invasive lobular carcinoma should be made on morphologic grounds; use of E-cadherin is not indicated in histologic typing of invasive carcinomas.³⁸¹

The genetic basis for the loss of E-cadherin expression in lobular carcinoma includes: (1) inactivating mutation of the E-cadherin gene *CDH1*, usually attributable to loss of heterozygosity on chromosome 16q or homozygous deletions of *CDH1*; (2) *CDH1* promoter hypermethylation; (3) truncating mutation in *CDH1*; and (4) transcriptional inactivation.⁴²⁶

The main differential diagnosis of invasive lobular carcinoma is with invasive carcinoma with ductal and lobular features. The small size and uniformity of the cells and their lack of cohesiveness are the most important distinguishing features. It should be remarked, however, that in some cases the distinction is difficult and to a large extent subjective, as borne out by the fact that the incidence of invasive lobular carcinoma ranges from 0.7% to 20% in the published series.⁴²⁷ As discussed earlier, LCIS involving adenosis can be a mimic of invasive lobular carcinoma. Myoepithelial cell markers are helpful in such cases. Other entities that can be confused with invasive lobular carcinoma are carcinoma with neuroendocrine features and malignant lymphoma. The latter possibility arises more often when invasive lobular carcinoma metastasizes to axillary nodes and other sites, particularly the orbit.⁴²⁸ In those situations cases may be misdiagnosed as large cell lymphoma or malignant histiocytosis because of the diffuse pattern of growth and the histiocyte-like appearance of the tumor cells. Immunoreactivity for cytokeratins and histochemical positivity with mucicarmine should eliminate any problems not resolved by the examination of the routinely stained slides.

Invasive Carcinoma With Ductal and Lobular Features

Carcinomas composed in part of a component with definite features of invasive ductal carcinoma and in part of a component with definite features of invasive lobular carcinoma do occur; more commonly seen are tumors with features neither definitively lobular nor definitively ductal (Fig. 36.96). It is acceptable to classify these tumors as invasive carcinoma with ductal and lobular features. They should be distinguished from cases in which two separate neoplasms of different microscopic appearances are present in the same breast. They should also be distinguished from so-called tubulo-lobular carcinoma, which has a reasonably distinct morphologic appearance (see next section).

Variants of Invasive Lobular Carcinoma

Pleomorphic invasive lobular carcinoma. This form of invasive breast carcinoma has the growth pattern of a classic breast carcinoma but exhibits a marked degree of nuclear pleomorphism (Fig. 36.97).⁴²⁹ Apocrine differentiation and focal signet ring morphology may also be seen. Pleomorphic invasive lobular carcinoma more frequently demonstrates a lack of hormone receptors and shows expression of

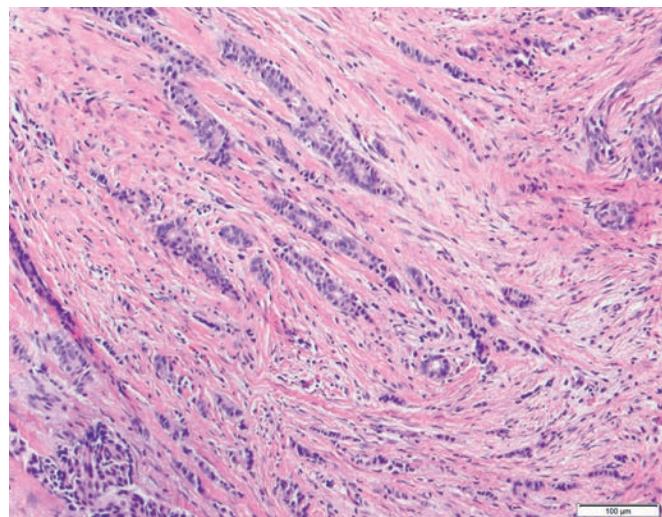


Figure 36.96 Invasive carcinoma with ductal and lobular features; in some areas there is gland formation, while in others, the tumor cells align in a single file (lower portion of field).

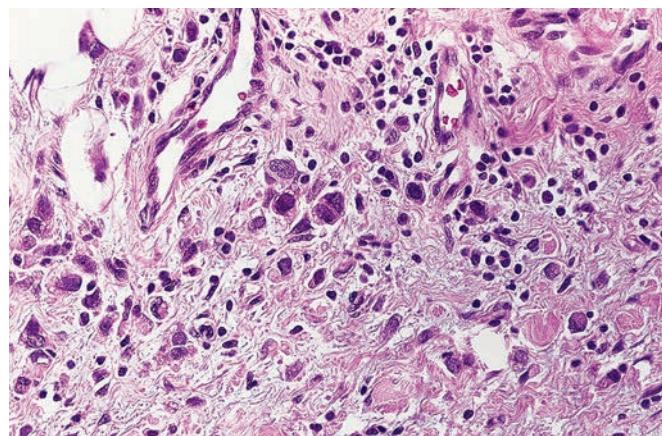


Figure 36.97 Pleomorphic variant of invasive lobular carcinoma.

HER2 and p53, while still demonstrating an absence of E-cadherin staining, as well as loss of the long arm of chromosome 16, in keeping with the lobular phenotype.^{383,384,430}

Signet ring carcinoma. Signet ring carcinoma is a type of breast carcinoma in which a significant number of tumor cells show intracytoplasmic mucin accumulation, resulting in the typical signet ring appearance (Fig. 36.98). It is important to separate this tumor from mucinous carcinoma (in which the mucin is extracellular) because of their differing prognoses.

Most cases of signet ring carcinoma show cytoarchitectural features (such as small cell size, uniformity, and cellular dyshesion) similar to those of classic invasive lobular carcinoma and sometimes coexist with it. Furthermore, it is not rare for LCIS or invasive lobular carcinoma to contain scattered signet ring cells. For these reasons, most cases of signet ring carcinoma are regarded as variants of invasive lobular carcinoma.⁴³¹

Immunohistochemically, signet ring carcinoma is positive for CK7 and MUC1 and usually negative for E-cadherin.⁴³²

Care must be taken with the challenging differential diagnosis of gastric signet ring adenocarcinoma, as invasive lobular carcinomas with signet ring cell features are known to metastasize to the stomach.

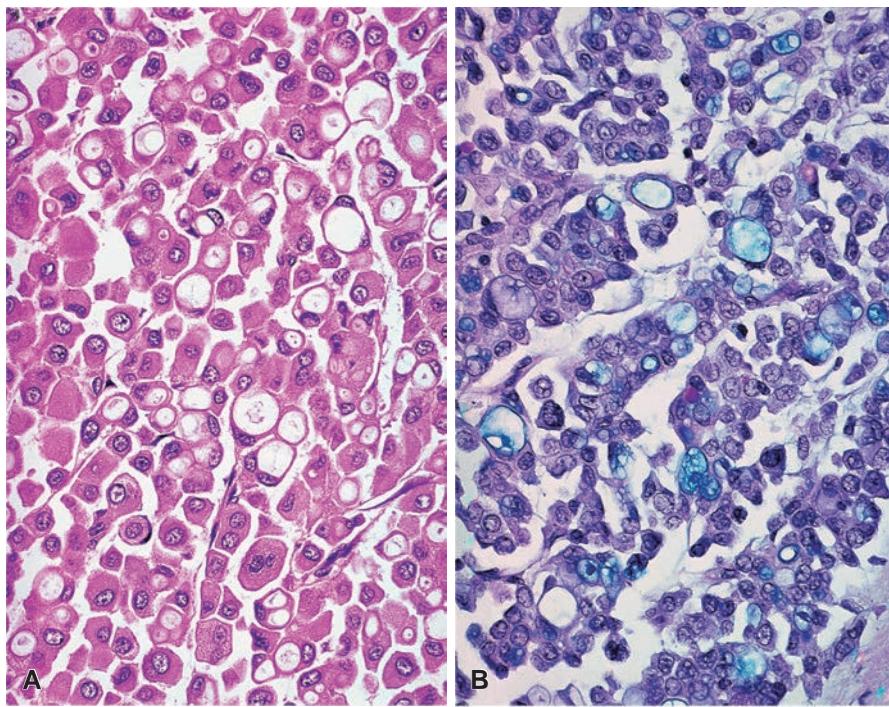


Figure 36.98 A, and B, Signet Ring Carcinoma of the Breast. This is regarded as a variant of lobular carcinoma. **B**, Alcian blue-PAS stain.

Rarely the converse of gastric metastasis to the breast has been reported.^{433,434}

Histiocytoid carcinoma. Histiocytoid carcinoma is characterized by a diffuse pattern of growth of bland tumor cells displaying abundant granular, foamy cytoplasm.⁴³⁵ It may simulate the appearance of an inflammatory process or of granular cell tumor.^{436,437} Histiocytoid carcinoma is viewed as a variant of invasive lobular carcinoma exhibiting apocrine differentiation, as evidenced by immunohistochemical reactivity for GCDFP-15 and absence of E-cadherin expression.^{436–438}

Histiocytoid carcinoma should also be distinguished from *lipid-rich carcinoma*. The latter is simply a form of breast carcinoma showing lipid accumulation in the cytoplasm of greater than 90% of the tumor cells (Fig. 36.99).^{439–441}

Other types. As long as the relatively bland and homogeneous cytologic appearance is maintained, cases having closely aggregated cells, solid pattern, trabecular pattern, and loose alveolar pattern have been accepted as invasive lobular carcinoma. Perhaps the most distinctive of these forms is the *alveolar variant*, in which the tumor cells are arranged in sharply outlined groups separated by fibrous tissue sometimes containing osteoclast-like giant cells.⁴⁴² The cytologic and/or architectural similarities between these various forms and classic invasive lobular carcinoma are undeniable. The problem, however, is that the more the concept of invasive lobular carcinoma is widened, and to some extent diluted, the less distinct the entity becomes and the less significant (or at least the less uniform) its clinical connotations.⁴⁴³

Tubular Carcinoma

Tubular carcinoma is a well-differentiated tumor more common among older women. Grossly, tubular carcinoma suggests malignancy by virtue of its poorly circumscribed margins and hard consistency similar to invasive ductal carcinomas of no special type. It is

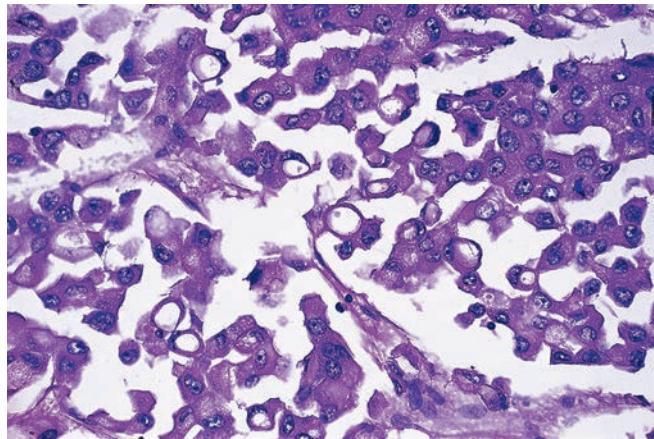


Figure 36.99 Lipid-Rich Carcinoma of the Breast. The cells show cytoplasmic vacuolation with nuclear displacement due to lipid accumulation. **A**, Intermediate power. **B**, High power.

characteristically small, with a mean diameter of about 1 cm.^{444,445} Microscopically, it simulates a benign condition (particularly radial scar but also microglandular adenosis) because of the well-differentiated nature of the glands, absence of necrosis or mitoses, and scanty pleomorphism. Clues to the diagnosis are the haphazard arrangement of the glands in the stroma with absence of any lobular configuration; frequent invasion of fat at the periphery of the lesion; cellular (but often also elastotic⁴⁴⁶) nature of the stroma; irregular and often angulated contours of the glands (Fig. 36.100); open lumina sometimes with basophilic secretion; apical “snouts” in the cytoplasm; lack of a myoepithelial cell component (well appreciated in immunostained preparations with myoepithelial cell antibodies such as p63 and SMMHC); lack of basement membrane; and occurrence

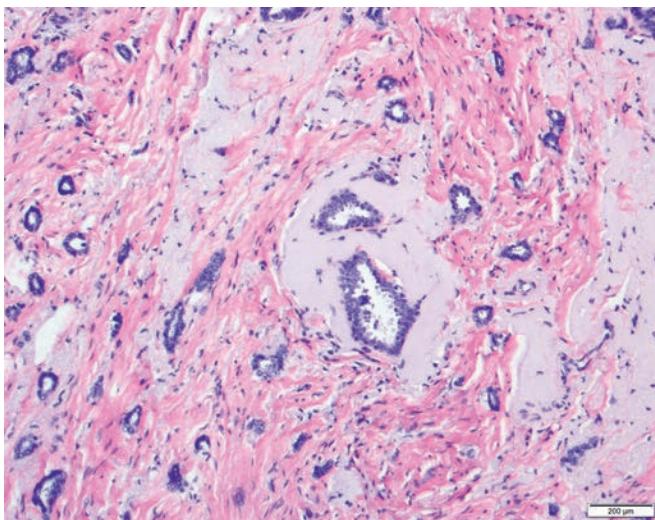


Figure 36.100 **Tubular Carcinoma of Breast.** The angulated shape of the glands percolating haphazardly through the cellular stroma are characteristic of this lesion. In this particular case, there is prominent stromal elastosis.

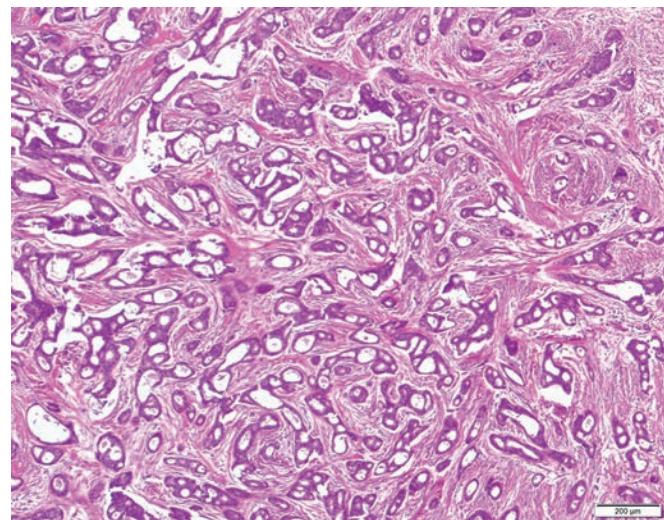


Figure 36.101 **Invasive Cribriform Carcinoma.** In this example, all the nests have a cribriform pattern. The irregular contour of the nests and the infiltrative growth pattern help distinguish this lesion from cribriform pattern DCIS.

in two-thirds of cases or more of low nuclear grade DCIS, often micropapillary or cribriform pattern.⁴⁴⁴ FEA also is frequently found in cases of tubular carcinoma. In fact, low-grade DCIS, ADH, and FEA are considered to be nonobligate precursor lesions of low-grade invasive carcinomas and tubular carcinomas in particular.^{118,447,448}

Because of the marked degree of cellular differentiation, it is not unusual for these tumors to be underdiagnosed as fibroadenoma or some other benign process on FNA material.⁴⁴⁹ They are more readily recognized in core needle biopsy specimens.

Metastases to axillary lymph nodes occur in approximately 10% of cases,⁴⁴⁴ but this does not appear to affect outcome, even in the absence of systemic chemotherapy.^{450–452} In a series by Rakha et al.,⁴⁵² only 7% of their 102 patients developed recurrent or metastatic disease during a median follow-up period of 127 months and these events were all found to be associated with an intervening recurrence of breast carcinoma of different histologic type and/or grade. Thus tubular carcinoma can be considered a special-type breast cancer with an exceptionally favorable prognosis.⁴⁵²

Sometimes, a tubular carcinoma pattern is seen in association with an ordinary invasive ductal carcinoma; however, the diagnosis of tubular carcinoma should be reserved for those tumors in which the tubular component makes up more than 90% of the tumor.

Tubulolobular carcinoma. This variant is characterized by the admixture of small tubular formations with cords of tumor cells growing in a lobular configuration.⁴⁵³ The *in situ* component, if present, may be of either lobular, ductal or both types.⁴⁵⁴ The immunohistochemical profile is intermediate between those of ductal and lobular carcinoma, in that it may show positivity for E-cadherin.⁴⁵⁴ This tumor is associated with a higher incidence of multifocality and positive axillary nodes than pure tubular carcinoma.^{455,456}

Invasive Cribriform Carcinoma

Invasive cribriform carcinoma is another special-type breast carcinoma, which, similar to tubular carcinoma, has an excellent prognosis.^{457,458} As the name indicates, the tumor has a cribriform appearance similar to that seen in the more common *in situ* counterpart, but it exhibits stromal invasion and lacks a myoepithelial cell layer (Fig. 36.101). This pattern is often seen in association with tubular

carcinoma, the relative proportion of the two elements determining the term used.⁴⁵⁸ The most important aspect of this particular tumor is the recognition that a cribriform lesion can be invasive, a potential diagnostic pitfall. In many cases, cribriform pattern DCIS is also present, but it is the size of the invasive component that should be reported for staging purposes. The invasive component can be recognized by the more infiltrative growth pattern extending between and around ducts and lobules, the irregular contour of some of the tumor cell nests and the presence of a desmoplastic-appearing stroma. DCIS, in contrast, has a growth pattern that conforms to the normal ductolobular architecture and more rounded contours to the nests; stromal changes are usually absent. If necessary, immunohistochemistry for myoepithelial cells can be used to separate the relative proportions of DCIS versus invasive cribriform carcinoma.

Mucinous Carcinoma

Mucinous carcinoma occurs over a wide age range (25–85 years), but the median age of 71 years is greater than that for invasive ductal carcinoma of no special type.⁴⁵⁹ Grossly, it is well circumscribed, fluctuant to palpation, and formed by a gelatinous mass held together by delicate septa (Fig. 36.102). Foci of hemorrhage may be seen. Microscopically, the classic and often quoted description is that of small clusters of tumor cells “floating in pools of mucin” (Fig. 36.103). These clusters may be solid, exhibit acinar formations, or form micropapillary structures.⁴⁶⁰ The mucin is almost entirely extracellular, and it may be of acid or neutral type.⁴⁶¹ Occasionally, mucinous carcinoma will consist almost entirely of mucin, and thorough sampling will be necessary to detect the neoplastic epithelium. An easily recognizable *in situ* component may be absent or inconspicuous (but see later section). Immunohistochemically, there is strong MUC2 cytoplasmic immunoreactivity and decreased MUC1 immunoreactivity compared with invasive ductal carcinoma of no special type.^{462,463} Both pure and mixed mucinous carcinomas of the breast often express WT1, a potential diagnostic trap with ovarian carcinoma.⁴⁶⁴ Hormone receptors are invariably positive, while HER2 is almost always negative.⁴⁶⁵

Interestingly, about a quarter to nearly one-half of mucinous carcinomas show features consistent with endocrine differentiation,

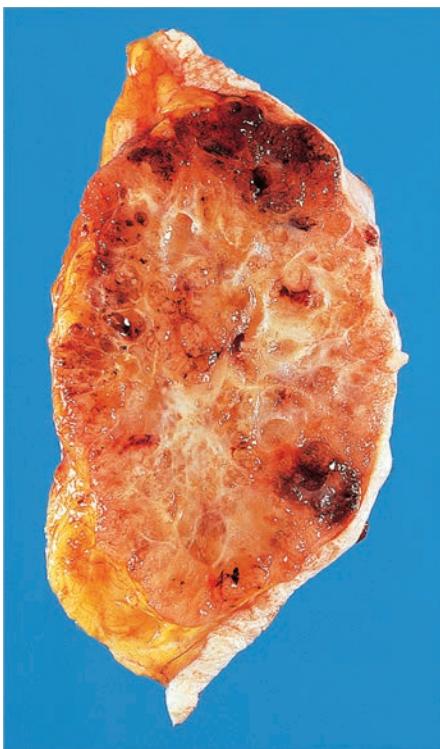


Figure 36.102 Typical Gelatinous Gross Appearance of Pure Mucinous Carcinoma. Note the sharply circumscribed quality of the tumor. (Courtesy of Dr RA Cooke, Brisbane, Australia. From Cooke RA, Stewart B. *Colour Atlas of Anatomical Pathology*. Edinburgh: Churchill Livingstone; 2004.)

such as synaptophysin and chromogranin immunoreactivity, and the presence of dense-core secretory granules by ultrastructural examination.^{466,467} This unexpected finding has raised the possibility of a link between mucinous carcinoma and neuroendocrine carcinoma.⁴⁶⁸ Some authors have suggested the existence of two types of mucinous carcinoma on the basis of being paucicellular or hypercellular and the absence or presence of endocrine differentiation, designated as type A and B, respectively (Fig. 36.103A, B and C, D respectively).⁴⁶⁶ There appears to be no influence of this separation on survival.⁴⁶⁹

On analysis of array-based CGH assays, pure mucinous carcinomas are a homogeneous group and cluster together, separately from invasive ductal carcinoma of no special type.^{465,468} They less frequently harbor gains of 1q and 16p and losses of 16q and 22q than grade- and ER-matched invasive ductal carcinomas of no special type. Gene expression profiling has shown that type B mucinous carcinomas and neuroendocrine carcinomas are part of a spectrum of lesions, whereas type A mucinous carcinoma is a discrete entity.⁴⁶⁸

It is important for prognostic reasons, and perhaps useful histogenetically, to restrict the term mucinous carcinoma to breast neoplasms exhibiting this feature throughout the tumor ("pure" mucinous carcinomas) and to exclude: (1) "mixed" tumors in which the mucinous pattern is admixed with an invasive ductal carcinoma (these having a prognosis analogous to the latter)⁴⁶⁵, and (2) signet ring carcinomas, even if technically speaking these are also "mucinous" tumors. The distinctiveness of signet ring carcinoma resides in the fact that the mucin remains within the cell, and the uniqueness of mucinous carcinoma is that most of the mucin is extracellular.

Pure mucinous carcinoma is associated with a very low incidence (2%–4%) of nodal metastases.^{451,459,470} The higher incidence reported

in some series is probably attributable to the inclusion of "mixed" mucinous tumors. Consequently, the pure form of mucinous carcinoma carries an excellent short-term prognosis. However, it has been shown that deaths from this tumor can occur greater than 25 years after therapy, indicating the need for long-term follow-up.^{451,471} As already indicated, several groups found no prognostic difference between mucinous carcinomas with endocrine-like features and those without,⁴⁷⁰ although others claim that the former are associated with favorable histologic and immunohistochemical parameters.⁴⁷²

A diagnostic challenge of which to be aware when encountering a mucinous lesion is the occurrence of extravasated mucin in association with benign or atypical lesions. "Mucocele-like lesion"⁴⁷³ is the occurrence of a cystically dilated duct filled with mucin that may rupture, resulting in extravasation of mucin into the stroma (Fig. 36.104). In many cases, the lining epithelium is attenuated, but in some mucocele-like lesions the lining epithelium is proliferative, with morphologic changes including UDH, ADH, and even DCIS. On occasion, this proliferative epithelium may become detached and "float" in the stromal mucin pools, mimicking mucinous carcinoma. The distinction can be challenging, particularly if the detached epithelium is from DCIS. Features favoring a mucocele-like lesion with detached epithelium over mucinous carcinoma are the linear arrangement of the epithelial fragments that have detached from the duct wall and the presence of myoepithelial cells.

On core needle biopsy specimens, mucinous lesions can be particularly difficult to categorize, given the knowledge that some mucinous carcinomas are hypocellular with abundant mucin. Most practitioners have recommended excision for mucinous lesions on core needle biopsy regardless of the identification of atypia⁴⁷⁴; however, more recent publications have moved toward recommending a more conservative approach to management for mucocele-like lesions without epithelial atypia that are radiologically concordant.^{475,476}

A further variation on the theme is represented by *mucinous cystadenocarcinoma*, an exceptionally rare tumor composed predominantly of tall columnar cells with abundant intracytoplasmic mucin and a multicystic gross quality similar to that of its ovarian counterpart.⁴⁷⁷

Carcinoma with Medullary Features

It is the recommendation of the WHO consensus panel convened in 2011 for the Classification of Tumors of the Breast that medullary carcinoma and atypical medullary carcinoma be included together under the descriptor "carcinoma with medullary features."⁴⁷⁸ These tumors tend to occur in younger women, with the average age reported to range from 42 to 52 years. It has also been reported that patients with *BRCA1* mutations are particularly likely to have carcinomas with medullary features.⁴⁷⁹ Grossly, carcinoma with medullary features is well circumscribed and may become large; as such it can be mistaken clinically, radiologically, and grossly for a fibroadenoma, but it lacks the trabeculation or whorling of the latter. Rather, the cut surface is solid, homogeneous, and gray, sometimes exhibiting small foci of necrosis (Fig. 36.105). Rare examples are partially or predominantly cystic.⁴⁸⁰ Microscopically, the borders are of the "pushing" type. The pattern of growth is diffuse, with minimal or no glandular differentiation. The tumor cells are large, with enlarged, pleomorphic nuclei, prominent nucleoli, and abundant mitoses (some of them atypical). The cell borders are indistinct, giving the tumor a syncytial or sheet-like appearance somewhat reminiscent of a germ cell tumor of the embryonal carcinoma type. This is accentuated by the observation that the tumor cells located at the periphery are more elongated and have a denser, more acidophilic cytoplasm, acquiring a vague resemblance to syncytiotrophoblast. Spindle cell morphology, bizarre tumor giant cells, extensive necrosis, and the absence of calcification

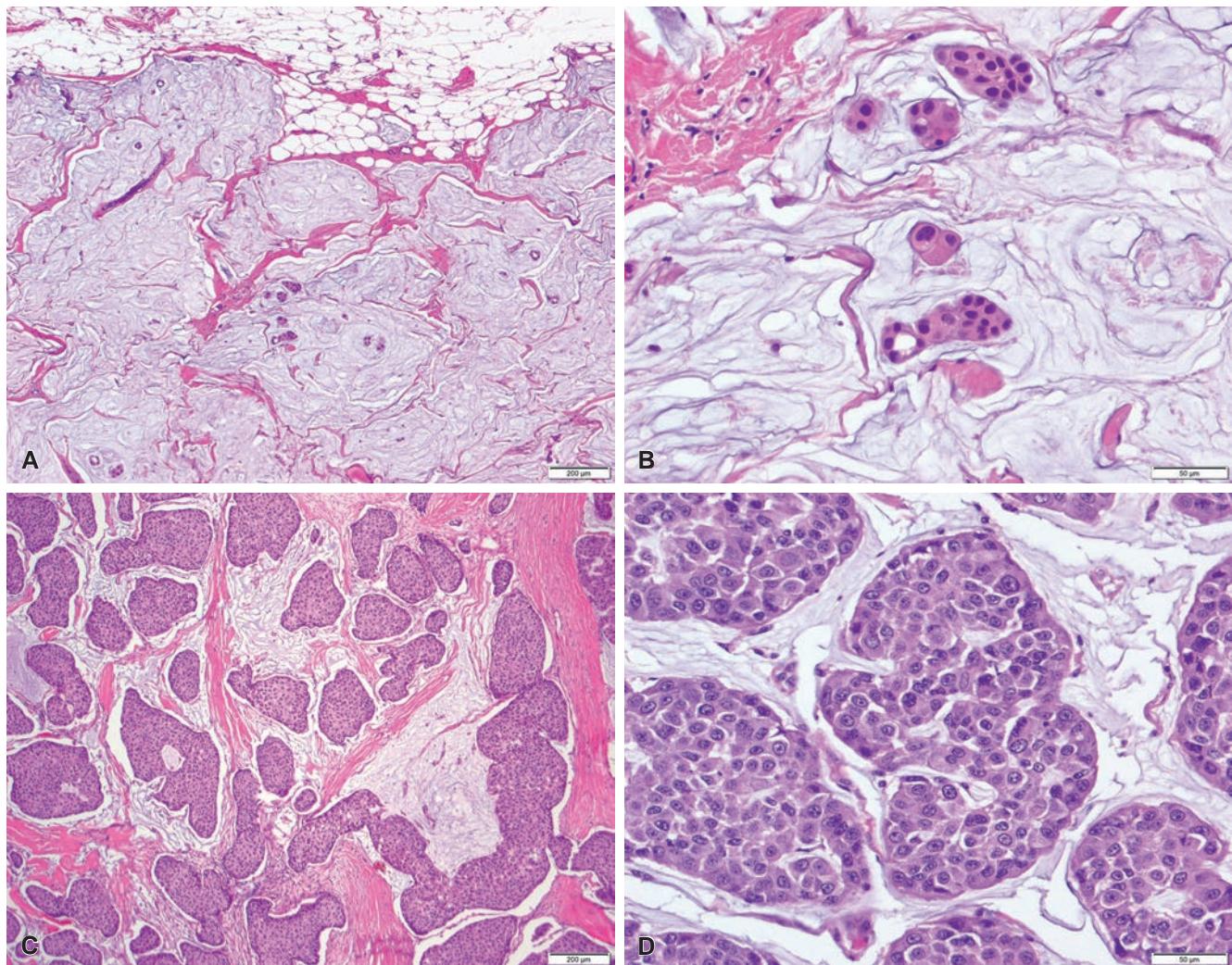


Figure 36.103 Mucinous Carcinoma of the Breast. Clusters of well-differentiated tumor cells are seen floating in a sea of mucin. Hypocellular variant, at low power (**A**) and high power (**B**). Hypercellular variant, at low power (**C**) and high power (**D**).

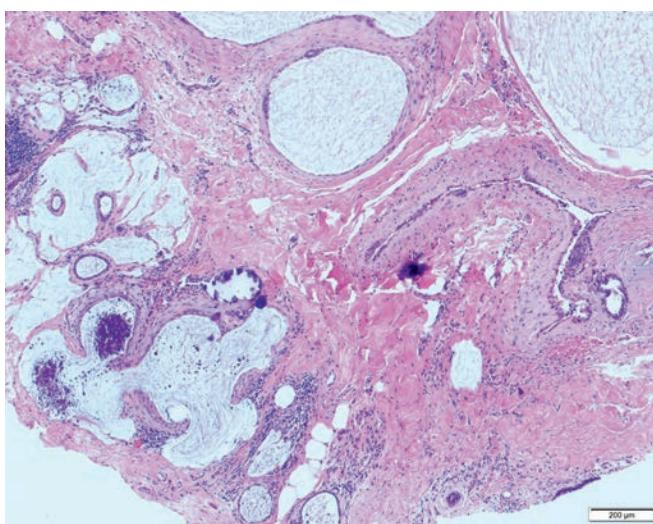


Figure 36.104 Mucocele-Like Lesion. Cystically dilated ducts are lined by an attenuated epithelium which are filled with mucin. Focally there is rupture with extravasation of mucin into the stroma. Note the association with calcifications in this case.

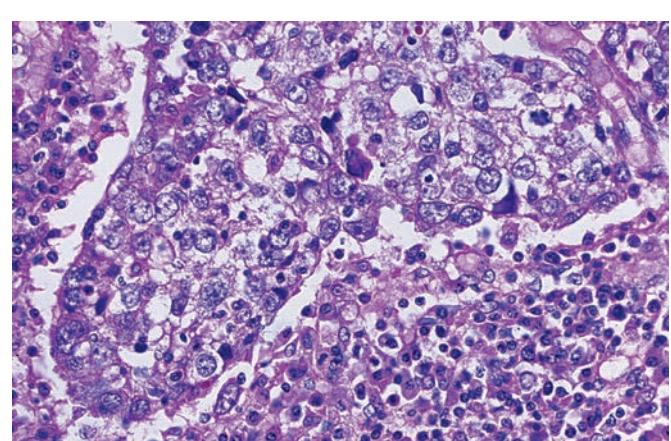


Figure 36.105 Carcinoma With Medullary Features. The large tumor cells grow in a “syncytial” fashion and are sharply separated from the surrounding stroma, which is heavily infiltrated by lymphocytes and plasma cells.

are other common features. A constant component is a prominent lymphoplasmacytic infiltrate, which is thought to represent a reaction of the host to the neoplasm. DCIS is usually minimal or absent.

Immunohistochemically, carcinomas with medullary features share the markers of ordinary invasive ductal carcinoma. They typically express CK7, often vimentin, S-100 protein, and p53, as well as HMW (basal) cytokeratins, and caveolin-1.⁴⁷⁸ They are almost invariably negative for hormone receptors, as well as HER2 ("triple negative" phenotype).⁴⁷⁸

Genetically, carcinomas with medullary features commonly show *TP53* gene mutation.⁴⁸¹ Although the gene expression profile of carcinoma with medullary features is considered to represent part of the basal-like carcinoma spectrum (see later)⁴⁸² and it shares genetic changes such as 1q and 8q gains and X losses with basal-like carcinomas not otherwise specified, it does show distinct molecular features, including higher numbers of gains and losses on array CGH analysis, as well as recurrent 10p, 9p, and 16q gains, 4p losses, and 1q, 8p, 10p, and 12p amplicons.⁴⁸¹

Axillary lymph node metastases are common, but they are usually few and limited to the low axillary group. The prognosis for "medullary carcinoma" is reported to be better than for the ordinary invasive ductal carcinoma, but given the low level of interobserver reproducibility for the diagnosis and the use of more descriptive terms for tumors with the aforementioned features, clinicians are increasingly treating these patients with the aggressive therapies used for patients with triple negative breast carcinoma.⁴⁷⁸ Newer gene expression profiling studies reveal immune signatures that appear to correlate with a better outcome in patients with triple negative breast carcinomas that have a prominent lymphoplasmacytic infiltrate.⁴⁸³

Invasive Micropapillary Carcinoma

Invasive micropapillary carcinoma is a distinct variant of invasive ductal carcinoma with important prognostic correlates.^{484,485}

Microscopically, it bears close similarity to micropapillary carcinoma of other organs, most notably ovary, and bladder.⁴⁸⁶ It is characterized by the formation of pseudopapillary structures lacking a fibrovascular core and by tubular structures free-floating in clear empty spaces (Fig. 36.106). Some of these spaces have been demonstrated to be lymphatic vessels, but the majority are newly formed clefts resulting from the inversion of polarity of the tumor cells (as evidenced by MUC1 and EMA staining).^{487,488} The nuclear grade is often high.⁴⁸⁹ Psammoma bodies are present in about one-half of the cases.⁴⁸⁴

Immunohistochemically, invasive micropapillary carcinoma is usually positive for ER and breast markers (mammaglobin, GCDFP-15, and GATA3) and negative for PAX8 and WT1, a panel that will facilitate distinction from metastatic serous carcinoma from the ovary.^{490,491} HER2 positivity is unusual, with fewer than 10% of cases showing overexpression/amplification.⁴⁸⁵ Lymph node metastases are the rule (their frequency being directly related to the presence of lymphatic vessel invasion⁴⁹²), local recurrence is high, but the survival rate is no different than that for stage- and grade-matched conventional invasive ductal carcinoma.^{493,494}

Carcinomas with Apocrine Differentiation

Carcinoma with apocrine differentiation is a rare form of breast malignancy (ranging from 1% to 4% of all cases), at least when defined as composed entirely or predominantly of apocrine-type epithelium.^{495,496} The large tumor cells have abundant eosinophilic, somewhat granular cytoplasm, which may contain eosinophilic or golden brown granules that are strongly PAS positive. The nuclei are vesicular, and nucleoli are prominent. Glandular differentiation is usually found, and the luminal aspect of the epithelial cells often

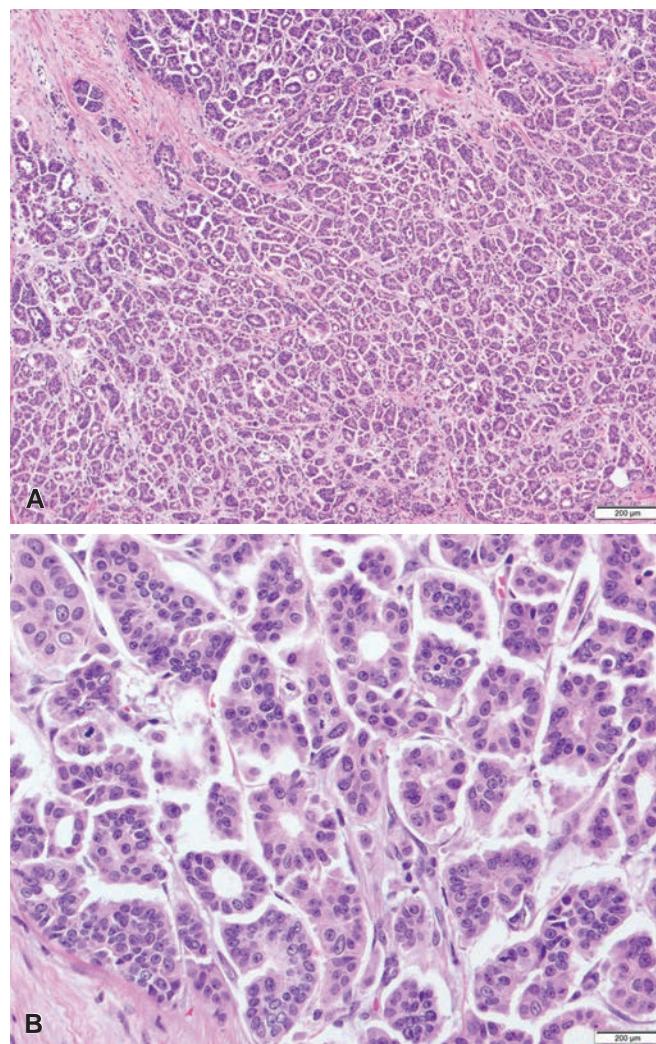


Figure 36.106 Invasive Micropapillary Carcinoma. **A**, At low power the tumor is characterized by the formation of micropapillary structures lacking a fibrovascular core and by tubular structures free-floating in clear empty spaces. **B**, At higher power the reverse polarity of the tumor cells can be appreciated.

have a characteristic bulbous expansion ("apocrine snout") (Fig. 36.107). Ultrastructurally, the cells of carcinoma with apocrine differentiation show prominent mitochondria (some with abnormal cristae).⁴⁹⁷ Immunohistochemically, there is diffuse reactivity for GCDFP-15 and androgen receptor.⁴⁹⁸ The gene coding for GCDFP-15 is located on chromosome 7q and is identical to the gene of prolactin-inducible protein (PIP); the expression of this gene in carcinomas with apocrine differentiation has been demonstrated with *in situ* hybridization techniques.⁴⁹⁹ Carcinoma with apocrine differentiation is usually ER negative; HER2 overexpression is common.

Since apocrine changes in the breast are usually indicative of benignity, even when the cells exhibit prominent nucleolar enlargement, the diagnosis of carcinoma with apocrine differentiation should be made only when the architectural features are clearly those of a carcinoma; a distinction more problematic for *in situ* than invasive apocrine lesions. It is also important to limit the diagnosis to malignant tumors in which the apocrine change is widespread, in view of the fact that focal apocrine differentiation can be detected in close to 10% of ordinary carcinomas.⁴⁹⁸ Finally, it should be noted that although carcinoma with apocrine differentiation is usually a

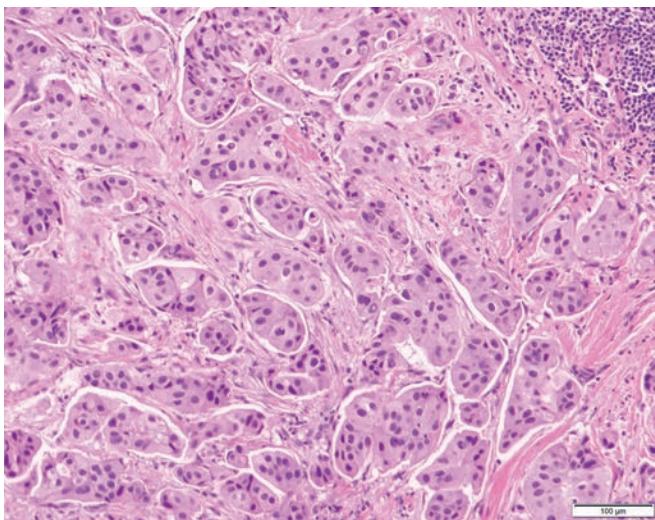


Figure 36.107 Carcinoma With Apocrine Differentiation. The large tumor cells have abundant eosinophilic, somewhat granular cytoplasm, which may contain eosinophilic or golden brown granules that are strongly PAS positive. The nuclei are vesicular and nucleoli are readily seen.

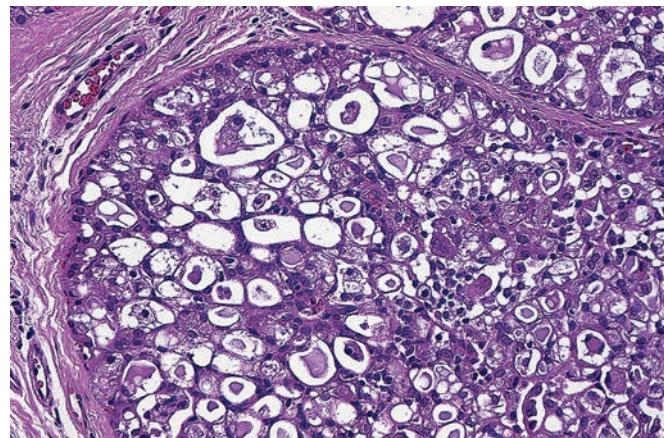


Figure 36.109 Secretory Carcinoma. The small uniform glands are filled by a secretory material.



Figure 36.108 Gross Appearance of Secretory Carcinoma. The tumor is well circumscribed and shows a variegated cut surface.

variant of either DCIS or invasive ductal carcinoma, apocrine differentiation has also been described in LCIS and invasive lobular carcinoma.⁵⁰⁰

Secretory Carcinoma

This rare form of breast carcinoma is seen primarily in children, but it can also occur in adults.^{501,502} Grossly, it is well circumscribed, with an average reported size of 3 cm (Fig. 36.108).⁵⁰³ The margins of the tumor are of the “pushing” type, and prominent hyalinization is often present in the central portion. The microscopic appearance

is distinctive (Fig. 36.109). Tubular, microcystic and solid patterns are variably present forming lumina filled with an eosinophilic, PAS-positive secretion surrounded by cells with vacuolated (sometimes “hypernephroid”), granular cytoplasm.^{502–504} Nucleoli may be prominent, but mitoses are scanty. Ultrastructurally, the tumor cells contain numerous membrane-bound intracytoplasmic secretory vacuoles.⁵⁰⁵

Immunohistochemically, there is strong reactivity for α -lactalbumin and S-100 protein, accompanied by variable expression of GCDFP-15 and CEA.⁵⁰⁶ Secretory carcinoma is typically triple negative (ER, PR, and HER2 negative). It has been hypothesized that there may be a histogenetic link between secretory carcinoma and a type of salivary gland tumor historically placed among the acinic cell carcinomas, a subset of which have more recently been recategorized as a mammary analogue secretory carcinoma due to the identification of a similar molecular genetic abnormality,⁵⁰⁷ namely a recurrent balanced chromosomal translocation, $t(12;15)(p13;q25)$, which leads to fusion of the *ETV6* and *NTRK3* genes as is found in secretory carcinoma of the breast.^{508,509} In fact, it is the identification of this gene fusion product that allows distinction of secretory carcinoma from acinic cell carcinoma of the breast.⁵⁰⁹

The overall prognosis is excellent, especially in younger patients, with most series quoting a 5-year survival rate close to 100%.^{502–504} Local recurrences and nodal metastases can develop, sometimes very late in the course of the disease.^{502–504} Death resulting from disseminated tumor has been recorded only exceptionally.⁵⁰² Secretory carcinoma has also been reported to occur in the axillary skin in the absence of a breast primary.⁵¹⁰

Carcinomas with Neuroendocrine Features

(including so-called carcinoid tumor). The clinical presentation of carcinoma with neuroendocrine features is no different from that of ordinary breast carcinoma. Specifically, none of the patients has had carcinoid syndrome, even in the presence of widespread disease. There are no distinctive gross features. Carcinomas with neuroendocrine features occur in older women and constitute less than 1% of all breast carcinomas.

Microscopically, the tumor cells are small, arranged in solid nests separated by delicate bands of fibrous tissue (Fig. 36.110). Ribbons and rosette-like formations are not typically seen in carcinoma with neuroendocrine features arising in the breast. Mitoses are generally rare. Mucin secretion may be present. The microscopic differential diagnosis includes the alveolar variant of invasive lobular carcinoma

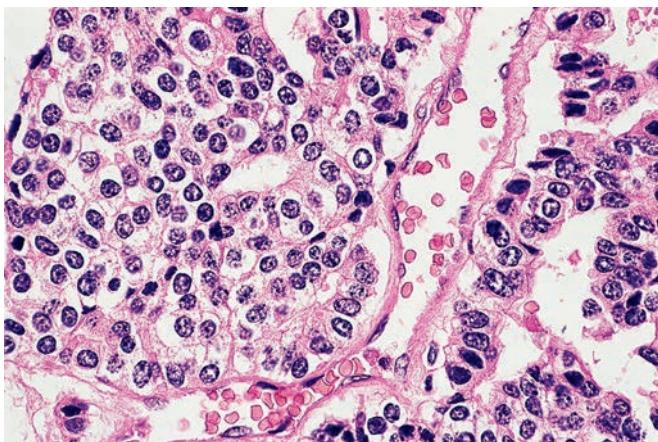


Figure 36.110 Breast carcinoma with neuroendocrine features.

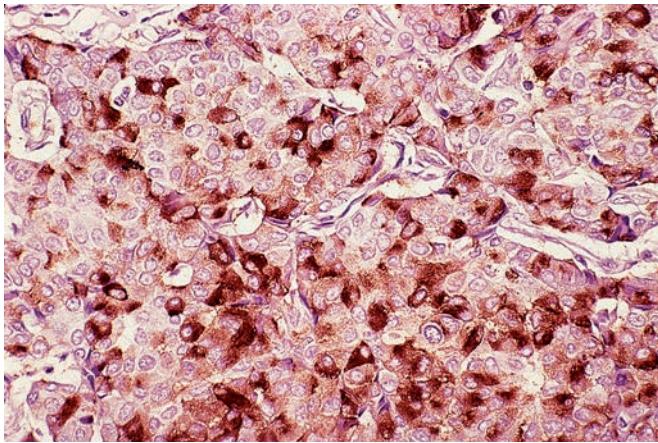


Figure 36.111 Strong reactivity for chromogranin in breast carcinoma with neuroendocrine differentiation.

and a metastasis to the breast of a neuroendocrine tumor located elsewhere. Identification of an intraductal component aids in establishing breast origin.

Of historical interest the tumor cells of neuroendocrine carcinoma of the breast are argyrophilic but not argentaffin positive and are found to contain dense-core secretory granules of various types ultrastructurally.^{511,512} The tumor cells demonstrate immunohistochemical positivity for chromogranin, synaptophysin, NSE, and CD56^{513–515} and in some instances for specific hormone peptides,⁵¹⁶ indicative of endocrine differentiation (Fig. 36.111).

It should be mentioned here that there are breast carcinomas of other morphologic patterns in which neuroendocrine features have been found.⁵¹⁷ Since markers of neuroendocrine differentiation are not routinely performed in breast pathology, the true incidence of this tumor is not known,^{513,518} though a recent report found between 10% and 30% of invasive ductal carcinomas of no special type expressed neuroendocrine markers.⁵¹⁹

Metaplastic Carcinoma

Metaplastic carcinoma is a generic term for breast carcinoma in which there is differentiation of the epithelial component into non-glandular elements. These include squamous differentiation and/or differentiation into mesenchymal elements.^{520,521} Given that the designation is so broad, the diagnosis is best used with a qualifier.



Figure 36.112 Gross Appearance of Metaplastic Carcinoma. A large, fleshy mass is seen protruding inside a cavity. Microscopically, this tumor showed an admixture of squamous and spindle cell elements.

The following categories, which overlap considerably with each other, are included:

1. *Metaplastic carcinoma with mesenchymal differentiation.* Grossly, this tumor tends to be well circumscribed (Fig. 36.112). Microscopically, the mesenchymal component may appear relatively well differentiated with minimal spindle cell atypia or may resemble its sarcomatous counterpart with areas of a chondrosarcoma, osteosarcoma, rhabdomyosarcoma, angiosarcoma, or a combination thereof.⁵²² There may be a gradual transition from carcinomatous to mesenchymal elements, or the separation between them can be abrupt. Tumors having overt carcinoma with abrupt transition to a cartilaginous and/or osseous matrix without an intervening spindle cell zone or osteoclastic giant cells have been referred to as *matrix-producing carcinomas*.^{522–524}

Immunohistochemically, the mesenchymal elements of these tumors have usually acquired vimentin positivity and other features of a mesenchymal nature ("phenotypic switch") but still retain epithelial markers, albeit focal and variable, a fact best demonstrated by employing several wide-spectrum cytokeratin antibodies.⁵²⁵

As in other sites, molecular studies support the interpretation that the recognizable epithelial and the mesenchymal components originate from the same stem cell.^{526,527}

2. *Spindle cell carcinoma.* The overt carcinomatous component of these tumors, when present, may be invasive ductal carcinoma or DCIS or it may be entirely squamous.⁵²⁸ The spindle cell component is composed of atypical spindle cells within a fibrocollagenous stroma with feathered, myxoid, angiod, and storiform patterns (Fig. 36.113).^{529,530} Merging of areas between the epithelial and the spindle components is common. The spindle cells are immunoreactive for cytokeratins and p63, albeit focal and variable in some cases.^{531,532}
3. *Fibromatosis-like metaplastic carcinoma.* These tumors are characterized by bland spindle cells with little to no cytologic atypia, resembling, as the name suggests, fibromatosis (Fig. 36.114). The spindle cells are arranged in fascicles that infiltrate into the surrounding fat and between ducts and lobules. On occasion, a central scar-like area may be present. Some of these tumors arise in connection with complex sclerosing lesions, sclerosing papillary lesions, or adenomyoepitheliomas.^{522,533}
4. *Metaplastic carcinoma with osteoclast-like giant cells.*⁵³⁴ When these cells appear in conjunction with mesenchymal elements, the

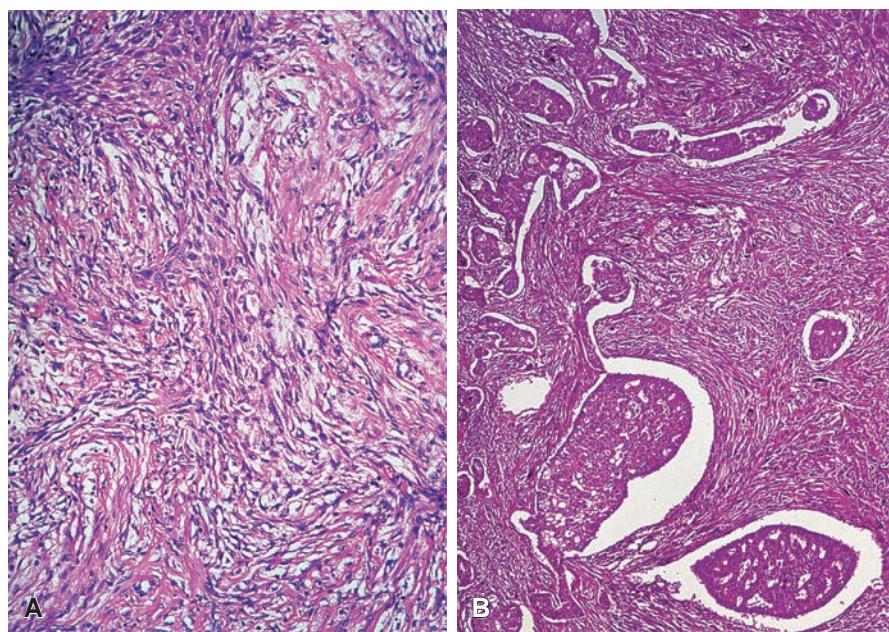


Figure 36.113 Metaplastic Carcinoma. The tumor shown in **(A)** exhibits a blending of the epithelial and spindle cell components making it more difficult to recognize this as a carcinoma, whereas that depicted in **(B)** has more readily recognizable epithelial elements admixed with the malignant spindle cell component.

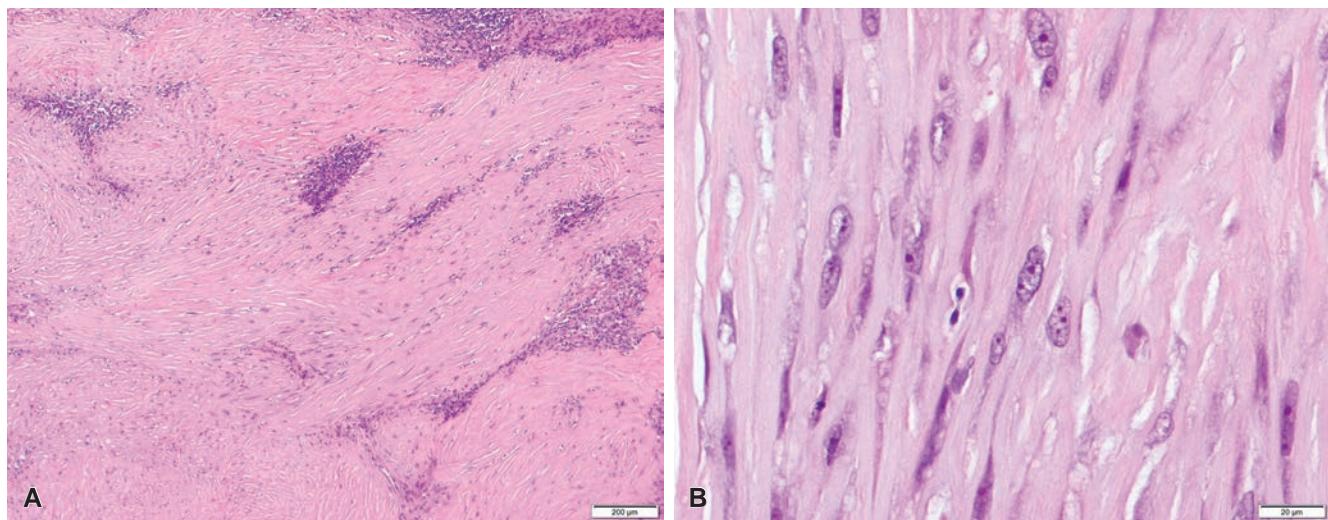


Figure 36.114 Low-grade Fibromatosis-like Metaplastic Carcinoma. **A**, At low power the tumor appears to be composed of bland spindle cells embedded in dense collagen resembling a scar. **B**, At high power the cytologic atypia of the spindle cells can be appreciated. The tumor cells were positive for cytokeratin (MNF116).

tumor should be regarded as a variant of metaplastic carcinoma. When osteoclast-like giant cells are seen in the stroma of what is otherwise a typical carcinoma lacking mesenchymal differentiation, the tumor is better classified as *invasive ductal carcinoma with osteoclast-like giant cells*. Interestingly, this particular tumor tends to have a reddish-brown appearance grossly and extravasated red blood cells on microscopic examination. All available evidence suggests that the osteoclast-like elements are of a non-neoplastic histiocytic nature and that they form from fusion of mononuclear precursors.^{535,536}

5. *Squamous cell carcinoma*. Squamous cell carcinoma is a rare variant of metaplastic carcinoma.^{522,537} Tumors of cutaneous origin and

those in which the squamous component is a portion of an otherwise typical phyllodes tumor should be excluded. It is also important not to misinterpret the syncytial areas of carcinoma with medullary features or the partial apocrine changes sometimes seen in other tumors as representing squamous change. The gross appearance of squamous cell carcinoma differs little from that of conventional breast carcinomas, although sometimes a large central cyst filled with keratin can be identified. Microscopically, most cases seem to represent instances of squamous metaplasia in invasive ductal carcinoma, indicating that squamous cell carcinoma is a special type of metaplastic carcinoma (Fig. 36.115).⁵³⁸ Occasionally, the tumor is accompanied by a prominent myxoid stroma.⁵³⁹

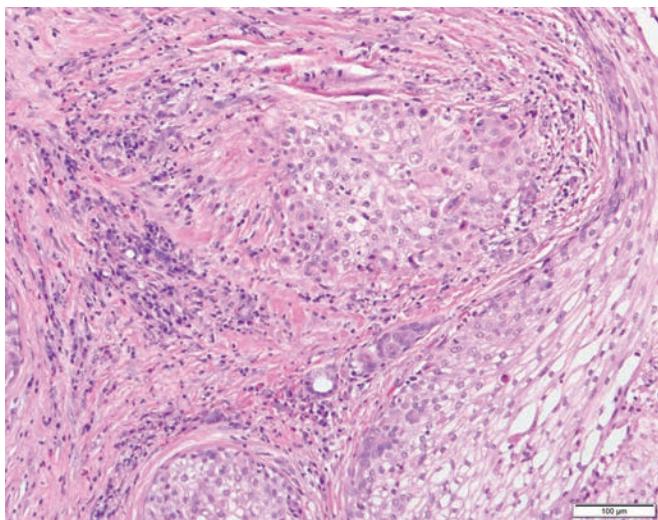


Figure 36.115 Metaplastic carcinoma, squamous cell type.

Two further variants are *acantholytic squamous cell carcinoma*, in which the lack of tumor cell cohesiveness results in a pseudovascular or pseudoglandular appearance (Fig. 36.116),⁵⁴⁰ and *low-grade adenosquamous carcinoma* (see next).

6. *Low-grade adenosquamous carcinoma*. Low-grade adenosquamous carcinoma is a well-differentiated tumor with dual glandular and squamous differentiation with squamous pearl or cyst formation infiltrating through a cellular stroma (Fig. 36.117). Local recurrence is common following conservative surgery, but nodal and distant metastases are exceptional.⁵⁴¹ Like fibromatosis-like metaplastic carcinoma, low-grade adenosquamous carcinoma may arise in association with adenomyoepithelioma and benign sclerosing lesions.^{533,541–544}

The differential diagnosis of metaplastic carcinoma includes phyllodes tumor, fibromatosis or scar, and less likely primary breast sarcoma. A broad panel of cytokeratin stains along with p63 is often necessary to aid in diagnosis of these challenging cases. As mentioned previously, metaplastic carcinomas vary with regard to which cytokeratin will be expressed and with regard to the extent of tumor cell positivity. In a well-sampled pure spindle cell lesion, unequivocal staining with cytokeratin or p63 is considered sufficient for the diagnosis of metaplastic carcinoma,⁵²² though it should be noted that it has been recently demonstrated that the stromal component of phyllodes tumor, particularly malignant phyllodes tumor may show focal staining with p63 (and/or p40) and/or cytokeratin immunostains.^{178,179} As such, caution should be exercised in rendering a definitive diagnosis based on the interpretation of these immunostains on core needle biopsy specimens of pure spindle cell lesions.

The behavior of metaplastic carcinoma compared with that of invasive ductal-type carcinoma of no special type is not well defined, though fibromatosis-like metaplastic carcinoma and low-grade adenosquamous carcinoma do appear to have a more indolent course.⁵³⁰ Metastases tend to occur via hematogenous spread rather than to lymph nodes.⁵³⁰

Inflammatory Carcinoma

The term “inflammatory carcinoma” is used in a clinical context for a type of breast carcinoma in which the breast is reddened and warm, with widespread edema of the skin, simulating the appearance of mastitis.⁵⁴⁵ A discrete breast mass is not always palpable. The clinical appearance is due to widespread carcinomatous emboli

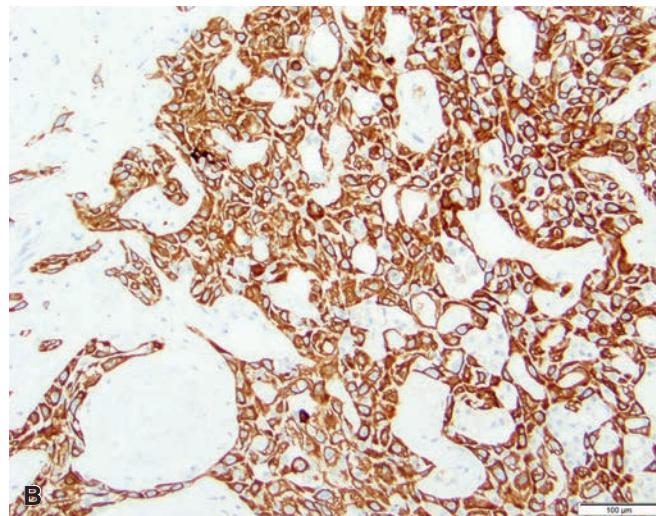
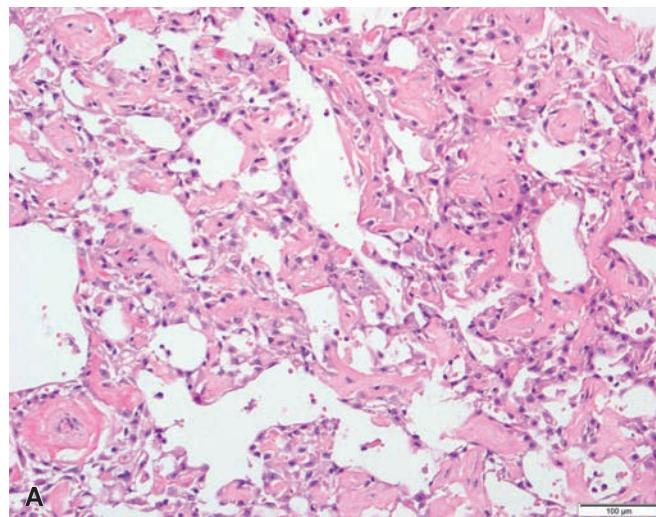


Figure 36.116 **A**, Metaplastic carcinoma, squamous cell type with acantholytic pattern mimicking angiosarcoma. **B**, Cytokeratin 903 immunostain.

involving the dermal lymphatic vessels (Fig. 36.118). However, patients may have inflammatory carcinoma clinically in the absence of pathologically identifiable dermal lymphatic involvement, at least on small punch biopsies of the skin; conversely, widespread permeation of dermal lymphatics can be seen in the absence of the clinical features of inflammatory carcinoma (so-called occult inflammatory carcinoma⁵⁴⁶). The underlying carcinoma is usually a high-grade invasive ductal carcinoma of no special type. Inflammatory carcinoma is staged as T4d. From a prognostic standpoint, the presence of dermal lymphatic permeation on microscopic examination is an ominous sign, whether the clinical appearance is that of an inflammatory carcinoma or not, though there is some improvement in survival outcome with the use of neoadjuvant chemotherapy.^{546,547}

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is similar to tumors of the same name occurring in the salivary gland and lung. It is important not to confuse this uncommon neoplasm with the much more common DCIS with cribriform pattern, with invasive cribriform carcinoma, or with collagenous spherulosis.^{548,549} Adenoid cystic carcinoma of

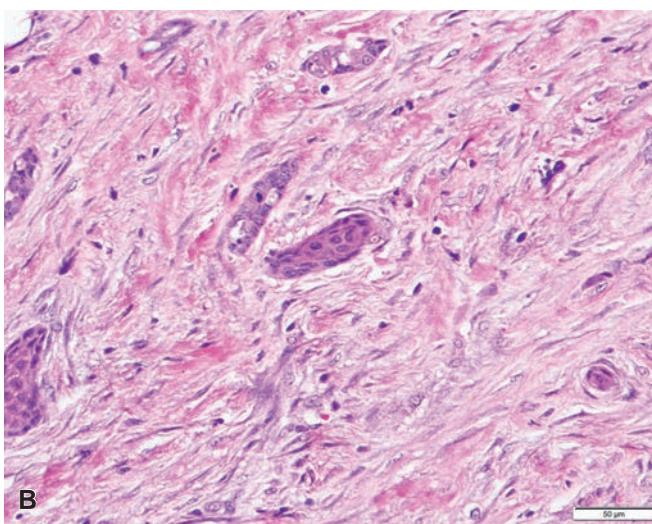
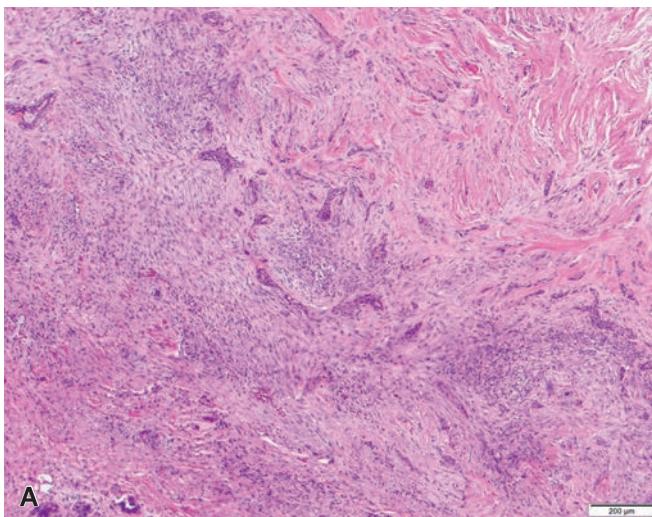


Figure 36.117 Low-grade Adenosquamous Carcinoma. **A**, At low power glands and squamous nests can be seen infiltrating haphazardly in a variably cellular and dense collagenous stroma. **B**, At high power the cytologic atypia and mitotic activity of the tumor cells is readily apparent.

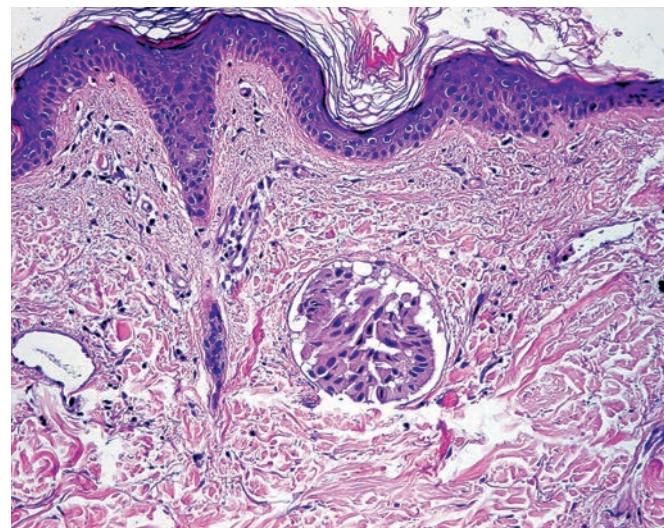


Figure 36.118 Large tumor embolus in a dermal lymph vessel in a case with the clinical appearance of inflammatory carcinoma.

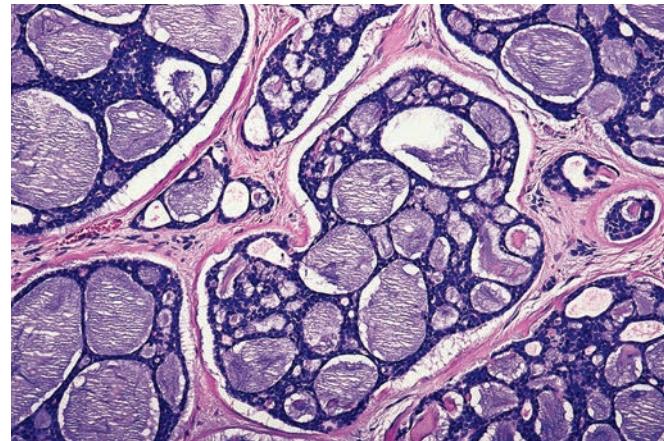


Figure 36.119 Adenoid Cystic Carcinoma. The appearance is similar to that of its more common homologue in salivary glands. The tumor is characterized by two types of cavity formation; true glandular lumina and pseudolumens containing basement membrane material surrounded by basal-myoeipithelial cells, a feature that is more pronounced in this image.

the breast shows, as in the salivary glands, two types of lumen formation: true glandular lumina lined by cells which are positive for CK7 and 8/18, and pseudolumens containing eosinophilic basement membrane material and/or basophilic mucin surrounded by basal-myoeipithelial cells which may express myoepithelial markers and basal cytokeratins (Fig. 36.119).⁵⁵⁰ Foci of sebaceous differentiation may also be seen.⁵⁵¹ Perineural involvement may be present. Adenoid cystic carcinomas are typically ER, PR, and HER2 negative (i.e., they are “triple negative” tumors,⁵⁵² although they should not be equated with mammary carcinomas now bearing that catchy designation).⁵⁵³ CD117 is usually expressed, mirroring the pattern of salivary gland adenoid cystic carcinoma; CD117 staining is not present in the previously mentioned simulators.^{554,555} Like the homologous tumor occurring in the salivary gland, a distinctive chromosomal translocation, t(6;9) resulting in *MYB-NFIB* gene fusion is commonly found and the presence of nuclear MYB staining with IHC can be used to confirm the diagnosis in histologically ambiguous cases.^{556,556a} Axillary lymph node metastases are extremely rare.^{557,558} Some patients have developed local recurrence or pulmonary metastases many years

after initial therapy,^{557,559} but the prognosis for this tumor as a group is remarkably good.⁵⁶⁰ The relationship between microscopic grading and prognosis is controversial.^{557,561,562}

A solid variant of adenoid cystic carcinoma with basaloid features has been described in which the glandular lumens and pseudolumens with basement membrane material are more subtle. The tumor cell nuclei are usually higher grade, and mitoses and necrosis may be present (Fig. 36.120). The prognosis for these tumors appears to be less favorable, albeit with limited data.^{561,562} As already mentioned, some cases of adenoid cystic carcinoma are seen in association with microglandular adenosis.¹⁹⁸

Acinic Cell Carcinoma

As the name indicates, acinic cell carcinoma is highly reminiscent of the homologous tumor of the salivary gland with variable growth patterns, which include microcystic, microglandular, and solid, occasionally with comedo necrosis. The cells have abundant granular eosinophilic or clear cytoplasm with round nuclei and prominent

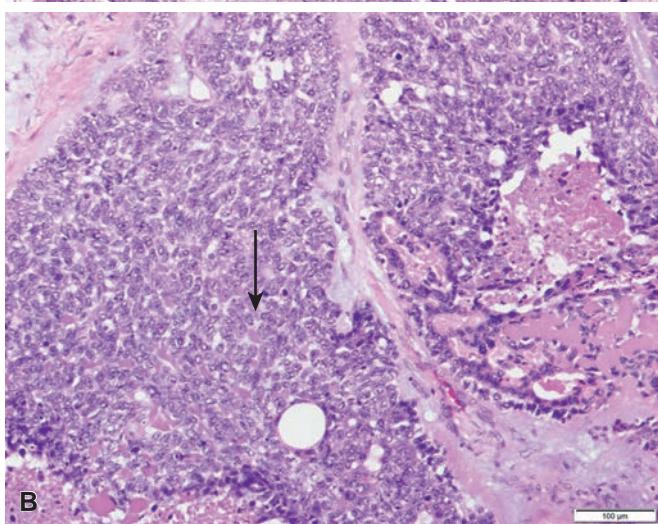
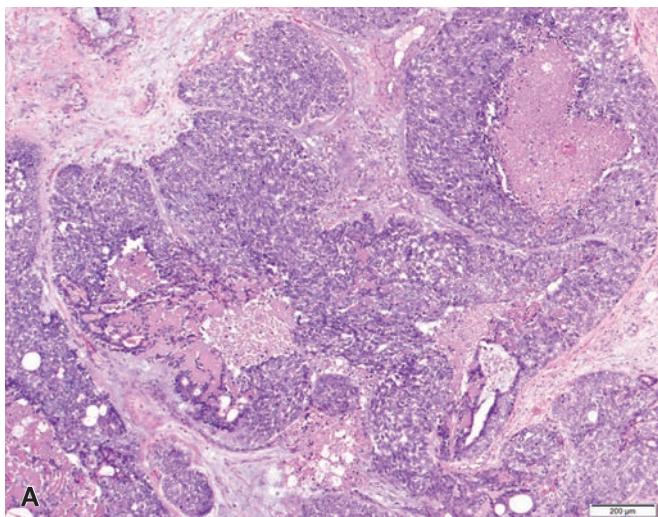


Figure 36.120 Solid Variant of Adenoid Cystic Carcinoma With Basaloid Features. **A**, At low power, solid nests of high-grade tumor cells with basaloid features and abundant necrosis are appreciated. Basement membrane material is also present at the lower left portion of the field. **B**, At higher power, pseudolumens with basement membrane material are confirmed to be present. The identification of true glandular lumens can be more challenging (arrow).

nucleoli (Fig. 36.121). The cytoplasmic granules are coarse and bright pink. The similarities extend to the ultrastructural and immunohistochemical features, which include positivity with α 1-antichymotrypsin, salivary gland amylase, and lysozyme.^{563,564} Like secretory carcinomas, for which they can be a mimic, acinic cell carcinomas are triple negative and positive for S-100 protein. Notably acinic cell carcinomas do not show the t(12:15) ETV6-NTRK3 rearrangement characteristic of secretory carcinoma.^{565,566}

Other rare malignant breast tumors with similar counterparts in the salivary gland are mucoepidermoid carcinoma,⁵⁶⁷ polymorphous (low-grade) adenocarcinoma,⁵⁶⁸ sebaceous carcinoma,⁵⁶⁹ oncocytic carcinoma,⁵⁷⁰ and basaloid carcinoma.⁵⁷¹

Glycogen-rich (clear cell) carcinoma is composed of large clear cells, which are found to contain abundant glycogen.⁵⁷²⁻⁵⁷⁶ The differential diagnosis includes other breast tumors with clear cytoplasm, including adenomyoepithelioma, lipid-rich carcinoma, histiocytoid carcinoma, metastatic renal cell carcinoma, and the exceptionally rare tumors of perivascular epithelioid cells (PEComa).⁵⁷²

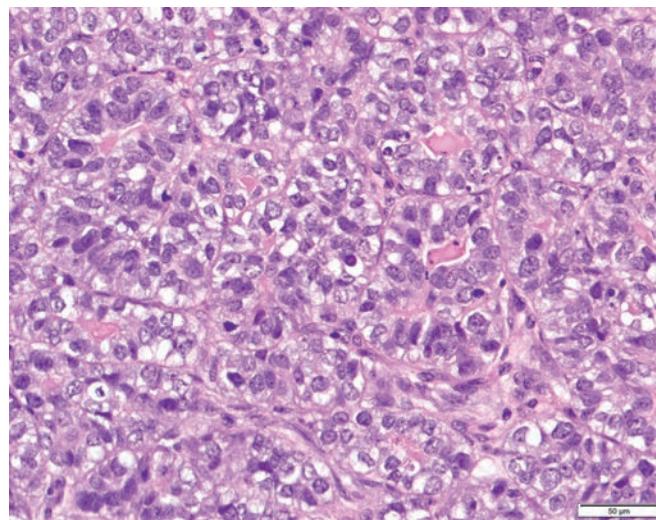


Figure 36.121 Acinic Cell Carcinoma of Breast. The cells have abundant eosinophilic or clear cytoplasm with round nuclei and prominent nucleoli. Coarse eosinophilic cytoplasmic granules can usually be identified.

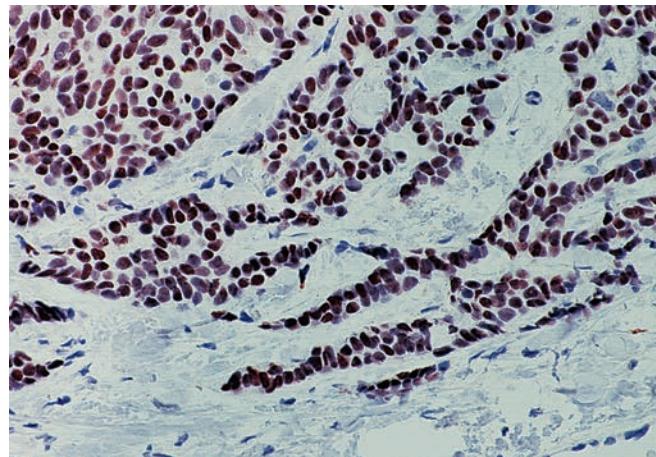


Figure 36.122 Immunostain for Estrogen Receptor in Invasive Ductal Carcinoma. Strong nuclear positivity of the tumor cells is shown.

Hormone Receptors

A crucial development in the treatment of breast carcinoma was the recognition that the presence of hormone (estrogen and progesterone) receptors in the tumor tissue correlates well with response to hormone therapy and chemotherapy.⁵⁷⁷ As a matter of fact, ER status is regarded as one of the most powerful predictive markers in breast cancer management.⁵⁷⁸ ER and PR are codependent variables, PR being a weaker predictor of response to endocrine therapy than ER.⁵⁷⁹ Initially, these hormone receptors were measured by the dextran-coated charcoal and sucrose gradient assay, but this has been replaced by the immunohistochemical method, on the grounds that it offers several important advantages (it does not require fresh tissue, it can be done with minute amounts of tumor, the location of the hormone receptor positivity can be visualized, etc.) (Fig. 36.122), correlation between the two methods is very good,^{580,581} and technical ease of the immunohistochemical assay. Efforts have been made to semiquantitate the immunohistochemical method by standardizing the technical procedure and reporting and by using appropriate controls.^{329,582,583} Delay in fixation has been reported to affect the results, whereas fixation time within reasonable boundaries

appears not to.⁵⁸⁴ The ASCO and CAP have published guideline recommendations for immunohistochemical testing of ER and PR in breast specimens.^{329,585} The guidelines have facilitated standardization of assay performance and reporting across laboratories in North America. Some of the more salient points of this document are the following:

- The pathologist must report the percentage of invasive tumor cells that are immunoreactive.
- Tumors having 1% or more invasive cancer cells staining are regarded as positive.
- The average intensity of the stain must be included (weak, moderate or strong).
- The pathologist must give an interpretation as to whether the sample is positive or negative.
- The use of a composite score based on percentage plus intensity (Allred, H, or Quick scores) is optional.
- Specimens should be placed in 10% neutral buffered formalin no later than 1 hour (but ideally much sooner) after being removed from the patient (cold ischemic time).
- Fixation time should be at least 6 hours and not longer than 72 hours.
- Normal breast cells in the sample should be used as internal positive controls and a comment about the adequacy of staining in the internal control provided.

Hormone receptors can also be evaluated in paraffin-embedded breast tissue by the *in situ* hybridization technique and by PCR.^{586,587}

About 80% of breast cancers are ER positive, so that an ER-negative rate of greater than 30% suggests that some problems exist with the assay which need to be investigated and resolved.

ER-positive breast carcinomas tend to be better differentiated tumors; conversely ER-negative breast carcinomas tend to have grade 3 histology, the exception being some special type tumors, such as adenoid cystic carcinoma and secretory carcinoma. Most carcinomas with medullary features, metaplastic, and apocrine carcinomas are ER negative, whereas mucinous, tubular, and lobular carcinomas have a high rate of ER positivity. In DCIS, high nuclear grade is the best morphologic predictor of ER-negative status.^{588,589} The positivity in LCIS is particularly strong, although this is not tested or reported in clinical practice.⁵⁹⁰ It is very unusual for an ER-negative cancer to become ER-positive at the time of recurrence or metastasis, whereas the reverse is more common, especially if there has been intervening tamoxifen therapy.

Hormone receptor positivity also correlates with bcl2 immunoreactivity⁵⁹¹ and absence of TP53 mutations⁵⁹² and correlates inversely with the presence of epidermal growth factor receptors (such as HER2).⁵⁹³

It should be pointed out that most breast carcinoma cells also have receptors for androgens, and that these may be found in the absence of estrogen and PR, a finding that is being exploited as a therapeutic option for patients with triple negative breast cancers.⁵⁹⁴

HER2

HER2 (c-erbB-2) is an oncogene that encodes a transmembrane glycoprotein with tyrosine kinase activity known as p185, which belongs to the family of epidermal growth factor receptors.⁵⁹⁵ Approximately 15% of invasive breast cancers show HER2 gene amplification and protein overexpression.⁵⁹⁶ Identification of HER2+ tumors is critically important in selecting patients for HER2-targeted therapies, such as trastuzumab. HER2 overexpression and amplification can be measured by immunohistochemistry or fluorescent *in situ* hybridization (FISH) (or its chromogenic equivalent), respectively,⁵⁹⁷ and a good correlation exists between these methods (Fig. 36.123).⁵⁹⁸

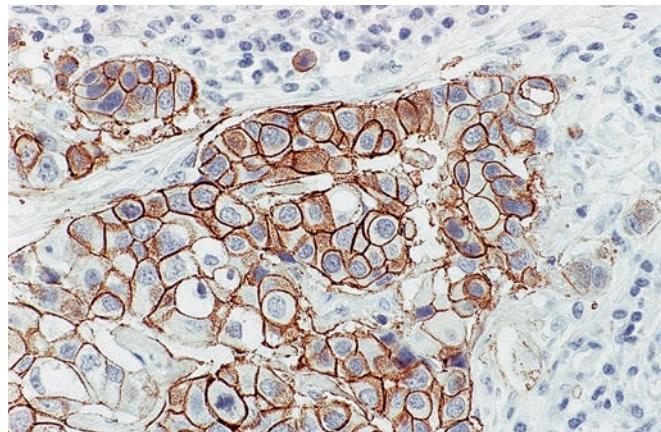


Figure 36.123 HER2-positive (3+) immunostain in high-grade invasive ductal carcinoma showing the required strong, complete, membranous pattern of staining in >10% of tumor cells.

The ASCO/CAP has published and updated guideline recommendations for HER2 testing in breast cancer.^{599,600} According to this joint document, a *positive* HER2 result is:

- immunohistochemical staining of 3+ (uniform, intense membrane staining of greater than 10% of invasive tumor cells), or
- a FISH result of more than six HER2 gene copies, or
- a FISH ratio (HER2 gene signals to chromosome 17 signals) of greater than 2.0.

A *negative* HER2 result is:

- immunohistochemical staining of 0 or 1+, or
- a FISH result of less than 4.0 HER2 copies per nucleus, or
- a FISH ratio of less than 2.0.

An *equivocal* HER2 result is:

- immunohistochemical staining of 2+ (weak and moderate membrane staining in greater than 10% of tumor cells), or
- a FISH ratio of less than 2.0 and a FISH result of ≥ 4.0 and less than 6.0 copies per nucleus.

In the event of an equivocal IHC result, reflex testing to FISH is recommended. If the FISH test is equivocal, either reflex test to IHC using the same specimen, test with an alternative ISH chromosome 17 probe, or order a new test (new specimen if available, ISH or IHC).

Many laboratory directors have concluded that the best approach to HER2 testing from the point of view of cost effectiveness is to start with the immunohistochemical procedure, which is scored according to the ASCO/CAP guideline summarized in Table 36.4.⁵⁹⁹ If the results are either 3+ or 0/1+, the determination can safely stop there, since the correlation with gene amplification or lack of it, respectively, as measured by FISH, is nearly 100%. If the IHC is 2+ (equivocal), the performance of FISH is recommended, and the result obtained tends to be regarded as the definitive result. Other laboratories perform both IHC and FISH on all cases because of the small possibility of a patient being HER2 positive by one or other of the tests.⁶⁰¹

HER2 positivity by either technique is a very good predictor of response to trastuzumab. HER2-positive tumors are typically high-grade tumors. HER2 amplification correlates inversely with estrogen and progesterone expression, though some hormone receptor positive tumors are also HER2 positive (~10% of all invasive breast carcinomas).⁵⁹⁶

HER2 heterogeneity is of sufficient importance that a CAP Expert Panel developed criteria to define it.⁶⁰² In 2009, this Expert

Table 36.4 Scoring of the immunohistochemical staining for HER2 overexpression

STAINING PATTERN	SCORE	ASSESSMENT
No staining is observed or faint, incomplete membrane staining is observed in ≤ 10% of tumor cells	0	Negative
Incomplete membrane staining that is faint/barely perceptible and within > 10% of tumor cells	1+	Negative
Weak and moderate complete membrane staining in >10% of tumor cells	2+	Equivocal
Circumferential membrane staining that is complete, intense, and within >10% of tumor cells	3+	Positive

Data from Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31(31):3997–4013.

Panel defined HER2 genetic heterogeneity as greater than 5% but less than 50% of invasive tumor cells, with an elevated ratio (then >2.2, now >2.0) in a dual probe ISH assay.⁶⁰² Approximately 20%–30% of cases are reported to be heterogeneous for HER2 amplification.^{603,604}

Before leaving the topic of ER, PR, and HER2 in breast carcinoma, a few words need to be said about tumors that are negative for all three markers which are referred to as **triple negative tumors**.^{605,606} Triple negative cancers overlap considerably with basal-like cancer (a tumor defined through gene-expression profiling studies, more fully discussed in the next section) and breast carcinomas arising in *BRCA1* mutation carriers. However, triple negative cancers are not synonymous with basal-like cancers—only 70%–80% of cases classified by gene expression profiling as basal-like show a triple negative phenotype, and conversely a similar, though not necessarily the same, proportion of triple negative cancers exhibit a basal-like gene expression profile.⁶⁰⁷ Triple negative breast cancers represent a heterogeneous group of tumors, which most characteristically exhibit the following features: morphologically usually high-grade invasive ductal carcinoma of no special type, high degree of aneuploidy, and greater tendency to metastasize to lungs and brain.^{605,606}

Molecular Genetics and Molecular Classification of Breast Cancer

Molecular Genetics

The development of invasive breast carcinoma involves multiple genetic alterations, as with other carcinomas of various anatomic sites. The genes most commonly affected, and consistently identified in breast cancer include: *PIK3CA*, *PTEN*, *AKT1*, *TP53*, *GATA3*, *CDH1*, *RB1*, *MLL3*, *MAP3K1*, and *CDKN1B*.⁶⁰⁸ In addition, some types of

breast carcinoma, such as secretory carcinoma, lobular carcinoma, and adenoid cystic carcinoma, exhibit distinctive genetic changes, as described in the respective sections.

Molecular Classification

The pioneering efforts of Perou and colleagues in 2000 to segregate breast cancers into distinct subgroups based on similarities in the gene expression profiles using a microarray platform has been enthusiastically embraced by the medical and scientific community, with the hope that this approach will provide new insights into the biology of breast cancers and impact therapeutic strategies.^{609,610} The subtyping reported by this group has evolved into a molecular classification of breast cancer.

The subtypes of breast cancers most widely recognized by their gene expression signature include: luminal (type A and B), HER2 enriched, basal-like, and normal breast-like. The last subtype may represent an artifact rather than a genuine subtype of breast cancer, resulting from lack or paucity of tumor in the tissue samples used for the microarray analysis. The main features of the four molecular subtypes are summarized in Table 36.5. Among the various subtypes, the basal-like subtype is associated with the worst prognosis.⁶¹⁰ Since the different molecular subtypes of breast cancers exhibit specific characteristics, it is thought that more specific and targeted forms of therapy could be developed. Efforts have been made to use immunohistochemistry as a surrogate (such as a panel including antibodies to ER, PR, HER2, cytokeratin 5/6, EGFR, Ki-67) to assign tumors to the various molecular subtypes (Table 36.6),^{611–614} but discordance is not uncommon, and there are currently no widely agreed upon criteria to define immunostain positivity for this purpose (particularly for Ki-67).

The current molecular classification of breast cancers still has drawbacks. The molecular subtypes were defined based on a relatively small number of cases, and some of the less common distinctive types of breast cancer (such as secretory carcinoma) were not included as part of the original analyses.^{468,615} The basal-like subtype is highly heterogeneous and encompasses some tumors with a favorable prognosis, such as secretory carcinoma and adenoid cystic carcinoma, necessitating the creation of a “low-grade” category of basal-like carcinoma.⁶¹⁵ It is too simplistic to try to subsume the many different types of breast carcinoma into a few molecular categories, ignoring the known distinctive types with characteristic morphology and biologic features (such as invasive lobular carcinoma and secretory carcinoma).⁶¹⁶ In fact, additional molecular subtypes have since been identified, such as molecular apocrine, or luminal androgen receptor and claudin-low.^{617–619}

Issues with standardization of analytic approaches, replication, attaining adequate sample size, and the evaluation of the clinical utility in heterogeneous populations apply to gene expression profiling studies as much as to any clinical trial with a component of pathologic testing and classification. In addition, how gene expression profiling can be applied to routine diagnosis and prognostication has yet to be fully determined. Further, although nearly every published microarray-based system can recognize molecular subtypes with similar survival and can also identify the basal-like subtype fairly consistently, the systems do not reliably assign the same patients to the same molecular groups for nonbasal-like tumors.⁶²⁰

Despite all the interest surrounding the molecular classification of breast cancers, currently the clinical value of characterizing invasive breast cancers beyond routine histologic type, histologic grade, and ER/PR/HER2 status has not been established; in fact it is these very characteristics that determine therapy.⁶¹⁴ Thus assignment of breast cancer cases to a molecular subtype is not a requirement at present,

Table 36.5 Major molecular subtypes of breast cancer determined by gene expression profiling

	MOLECULAR SUBTYPE			
	LUMINAL A-LIKE	LUMINAL B-LIKE	HER2-ENRICHED	BASAL-LIKE ^a
Gene expression pattern	Expression of luminal (low-molecular-weight) cytokeratins, and high expression of hormone receptors and associated genes	Expression of luminal (low-molecular-weight) cytokeratins and moderate to weak expression of progesterone receptor and associated genes	High expression of <i>HER2</i> and other genes in amplicon on 17q12 Low expression of ER and associated genes	High expression of basal epithelial genes, basal cytokeratins Low expression of ER and associated genes Low expression of <i>HER2</i> related genes
Clinical and biologic features	~60% of invasive breast cancers ER/PR positive HER2 negative Low proliferation rate	~10% of invasive breast cancers ER positive, PR low positive HER2 expression variable (positive or negative) Intermediate or high proliferation rate (Ki-67 high) Luminal B tends to be higher histologic grade than luminal A	~15% of invasive breast cancers ER/PR negative HER2 positive (though not all HER2 enriched by molecular subtype are HER2+ by clinical definition) High proliferation rate <i>TP53</i> mutation common More likely to be high grade and node positive	~15% of invasive breast cancers Most ER/PR and HER2 negative (“triple negative”) High proliferation rate <i>TP53</i> mutation common; <i>BRCA1</i> dysfunction (germline, sporadic) Particularly common in African-American women
Histologic correlation	Tubular carcinoma Cribiform carcinoma Low grade invasive ductal carcinoma NST ^b Classic lobular carcinoma	Invasive ductal carcinoma NST Micropapillary carcinoma	High-grade invasive ductal carcinoma NST	High-grade invasive ductal carcinoma NST Metaplastic carcinoma Carcinoma with medullary features
Treatment response and outcome	Respond to endocrine therapy Chemotherapy generally not indicated Good prognosis	Respond to endocrine therapy (tamoxifen and aromatase inhibitors) Response may not be as good as for luminal A Response to chemotherapy variable (greater than luminal A) Prognosis not as good as for luminal A	Respond to trastuzumab (Herceptin) Respond to anthracycline-based chemotherapy Generally poor prognosis, but better with HER2-targeted therapies	No response to endocrine therapy or trastuzumab (Herceptin) Appear to be sensitive to platinum-based chemotherapy and PARP inhibitors Generally poor prognosis (but not uniformly poor)

ER, Estrogen receptor; *PARP*, poly-adenosine diphosphate-ribose polymerase; *PR*, progesterone receptor; *NST*, no special type.

^aThere is a low-grade group of basal-like tumors that similarly express basal-type (high-molecular-weight) cytokeratin and have a triple negative phenotype, but with low proliferation (e.g., adenoid cystic carcinoma, secretory carcinoma).

^bWhile classic lobular carcinoma usually exhibits luminal A features, pleomorphic lobular carcinoma often exhibits features of other molecular subtypes.

Table 36.6 Use of immunohistochemistry as surrogate marker for the molecular subtypes of breast cancer

	MOLECULAR SUBTYPE			
IMMUNOPROFILE	LUMINAL A	LUMINAL B	HER2 ENRICHED	BASAL-LIKE
ER, PR	ER+ and PR high+	ER+ and PR low or intermediate+	ER-, PR-	ER-, PR-
HER2	HER2-	HER2+ or HER2-	HER2+	HER2-
Others	Low Ki-67 (<14%)	Ki-67 ≥14%		CK5/6 and/or EGFR+

EGFR, Epidermal growth factor receptor; *ER*, estrogen receptor; *PR*, progesterone receptor.

Modified from Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol*. 2015;26(8):1533–1546.

though oncologists likely use the information provided in the pathology report to categorize tumors into their surrogate molecular subtypes.⁶²¹

Oncologists treating patients with luminal-type breast cancers, that is, those with hormone receptor positive tumors, may opt for one of the genomic prognostic tests (e.g., Oncotype Dx, MammaPrint, PAM50, see later) to determine the need for adjuvant chemotherapy. Despite the relatively high cost of these tests, the human and economic benefits derived from a decision to avoid chemotherapy when the test result indicates a low risk of recurrence are enormous.^{613,622-624}

Extent, Local Recurrence, and Metastases

Breast carcinoma spreads by direct invasion, by the lymphatic route, and by the hematogenous route. Some of these metastases are already present at the time of diagnosis, and others become manifest clinically months, years, or decades after initial diagnosis and treatment. Local invasion can occur into the nipple, skin, pectoralis fascia and muscle, or other structures of the chest wall.

The frequency of microscopic extension beyond the gross confines of the tumor was evaluated by Rosen et al. by performing a simulated "local excision" with a 2-cm gross margin in mastectomy specimens. Of 18 mastectomies performed for carcinoma measuring less than 1 cm, residual invasive carcinoma was found in 11% and residual DCIS in an additional 22%; this is particularly so for invasive lobular carcinoma.^{625,626} The importance of a thorough pathologic evaluation of extent of breast carcinoma and the status of the margins is paramount because of the large number of conservative surgical procedures being performed.^{627,628}

A somewhat related problem is that of microscopic involvement of the nipple by DCIS, since this structure is left in place when a local excision is carried out. Nipple involvement has been found in about 12% of all clinically detectable invasive carcinomas,⁶²⁹ which is increasingly relevant in an era of nipple-sparing mastectomy. Evaluation of the shaved resection margin below the nipple is indicated in this procedure.⁶³⁰

Local recurrence following mastectomy appears as superficial nodules in or near the surgical scar or as subcutaneous parasternal nodules. Their malignant nature should always be documented by biopsy because the condition can be closely simulated by foreign body granulomas and infectious processes.

Tumor recurrence following local excision usually develops in the same breast quadrant, a fact that led some authors to recommend a primary excision technique that removes en bloc the tumor mass and the associated duct system.⁶³¹ However, contemporary excisions are more conservative because of the frequent use of adjuvant radiation therapy.

The two lymph node stations typically involved by metastatic breast carcinoma are the axilla and the internal mammary chain, with the supraclavicular area representing an extension of the former. It should be remembered that it is not too unusual also to find lymph nodes within the substance of the mammary gland ("intramammary lymph nodes"). Axillary lymph node metastases are present in approximately 30% of cases⁶³² and are divided into levels according to their topographic relation with the insertion of the pectoralis minor muscle: low or proximal, medium, and high or distal. When extensively involved by metastatic carcinoma, the axillary lymph nodes are palpable, but the margin of error with clinical examination is high. Careful dissection and microscopic examination of the submitted lymph nodes by the pathologist is important for accurate staging of the patient. Supraclavicular lymph node involvement is reported to be present in close to 20% of patients with axillary lymph node involvement but is almost zero in cases with negative axillae.⁶³³

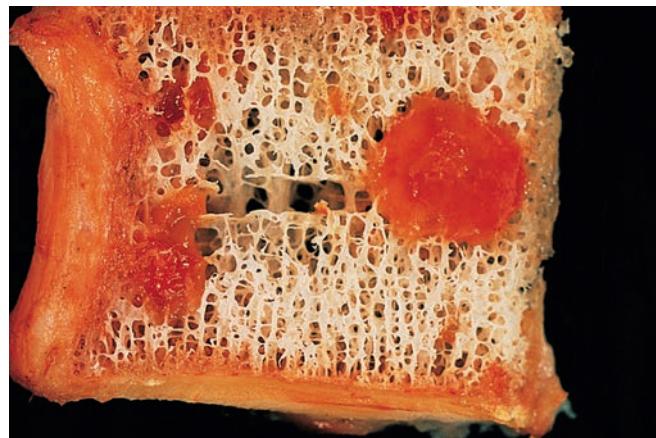


Figure 36.124 Breast Carcinoma Metastatic to Vertebra. The normal bone marrow has been flushed out by placing a thin slice of tissue under a strong jet of water.

The second major lymph node drainage area is to the internal mammary chain, which lies at the anterior ends of the intercostal spaces by the side of the internal thoracic artery. The overall incidence of metastatic involvement of this chain in patients with clinically detectable axillary lymph node metastases is approximately 20%.⁶³⁴ Rarely, a metastatic lymph node will appear entirely necrotic and may simulate an infectious process; immunostains for keratin may be useful in aiding detection of necrotic tumor cells.

Distant metastases are seen most commonly in the skeletal system (Fig. 36.124), lung and pleura, liver, ovary, adrenal gland, and central nervous system (including leptomeninges and eyes)^{635,636} and vary according to breast cancer subtype, with the hormone receptor-positive, HER2-negative subtype having a higher rate of lymph node metastasis at diagnosis than the triple negative subtype.⁶³⁷ Invasive lobular carcinoma (including the signet ring variant) has a propensity to metastasize to the abdominal cavity, particularly to the gastrointestinal tract (Fig. 36.125), ovaries, and serosal surfaces.^{638,639}

In the presence of metastatic deposits of unknown source to lung and other sites, immunoreactivity for breast markers GCDFP-15, gammaglobulin, GATA3, as well as hormone receptors, strongly suggests a breast primary.^{412,640-642} Metastases of breast carcinoma to the ovary are likely to be positive for the aforementioned breast markers and negative for WT1, CA125, and PAX8, whereas the reverse is true, with the exception of ER, for primary ovarian carcinoma.^{412,643,644}

The pattern of metastatic spread of breast carcinoma as evaluated by Fisher et al.⁶⁴⁵ in a large randomized series of patients treated with various modalities brought them to the following conclusions: there is no orderly pattern of tumor dissemination; regional nodes are ineffective as barriers to tumor spread and, when positive, are more an indicator of a particular host-tumor relationship than the instigator of distant metastases; hematogenous spread is of considerable importance in tumor dissemination; complex host-tumor interrelationships affect every facet of the disease; operable breast carcinoma is a systemic disease; and variations in local-regional therapy are unlikely to substantially affect survival.⁶⁴⁶

Occult Breast Carcinoma

Sometimes a single enlarged axillary lymph node in an adult female is found to be involved by metastatic nonlymphoid tumor in the presence of a clinically and radiographically normal breast, with no evidence of tumor elsewhere. When this situation arises, the diagnosis will be metastatic breast carcinoma or metastatic malignant melanoma

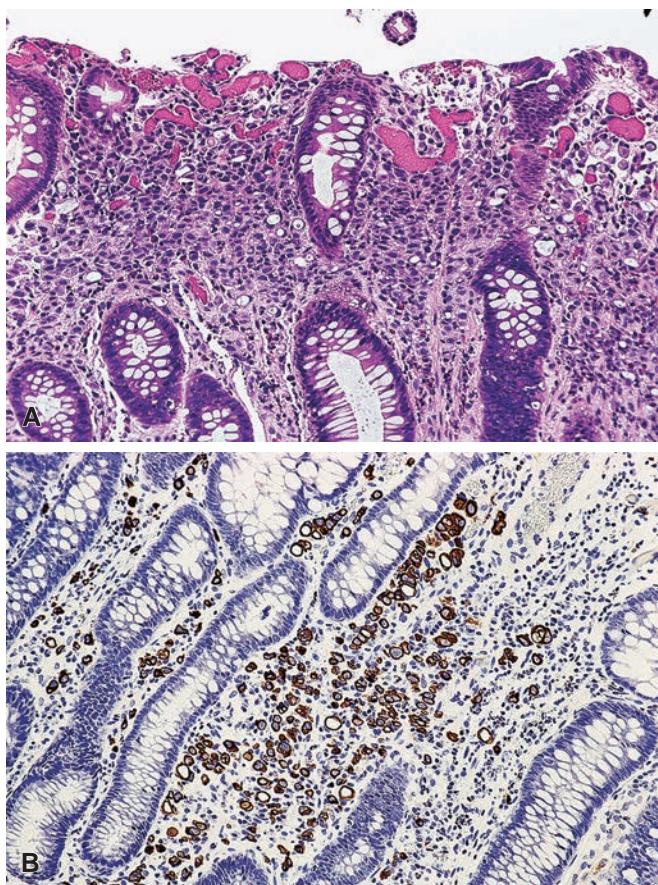


Figure 36.125 **A** and **B**, Metastasis of mammary lobular carcinoma to lamina propria of large bowel mucosa. **B**, Cytokeratin 7 immunostain.

in over 90% of cases. Making the distinction between carcinoma and melanoma should be possible in nearly every case from the combination of morphologic features and immunohistochemical stains, including cytokeratins, GCDFP-15, mammaglobin, GATA3, S-100 protein, HMB-45, and other markers. A note of caution is in order regarding the interpretation of the immunostains, since S-100 protein (originally thought to be very distinctive of melanoma in this situation) is now known to stain a high number of breast carcinomas and, some melanomas may show aberrant expression of cytokeratin. MRI is indicated to attempt to establish the location of the tumor. If the combined approach has shown that: (1) the tumor is a carcinoma rather than a melanoma; (2) the appearance of this carcinoma is compatible with breast origin; and (3) there is no clinicoradiographic evidence of tumor elsewhere, treatment options include ipsilateral mastectomy, whole breast irradiation, and even chemotherapy.⁶⁴⁷⁻⁶⁴⁹ A primary tumor, which can be extremely small, will be found in most cases.⁶⁴⁷⁻⁶⁴⁹ It appears from the limited data available that those women who undergo mastectomy fare better than those who elect to have breast irradiation.^{647,649}

Occasionally, occult carcinomas are found on routine microscopic examination of a reduction mammoplasty specimen.²⁶² As already pointed out, these are almost always *in situ* rather than invasive tumors.

Sentinel Lymph Node

First pioneered in the early 1990s, the technique of sentinel lymph node biopsy for the evaluation and management of breast

carcinoma has gained enormous popularity and has become the standard of care.⁶⁵⁰ The procedure is based on the concept that if the sentinel node is negative, the other nodes of that group will also be negative in nearly all instances, whereas if it is positive, the chance that there will be additional metastases in that nodal group is about one-third.^{344,651,652} In most substantial series the size of the primary tumor and the presence of lymphovascular invasion have been found to be significant predictors of positive sentinel lymph nodes.^{653,654} The goal of sentinel lymph node examination is to identify macrometastases (>2 mm), which can be achieved by sectioning the lymph nodes at 2-mm intervals and examining one H&E section.⁶⁵⁵ The use of enhanced techniques, such as step-sectioning or performing immunostains for cytokeratin to identify occult metastases, are not routinely indicated, as their identification does not translate into additional clinical benefit.^{656,657} Molecular evaluation with RT-PCR (searching for the mammaglobin genes *MGB1* and *MGB2* or *CK19* mRNA) offers an alternate method for identifying lymph node metastases⁶⁵⁸; however, these techniques have not been widely adopted in the United States, for the reasons stated previously.

Pitfalls in the interpretation of lymph nodes include keratin-positive reticulum cells indigenous in the lymph node (which may become quite hyperplastic and which have a typical dendritic morphology; use of AE1/AE3 and avoiding CAM5.2 will prevent this error), benign glandular inclusions, endosalpingiosis and other epithelial tissue, as well as traumatic displacement of breast epithelium.^{27,659,660} Of these various traps, the one that presents the greatest challenge is that of *mechanical transport*, that is, the possibility that the biopsy procedure may push either normal or neoplastic epithelial cells into mammary lymphatic spaces, from which they could find their way into the sentinel lymph node.^{659,660} This phenomenon likely does occur, as supported by the fact that it is seen more commonly in those patients in whom such instrumentation procedures were carried out.⁶⁶¹ It is also credible that it may involve both tumor and normal cells. Alas, it is also too evident that the distinction between normal and neoplastic epithelial cells for these isolated nodal-based epithelial cells is anything but easy.^{662,663} Suffice it to say that, for practical purposes, it has been recommended that the term *micrometastases* be applied to a cluster of tumor cells greater than 0.2 mm (>200 cells) but ≤2 mm and that the term *isolated tumor cells* be used for the presence of single cells interpreted as malignant totaling fewer than 200 cells or ≤0.2 mm in greatest dimension. Cells that appear degenerated and that are associated with hemosiderin-laden macrophages are favored to be displaced.

As mentioned previously, the identification of isolated tumor cells and even micrometastases has little impact on patient management; further, the management of the axilla in patients with 1–3 lymph nodes with macrometastases and no extranodal extension has evolved to become less invasive. The ACSOG Z0011 trial demonstrated no significant differences in outcome for patients with the aforementioned findings undergoing completion axillary dissection versus those managed with wide local excision, whole breast irradiation, and sentinel lymph node biopsy alone.³⁴⁴ This has translated into fewer intraoperative sentinel lymph node evaluations and fewer completion axillary dissections.^{664,665}

Staging of Breast Carcinoma

The most widely used clinical staging system for breast carcinoma is the one adopted by both the International Union for Cancer Control (UICC) and the American Joint Commission on Cancer (AJCC). It is based on the TNM system (T, tumor; N, nodes; M, metastases) and is shown in (Table 36.7).⁶⁶⁶ There are two stage group tables: the anatomic stage group table and the prognostic

Table 36.7 Definitions of AJCC TNM for breast carcinoma

Definition of Primary Tumor (T) — Clinical and Pathological		Definition of Regional Lymph Nodes — Clinical (cN)†	
T CATEGORY	T CRITERIA	CN CATEGORY	CN CRITERIA
TX	Primary tumor cannot be assessed	cN2	Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
T0	No evidence of primary tumor	cN2a	Metastases in ipsilateral Level I, II axillary lymph nodes fixed to one another (matted) or to other structures
Tis (DCIS)*	Ductal carcinoma in situ	cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.	cN3	Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with Level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
T1	Tumor ≤ 20 mm in greatest dimension	cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
T1mi	Tumor ≤ 1 mm in greatest dimension	cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
T1a	Tumor > 1 mm but ≤ 5 mm in greatest dimension (round any measurement 1.0-1.9 mm to 2 mm)	cN3c	Metastases in ipsilateral supraclavicular lymph node(s)
T1b	Tumor > 5 mm but ≤ 10 mm in greatest dimension		
T1c	Tumor > 10 mm but ≤ 20 mm in greatest dimension		
T2	Tumor > 20 mm but ≤ 50 mm in greatest dimension		
T3	Tumor > 50 mm in greatest dimension		
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4		
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4	pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathological study or previously removed)
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criterial for inflammatory carcinoma	pN0	No regional lymph node metastasis identified or ITCs only
T4c	Both T4a and T4b are present	pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
T4d	Inflammatory carcinoma	pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
Definition of Regional Lymph Nodes — Clinical (cN)†		Definition of Regional Lymph Nodes — Pathological (pN)¶	
cN CATEGORY	cN CRITERIA	pN CATEGORY	pN CRITERIA
cNX‡	Regional lymph nodes cannot be assessed (e.g., previously removed)	pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases by sentinel node biopsy
cN0	No regional lymph node metastases (by imaging or clinical examination)	pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN1	Metastases to movable ipsilateral Level I, II, axillary lymph node(s)	pN1a	Metastases in 1-3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
cN1mi§	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)	pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
		pN1c	pN1a and pN1b combined

Table 36.7 Definitions of AJCC TNM for breast carcinoma—cont'd

Definition of Regional Lymph Nodes — Pathological (pN)¶		Definition of Regional Lymph Nodes — Pathological (pN)¶	
pN CATEGORY	pN CRITERIA	pN CATEGORY	pN CRITERIA
pN2	Metastases in 4-9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases	pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging); or pN2a in the presence of pN1b
pN2a	Metastases in 4-9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)	pN3c	Metastases in ipsilateral supraclavicular lymph nodes
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes	Definition of Distant Metastasis (M)	
pN3	Metastases in 10 or more axillary lymph nodes; or in infraclavicular (Level III axillary) lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive Level I, II axillary lymph nodes; or in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes	M0	No clinical or radiographic evidence of distant metastases**
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); or metastases to the infraclavicular (Level III axillary lymph) nodes	cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
		M1	Distant metastases detected by clinical and radiographic means (cM) and/or histologically proven metastases larger than 0.2 mm (pM)

From Amin M, Edge S, Greene F, et al. (Eds.). AJCC Cancer Staging Manual. Ed. 8. New York: Springer; 2017.

*Note: Lobular carcinoma *in situ* (LCIS) is a benign entity and is removed from TNM staging in the AJCC Cancer Staging Manual, 8th edition.

†Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or fine needle aspiration/core needle biopsy respectively.

‡The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.

§cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy.

¶Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy respectively; with NO further resection.

**Note that imaging studies are not required to assign the cM0 category.

stage group table. Cancer registries and U.S. physicians must use the prognostic stage group table for reporting. Pathology synoptic reports need only report the biomarker status so that the prognostic stage group table may be appropriately assigned.

Therapy for Breast Carcinoma

Therapy for breast carcinoma includes surgery, radiation therapy, hormonal therapy, chemotherapy, and targeted therapy, depending on the type and extent of the disease.⁶⁶⁷

Surgical therapy, historically synonymous with Halsted's radical mastectomy, now includes a wide variety of options, such as partial mastectomy (lumpectomy, segmentectomy, or quadrantectomy, i.e., breast-conserving surgeries) and total (simple) mastectomy. The procedure selected is influenced by many factors, including tumor stage, patient preference and breast size, the surgeon's practice, whether or not reconstructive surgery is available, and geographic region.⁶⁶⁸⁻⁶⁷⁰

Radiation therapy is often employed as a postoperative adjunct (especially in more limited operations), as well as for control of locally recurrent disease.^{671,672}

Microscopic evaluation of all surgical margins in breast-conserving surgery and of the deep margin in mastectomy is critical to determining the need for additional surgery and/or radiation therapy. A recent meta-analysis has endorsed the definition of ink on tumor (either invasive or DCIS) as being required for a positive margin in patients with invasive carcinoma being treated with breast-conserving surgery and whole breast irradiation. Anything less should be reported as a negative margin and the distance in millimeters reported.⁶⁷³ Several studies have shown that patients with positive margins are more likely to develop local recurrence, as well as distant failure.⁶⁷⁴⁻⁶⁷⁶ For margin-negative cases, the likelihood of ipsilateral breast failure and distant metastases is related to the amount of carcinoma near the margins.⁶⁷⁷ Margin width is also a factor influencing recurrence among women with DCIS, particularly among those who forgo radiation

therapy.⁶⁷⁸ A recent meta-analysis indicates that a 2-mm margin is desirable for patients with DCIS.⁶⁷⁹ There is no requirement to report the margin status for classical LCIS, though reporting of margin status is recommended for the variant forms of LCIS, such as pleomorphic LCIS.

Endocrine therapy is the standard of care for all patients with ER-positive breast cancer.⁶⁸⁰ At present, administration of a selective estrogen receptor modulator (SERM, e.g., tamoxifen) or an aromatase inhibitor in postmenopausal women (e.g., anastrazole) is the standard of care for early-stage, hormone receptor-positive breast carcinoma, usually combined with irradiation, with or without adjuvant chemotherapy, depending on the patient's age and other parameters.⁶⁸⁰ Hormonal therapy, which had historically included the options of bilateral oophorectomy, adrenalectomy, and hypophysectomy, is now largely dependent on the aforementioned antiestrogen drugs.

Trastuzumab (Herceptin), a humanized monoclonal antibody against the HER2 receptor, is a form of targeted therapy that is effective for breast cancers that are HER2 positive (score 3+ by immunohistochemistry or HER2 amplified by FISH studies). Although originally used only for patients with metastatic disease, the drug is now standard of care as an adjuvant agent for early-stage breast cancer as well.⁶⁸¹ Furthermore, newer agents against HER2 and its related receptors are becoming increasingly available either as alternate therapeutic options or as second-line therapy at the time of recurrence or metastasis.

Chemotherapy has had a significant impact on the survival of patients with metastatic breast carcinoma, the best results having been obtained with combination regimens. In addition, chemotherapy is currently used as an adjunct following local treatment, with curative intent, in patients with positive axillary nodes. The interested reader should refer to clinical texts for further information.⁶⁸² The value of platinum-based chemotherapeutic agents and of PARP inhibitors for treatment of breast cancers with specific DNA repair defects, including those arising in carriers of *BRCA1* or *BRCA2* mutation and basal-type breast cancers, have also shown promise.⁶⁸³

Effects of Therapy on the Tumor and on Normal Breast

Radiation therapy of breast carcinoma may result in bizarre nuclear changes, formation of giant tumor cells, naked nuclei, and abnormal mitotic figures. Extensive tumor necrosis may develop, which can become surrounded by a thick fibrous wall. It is important to remember that morphologic viability is not necessarily equivalent to biologic viability (i.e., the capacity of the tumor cell to replicate). In the non-neoplastic breast, the most characteristic irradiation effect is atypia of epithelial cells in the terminal ductules, associated with lobular sclerosis and atrophy (Fig. 36.126).⁶⁸⁴ These postradiation changes can persist for years.⁶⁸⁵

Treatment of ER-positive tumors with endocrine therapy leads to prominent stromal fibrosis and hyalinization, an increase in the amount of elastic tissue, and degenerative changes in the tumor cells. The latter are manifested by cytoplasmic vacuolization, rupture of cell membranes, nuclear aberrations, and eventual necrosis. These changes may occur both in the primary tumor and in the metastases, and can be very patchy, in the sense of showing morphologically unaffected cells lying side by side with highly altered cells.

Chemotherapy can also induce striking morphologic changes in the tumor cells (Fig. 36.127), including such a degree of vacuolization as to simulate histiocytes. It also results in atrophy of the TDLU, with occasional atypia of the normal epithelial cells.⁶⁸⁶ In most instances, treatment with neoadjuvant chemotherapy does not affect the histologic grading of the carcinoma; however, in some cases

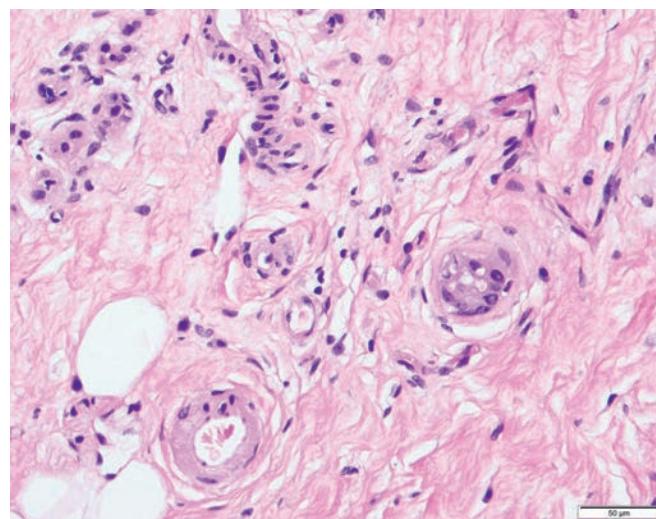


Figure 36.126 Radiation Effect in Non-Neoplastic Breast. The epithelial cells of the lobules show cytomegaly with smudgy nuclear features and cytoplasmic vacuolation associated with lobular sclerosis and atrophy. Note the absence of any epithelial proliferation.

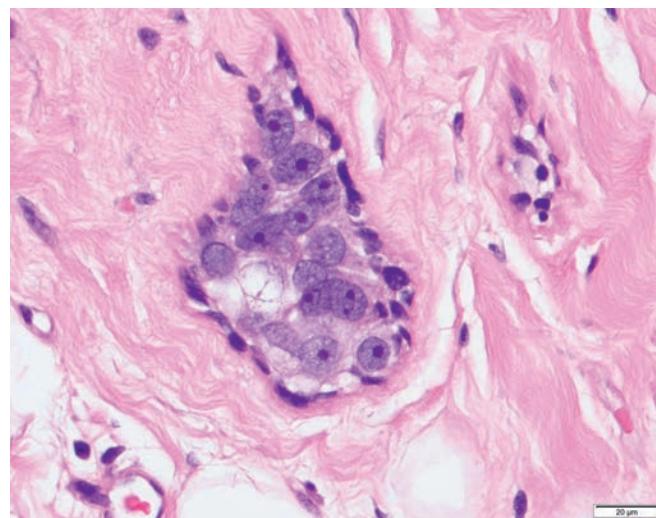


Figure 36.127 Chemotherapy Effect. Residual ductal carcinoma showing the effects of chemotherapy: nuclear enlargement, prominent nucleoli, and cellular vacuolization.

the tumor may appear to be higher grade (due to greater nuclear pleomorphism) or even lower grade (due to the identification of fewer mitoses).⁶⁸⁷ The microscopic features of the treated tumor correlate poorly with patient outcome.⁶⁸⁷ In some cases the residual tumor is present exclusively or predominantly as lymphatic emboli, a prognostically unfavorable feature.⁶⁸⁸

Guidelines have been published detailing appropriate gross examination, sampling, and reporting of breast carcinomas after neoadjuvant therapy.⁶⁸⁷ In such patients, careful examination of the tumor bed, which is characterized by a hyalinized vascular stroma with fibroelastosis and edema infiltrated by histiocytes (Fig. 36.128), is critical to confirming the degree of pathologic response, particularly in the absence of any residual foci of invasive carcinoma. There are a variety of classification schemes in use to score the degree of tumor response with the two best known being the Residual Cancer Burden score and the Miller-Payne grade (Table 36.8).^{689,690}

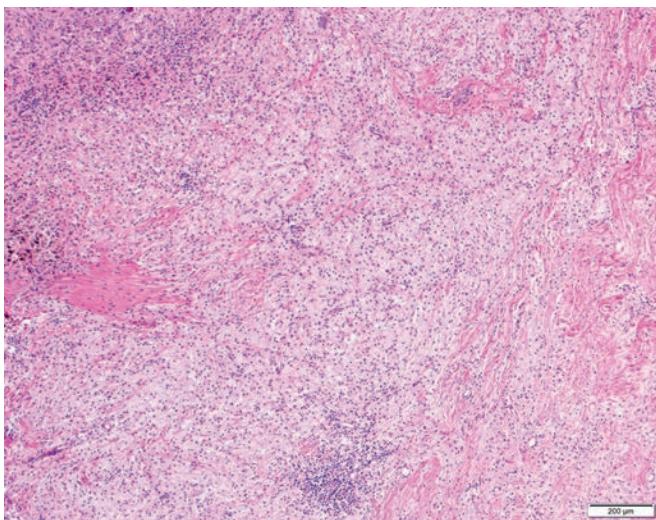


Figure 36.128 Tumor bed which is characterized by a hyalinized vascular stroma with fibroelastosis and edema infiltrated by histiocytes. Lymphocytes and hemosiderin are also noted in this field.

Table 36.8 Classification of neoadjuvant-treated breast cancers

Residual Cancer Burden (RCB) ⁶⁸⁹ Used in conjunction with MD Anderson Website Calculator (http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3)	
CATEGORY	DEFINITION
RCB-0 (pCR)	No carcinoma in breast or lymph nodes
RCB-I	Partial response
RCB-II	Partial response
RCB-III	Chemoresistant
Miller-Payne System	
GRADE	DESCRIPTION OF RESPONSE
Grade 1	No change or some alteration to individual malignant cells, but no reduction in overall cellularity
Grade 2	A minor loss of tumor cells but overall cellularity remains high; up to 30% loss
Grade 3	Between an estimated 30% and 90% reduction in tumor cell volume
Grade 4	A marked disappearance of tumor cells (>90% reduction); only small clusters or widely dispersed individual cells remain
Grade 5	No malignant cells identifiable; only tumor bed present. May have DCIS or LVI present

DCIS, Ductal carcinoma in situ; LVI, lymphovascular space invasion.

Data from Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol*. 2007;25(28):4414–4422; and Ogston KN, Miller ID, Payne S, et al. A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival. *Breast*. 2003;12(5):320–327.

Another “treatment-related” effect worthy of comment relates to the use of breast implants for reconstructive purposes. The implants frequently develop a fibrous capsule around them, and the inside surface of this capsule has a tendency to undergo *synovial metaplasia*, which on occasion may become quite hyperplastic. Sometimes, the capsule is surrounded by benign squamous epithelium,⁶⁹¹ and, very rarely, implant-associated anaplastic lymphoma may occur (see later).^{692,693}

Prognosis

The prognosis of breast carcinoma is related to a huge number of clinical and pathologic features, some of which are discussed later, often with conflicting reports as to the level of risk associated with any particular putative prognostic factor.

Patient age. Older, postmenopausal women have the best prognosis as these patients tend to have the better differentiated, ER-positive, screen-detected tumors presenting at a lower stage, though, of course, this age group will have competing morbidities that will affect survival data. As far as tumors occurring in young women (≤ 35 or < 40 years of age), studies have shown young age to be an independent risk factor associated with a propensity for recurrence and distant metastases despite more aggressive therapies, related to the fact that these patients tend to have adverse histologic features, often have had delays in diagnosis, and thus present at a later/higher stage.^{694–697}

BRCA. Early studies suggested that breast carcinomas developing in *BRCA1* mutation carriers were associated with worse overall survival if adjuvant therapy was not given, but a large study of Israeli women carriers of *BRCA1* and *BRCA2* mutations showed that their breast cancer-specific death rates were similar to those of noncarriers.⁶⁹⁸ At this time, mutation status is not considered to be an independent predictor of clinical outcome.⁶⁶⁶

Pregnancy and oral contraceptives. There is general agreement that carcinoma of the breast manifesting during pregnancy or lactation is generally an aggressive tumor with low expression of hormone receptors and high expression of HER2 and that it is associated with an overall poorer prognosis.^{699,700} However, it has been found that this difference does not reach statistical significance when evaluated stage for stage.^{701,702}

No convincing evidence has been found that prior use of oral contraceptive agents has an effect on the evolution or survival of patients with breast carcinoma.⁷⁰³

Early diagnosis. The relative 5-, 10-, and 20-year survival rates for asymptomatic breast carcinomas detected in a large screening project (Breast Cancer Demonstration Detection Project) were 87%, 79%, and 78.2%, respectively.^{311,704} These figures are much higher than those for clinically detectable carcinoma and relate to the fact that the tumors were small in most cases, were usually devoid of axillary metastases, and included a high percentage of microscopically favorable types.

Size. The diameter of the primary tumor shows a good correlation with the incidence of nodal metastases and with survival rate, with the notable exception of basal-like carcinomas which do not follow the “size-node rule,” that is, small triple negative cancers may be lymph node positive and vice versa.^{605,611,705,706} As a matter of fact, this easily, quickly, and cheaply determined parameter has been found to be one of the strongest predictors of dissemination and rate of relapse in node-negative breast carcinomas.⁷⁰⁷ It should be noted that in tumors having both DCIS and an invasive component, the size of the latter, as measured microscopically, is a better predictor than is the total tumor size, hence the staging guideline for reporting microscopic size of the invasive component as the T-stage.^{666,706,708}

Site. No relationship has been found in most studies between prognosis and the quadrant location of the primary tumor. However, in one large study, it was found that medial location of the tumor was associated with a risk of tumor-related death when compared with lateral location but not with local tumor control.^{709–711}

Histologic type. There is no significant prognostic difference between ordinary invasive ductal and invasive lobular carcinoma.⁷¹² Morphologic variants of invasive ductal carcinoma with a more favorable prognosis are tubular carcinoma, invasive cribriform carcinoma, pure mucinous carcinoma, adenoid cystic carcinoma, and secretory carcinoma.^{210,713} A variant of invasive lobular (and sometimes ductal) carcinoma associated with a poor prognosis is signet ring carcinoma and the prognosis of inflammatory carcinoma (as defined microscopically, see next) is also particularly ominous. Metaplastic carcinomas show similar survival rates to invasive carcinomas of no special type.²¹⁰

Microscopic grade. Since both architecture and cytology have been found to correlate with prognosis, Elston and Ellis championed a modification of the original Bloom and Richardson⁷¹⁴ and Black et al.⁷¹⁵ grading schemes, which were based on tubule formation and degree of nuclear atypia, respectively. This has come to be known as the Nottingham modification of the Bloom–Richardson system; it also incorporates evaluation of mitotic activity.⁷¹⁶ In this scheme, the grade is obtained by adding up the scores for tubule formation, nuclear pleomorphism, and mitotic count, each of which is given 1, 2, or 3 points. This is translated into the final grade by formulae outlined in **Box 36.1** and **Tables 36.9** and **36.10**. The utility of this and related grading systems has been convincingly and repeatedly proven^{717,718} to the point that incorporation of this information into the routine pathology report has become a requirement.⁶⁶⁶ Further, an acceptable degree of interobserver reproducibility has been achieved when the criteria are applied.^{719,720} The system was largely conceived for invasive ductal carcinoma NST, but it can also be applied to

Box 36.1 Microscopic grading of breast carcinoma: Nottingham modification of the Bloom–Richardson system

Tubule formation

- 1 point: Tubule formation in >75% of the tumor
- 2 points: Tubule formation in 10%–75% of the tumor
- 3 points: Tubule formation in <10% of the tumor

Nuclear pleomorphism

- 1 point: Nuclei with minimal variation in size and shape
- 2 points: Nuclei with moderate variation in size and shape
- 3 points: Nuclei with marked variation in size and shape

Mitotic count

- 1, 2, or 3 points, according to **Table 36.9**.

Table 36.9 Assignment of points for mitotic counts according to the field diameter

Field diameter (mm)	0.44	0.59	0.63
Mitotic count			
1 point	0–5	0–9	0–11
2 points	6–10	10–19	12–22
3 points	>11	>20	>23

the special types of ductal carcinoma and to invasive lobular carcinoma.⁷²¹

Tumor-infiltrating lymphocytes (TILs). Emerging data indicate that patients with breast carcinomas demonstrating a prominent lymphocytic reaction, particularly triple negative and HER2-positive tumors, have a better response to neoadjuvant chemotherapy than those tumors without.⁷²² Similarly, patients with triple negative or HER2-positive tumors and a prominent lymphocytic reaction receiving adjuvant chemotherapy appear to have a survival advantage over those without TILs.^{722,723} No significant differences are noted for patients with hormone receptor-positive, HER2-negative disease according to TIL status.⁷²² At this point in time, however, there are no agreed-upon criteria for counting TILs or on how to report an “immune-score.”

HER2. As already stated, overexpression or amplification of HER2 as determined either by immunohistochemistry or by FISH is an excellent predictor of response to trastuzumab (or other HER2-targeted therapies). Although it identifies a subset of patients with poor prognosis, HER2 status correlates closely with tumor grade and as such loses much of its independent prognostic significance in multivariate analysis.^{724,725}

Skin invasion. Breast carcinomas in which invasion of the overlying skin has occurred are associated with a decreased survival rate.⁷²⁶ Invasion of dermal lymphatic vessels as a determinant of the “inflammatory carcinoma” picture is a particularly ominous prognostic sign.

Lymphatic tumor emboli. The presence of tumor emboli in lymphatic vessels within the breast is associated with an increased risk of distant recurrence; an association made stronger with immunohistochemical confirmation of the lymphatic nature of the involved spaces (e.g. with D2-40).^{727,728}

Blood vessel emboli. This finding shows a high correlation with tumor size, histologic grade, tumor type, lymph node status, development of distant metastases, and poor prognosis.⁷²⁹

Paget disease. The presence or absence of Paget disease in invasive ductal carcinoma is of no prognostic relevance.⁷³⁰

ER. Patients with ER-positive tumors have a longer disease-free survival than others.

DNA ploidy. Despite numerous studies evaluating DNA ploidy with flow cytometry, it is yet unclear whether this parameter adds *independent* information of therapeutic or prognostic value once the size of the tumor, microscopic grading, lymph node status, and hormone-receptor status have been taken into account; this ancillary information is not provided in routine clinical practice.^{731–733}

Cell proliferation. This parameter, whether measured by the old-fashioned mitotic count, by MIB-1 (Ki-67) or analogous immunostain, by determination of S-phase fraction by flow cytometry, or by molecular-based testing such as PCR or gene expression profiling, has emerged as a very important prognostic determinant, particularly for ER-positive cases, hence its inclusion in the combined grading scheme espoused by Elston.⁷¹⁶ Many view it as the most important component of that system, which is being supported by evidence from innumerable gene expression profiling panels which all

Table 36.10 Final grading score

SUM OF POINTS	FINAL GRADE
3–5	1
6–7	2
8–9	3

demonstrate that proliferation-related genes are the main drivers in each of the gene signatures.^{734,735}

Axillary lymph node metastases. This is one of the most important prognostic parameters. Not only is there a sharp difference in survival rates between patients with positive and negative nodes, but the survival rate also depends on the level of axillary node involved (low, medium, or high), the absolute number (fewer than four versus four or more), the amount of metastatic tumor and the presence or absence of extranodal extension.⁶⁵⁵ There is no clinical significance to the presence of "micrometastases" (>0.2 to ≤ 2 mm) or "isolated tumor cells" (≤ 0.2 mm) as demonstrated in the NSABP (National Surgical Adjuvant Breast and Bowel Project) B32 trial.⁷³⁶ For prognostic purposes, the best grouping seems to be the following: negative nodes, one to three positive nodes, and four or more positive nodes.

Internal mammary lymph node metastases. Survival in patients with involvement of this lymph node group is lower than in those without such involvement, especially if only patients with one to three positive axillary nodes are evaluated.⁷³⁷

Circulating tumor cells. There is increasing evidence that the presence and number of tumor cells in the bloodstream provide independent prognostic information on progression-free and overall survival in patients with early-stage and metastatic breast cancer.⁷³⁸

Local recurrence. Early studies showed this to be a sign of ominous prognosis. However, more recent data on larger series indicate that risk of death after local recurrence is related to the stage at initial breast cancer diagnosis.⁷³⁹

Type of therapy. This is too complex and multifactorial an issue to be adequately addressed here. Available evidence suggests that the outcome in breast carcinoma depends on both the nature of the individual tumor and on the type of therapy given, in addition to those factors discussed previously. A complicating factor in evaluating therapeutic results is the marked variation in the natural history of the disease among individuals, which renders imperative the use of carefully randomized studies.^{740,741} The results of six large prospective randomized clinical trials have clearly demonstrated that the combination of breast-conserving surgery and radiation therapy provides survival rates equivalent to those following mastectomy.⁷⁴²

Surgical margins. Microscopically positive surgical margins in specimens from conservative breast excisions are associated with a higher risk of ipsilateral tumor recurrence.^{628,673,743} Definitions of "positive" and "close" margins have varied in the literature, but a recent guideline statement by a multidisciplinary group of experts recommends use of "ink on tumor" as the definition of a positive margin in patients with invasive breast carcinoma. All else should be reported as a negative margin, with the distance to the margin reported in millimeters.⁶⁷³ It is anticipated that standardizing the definition of a positive margin will result in less arbitrary decision-making regarding the need for reexcision. Early indications are that there has been a change in surgical practice with a reduction in reexcision rates reported.⁷⁴⁴ Some surgeons excise multiple separate "cavity margins" (from the wall of the residual cavity during the same surgical procedure) and regard them as the "final margins" that supersede the initial margins from the excised specimen.⁷⁴⁵

Gene expression profiling. There are many studies reporting the use of microarray analysis to select tumor gene signatures for separating patients into meaningful prognostic/predictive groups that will potentially help with selection of therapy.^{609,746-749} Two popular commercially available tests are: (1) MammaPrint (70-gene expression analysis by microarray); and (2) Oncotype DX (analysis of expression of 16 cancer-related genes and 5 reference genes by reverse transcription quantitative PCR). Both may be performed on formalin-fixed paraffin-embedded tissue.⁷⁵⁰ A third test, PAM50

Prosigna assay, has recently come to market; it utilizes nanostring technology, as well as providing prognostic and predictive information, the test also classifies the tumor according to its intrinsic molecular subtype. This test will be available for laboratories to perform themselves, in contrast to the Oncotype Dx and MammaPrint assays, which are performed in single, commercial laboratories. It should be noted that almost all the gene signatures are applicable to hormone receptor-positive tumors with the decision point being whether or not to give the patient chemotherapy in addition to antiestrogen therapy.^{623,749,751} Recent data from two prospective clinical trials indicate that chemotherapy may be safely omitted in patients with a low recurrence score on Oncotype Dx or a good prognosis signature on testing by MammaPrint.⁵²³ Results guiding management of patients in the intermediate risk group have not yet been reported.

Salivary Gland and Skin Adnexal-Type Tumors (Including Myoepithelial Tumors)

A small proportion of benign and malignant tumors of the breast have an appearance analogous to, or at least reminiscent of, that more commonly seen in salivary glands or skin adnexa, particularly sweat glands.⁷⁵² This should not be too surprising, since the breast is a modified sweat gland and a close analogy exists between sweat gland tumors and salivary gland neoplasms. Some of the malignant tumors in this category share many of the features of ordinary breast carcinoma and therefore have been discussed in the preceding section. However, they could have been included here because of the histogenetic link they seem to have (at least at the conceptual level) with benign tumors of salivary gland and/or their skin adnexal-type morphology.

The benign tumors in this category include **eccrine spiradenoma** (which, as in the skin, may undergo malignant transformation), **syringomatous squamous tumors** (to be distinguished from low-grade adenosquamous carcinoma), **papillary syringocystadenoma**, **dermal-type cylindroma** (not to be equated with adenoid cystic carcinoma), **eccrine acrospiroma** (including nodular, solid-cystic, and clear cell hidradenoma), and **pleomorphic adenoma**. The latter, which is very rare in humans but relatively common in female dogs, has been interpreted by some as a variant of intraductal papilloma, but its appearance is quite similar to that of pleomorphic adenoma of salivary glands (benign mixed tumor) or of cutaneous sweat glands (chondroid syringoma) (Fig. 36.129). This tumor can arise as single or multiple nodules sometimes in a background of usual ductal hyperplasia, or in association (possibly coincidental) with breast carcinoma. An association with metaplastic carcinoma has not been well defined.^{753,754}

A more complicated issue is represented by breast tumors of probable myoepithelial nature. First, it should be recognized that myoepithelial participation is an integral component of benign proliferative breast diseases (such as sclerosing adenosis, UDH, intraductal papilloma, and nipple adenoma) and that, in some instances, it dominates the histologic picture. Second, myoepithelial cells are a normal constituent of ducts and lobules, and therefore one might question whether these neoplasms should even be regarded as of salivary or sweat gland type. They are discussed here because the morphologic variations they exhibit and classification problems they elicit are very similar to those they pose in the salivary glands (see Chapter 12). **Adenomyoepithelioma** is a small (average diameter 1 cm), firm, well-circumscribed, often multilobulated tumor composed microscopically of cells of polygonal shape and optically clear to eosinophilic cytoplasm, arranged in nests within which

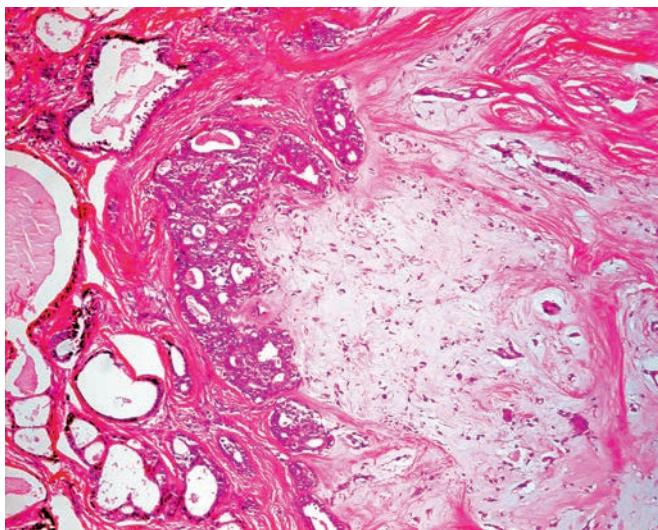


Figure 36.129 Pleomorphic Adenoma/Benign Mixed Tumor of the Breast. A prominent myxochondroid stroma is interspersed among the glandular structures.

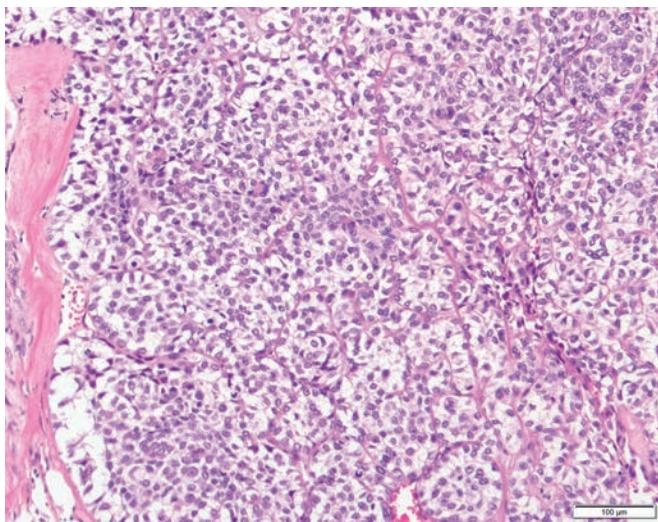


Figure 36.130 Adenomyoepithelioma. This well-circumscribed, multilobulated tumor is composed of polygonal cells with optically clear cytoplasm, arranged in nests. The gland-forming epithelial cells, with more eosinophilic cytoplasm, are harder to appreciate.

gland-forming epithelial cells may be appreciated.⁷⁵⁵ The patterns of growth may be spindle cell (myoid), tubular, or lobulated (Fig. 36.130).⁷⁵⁵⁻⁷⁵⁷ The behavior is generally benign, with local recurrence reported but no instances of metastatic spread.^{756,758} Fully malignant myoepithelial tumors arising in association with adenomyoepithelioma (malignant myoepithelioma and/or myoepithelial carcinoma) are better classified as metaplastic carcinomas given the considerable overlap in expression of myoepithelial and epithelial markers in these tumors; a classification change that is largely semantic.²¹⁰

Stromal and Vascular Tumors and Tumorlike Conditions

Primary angiosarcoma of the breast is an extremely rare tumor of young to middle-aged women.⁷⁵⁹ Mammographically, it presents as

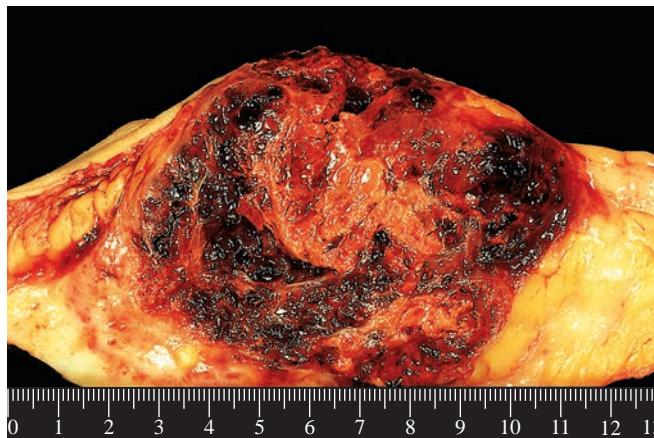


Figure 36.131 Typical Hemorrhagic Gross Appearance of Angiosarcoma of Breast. (Courtesy of Dr Pedro J Grases Galofrè. From Grases Galofrè P. *Patología ginecológica, Bases para el diagnóstico morfológico*. Barcelona: Masson; 2002.)

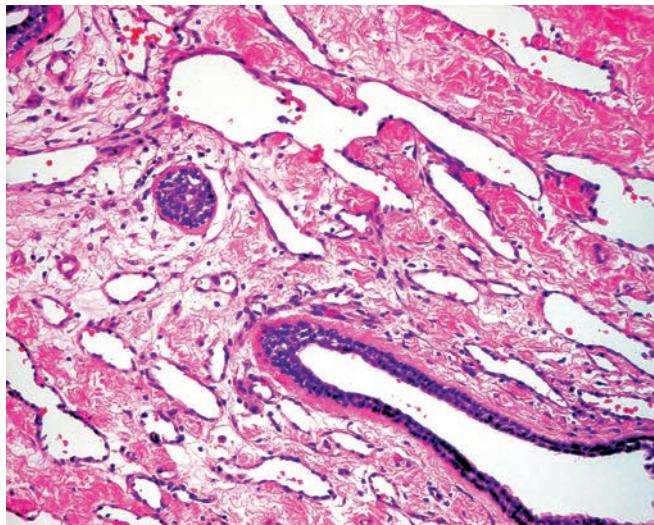


Figure 36.132 Well-Differentiated Angiosarcoma of Breast.

a solitary mass without associated calcifications.⁷⁶⁰ Grossly, the tumor is soft, spongy, and hemorrhagic (Fig. 36.131). Microscopically, the diagnostic areas are characterized by anastomosing vascular channels lined by atypical endothelial cells infiltrating through the breast parenchyma (Fig. 36.132). The appearance may vary, even in the same tumor, from that of a highly undifferentiated solid neoplasm to one that is extremely bland cytologically. However, close examination will usually reveal that even the better differentiated areas exhibit the telltale sign of angiosarcoma (i.e., inter-anastomosing vascular channels and endothelial cell atypia) (Figs. 36.133 and 36.134; see also Fig. 36.132). The tumor is thought to be of blood vessel rather than lymphatic vessel nature. Occasionally, the tumor is more epithelioid appearing and may mimic a high-grade invasive ductal carcinoma; a pitfall that may be compounded by aberrant keratin expression.⁷⁶¹ Curiously, some cases of breast angiosarcoma have been found to express ER.⁷⁶² The differential diagnosis of angiosarcoma includes metaplastic carcinoma, in particular, the acantholytic variant of squamous cell carcinoma (see Fig. 36.116), hemangioma (see following discussion), and pseudoangiomatous stromal

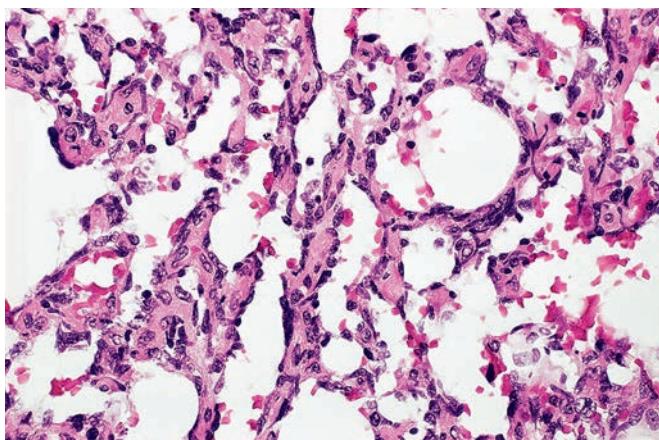


Figure 36.133 Complex anastomosing vascular pattern in angiosarcoma of breast.

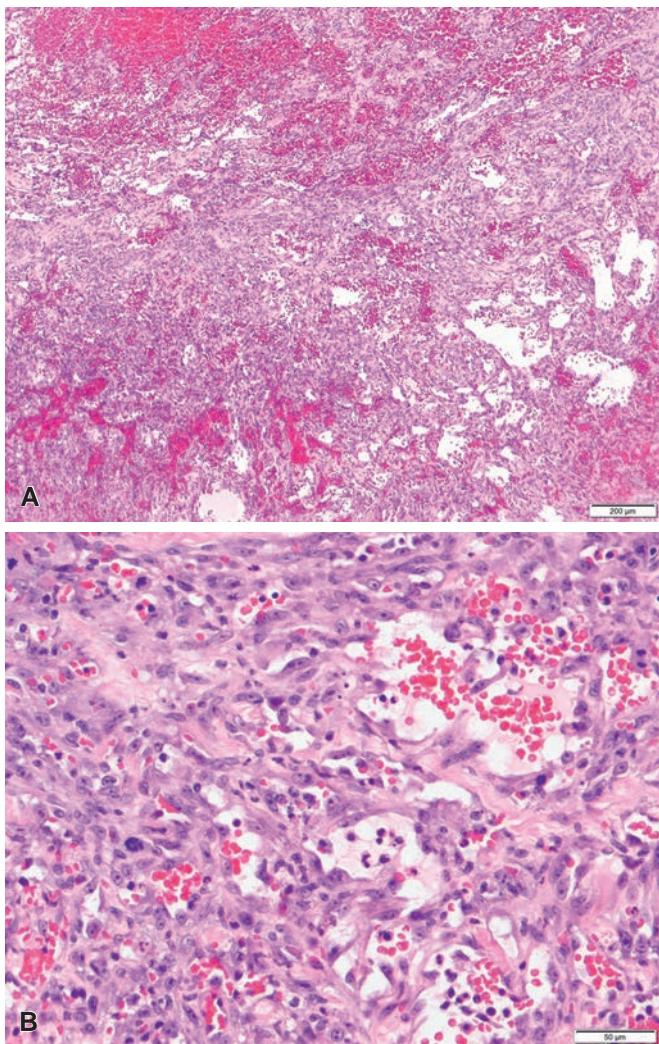


Figure 36.134 Poorly Differentiated Angiosarcoma of Breast. **A**, At low power, the interanastomosing vascular channels are apparent, as well as areas of solid growth and “blood lakes.” **B**, High power, showing the significant endothelial cell atypia and brisk mitotic activity.

hyperplasia (PASH). Immunostaining for MIB-1 (Ki-67) is said to be of utility in distinguishing the better differentiated angiosarcomas from hemangiomas.⁷⁶³

A useful immunohistochemical panel for angiosarcoma should include vascular markers, such as ERG, CD34, and CD31, as well as cytokeratins and, on occasion p63, if the differential diagnosis includes metaplastic carcinoma and/or high-grade invasive ductal carcinoma. Note that some angiosarcomas, particularly the epithelioid variant, may show aberrant cytokeratin expression.

The overall prognosis of angiosarcoma is poor, with most patients developing metastases via hematogenous dissemination.⁷⁶⁴ Donnell et al.⁷⁶⁵ demonstrated that good correlation exists between microscopic grade and outcome. In their series, the 5-year disease-free survival was 33%; 10 of their 13 patients with grade I lesions were alive and well. The relationship of grading with prognosis has been confirmed in some, but not all, series.⁷⁶⁶⁻⁷⁶⁸

Post-mastectomy; post-lymphedema lymphangiosarcoma was a rare dreadful complication developing in the soft tissues of the upper extremity as a result of longstanding lymphedema following radical mastectomy or, exceptionally, segmental mastectomy⁷⁶⁹ (Stewart-Treves syndrome). This is hardly seen now, though it has been replaced by another type of iatrogenic process, this time following radiation therapy for carcinoma of the breast, as described in the following paragraph.

Post-radiation vascular proliferations. Following the administration of radiation therapy to patients with breast carcinoma who have been treated with conservative surgery, the overlying skin can develop a variety of vascular proliferative lesions, which range from lymphangioma-like nodules to angiosarcoma,⁷⁷⁰ with intermediate forms that have been descriptively named *atypical vascular lesions*.⁷⁷¹⁻⁷⁷⁷ Atypical vascular lesions are characterized by a proliferation of vascular channels located in the dermis and arrayed in a wedge-like manner. There is little if any endothelial cell atypia and they tend to run a benign clinical course, at least on a short-term basis. Some reports indicate that these lesions may evolve into angiosarcomas.⁷⁷⁸

Recent work has demonstrated that *post-radiation angiosarcomas* frequently show *MYC* amplification which potentially could be used to distinguish these lesions from primary angiosarcomas and atypical vascular lesions, which do not demonstrate amplification of this oncogene.⁷⁷⁹⁻⁷⁸² Post-radiation angiosarcomas, too, are preferentially located in the skin rather than the breast parenchyma itself.⁷⁸³ The histologic features are as described for primary angiosarcomas, and the prognosis is poor. In contrast to angiosarcoma of the Stewart-Treves type, the interval between the radiation and the development of this tumor is short and lymphedema is minimal or absent.⁷⁸⁴

Benign vascular tumors can also develop within the breast parenchyma, contradicting the old adage that virtually all vascular tumors of the breast are malignant. Although the bland microscopic appearance of some angiosarcomas of the breast cannot be overemphasized, it is also true that a number of perfectly benign vascular tumors can occur in the breast. To begin with, hemangiomas of various types that share the features of those seen elsewhere in the body can develop in the overlying skin and subcutaneous fat. The most likely to be overdiagnosed is *angiolipoma* because sometimes it can be very cellular and the adipose tissue component can be inconspicuous.^{785,786} The presence of fibrin thrombi in the vessels and absence of breast parenchyma indicating location in the subcutaneous tissue are important diagnostic clues on core needle biopsy⁷⁸⁷; encapsulation is often subtle in these specimens.

Perilobular hemangioma is usually an incidental microscopic finding; it is characterized by dilated capillary-sized vessels in a perilobular location, without anastomoses or cellular atypia.⁷⁸⁸ Autopsy studies have shown that it is a relatively common lesion, having been found in 11% of all breasts.⁷⁸⁹ Other *hemangiomas* are not perilobular in

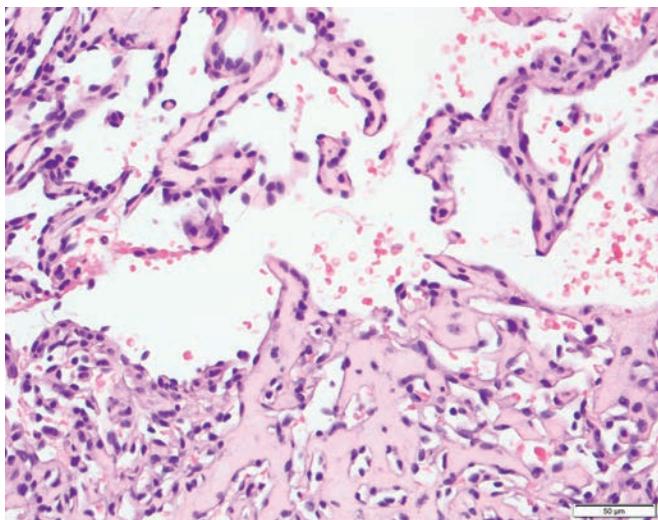


Figure 36.135 Papillary Endothelial Hyperplasia. High-power view showing a pattern of vascular anastomosis and prominent endothelial cells, which may be a mimic for low-grade angiosarcoma.

location; they also tend to be small but can reach a diameter of 2 cm.⁷⁹⁰ There are also *venous hemangiomas*.⁷⁹¹ Hemangiomas having a diffuse quality (although without anastomosing channels) have been referred to as *angiomatosis*.⁷⁹² *Epithelioid hemangioma* and *intravascular papillary endothelial hyperplasia (Masson tumor)* can also be located within the breast parenchyma (Fig. 36.135); the latter can be a mimic for low-grade angiosarcoma.

Other Malignant Stromal Tumors

Primary breast sarcoma is an extremely rare tumor. In fact, with the exception of angiosarcoma, any sarcomatous appearing tumor of the breast should be thoroughly worked up to exclude metaplastic carcinoma or the stromal component of a malignant phyllodes tumor before the diagnosis is rendered. Grossly, primary breast sarcomas appear solid, grayish white, and homogeneous. Necrosis may be present. Microscopically, most of them have the features of fibrosarcoma; focal osseous metaplasia can occur. Infiltrative margins and severe atypia indicate a greater tendency for local recurrence and distant metastases.⁷⁹³ Many of these sarcomas do not match precisely the appearance of those arising in the usual soft tissue locations, probably owing to the fact that they are composed of a specialized type of stroma. Reported cases of CD10-positive mammary sarcomas are examples of this phenomenon.⁷⁹⁴ Having said that, it ought to be acknowledged that tumors with an appearance equivalent to that of various types of sarcomas of somatic soft tissues do exist.⁷⁹⁵ They include but are not limited to *liposarcoma*, *leiomyosarcoma*, *rhabdomyosarcoma* (though most such tumors are metastatic), *fibrosarcoma*, *chondrosarcoma*, and *osteosarcoma*.

Lymphoid Tumors and Tumorlike Conditions

Malignant lymphoma can present as a primary mammary neoplasm or involve the breast as part of a systemic process.⁷⁹⁶ Lymphoma can also occur in association with breast implants (see below).^{692,693} Grossly, lymphoma of the breast is fleshy and tan-white in color. It is not accompanied by skin retraction or nipple discharge. Multiple nodules are sometimes encountered. The involvement is bilateral in 10% of patients. In adult patients, primary lymphomas of the breast

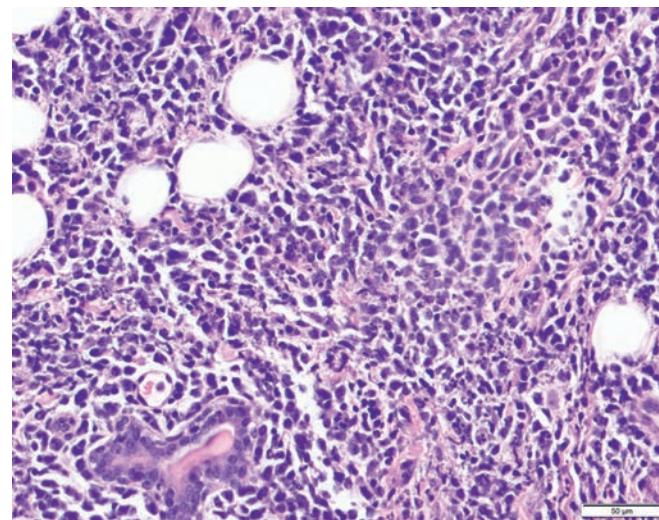


Figure 36.136 Diffuse Large B-cell Lymphoma of Breast. The breast parenchyma is infiltrated by a population of abnormal lymphoid cells which are medium and large in size, with irregular nuclear contours. Numerous apoptotic cells are seen.

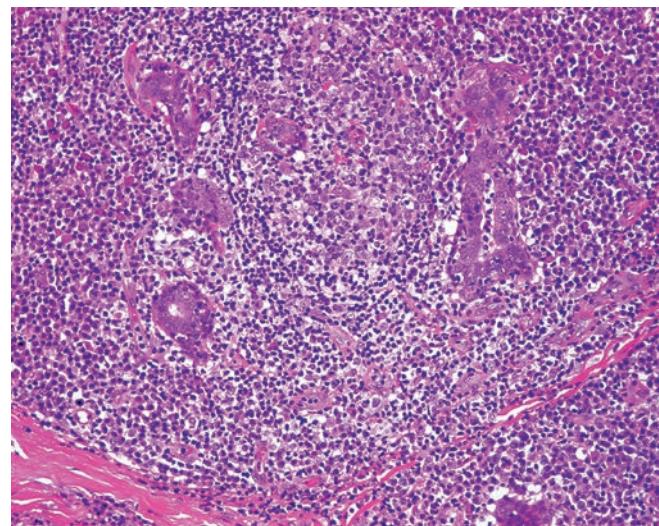


Figure 36.137 Extranodal Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT Lymphoma) of Breast. Some of the neoplastic lymphocytes infiltrate the glandular structures.

are nearly always of non-Hodgkin type and are usually composed of B cells,⁷⁹⁶ although examples of T-cell lymphoma are also on record.^{797,798} The B-cell lymphomas can be composed of either large or small cells^{799,800} and usually show a nongerminat center phenotype.⁸⁰¹ Most primary breast lymphomas are of the diffuse large B-cell type (Fig. 36.136); other types include extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) and follicular lymphoma (Fig. 36.137).⁷⁹⁶ Rare types of lymphoma include Burkitt lymphoma, lymphoblastic lymphoma, and implant-associated anaplastic large cell lymphoma (see later). Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) shows the typical tendency to surround and invade the wall and lumina of the epithelial structures, resulting in the so-called "lymphoepithelial lesion." Immunohistochemical studies demonstrate the characteristic profile of the lymphoma as found at other sites.⁸⁰⁰ Be aware that the targetoid pattern sometimes seen around the ducts in extranodal

marginal zone lymphoma of mucosa-associated lymphoid tissue may simulate the appearance of invasive lobular carcinoma; in such cases, stains for CD45, CD20, and cytokeratin should solve the diagnostic dilemma. The survival of patients with breast lymphoma is related to stage and microscopic type.^{796,799}

“*Pseudolymphoma*” has been described in the breast. As in other organs, its position in relation to extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue has become fuzzy. Some cases seem clearly reactive on morphologic and immunohistochemical grounds, perhaps representing an exuberant local reaction to injury.^{802–804} Some cases may represent part of the spectrum of IgG4-related disease.^{53,54} Other cases, instead, are composed of a monotonous small lymphocytic population and not easily separable from low-grade lymphomas. In some instances, the noncommittal diagnosis of *small lymphocytic proliferation* may be the best approach, followed by a recommendation for no further therapy if no systemic evidence of lymphoma is encountered. As far as the term *pseudolymphoma* is concerned, it is probably better to avoid it altogether.

Involvement of the breast by **Burkitt lymphoma** in African children has resulted in the formation of huge bilateral masses. Bilateral Burkitt-type lymphoma has also been seen in young women during pregnancy.⁸⁰⁵

Hodgkin lymphoma primary in the breast is exceptional. Most cases of Hodgkin lymphoma involving the breast represent secondary involvement in stage IV disease.

Plasmacytoma has been seen presenting as a primary breast mass, sometimes associated with a serum monoclonal protein.⁸⁰⁶

Intravascular lymphoma can involve the breast and bear an uncanny resemblance to high-grade DCIS, as Dr. Rosai admitted learning the hard way at a seminar in which he participated many years ago.^{807,808}

Anaplastic large cell lymphoma can also involve the breast.⁸⁰⁹ Notably, the majority of the reported cases have developed around a breast prosthesis (“implant-associated”). **Implant-associated anaplastic large cell lymphoma** is a recently reported distinct entity, very different from systemic ALK-negative anaplastic large cell lymphoma. There appears to be no relation to the indication for the implant, or the duration since the implant was placed; recent data indicate a significant association with textured implants. Limited data indicate a relatively indolent course, managed with implant removal and observation, unless associated with a mass-forming lesion, in which case a more aggressive course may ensue.^{692,693,809}

Myelocytic leukemia of either acute or chronic type can present as a localized mass (granulocytic or myeloid sarcoma) in the breast and be microscopically confused with large cell lymphoma (Fig. 36.138).⁸¹⁰ The most important clue to the diagnosis in H&E sections is the presence of eosinophilic myelocytes and metamyelocytes, identified by their round or slightly indented nucleus and bright eosinophilic cytoplasmic granules. The diagnosis can be confirmed with immunostains for myeloperoxidase or CD117.⁸¹¹

Extramedullary hematopoiesis can exceptionally present in the form of a mass lesion in the breast in patients with idiopathic myelofibrosis or following neoadjuvant chemotherapy.^{812,813}

Other Primary Tumors and Tumorlike Conditions

Basal cell carcinomas, **squamous cell carcinomas**, **keratinous cysts**, and **sweat gland tumors** may arise in the skin of the nipple or other sites in the breast, but they are not considered primary breast tumors.

Mammary hamartoma is defined as combination of ducts, lobules, collagenous stroma, and adipose tissue present as a relatively circumscribed lesion. Its identification is said to depend on the

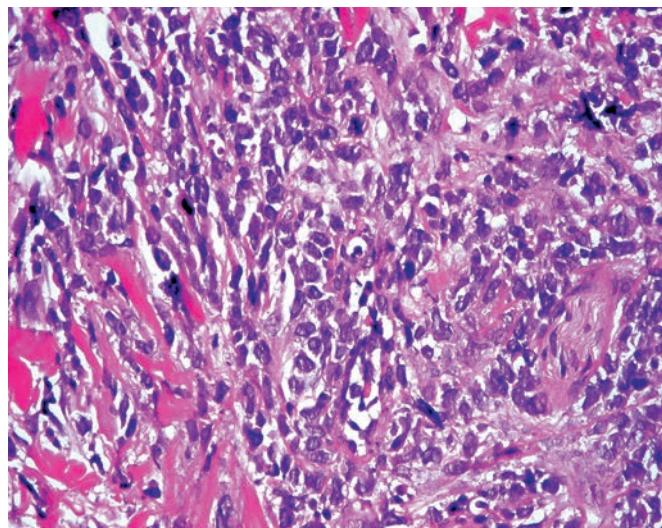


Figure 36.138 Granulocytic Sarcoma of Breast. It is easy to misdiagnose this lesion as a large cell lymphoma.



Figure 36.139 Gross Appearance of So-Called Hamartoma. There is a combination of cystic dilation of ducts, fibrosis, and entrapment of adipose tissue. This lesion is more distinctive and impressive grossly than microscopically.

combination of clinical, radiologic, and pathologic criteria.^{814,815} Morphologically, lesions that have been thought to be hamartomas on mammography may exhibit a wide diversity of appearances, the common denominator, by definition, being the admixture of epithelial and stromal elements, the latter including fat (Figs. 36.139 and 36.140).^{816–818} A reproducible immunohistochemical profile has not been reported.⁸¹⁹ *Myoid hamartoma*^{817,820} (which can contain epithelioid smooth muscle cells⁸²¹) and *chondrolipoma* (a benign lesion composed of an admixture of fat, cartilage, and sometimes bone) are two other processes straddling the fence between malformation and benign neoplasia.

Granular cell tumor is important because of its ability to simulate grossly the appearance of invasive carcinoma.^{822–824} It is usually small, but it may reach a size of 10 cm or more. On cut section, it is firm, homogeneous, and white or grayish yellow. As a rule, it is not attached to the overlying skin, but it may be fixed to the underlying fascia. The behavior is benign, and the treatment is local excision.^{822,825}

Myofibroblastoma is a benign mesenchymal tumor originally described in the male breast but also occurring in the female organ.^{826,827} Grossly, it is well circumscribed and usually small,

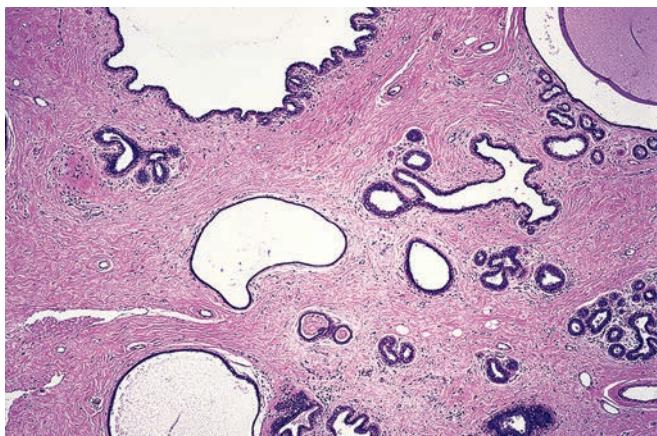


Figure 36.140 Glandular epithelium and fibrous stroma with distorted arrangement in hamartoma of breast.

although on occasion it can reach a large size. Microscopically, uniform, bland-looking spindle cells are arranged in short fascicles separated by broad bands of hyalinized collagen (Fig. 36.141).^{826–828} Focally, there may be smooth muscle, cartilaginous, or adipose metaplasia. The appearance is very reminiscent of both solitary fibrous tumor and spindle cell lipoma, the suggestion having been made that there is a close histogenetic link between these neoplasms.^{828–830} This hypothesis is further supported by the finding of genetic rearrangement or deletion of 13q14 and loss of Rb expression by immunohistochemistry in this group of lesions.^{828,831,832} Immunoreactivity for desmin and CD34 is reported in the majority of cases.⁸²⁸ ER and bcl-2 are also strongly expressed.⁸²⁶

There are several variants described, for example, *epithelioid* and the *deciduoid* myofibroblastoma. The former may be a mimic for invasive lobular carcinoma, particularly on core needle biopsy; an error that may be compounded by ER expression of the lesional cells.

Solitary fibrous tumor has been reported in the breast. Its morphologic and immunohistochemical features are the same as those reported for solitary fibrous tumor occurring at other sites and blend with those of spindle cell lipoma and myofibroblastoma.⁸³³ Immunoreactivity for CD34, bcl-2, and especially STAT6 are helpful in confirming the diagnosis.⁸³³

Leiomyoma usually involves the nipple and is often painful⁸³⁴; occasionally, it is seen within the breast substance.⁸³⁵ Some have been reported as having epithelioid features and granular changes.⁸³⁶

Benign peripheral nerve tumors of both *schwannoma* and *perineurioma* types have been described. *Traumatic neuromas* with *granular cell changes* have been observed in mastectomy scars.⁸³⁷

Perivascular epithelioid cell neoplasm (PEComa; clear cell ["sugar"] tumor) has been reported in the breast.⁸³⁸ This a neoplasm characterized by HMB45-positive epithelioid smooth muscle cells.

Nodular fasciitis is rarely seen within the breast, its appearance and behavior being similar to those of its more common soft tissue counterpart. It should be included in the differential diagnostic consideration of spindle cell lesions of the breast.

Fibromatosis (extra-abdominal desmoid tumor) can also be found within the substance of the breast (Fig. 36.142). Morphologically it is composed of long, sweeping fascicles of bland spindle cells that entrap the native ducts and lobules. Lymphoid infiltrates are commonly seen at the periphery of the lesion (Fig. 36.143). It shares with its homologue in the somatic soft tissue a tendency for infiltration, local aggressiveness, and local recurrence.⁸³⁹ This is also true at the molecular level, in that they have a similar spectrum of

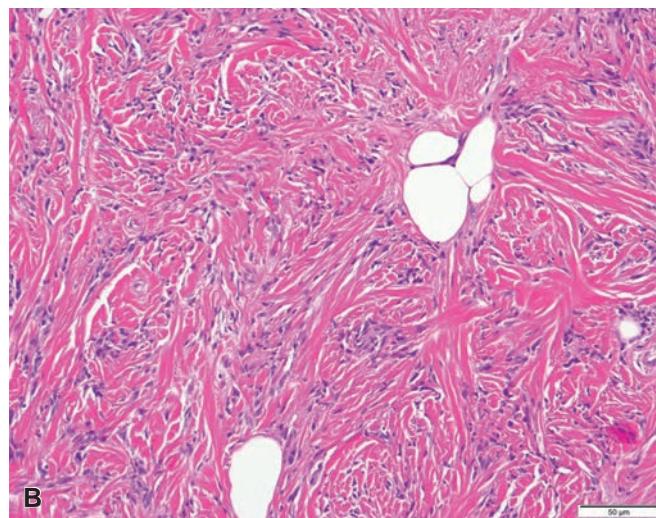
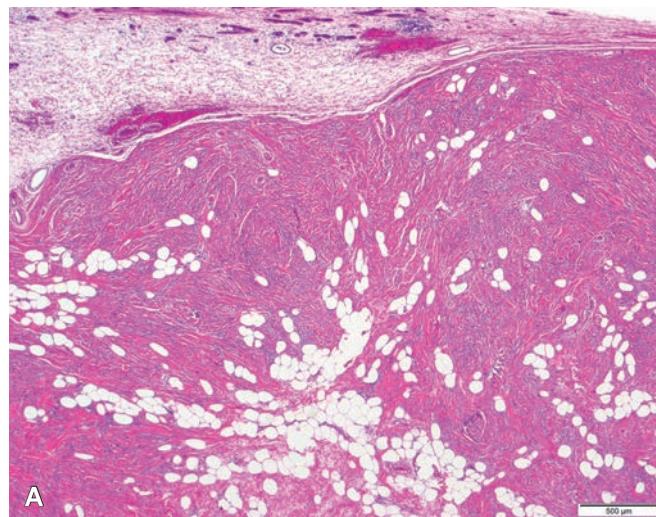


Figure 36.141 Myofibroblastoma. **A**, At low power, the well-circumscribed margin of this bland spindle cell tumor is appreciated. **B**, At high power, the spindle cells are bland, arranged in short fascicles separated by broad bands of collagen.

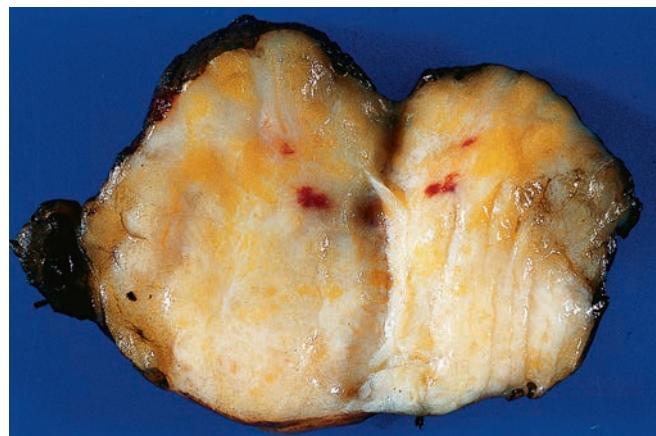


Figure 36.142 Gross appearance of fibromatosis involving breast. The mass is solid and ill defined.

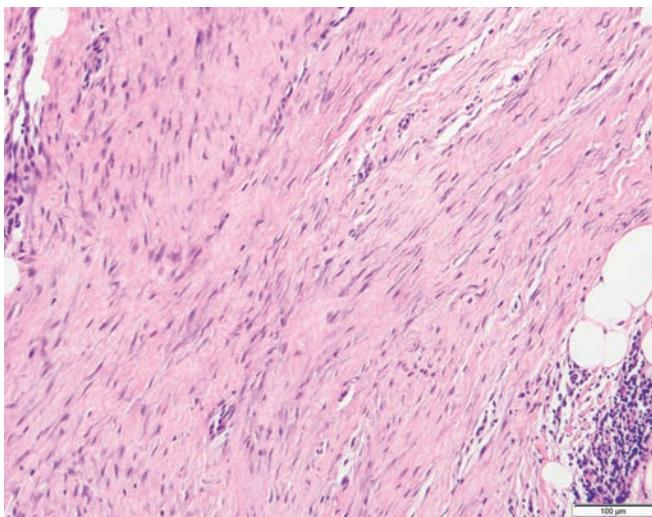


Figure 36.143 Fibromatosis. The lesion is composed of long, sweeping fascicles of bland spindle cells that entrap the native ducts and lobules. Lymphoid infiltrates are commonly seen at the periphery of the lesion.

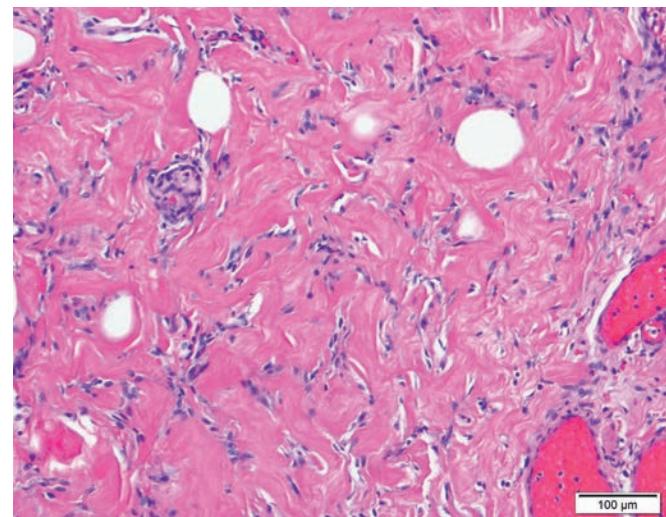


Figure 36.144 Pseudoangiomatous Stromal Hyperplasia. Thin channels lined by spindle cells are seen scattered within a hyalinized stroma.

CTNNB1 (β -catenin) and *APC* gene alterations.⁸⁴⁰ Reports of mammary fibromatosis occurring in or around the capsule of a grossly intact implant have not been able to establish a significant pathogenetic relationship.⁸⁴¹

Cases of mammary fibromatosis occurring during childbearing age are, in general, more cellular than those seen after menopause,⁸⁴² being infiltrative, aggressive, and prone to local recurrence.⁸³⁹ Fibromatosis should be distinguished from low-grade fibromatosis-like metaplastic carcinoma and scarring secondary to (surgical) trauma. Nuclear staining with β -catenin may be useful in confirming the diagnosis of fibromatosis, though it should be noted that this is not specific for the lesion as phyllodes tumor and metaplastic carcinoma may also stain with β -catenin.

Pseudoangiomatous stromal hyperplasia (PASH) is characterized by a proliferation of stromal spindle cells of fibroblastic/myofibroblastic nature associated with the formation of clefts that simulate vascular channels (Fig. 36.144).^{843,844} It is a common finding identified in nearly one-third of breast biopsies. PASH may present as a mass on mammographic and ultrasound studies; on MRI it is more likely to present as an area of non-mass-like enhancement. It is prudent to rule out other possible pathologies before diagnosing PASH as the imaging correlate for a targeted mass. Occasionally, the myofibroblasts may aggregate into fascicles; this appearance has been referred to as fascicular PASH. The spindle cells are immunoreactive for vimentin and CD34 and negative for vascular markers, such as ERG and CD31. In addition, they show intense positivity for PR. The latter finding suggests that PASH represents a localized form of stromal overgrowth with a hormonal (primarily progestogenic) pathogenesis.⁸⁴⁵

Multinucleated giant cells of reactive appearance are sometimes found incidentally in the normal mammary stroma or in the stroma of fibroadenomas^{150,846}; they are of no clinical significance and are probably analogous to those seen in non-neoplastic polypoid stromal lesions located beneath mucosal membranes, such as the nasal cavity, oral cavity, anus, and lower female genital tract (Fig. 36.145).⁸⁴⁶ Recognition of these cells for what they are and not mistaking them for a malignant process is the reason for mentioning them here.

Inflammatory myofibroblastic tumor may involve the breast, its microscopic features being analogous to those seen in other, more common sites.^{847,848}

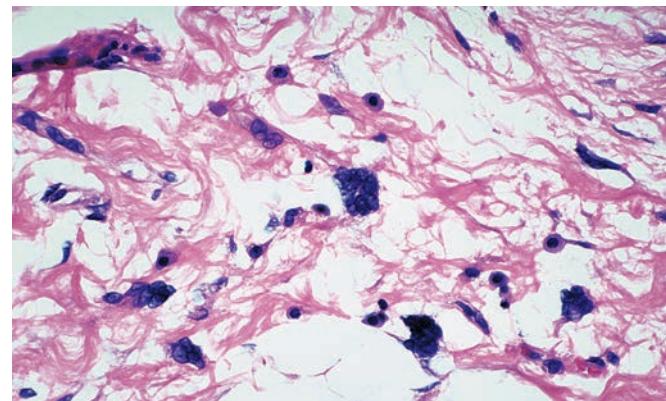


Figure 36.145 Bizarre Multinucleated Cells in Mammary Stroma. This non-neoplastic change is analogous to that more often seen in the stroma of the upper aerodigestive tract and in the genital tract.

Amyloidosis can appear as a solitary nodule within the breast parenchyma (so-called amyloid tumor).^{849,850}

Rosai–Dorfman disease and **Erdheim–Chester disease** can also present under exceptional circumstances as breast masses, the former either as an isolated event or as a component of systemic disease.^{851,852}

Juvenile xanthogranuloma can affect the breast of children and, exceptionally, of adult patients.⁸⁵³

Nodular mucinosis presents as a circumscribed area of myxoid stromal change near the nipple.⁸⁵⁴ It should be distinguished from mucinous carcinoma and mucocle-like lesion.

Metastatic Tumors

Metastatic malignant tumors rarely affect the breast except when widely disseminated.⁸⁵⁵ They typically appear as superficial, well-defined multinodular masses. Malignant melanoma and carcinoma of the lung, ovary, kidney, and stomach are the most common sources.^{856,857} Most of the lung tumors are of the small cell neuroendocrine type. Breast metastases have also been documented from better differentiated neuroendocrine tumors, such as from the bronchus or small bowel, pancreatic (neuro)endocrine tumor, thyroid

medullary carcinoma, and even carcinoid tumor arising from a tailgut cyst.⁸⁵⁸⁻⁸⁶²

One should not forget in this listing the metastases from contralateral breast carcinoma, which is not an infrequent finding in autopsy series.⁸⁵⁵ Azzopardi has made the interesting observation that the presence of elastosis has not been documented in association with metastatic disease of the breast.²²

Metastatic carcinomas to the breast can simulate primary malignant tumors of this organ; exceptionally, they greatly mimic the appearance of DCIS.⁸⁶³ In an era of increasing use of neoadjuvant chemotherapy, it is important to consider metastasis when encountering a tumor of the breast with unusual morphology, extensive lymphovascular invasion in the presence of a small "invasive" component, an absence of an *in situ* component and/or a triple negative immunophenotype. If doubt exists as to whether the tumor represents a breast primary, a panel of breast markers (GCDFP-15, mammaglobin, GATA3) may be appropriate. Of course, eliciting a history of prior malignancy at another site and comparing the morphology may be the most helpful tool.

In children, the most common malignant tumor to metastasize to the breast (hematolymphoid malignancies excluded) is rhabdomyosarcoma, particularly of the alveolar type.⁸⁶⁴⁻⁸⁶⁶

Breast Diseases in Children and Adolescents

The most common breast "mass" for which clinical consultation is sought in this age group is actually not a pathologic condition at all but rather precocious, sometimes predominantly unilateral, breast development.⁸⁶⁷ Should such a "mass" be inadvertently removed, no development of the breast will occur.

Fibroadenoma is the most common pathologic condition of the breast between puberty and 20 years of age but is exceptional before puberty.⁸⁶⁷

Virginal hypertrophy (gigantomastia; macromastia) may result in massive unilateral or bilateral enlargement.⁸⁶⁷ Microscopically, it is characterized by a combined proliferation of ducts and stroma with little, if any, lobular participation (Fig. 36.146).⁸⁶⁶

Pseudoangiomatous stromal hyperplasia is generally a disorder of adult life, but cases have been documented in adolescents and children (including a 3-year-old boy).⁸⁶⁸

So called fibrocystic change is practically never seen in this age group. However, highly proliferative epithelial lesions can develop, such as papillomas and usual duct hyperplasia, similar to those seen

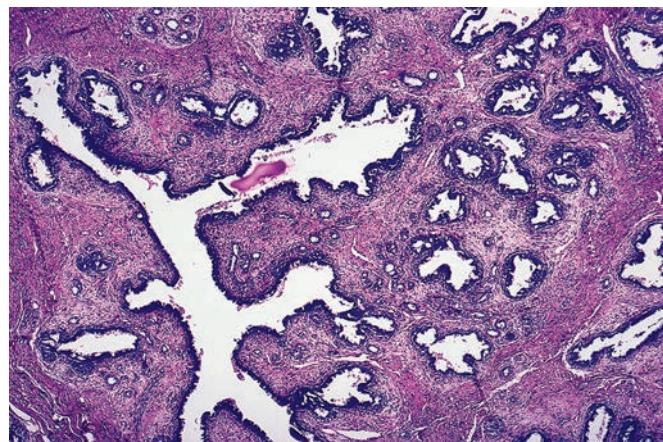


Figure 36.146 So-called "virginal hypertrophy" of breast, showing proliferative changes in epithelium and stroma.

in the adult breast, with or without associated sclerosis and ductular distortion.⁸⁶⁹ Wilson et al.⁸⁷⁰ studied 74 patients with a process they termed *papillary duct hyperplasia*, which they distinguish from the juvenile papillomatosis described later. They found that 28% of the patients had a family history of breast carcinoma but that none of the patients had developed carcinoma at the time of the last follow-up.

Juvenile papillomatosis ("Swiss cheese" disease) is usually seen in young individuals (average age 19 years) but occurring in a wide age range (10–44 years). Clinically, the localized, multinodular masses simulate the appearance of fibroadenoma. Grossly, the clustering of cysts results in a cut surface appearance reminiscent of Swiss cheese—hence the alternative designation for this entity (Fig. 36.147). Microscopically, there is florid epithelial hyperplasia (sometimes with atypia and/or focal necrosis), cysts with or without apocrine metaplasia, duct stasis, and sclerosing adenosis (Fig. 36.148).^{871,872} A family history of breast carcinoma is reported in 58% of cases, and 10% of the patients subsequently develop breast carcinoma.^{872,873}



Figure 36.147 Juvenile Papillomatosis (Swiss Cheese Disease). The gross appearance is that of clustered cystic formations.

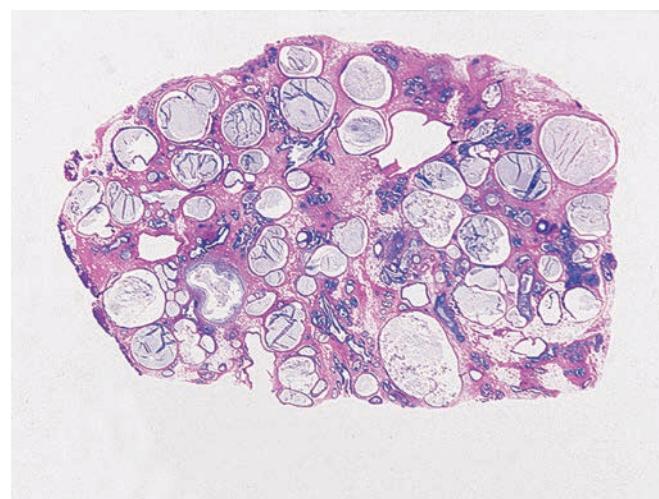


Figure 36.148 Juvenile Papillomatosis (Swiss Cheese Disease). Whole-mount view showing variously sized cystic formations, alternating with solid epithelial proliferations.

Carcinoma of the pre-pubertal breast is very rare; most cases are of the so-called secretory type (see earlier description). A few tumors have the appearance of ordinary invasive ductal carcinomas.

In the presence of a high-grade malignant round cell tumor of the breast in a child or adolescent, the possibility should be considered that it may be a solid variant of alveolar rhabdomyosarcoma, whether primary or metastatic.¹⁵⁶

Breast Diseases in Males

Gynecomastia

Gynecomastia is defined as the enlargement of the male breast resulting from hypertrophy and hyperplasia of both glandular and stromal components. It may result from numerous causes, which share a background of relative increase in estrogenic activity (whether endogenous or exogenous), decrease in androgenic activity, or both.^{874,875} Development of gynecomastia before 25 years of age is usually related to hormonal pubertal changes, whereas development in later years may be caused by hormonally active tumors (Leydig cell tumor of testis, hCG-secreting germ cell tumors, lung carcinoma, or others), cirrhosis, or medications (digitalis, reserpine, phenytoin, and others).⁸⁷⁶ Cases have also been reported in type 1 neurofibromatosis.⁸⁷⁷ Clinical gynecomastia developing in diabetic patients may have the features of diabetic or lymphocytic mastopathy, as seen in females.⁸⁷⁸ Many cases are idiopathic.

Clinically, gynecomastia is usually centered behind the nipple, an important point in the differential diagnosis with carcinoma, which tends to be located eccentrically.⁸⁷⁴ It may be unilateral (at least at the clinical level, the left breast being more commonly involved than the right) or bilateral. Pubertal and hormone-induced gynecomastias tend to be bilateral, whereas idiopathic and nonhormonal drug-induced gynecomastias are usually unilateral.

On ultrasound examination, gynecomastia may appear as a hypoechoic or hyperechoic mass or be of mixed echogenicity.⁸⁷⁹ Mammographic examination reveals a round, retroareolar density with stranded extensions into the deeper adipose tissue.⁸⁷⁹ The gross appearance is characteristic. The mass is oval, disk shaped, of elastic consistency, and with well-circumscribed borders. Microscopically, the ducts show a variable and sometimes very prominent degree of epithelial hyperplasia and are surrounded by a prominent edematous

stroma, which results in a typical "halo" effect (Fig. 36.149). This stroma contains large amounts of acid mucopolysaccharides (mainly hyaluronic acid) of a type similar to that seen in fibroadenoma of the female breast.⁸⁸⁰ The immunophenotype parallels that of normal breast stroma.⁸⁸¹ There may be PASH and focal squamous metaplasia; formation of lobules may be observed.^{874,882} Exceptionally, a population of clear or globoid cells immunoreactive for GCDFP-15 may be present within the ducts.⁸⁸³

The microscopic changes are related to the duration of the gynecomastia. Cases of short duration tend to have a prominent hyperplastic epithelial component, often with micropapillary ("gynecomastoid") architecture, and stromal edema, whereas those of long duration have prominent stromal fibrosis.⁸⁸⁴ Occasionally ADH may be present; however, the clinical significance of the diagnosis in this setting is unknown.⁸⁸⁵ The possible relationship between gynecomastia and carcinoma is discussed later. Changes morphologically similar to those of gynecomastia can be seen in the female breast ("gynecomastoid hyperplasia").

Myofibroblastoma

Myofibroblastoma is the term used for a benign stromal neoplasm composed of myofibroblasts and collagen first described by Toker et al.⁸⁸⁶ Originally thought to involve primarily the male breast, it is now known to occur in the female breast with a higher frequency.⁸⁸⁷

Carcinoma

In the United States, only 1% of all breast carcinomas occur in males, but in some Arab countries the incidence rises to nearly 10%.⁸⁸⁸⁻⁸⁹¹ An increased incidence of breast carcinoma is seen in patients with Klinefelter syndrome.⁸⁹² Familial cases have also been recorded, particularly among *BRCA2* mutation carriers.^{893,894} Cases of primary breast carcinoma have occurred in patients with prostatic carcinoma treated with estrogens.^{875,895} A definitive relationship between gynecomastia and breast carcinoma has not been demonstrated.

Clinically, most breast carcinomas present in elderly men as breast masses, with or without associated nipple abnormalities.⁸⁹⁶ Nipple discharge in an adult male, especially if bloody, should arouse a strong suspicion of carcinoma. Skin involvement by direct extension and Paget disease are much more common in males.

Imaging studies demonstrate findings as described earlier for the radiographic identification of breast cancer in female patients; namely a spiculated mass on mammography and a hypoechoic mass, taller-than-wide, with posterior shadowing on ultrasound examination.⁸⁷⁹ Similarly, grossly, microscopically, and immunohistochemically, carcinomas of the male breast are like those seen in females. As such, they can be *in situ* or invasive, low grade, or high grade. All of the microscopic types and molecular subtypes identified in the female breast have been encountered in males. The incidence of papillary carcinoma is higher than in females.^{889,897} The least common of the major categories is invasive lobular carcinoma, only a few cases having been described.^{897,898}

Breast carcinoma is diagnosed on core needle biopsy in most patients, with the most important differential diagnosis for a breast mass in a male patient being gynecomastia. The incidence of positivity for ER is higher than in females.⁸⁹⁹

The overall survival rate is lower than for breast carcinoma occurring in females but, as is often the case, the differences tend to disappear when the tumors are compared stage by stage.^{888,889} Indeed, the prognosis of breast cancer in males, like that in females, is heavily influenced by clinical stage, histologic grade, and receptor status. It also correlates with mitotic activity, DNA ploidy, and p53 status.^{900,901}

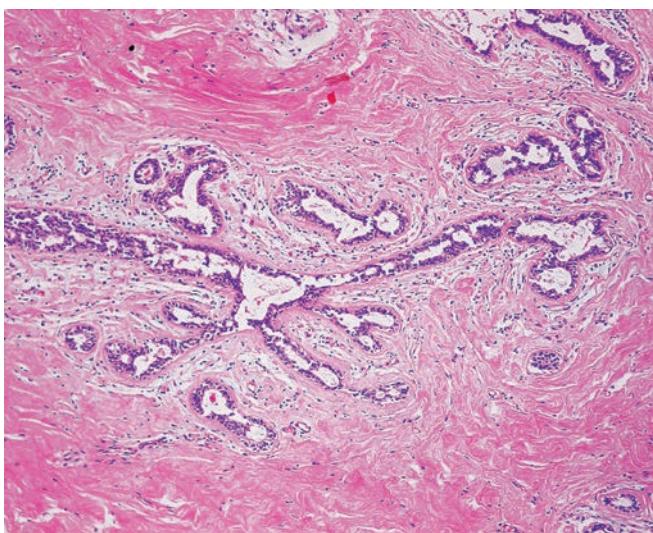


Figure 36.149 Epithelial proliferation surrounded by a hypocellular myxoid halo in gynecomastia.

Other Lesions

Mammary duct ectasia and sclerosing adenosis can occur in the male breast. Fibroadenoma (sometimes bilateral), phyllodes tumor, PASH, and nodular fasciitis have also been reported.^{902,903} **Nipple adenoma and intraductal papilloma** have been seen on several occasions. There are also reports of leiomyoma and leiomyosarcoma of the nipple⁹⁰⁴ and **neurofibromatosis** in a child whose condition simulated gynecomastia.⁹⁰⁵

Metastatic carcinoma to the male breast commonly originates from the prostate, is often bilateral, and is almost always seen following estrogen therapy.⁸⁹⁵ As such, it occurs against a background

of gynecomastia. Some of these cases have been confused with primary breast carcinoma. Immunohistochemical stains for PSA and prostatic acid phosphatase are helpful in the differential diagnosis. The matter is complicated by the fact that the normal mammary duct epithelium of males and the hyperplastic epithelium of gynecomastia are often immunoreactive for PSA (but not for prostatic acid phosphatase). Male breast carcinoma is typically negative for both markers; though PSA positivity has been reported in an FNA specimen from a primary breast carcinoma.^{906,907}

The most common type of nonepithelial tumor to metastasize to the male breast is malignant melanoma.⁸⁹⁷

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Normal Anatomy

The lymph node is one of the major anatomic components of the immune system.^{1,2}

The three major regions of a lymph node are the *cortex*, *paracortex*, and *medulla* (Fig. 37.1A). The cortex is situated beneath the capsule and represents the compartment where most lymphoid follicles reside and is composed of primarily B lymphocytes and follicular dendritic cells. The medulla, close to the hilum, grows in the form of cords. It is rich in lymph sinuses, arteries, and veins but contains only a minor lymphocytic component that is a mix of B and T lymphocytes. The appearance of the follicles varies according to

their state of activity. Primary follicles appear as round aggregates of small lymphocytes with little cytoplasm; secondary follicles appear following antigenic stimulation and are characterized by the presence of germinal centers surrounded by mantle zones.³ The germinal center cells are predominantly B lymphocytes known as follicular center cells (centroblasts and centrocytes or small and large cleaved and noncleaved cells), macrophages, and follicular dendritic cells, but a population of T follicular-helper cells also reside normally in this compartment. The germinal center contains pale-staining large cells on hematoxylin and eosin (H&E) sections that are normally highly proliferative and shows polarization toward the side of antigen stimulation. The surrounding mantle zone B lymphocytes are small

Abstract

The disorders that may present in lymph nodes are diverse and include infectious diseases, neoplasms, and reactive responses to injury elsewhere. This chapter reviews the histologic patterns of various reactive conditions that involve lymph nodes, as well as the hematologic neoplasms that may primarily involve lymph nodes. The approach to the immunophenotypic evaluation as well as the role of molecular genetic studies, particularly in the hematopoietic neoplasms, are reviewed. In addition, unusual inclusions and disorders that may mimic malignancy in lymph nodes are discussed.

Keywords

Malignant lymphoma,
Hodgkin lymphoma,
Reactive follicular hyperplasia

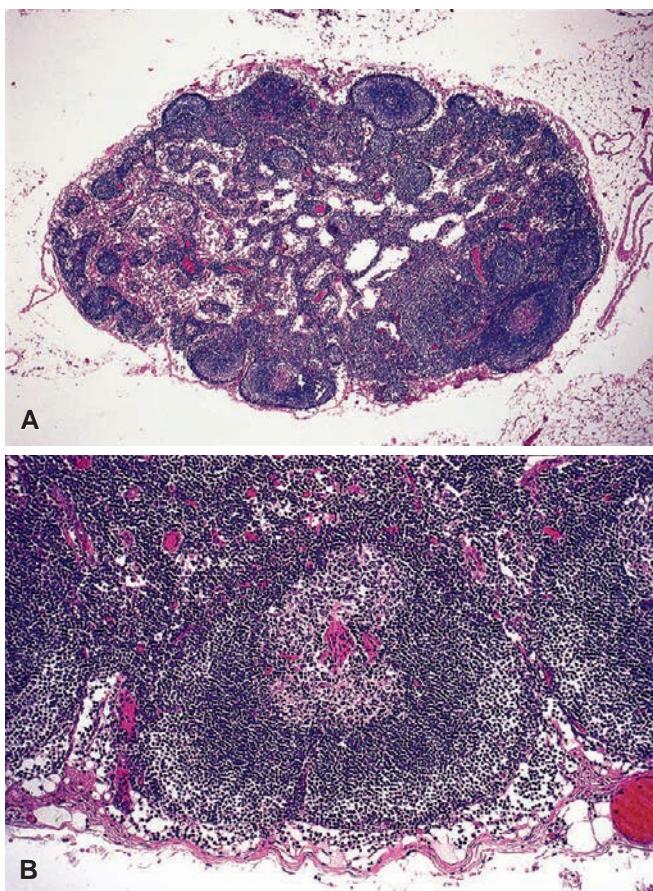


Figure 37.1 Normal Lymph Node. **A**, The morphologic differences among the various nodal compartments are particularly evident in mesenteric lymph nodes, of which this is an example. **B**, Secondary lymphoid follicle with obvious polarity of the germinal center.

and stain dark blue and contain little cytoplasm (see Fig. 37.1B).¹ Proliferated germinal centers are always indicative of humoral antibody production. Under conditions of intense antigenic stimulation, they also can appear within the medullary cords.⁴

The paracortex is the zone situated between the cortex and the medulla, which contains the mobile pool of T lymphocytes responsible for cell-mediated immune responses.¹ A characteristic feature is the presence of postcapillary venules, which are identifiable by their lining of high endothelial cells and the presence of lymphocytes migrating through their cytoplasm. Another cell type present in the paracortex is the interdigitating dendritic cell, a member of the accessory immune system. Expansion of the paracortex is indicative of a cell-mediated immunologic reaction. The number of lymphocytes within the lumen and wall of postcapillary venules gives a rough indication of the degree of lymphocyte recirculation.⁵

Afferent lymph vessels penetrate the nodal capsule to open into the marginal sinus; this communicates with an intricate intranodal sinus network that merges into efferent lymph vessels exiting the node at the hilum. The endothelial lining of the outer (subcapsular) side of the marginal sinus is nonphagocytic and similar to that of the afferent and efferent vessels; the lining of the intranodal sinuses has strong phagocytic properties. The main arteries and veins pass through the hilum and radiate to the medulla, paracortex, and inner part of the cortex; other blood vessels penetrate the capsule to supply the superficial cortex and a small area surrounding the trabeculae.

The morphologic and phenotypic features of the various populations of lymphoid cells and cells of the accessory immune system

are discussed in the next sections and in connection with the respective proliferative pathologic changes affecting these populations.

Lymph Node Evaluation

The proper examination of a lymph node is a complicated task that may require the performance of a variety of specialized procedures depending on the nature of the case.

Biopsy

Selection of the lymph node to be biopsied is of great importance. In cases of generalized lymphadenopathy, inguinal nodes are to be avoided whenever possible because of a high frequency of nonspecific chronic inflammatory and fibrotic changes. Axillary or cervical nodes are more likely to be informative. Whenever possible, the largest lymph node in the region should be excised. Small superficial nodes may show only nonspecific hyperplasia, whereas a deeper node of the same group may show diagnostic features.

The surgeon biopsying intra-abdominal nodes or large cervical or axillary masses should have a frozen section or touch preparations performed to be certain that the tissue is representative—not necessarily to obtain a specific diagnosis at this point. This may save a second biopsy.

Adherence to a strict technique for the preparation of lymph nodes in the pathology laboratory is of paramount importance (see later).⁶ The specimen should be received fresh in the laboratory immediately after excision, bisected as soon as it is received, and sampled for the appropriate studies. The portion to be embedded in paraffin (which should not exceed 3 mm in thickness) can be placed in 10% buffered formalin and/or a mercury-containing fixative such as B5. As a routine procedure, initial examination of a preparation stained with H&E is perfectly adequate, followed by whatever additional stains and special techniques the nature of the case may require (which may range from very many to none).

A technique that complements the study of tissue sections and that is too often neglected is the examination of touch preparations from the cut surface of the fresh lymph node stained with Giemsa or Wright solution. This is particularly useful in the evaluation of lymphoma and leukemia, and in the initial triage of the specimen (such as sending tissue for culture if granulomas are seen). For instance, granulocytic leukemia can closely simulate large cell lymphoma in a hematoxylin–eosin-stained section, but an imprint may readily distinguish the two conditions.

Needle Biopsy

Core needle biopsy is adequate for the diagnosis of metastatic carcinoma. Although not preferred for the evaluation of primary lymphoid disorders, core biopsies are increasingly used nowadays, putting pressure on the pathologist to render a diagnosis based on limited amounts of tissue. Compression artifact is very common in core biopsies, with the cells appearing smaller and the nuclei appearing darker compared with those seen in excisional biopsies. Very often, flow cytometry immunophenotyping and more extensive immunohistochemical evaluation are required to maximize the information obtainable from the biopsies.

Fine-needle aspiration of lymph nodes is particularly useful for the documentation of metastatic carcinoma (Fig. 37.2). It is used most often in cervical lymph nodes⁷ but also in other locations, including intra-abdominal and retroperitoneal regions.⁸ The cytologic diagnosis of malignant lymphoma can be made in 50%–75% of the cases, the accuracy being greatest in the high-grade lesions (see Fig. 37.2).⁹ A primary diagnosis of malignant lymphoma based on

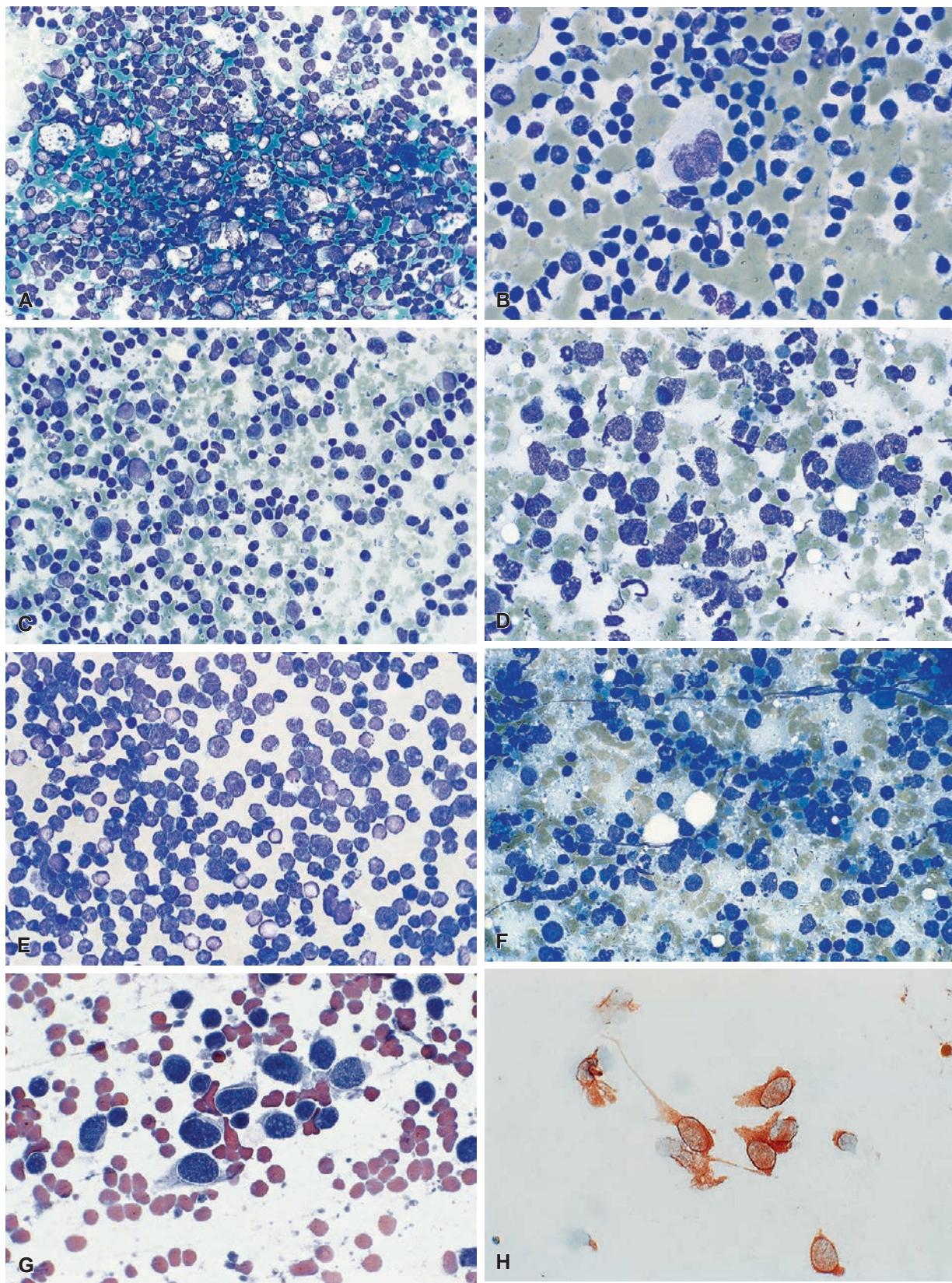


Figure 37.2 Appearance of Various Lymph Node Diseases as Seen in Fine Needle Aspiration Specimens. **A**, follicular hyperplasia; **B**, Hodgkin lymphoma (Reed-Sternberg cell); **C**, small lymphocytic lymphoma/chronic lymphocytic leukemia; **D**, follicular lymphoma, grade 3; **E**, lymphoblastic lymphoma; **F**, metastatic pulmonary small cell carcinoma; **G**, metastatic alveolar rhabdomyosarcoma; **H**, same case as **G** immunostained for desmin. (Courtesy of L. Alasio, Milan, Italy.)

cytology morphology, however, is not adequate, and all cases undergoing fine-needle aspiration for possible lymphoma should have an aspirate sample submitted for flow cytometry immunophenotyping, and preferably, be accompanied by a core biopsy for architectural evaluation. Even with this combination, complete lymphoma classification may not be possible in up to 35% of cases, requiring an excisional biopsy. The fine-needle aspiration technique has been found most useful for the selection of a representative node for biopsy, for the diagnosis of recurrent lymphoma, for staging the extent of the disease, for monitoring treatment and to collect material for ancillary testing. Hemorrhage, necrosis, and myofibroblastic proliferation may develop along the needle tract; the latter should not be confused with Kaposi sarcoma or other neoplasms.

Infectious Disease Examination

If there is a possibility that the node contains an infectious process, an adequate, steriley collected sample of the biopsied lymph node must be sent directly for bacteriologic, fungal, and viral studies or at least be placed in a sterile Petri dish in the refrigerator. If permanent sections show an inflammatory process, the material can then be retrieved and studied for infectious diseases. For some reason, this technically trivial step is the one most commonly forgotten; but molecular assays to identify infectious agents may now be performed on formalin-fixed, paraffin-embedded tissues¹⁰⁻¹³ and should be considered if the histologic changes suggest an infectious etiology, even if cultures are negative.

Immunophenotyping

Phenotyping of lymphoid disorders has evolved into a highly complex field, as a result of the enormous cellular diversity within the immune system and the huge number (over 1000) of markers that have become available for this purpose.

Rosetting tests with coated or uncoated red blood cells and polyclonal antibodies, which were so useful for the early characterization of lymphomas, have been all but replaced by the use of monoclonal antibodies. These have received a multitude of designations, which are more dependent on the manufacturer's source than the features of the antibody. Fortunately, an internationally agreed-upon nomenclature (the CD system, which stands for *cluster designation* or *cluster of differentiation*) has evolved, and this has allowed for better communication among the various laboratories. Over 300 CD antigens have been identified. Many of these monoclonal antibodies are now applicable to paraffin sections (Table 37.1). A detailed discussion of these tests and their optimal use in the differential diagnosis of hematolymphoid disorders is outside the scope of this book.

Immunophenotyping can be performed by flow cytometry (requiring fresh tissue) or on paraffin-embedded materials.^{14,15} Two major advantages of the former are rapid availability of results, and excellent assessment of surface immunoglobulin and hence B-cell clonality. The disadvantages are the need for immediate handling of fresh tissue, and suboptimal architectural-morphologic correlation.

Molecular Genetic and Cytogenetic Studies

Gene Rearrangement Analysis

Individual T and B lymphocytes normally undergo rearrangements of antigen receptor genes as part of normal maturation, resulting in the development of unique immunoglobulin or T-cell receptor molecules. The vast majority of mature B cells have undergone rearrangement of the immunoglobulin heavy chain (IGH) gene and

the immunoglobulin kappa light chain (IGK) gene, and approximately one-third of B cells have also undergone rearrangement of the immunoglobulin lambda (IGL) gene. Maturing T cells normally rearrange the T-cell receptor gamma and delta genes (TRG and TRD, respectively), and most cells then undergo rearrangement of the T-cell receptor alpha and beta genes (TRA and TRB, respectively). These mature T cells express the alpha and beta proteins and are termed α/β T cells. A small percentage of normal T cells fail to undergo TRA and TRB rearrangements, resulting in expression of surface gamma and delta proteins and these cells are termed δ/γ T cells. The gene rearrangement process results in editing of the original germline DNA to move one variable or V-region of the gene in contact with a single joining or J-region, sometimes with an individual diversity or D-region in between the two (Fig. 37.3). Varying numbers of small nucleotides are added between these regions. This shuffling of V-, D-, and J-regions results in variation in size of an individual reactive lymphocyte's antigen receptor gene, while clonal populations will have large numbers of cells with identically sized gene rearrangements. Molecular genetic assays attempt to capitalize on this difference between reactive and clonal populations, but some normal antigen responses may result in oligoclonal proliferations that can result in false positive results.

Mature B-cell lymphomas almost always show clonal rearrangements of the immunoglobulin genes, although rare cases may show simultaneous rearrangements of T-cell receptor genes.¹⁶ Mature T-cell lymphomas almost always show clonal rearrangements of the T-cell receptor genes, but rare cases may show simultaneous rearrangements of the immunoglobulin genes, an occurrence which is particularly common in angioimmunoblastic T-cell lymphoma (AITL) (20%–30%), probably due to the presence of an associated B-cell proliferation.¹⁷ However, precursor lymphoblastic lymphomas frequently show cross-lineage antigen receptor gene rearrangements.¹⁸

Analysis of the immunoglobulin and T-cell receptor gene status in lymphoid proliferations may help in determining clonality, which generally but not invariably indicates a neoplastic process,¹⁹ and in determining lineage in mature lymphoid proliferations, with the caveats of possible cross-lineage gene rearrangements.^{16,20} Demonstration of clonal immunoglobulin or T-cell receptor gene rearrangements is most commonly achieved by methods using the polymerase chain reaction (PCR) technique, which has superseded the much more laborious and demanding Southern blot technique.²¹ Although PCR is a highly sensitive technique, being able to demonstrate even minor clonal populations, there can be significant false-negative results due to imperfect annealing of the consensus primers with the target DNA sequences which can be particularly difficult when fragmented DNA from formalin-fixed, paraffin-embedded tissue is used.^{16,22,23} However, false-negative results can be significantly reduced by using multiple primer pairs against the antigen receptor gene target, such as using the BIOMED-2 primers.^{18,24} False-positive results also occur with these assays, often related to oligoclonal proliferations or small numbers of lymphocytes in the specimens.²⁵ Newly developed next-generation sequencing assays appear to be useful in overcoming some of these obstacles.²⁶

Chromosomal Translocation

In addition to clonal rearrangements of antigen receptor genes, a subset of non-Hodgkin lymphomas are associated with nonrandom chromosomal translocations, the more common of which are summarized in Table 37.2. Although most are not entirely specific for a single lymphoma type, their detection may be useful in the proper clinical setting which is discussed in more detail with the various lymphoma types.

Text continued on p. 1538

Table 37.1 Principal antibodies applicable on paraffin tissue sections for lymphoid proliferations

CD ANTIGEN AND/ OR ANTIBODY	PREDOMINANT NORMAL CELL REACTIVITY	REACTIVITY IN NEOPLASMS	COMMENT/CAUTION
Leukocytes			
CD45RB Leukocyte common antigen	B cells and most T cells, macrophages, myeloid cells	Most lymphomas and leukemias	Plasma cell neoplasms and Reed–Sternberg cells usually unreactive; some lymphoblastic and anaplastic large cell lymphomas unreactive
B Lymphocytes			
C20 (L26)	B cells, except plasma cells	Most B-cell lymphomas; L&H cells in NLPHL; some Reed–Sternberg cells in ~20% of classic Hodgkin lymphomas; rare T-cell lymphomas	Plasmablastic and plasma cell neoplasms usually unreactive; epithelium of some thymomas may stain
Immunoglobulin light chains	B cells and plasma cells	B-cell and plasma cell neoplasms	Cytoplasmic Ig often detectable in paraffin sections; surface Ig often requires flow cytometry or frozen tissue
CD79A	B cells, including most plasma cells	Most B-cell lymphomas; B-lymphoblastic leukemias	CD79A is associated with antigen receptor (Ig) on B cells in a similar manner as CD3 on T cells
PAX5	B cells, except most plasma cells	B-cell neoplasms, including B-lymphoblastic neoplasms; L&H cells in NLPHL; Reed–Sternberg cells in classic Hodgkin lymphoma show moderate to weak staining	Plasma cell neoplasms are usually unreactive
OCT2	B cells, including plasma cells	B-cell neoplasms, including plasma cell and plasmablastic neoplasms; strong nuclear expression in L&H cells of NLPHL; weak or absent staining in classical Hodgkin lymphoma	
BOB.1	B cells, including plasma cells	B-cell neoplasms, including plasma cell and plasmablastic neoplasms; weak or absent staining in classical Hodgkin lymphoma	Some T-cell lymphomas can be BOB.1 positive
B Lymphocyte Differentiation Stage			
CD10 (CALLA)	Precursor B cells, follicular center B cells; follicular center T helper cells; granulocytes	Many B-cell and some T-cell lymphoblastic lymphomas/leukemias; follicular lymphoma; Burkitt lymphoma; some large B-cell lymphomas; angioimmunoblastic T-cell lymphoma	Useful in separating follicular from other low-grade B-cell lymphomas; expressed by subset of myeloma; reactive with a variety of nonhematolymphoid neoplasms
BCL6	Follicular center B cells; follicular center T-helper cells; rare subpopulations of T cells	Follicular lymphoma; Burkitt lymphomas; some large B-cell lymphomas; angioimmunoblastic T-cell lymphoma; anaplastic large cell lymphoma	
MUM1	Plasma cells and plasmablasts; subpopulation of BCL6 follicular center B cells; small percentage of activated T cells	Plasma cell and plasmablastic neoplasms; lymphoplasmacytic lymphoma; diffuse large B-cell lymphoma (75% of cases); other B-cell lymphomas (variable); some T-cell lymphomas (variable)	MUM1 may be positive in nonhematolymphoid neoplasms, such as malignant melanoma
CD138	Plasma cells and plasmablasts; some immunoblasts	Plasma cell and plasmablastic neoplasms; some large B-cell lymphomas	CD138 is positive in normal epithelial cells and many nonhematolymphoid neoplasms

Table 37.1 Principal antibodies applicable on paraffin tissue sections for lymphoid proliferations—cont'd

CD ANTIGEN AND/ OR ANTIBODY	PREDOMINANT NORMAL CELL REACTIVITY	REACTIVITY IN NEOPLASMS	COMMENT/CAUTION
CD23	Mantle zone B cells, subset of follicular dendritic cells	CLL/small lymphocytic lymphomas usually reactive; follicular lymphoma (some cases); mediastinal large B-cell lymphoma; follicular dendritic cell tumor	Low-affinity Fc receptor for IgE; upregulated by EBV infection
T and NK Lymphocytes			
Cytoplasmic CD3 (detected by polyclonal or monoclonal antibody)	T cells and NK cells	Most T-cell and NK-cell lymphomas; exceptional cases of B-cell lymphoma can be CD3+	CD3 demonstrable in paraffin sections represents cytoplasmic CD3; this is present in T cells as well as NK cells. Surface CD3, which is typically positive in T cells but negative in NK cells (and their neoplasms), requires fresh or frozen tissue for demonstration.
CD2	T cells, NK cells	Most T-cell and NK-cell lymphomas and leukemias; few myeloid leukemias; systemic mastocytosis	CD2 is the sheep erythrocyte receptor
CD5	T cells, weak expression by small B-cell subset	Most T-cell lymphomas and leukemia; chronic lymphocytic leukemia/small lymphocytic lymphoma; mantle cell lymphoma; rare subset of diffuse large B-cell lymphoma	CD5-reactive B cells may be elevated in autoimmune disorders; expression of CD5 by diffuse small B-cell neoplasms useful in diagnosis; CD5 typically negative in NK cells and their neoplasms; CD5 can be expressed in nonhematolymphoid neoplasms, such as thymic carcinoma
CD7	Most T cells, NK cells	Most T-cell and some NK-cell lymphomas and leukemias; some myeloid leukemias	Earliest expressed antigen in T-cell ontogeny and one of the best T-cell markers for lymphoblastic neoplasms; most commonly deleted antigen in peripheral T-cell malignancy, particularly mycosis fungoides
TCR β	Expressed by over 95% of mature T cells	Many T-cell lymphomas	NK cells and their neoplasms are unreactive
TCR γ	Expressed by a small population of mature T cells, often in extranodal sites	T-cell lymphomas of gamma/delta type, usually extranodal	NK cells and their neoplasms are unreactive
CD56	NK cells, minor subpopulation of T cells, neural tissues	NK-cell lymphomas; some peripheral T-cell lymphomas; some plasma cell neoplasms	Also reacts with neural and neuroendocrine cells and their neoplasms
CD43	T cells, macrophages, Langerhans cells, myeloid cells, minor subset of B cells	Most T-cell lymphomas; some B-cell lymphomas (CLL/small lymphocytic lymphoma, mantle cell lymphoma some marginal zone lymphomas); myeloid leukemias; histiocytic neoplasms; Langerhans cell histiocytosis; some plasma cell neoplasms	Coexpression on B cells is helpful for diagnosis, but caution should be used in interpreting partial coexpression due to heterogeneity of cell types that react with CD43

Continued

Table 37.1 Principal antibodies applicable on paraffin tissue sections for lymphoid proliferations—cont'd

CD ANTIGEN AND/ OR ANTIBODY	PREDOMINANT NORMAL CELL REACTIVITY	REACTIVITY IN NEOPLASMS	COMMENT/CAUTION
T- or NK-Cell Subset or Differentiation Stage			
CD57	Some NK cells; subset of germinal center T cells	T-cell large granular lymphocyte leukemia; rare cases of T-lymphoblastic neoplasm	CD57+ cells often rosette around L&H cells in NLPHL
PD1	Follicle helper T cells	Angioimmunoblastic T-cell lymphoma	PD1+ cells frequently rosette around L&H cells in NLPHL
CD4	Most helper/inducer T cells, many macrophages, many dendritic cells	Many peripheral T-cell lymphomas; histiocytic neoplasms; Langerhans cell histiocytosis	
CD8	Most cytotoxic/suppressor T cells, subset of NK cells, splenic sinus lining cells	Minority of peripheral T-cell lymphomas	
Precursor Cell Marker			
Terminal deoxynucleotidyl transferase (TdT)	Precursor cells in marrow B-cell precursors, cortical thymocytes	Most lymphoblastic lymphomas and leukemias of a T or B lymphoblastic lineage; some myeloid leukemias	Useful as marker of precursor cell
CD34	Various cell types, including endothelial cells and immature hematopoietic cells	Vascular tumors, gastrointestinal stromal tumors, many lymphoblasts and myeloblasts	May confirm immaturity in rare TdT negative lymphoblastic proliferations
Hodgkin Lymphoma-Associated			
CD30	Some activated B and T cells, some plasma cells	Reed–Sternberg cells in most cases of classic Hodgkin lymphoma; anaplastic large cell lymphomas; some B- and T-cell lymphomas	Embryonal carcinomas and few other nonhematolymphoid neoplasms reactive
CD15 (Leu-M1)	Granulocytes, some macrophages	Reed–Sternberg cells in most cases of classic Hodgkin lymphoma; large cells in some B- and T-cell lymphomas; histiocytic neoplasms; some myeloid leukemias	Many carcinomas reactive; CMV-infected cells reactive; antibody of IgM isotype and thus may benefit from isotype-specific detection; L&H cells usually unreactive
Accessory Cells			
CD68	Macrophages and monocytes; myeloid cells positive with KP1 but not PGM1 antibody	True histiocytic neoplasms; monocytic leukemias; myeloid leukemias positive with KP1	Reactive in granular cell tumors, some melanomas, malignant fibrous histiocytomas, and renal cell carcinomas
CD163	Macrophages except those of germinal centers and splenic white pulp	Histiocytic neoplasms; acute monocytic leukemia	Dendritic cells and their tumors are unreactive
Lysozyme	Macrophages, myeloid cells	Histiocytic neoplasms; many myeloid leukemias	Reactive with many nonhematolymphoid neoplasms
S100 protein	Langerhans cells, interdigitating (IDRC) and sometimes follicular dendritic cells	Langerhans cell histiocytosis; IDRC tumors; rare T-cell lymphomas; histiocytic neoplasms; Rosai–Dorfman disease	Reactive with many nonhematolymphoid neoplasms
CD1a	Cortical thymocytes, Langerhans cells	Some T-lymphoblastic lymphomas/ leukemias; Langerhans cell histiocytosis	
CD207 (langerin)	Langerhans cells	Langerhans cell histiocytosis	

Table 37.1 Principal antibodies applicable on paraffin tissue sections for lymphoid proliferations—cont'd

CD ANTIGEN AND/ OR ANTIBODY	PREDOMINANT NORMAL CELL REACTIVITY	REACTIVITY IN NEOPLASMS	COMMENT/CAUTION
CD21	Mantle and marginal zone B cells, follicular dendritic cells	Some B-cell lymphomas; follicular dendritic cell tumors	C3d (CR2) complement receptor; receptor for EBV; expanded CD21-positive follicular dendritic cell networks characteristic of angioimmunoblastic T-cell lymphoma
CD35	Mantle and marginal zone B cells, follicular dendritic cells, some macrophages	Some B-cell lymphomas; follicular dendritic cell tumors; some myeloid leukemias	C3b (CR1) complement receptor
Miscellaneous			
BCL2	Nongerminal center B cells, most T cells, plasma cells	Overexpressed in most follicular lymphomas and some diffuse large B-cell lymphomas; also expressed in many other lymphomas and leukemias	Most useful in differentiating follicular lymphoma from reactive follicular hyperplasia
Cyclin D1	Some histiocytes; normal lymphoid cells are negative	Mantle cell lymphoma; proliferation centers of some cases of CLL/small lymphocytic lymphoma; some plasma cell neoplasms; hairy cell leukemia	Cyclin D1 is expressed in many nonhematolymphoid neoplasms but is useful in confirming mantle cell lymphoma in a CD5 positive small B-cell proliferation
ALK	None	ALK+ anaplastic large cell lymphoma; ALK+ large B-cell lymphoma	ALK also positive in some cases of inflammatory myofibroblastic tumor
Myeloperoxidase	Myeloid cells	Myeloid leukemias	Most sensitive and specific marker for myeloid neoplasms

ALK, Anaplastic lymphoma kinase; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma.

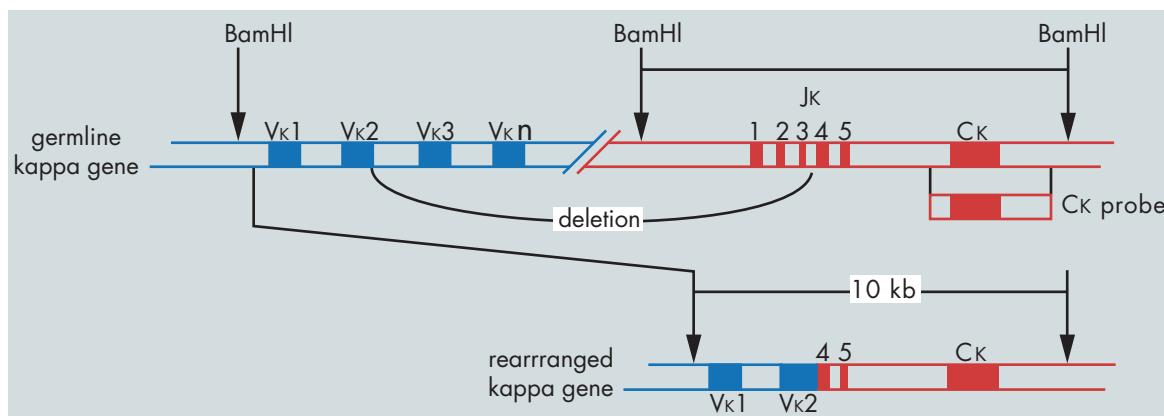


Figure 37.3 Schematic representation of an immunoglobulin gene rearrangement, in this case the kappa (IGK) gene. The germline configuration of the kappa light chain gene (upper line) consists of numerous variable gene segments (V-kappa, 1–n), five joining gene segments (J-kappa, 1–5), and a single constant region gene segment (C-kappa). To assemble a functional light chain gene (lower line), select V and J segments are juxtaposed with each other by deletion of the intervening DNA. The deletion reconfigures restriction enzyme cutting sites upstream of J-kappa, changing the size of the *Bam*H1 fragment detected with a C-kappa hybridization probe (12 kb germline vs. 10 kb rearranged in figure) when examined by Southern blot analysis. Current polymerase chain reaction method target detection of the rearranged product (lower line). (From Warnke RA, Weiss LM, Chan JKC, et al. *Tumors of the Lymph Nodes and Spleen. Atlas of Tumor Pathology*, series 3, fascicle 14. Washington, DC: Armed Forces Institute of Pathology; 1995.)

Table 37.2 Recurrent chromosomal abnormalities in lymphomas

CHROMOSOMAL ABNORMALITY	MOST FREQUENT TYPES OF LYMPHOMA	ANTIGEN RECEPTOR GENE	ONCOGENE
t(8;14)(q24;q32.33)	Burkitt lymphoma, some high-grade	IGH	MYC
t(2;8)(2p11.2;q24)	B-cell lymphomas, and rarely diffuse	IGK	MYC
t(8;22)(q24;q11.2)	large B-cell lymphoma	IGL	MYC
t(14;18)(q32.33;q21.3)	Follicular lymphoma; subset of diffuse large B-cell lymphomas and high grade B-cell lymphomas	IGH	BCL2
t(11;14)(q13;q32.33)	Mantle cell lymphoma	IGH	CCND1 (cyclin D1)
t(3;v)(q27;v) ^a	Large B-cell lymphoma; some high grade B-cell lymphomas; small subset of follicular lymphomas	IGH, IGK, IGL, others	BCL6
t(14;v)(q11.2;v)	T-lymphoblastic lymphoma; adult T-cell leukemia/lymphoma	TRA	Several
t(7;v)(q34;v)	T-lymphoblastic lymphoma	TRB	Several
t(2;5)(p23;q35.1) and t(5;v)(q35.1;v)	Anaplastic large cell lymphoma, ALK+	NA	NPM-ALK fusion gene
t(11;18)(q22;q21)	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	NA	BIRC3-MALT1 fusion gene
t(14;18)(q32.33;q21)		IGH	MALT1
t(3;14)(p13;q32.33)		IGH	FOXP1
t(1;14)(p22;q32.33)		IGH	BCL10

^aVariable.

NA, Not applicable.

Chromosomal translocations are most often detected by conventional cytogenetics, direct or reverse transcriptase PCR, and fluorescence in situ hybridization (FISH). Each of these techniques has its own advantages and limitations. However, the FISH technique, either using break-apart probe or dual-fusion probes, generally offers the highest sensitivity and can often be performed in formalin-fixed, paraffin-embedded tissue.^{27,28}

Chromosome Copy Change and Chromosomal Gain or Deletion

Increase in copies of entire chromosomes is common in certain lymphoma types, such as trisomy 3 or trisomy 18 in extranodal marginal zone lymphoma, and trisomy 12 in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).^{29,30} Lymphomas can also exhibit deletions or gains of specific regions of chromosome, such as del 6q21–25 in extranodal NK/T-cell lymphoma, del 6q23.3 in marginal zone lymphoma, and gain of 3q26 in mantle cell lymphoma.³¹ These chromosomal changes can be demonstrated by conventional cytogenetics, FISH, or single nucleotide polymorphism (SNP) microarrays but are usually less helpful diagnostically when compared to gene rearrangement studies or detection of chromosomal translocations.

Gene Mutation, Amplification, and Hypermethylation

Point mutations in specific genes are characteristic of some lymphoma types, including activating mutations of proto-oncogenes, such as point mutations in genes involved in regulation of the nuclear factor kappa B (NF κ B) in some cases of diffuse large B-cell lymphoma (DLBCL), and inactivating mutations of tumor suppressor genes, such as A20 in various lymphoma types.^{32–35} An inactivating mutation in

a tumor suppressor gene is often accompanied by chromosomal/gene deletion in the remaining allele, resulting in complete loss of function of the gene.^{33,35} Tumor suppressor genes are alternatively inactivated in some lymphomas through hypermethylation of the gene promoters, such as p16 in mantle cell lymphoma.³⁶ Gene amplifications are found in some lymphomas, such as REL in DLBCL.³⁷

Gene Expression Profiling

Some highly publicized studies have demonstrated the use of molecular profiling with the microarray technology to segregate DLBCLs into subtypes³⁸ and to predict survival after chemotherapy.³⁹ Although microarray-based gene expression profiling has provided tremendous information on various lymphoma types, this technology has not been reproducibly applied in the diagnostic setting.³⁸ Instead, immunohistochemical algorithms⁴⁰ predictive of gene expression profiling results have become routine while new methods of detecting complex molecular lymphoma subtypes are being developed.

Primary Immunodeficiencies

Primary immunodeficiency syndromes are congenital abnormalities of the immune system that most often result in an increased risk of infection but are now also known to be associated with an increased risk for developing malignant lymphoma.^{41,42} Over 250 genetic abnormalities have been identified in association with primary immunodeficiency, and the range of these defects and disorders is beyond the scope of this textbook. However, the genetic defects result in a decrease in number and/or function of normal B, T, and/or NK cells or their subsets. While loss of T cells, a feature of some types of severe combined immunodeficiency, is most striking in the

thymus, lymph nodes also often demonstrate loss of the normal immunoarchitecture. This may also include complete loss of B-cell follicles or the presence of “naked” germinal centers without normal mantle zones. Some disorders, such as Omenn’s syndrome,⁴³ have normal or elevated numbers of T cells despite genetic mutations that impact T-cell function. Rare X-linked disorders associated with mutations of *SH2D1A* and *BIRC4* are associated with an Epstein–Barr virus (EBV) positive, fatal infectious mononucleosis-like proliferation that affects young males.⁴⁴

Autoimmune lymphoproliferative syndrome (ALPS; Canale–Smith disease) occurs in young males with lymphadenopathy and hepatosplenomegaly and an average age of onset of 3 years.^{45,46} It is an inherited disorder due to defects in FAS-mediated apoptosis and characterized in most instances by lymphadenopathy, splenomegaly, hypergammaglobulinemia, and autoimmune phenomena.^{45,47} Most patients present in childhood, but cases of adult onset are on record.⁴⁸ Most patients with ALPS have germline, and less commonly somatic, mutations of *FAS* (*TNFRSF6*), *FASL*, or *CASP10* genes.⁴⁹ Four subtypes of this condition have been described.⁴⁹

Microscopically, the main change in the affected lymph nodes is a marked paracortical expansion by a mixed population of small- and intermediate-sized lymphocytes and numerous large immunoblasts.^{50,51} The interfollicular areas are expanded by a proliferation of T cells that lack both CD4 and CD8 (“double negative”) with increased S100 positive dendritic cells.⁵² This expansion can be so extensive as to simulate a lymphoma. In addition, there is often florid follicular hyperplasia, frequently accompanied by focal progressive transformation of germinal centers. A polyclonal plasmacytosis is also common.⁵¹

An increased incidence of malignant lymphoma has been detected in this population.⁵³ Interestingly, as many as 41% of patients with type Ia ALPS have Rosai–Dorfman disease (RDD)-like changes in their lymph nodes, raising the possibility that RDD may be related to ALPS and possibly represent a forme fruste of it.⁵²

While the morphologic features of most primary immunodeficiency syndromes are nonspecific, the findings of recurrent atypical hyperplasia or persistent infectious mononucleosis-like changes in a young person should warrant further clinical and genetic evaluation for an underlying immune defect.⁵⁴

Patterns of Hyperplasia

The various components of the lymph node react to various known and unknown stimuli by undergoing reactive changes, some being the expression of an inflammatory reaction and some being indicative of an immune response. The two are often present together. A similar microscopic picture may result from a variety of causes, but some agents produce a characteristic microscopic picture. When the hyperplastic change is very intense, the differential diagnosis with malignant lymphoma may become difficult^{55,56} and may require the application of immunophenotyping and molecular genetic methods.⁵⁷

Although most lymph node reactions involve several compartments, it is useful to evaluate these compartments individually, not only because their presence and relative intensity correlate with various specific disorders (thus providing important etiologic clues), but also because each of them raises differential diagnostic problems with different types of malignant processes. From a topographic and functional standpoint, the major patterns of reactive lymphoid proliferations are *follicular/nodular*, *interfollicular/paracortical*, *diffuse*, *sinus*, and *mixed*. These patterns also apply to the various types of malignant lymphoma (Table 37.3).

Follicular Hyperplasia

The criteria laid down in the classic article by Hicks et al.⁵⁸ and further elaborated by Nathwani et al.⁵⁹ remain extremely useful and reliable to distinguish reactive follicular hyperplasia from follicular lymphoma (Table 37.4). In general, reactive follicles vary considerably in size and shape; their margins are sharply defined and surrounded by a mantle of small lymphocytes often arranged circumferentially with an onion-skin pattern and sometimes concentrating on one pole of the follicle (corresponding to the side of the antigenic stimulation); the follicles are composed of an admixture of small and large lymphoid cells with irregular (elongated and cleaved) nuclei; mitoses are numerous; and phagocytosis of nuclear debris by histiocytes is prominent, resulting in a starry sky pattern. The lymphoid tissue present between the follicles is distinctly different from that of the follicles themselves (although this also may be true

Table 37.3 Differential diagnosis of reactive proliferations based upon recognition of predominant pattern in lymph node at low magnification

FOLLICULAR/ NODULAR	INTERFOLLICULAR/ PARACORTICAL	DIFFUSE	SINUS	MIXED/OTHER
Non-Neoplastic				
Reactive follicular hyperplasia	Immunoblastic proliferations	Immunoblastic proliferations	Sinus hyperplasia	Mixed hyperplasia
Explosive follicular hyperplasia (HIV)	Viral lymphadenitis (EBV, CMV, herpes)	Viral lymphadenitis (EBV, CMV, herpes)	Rosai–Dorfman disease	Dermatopathic lymphadenopathy
Progressive transformation of germinal centers	Post-vaccination lymphadenitis	Post-vaccination lymphadenitis	Lymphangiogram effect	Toxoplasmosis
Castleman disease	Drug sensitivity, e.g., diphenylhydantoin (Dilantin)	Drug sensitivity, e.g., diphenylhydantoin	Whipple disease	Cat-scratch disease
Rheumatoid lymphadenopathy			Vascular transformation of sinuses	Systemic lupus erythematosus
Luetic lymphadenitis			Hemophagocytic syndrome	Kawasaki disease
Kimura disease				Kikuchi lymphadenitis
				Granulomatous lymphadenitis
				Inflammatory pseudotumor

CMV, Cytomegalovirus; EBV, Epstein–Barr virus.

Modified from Warnke RA, Weiss LM, Chan JKC, et al. *Tumors of the Lymph Nodes and Spleen. Atlas of Tumor Pathology*, series 3, fascicle 14. Washington, DC: Armed Forces Institute of Pathology; 1995.

Table 37.4 Architectural and cytologic features of follicular lymphoma and of reactive follicular hyperplasia

FOLLICULAR LYMPHOMA	REACTIVE FOLLICULAR HYPERPLASIA
Architectural Features	
Complete effacement of normal architecture	Preservation of nodal architecture
Even distribution of follicles throughout cortex and medulla	Follicles more prominent in cortical portion of lymph node
Slight or moderate variations in size and shape of follicles	Marked variations in size and shape of follicles with presence of elongated, angulated, and dumbbell-shaped forms
Fading of follicles	Sharply demarcated reaction centers
Massive infiltration of capsule and pericapsular fat with or without formation of neoplastic follicles outside capsule	No, or only moderate, infiltration of capsule and pericapsular fat tissue with inflammatory cells that may be arranged in perivascular focal aggregates (when associated with lymphadenitis)
Condensation of reticulin fibers at periphery of follicles	Little or no alteration of reticular framework
Cytologic Features	
Follicles composed of neoplastic cells exhibiting cellular pleomorphism with nuclear irregularities	Centers of follicles (germinal centers) composed of lymphoid cells, histiocytes, and "reticulum cells," with few or no cellular and nuclear irregularities
Lack of phagocytosis	Active phagocytosis in germinal centers
Relative paucity of mitotic figures usually without significant difference in their number inside and outside the follicles; occurrence of atypical mitoses	Moderate to pronounced mitotic activity in germinal centers; rare or no mitoses outside germinal centers; no atypical mitoses
Similarity of cell type inside and outside follicles	Infiltration of tissue between germinal centers with inflammatory cells (when associated with lymphadenitis)

Slightly modified from Rappaport H, Winter WJ, Hicks EB. Follicular lymphoma. A re-evaluation of its position in the scheme of malignant lymphoma, based on a survey of 253 cases. *Cancer*. 1956;9:792-821.

for follicular lymphoma); it is composed of a mixture of small lymphocytes, large lymphoid cells, prominent postcapillary venules, and sometimes a prominent component of mature plasma cells (Fig. 37.4).

Follicular hyperplasia can accompany a large number of inflammatory and noninfectious conditions. When the reactive follicles are particularly large ("giant"), particularly if there is associated zonal or single cell necrosis and a polymorphous, plasmacytoid paracortical expansion, infection by EBV should be suspected.

It should be kept in mind that follicular hyperplasia may coexist in the same node with follicular lymphoma or other types of malignant lymphoma.

The immunophenotypic differences between follicular hyperplasia and follicular lymphoma are discussed later, but the B-cells reactive follicles should not express BCL2 and should not harbor the *IGH/BCL2* fusion. However, immunoglobulin gene rearrangement studies may detect clonal or oligoclonal populations in reactive follicular hyperplasia, especially in association with EBV infection, and this test alone should not be used to diagnose lymphoma.

Progressively and Regressively Transformed Germinal Centers

Progressively transformed germinal centers are the morphologic expression of a distinct type of follicular hyperplasia. They usually are seen in conjunction with more typical reactive germinal centers and are often located more centrally within the node (Fig. 37.5).⁶⁰ They are large and contain numerous small lymphocytes, the borders are indistinct, and the interphase between the germinal center and the

cuff of small lymphocytes is blurred. However, residual starry sky macrophages are present, together with scattered large lymphoid cells (cleaved and noncleaved) and occasional collections of epithelioid cells at the periphery.⁶¹ There is an increased network of follicular dendritic cells, a larger number of mantle zone lymphocytes, and a relatively large number of T lymphocytes.⁶² While multiple transformed germinal centers may be present, they do not form a distinct mass within the lymph node and are admixed with the more typical, small reactive follicles. Remnants of residual, BCL2-negative germinal center B cells remain within the transformed follicles and the surrounding mantle zones retain IgD-positive cells. Evaluation of these features should allow the differential diagnosis between progressively transformed germinal centers and follicular lymphoma to be made with ease in most instances; however, cases exist in which this is extremely difficult on the basis of routinely stained sections,⁶³ and immunohistochemical studies are warranted in most cases.

Progressively transformed germinal centers can occur as an isolated self-limited reactive process, particularly in young men.^{63,64} However, they also show an interesting and still poorly understood relation with nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), which may manifest itself in three ways: they may precede the development of NLPHL, they may accompany NLPHL in involved nodes, or they may appear in the absence of NLPHL in recurrent post-therapy adenopathy done for the latter.⁶⁵⁻⁶⁷ Indeed, the main differential diagnosis of progressively transformed germinal centers is with NLPHL, which should be suspected if T-cell rosettes are prominent, if large B cells extend beyond the transformed germinal center or if the expanded nodules form tumor masses that displace

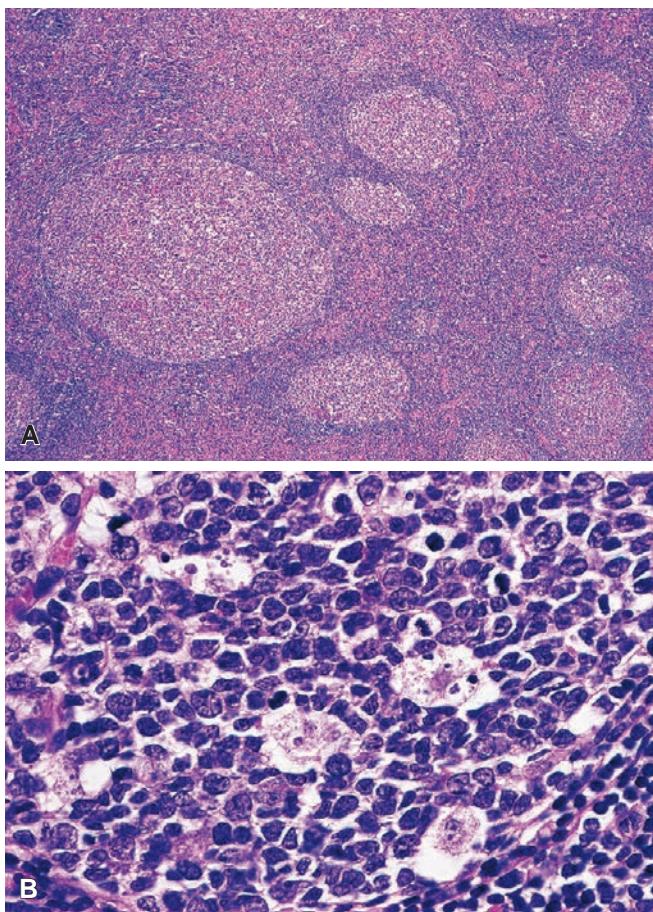


Figure 37.4 Follicular Hyperplasia. **A**, Low-power view showing marked differences in size of germinal centers, their well-circumscribed character, and the fact that they are surrounded by a well-defined mantle. **B**, High-power view showing numerous “tingible body” macrophages.

adjacent reactive or normal lymph node tissue. A thorough search for the atypical cells seen in NLPHL (see later) should then be undertaken.⁶⁸

Regressively transformed germinal centers are small, practically devoid of lymphoid cells, and composed of follicular dendritic cells, vascular endothelial cells, and hyalinized periodic acid-Schiff (PAS)-positive intercellular material. These abnormal centers have an onion-skin appearance on low-power examination. Regressively transformed germinal centers are particularly prominent and numerous in Castleman disease (see later) but may also be seen with HIV infection or in association with AITL. A peculiar form of regressive germinal centers with “follicular dendritic cells only” has been described in organ transplant recipients.⁶⁹

Mantle/Marginal Zone Hyperplasia

This pattern of hyperplasia, which blends with the lymphoid subtype of hyaline vascular Castleman disease, is characterized by a monomorphic proliferation of small lymphoid cells with round nuclei and clear cytoplasm which may be arranged in a nodular, inverse follicular, and/or marginal zone pattern. The main differential diagnosis is with the rare mantle zone pattern of mantle cell lymphoma and the monocyteoid B-cell pattern of some cases of nodal marginal zone lymphoma. Features in favor of benignancy at the H&E level are the lack of pericapsular infiltration, preservation of

sinuses, scattered reactive follicles, and paracortical nodular hyperplasia.⁷⁰ In addition, reactive “monocyteoid B cells” are frequently BCL2 negative and contain admixed neutrophils. In contrast, the cells of marginal zone lymphoma are usually BCL2 positive and show aberrant coexpression of CD43 in approximately 40% of cases.^{71,72} Mantle cell lymphoma shows aberrant coexpression of CD5 and CD43 on the B cells in the vast majority of cases as well as nuclear expression of cyclin D1, all features that are absent in reactive proliferations.

Paracortical Hyperplasia

Expansion of the paracortical (interfollicular) region can be nodular or diffuse. The nodular form is characteristic of dermatopathic lymphadenitis, while viral lymphadenitis, drug reactions, postvaccinal proliferations, and immunoblastic proliferations in general tend to be more diffuse (Fig. 37.6). The differential diagnosis of the diffuse form is often with peripheral T-cell lymphoma. These specific types of hyperplasia are discussed in more detail later.

Sinus Hyperplasia

The sinuses appear dilated and prominent in various disorders. The most common and least significant is *sinus hyperplasia* (sinus histiocytosis, sinus “catarrh”) seen in nodes draining infectious or neoplastic processes and characterized by an increased number of macrophages in the lumen (Fig. 37.7). Other reactive disorders involving primarily the sinuses are RDD/sinus histiocytosis with massive lymphadenopathy (SHML), Langerhans cell histiocytosis (LCH), Whipple disease, vascular transformation of sinuses, and hemophagocytic syndromes.

Granulomatous Inflammation

There are a large number of diseases that can result in granulomatous formations in lymph nodes. They include various types of infection, foreign body reactions, aberrant immune reactions, sarcoidosis, and secondary responses in lymph nodes draining carcinoma^{73,74} or in patients with Hodgkin lymphoma and other lymphomas, whether the node is involved by the malignancy or not,⁷⁵⁻⁷⁷ and associated with metastatic seminoma. Sometimes the appearance of the granulomas is such that a specific diagnosis can be strongly suggested on the basis of the hematoxylin–eosin-stained slide.⁷⁸ Features of importance in this regard are the presence and type of necrosis; presence, number, and size of Langhans giant cells; size, shape, and distribution of the granulomas; and type of associated changes in the intervening tissue. In most cases, however, a combination of clinical, morphologic, and culture data is necessary to determine the etiology of the granulomas. It is therefore important that any node suspected of harboring a granulomatous process be sampled for culture analysis in addition to being subjected to the standard microscopic examination.

Other Cell Types Involved in Nodal Hyperplasia

Monocyteoid B Cells

Monocyteoid B-cell hyperplasia, a variation on marginal zone hyperplasia mentioned previously, is characterized by the filling of the sinuses by small lymphoid cells with round or angulated nuclei and clear cytoplasm, sometimes admixed with neutrophils (Fig. 37.8). It was originally described as *immature sinus histiocytosis*, but marker studies have shown that these monocyteoid clear cells are of

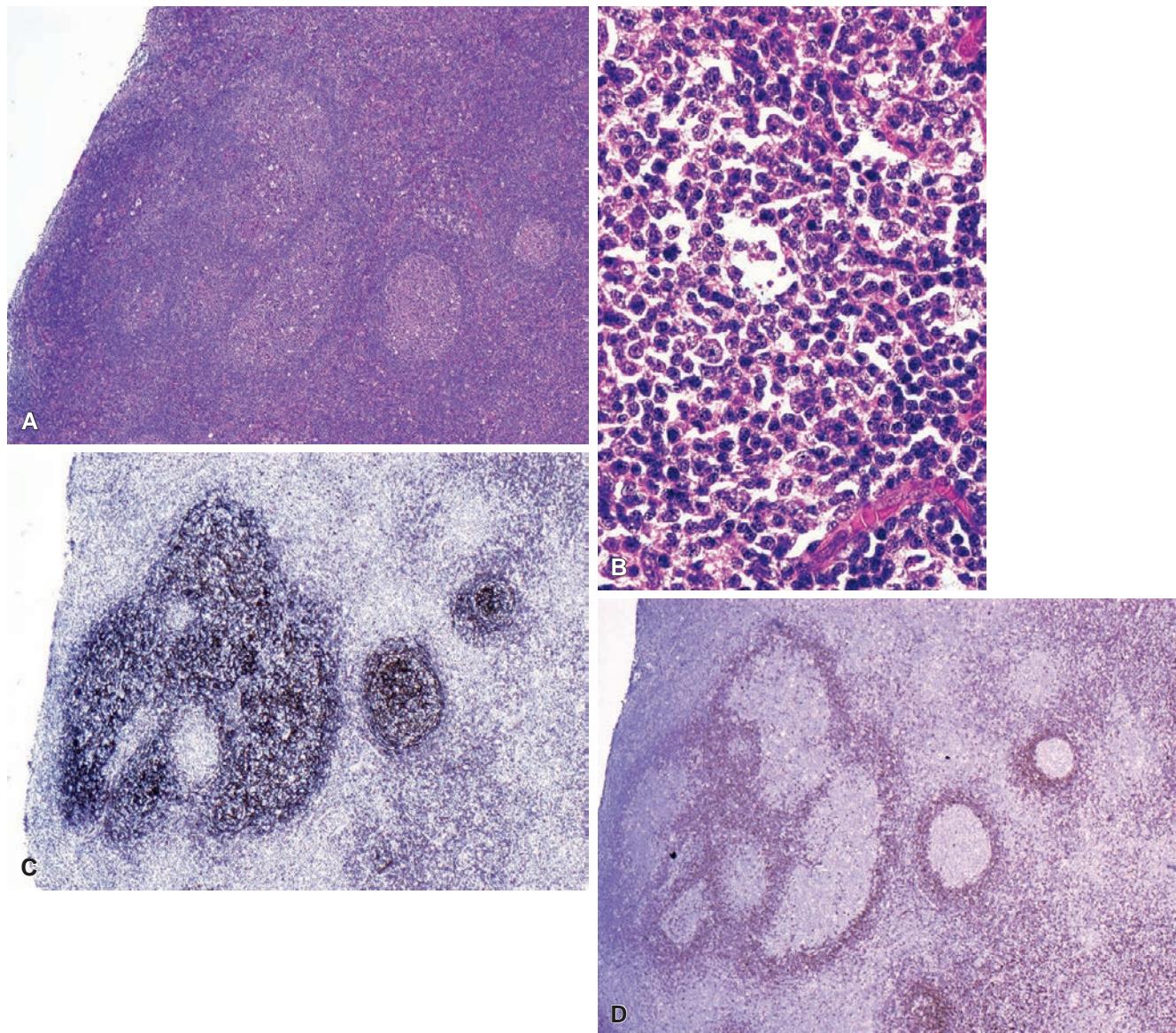


Figure 37.5 Progressively Transformed Germinal Centers. **A**, Low-power view showing that this formation is larger and less well defined than the adjacent hyperplastic follicles. **B**, High-power view showing cytologic composition not too dissimilar from that of ordinary hyperplastic follicles. **C**, CD21 staining highlights the expanded and disrupted follicular dendritic cell network of follicle. **D**, IgD staining shows preserved mantle zones with infiltration into the transformed germinal center.

B-cell type.^{79,80} This alteration occurs most frequently in toxoplasmosis, but it has also been seen in many other reactive disorders, including cat-scratch disease,⁸¹ infectious mononucleosis, AIDS, and autoimmune disorders⁸²; it may also accompany malignant lymphomas, including Hodgkin lymphoma.⁸³ It should be distinguished from other nodal lesions featuring cells with clear cytoplasm (such as peripheral T-cell lymphomas, hairy cell leukemia, and mastocytosis) and also from a type of malignant lymphoma composed of cells with features of monocyteid B cells (nodal marginal zone B-cell lymphoma).⁸⁴

Plasmacytoid Dendritic Cells

Clusters of cells with plasmacytoid cytoplasm, fine nuclear chromatin pattern, and small nucleoli are sometimes seen in a variety of reactive nodal lesions (Fig. 37.9). Pyknosis and starry sky pattern may be

present.⁸⁵ These cells were originally interpreted as T-associated plasma cells and later as a subtype of T cells, but then as macrophages/monocytes (plasmacytoid monocytes), and more recently as a special form of dendritic cells.⁸⁶⁻⁸⁸ They are particularly common in Kikuchi necrotizing lymphadenitis and Castleman disease,^{89,90} but they can also be seen in other lymphadenitides⁹¹ and in association with chronic myelomonocytic leukemia. Neoplasms of blastic plasmacytoid dendritic cells also occur.

Polykaryocytes

The term *polykaryocyte* is used for a type of multinucleated giant cell found in lymphoid tissues, of which the Warthin-Finkeldey giant cell of measles is the paradigm. These cells can be found in lymph nodes in association with a variety of reactive and neoplastic disorders.

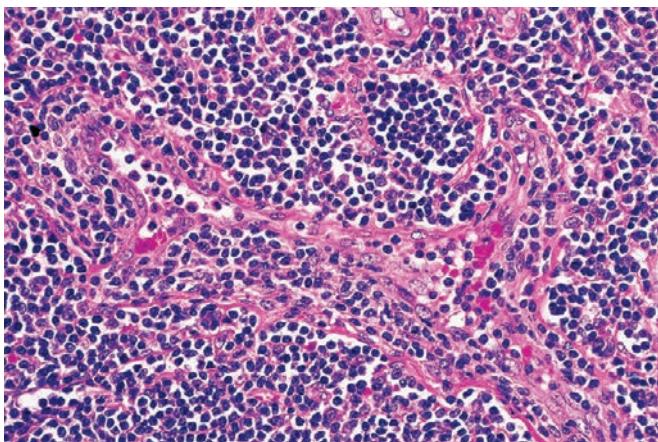


Figure 37.6 Paracortical hyperplasia, identified by the prominence of postcapillary venules.

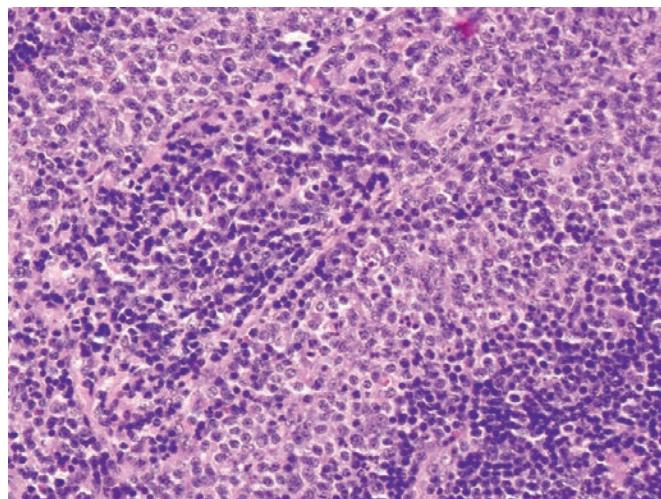


Figure 37.8 Monocyteoid B-Cell Hyperplasia in a Case of Toxoplasmic Lymphadenitis. Clusters of small to medium-sized cells are present with clear cytoplasm. Note the presence of admixed neutrophils and nuclear remnants, a feature of reactive monocyteoid B-cells.

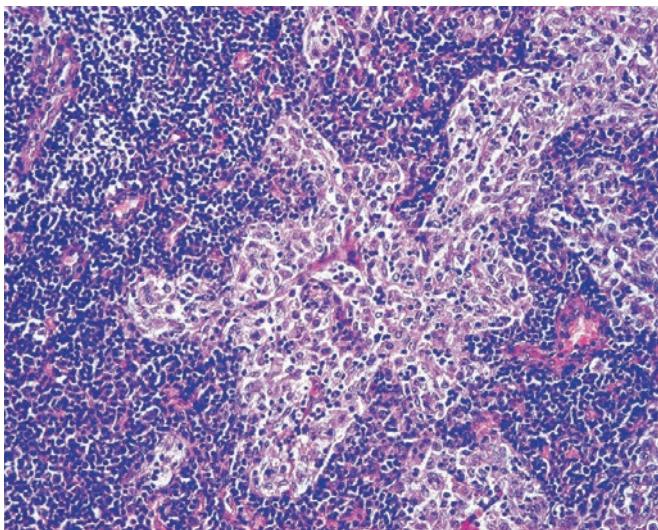


Figure 37.7 Sinus Hyperplasia. The cells present in the sinus represent an admixture of histiocytes and sinus lining cells.

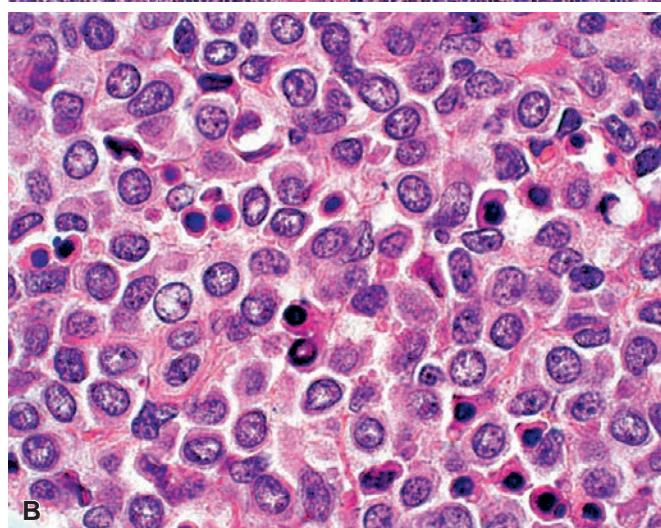
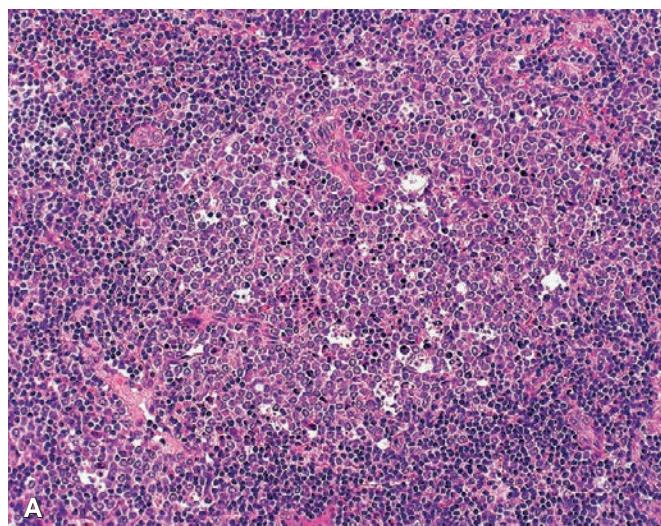


Figure 37.9 Plasmacytoid monocytes as seen on low (A) and high power (B).

They measure 25–150 μm in diameter and have as many as 60 nuclei arranged in grapevine clusters.⁹² Their cytoplasm is very scanty (Fig. 37.10). Although some early studies suggested a T-cell phenotype, more recent evaluations are in keeping with the hypothesis that these cells are multinucleated forms of follicular dendritic cells, a possibility that fits much better their morphologic appearance.⁹³

Inflammatory/Hyperplastic Diseases

Acute Nonspecific Lymphadenitis

The typical case of acute nonspecific lymphadenitis is rarely biopsied. Microscopically, the earliest change is sinus dilation resulting from increased flow of lymph, followed by accumulation of neutrophils, vascular dilation, and edema of the capsule. *Suppurative lymphadenitis* is a feature of staphylococcal infection, mesenteric lymphadenitis, lymphogranuloma venereum, and cat-scratch disease. *Necrotizing features* may be seen in bubonic plague, tularemia, anthrax, typhoid fever, melioidosis, and the entity known as Kikuchi necrotizing lymphadenitis (see next section).

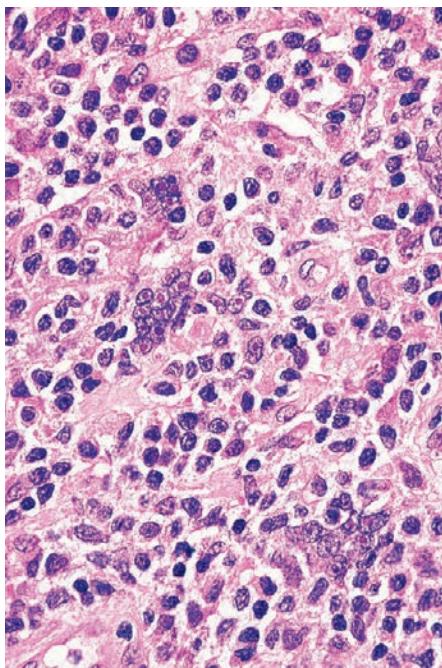


Figure 37.10 So-Called Polykaryocytes. These cells are characterized by numerous clustered nuclei.

Kikuchi Necrotizing Lymphadenitis

Kikuchi necrotizing lymphadenitis (Kikuchi lymphadenitis; Kikuchi-Fujimoto disease) is seen most commonly in Japan and other Asian countries,⁹⁴ but it also occurs elsewhere, including the United States and Western Europe. Most patients are young women with persistent, painless cervical lymphadenopathy of modest dimensions that may be accompanied by fever.⁹⁵ Microscopically, the affected nodes show focal, well-circumscribed, paracortical necrotizing lesions. There are abundant karyorrhectic debris, scattered fibrin deposits, and collections of mononuclear cells⁹⁶ with cellular debris but an absence of intact neutrophils (Fig. 37.11). Special studies have shown that the necrosis is the expression of cytotoxic lymphocyte-mediated apoptotic cell death.^{97,98} Plasma cells are very scanty, and intact neutrophils are absent, a feature of diagnostic importance.^{99,100} Instead, plasmacytoid dendritic cells, macrophages, and activated T cells are often numerous.^{89,101} When these cells are abundant, the appearance may simulate that of malignant lymphoma.^{102–104} The main lesional cells include histiocytes (CD68 and CD163+) that contain cytoplasmic myeloperoxidase and are associated with aggregates of plasmacytoid dendritic cells (TCL1 and CD123+).^{87,105} On occasion, a prominent secondary xanthomatous reaction is seen and may be prominent.¹⁰⁶ Such cases may lack areas of necrosis, but the apoptotic debris without neutrophils remains in association with the xanthomatous change. Ultrastructurally, tubuloreticular structures and intracytoplasmic rodlets similar to those described in lupus erythematosus are often found.¹⁰⁷

The diagnosis can be made or at least suspected in material from fine-needle aspiration because of the prominence of phagocytic histiocytes with peripherally placed ("crescentic") nuclei and medium-sized cells with eccentrically placed nuclei consistent with plasmacytoid dendritic cells.¹⁰⁸

The evolution is generally benign and self-limited. However, cases have been described with recurrent lymphadenopathy or accompanied by skin lesions.^{109,110} Isolated fatal cases are also on record.¹¹¹ The etiology is unknown. The most important differential diagnosis is

with malignant lymphoma with secondary necrosis and the admixed T-cell component with large crescentic histiocytes may be overinterpreted as a peripheral T-cell lymphoma. Lupus lymphadenitis may demonstrate features identical to Kikuchi lymphadenitis, and the possibility of lupus should be investigated in all cases.¹¹² The hematoxylin bodies of lupus, which are not always present, should not be seen with Kikuchi disease.

Chronic Nonspecific Lymphadenitis

The morphologic features and the very concept of chronic lymphadenitis merge with those of hyperplasia. The general features of chronic lymphadenitis are follicular hyperplasia; prominence of postcapillary venules; increased number of immunoblasts, plasma cells, and histiocytes; and fibrosis. The capsule may appear inflamed and/or fibrotic, and the process may extend into the immediate perinodal tissues. In some cases, one may find an undue predominance in the number of eosinophils, foamy macrophages, and/or mast cells. Terms such as *eosinophilic* or *xanthogranulomatous lymphadenitis* have been sometimes used, depending on the type of the infiltrate.¹¹³ The presence of numerous eosinophils in a lymph node should raise the possibility of Langerhans cell histiocytosis, parasitic infections, Hodgkin lymphoma, autoimmune disorders, and Kimura disease. Eosinophils can also be numerous in epithelioid hemangioma/angiolympoid hyperplasia with eosinophilia (which may rarely involve lymph nodes), Churg–Strauss disease, T-cell lymphomas, and various chronic eosinophilic neoplasms.

Tuberculosis

Lymph nodes involved by tuberculosis may become adherent to each other and form a large multinodular mass that can be confused clinically with metastatic carcinoma (Fig. 37.12). The most common location of clinically apparent lymphadenopathy is the cervical region ("scrofula"), where a draining sinus that communicates with the skin ("scrofuloderma") may form.¹¹⁴ Microscopically, the appearance ranges from multiple small epithelioid granulomas reminiscent of sarcoidosis to huge caseous masses surrounded by Langhans giant cells, epithelioid cells, and lymphocytes. Demonstration of the organisms by special stains, cultures, or PCR is necessary to establish the diagnosis.¹¹⁵

Atypical Mycobacteriosis

Atypical mycobacteria are a common cause of granulomatous lymphadenitis. In the United States, caseating granulomatous disease in a cervical lymph node of a child unaccompanied by pulmonary involvement is more likely to be caused by an atypical mycobacterium. The process typically involves lateral nodes in the midportion of the neck. Drainage may continue for months or years in the absence of specific therapy, and healing may result in scarring and contractures. Microscopically, the host reaction may be indistinguishable from that of tuberculosis, but often the granulomatous response is overshadowed by suppurative changes.^{116–118} A nontuberculous mycobacterial etiology should also be suspected if the granulomas are ill-defined (nonpalisading), irregularly shaped, or serpiginous.^{50,117} An acid-fast stain should be performed in every granulomatous and suppurative lymphadenitis of unknown etiology, especially if the patient is a child or an HIV-infected individual.¹¹⁹ The final identification of the organism rests on the culture or molecular characteristics.

In immunosuppressed patients, mycobacterial infections may result in a florid spindle cell proliferation that can simulate a neoplastic process (*mycobacterial spindle cell pseudotumor*).¹²⁰

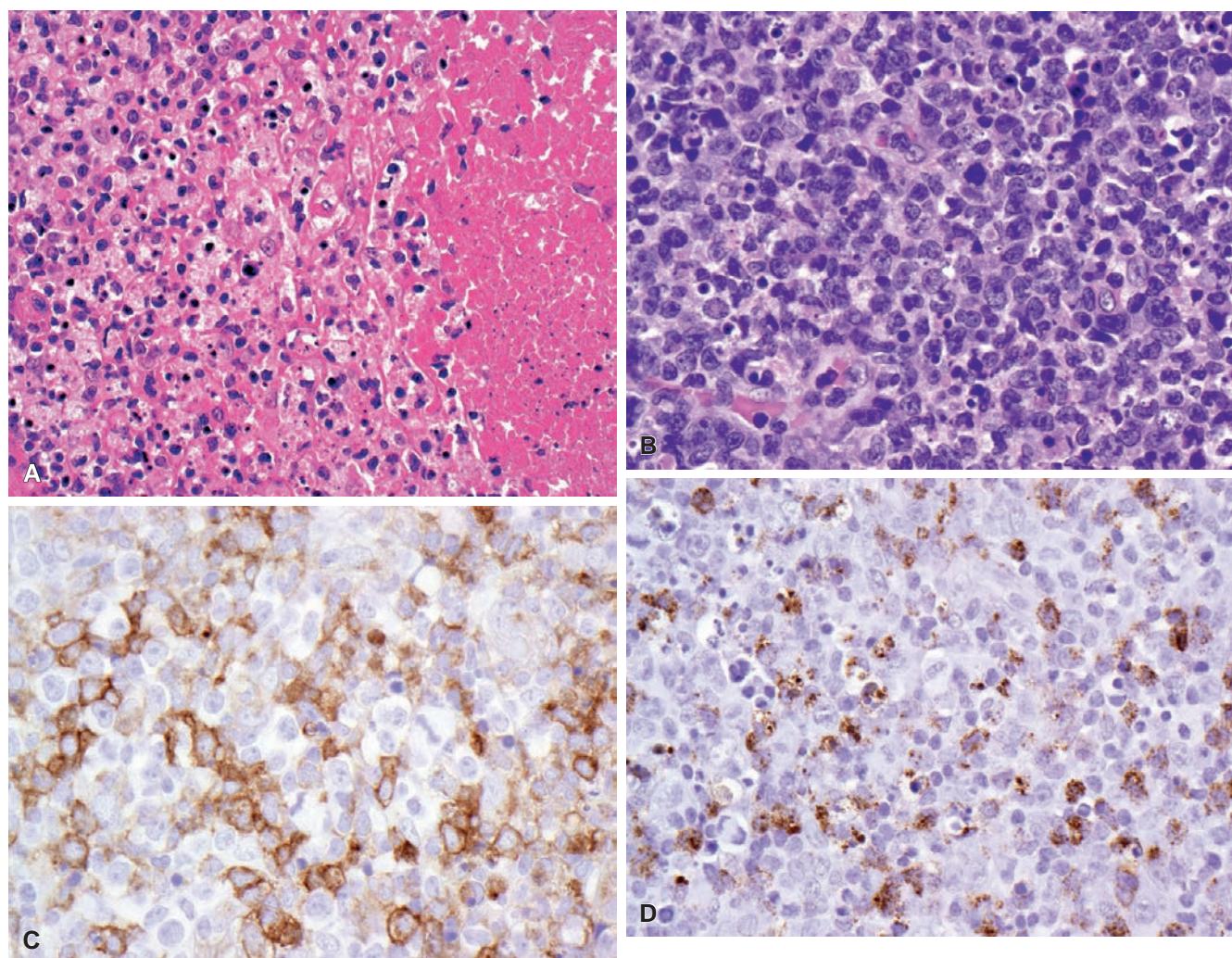


Figure 37.11 Necrotizing Lymphadenitis (Kikuchi-Fujimoto Disease). **A**, The most common pattern shows necrosis with karyorrhexis/pyknosis with nuclear debris but no neutrophils. **B**, Other cases show a more mononuclear infiltrate with debris without zonal necrosis. **C**, Increased numbers of CD123-positive cells, and **D**, myeloperoxidase positive histiocytes, support the diagnosis.



Figure 37.12 Large adherent tuberculous lymph nodes containing extensive foci of caseation necrosis.

Sarcoidosis

The enigmatic clinicopathologic entity known as sarcoidosis has a worldwide distribution.¹²¹ Scandinavian countries are particularly affected.¹²² In the United States, the disease is 10–15 times more common in blacks than in whites. Practically every organ can be involved, but the ones most commonly affected are lung, lymph nodes, eyes, skin, and liver.^{123–125} Erythema nodosum often precedes or accompanies the disease. Functional hypoparathyroidism is the rule, although a few cases of sarcoidosis coexisting with primary hyperparathyroidism have also been reported.^{126,127} This seems to be due to the secretion of a parathyroid hormone (PTH)-related protein by the cells in the granuloma.¹²⁸

Microscopically, the basic lesion is a small granuloma mainly composed of epithelioid cells, with scattered Langhans giant cells and lymphocytes (Fig. 37.13).¹²⁹ As a general rule, the Langhans giant cells are smaller and have fewer nuclei than those typically seen in tuberculosis. Necrosis is either absent or limited to a small central fibrinoid focus ("hard" granulomas); a "necrotizing" variant of sarcoidosis exists, but this is usually extranodal. Schaumann bodies, asteroid bodies, and calcium oxalate crystals are sometimes found

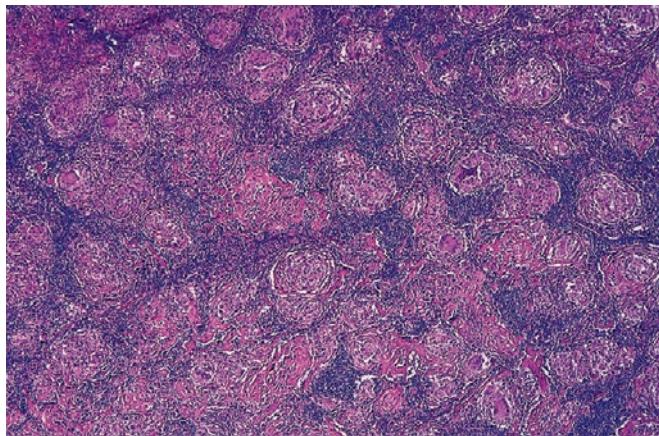


Figure 37.13 Numerous confluent non-necrotizing granulomas mainly composed of epithelioid cells in a lymph node affected by sarcoidosis.

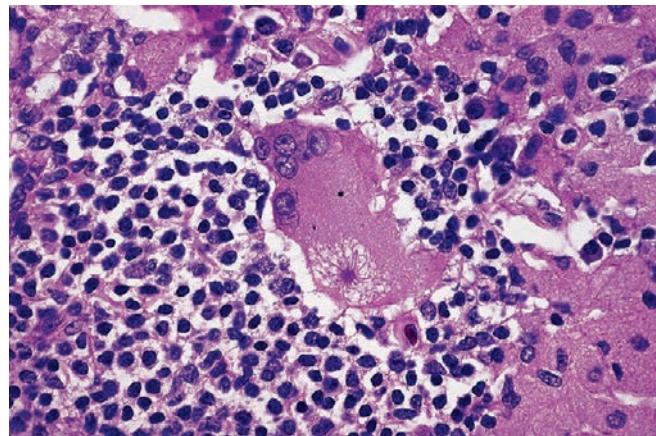


Figure 37.14 Asteroid body in the cytoplasm of a multinucleated giant cell in sarcoidosis.

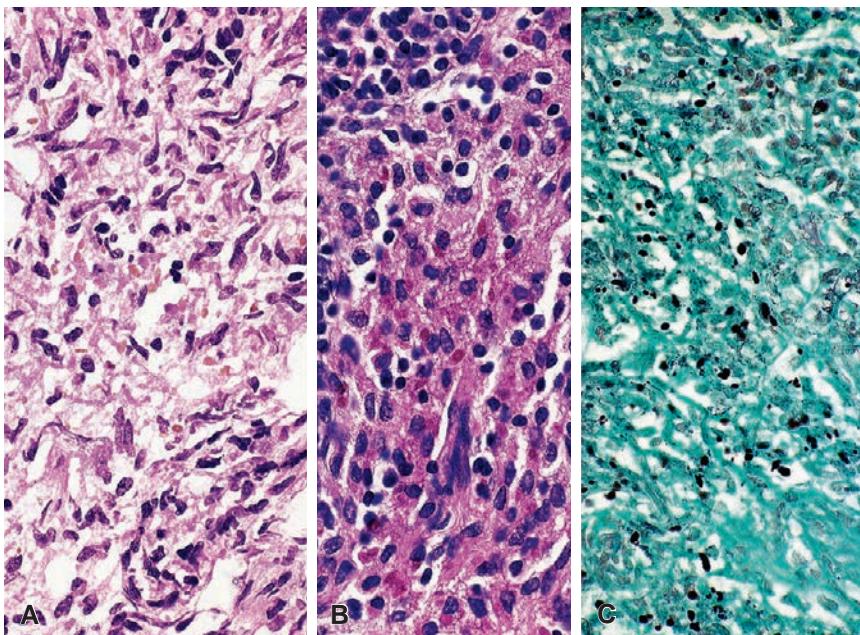


Figure 37.15 Hamazaki-Wesenberg bodies in a lymph node with sarcoidosis, as shown in (A) hematoxylin-eosin, (B) periodic acid-Schiff, and (C) Gomori methenamine-silver stains.

in the cytoplasm of the giant cells (Figs. 37.14 and 37.15).¹³⁰ Schaumann bodies are round, have concentric laminations, and contain iron and calcium. Ultrastructurally, asteroid bodies are composed of radiating filamentous arms enveloped by "myelonoid" membranes.¹³¹ Elemental analysis has shown calcium, phosphorus, silicon, and aluminum in these formations.^{129,131} Peculiar PAS-positive inclusions known as Hamazaki-Wesenberg, yellow, or ovoid bodies were claimed to be specific for sarcoidosis, but subsequent histochemical and ultrastructural studies¹³² have shown that they have no etiologic or pathogenetic significance. They probably represent large lysosomes containing hemolopofuscin material and are found in a large variety of conditions.^{130,133} None of these inclusions is specific for sarcoidosis. From a pathologic standpoint the diagnosis of sarcoidosis is always one of exclusion. A noncaseating granulomatous inflammation in the lymph nodes or skin microscopically indistinguishable from sarcoidosis can be seen in tuberculosis, atypical mycobacteriosis (including swimming pool granuloma), fungus diseases, leprosy,

syphilis, leishmaniasis, brucellosis, tularemia, chalazion, zirconium granuloma, berylliosis, Crohn disease, and Hodgkin lymphoma; in nodes draining a carcinoma; and in several other conditions.¹³⁴ Only when all these possibilities have been excluded and the clinical picture is characteristic is there justification in labeling a case as consistent with sarcoidosis.

Most of the lymphocytes present in the sarcoidal granulomas are CD4-positive T cells; both these cells and the epithelioid histiocytes exhibit features of proliferation and/or activation, as shown by their immunocytochemical positivity with the Ki-67 antibody and for interleukin-1, respectively.^{135,136} Pathogenetically, sarcoidosis is thought to represent a dysfunction of circulating T cells with overactivity of B cells.¹³⁷ The association of particular human leukocyte antigens (HLAs) with sarcoidosis suggests a role for HLA-linked immune response genes and disease susceptibility.¹³⁸ Specifically, it has been shown that certain types of genetic polymorphism are associated with increased risk of disease or affect disease presentation.¹³⁹

The Kveim test for sarcoidosis is an intradermal reaction that occurs following inoculation with an extract of human spleen involved with the disease. It is positive in 60%–85% of patients with sarcoidosis, and the number of false-positive results is small. The test is regarded as positive when a biopsy of the area taken 4–6 weeks after inoculation shows microscopically sarcoid-type granuloma. A trial employing a single test suspension among 2400 subjects in 37 countries on six continents showed a similar level of reactivity and microscopic appearance from country to country, supporting the concept that sarcoidosis is the same disease the world over. The Kveim test is rarely practiced today because of lack of availability of the antigen. The etiology and pathogenesis of sarcoidosis remain elusive.¹⁴⁰

Fungal Infections

Fungal infections of lymph nodes may present as chronic suppurative lesions, as granulomatous processes, or as a combination of the two. The most important fungal lymphadenitis is *histoplasmosis*, which in addition to the previously mentioned patterns can also result in widespread nodal necrosis and in marked diffuse hyperplasia of sinus histiocytes (Fig. 37.16). Other fungal diseases known to result in lymphadenitis are blastomycosis, paracoccidioidomycosis, coccidioidomycosis, and sporotrichosis.¹⁴¹ To these, one should add opportunistic infections such as cryptococcosis, aspergillosis, mucormycosis, and candidiasis.

The fungal organisms can usually be demonstrated with Gomori methenamine silver (GMS) or PAS–Gridley stains, but sometimes their number is so small that they can be detected only in cultures or by molecular testing.¹⁰

Toxoplasmosis

Toxoplasmosis, one of the most common parasitic infections of humans and other warm-blooded animals, is caused by the protozoan

parasite *Toxoplasma gondii*.¹⁴² Toxoplasmic lymphadenitis (formerly known as Piroinger–Kuchinka lymphadenitis), in its most typical form, involves the posterior cervical nodes of young women.¹⁴³ On palpation, the nodes are firm and only moderately enlarged. Microscopically, the nodal architecture is rather well preserved. The typical triad of the disease, which is not present in all cases, is constituted by: (1) marked follicular hyperplasia, associated with intense mitotic activity and phagocytosis of nuclear debris; (2) small, loose collections of epithelioid histiocytes, located within the hyperplastic follicles and at the periphery, encroaching on and blurring their margins; and (3) distention of marginal and cortical sinuses by monocytoid B cells (Fig. 37.17). An additional feature is the presence of immunoblasts and plasma cells in the medullary cords.¹⁴⁴ Variations on the theme include presence in

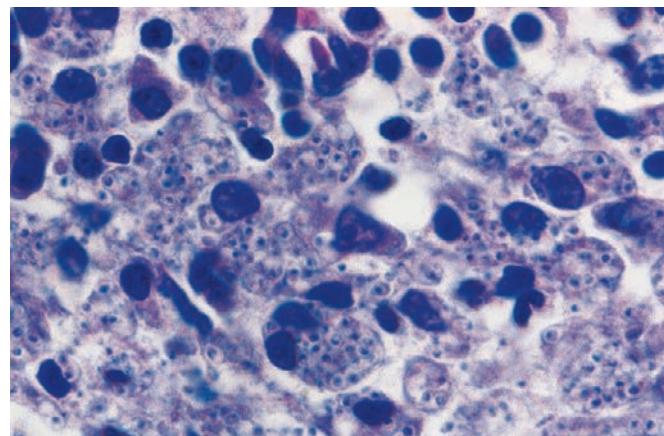


Figure 37.16 Numerous *Histoplasma* organisms in the cytoplasm of histiocytes.

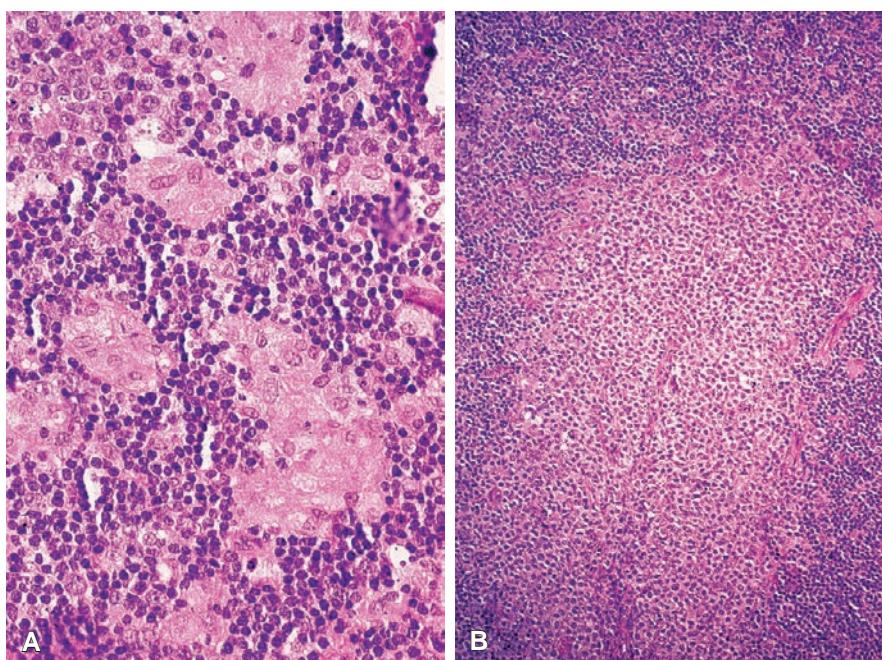


Figure 37.17 Toxoplasmosis of Lymph Node. **A**, Small noncaseating granulomas composed of epithelioid cells are located at the periphery of a hyperplastic follicle. This picture is almost pathognomonic of this disease. **B**, An area of massive monocyteid B-cell hyperplasia.

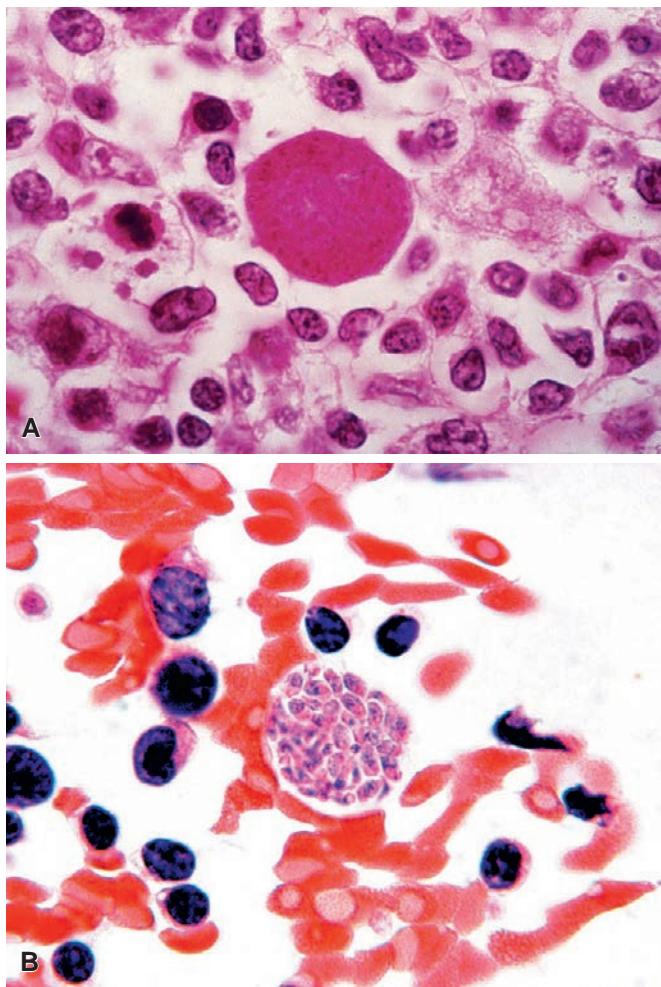


Figure 37.18 *Toxoplasma* cyst as seen in a microscopic section, (A) and a touch preparation (B). This is a very unusual finding in lymph nodes affected by the disease.

the granulomas of necrosis or more than an occasional Langhans giant cell.

It is extremely rare to find *Toxoplasma* organisms in the lymph node by morphologic examination, immunohistochemistry, or PCR (Fig. 37.18).^{145,146} This finding contrasts sharply with the results obtained in toxoplasmic encephalitis and myocarditis¹⁴⁶ and suggest that the lymph node findings may be an immunologic response to infection at other sites. The combination of microscopic features described correlates remarkably well with serologic studies. Of 31 cases studied by Dorfman and Remington¹⁴⁷ the Sabin-Feldman dye test was positive in all and the IgM immunofluorescent antibody test was positive in 97% of the cases.

If the diagnosis of toxoplasmic lymphadenitis is suspected from the microscopic pattern, it should be confirmed serologically, keeping in mind that these tests may be normal in the early stages of the disease.¹⁴⁸

The differential diagnosis of toxoplasmosis includes other infectious diseases and the lymphocyte predominant form of Hodgkin lymphoma. In this regard, Miettinen and Franssila¹⁴⁹ have made the interesting point that occurrence of collections of epithelioid cells *within* germinal centers seems to be a nearly specific feature for toxoplasmosis.

Syphilis

Generalized lymphadenopathy is a common finding in secondary syphilis, whereas localized node enlargement can be seen in the primary and tertiary stages of the disease. In secondary syphilis, the changes are those of a florid follicular hyperplasia. In primary syphilis, the combination of changes may result in a mistaken diagnosis of malignant lymphoma. Most of the cases have presented as solitary inguinal lymphadenopathy.¹⁵⁰ There are capsular and pericapsular inflammation and extensive fibrosis, diffuse plasma cell infiltration with extension often into or beyond the capsule, proliferation of blood vessels with endothelium swelling and inflammatory infiltration of vessel walls (phlebitis and endarteritis), and follicular hyperplasia (Fig. 37.19).¹⁵⁰ Rarely, noncaseating granulomas and abscesses are present. Exceptionally, the appearance is that of a nodal inflammatory pseudotumor, the message being that spirochetes should be searched for whenever making that diagnosis in a nodal biopsy, by histochemical or immunohistochemical stain.¹⁵¹

The morphologic features of syphilitic infection are not substantially different when occurring in HIV-infected patients¹⁵² and can be identified in most cases by the Warthin-Starry or Levaditi stains, by immunofluorescence techniques applied to imprint preparations, or immunohistochemical staining on paraffin section.¹⁵³ The organisms are most frequently found in the wall of blood vessels. Detection of *Treponema pallidum* is now also feasible in lymph node biopsies and fine needle aspirations by PCR.¹⁵⁴

Leprosy

Lymph nodes involved by the lepromatous type of leprosy have a very characteristic microscopic appearance. The main change is the progressive accumulation of large, pale, rounded histiocytes ("lepra" or "Virchow" cells), without granuloma formation and with minimal or no necrosis (Fig. 37.20). Wade-Fite and Fite-Faraco stains (which are modified Ziehl-Neelsen reactions) demonstrate packing of the cytoplasm by acid-fast organisms, which can also be demonstrated by a fluorescent method,¹⁵⁵ and by PCR.¹⁵⁶

Mesenteric Lymphadenitis

Mesenteric (Masshoff) lymphadenitis is produced by *Yersinia pseudotuberculosis* or *Yersinia enterocolitica*, two gram-negative polymorphic coccoid or ovoid motile organisms.¹⁵⁷⁻¹⁶⁰ It is a benign, self-limited disease that can clinically simulate acute appendicitis. Microscopically, there are capsular thickening and edema, increase of immunoblasts and plasma cells in the cortical and paracortical region, dilation of sinuses with accumulation of large lymphocytes within, and germinal center hyperplasia.^{161,162} In the lymphadenitis produced by *Y. pseudotuberculosis*, small granulomas and abscesses are commonly present, whereas this is unusual in infection caused by *Y. enterocolitica*.¹⁶² These nodal changes are accompanied by inflammatory changes of the terminal ileum and cecum. Ideally, the diagnosis should be confirmed with cultures. Too often, the diagnosis of mesenteric lymphadenitis is made on normal or mildly hyperplastic nodes in an attempt to explain why a patient with the clinical picture of acute appendicitis has a normal appendix.

The organism can be identified by PCR. Interestingly, *Yersinia* DNA has been detected in mesenteric lymph nodes in patients with Crohn disease.¹⁶³

Cat-Scratch Disease

Cat-scratch disease is characterized by a primary cutaneous lesion and enlargement of regional lymph nodes, usually axillary or cervical

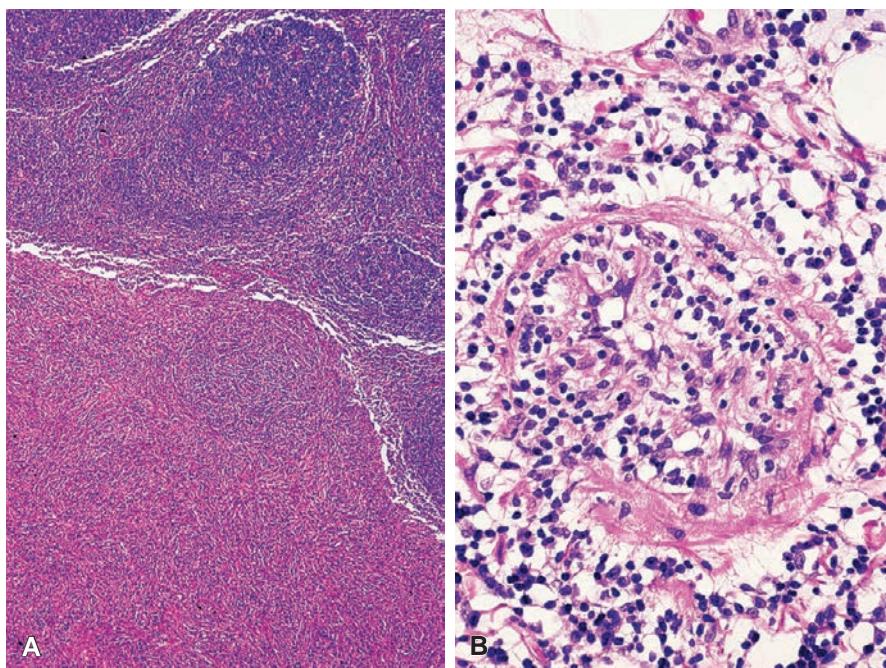


Figure 37.19 Syphilis of Lymph Node. **A**, Follicular hyperplasia associated with striking pericapsular inflammation and fibrosis. **B**, The prominent vasculitis seen in this field is an important clue to the diagnosis.

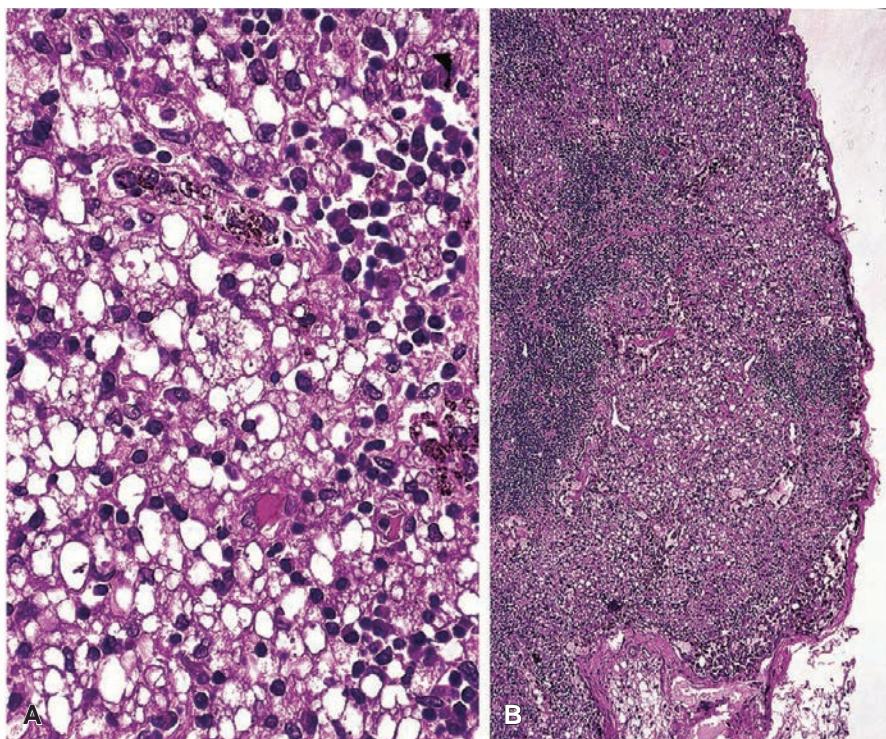


Figure 37.20 **A** and **B**, Lymph node involvement by lepromatous leprosy. The sinuses are massively dilated as a result of the accumulation of foamy histiocytes.

(Fig. 37.21).¹⁶⁴ The changes in the nodes vary with time. Early lesions have histiocytic proliferation and follicular hyperplasia, intermediate lesions have granulomatous changes, and late lesions have abscesses of various sizes (Fig. 37.22).¹⁶⁵ These abscesses are very suggestive of the diagnosis because of their pattern of central, sometimes stellate

necrosis with abundant neutrophils, surrounded by a palisading of histiocytes.¹⁶⁶ However, similar abscesses can be seen in lymphogranuloma venereum. Another common feature of lymph nodes with cat-scratch disease is the packing of sinuses by monocyteoid B cells, which, together with the follicular hyperplasia, may simulate

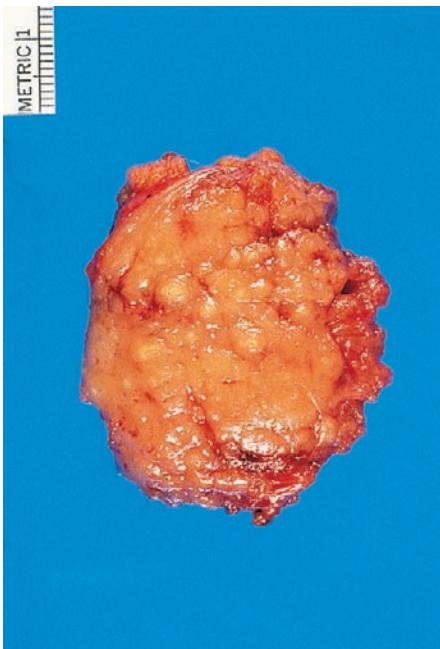


Figure 37.21 Lymph Node Involved by Cat-Scratch Disease.

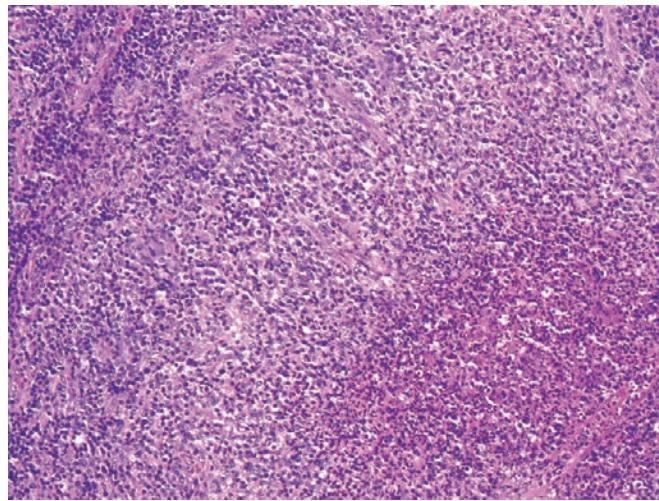


Figure 37.22 Cat-scratch disease with an area of stellate necrosis with neutrophils surrounded by histiocytes.

toxoplasmosis.⁸¹ However, clusters of perifollicular and intrafollicular epithelioid cells are absent.⁵⁵

The primary lesion is a red papule in the skin at the site of inoculation, usually appearing between 7 and 12 days following contact. It may become pustular or crusted. Microscopically, there are foci of necrosis in the dermis surrounded by a mantle of histiocytes. Multinucleated giant cells, lymphocytes, and eosinophils are also present.¹⁶⁷

The agent of cat-scratch disease is a coccobacillary pleomorphic extracellular bacterium that can be identified with the Warthin-Starry silver stain or by immunohistochemistry, particularly in those cases exhibiting extensive necrosis.^{168–170} This organism, which has also been detected ultrastructurally,¹⁷¹ was originally designated *Rochalimaea henselae* and has been renamed *Bartonella henselae*. The diagnosis can be confirmed by serology, immunohistochemistry, or PCR.^{172–175}

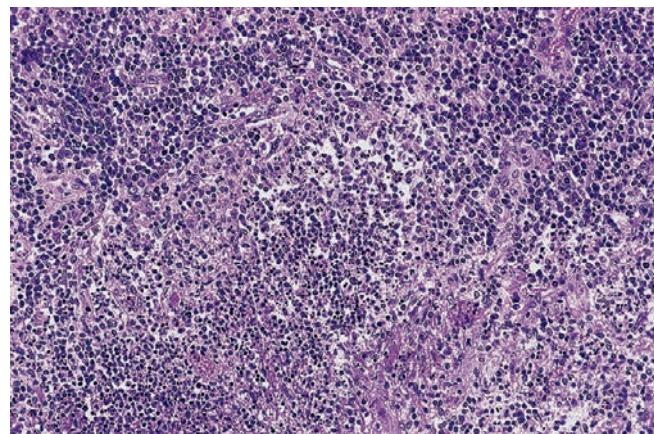


Figure 37.23 Necrotizing granuloma in a lymph node affected by lymphogranuloma venereum, showing features similar, if not identical, to cat-scratch disease.

Rare complications of the disease include granulomatous conjunctivitis ("oculoglandular syndrome of Parinaud"), thrombocytopenic purpura, and central nervous system manifestations.¹⁷⁶

Lymphogranuloma Venereum

This sexually transmitted disease (not to be confused with granuloma inguinale) is caused by *Chlamydia trachomatis* organisms corresponding to serotypes L1, L2, and L3.¹⁷⁷ The initial lesion is a small (2–3 mm), painless genital vesicle or ulcer that often goes unnoticed and heals in a few days. This is followed by inguinal adenopathy, which can be very prominent. As mentioned, the morphologic features are similar to cat-scratch disease, although the site of disease is a helpful clue to the diagnosis. The earliest microscopic change in an affected node is represented by tiny necrotic foci infiltrated by neutrophils. These enlarge and coalesce to form the stellate abscess that represents the most characteristic feature of this disease (Fig. 37.23). In later stages, epithelioid cells, scattered Langhans giant cells, and fibroblasts are seen to line the abscess walls. Confluence of these abscesses is common, and cutaneous sinus tracts may develop. The healing stage is represented by nodules with dense fibrous walls surrounding amorphous material.¹⁷⁸

The microscopic picture just described is not pathognomonic of this disease. Similar changes can occur in cat-scratch disease, atypical mycobacteriosis, and tularemia. Therefore a presumptive diagnosis of lymphogranuloma venereum should be confirmed with the Frei test (a delayed hypersensitivity skin test using purified "lygranum" chlamydial antigen), complement fixation, immunofluorescence, or molecular testing.^{177,179–181}

Tularemia

Tularemia is a bacterial disease produced by *Francisella tularensis*, an extremely virulent pathogen,^{182–184} which has recently gained notoriety as a potential biowarfare agent.^{185,186} In the ulceroglandular form of the disease, prominent lymphadenopathy occurs; this predominates in the axillary region when mammalian vectors are involved and in cervical or inguinal regions with arthropod vectors.¹⁸⁷ A history of handling rabbits suggests the diagnosis in the first instance. The diagnosis is supported by a rise in hemagglutinin titers.^{183,188}

Microscopically, the picture in the acute phase is that of an intense lymphadenitis with widespread necrosis, sometimes associated with

irregularly shaped microabscesses and granulomas.¹⁸⁵ In the more chronic forms, there is a granulomatous reaction that in some cases may have a frankly tuberculosis-like appearance.¹⁸⁹ Although the histologic and cytologic features are not specific, fine-needle aspiration specimens may be useful to obtain material for molecular identification of the organism.¹⁹⁰

Brucellosis

Brucellosis is caused by *Brucella abortus*, *melitensis*, or *suis*.¹⁹¹ In the United States it has evolved from an occupational to a food-borne illness related to consumption of milk and cheese.¹⁹² The most common clinical manifestations are fever, hepatomegaly, and splenomegaly.¹⁹³ Lymphadenopathy is uncommon and, when present, usually of modest dimensions. Microscopically, there may be nonspecific follicular hyperplasia and clusters of epithelioid histiocytes sometimes forming large noncaseating granulomas. This is accompanied by a polymorphic infiltrate containing eosinophils, plasma cells, and immunoblasts. When the latter are numerous, the microscopic picture may show a vague resemblance to Hodgkin lymphoma.

A definitive diagnosis can only be made by recovery of the organism with bacteriologic or PCR techniques¹⁹⁴ or the detection of a high agglutination titer.¹⁹⁵

Acquired Immunodeficiency Syndrome–Related Lymphadenopathy

The lymph node abnormalities in AIDS patients can be of various types. They include mycobacterial and other opportunistic infections (some resulting in spindle cell pseudotumors),^{120,196} Kaposi sarcoma, malignant lymphomas of either Hodgkin or non-Hodgkin type, and *florid reactive hyperplasia*.^{197–199} The lymphomas, discussed later, and reactive hyperplasia are the most common (Fig. 37.24). Hyperplasia

may be accompanied by collections of monocyteid B cells in the sinuses, neutrophils, and features of dermatopathic lymphadenopathy. In many of the cases, the reactive germinal centers show a feature termed *follicle lysis*, characterized by invagination of mantle lymphocytes into the germinal centers, and this feature is often associated with interfollicular hemorrhage. Follicle lysis is associated with disruption of these centers ("moth-eaten appearance") and a distinctive clustering of large follicular center cells,^{200,201} resulting in an appearance that has been termed *explosive follicular hyperplasia*. Ultrastructurally, a prominence of follicular dendritic cells exhibiting alterations of their fine processes has been described;²⁰² it has been suggested also on the basis of immunohistochemically (fascin stain) that the AIDS virus preferentially infects these cells.^{203,204} It has been suggested that the polykaryocytes (Warthin–Finkeldey cells) that are sometimes seen in HIV-infected nodes are a multinucleated form of follicular dendritic cell.⁹³ Immunohistochemically, positive stain for the HIV core protein P24 has been documented within the abnormal germinal centers.^{205,206}

This combination of follicular changes is not pathognomonic of AIDS, but the possibility of this disease should be considered and investigated whenever they are found, such as by immunostaining for P24 or by serologic study.²⁰⁵

Some lymph nodes in untreated AIDS patients may also show advanced lymphocyte depletion, with or without abnormal (regressively transformed) germinal centers.^{200,202}

The interfollicular tissue may show prominent vascular proliferation, the resulting picture acquiring a vague resemblance to Castleman disease. It is important to search in these areas and in the subcapsular region for the earliest signs of development of Kaposi sarcoma.²⁰⁷ These changes should be distinguished from those of vascular transformation of the sinuses.

A rough relationship has been found among the pattern of nodal reaction, the cell suspension immunophenotypic data, and the patient's HIV status.^{208,209}

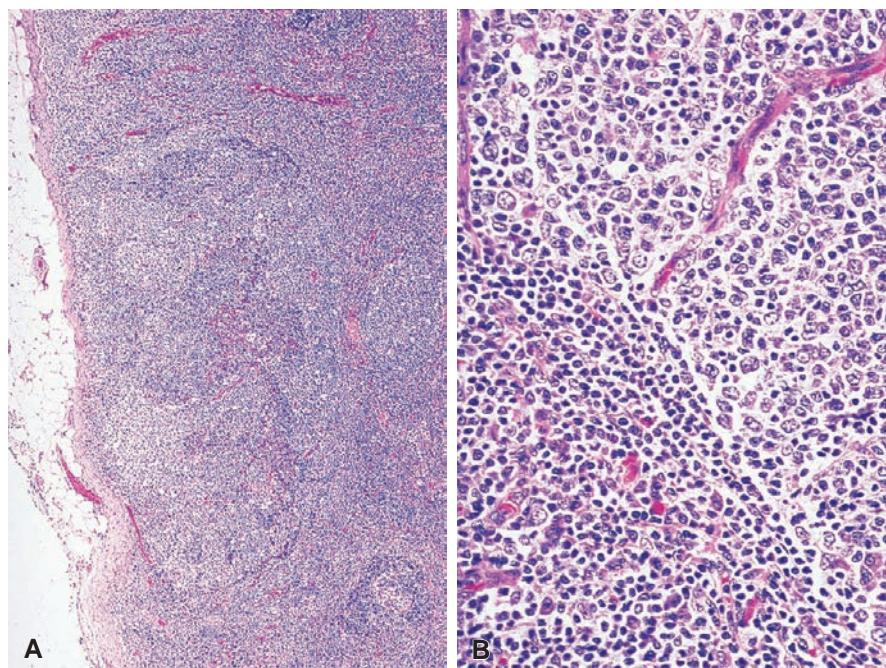


Figure 37.24 Low-power (A) and high-power (B) microscopic views of AIDS-related lymphadenopathy. The depicted germinal center shows disruption of its architecture by intrusion of small lymphocytes from the mantle zone. This is a common but not pathognomonic feature of this disease.

The term *chronic lymphadenopathy syndrome* has been defined as an unexplained enlargement of nodes of at least 3 months' duration at two or more extrainguinal sites in an individual at risk for AIDS.²¹⁰ The microscopic picture is similar to that described previously.²¹¹ Overall, up to a fourth of the patients have developed AIDS on follow-up, cachexia and weight loss being the clinical signs of this progression.^{212,213}

The HIV-associated lymphoproliferative diseases of lymph nodes are discussed later in this chapter.

Infectious Mononucleosis

The etiologic agent of classic infectious mononucleosis is EBV,²¹⁴ but other agents may be involved in atypical cases.²¹⁵ It is rare for the pathologist to see a lymph node from a patient with a typical clinical picture because in most instances the presumptive clinical diagnosis is confirmed by examination of the peripheral blood and serologic evaluation without need of a lymph node biopsy.²¹⁶ It is in the atypical case, presenting with lymphadenopathy without fever, sore throat, or splenomegaly, that the clinician will perform a lymph node biopsy to rule out the possibility of malignant lymphoma.

Microscopically, nodes and other lymphoid organs affected by infectious mononucleosis can be confused with malignant lymphoma because of the effacement of the architecture; infiltration of the trabecular, capsule, and perinodal fat; and the marked proliferation of immunoblasts, immature plasma cells, and mature plasma cells ("polymorphic B-cell hyperplasia") (Figs. 37.25 and 37.26). These features are particularly prominent when the disease develops in transplant recipients or other immunosuppressed patients.²¹⁷ Necrosis may also be present; this is usually only focal, but in immunodeficient children it may be massive.

Features of importance in the differential diagnosis with lymphoma include the predominantly sinus distribution of the large lymphoid cells, follicular hyperplasia with marked mitotic activity and phagocytosis (these follicles being usually small), increase in the number of plasma cells, often polymorphic in appearance, and vascular proliferation.²¹⁸ Another important feature is the fact that, although the nodal architecture may appear effaced, the sinus pattern remains intact or even focally accentuated. Another characteristic feature of this disease is the presence in the sinuses of clusters or "colonies" of lymphocytes in graduated sizes, from the small lymphocyte to the large lymphoid cell or immunoblast, often with plasmacytoid features.²¹⁹ The immunoblasts usually have only one large vesicular

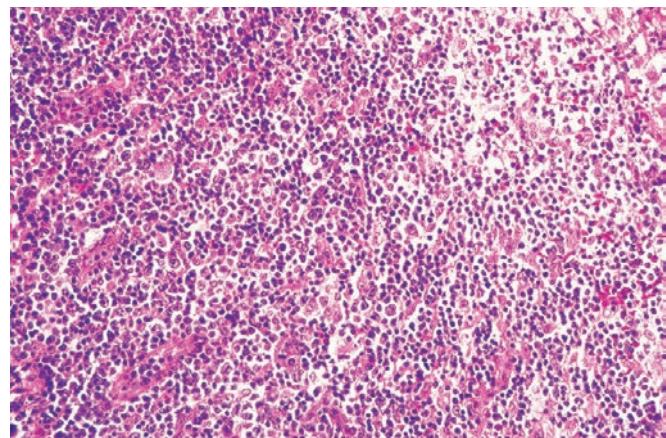


Figure 37.25 Lymph Node Involved by Infectious Mononucleosis. There is a marked effacement of the architecture by a polymorphic lymphoid infiltrate.

nucleus with a thin nuclear membrane and one or two prominent amphophilic or basophilic nucleoli. A paranuclear "hof" is often seen. When binucleated, this cell may closely resemble a Reed-Sternberg cell and result in a mistaken diagnosis of Hodgkin lymphoma (see Fig. 37.26).^{220,221} A combination of immunophenotyping and *in situ* hybridization for EBV should resolve the issue in most cases (Fig. 37.27),²²²⁻²²⁴ but it should be recognized that many enlarged, EBV-infected cells that may morphologically mimic Hodgkin cells will also express CD30²²⁵ and the neoplastic cells of approximately 40% of cases of classical Hodgkin lymphoma will be EBV positive. The EBV infection in Hodgkin disease, however, is largely restricted to the neoplastic cells, while in infectious mononucleosis the EBV positive cells are more variable in size and include small cells. Because of the morphologic overlap between infectious mononucleosis and Hodgkin lymphoma and even DLBCL, extreme caution should be used before diagnosing either malignancy in immunocompetent adolescent or young adults in the head and neck region, especially on a tonsil biopsy.

Other Viral (Including Postvaccinal) Lymphadenitides

Lymph nodes draining an area of the skin subjected to smallpox vaccination can enlarge and become painful. If removed and examined microscopically, they can be easily confused with lymphoma, especially if the history of vaccination is overlooked. Of 20 cases of postvaccinal lymphadenitis reported by Hartsock,²²⁶ 13 were located in the supraclavicular region on the side of the vaccination. The largest node measured 6 cm in diameter. The interval between the vaccination and the biopsy varied between 1 week and 3 months.

Microscopically, the changes are those of a diffuse or nodular paracortical expansion, with mixed cellular proliferation, consisting of eosinophils, plasma cells, and a large number of immunoblasts. The alterations are accompanied by vascular and sinus changes and focal discrete necrosis. The most important histologic feature of postvaccinal hyperplasia is the presence of numerous immunoblasts scattered among the lymphocytes and imparting to the lymphoid tissue a mottled appearance (Fig. 37.28). Hartsock²²⁶ noted that follicular hyperplasia was present only in those nodes removed more than 15 days after vaccination. These changes have been reproduced experimentally.²²⁶

Viral lymphadenitis resulting from *herpes simplex infection* may be localized²²⁷ or generalized.²²⁸ The morphologic features are similar to those of postvaccinal lymphadenitis, particularly in reference to the marked immunoblastic proliferation.^{229,230} Intranuclear viral inclusions may be found, especially at the edge of necrotic areas.²³¹⁻²³³ The nodal changes seen in herpes zoster lymphadenitis and infectious mononucleosis are of similar nature; the latter are discussed under a separate heading (see preceding section). It is likely that analogous morphologic changes occurring in the absence of these clinical conditions are, in most cases, the result of some unidentified viral infection.

Prominent regional lymphadenopathy also may follow the administration of live attenuated measles virus vaccine. Microscopically, the typical multinucleated giant cell of Warthin-Finkeldey (polykaryocytes) may be found (see Fig. 37.10).²³⁴

Mucocutaneous Lymph Node Syndrome

Mucocutaneous lymph node syndrome, also known as Kawasaki syndrome, is a febrile disorder of unknown etiology usually affecting children, originally described in the Japanese literature but having a worldwide distribution.²³⁵ Fever, cervical lymphadenopathy, pharyngeal and conjunctival inflammation, and erythematous skin

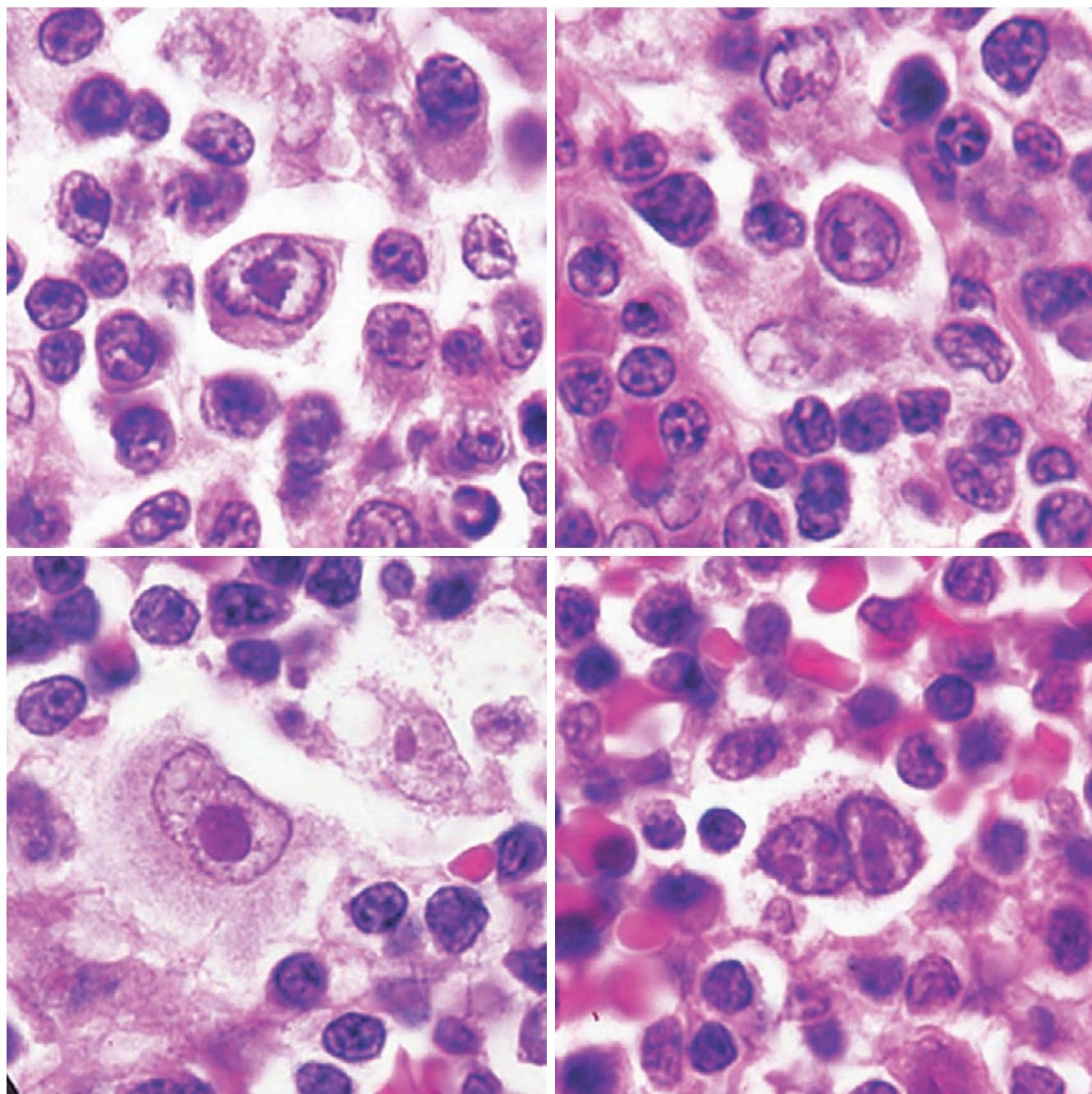


Figure 37.26 Various types of immunoblast seen in a lymph node involved by infectious mononucleosis. The binucleated form (shown in the fourth image) can simulate Reed–Sternberg cells. Note the basophilic character of the nucleus and the presence of a paranuclear hof. Also note the variability in size of background lymphocytes that also demonstrate a plasmacytoid appearance. This variability is characteristic of infectious mononucleosis.

rashes are the most common clinical symptoms. Sometimes lymphadenopathy represents the dominant manifestation of the disease.²³⁶ Arthritis is present in approximately 40% of the cases. Coronary arteritis may lead to fatal complications. The etiology is unknown, but an infectious agent is suspected.

Microscopically, the affected lymph nodes often show fibrin thrombi in the smaller vessels accompanied by patchy infarcts/areas of nongranulomatous necrosis with or without neutrophils.^{237,238} These changes have been interpreted as the expression of an acute

vasculitis. The main differential diagnosis is Kikuchi necrotizing lymphadenitis, but the presence of thrombi would favor Kawasaki disease. Persistent damage to the coronary arteries occurs in approximately one-fourth of untreated children.²³⁹

Lupus Erythematosus

The lymph node changes in lupus erythematosus are generally of a nonspecific nature and consist of moderate follicular hyperplasia

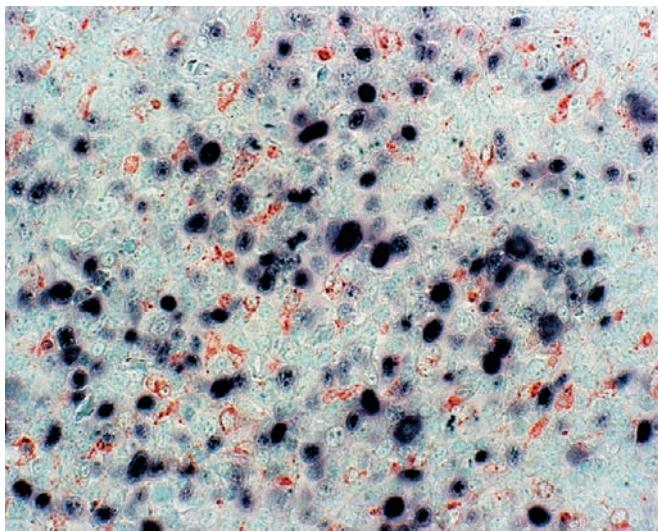


Figure 37.27 Demonstration of EBV EBER by *in situ* hybridization in a case of infectious mononucleosis. Note that both large and small cells are positive, in contrast to EBV+ Hodgkin lymphoma in which the EBV is primarily in large cells.

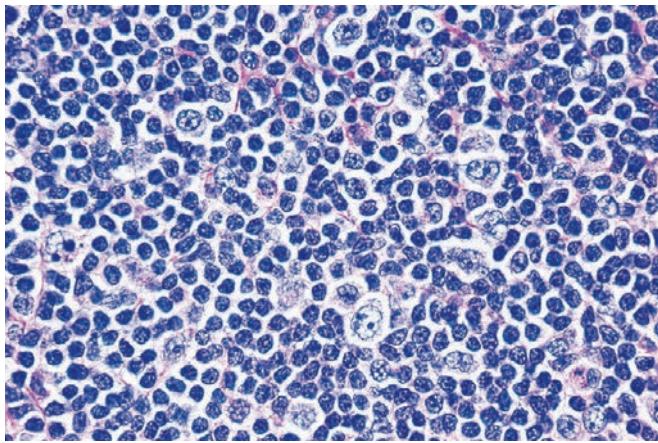


Figure 37.28 Viral lymphadenitis showing scattered immunoblasts resulting in a "salt-and-pepper" appearance.

associated with increased vascularization and scattered immunoblasts and plasma cells; some of the latter contain PAS-positive cytoplasmic bodies that represent sites of immunoglobulin production.²⁴⁰ Occasionally, one encounters a peculiar form of necrosis characterized by the deposition of hematoxyphilic material in the stroma, in the sinuses, and on the wall of blood vessels (Fig. 37.29).²⁴¹ These have been found to be composed of DNA derived from karyorrhectic nuclear material, presumably from lymphocytes. As mentioned previously, the microscopic appearance of lupus lymphadenitis may be indistinguishable from that of Kikuchi disease,²⁴² and some patients originally diagnosed with Kikuchi disease may actually represent an early presentation of systemic lupus erythematosus.¹¹² The presence of hematoxylin bodies is considered relatively specific for lupus over Kikuchi disease. On occasion the changes of lupus are morphologically similar to those of either the hyaline vascular or intermediate types of Castleman disease.^{243,240} In other instances, Warthin-Finkeldey-like polykaryocytes have been numerous.²⁴⁴ The immunophenotype of lupus lymphadenitis is nonspecific.²⁴¹

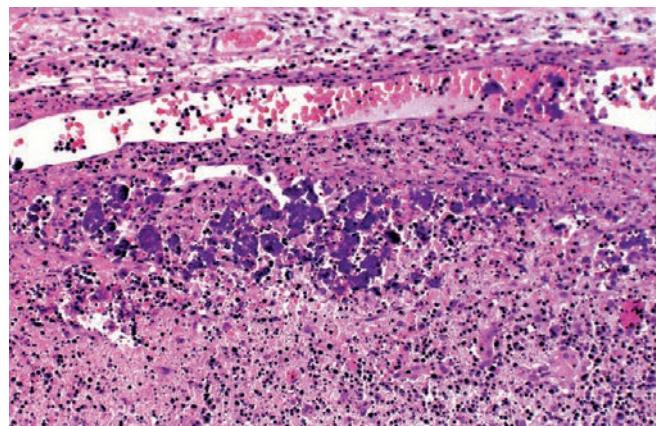


Figure 37.29 Large accumulations of DNA-containing basophilic material in the subcapsular region of a lymph node in a patient with systemic lupus erythematosus.

Rheumatoid Arthritis

Most patients with rheumatoid arthritis have generalized lymphadenopathy at some time during their illness.²⁴⁵ The lymph node enlargement may precede the arthritis and raise the clinical suspicion of lymphoma.

Microscopically, the most important changes are follicular hyperplasia and plasma cell proliferation, with formation of Russell bodies.²⁴⁶ Vascular proliferation is also a consistent finding. The appearance may be quite similar to that of the plasma cell type of Castleman disease. Small foci of necrosis and clumps of neutrophils are seen in some instances. The capsule is often infiltrated by lymphocytes. Immunohistochemically, the plasma cell proliferation is polytypic.²⁴⁷ Adult-onset Still disease can also result in an intense hyperplastic change that can vaguely resemble peripheral T-cell lymphoma.²⁴⁸ Other immune-mediated diseases, such as lupus erythematosus, polyarteritis nodosa, and scleroderma, are usually not associated with this type of lymph node abnormality.

Patients with rheumatoid arthritis treated with gold compounds can develop **gold-associated lymphadenopathy**.²⁴⁹ They are also said to have a slightly increased incidence of malignant lymphomas.^{250,251}

Castleman Disease

Castleman disease (giant lymph node hyperplasia) represents a morphologically distinct lymph node proliferation that in most cases is of unknown etiology. It occurs most commonly in adults, but it can also affect children.²⁵² Two major clinical and microscopic categories have been described that do not always correlate with each other.^{253,254} The first microscopic category, designated as *hyaline-vascular type* or *angiofollicular*, shows large follicles scattered in a mass of lymphoid tissue. The follicles show marked vascular proliferation and hyalinization of their abnormal germinal centers; they have been confused with Hassall corpuscles and with splenic white pulp, prompting in the first case a mistaken diagnosis of thymoma and in the second of ectopic spleen (Fig. 37.30). Their appearance corresponds to that of regressively transformed germinal centers. Many of the large cells with vesicular nuclei present in the hyaline center are follicular dendritic cells, as evidenced by their strong immunoreactivity for CD21 and CD35.²⁵⁵ There is a tight concentric layering of lymphocytes at the periphery of the follicles (corresponding to the mantle zone), resulting in an onion-skin appearance. The interfollicular stroma is also prominent, with

numerous hyperplastic vessels of the postcapillary venule type and an admixture of plasma cells, eosinophils, and immunoblasts, as well as tight collections of CD123-positive plasmacytoid dendritic cells and frequently admixed TdT-positive T cells.^{256–259} Sinuses are characteristically absent. In the variant of the hyaline-vascular type described as the *lymphoid subtype*, the follicles have a marked expansion of the mantle zone and small, relatively inconspicuous germinal centers. This variant of Castleman disease merges with the process known as *mantle zone hyperplasia*, and it is the one more likely to be confused with malignant lymphoma of either follicular or mantle cell type. Immunohistochemically, there is polyclonal immunoglobulin production by plasma cells, and large numbers of suppressor T cells are found in the interfollicular areas. An aberrant phenotype of Ki-B3–negative B lymphocytes has been detected in the mantle zone cells.²⁶⁰

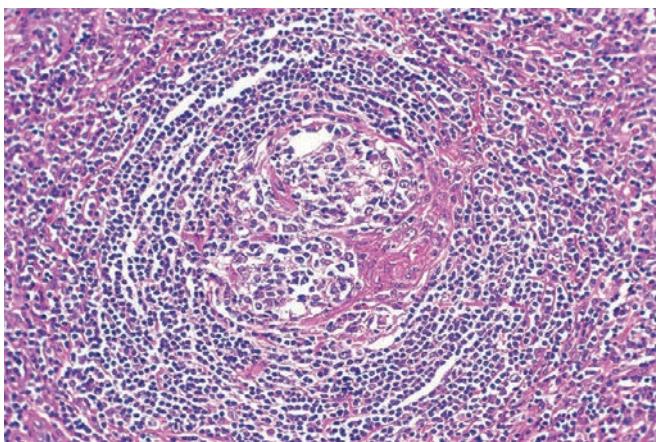


Figure 37.30 Castleman Disease of Hyaline Vascular Type. There is a prominent germinal center showing well-developed changes.

The second major morphologic category of Castleman disease is known as the *plasma cell type*.²⁵⁴ It is characterized by a diffuse plasma cell proliferation in the interfollicular tissue, sometimes accompanied by numerous Russell bodies. The hyaline-vascular changes in the follicles are inconspicuous or absent; instead, one often encounters in the center of these follicles a deposition of an amorphous acidophilic material that probably contains fibrin and immune complexes. The overall appearance is reminiscent of that seen in the lymph nodes from patients with rheumatoid arthritis (Fig. 37.31). The abundant expression of interleukin-6 that has been detected in this condition is thought to be responsible for the marked plasma cell infiltration.²⁶¹

Based on clinical presentation, Castleman disease has been divided into a solitary and a multicentric form. The *solitary form* presents as a mass located most commonly in the mediastinum but also described in the neck, lung, axilla, mesentery, broad ligament, retroperitoneum, soft tissues of the extremities (including subcutis and skeletal muscle),²⁶² nasopharynx, meninges, and several other sites.²⁶³ Grossly, it is round, well circumscribed, with a solid gray cut surface and can measure 15 cm or more in diameter (Fig. 37.32). Although this form by definition presents as a single mass, microscopic changes suggesting an early stage of the same process are sometimes seen in adjacent nodes. Microscopically, over 90% of the cases are of the hyaline-vascular type (including the lymphoid subtype), and the remainder are of the plasma cell type. The former is usually asymptomatic, whereas the plasma cell type is often associated with fever, anemia, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, and hypoalbuminemia. The disease reported in Asia as *idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinemia* is probably different from the plasma cell type of Castleman disease but may represent IgG4-related lymphadenopathy in a significant proportion of cases.^{264,265} The treatment of solitary Castleman disease is surgical excision, which has been found to result in rapid regression of the associated abnormalities whenever present.²⁶⁶

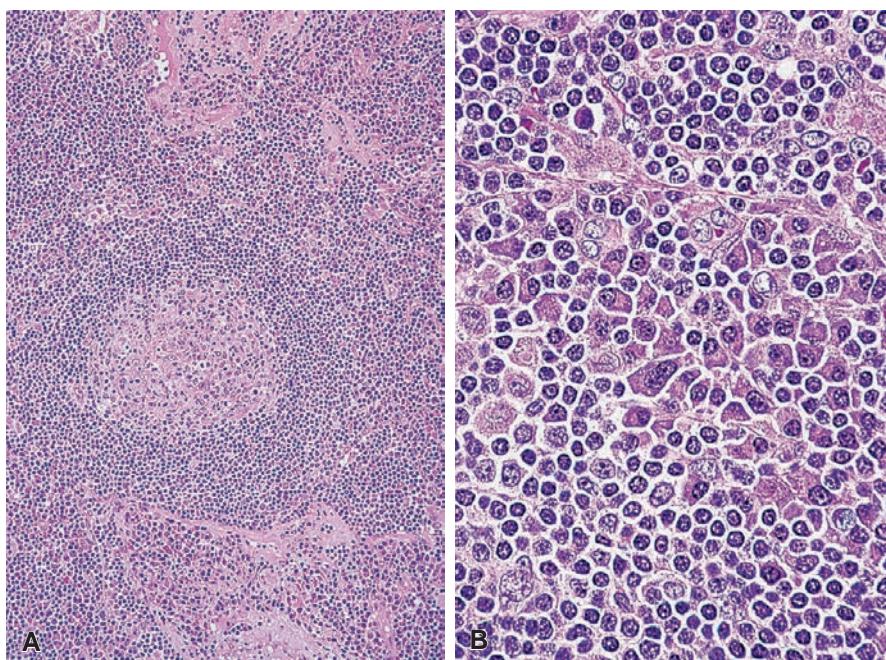


Figure 37.31 Castleman Disease of Plasma Cell Type. **A**, Low-power view showing follicular hyperplasia without hyaline vascular changes. **B**, High-power view of the interfollicular region showing a massive infiltration by plasma cells. Some of these plasma cells show multinucleation and mild nuclear atypia.

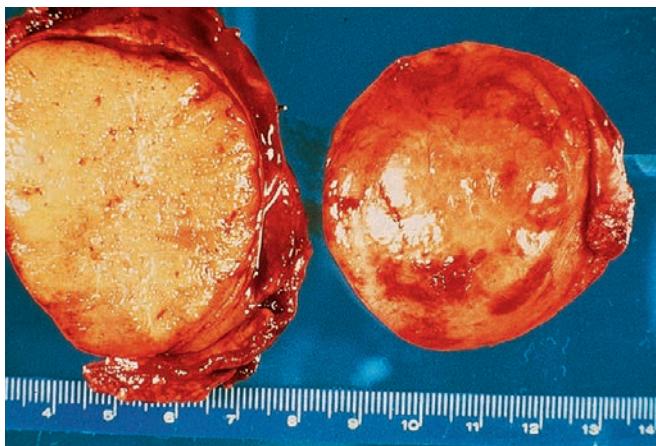


Figure 37.32 Gross appearance of Castleman disease of the hyaline-vascular type.

The *multicentric* or *systemic* form is nearly always of the plasma cell type,²⁶⁷ although occasional examples of the hyaline-vascular type (involving even the skin) are on record.²⁶⁸ It presents with generalized lymphadenopathy and may also involve the spleen.^{269–271} The etiology is unknown, the two main hypotheses (not mutually exclusive) being abnormal immune response and viral infection.²⁷² Regarding the latter, a definite link has been documented between HHV8 and multicentric Castleman disease (this virus being also linked to Kaposi sarcoma and primary effusion sarcoma and can be identified by immunohistochemistry).^{273–275} Cases of HHV8+ Castleman disease are said to be characterized morphologically by dissolution of the lymphoid follicles.²⁷⁶ It has been hypothesized that HHV8 induces the changes of Castleman disease through the production of interleukin-6.^{277,278}

Sometimes multicentric Castleman disease is seen in association with the POEMS syndrome, an acronymic designation for polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes.^{279,280} The latter include a distinctive vascular lesion known as glomeruloid hemangioma.²⁸¹ In other instances, Castleman disease has been reported in association with amyloid deposits.^{282,283}

The long-term prognosis of systemic Castleman disease is poor; the disease tends to persist for months or years and to result sometimes in renal or pulmonary complications.²⁸⁴ Furthermore, some of the patients have been found to have Kaposi sarcoma. Indeed, the coexistence of multicentric Castleman disease and Kaposi sarcoma in the same tissue sample is not an uncommon phenomenon.²⁸⁵ Other cases have developed large cell lymphomas with plasmablastic features, most of which are associated with HHV8 infection. Evidence of clonal rearrangement for immunoglobulin and T-cell receptor genes has been found in cases of systemic Castleman disease together with copies of the EBV genome; no such features having been detected in the solitary form of the disease.^{286–289} This suggests that multicentric Castleman disease is a disorder different from the classic localized type and one that may evolve into a clonal lymphoproliferation. Some authors actually regard it as a lymphoproliferative process rather than a reactive/inflammatory condition.

An important theme of the hyaline-vascular type of Castleman disease is the active participation of a variety of nonlymphoid cellular components. One such component is the follicular dendritic cell, which is prominently present in the hyalinized nodules that characterize the disease and which is thought by some authors to be at the core of the pathogenesis of this disorder (Fig. 37.33).^{290,291} These cells can become atypical ("dysplastic") both in the abnormal germinal centers and in the intervening tissue²⁹¹ and can manifest cytogenetic

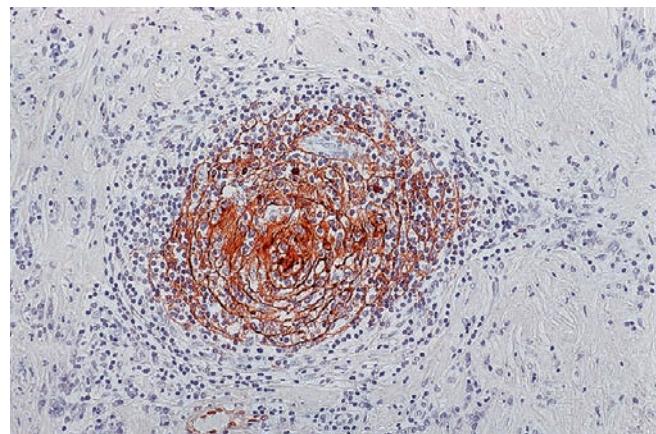


Figure 37.33 Prominent network of CD21-positive dendritic follicular cells in the abnormal germinal center of Castleman disease.

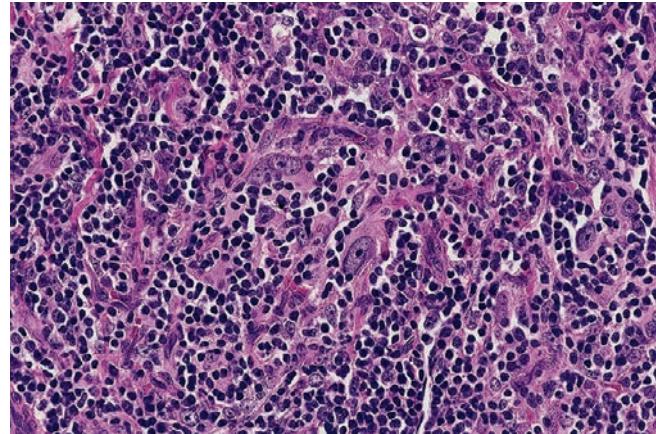


Figure 37.34 "Dysplasia" of Reticular/Dendritic Cells in Castleman Disease. These cells were immunoreactive for desmin.

and molecular evidence of clonality (Fig. 37.34).^{292–294} Furthermore, they may result in the formation of full-blown follicular dendritic cell tumors.^{295,296} Another type of proliferation involves the vascular and related contractile (myoid) elements that are present in the interfollicular tissue. Cases of Castleman disease in which these elements are unduly prominent have been referred to as *stroma rich* (Fig. 37.35).²⁹⁶ Further proliferation of this component results in the formation of *angiomoid proliferative lesions*,²⁹⁶ and of lesions that have been referred to as *angiomatous hamartomas* (Fig. 37.36)²⁹⁷ or *vascular neoplasms*, the latter sometimes having hemangiopericytoma-like features.²⁹⁸ Finally, cases have been described of high-grade spindle cell sarcomas arising in Castleman disease, which have been originally interpreted as of probable vascular nature because of the presence of myoid tumor cells adjacent to vascular structures (Fig. 37.37).²⁹⁹ Whether these myoid cells are truly vessel related or whether they originate from yet another member of the reticulum/dendritic cell family (so-called fibroblastic reticulum cells, myoid reticulum cells, or dycthyocytes) is not clear.

In the light of the above information, one might conclude that the neoplastic potentialities of Castleman disease tend to manifest themselves mainly through the development of lymphoid tumors in the plasma cell type and of dendritic/stromal tumors in the hyaline-vascular type. However exceptions occur, in the sense that isolated cases of the latter have been accompanied or preceded by

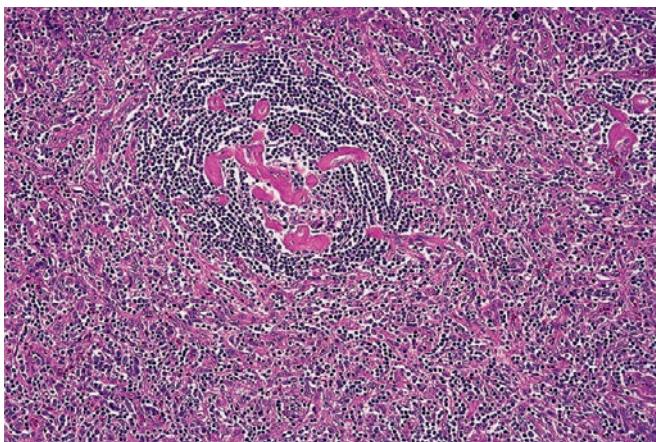


Figure 37.35 Castleman disease of hyaline vascular type with a prominent stromal component which is richly vascularized ("stroma-rich" variant).

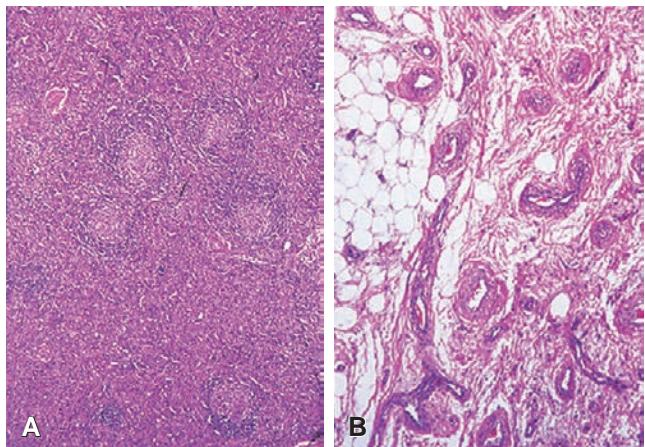


Figure 37.36 Castleman disease associated with vascular proliferation in the surrounding soft tissues. (Courtesy of Dr. Pietro Muretto, Pesaro, Italy.)

plasmacytoma,^{300,301} follicular lymphoma,^{302,303} and particularly Hodgkin lymphoma.^{304–306}

Drug Hypersensitivity

Antiepileptic drugs derived from hydantoin, such as diphenylhydantoin (Dilantin) and mephenytoin (Mesantoin), can result in a hypersensitivity reaction manifested by skin rash, fever, generalized lymphadenopathy (mainly cervical), and peripheral eosinophilia. The reaction, which is quite uncommon, tends to occur within the first few months of therapy. The changes disappear if the drug is discontinued. The nodal enlargement can occur in the absence of some of the other manifestations of the drug reaction.

Microscopically, partial effacement of the architecture by a polymorphic cellular infiltration is seen.³⁰⁷ Histiocytes, immunoblasts, eosinophils, neutrophils, and plasma cells are all present. Some of the immunoblasts have atypical nuclear features, including rare cases with Reed–Sternberg-like cells. Foci of necrosis were noted in the classic article by Salzstein and Ackerman in which this condition was first described.³⁰⁸ In some of the cases, the microscopic appearance may mimic viral infections, postvaccinal lymphadenopathy and even angioimmunoblastic T-cell lymphoma and classical Hodgkin lymphoma. Detailed medication history and clinical information

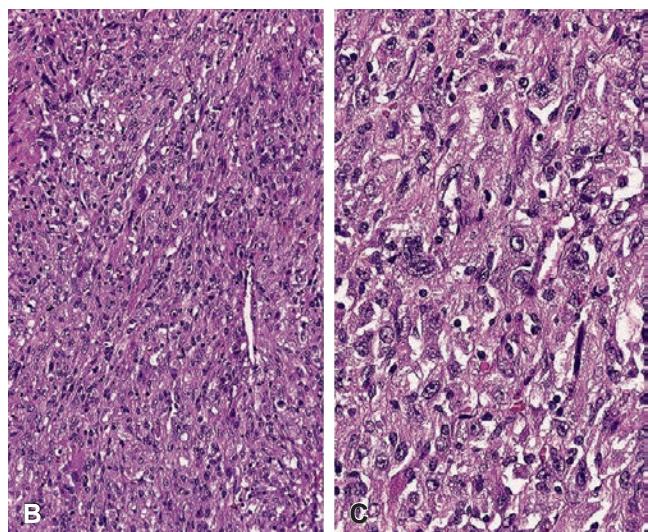


Figure 37.37 Castleman Disease Complicated by the Development of Sarcoma. **A**, Gross appearance of a case located in the perirenal region. **B**, Microscopic appearance of another case. The tumor has a vaguely hemangiopericytomatous quality. **C**, High-power view.

is needed to diagnose appropriately and the diagnosis might only be confirmed with clinical resolution after discontinuation of the drug.

Dermatopathic Lymphadenitis

Dermatopathic lymphadenitis (lipomelanosis reticularis of Pautrier) is a form of nodal hyperplasia usually secondary to a generalized dermatitis, particularly those with exfoliative features. Pathogenetically, it represents a T-cell response to skin antigens processed and presented by interdigitating dendritic cells. It may occur in any skin disorder in which itching and scratching are prominent; this includes inflammatory dermatoses such as psoriasis and neoplastic diseases such as mycosis fungoides. Rarely, the morphologic changes of dermatopathic lymphadenitis are seen in the absence of clinical skin disease.³⁰⁹

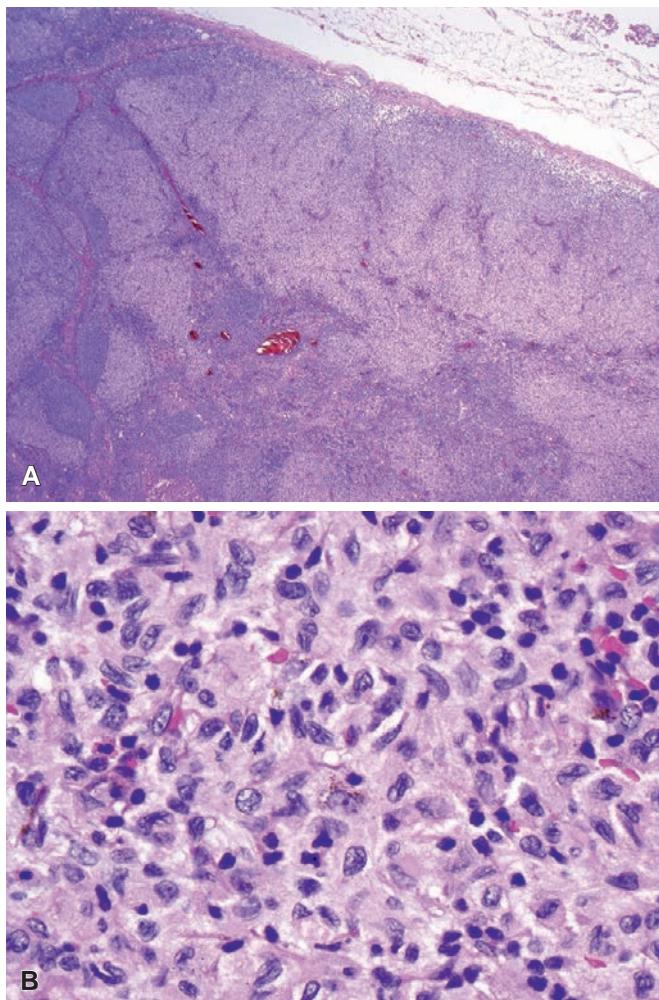


Figure 37.38 Dermatopathic Lymphadenitis. **A**, Massive expansion of the paracortical region, resulting in a wide, pale area between the capsule and the lymphoid follicles. **B**, High-power view of the paracortical region showing numerous cells with oval vesicular nuclei, which correspond to an admixture of interdigitating dendritic cells and Langerhans cells with nuclear grooves. Scattered cells containing pigment are also present.

Grossly, the lymph node is enlarged, the cut surface bulging, and the color pale yellow. In florid cases, black linear areas are seen in the periphery, representing clumps of melanin pigment and simulating the appearance of malignant melanoma.

Microscopically, the nodal architecture is preserved. The main change is represented by a marked pale widening of the paracortical zone, which stands out prominently on low-power examination (Fig. 37.38).³¹⁰ Most of the large nonlymphoid cells occupying this area are thought to be of three types: histiocytes, Langerhans cells, and interdigitating dendritic cells marking with a mix of CD163, CD1a, langerin, and S100 positivity.^{311,312} Many of the histiocytes contain phagocytosed melanin and neutral fat in their cytoplasm. Plasma cell infiltration and follicular hyperplasia are often present. A scattering of eosinophils also may be seen.

Nodes affected by dermatopathic lymphadenitis may be confused with Hodgkin lymphoma, mycosis fungoïdes, monocytic leukemia, or LCH. The differential diagnosis with mycosis fungoïdes is of particular concern because of the fact that mycosis fungoïdes is one of the cutaneous disorders that can be associated with dermatopathic lymphadenitis.^{313,314} Diagnostic assistance can be obtained from

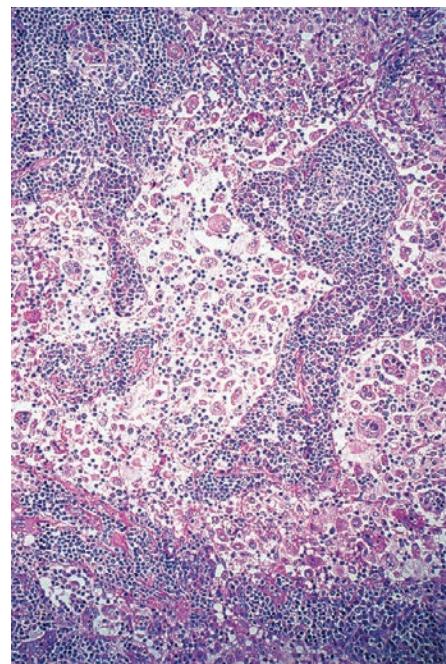


Figure 37.39 Rosai-Dorfman Disease. Low-power view showing massive distension of the sinuses by the histiocytic infiltrate.

immunohistochemistry and molecular pathology. Dermatopathic lymph nodes that are also involved by mycosis fungoïdes may show loss of CD7 and CD62L expression, and sometimes also loss of the pan-T-cell markers CD5, CD3, and CD2.³¹⁵ At the molecular level, clonal rearrangements of T-cell receptor genes may be demonstrated in cases involved by mycosis fungoïdes.³¹⁶ The presence of dermatopathic lymphadenitis in a patient with known mycosis fungoïdes, even in the absence of involvement by mycosis fungoïdes, is considered an abnormal finding and results in an N1 staging status and the need for molecular studies for T-cell receptor gene rearrangements.^{317,318}

Rosai-Dorfman Disease

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy (SHML), presents in its most typical form as massive, painless, bilateral lymph node enlargement in the neck, associated with fever, leukocytosis, elevated erythrocyte sedimentation rate, and polyclonal hypergammaglobulinemia.^{319,320} Most cases occur during the first or second decade of life, but any age group can be affected. A few cases have affected two members of the same family.³²¹ There is a predisposition for the condition in blacks. Although the disease has a widespread geographic distribution and most of the reported cases have been from the United States and Western Europe, there is a disproportionately high number of cases from Africa and the Caribbean region.³¹⁹ The cervical region is by far the most common and most prominent site of involvement, but other peripheral or central lymph node groups can be affected, with or without cervical disease.

Grossly, the nodes are matted together by prominent perinodal fibrosis. Their cut surface varies from gray to golden yellow, depending on the amount of fat present.

Microscopically, there is a pronounced dilation of the lymph sinuses, resulting in partial or complete architectural effacement (Fig. 37.39). These sinuses are occupied by lymphocytes, plasma cells, and—most notably—by numerous cells of histiocytic appearance

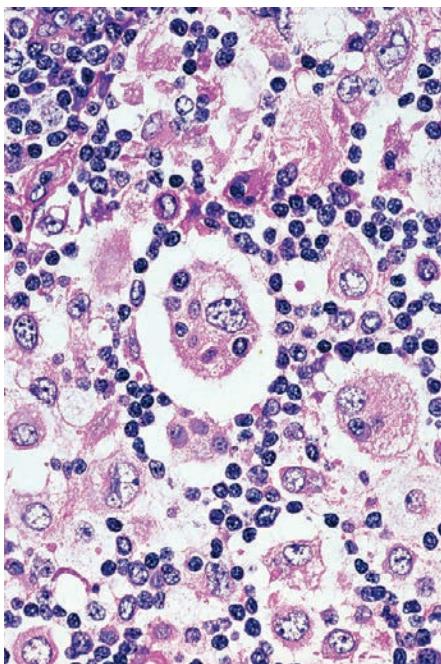


Figure 37.40 Rosai–Dorfman Disease. High-power view showing lymphocytophagocytosis by the sinus histiocytes.

with a large vesicular nucleus and abundant clear or lightly eosinophilic cytoplasm that may contain large amounts of neutral lipids. Many of these histiocytes have within their cytoplasm numerous intact lymphocytes, a feature that has been designated as emperipoleisis or lymphocytophagocytosis. Although not specific, this is a constant feature of RDD (as least in the lymph node location) and is therefore of great diagnostic significance (Fig. 37.40). Sometimes other cell types are present within the cytoplasm of the histiocytes, such as plasma cells and red blood cells.

The intersinus tissue exhibits a variable but sometimes impressive number of mature plasma cells, some of which may contain Russell bodies. Capsular and pericapsular inflammation and fibrosis are common, but intranodal fibrosis is minimal or absent. In a minority of cases, small microabscesses or foci of necrosis are found within the dilated sinuses. Ultrastructurally, the histiocytes located in the sinuses have extensive pseudopodia and lack Birbeck granules; viral particles or other evidence of infection is consistently lacking. The sinus histiocytes contain cytoplasmic fat (Fig. 37.41) and are strongly reactive for S100 protein³²² and CD68 (Fig. 37.42) but negative for CD1a; some of them are also positive for immunoglobulin, presumably phagocytosed from the surroundings. Their immunohistochemical profile (including the adhesion molecules pattern) suggests that they are monocytes that have been recently recruited from the circulation.^{323–326} The plasma cells show a polyclonal pattern of immunoglobulin expression. Some cases show an increase in IgG4-positive plasma cells and the relationship between RDD and IgG4-related disease requires clarification.^{327–329} The lymphocytes present are an admixture of B and T cells.

In over one-fourth of the cases, RDD involves extranodal sites.³¹⁹ This usually occurs in the presence of massive lymphadenopathy, and the disease is therefore easily recognized. However, in some cases these extranodal manifestations represent the predominant or even exclusive manifestation of the disease. Practically all organ systems have been recorded as being the site of the disease. The most common are eyes and ocular adnexa (especially orbit),³³⁰ head and neck region,³³¹ upper respiratory tract,^{332,333} skin and subcutaneous

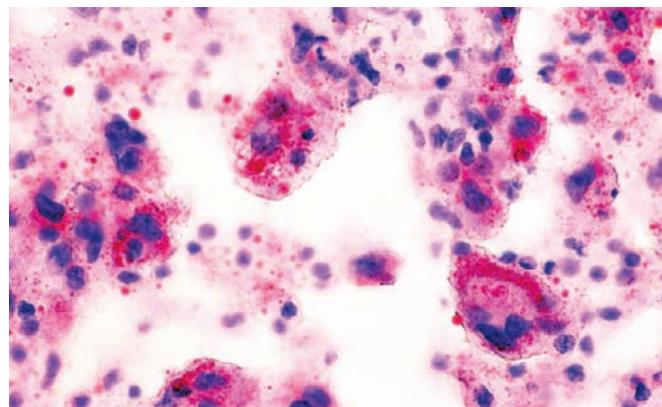


Figure 37.41 Rosai–Dorfman Disease. Oil red O stain showing abundant neutral lipid in the cytoplasm of the histiocytes.

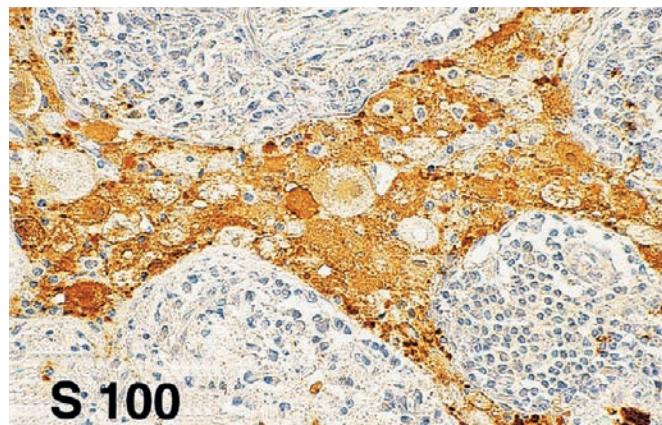


Figure 37.42 Strong immunoreactivity of the sinus histiocytes for S100 protein in Rosai–Dorfman disease.

tissue (perhaps more commonly in Asia),^{334–339} skeletal system,³⁴⁰ and central nervous system.^{341–343} However, the disease has been reported in many other sites, including gastrointestinal tract,^{344–346} pancreas,³⁴⁷ salivary glands,³⁴⁸ genitourinary tract, thyroid,³⁴⁹ mediastinum,³⁵⁰ breast,^{351,352} uterine cervix,³⁵³ and bone marrow.³⁵⁴ In some instances, widespread nodal and extranodal dissemination is found.³⁵⁵ Organs that stand out because of their almost universal sparing by the disorder are lung, and spleen, and bone marrow (the latter exclusive of the focal bone lesions mentioned previously). The histopathologic features of RDD in extranodal sites are similar to the nodal disease except for the fact that fibrosis tends to be more pronounced and emperipoleisis less conspicuous.

The etiology of RDD remains unknown, the two most likely possibilities (not mutually exclusive) being infection by a virus or some other microorganism and the manifestation of a subtle undefined immunologic defect. It has been suggested that stimulation of monocytes/macrophages via macrophage colony-stimulating factor (M-CSF) leading to immune suppressive macrophages may be the main pathogenetic mechanism.³⁵⁶ Despite some suggestive early data derived from serologic tests, most studies fail to demonstrate an infectious etiology.^{357,358} Molecular studies done on involved tissue have failed to show evidence of clonality, in keeping with their presumed reactive nature. This contrasts with the findings in at least some studies of LCH, a disease that it otherwise resembles in many clinical, morphologic, and phenotypic aspects,^{325,359,360} and with which it can coexist.^{361,362}

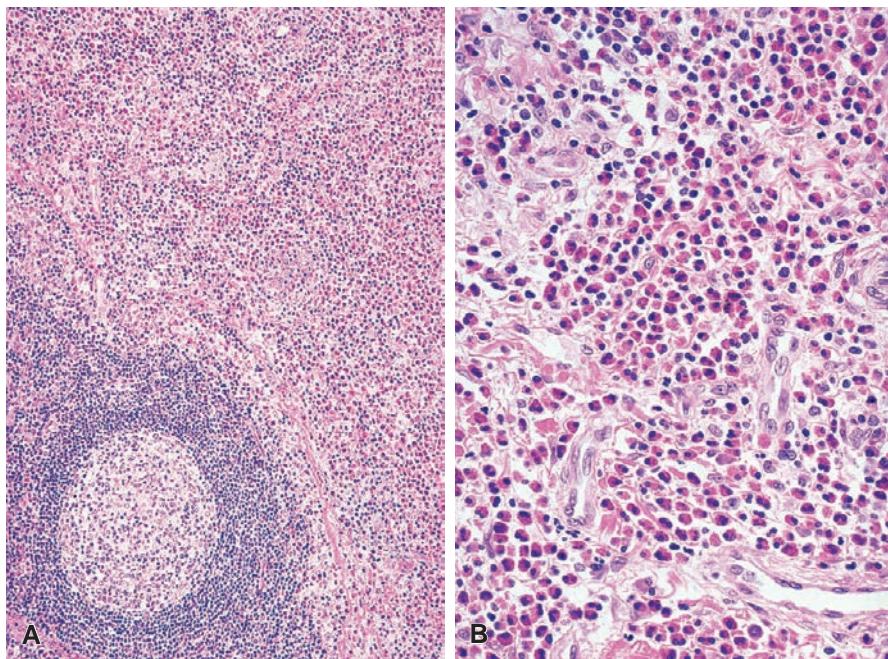


Figure 37.43 A and B. Lymph node involvement by Kimura disease. There is follicular hyperplasia and massive perinodal inflammation, which is predominantly composed of eosinophils. (Courtesy of Dr. T.-T. Kuo, Taipei, Taiwan.)

RDD is relatively unaffected by therapy, although chemotherapy has proved effective in some cases^{363–365} occasionally with allegedly complete and permanent results.³⁶⁶ In many cases, RDD undergoes quick and complete spontaneous resolution. In others, it follows a protracted clinical course for years or decades. The latter is particularly true in cases with widespread extranodal involvement. In some instances the disease disappears, only to come back years later at another site. Some patients have died as a result of RDD, either because of extensive disease affecting vital organs or because of complications related to the immunologic abnormalities that may be present,^{367,368} such as amyloidosis.³⁶⁹

The differential diagnosis of RDD includes nonspecific sinus hyperplasia (in which the cells lack emperipoleisis and are S100 protein-negative), LCH (in which the cells are positive for S100 protein, langerin, and CD1a), leprosy, rhinoscleroma (with which it can apparently coexist³⁷⁰), and metastatic malignant melanoma. Perhaps the condition that resembles it most is the sinus histiocytosis induced by cobalt-chromium and titanium that can occur in pelvic lymph nodes after hip replacement.³⁴⁴

It should also be noted that focal RDD-like changes can sometimes be seen in lymph nodes involved by other processes, such as Hodgkin³⁷¹ or non-Hodgkin lymphoma, a phenomenon analogous to that sometimes seen in LCH.³⁷² Similar changes can also occur in lymph nodes involved by ALPS.⁵²

Kimura Disease

Kimura disease is an inflammatory disorder of unknown etiology seen in an endemic form in Asia³⁷³ but also in other parts of the world, including the United States and Europe.³⁷⁴ It usually presents as a mass lesion in the subcutaneous tissue of the head and neck region or the major salivary glands, often associated with regional lymphadenopathy. Sometimes lymph node enlargement is the only manifestation of the disease.

Microscopically, the involved nodes show marked hyperplasia of germinal centers, a few of which may be of the progressively

transformed type. These germinal centers are often well vascularized and contain polykaryocytes, interstitial fibrosis, and deposition of a proteinaceous material. There is also extensive infiltration by mature eosinophils, with occasional formation of eosinophilic abscesses (Fig. 37.43). Hyalinized vessels are often seen in the paracortical region, and there is a variable degree of sinus and paracortical sclerosis. An increase in the number of plasma cells and mast cells has been noted in the paracortex,³⁷⁵ together with proliferation of postcapillary venules.³⁷⁴ Some cases are associated with increases in IgG4-positive plasma cells, a feature of unclear significance.³⁷⁶

Despite early statements to the contrary, current evidence strongly suggests that Kimura disease and the disease known to dermatologists as angiolympoid hyperplasia with eosinophilia are different entities (see Chapter 3); specifically, the former disorder lacks the epithelioid (histiocytoid) endothelial cells that are the morphologic hallmark of the latter.^{377–380} The differential diagnosis of Kimura disease includes parasitic infections as well as tissue manifestations of chronic eosinophilic leukemia and the related clonal eosinophilic disorders reviewed in Chapter 39.

Chronic Granulomatous Disease

Chronic granulomatous disease is the result of a genetically determined enzymatic defect of granulocytes and monocytes.^{381–383} These cells ingest microorganisms but are unable to destroy them because of their inability to generate superoxide anion (O_2^-). This is due to a defect in any one of five components of NADPH oxidases, the enzyme responsible for the generation of the anti-microbial oxidants.³⁸² A pattern of X-linked inheritance is seen in approximately 65% of the patients and results from mutations in the gene that encodes the $g91\text{-phox}$ subunit of the cytochrome b558 component of the oxidase. The remaining 35% of patients inherit the disease in an autosomal recessive manner resulting from mutations in the genes that encode the other three oxidase components.^{384–386}

The traditional laboratory technique for the detection of the disease is the nitro blue tetrazolium test although detection of dihydrorhodamine oxidation can be performed by flow cytometry.^{383,387}

The main clinical features are recurrent lymphadenitis, hepatosplenomegaly, skin rash, pulmonary infiltrates, anemia, leukocytosis, and hypergammaglobulinemia.³⁸⁸⁻³⁹⁰ Microscopically, granulomas with necrotic purulent centers are seen in lymph nodes and other organs. They closely simulate the appearance of cat-scratch disease and lymphogranuloma venereum. Collections of histiocytes containing a lipofuscin-like pigment are also commonly observed and represent an important clue to the diagnosis.³⁹¹

Lipophagic Reactions

Accumulation of neutral lipid with formation of foamy macrophages (xanthoma cells) can be seen as an inconsequential secondary event in a variety of inflammatory and neoplastic conditions of lymph nodes, including LCH, RDD, Erdheim–Chester disease, and Hodgkin lymphoma. There are, in addition, conditions in which the **lipophagic granuloma** is the primary alteration. The lipophagic granuloma is defined as a collection of mononuclear and multinucleated giant cells, both of them exhibiting a cytoplasmic foamy appearance and lacking a significant participation of other cell types. By far the most common situation in which this occurs (so common as to be nearly universal, at least in Western countries) is represented by the incidental microscopic finding in periportal and mesenteric nodes in asymptomatic individuals, probably the result of mineral oil ingestion (Fig. 37.44).³⁹² Boitnott and Margolis³⁹³ found this change in 78% of a series of 49 autopsied adults. Their chemical and histochemical studies showed that the oil droplets represent deposits of liquid-saturated hydrocarbons. Mineral oil is extensively used in the food processing industry, as a release agent and lubricant in capsules, tablets, bakery products, and dehydrated fruits and vegetables. Lipophagic granulomas of an extensive degree have been reported

in association with long-term total parenteral nutrition therapy for short bowel syndrome.³⁹⁴

Whipple disease can result in marked enlargement of mesenteric lymph nodes, with formation of numerous lipophagic granulomas.³⁹⁵ Collections of histiocytes containing a PAS-positive glycoprotein are also present.³⁹⁶ Under oil immersion and with electron microscopy, the characteristic bacillary bodies can be identified. Collections of PAS-positive histiocytes can also develop in peripheral nodes and may be the first clue to the diagnosis in a patient with gradual weight loss, weakness, and polyarthritis. Steatorrhea, the other classic symptom of the disease, may appear only in a later stage. In the presence of suggestive findings in routinely stained sections, confirmation of the diagnosis can now be obtained by the demonstration of the responsible organism (*Tropheryma whipplei*) by immunohistochemistry or PCR.³⁹⁷⁻³⁹⁹

Lymphangiography, a procedure now largely abandoned, induces a lipophagic granulomatous reaction that may persist for several months. The sinuses are markedly distended and lined by histiocytes, many of which are multinucleated. Eosinophils may be present in appreciable numbers in the medullary cords. This is preceded by a predominantly neutrophilic infiltration.⁴⁰⁰

Malignant Lymphoma

Malignant lymphoma is the generic term given to tumors of the lymphoid system and specifically of lymphocytes and their precursor cells, whether of T, B, or null phenotypes. Tumors now known to be composed of histiocytes, and other cells of the accessory immune system were previously included in the category of malignant lymphoma but are now regarded separately for both conceptual and practical reasons. Many tumors that were designated in the past as histiocytic lymphomas or reticulum cell sarcomas, however, are in reality of lymphocytic nature and therefore true malignant lymphomas and an interrelationship between some true histiocytic tumors and malignant lymphomas is becoming clear.⁴⁰¹

Although some overlapping exists, the term *malignant lymphoma* is reserved for those neoplastic processes that initially present as localized lesions and are characterized by the formation of gross tumor nodules. Conversely, neoplastic lymphoid proliferations that are systemic and diffuse from their inception are usually termed leukemias (see Chapter 39).

The malignant lymphomas can be divided into two major categories: Hodgkin lymphoma and all the others, which, for lack of a better term, are known collectively as non-Hodgkin lymphomas.⁴⁰²⁻⁴⁰⁶ Both groups are further subdivided into several more or less distinct subcategories, with the most currently and widely accepted classification being the 2016 WHO revision.⁴⁰⁷ This classification has incorporated a wealth of information gathered from the fields of immunophenotyping, molecular genetics, genomics, and proteomics but also relies on clinical information and morphology. While other classification systems, including those of Rappaport, Kiel, and the so-called Working Formulation,⁴⁰⁸⁻⁴¹⁰ have historic significance, they should no longer be used.

Hodgkin Lymphoma

The disease originally described by Thomas Hodgkin in 1832 and which Samuel Wilks first proposed to be called Hodgkin's disease makes one of the richest chapters of history of oncologic pathology.⁴¹¹⁻⁴¹⁴ The original color illustrations have become icons,⁴¹⁵ and the original cases, still housed at the pathology museum of Guy's Hospital in London, have been "exhumed" and studied microscopically and immunohistochemically, and the diagnosis has been confirmed (at least in some of the cases) after well over a

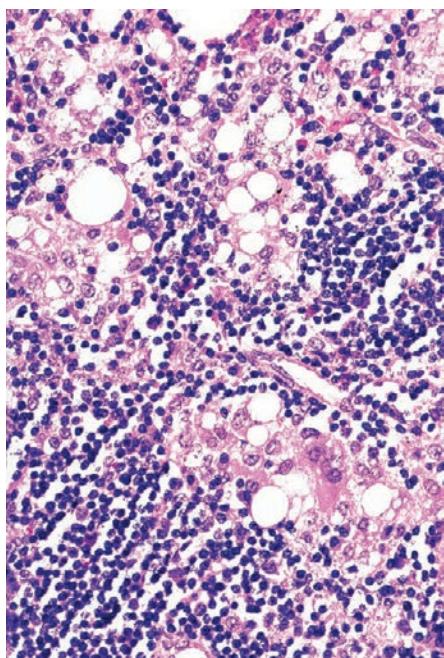


Figure 37.44 Lymph Node Containing Lipophagic Granulomas. The change is manifested by the presence of mononuclear and multinucleated histiocytes located in the sinuses and containing large cytoplasmic vacuoles.

century of fixation.⁴¹⁶ The interest in this enigmatic disease remains unabated, having been quoted as the paradigm for the emerging science of "molecular morphology."⁴¹⁴

The conventional definition of Hodgkin's disease, now termed Hodgkin lymphoma, is that of a type of malignant lymphoma in which Reed-Sternberg cells are present in a "characteristic background" of reactive inflammatory cells of various types, accompanied by fibrosis of a variable degree. This definition still applies, at least in part, for cases of so-called classical Hodgkin lymphoma, but it is now recognized that cases of nodular lymphocyte predominance Hodgkin lymphoma (NLPHL) are distinct from this group. While identification of typical Reed-Sternberg cells is useful for the initial diagnosis of classical Hodgkin lymphoma, cells with similar features may be seen in other neoplasms, including some non-Hodgkin lymphomas and a diagnosis of Hodgkin lymphoma, in some cases, can be made without identification of cells with the classic binucleated Reed-Sternberg appearance. As far as the "characteristic background" or "appropriate milieu" is concerned, it is highly variable, but in classical Hodgkin lymphoma, it lacks the monomorphic appearance of most other malignant lymphomas. Mature lymphocytes, eosinophils, plasma cells, and histiocytes may all be present in greater or lesser amount, depending on the microscopic type. Many of the Reed-Sternberg cells are surrounded by T lymphocytes arranged in a rosettelike fashion.

Most cases of classical Hodgkin lymphoma and all cases of NLPHL are derived from B cells,⁴¹⁷⁻⁴²⁰ and approximately 40% of cases of classical Hodgkin lymphoma cases are associated with EBV infection.⁴²¹ Individuals with a history of infectious mononucleosis have an increased incidence of Hodgkin lymphoma;^{422,423} patients with Hodgkin lymphoma have an altered antibody pattern to EBV prior to diagnosis;⁴²⁴ marked phenotypic similarities exist between infectious mononucleosis and Hodgkin lymphoma;⁴²⁵ and EBV genomes have been identified in Reed-Sternberg cells at least 40% of the cases (particularly in the mixed cellularity subtype, in young patients, and/or in developing countries) (Fig. 37.45).⁴²⁶⁻⁴³⁰ There is also evidence for a genetic susceptibility factor.⁴³¹

Gross Features

Except for the very early stages, lymph nodes involved by Hodgkin lymphoma are enlarged, sometimes massively so. The gross

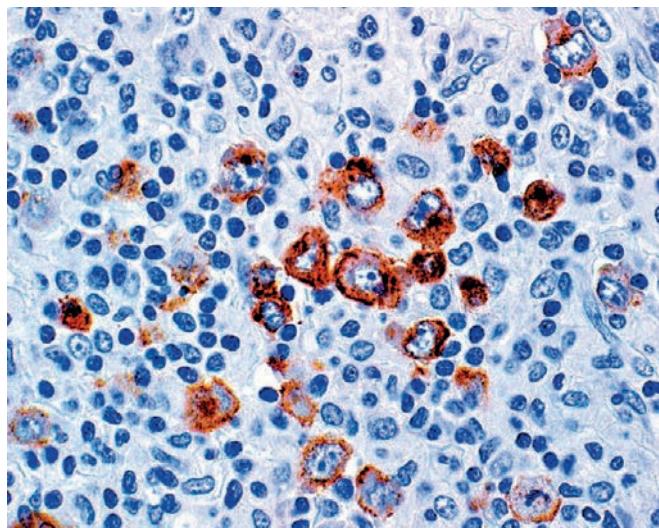


Figure 37.45 Presence of the EBV in the neoplastic cells of Hodgkin lymphoma as demonstrated immunohistochemically by the detection of LMP1 antigen.

appearance is somewhat dependent on the microscopic subtypes (see later section). The consistency varies from soft to hard depending on the amount of fibrosis. Some degree of nodularity is often appreciated, particularly in the nodular sclerosis form (Fig. 37.46). Foci of necrosis may be present. Except for NLPHL, the cut surface of the node has a more heterogeneous appearance than most non-Hodgkin lymphomas. In advanced cases, several nodes from the same group become matted together, a feature spectacularly demonstrated in the drawing that accompanied Hodgkin's classic article.

Classical Hodgkin Lymphoma

Reed-Sternberg Cell

The classic Reed-Sternberg cell, as seen in all subtypes of classic Hodgkin lymphoma (but not in NLPHL, see later), is a large cell (20–50 µm in diameter or more) with abundant weakly acidophilic or amphophilic cytoplasm, which may appear homogeneous or granular and which lacks a pale zone in the Golgi area (Fig. 37.47). The nucleus is bilobed or polylobed so that the cell appears binucleated or multinucleated; it is possible that in some cases bona fide



Figure 37.46 A and B, Gross appearance of lymph nodes involved by Hodgkin lymphoma. Note nodularity and sclerosis.

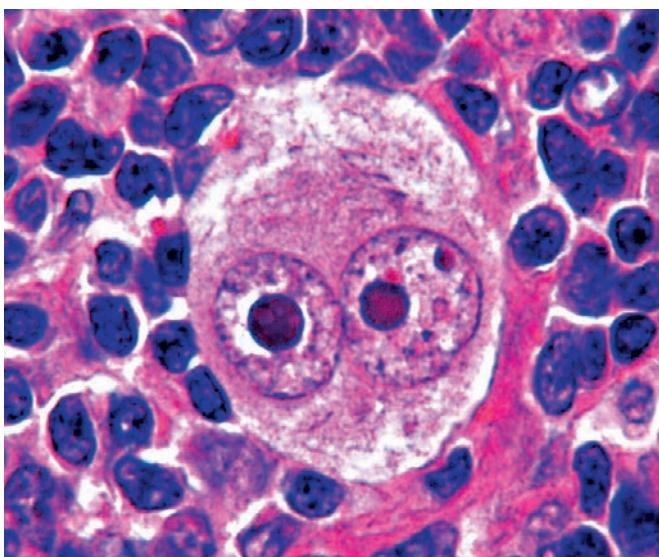


Figure 37.47 Spectacular example of a Reed–Sternberg cell. (Courtesy of Dr. Fabio Faccettini, Brescia, Italy.)

binucleation or multinucleation actually occurs (Fig. 37.48). The nuclear membrane is thick and sharply defined. The nuclear pattern is usually vesicular but with some coarse chromatin clumps scattered throughout. There is a very large, variously shaped, but usually rounded, highly acidophilic central nucleolus surrounded by a clear halo. In the most typical example of the Reed–Sternberg cell, the two nuclear lobes face each other (“mirror image”), resulting in the oft-cited “owl eye” appearance. When multilobation occurs, the appearance has been likened to that of an “egg basket.” Cells with this set of features but lacking nuclear lobation have been referred to as mononuclear variants of Reed–Sternberg cells or Hodgkin cells. It has been stated that the minimal requirement for a diagnostic Reed–Sternberg cell is a bilobed nucleus in which at least one of the lobes has a prominent acidophilic nucleolus. At the other end of this spectrum is the Reed–Sternberg cell of giant size and highly pleomorphic hyperchromatic nuclei, having an appearance such as to simulate the cells of anaplastic carcinoma or one of the pleomorphic sarcomas. Another type of Reed–Sternberg cell, characterized by a darkly staining and retracted quality, is referred to as the mummified or necrobiotic variant and appears to be the morphologic expression of apoptosis (Fig. 37.49). Additional morphologic variations of Reed–Sternberg cells exist, and these will be discussed with the various types of Hodgkin lymphoma.

The Reed–Sternberg cell of Hodgkin lymphoma needs to be distinguished from other multinucleated cells that may be present in lymph nodes. Megakaryocytes can simulate it closely in hematoxylin–eosin-stained sections, but they can be identified by the presence of a strongly PAS-positive substance in their cytoplasm and their different immunophenotype, which includes positivity for Factor VIII-related antigen and CD61. Cells morphologically very similar to Reed–Sternberg cells, representing pleomorphic immunoblasts, can be seen in infectious mononucleosis and other viral diseases.²²¹ Neoplastic cells from a variety of epithelial and mesenchymal tumors also can resemble Reed–Sternberg cells.⁴³² Finally, some malignant lymphomas of non-Hodgkin type may be accompanied by cells with the appearance of Reed–Sternberg cells. In all of these disorders—and especially in the lymphomas—it is of the utmost importance to examine not only the putative Reed–Sternberg cells but also the background in which they are situated. The more cytologically atypical the lymphoid population, the less likely is the

diagnosis of Hodgkin lymphoma. Despite these fairly distinctive morphologic features, a diagnosis of Hodgkin lymphoma is no longer made based on morphology alone and should be confirmed by demonstration of the characteristic immunophenotype of the neoplastic cells (see later).

The immunohistochemical profile of the Reed–Sternberg cell and mononuclear variants in classic Hodgkin lymphoma have been summarized in numerous studies.^{433–447} While variability in antigen expression exists, immunohistochemical studies, usually by paraffin section immunohistochemistry, are essential for proper diagnosis and to exclude disorders that may morphologically mimic classical Hodgkin lymphoma. The vast majority of cases are CD30 positive (Fig. 37.50), and caution should be taken if there is not fairly strong expression of CD30 in most if not all atypical large cells. CD15 expression, in membrane, Golgi, or cytoplasmic patterns, is reported in up to 80% of cases but appears to be slightly less common in the author’s experience. The neoplastic cells of classical Hodgkin lymphoma are CD45 negative, but interpretation of CD45 staining is often difficult unless large numbers of back-to-back neoplastic cells are present in the specimen. Although classical Hodgkin lymphoma is usually derived from a B cell, expression of B-cell antigens is inconsistent and typically variable. CD20 expression is reported in approximately 20% of cases, but even those cases show variable expression with some neoplastic cells usually negative. A finding of strong and uniform CD20 expression should raise consideration for an alternative diagnosis. The B-cell transcription factor PAX5 demonstrates weak nuclear positivity in at least 90% of cases, but expression of other transcription factors, specifically OCT2 and BOB1, is usually not present or minimal. Individual pan-T cell markers may rarely be expressed, but strong expression of multiple T-cell antigens should suggest a T-cell neoplasm.

Molecular studies are usually of limited utility in the diagnosis of classical Hodgkin lymphoma. Most cases yield a germline configuration for immunoglobulin heavy and light chain genes and the T-cell receptor genes, but this simply results from a dilution factor by the non-neoplastic cells; indeed, studies of cases with an increased number of Reed–Sternberg cells and their variants show clonal rearrangements, usually of the IGH,^{448–452} while cases studied after microdissection also reveal evidence of B-cell clonality.^{417,420}

General and Clinical Features

Classical Hodgkin lymphoma accounts for 20%–30% of all malignant lymphomas in the United States and Western Europe but a much lower percentage in Japan and other Asian countries.⁴⁵³ There is a wide range in age incidence, which varies according to geographic location. In the United States, there is a bimodal distribution, with a peak at 15–40 years and a second, smaller peak in the seventh decade. In Japan, the peak in young adulthood is absent. In poorly developed countries, there is a high incidence in children, a relatively low incidence in the 15- to 40-year age group, and a third peak later in life.^{454,455} There is a male preponderance (approximately 1.5:1) in all microscopic types except nodular sclerosis. The disease may present in a variety of ways, the most common (approximately 90% of the cases) being painless enlargement of superficial (usually cervical) lymph nodes. Fever, night sweats, and loss of weight (so-called B symptoms) occur in approximately 25% of the cases; their presence influences the clinical staging. Pruritus is also frequent.

Nodular sclerosis is by far the most common type of Hodgkin lymphoma in the United States. It characteristically presents in the neck and/or mediastinum of young females.⁴⁵⁶ Lymphocyte depletion Hodgkin lymphoma may present in adults or elderly patients as a febrile illness with pancytopenia or lymphocytopenia, hepatomegaly, abnormal liver function tests, and no peripheral lymphadenopathy,⁴⁵⁷ or it may manifest the usual clinical presentation of Hodgkin

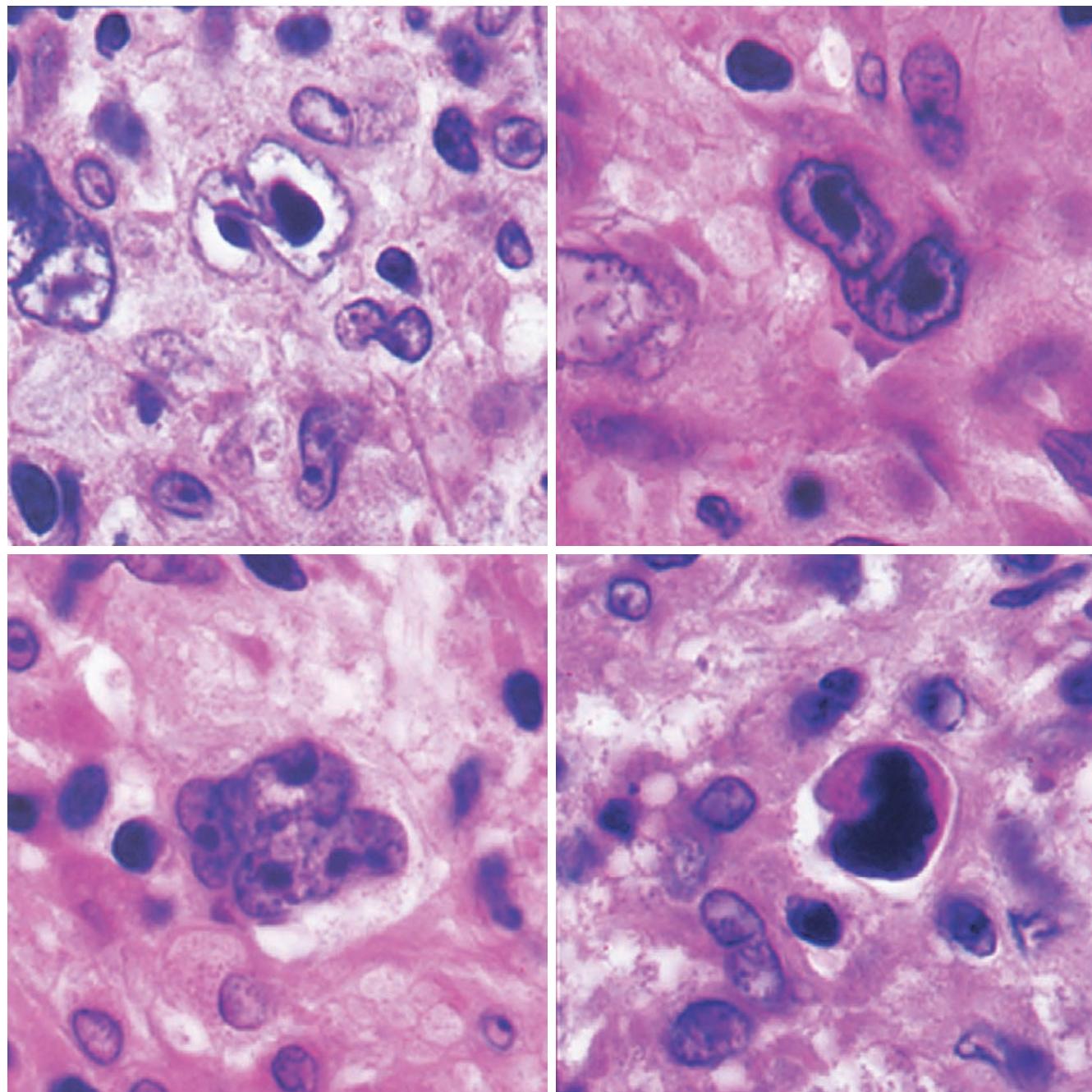


Figure 37.48 Various Appearances of Reed-Sternberg Cells. The cell located at the bottom right has a “mummified” appearance.

lymphoma.⁴⁵⁸ This form is extremely rare in children, in whom nodular sclerosis and lymphocyte predominance predominate greatly.^{459,460}

Mediastinal involvement is the rule in nodular sclerosis and is inconstant in mixed cellularity and lymphocyte depletion.⁴⁶¹ The risk of abdominal involvement is greater in patients with B symptoms and in lymphocyte depletion or mixed cellularity types; the lowest risk is for asymptomatic females with nodular sclerosis histology (6%).⁴⁶²

The diagnosis of Hodgkin lymphoma should be questioned for any lymphoma initially involving Waldeyer's ring, the skin, and the gastrointestinal tract or presenting below the diaphragm.

Most of these cases are examples of non-Hodgkin lymphomas with Hodgkin-like cells.

Patients with Hodgkin lymphoma often have defects in cellular immunity, which leads to an increased susceptibility to some infections.⁴⁶³ However, a diagnosis of Hodgkin lymphoma should be viewed with suspicion if it presents as a complication of a natural immune deficiency, immunosuppression, or other immune diseases. Although clear cases of this association exist (particularly in patients with ataxia-telangiectasia and with HIV infection),^{464,465} most of these cases actually represent other neoplasms. HIV-associated Hodgkin lymphoma tends to present at a high stage and to run an aggressive clinical course.⁴⁶⁶

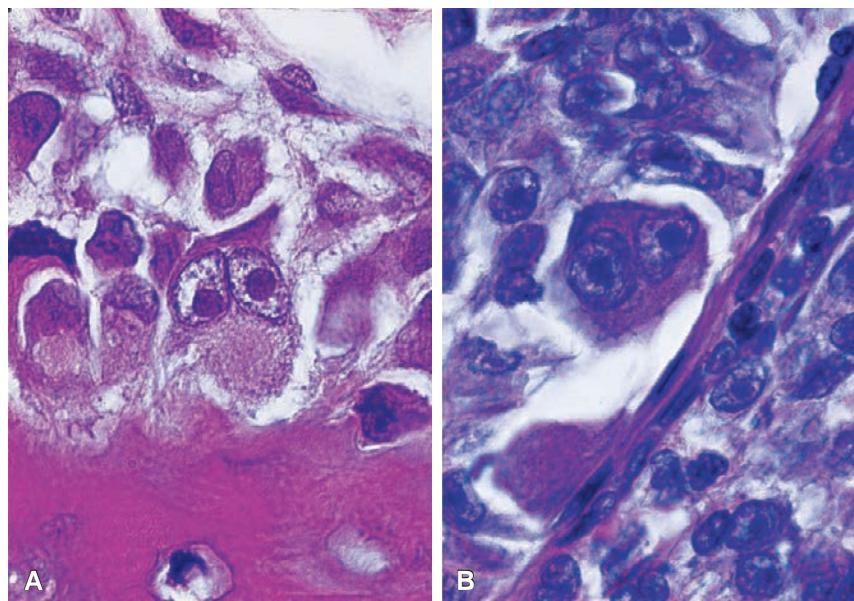


Figure 37.49 Reed-Sternberg-like cells in malignant melanoma (A), and osteoblastoma (B).

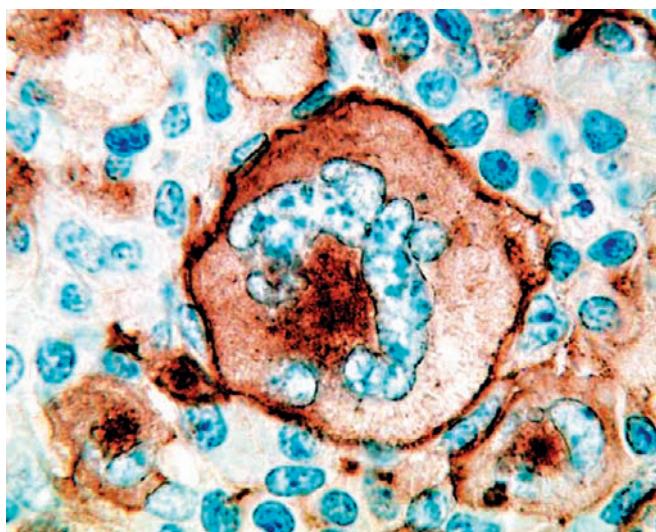


Figure 37.50 Membrane and Golgi-type immunoreactivity for CD30 in a Reed-Sternberg cell. (Courtesy of Dr. Fabio Facchetti, Brescia, Italy.)

Spread

Most cases of classical Hodgkin lymphoma begin in lymph nodes above the diaphragm and spread from there to other lymph node groups and to extranodal sites. Important information has been acquired in regard to the frequency and significance of this spread as a result of an aggressive diagnostic approach, particularly with the use of laparotomy as a routine staging procedure.^{467,468}

1. **Direct extension.** The disease may spread to the perinodal tissues, sometimes extensively, and result in a fusion of the involved nodes. In advanced cases, direct invasion of skin, skeletal muscle, and other sites can occur. Mediastinal Hodgkin lymphoma can extend by continuity into the large vessels, lung, and chest wall.⁴⁶⁹
2. **Other lymph node groups.** Most cases of classical Hodgkin lymphoma spread by involvement of adjacent lymph node groups.⁴⁷⁰ This

contiguous manner of spread is particularly common in the nodular sclerosis type.⁴⁶⁹ Nodal spread has been evaluated with lymphangiogram, CT scan, and staging laparotomy. When it was carried out with some frequency, lymphangiography had an overall diagnostic accuracy in excess of 90%; it was more effective in detecting involvement below the level of the second lumbar vertebra but inconsistent for nodes situated higher in the periaortic area. Approximately 30% of patients with negative lymphangiograms in whom the para-aortic nodes were left untreated later demonstrated disease below the diaphragm.⁴⁷¹ Of the nodes biopsied at laparotomy during the course of a staging procedure, the most likely to be involved were those located in the splenic hilum and retroperitoneum. Mesenteric nodes are almost always spared.

3. **Spleen.** A spleen weighing 400 g or more is practically always histologically positive. The converse is not true: spleens below this weight are involved in a high proportion of cases. The focal nature of the disease calls for a careful gross examination of this organ. The specimens should be sectioned throughout in thin slices, and every suspicious area should be examined microscopically. If no nodules are detected on gross inspection, the chances of finding Hodgkin lymphoma in random microscopic sections are negligible. Splenic involvement is thought to represent a critical stage in the spread of Hodgkin lymphoma and is an early manifestation of blood vessel dissemination. The approximate number of tumor nodules present in the spleen should be indicated because of their relation to prognosis; specifically, it should be stated whether there are five or more.
4. **Liver.** Hepatic disease is almost invariably associated with splenic and retroperitoneal lymph node involvement and with so-called B symptoms. Clinical assessment of liver involvement is quite unreliable. Care should be exercised in distinguishing involvement by Hodgkin lymphoma from benign lymphoid aggregates, some of which may show mild atypia.⁴⁷²
5. **Bone marrow.** This is discussed in Chapter 39.
6. **Others.** Practically any other organ can show secondary involvement by Hodgkin lymphoma, such as the lung, skin, gastrointestinal tract, and central nervous system (see respective chapters).

Microscopic Types

A variety of classification systems for Hodgkin lymphoma have been proposed and historically accepted,^{473–475} with numerous histologic subtypes described. The 2016 WHO classification, however, is the currently accepted nomenclature system for this disease and should be used for all cases.⁴⁰⁷ NLPHL is now recognized to be morphologically, biologically, and clinically distinct from more traditional types of Hodgkin lymphoma, termed classical Hodgkin lymphoma, and it is described separately later. With current therapy, the histologic subtypes of classical Hodgkin lymphoma have no clinical or prognostic significance and, especially on small needle biopsies, a simple diagnosis of "classical Hodgkin lymphoma" is appropriate for patient care.

As mentioned, the category of classical Hodgkin lymphoma subsumes all types of Hodgkin lymphoma except for NLPHL. It is regarded as a nosologic entity because of the similar immunophenotype of the tumor cells. The differences consist in sites of involvement, clinical features, growth pattern, presence of fibrosis, composition of cellular background, number and degree of atypia of the tumor cells, and prevalence of EBV infection. These subtypes are nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted.

Nodular sclerosis Hodgkin lymphoma is characterized in its fully developed stage by broad bands of birefringent collagen separating the lymphoid tissue in well-defined nodules (Fig. 37.51). These fibrous bands, which have a birefringent quality when examined under polarized light, often center around blood vessels. In addition to the classic Reed–Sternberg cell, nodular sclerosis Hodgkin lymphoma also displays a variant known as *lacunar* cells (Fig. 37.52). This cell type is quite large (40–50 μ m in diameter), with an abundant clear cytoplasm and multilobulated nuclei having complicated infoldings and nucleoli of smaller size than those of the classic Reed–Sternberg cell. The "frail" cytoplasm of these cells is retracted close to the nuclear membrane so that the cell appears to be floating in a "lacuna." This is the result of an artifact induced by formalin fixation, inasmuch as it is absent in tissues fixed in B5 or Zenker. In some cases, there is clustering of these lacunar cells, particularly around areas of necrosis. They form sheets and cohesive nests, to the point that a mistaken diagnosis of large cell non-Hodgkin lymphoma, carcinoma, germ cell tumor, or thymoma can be made. Cases of nodular sclerosis Hodgkin lymphoma showing prominence of this feature have been referred to as the *syncytial*, *sarcomatoid*, or *sarcomatous* variant.⁴⁷⁶

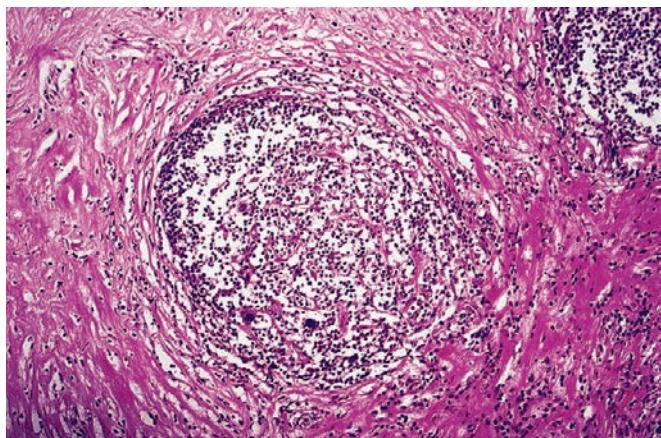


Figure 37.51 A Typical Case of Nodular Sclerosis Hodgkin Lymphoma. The lymphoid nodule is encased in dense fibrohyaline tissue.

The composition of the non-neoplastic infiltrate varies widely, to the point that some authors have proposed to subdivide nodular sclerosis Hodgkin lymphoma into lymphocyte predominant, mixed cellularity, and lymphocyte depletion categories, and this subdivision carried some prognostic implications in the past. Along similar lines, the British National Lymphoma Investigation group proposed to divide cases of nodular sclerosis Hodgkin lymphoma into two grades. In their scheme, cases were assigned to the allegedly more aggressive grade II if any of these features are present: (1) a "reticular" or "pleomorphic" pattern of lymphocytic depletion in over 25% of the cellular nodules; (2) a "fibrohistiocytic" pattern of lymphocyte depletion in over 80% of the cellular nodules; and (3) the presence of numerous bizarre and highly anaplastic Reed–Sternberg and Hodgkin cells without lymphocyte depletion in over 25% of the nodules.⁴⁷⁷ Grade II lesions include the already mentioned "syncytial" variant of other authors. With current therapy, these subtypes of nodular sclerosis Hodgkin lymphoma have no prognostic significance and such subtyping is not necessary.⁴⁷⁸

By electron microscopy, nodular sclerosis Hodgkin lymphoma shows abundant collagen fibers together with myofibroblasts;⁴⁷⁹ it has been suggested that the latter contribute to the retraction seen in this condition. In regard to the fibrosis, it should be kept in mind that practically all types of Hodgkin lymphoma can exhibit some degree of this change, particularly after therapy and recurrent cases of classical Hodgkin lymphoma should not be further subtyped.

In **mixed cellularity** Hodgkin lymphoma, a large number of eosinophils, plasma cells, and atypical mononuclear cells are admixed with classic Reed–Sternberg cells, which tend to be numerous. Focal necrosis may be present, but fibrosis should be minimal or absent (Fig. 37.53). This type tends to occur more frequently in the head and neck region and be associated with EBV infection of the Hodgkin cells.

The **lymphocyte-rich** type is characterized by the presence of Reed–Sternberg cells scattered against a nodular (most commonly) or diffuse background, largely composed of small B lymphocytes (in contrast to the striking T-cell background of other classical Hodgkin lymphoma types) and practically devoid of eosinophils and neutrophils.⁴⁸⁰ The main differential diagnosis is with NLPHL, and is primarily based on the presence of cells with the typical morphologic and immunohistochemical features of classic Hodgkin cells.

The **lymphocyte-depletion** group, which comprises less than 5% of all cases of Hodgkin lymphoma, includes two morphologically different subtypes, designated as "diffuse fibrosis" and "reticular" in the original Lukes classification. In the diffuse fibrosis subtype, the number of lymphocytes and other cells progressively decreases as the result of heavy deposition of collagen fibers. The reticular subtype is characterized by a very large number of diagnostic Reed–Sternberg cells (many of them of bizarre configuration) among atypical mononuclear cells and other elements (Fig. 37.54). Areas of necrosis are more common than in other types. The "reticular" subtype of lymphocyte depletion Hodgkin lymphoma needs to be distinguished from non-Hodgkin lymphoma of large cell type (including anaplastic large cell lymphoma [ALCL]) and from the variant of nodular sclerosis Hodgkin lymphoma with aggregates of lacunar cells.⁴⁸¹

The immunophenotypic profile of the neoplastic cells in classic Hodgkin lymphoma is described in a preceding section on "Reed–Sternberg cells." The background lymphocytes are predominantly T cells with the exception of lymphocyte-rich classical Hodgkin lymphoma.

While relapsed Hodgkin lymphoma often retains the same immunophenotypic and morphologic features as the primary disease, radiation and chemotherapy may result in morphologic

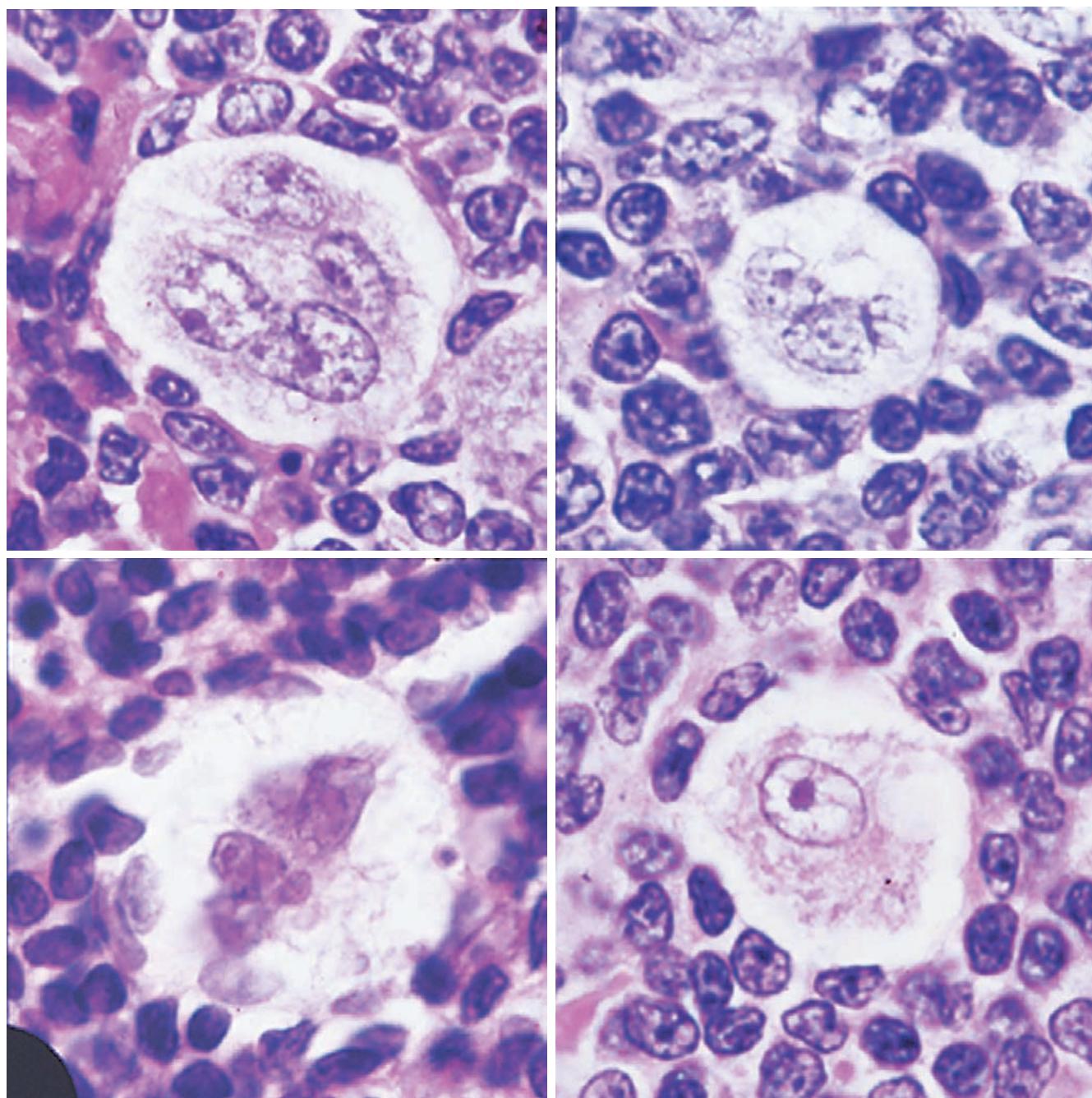


Figure 37.52 Various appearances of lacunar cells in nodular sclerosis Hodgkin lymphoma.

changes that differ from the untreated disease.^{482–484} Additionally, some cases relapse with higher numbers of neoplastic cells, more typical of lymphocyte-depleted Hodgkin disease, but an attempt to reclassify relapsed disease is confusing and not advised. Such cases should be studied by immunohistochemistry to confirm that they represent recurrent disease rather than a new neoplasm but are probably best diagnosed simply as recurrent classical Hodgkin lymphoma.

Other Microscopic Features

There are some microscopic variations on the theme of classical Hodgkin lymphoma worth mentioning, mainly because lack of knowledge of their occurrence may result in mistaken diagnoses.

1. *Foamy macrophages.* Clumps of foamy macrophages resulting in a xanthogranulomatous appearance may be found, particularly in the nodular sclerosis form.⁴⁸⁵
2. *Eosinophils.* In some instances, the intensity of eosinophilic infiltration is massive and accompanied by so-called eosinophilic microabscesses. Such cases may be confused with LCH, hypersensitivity reaction, or “allergic granulomatosis.”
3. *Other inflammatory cells.* S100 protein-positive dendritic cells,⁴⁸⁶ mast cells,⁴⁸⁷ and monocyteoid B cells⁴⁸⁸ may be very numerous.
4. *Focal interfollicular involvement.* In the early stages of the disease, only focal involvement of a lymph node may be encountered,⁴⁸⁹ often restricted to the paracortical region between florid

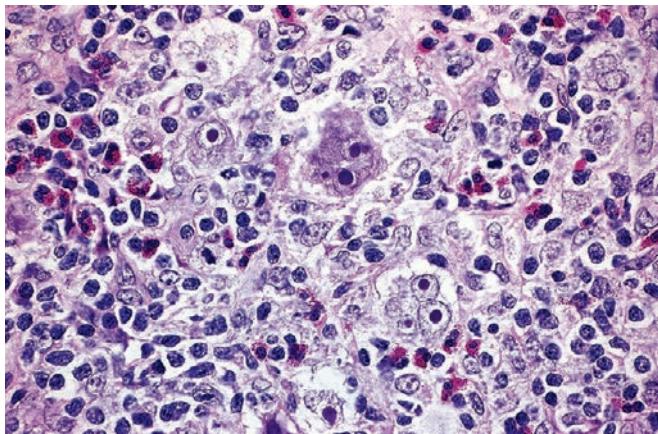


Figure 37.53 Mixed Cellularity Hodgkin Lymphoma. Several diagnostic Reed-Sternberg cells are seen admixed with a polymorphic lymphoid infiltrate rich in eosinophils.

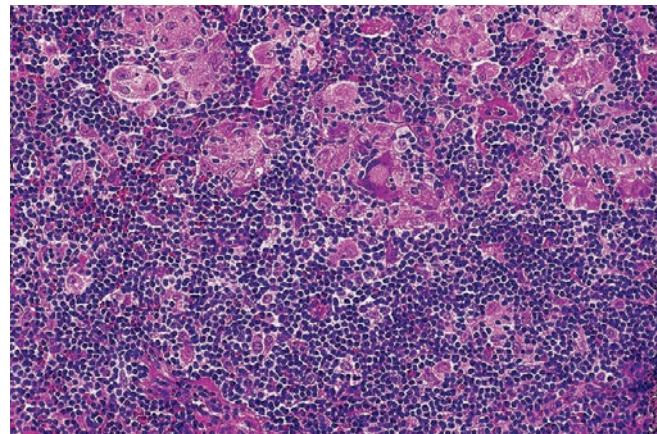


Figure 37.55 Hodgkin Lymphoma Accompanied by Numerous Sarcoid-Like Granulomas. The presence of this component can obscure the basic nature of the disease.

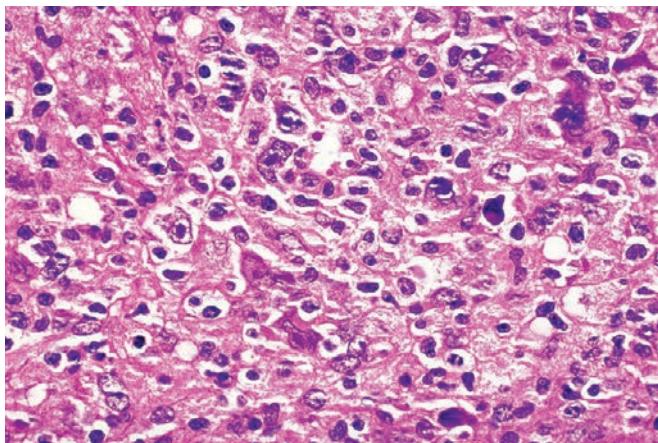


Figure 37.54 Lymphocyte Depletion Type of Hodgkin Lymphoma. Numerous atypical cells are present in a densely fibrotic stroma. Lymphocytes are scanty.

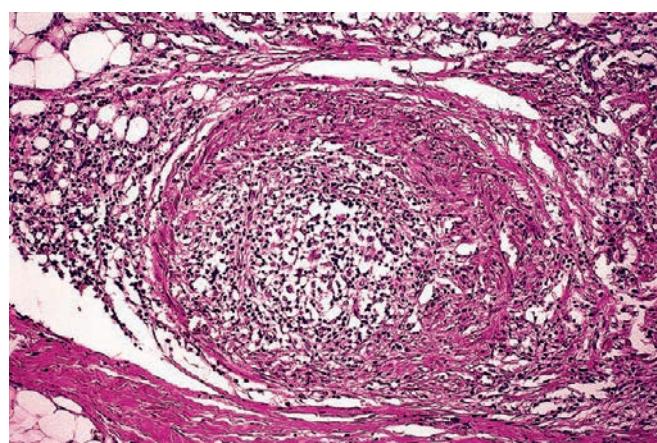


Figure 37.56 Blood Vessel Invasion in Hodgkin Lymphoma.

- hyperplastic follicles; this pattern has been referred to as *interfollicular Hodgkin lymphoma*.⁴⁹⁰
5. *Follicular involvement.* Sometimes the nodal involvement by Hodgkin lymphoma is mainly in the germinal centers, the appearance being reminiscent of NLPHL.⁴⁹¹
 6. *Castleman disease-like features.* Cases of Hodgkin lymphoma may be accompanied or preceded by a plasmacytic infiltrate and abnormalities of germinal centers closely resembling those seen in plasma cell type Castleman disease, probably attributable to interleukin-6 secretion by Reed-Sternberg cells.
 7. *Fibrosis.* In cases of nodular sclerosis Hodgkin lymphoma but sometimes also in other types, the amount of fibrosis can be such as to simulate the appearance of one of the inflammatory fibroscleroses (such as sclerosing mediastinitis or retroperitoneal fibrosis).
 8. *Spindle cell proliferation.* In rare cases of Hodgkin lymphoma, there is a proliferation of oval to spindle cells of such a degree as to simulate fibrosarcoma, malignant fibrous histiocytoma, or a follicular dendritic cell tumor; such lesions have been referred to as *fibrosarcomatous or fibroblastic Hodgkin lymphoma*. Some of these spindle cells have a degree of nuclear atypia such as to indicate their neoplastic nature and relationship with Reed-Sternberg and Hodgkin cells; indeed, most of these

lesions would be included in the grade II category of nodular sclerosis Hodgkin lymphoma proposed by the British National Lymphoma Investigation Group. Others are of a reactive nature and stromal derivation (i.e. made up of fibroblasts and myofibroblasts).⁴⁹²

9. *Noncaseating granulomas.* These formations are sometimes present in nodes and other organs involved by Hodgkin lymphoma. Occasionally they are so numerous as to obscure the diagnostic features of the disease (Fig. 37.55). In other instances, these granulomas may be seen within otherwise uninvolved organs of patients with Hodgkin lymphoma.⁷⁷ Their significance is unknown. Perhaps they represent an expression of delayed hypersensitivity. Some seen in the past were reactions to the contrast material used in lymphangiography.⁴⁹³ Their presence does not indicate involvement of that organ by Hodgkin lymphoma and should therefore not influence the staging criteria. Actually, it has been suggested that, within a given stage, the presence of these granulomas is associated with a better prognosis.⁴⁹⁴
10. *Vascular invasion.* Blood vessel infiltration has been detected microscopically in 6%–14% of the cases of Hodgkin lymphoma by the use of elastic tissue stains (Fig. 37.56).⁴⁹⁵ This finding is said to be associated with an increased incidence of extranodal organ involvement,⁴⁹⁶ but the statement and the very validity of the observation have been questioned.

Molecular Genetics

In almost all cases of classical Hodgkin lymphoma, clonal immunoglobulin gene rearrangements can be demonstrated in microdissected neoplastic (Reed–Sternberg) cells or tissue samples rich in neoplastic cells; only exceptionally are clonal T-cell receptor gene rearrangements present instead.^{417,497–499} The variable regions of the immunoglobulin genes frequently show hypermutation but not ongoing mutations. Remarkably, immunoglobulin mRNA transcripts are usually absent, which may result from functional defects in immunoglobulin gene regulatory elements or crippling mutations in the immunoglobulin genes.^{500,498} That is, the neoplastic cells are compatible with germinal center B cells that have lost the capacity to express a functional antigen receptor, but which differ from their normal counterpart in having been rescued from apoptosis by various mechanisms, such as presence of EBV or aberrant activation of the NFκB pathway.^{501–503}

Cytogenetic studies of classic Hodgkin lymphoma reveal complex karyotypes, commonly featuring hyperdiploidy or hypertetraploidy.^{504,505} Recent FISH studies have shown rearrangements of the immunoglobulin genes in approximately 20% of cases, involving variable partners genes which may include *BCL2*, *BCL3*, *BCL6*, *REL*, *MYC*, *MHCT2A*, and unidentified genes,^{506–508} and mutations of other genes, including NFκB.^{509,510}

About 40% of cases of classic Hodgkin lymphoma are associated with EBV, which can be demonstrated by EBV-LMP1 immunohistochemistry or EBV-encoded early RNA (EBER) in situ hybridization.⁵¹¹ The association with EBV is stronger at the extremes of age, that is children/young adults and elderly adults, and in the mixed cellularity subtype. Of note, the overall frequency of EBV association is much higher in individuals with immunodeficiency (approximately 100%) or from developing countries (80%–100%).^{512–515}

Nodular Lymphocyte Predominant Hodgkin Lymphoma

In NLPHL, the predominant cell is an irregular, medium-sized B lymphocyte (L&H or popcorn cell), with or without an accompanying population of benign-appearing histiocytes.^{516,517} Postcapillary venules with high endothelium may be prominent.^{518,519} The lymph node architecture is partially or totally effaced, and the infiltrate has a variously well-developed nodular pattern of growth.⁵²⁰ The nodularity may be so pronounced as to simulate on low power the appearance of follicular lymphoma; however, the nodules of NLPHL are more irregular in size and staining quality, and the admixture of lymphocytes and epithelioid cells gives them a mottled appearance (Fig. 37.57). A rim of uninvolved or hyperplastic lymphoid tissue which may include progressively transformed germinal centers may be present but reactive follicles are not admixed with the large tumor nodules. Eosinophils, plasma cells, and foci of fibrosis are scanty or absent. Classic Reed–Sternberg cells are usually absent. One sees instead a variable but usually large number of a type of Reed–Sternberg cell (the L&H cell, LP cell, or “popcorn” cell) characterized by a folded, multilobed nucleus with smaller nucleoli. These cells are most commonly found within the nodules but tend to also spill into the internodular areas. If numerous typical Reed–Sternberg cells are found in a node with a lymphocyte predominant background, the case probably belongs in the classical Hodgkin lymphoma category (lymphocyte-rich subtype). Occasionally, the L&H cells predominate at the margins of the nodules, creating a “wreath” around them. In others, they may cluster in large confluent sheets resembling diffuse large cell lymphoma.⁵²¹

Poppema et al.^{61,522,523} first proposed that cases of NLPHL arise from B-cell regions of the node and specifically from progressively transformed germinal centers. They supported their theory by showing

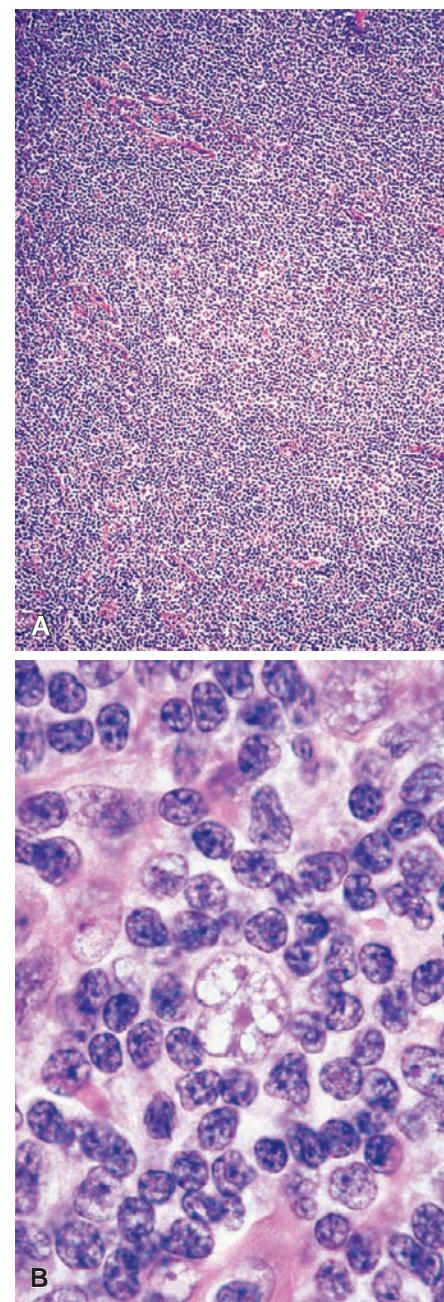


Figure 37.57 Lymphocyte Predominant Hodgkin Lymphoma. **A**, Low-power view showing a mottled appearance of the node. **B**, High-power view showing the lymphocytic and/or histiocytic (L&H) type of cell (“popcorn” cell) that is characteristic of this condition.

that the L&H cell that is characteristic of this condition is of B-cell lineage, and this has been confirmed by many others.^{524–526} L&H cells express the pan-B-cell markers CD19, CD20, CD22, CD79A, PAX5, and OCT2.^{525,527,528} They are also positive for CD45RB (LCA) but consistently negative for T-cell markers. They commonly express epithelial membrane antigen (EMA) and generally lack CD30 and CD15 expression. The neoplastic cells characteristically occur within nodules of small B cells (CD20+) with expanded follicular dendritic cell networks and spill out into the T-cell zones. OCT2 nuclear staining is usually strong in the tumor cells and highlights their expansion beyond the B-cell nodules. These “popcorn” cells are

typically rosetted by follicular helper T (TFH) cells which express CD3, PD1, BCL6, and CD57.^{529,530}

NLPHL should be sharply separated (also on epidemiologic and clinical grounds) from classical Hodgkin lymphoma, even if occasionally the two are seen to coexist.^{531,532} Although usually a rather indolent tumor, some cases will transform to DLBCL and such cases have been demonstrated to be clonally related.⁵³³

The differential diagnosis between NLPHL and T-cell/histiocyte-rich B-cell lymphoma, which is discussed in more detail later, may not be resolvable on small biopsies. A nodular pattern with background small B cells and associated follicular dendritic cells networks support NLPHL when this differential diagnosis arises.

Molecular Genetics

Microdissected neoplastic (L&H/LP) cells exhibit clonal rearrangements of the immunoglobulin genes, which show hypermutation and ongoing mutations, compatible with transformed antigen-selected germinal center B cells.^{418,502,534,535} The rearranged immunoglobulin genes are functional, and can be transcribed into immunoglobulin mRNA, and further translated to immunoglobulin.^{535,536}

Cytogenetic studies reveal complex karyotypes, often in the diploid range, with the commonest abnormalities being gain or partial gain of 1q, loss of chromosome 4q28–q32, and rearrangement involving 3q27 (shown to implicate *BCL6*, which is fused with a variety of partner genes, including the *IGH* gene at 14q32).^{537–539} Array comparative genomic hybridization (CGH) studies have demonstrated gains in 2p16.1, the site of *REL*, and losses at 2p11.2 and 9p11.2, features similar to T-cell/histiocyte-rich large B-cell lymphoma.⁵⁴⁰

Although the vast majority of cases of NLPHL are not associated with EBV, a few rare cases have been recently reported.^{541,542}

Non-Hodgkin Lymphoma

The 2016 WHO classification contains numerous categories of non-Hodgkin lymphomas that are listed in **Box 37.1**. While most of these involve lymph nodes, some are primarily extranodal diseases and those are discussed in more detail in other chapters. As mentioned, the WHO classification is based on a combination of clinical features, morphology, immunophenotyping, and genetics to define disease entities; morphology alone is no longer sufficient to make a lymphoma diagnosis.

The non-Hodgkin lymphomas are grouped into general categories of B-cell lineage or T/NK-cell lineage diseases and these are further grouped into mature and precursor neoplasms. The precursor neoplasms represent lymphoblastic leukemias/lymphomas and are grouped together because of similarities in the disease despite variations in their clinical presentation (leukemic, tissue based, or both).

Precursor Lymphoid Neoplasms

Lymphoblastic lymphomas represent the tissue-based presentation of either T- or B-lymphoblastic leukemia/lymphoma. The leukemic presentations are discussed in more detail in Chapter 39. Most lymphoblastic leukemias are of precursor T-cell lineage.

Lymphoblastic lymphoma is seen primarily in children and adolescents, but it also occurs in adults.^{543,544} T-lymphoblastic lymphoma has a distinctive clinical presentation. In approximately half of the cases there is a mediastinal mass in the thymic region (the old Sternberg sarcoma). The clinical course of the untreated disease is extremely aggressive, with rapid multisystem dissemination and development of a leukemic blood picture,⁵⁴⁵ and death after a few months.⁵⁴⁶ Grossly, the tumor is whitish and soft and often exhibits foci of hemorrhage and necrosis. Microscopically, there is a diffuse and relatively monomorphic pattern of proliferation, broken

only by a focal starry sky appearance in some of the cases. The tumor often extends outside the node or thymus to invade the adipose tissue in a diffuse fashion. Permeation of the wall of blood vessels in a targetoid fashion is another characteristic feature. The neoplastic cells have scanty cytoplasm and a nucleus that has a round contour (instead of the angulated shape typical of follicular lymphoma) that, on close examination, shows in some cases the presence of delicate convolutions resulting from multiple small invaginations of the nuclear membrane. Oil-immersion examination of well-prepared, very thin sections is necessary to demonstrate this feature, which may be present in only a small percentage of the tumor cells or sometimes practically absent (Fig. 37.58).⁵⁴⁶ The chromatin is finely stippled, and nucleoli are inconspicuous. Mitotic activity is extremely high. These convoluted cells are similar to the cerebroid cells of mycosis fungoides–Sézary syndrome (as one might assume from their similar names) but differ from the latter because the nuclear membrane is thinner, the chromatin more dispersed, and the invaginations more delicate. Actually, the need for distinction between these two cell types is more theoretical than real because of the fact that the two diseases are vastly different in their clinical presentation.

Remnants of thymus often are found in the mediastinal mass, and this may lead to a mistaken diagnosis of thymoma; in this regard, it should be remembered that thymoma is very infrequent in children and that, when it occurs, it is characterized by a population of small or activated lymphocytes but not convoluted ones. When lymphoblastic lymphoma spreads to lymph nodes, it preferentially involves the paracortical (thymic-dependent) zone.

The immunohistochemical hallmark of lymphoblastic lymphoma is TdT, a marker for precursor lymphoid cells. The precursor T-cell cases express pan-T antigens, such as CD1, CD2, CD7, cytoplasmic CD3, and CD43, but usually do not express surface CD3.⁵⁴⁷ The latter feature is of importance if flow cytometry immunophenotyping is performed without study of cytoplasmic markers but is not a major concern by immunohistochemistry, with routinely detects cytoplasmic CD3. Approximately one-third of cases of T-lymphoblastic leukemia/lymphoma will express CD10, which may cause confusion with a B-cell lymphoma. CD34 expression may also be present and is useful for rare cases that demonstrate weak or negative TdT expression. Positivity is also consistently encountered for CD99.

Translocations involving the alpha and delta T-cell receptor loci at 14q11.2, the beta locus at 7q35, and the gamma locus at 7p14–15 with a variety of partner genes (such as *MYC*, *TAL1*, *RBTN1*, *RBTN2*, and *HOX11*), leading to a dysregulation of transcription of the latter, are relatively common in T-lymphoblastic leukemia/lymphoma. *NOTCH1* and/or *NOTCH1* pathway mutations are identified in the majority of cases.⁵⁴⁸ Rare cases may be associated with eosinophilia and translocations involving *FGFR1*, particularly t(8;13)(p11;q12). Such cases are considered a distinct entity in the WHO classification (myeloid/lymphoid neoplasms with *FGFR1* rearrangement) and may relapse with a significantly different immunophenotype.⁵⁴⁹ While cases presenting as leukemia or as lymphoma are similar in most regards, one study has found upregulation of *BCL2*, *S1PR1*, and *ICAM1* in cases with a tissue-based presentation, suggesting a role in homing of tumor cells to tissue rather than marrow in these patients.⁵⁵⁰

In 15%–20% of the cases of lymphoblastic lymphoma, the tumor cells are precursor B cells expressing CD19 and CD79A and most are CD10 positive.⁵⁵¹ They also usually express TdT but not surface immunoglobulin, and many are CD20 negative. These cases usually do not present in the mediastinum. These are predominantly extranodal tumors with low propensity for leukemic involvement.⁵⁵² The genetic changes of B-lymphoblastic lymphoma are similar to

Box 37.1 2016 World Health Organization classification of mature lymphoid neoplasms

Provisional entities are in italics. Only entities that primarily involve lymph nodes are discussed in this chapter.	Lymphomatoid granulomatosis
Mature B-cell neoplasms	Primary mediastinal (thymic) large B-cell lymphoma
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Intravascular large B-cell lymphoma
Monoclonal B-cell lymphocytosis	ALK+ large B-cell lymphoma
B-cell prolymphocytic leukemia	Plasmablastic lymphoma
Splenic marginal zone lymphoma	Primary effusion lymphoma
Hairy cell leukemia	<i>HHV8+ DLBCL, NOS</i>
<i>Splenic B-cell lymphoma/leukemia, unclassifiable</i>	Burkitt lymphoma
<i>Splenic diffuse red pulp small B-cell lymphoma</i>	<i>Burkitt-like lymphoma with 11q aberration</i>
<i>Hairy cell leukemia variant</i>	High-grade B-cell lymphoma with <i>MYC</i> and <i>BCL2</i> and/or <i>BCL6</i> rearrangements
Lymphoplasmacytic lymphoma	High-grade B-cell lymphoma, NOS
<i>Waldenström macroglobulinemia</i>	B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma
Monoclonal gammopathy of undetermined significance (MGUS), IgM+	Mature T-cell and NK cell neoplasms
<i>μ heavy chain disease</i>	T-cell prolymphocytic leukemia
<i>γ heavy chain disease</i>	T-cell large granular lymphocytic leukemia
<i>α heavy chain disease</i>	<i>Chronic lymphoproliferative disorder of NK cells</i>
<i>MGUS, IgG/A+</i>	Aggressive NK cell leukemia
Plasma cell neoplasms	Systemic EBV+ T-cell lymphoma of childhood
<i>Solitary plasmacytoma of bone</i>	Hydroa vacciniforme-like lymphoproliferative disorder
<i>Extraosseous plasmacytoma</i>	Adult T-cell leukemia/lymphoma
<i>Monoclonal immunoglobulin deposition diseases</i>	Extranodal NK/T-cell lymphoma, nasal type
<i>Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)</i>	Enteropathy-associated T-cell lymphoma
<i>Nodal marginal zone lymphoma</i>	Monomorphic epitheliotrophic intestinal T-cell lymphoma
<i>Pediatric nodal marginal zone lymphoma</i>	<i>Indolent T-cell lymphoproliferative disorder of the GI tract</i>
<i>Follicular lymphoma</i>	Hepatosplenic T-cell lymphoma
<i>In situ follicular neoplasia</i>	Subcutaneous panniculitis-like T-cell lymphoma
<i>Duodenal-type follicular lymphoma</i>	Mycosis fungoïdes
<i>Pediatric-type follicular lymphoma</i>	Sézary syndrome
<i>Large B-cell lymphoma with IRF4 rearrangement</i>	Primary cutaneous CD30+ T-cell lymphoproliferative disorders
<i>Primary cutaneous follicle center lymphoma</i>	Primary cutaneous $\gamma\delta$ T-cell lymphoma
<i>Mantle cell lymphoma</i>	<i>Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma</i>
<i>In situ mantle cell neoplasia</i>	<i>Primary cutaneous acral CD8+ T-cell lymphoma</i>
<i>Diffuse large B-cell lymphoma (DLBCL), not otherwise specified</i>	<i>Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder</i>
<i>Germinal center B-cell type</i>	Peripheral T-cell lymphoma, NOS
<i>Activated B-cell type</i>	Angioimmunoblastic T-cell lymphoma
<i>T-cell/histiocyte-rich large B-cell lymphoma</i>	<i>Follicular T-cell lymphoma</i>
<i>Primary DLBCL of the central nervous system</i>	<i>Nodal peripheral T-cell lymphoma with TFH phenotype</i>
<i>Primary cutaneous DLBCL, leg-type</i>	Anaplastic large cell lymphoma, ALK+
<i>Epstein-Barr virus (EBV) + DLBCL, NOS</i>	Anaplastic large cell lymphoma, ALK-
<i>EBV+ mucocutaneous ulcer</i>	<i>Breast-implant associated anaplastic large-cell lymphoma</i>
<i>DLBCL associated with chronic inflammation</i>	

Data from Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-2390.

B-lymphoblastic leukemia and are discussed in more detail in Chapter 39.

The differential diagnosis of lymphoblastic lymphoma includes the already mentioned thymoma when in a mediastinal location, as well as Ewing sarcoma/ peripheral neuroectodermal tumor (PNET), Burkitt lymphoma, and the blastoid variant of mantle cell lymphoma.⁵⁵³⁻⁵⁵⁶ Other than thymoma, the detection of TdT should exclude the other possibilities. Non-mass-forming TdT-positive proliferations, however, may occur in lymph nodes and tonsils, often in association with other disorders, and are not by themselves evidence of lymphoblastic lymphoma.⁵⁵⁷ Similarly, some more diffuse lymphoblastic proliferations, especially in extranodal sites, have been identified as having an indolent clinical course and correlation with clinical findings is essential for proper classification of these rare cases.⁵⁵⁸

Mature Lymphoid Neoplasms of B Lineage

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma and Related Disorders

Similar to the lymphoblastic neoplasms, CLL and SLL are considered to represent different manifestations of the same disease. CLL is discussed in more detail in Chapter 39 but now requires a presence of $\geq 5 \times 10^9/L$ neoplastic cells in the blood⁴⁰⁷ and is also usually accompanied by bone marrow involvement, with or without other tissue involvement. The term SLL is reserved for rare cases that present with only tissue involvement and such a diagnosis should trigger an evaluation of the peripheral blood for evidence of CLL. SLL preferentially occurs in middle-aged and elderly individuals.^{559,560} The patients often have few or no symptoms, the evolution is

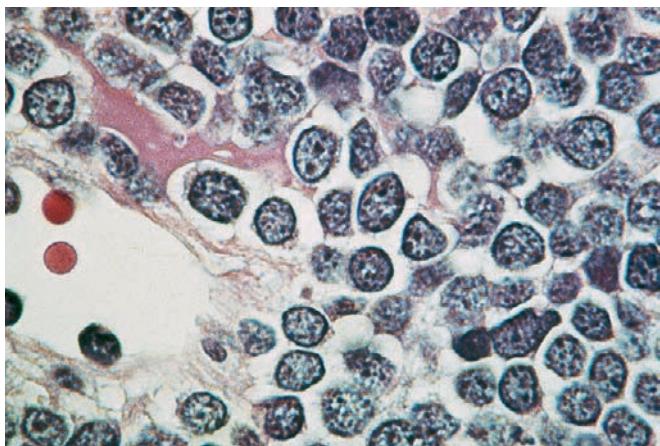


Figure 37.58 Lymphoblastic Lymphoma. The immature lymphoma cells have fine nuclear chromatin more characteristic of blasts over large mature B cells.

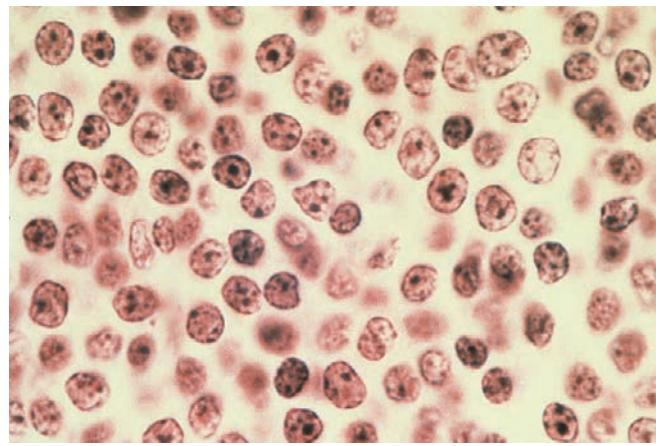


Figure 37.60 High-Power View of Small Lymphocytic Lymphoma. There is some variability in cell size. The nuclear contours are regular, the chromatin is clumped, and nucleoli are inconspicuous.

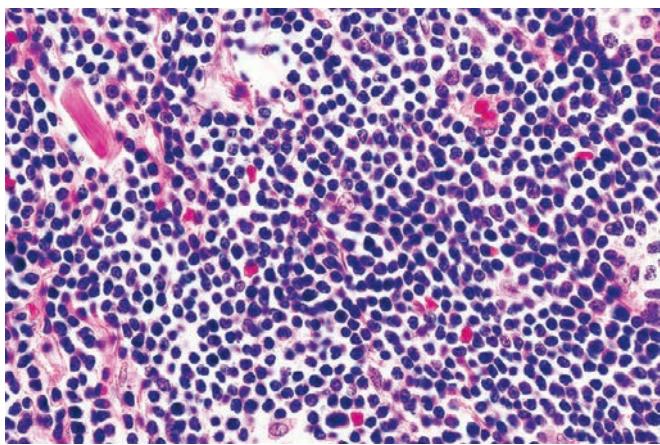


Figure 37.59 Low-Power View of Small Lymphocytic Lymphoma. A proliferation of small lymphocytes effaces the architecture of the node.

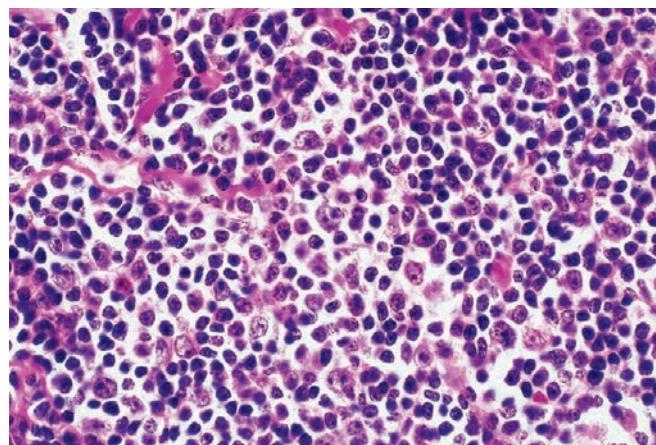


Figure 37.61 So-called proliferation center in a lymph node involved by small lymphocytic lymphoma.

prolonged, and the survival is very good. It is not unusual to find the disease incidentally in lymph node dissections done for carcinoma of one type or another.⁵⁶¹

The architecture of the node in most cases of SLL is massively effaced by a population of predominantly small round lymphocytes with clumped chromatin, inconspicuous nucleoli, barely visible cytoplasm, and scanty mitotic activity (Figs. 37.59 and 37.60). There are also variable numbers of larger cells (prolymphocytes and paraimmunoblasts) with vesicular nuclei and distinct nucleoli, singly or in small aggregates, termed proliferation centers (Fig. 37.61).^{562–565} The presence of proliferations centers and of a heterogeneous mixture of small lymphocytes with prolymphocytes/paraimmunoblasts is characteristic of SLL as opposed to mantle cell lymphoma.

Lymph node infiltration is usually diffuse, but on occasion a similar infiltrate is confined to the marginal zone, the perifollicular regions, or the interfollicular regions surrounding benign lymphoid follicles, the latter pattern being referred to as *interfollicular SLL*.^{566–568} Such cases might be considered partial lymph node involvement by monoclonal B-cell lymphocytosis (MBL) (see later). Extranodal extension of SLL is seen in approximately one-third of the cases.⁵⁶⁹

By definition, SLLs are always of mature B-cell lineage.⁵⁷⁰ Monoclonal immunoglobulins, including both IgM and IgD types, are

consistently found on their surface, but both surface heavy and light chain expression is characteristically dim compared to normal B lymphocytes and most other B-cell lymphomas. They are usually weakly CD20+ with aberrant expression of CD5+ and CD43+. They also usually express CD23, as well as CD200, BCL2, and LEF1, but are negative for CD10, cyclin D1, and SOX11.^{571–576} At the molecular level, Ig heavy and light chain genes are rearranged. While most tumors are slow growing and demonstrate a negative karyotype on routine analysis, cytogenetic abnormalities are detectable in approximately 80% of cases by FISH analysis and these findings have prognostic significance.⁵⁷⁷ The presence of somatic hypermutations in IGH is also a good prognostic indicator^{578,579} (often correlating with the absence of ZAP70 expression), and a variety of gene mutations and array CGH findings with potentially prognostic importance have been identified, including mutations of *NOTCH1* and *SF3B1*.^{580–584} These prognostic markers are discussed in more detail with CLL in Chapter 39. On occasion one sees cases of SLL with admixed typical Reed–Sternberg cells. Such cases may relapse as classical Hodgkin lymphoma but should not be diagnosed as a composite lymphoma unless there are discrete areas of typical classical Hodgkin lymphoma.⁵⁸⁵ A development of even greater clinical significance is the transformation of a SLL into another lymphoma, usually DLBCL (Figs. 37.62 and 37.63).⁵⁸⁶ This occurrence has been

traditionally known as *Richter syndrome*^{587,588} and is accompanied by a precipitous decline in the clinical course.

Monoclonal B-cell lymphocytosis (MBL) is generally defined by peripheral blood findings of less than $5 \times 10^9/L$ monotypic B-cells⁵⁸⁹ but may also infiltrate tissues. Most cases have an immunophenotype similar to CLL/SLL, and similar infiltrates found in lymph nodes without nodal enlargement are probably best classified as MBL rather than partial involvement by SLL unless more extensive disease is identified in the blood or elsewhere.⁵⁹⁰

B-prolymphocytic leukemia is a rare disorder that is defined by peripheral blood findings with 55% or more circulating B-lineage prolymphocytes⁵⁹¹ but can involve lymph nodes in a diffuse or vaguely nodular pattern. Prolymphocytes are small- to medium-sized cells

with a central, prominent nucleolus and usually also show an increased proliferation rate. Most cases differ from CLL/SLL by demonstrating bright immunoglobulin heavy and light chains, bright CD20 expression, and lack of CD5 and CD23 expression. Some cases of mantle cell lymphoma in a leukemic phase may mimic these features but will demonstrate nuclear expression of cyclin D1,⁵⁹² which should not be seen in B-cell prolymphocytic leukemia.

Lymphoplasmacytic Lymphoma

Lymphoplasmacytic lymphoma is an indolent neoplasm of small B-lymphocytes with admixed plasmacytoid lymphocytes and plasma cells.^{593,594} By definition, other lymphomas of small B cells, which may also have a plasmacytoid component, must be excluded before the diagnosis can be made. The bone marrow and spleen are frequently involved, with lymph node involvement in a smaller percentage of cases. Most patients have elevations of monotypic IgM, which may cause hyperviscosity, and meet clinical criteria for Waldenström's macroglobulinemia. Two patterns of lymph node involvement by lymphoplasmacytic lymphoma have been described, but the first is probably more specific. This generally diffuse infiltration of mostly small cells with admixed plasmacytoid cells often includes small plasma cells with intranuclear inclusions or Dutcher bodies (Fig. 37.64). Reactive mast cells are commonly admixed with the lymphoplasmacytic cells. The extent of the plasma cell proliferation can be quite variable, ranging to very little to sheets of small plasma cells. These cases may show a prominent interfollicular component with residual germinal centers. A more polymorphous type has also been described with epithelioid histiocytes and more variably sized plasmacytoid cells. This latter group appears to include cases of so-called polymorphous immunocytoma (Fig. 37.65), which has subsequently been shown to be a nonspecific pattern that includes a variety of lymphoma types of both T- and B-cell lineage.

The neoplastic cells in lymphoplasmacytic lymphoma show CD20 expression on at least the more mature lymphocyte component and



Figure 37.62 Gross appearance of lymph nodes involved by chronic lymphocytic leukemia/small lymphocytic lymphoma with anaplastic transformation (so-called Richter syndrome).

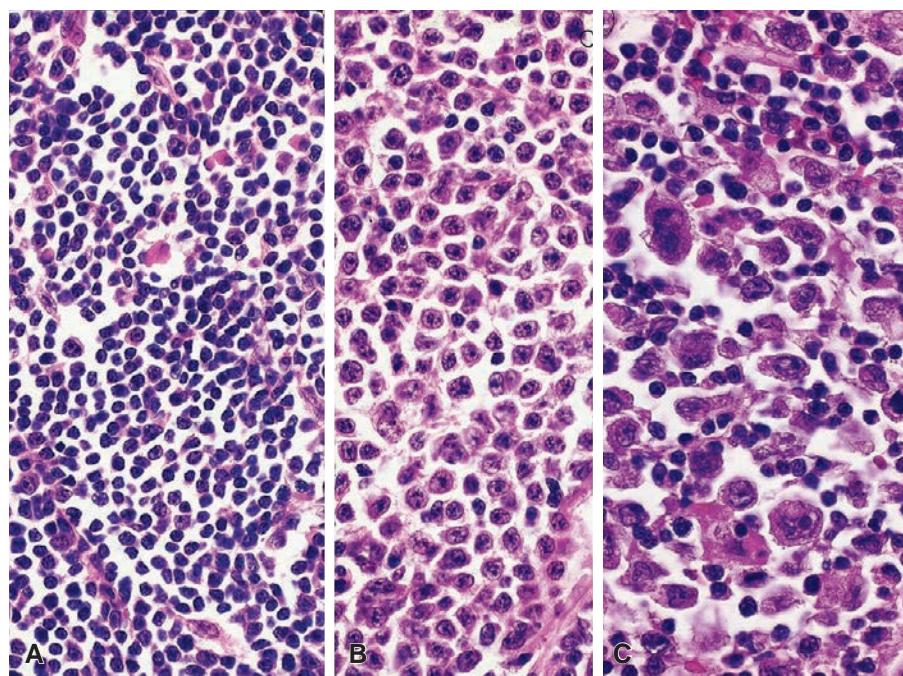


Figure 37.63 Various morphologic types of lymph node involvement by chronic lymphocytic leukemia/small lymphocytic lymphoma: **A**, monotonous infiltrate of small mature lymphocytes; **B**, increased prolymphocytes, with slightly larger nuclei and more open chromatin; **C**, large pleomorphic tumor cells (so-called Richter syndrome).

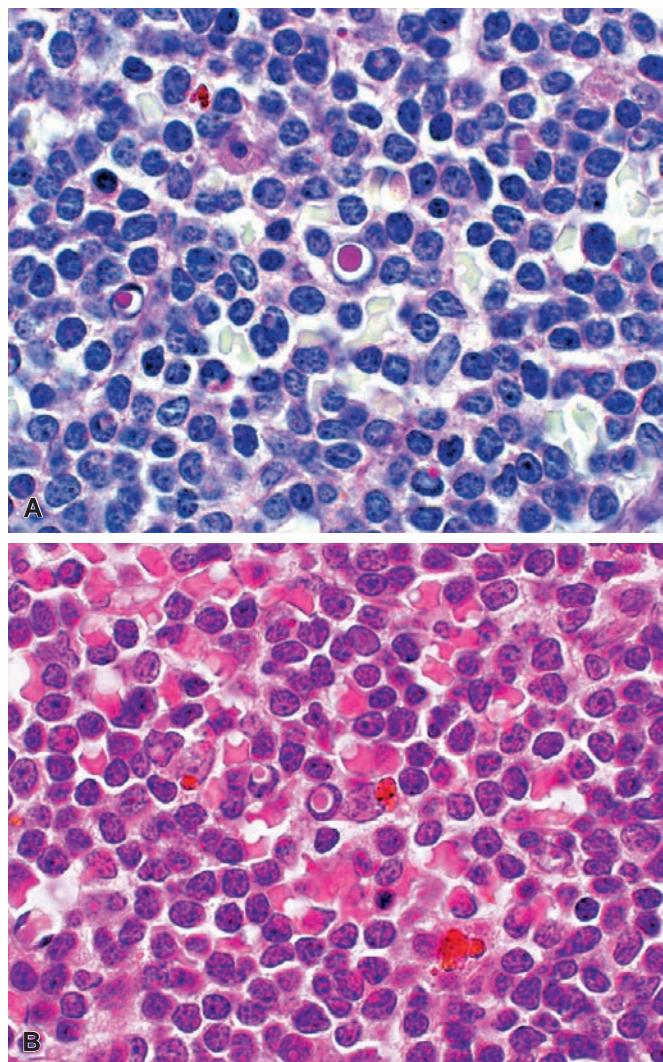


Figure 37.64 Intranuclear immunoglobulin inclusions (Dutcher bodies) in a lymph node affected by lymphoplasmacytoid lymphoma as seen after hematoxylin-eosin (**A**) and PAS stains (**B**).

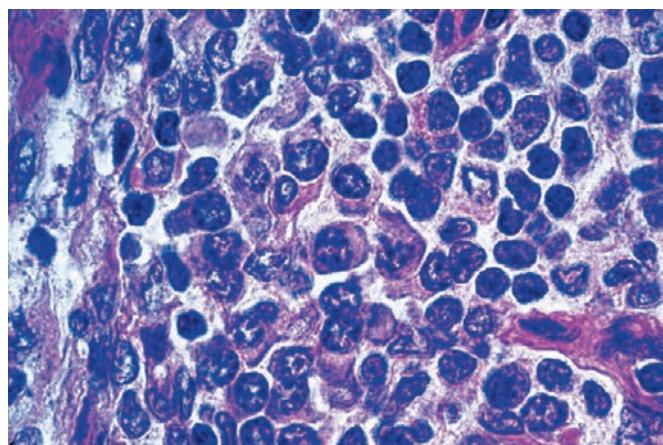


Figure 37.65 Malignant lymphoma composed of lymphocytes and immature plasmacytoid forms (so-called pleomorphic immunocytoma).

monotypic light chain expression in the plasmacytoid cell component. The B cells generally lack CD5 and CD10 expression and are cyclin D1 and CD103 negative. This immunophenotype, however, is nonspecific and can be seen in a variety of B-cell lymphomas, most notably marginal zone lymphoma.

Mutations in *MYD88* have been recently described in over 90% of cases of lymphoplasmacytic lymphoma^{595,596} with features described previously for the diffuse type (but not the polymorphous type). While a small percentage of other lymphomas of small B cells will have this mutation, its detection in the proper clinical and morphologic setting is helpful in confirming a diagnosis of lymphoplasmacytic lymphoma.

The differential diagnosis of lymphoplasmacytic lymphoma ranges from marginal zone lymphoma to plasma cell myeloma. As mentioned, detection of a mutation in *MYD88* would favor lymphoplasmacytic lymphoma or marginal zone lymphoma; this finding is not entirely sensitive or specific, and it may not be possible to resolve this differential diagnosis on small biopsies. Some cases of plasma cell myeloma may have a prominent lymphoid component and even express IgM (in contrast to most myeloma cases that are IgG or IgA producing).⁵⁹⁷ These lymphoid predominant myeloma cases may have cyclin D1 translocations and express the cyclin D1 protein, which is not a feature of lymphoplasmacytic lymphoma. Recognition of clinical features of plasma cell myeloma, including lytic bone lesions, may be the only means of differentiating these unusual types of myeloma from lymphoplasmacytic lymphoma.

Heavy Chain Diseases

The so-called heavy chain diseases are monoclonal plasma cell and B-lymphocyte proliferations that do not typically express immunoglobulin light chains and only express heavy chains.⁵⁹⁸ While rare, they can mimic other lymphoma types and may involve lymph nodes. *Mu heavy chain disease* resembles CLL/SLL but usually lacks light chains. *Gamma heavy chain disease* may show a variety of tissue presentations, including mimicking lymphoplasmacytic lymphoma, marginal zone lymphoma, and even T-cell lymphomas and Hodgkin lymphoma.⁵⁹⁹ It does not, however, show mutations of *MYD88*.⁶⁰⁰ *Alpha heavy chain disease* is a subtype of extranodal marginal zone lymphoma, usually involving the gastrointestinal tract, but may involve regional lymph nodes as well.⁶⁰¹

Nodal Marginal Zone B-Cell Lymphoma

Marginal zone B-cell lymphoma is the general term used to designate a group of low-grade B-cell lymphomas composed of a heterogeneous population of small B cells. The concept represents a grouping of entities that had been described separately, most of them at extranodal sites.⁶⁰² There appears to be considerable clinical, morphologic, and immunohistochemical overlap among the three entities (extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue [MALT lymphoma], nodal marginal zone lymphoma, and splenic marginal zone lymphoma).⁶⁰³ Consequently, the proposal has been made that they represent a related family of neoplasms showing morphologic evidence of differentiation into cells of marginal zone type.^{604,605} These cells are thought to have the capacity to mature into both monocyteoid B cells and plasma cells and to display tissue-specific homing patterns. A corollary of this proposal is that the various clinical syndromes may be the result of the homing pattern of the specific neoplastic clone.⁶⁰² The three main categories of marginal zone lymphoma, however, are distinct and differ, especially on the genetic level. Extranodal and splenic marginal zone lymphomas are discussed elsewhere in association with their anatomic sites, but nodal marginal zone lymphoma is covered here.

Nodal marginal zone lymphoma, previously termed monocyteoid B-cell lymphoma, is a tumor of small to medium-sized postgerminal

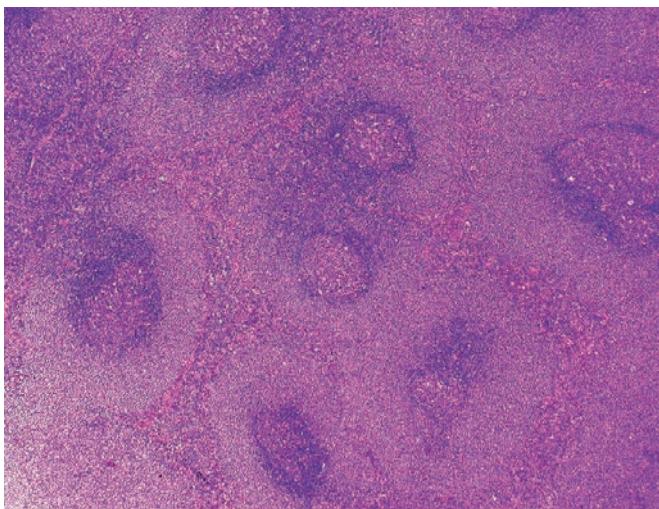


Figure 37.66 Lymph node involvement by marginal zone B-cell lymphoma with a prominent perifollicular or marginal zone pattern. There are numerous residual, non-neoplastic germinal centers.

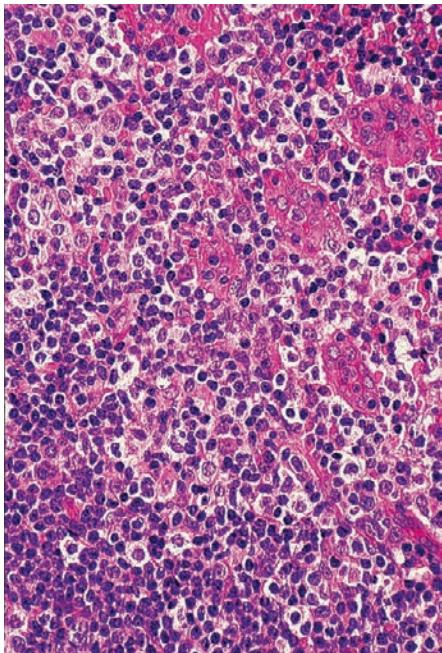


Figure 37.67 Lymph node involvement by marginal zone B-cell lymphoma with small lymphoma cells with clear cytoplasm. This tumor also affected the thymus gland. (Courtesy of Dr. John Chan, Hong Kong.)

center B lymphocytes with round or slightly indented nuclei and relatively abundant clear cytoplasm, usually located in lymph nodes, hence its designation as nodal (Figs. 37.66 and 37.67).⁶⁰⁶ The tumor cells have been regarded as the neoplastic counterpart of the monocytoid B lymphocytes found in lymph node sinuses in toxoplasmosis and other reactive disorders.⁶⁰⁷ Plasmacytoid features are prominent in some cases. The pattern of involvement is predominantly perifollicular or interfollicular,⁶⁰⁸ but cases have been seen with “follicular colonization” and with “floral” features.⁶⁰⁹ Clinically, the disease is more common in women and can be localized or generalized at presentation.⁶¹⁰ Some patients have suffered from autoimmune disorders such as Sjögren disease. In all cases, the possibility of nodal spread from an extranodal marginal zone lymphoma has to

be excluded by clinical work-up. Histologic transformation to large cell lymphoma has been documented in some cases.

The neoplastic cells of nodal marginal zone lymphoma are monotypic, mature B-cells that express CD19, CD20, CD79A, and PAX5 and are weakly positive for BCL2.⁶¹¹⁻⁶¹³ They usually lack CD5 and are negative for CD10, CD23, and cyclin D1. Approximately 40% of cases show aberrant coexpression of CD43 on the B-cells.⁷² CD21 or CD23, while negative on the neoplastic cells, may highlight expanded follicular dendritic cell networks that are infiltrated by the lymphoma cells (follicular colonization). Plasma cells are monotypic in some but not all cases.

There are no specific genetic markers for nodal marginal zone lymphomas.⁶¹⁴ They demonstrate clonal immunoglobulin gene rearrangements, similar to other B-cell neoplasms but do not usually demonstrate the recurring cytogenetic abnormalities associated with extranodal marginal zone lymphoma. Abnormalities of chromosome 3, including trisomy 3, are common but nonspecific in nodal marginal zone lymphoma. Mutations of *MYD88* are uncommon in this disease.

Pediatric nodal marginal zone lymphoma is a provisional entity in the 2016 WHO classification that occurs as localized disease, usually in cervical lymph nodes.^{407,615} Patients have a median age of 16 years with a marked male predominance. Because of the very indolent and localized nature of such proliferations in contrast to the more systemic presentation of usual type nodal marginal zone lymphoma, this provisional designation has been proposed.

Follicular Lymphoma

Follicular (nodular) lymphoma is a B-cell neoplasm that recapitulates the architectural and cytologic features of the normal germinal center.⁶¹⁶ This tumor comprises up to 40% of all adult non-Hodgkin lymphomas in the United States, but in other countries the relative incidence is much lower. Most cases occur in elderly individuals. It is very unusual under 20 years of age and relatively uncommon in patients of African descent.⁶¹⁷

Grossly and at low-power examination, the most distinctive feature of these tumors is the nodular pattern of growth (Figs. 37.68 and 37.69). The morphologic features that are useful in the differential diagnosis of follicular lymphoma and reactive follicular hyperplasia were described earlier in this chapter. With progression of the disease, this distinct nodularity becomes blurred, and eventually most of the proliferation acquires a diffuse pattern. The cytologic composition of the neoplastic nodules is characterized by a mixture in different proportions of small and large lymphoid cells, both of which resemble their normal follicular counterparts.⁶¹⁸ The small cells have scanty cytoplasm and an irregular, elongated cleaved nucleus with prominent indentations and infoldings; the size is similar to or slightly larger than that of normal lymphocytes, the chromatin is coarse, and the nucleolus is inconspicuous (Figs. 37.70-37.72). These cells have been variously referred to as centrocytes, poorly differentiated lymphocytes, and small cleaved follicular center cells. The large cells are 2 or 3 times the size of normal lymphocytes; they have a distinct rim of cytoplasm and a vesicular nucleus with one or three nucleoli often adjacent to the nuclear membrane. These cells, which have a rapid turnover rate and probably represent the proliferating component of the tumor, have been designated over the years as germinoblasts, centroblasts, histiocytes, large (cleaved or noncleaved) follicular center cells, large lymphoid cells, and lymphoblasts. Some may be binucleated and simulate Reed-Sternberg cells.⁶¹⁹ Another type of large cell seen in follicular lymphoma is the non-neoplastic follicular dendritic cell. It is recognized because of its finely dispersed chromatin, the lack of identifiable cell boundaries, and the inconspicuousness of the nucleolus.

Immunohistochemically, the follicles of follicular lymphoma (including all its variants) are composed of a monoclonal population

of mature B cells admixed with variable numbers of non-neoplastic small T cells, macrophages, and follicular dendritic cells, corresponding to the cellular composition of a normal germinal center (Fig. 37.73).^{620,621} The tumor cells express pan-B antigens, such as CD19, CD20, CD22, PAX5, and CD79A, in addition to HLA-DR. They also



Figure 37.68 Gross Appearance of a Lymph Node Affected by Follicular Lymphoma. The neoplastic nodules bulge onto the surface. (Courtesy of Dr. R. A. Cooke, Brisbane, Australia; from Cooke RA, Stewart B. *Colour Atlas of Anatomical Pathology*. Edinburgh: Churchill Livingstone; 2004.)

express surface and/or cytoplasmic immunoglobulins (usually of the IgM type) with light chain restriction. CD10, a germinal center cell marker that is also present in lymphoblastic proliferations, Burkitt lymphoma, and some large B-cell lymphomas, is detected in approximately 60%–70% of the cases.⁶²² This marker can aid in distinction from reactive follicular hyperplasia when significant numbers of CD10+ cells are found in the interfollicular zone as an indication of interfollicular invasion. Other germinal center cell markers, such as BCL6, HGAL, and LMO2, are expressed in most cases. CD5 and CD43 are usually negative.

The BCL2 protein can be identified immunohistochemically in approximately 85% of cases⁷¹ and is thus one of the most useful markers for the differential diagnosis with reactive follicular hyperplasia (BCL2 negative), although it is important to realize that BCL2 negativity does not totally rule out follicular lymphoma.^{621,623,624} Immunostaining for BCL2 cannot be used for distinction of follicular lymphoma from other low-grade B-cell lymphomas, because the latter are commonly BCL2 positive; to deal with such a diagnostic problem, immunostaining for follicular center cell markers such as CD10 and BCL6 is more helpful.^{625,626}

Follicular lymphoma shows clonal rearrangements of the immunoglobulin genes, which also feature hypermutations and ongoing somatic mutations, as characteristic of follicle center B cells.⁶²⁷

The hallmark genetic alteration of follicular lymphoma is t(14;18) (q32;q21), found in 90% of cases.⁶²⁸ The chromosomal translocation juxtaposes IGH with the BCL2 gene, driving overexpression of BCL2 protein, an anti-apoptotic molecule located in the inner mitochondrial membrane whose expression is typically switched off in normal follicle center B cells.^{629–631} As a result of aberrant BCL2 expression, the neoplastic follicle center cells do not undergo apoptosis. Thus follicular lymphoma results more from cell accumulation than cell proliferation. Although BCL2 rearrangement is also seen in some cases of DLBCL, demonstration of this molecular alteration provides a good support for a diagnosis of follicular lymphoma in the appropriate context, such as distinction from atypical follicular hyperplasia, marginal zone lymphoma with follicular growth pattern

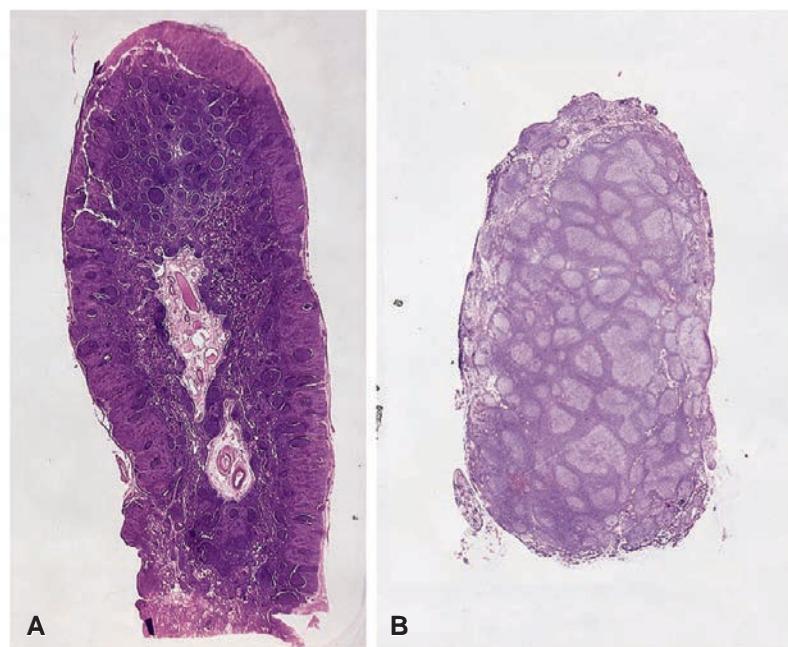


Figure 37.69 Even distribution of neoplastic follicles in follicular lymphoma (B), as opposed to the predominantly cortical distribution typical of follicular hyperplasia (A).

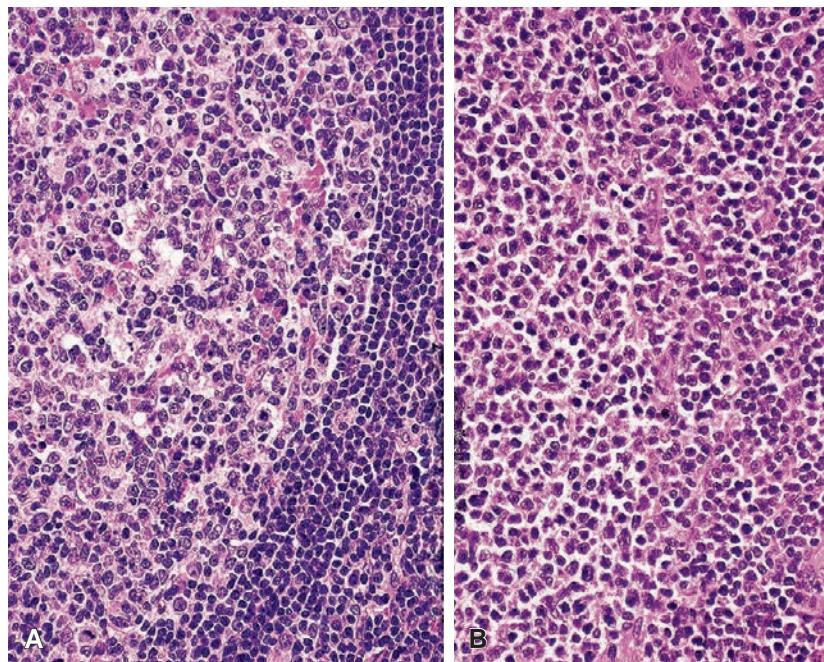


Figure 37.70 Fuzzy edge of neoplastic nodule of follicular lymphoma (B), as opposed to sharp edge bound by the mantle zone in follicular hyperplasia (A).

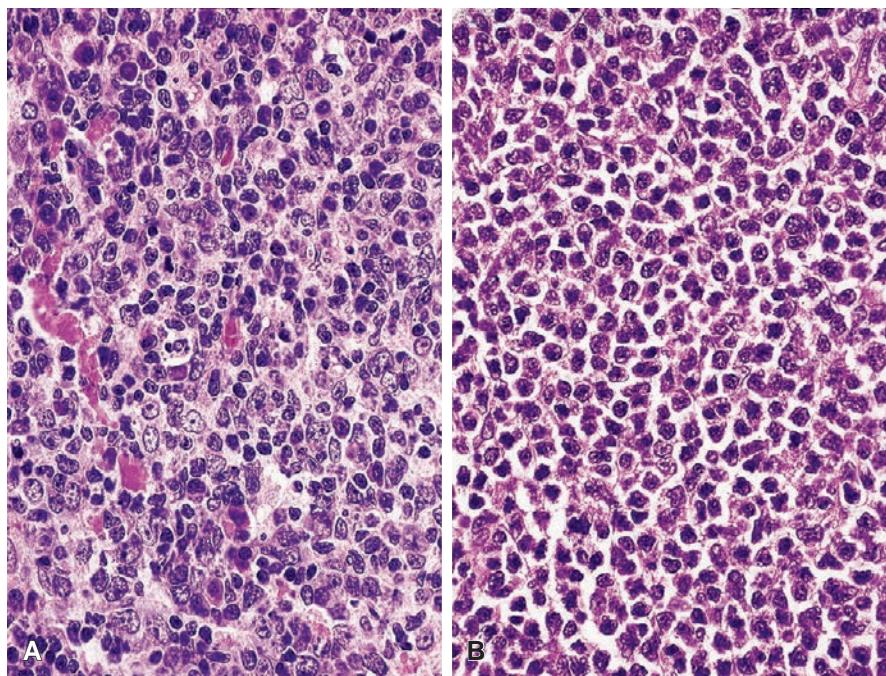


Figure 37.71 Homogeneous population of small cleaved cells in follicular lymphoma (B), as opposed to the polymorphic composition seen in follicular hyperplasia, including the presence of tingible-body macrophages (A).

and mantle cell lymphoma. For this purpose, FISH is more sensitive than PCR.^{628,632} Certain types of follicular lymphoma uncommonly or do not exhibit *BCL2* rearrangement, including pediatric follicular lymphoma, primary cutaneous follicle center lymphoma, and grade 3b follicular lymphoma (see later).⁶³³⁻⁶³⁸

The presence of *t*(14;18) alone appears to be insufficient for the development of follicular lymphoma, because this is rarely the sole genetic aberration and even healthy subjects commonly harbor low

numbers of B lymphocytes with *t*(14;18).⁶³⁹⁻⁶⁴³ Common additional genetic changes include *-1p36, +2p15, +6q, +7p, +7q, -9p, +12q, -17p, +18q, and +X*, with some of them, such as *-1p36, -6q, -9p, and +18q*, being associated with a worse prognosis.⁶⁴³⁻⁶⁴⁶

BCL6 translocation occurs in approximately 10% of the cases, usually mutually exclusive to *BCL2* translocation.^{637,647} This is correlated with grade 3b histology, high proliferative index, and infrequent expression of CD10 and *BCL2*.^{635,648,649} Follicular

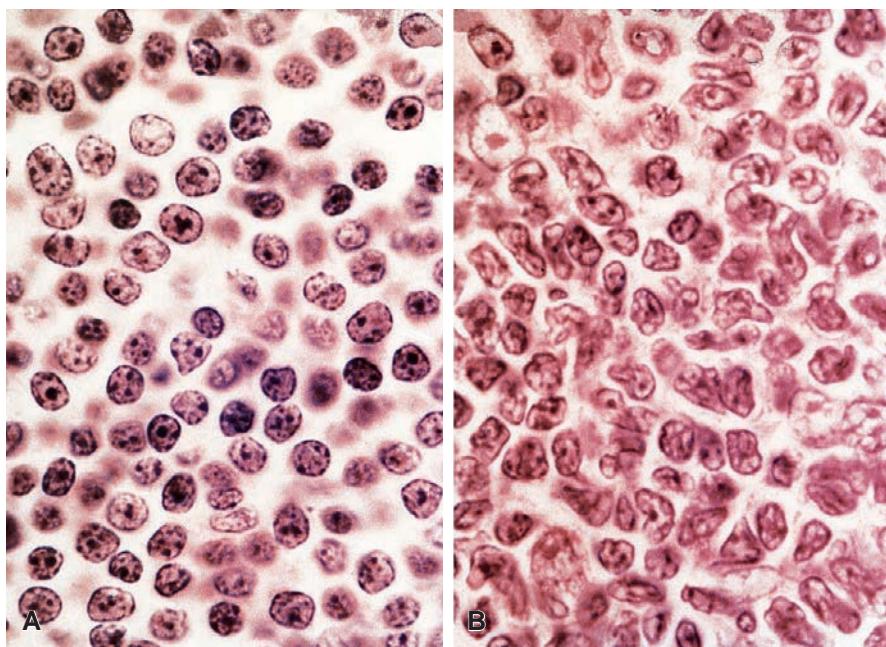


Figure 37.72 Marked contrast between the cleaved cells of follicular lymphoma (B) and the regular mature lymphocytes of small lymphocytic lymphoma (A).

lymphomas with del6q23–26 or del17p at presentation are at increased risk of transformation to high-grade B-cell lymphoma.⁶³¹ Genetic changes that mediate such a transformation may include MYC translocation, TP53 mutation, BCL2 mutation, deletions of 9p21 involving P16 and P15, and mutation of the 5' noncoding region of BCL6.^{650–652}

The gene expression profile of follicular lymphoma recapitulates that of normal germinal center B cells and furthermore clusters close to resting B cell samples, in keeping with its indolent nature.³⁸ On microarray analysis, the immune response-1 signature, reflecting presence of a complex infiltrate of T cells and other immune cells, predicts long survival, while immune response-2 signature, reflecting a significant infiltrate of monocytes and dendritic cells, predicts short survival.⁶⁵³

Depending on the relative proportion of small and large cells, typical follicular lymphomas are subdivided into two categories. Because of reproducibility issues in grading and a lack of prognostic significance, low-grade cases are now designated as grade 1/2 and are defined by the presence of 15 or fewer centroblasts (large B cells) per high-power field. Grade 3 is defined as more than 15 centroblasts per high-power field and are further subdivided into grades 3a and 3b. Cases with admixed centrocytes (small cleaved B cells) are referred to as grade 3a, which is most common, while cases with solid sheets of centroblasts are referred to as grade 3b.

Several important clinical differences exist between these groups.^{654,655} Patients with grade 1/2 follicular lymphoma are often asymptomatic, usually have generalized disease (often involving extranodal sites, such as the liver and bone marrow), and have a good prognosis,⁶⁵⁶ to the point that some authors advise against aggressive treatment for them.^{657–662} Grade 3 tumors are more commonly localized at the time of presentation but run a more aggressive clinical course^{617,663} and are more likely to lose their nodular pattern of growth and become diffuse.

The extranodal spread of follicular lymphoma is quite predictable. In the spleen, it tends to affect the B-derived lymphoid follicles located eccentrically in the white pulp. In the liver, the infiltrate is

predominantly periportal. The bone marrow infiltrates tend to have a paratrabecular location. In the skin, there is an extensive dermal infiltrate without particular relation to vessels or adnexa.

In some cases of follicular lymphoma (particularly grade 1/2), malignant cells are found in the peripheral blood; hematologists refer to them by the inelegant term “buttock” cells because of their prominent nuclear cleft (Fig. 37.74). No prognostic significance has been assigned to this finding.

Specimens from subsequent biopsies or autopsy from patients with grade 1/2 follicular lymphomas may show a similar microscopic appearance or a progression to grade 3 or to DLBCL.^{664,665} A more ominous development is represented by the occasional “blastic” or “blastoid” transformation of follicular lymphoma, in which the tumor cells resemble those of Burkitt or lymphoblastic lymphoma; this is accompanied by a highly aggressive clinical course.⁶⁶⁶ The resulting high-grade malignant tumor may also express CD30 but remains a mature B-cell neoplasm and not true ALCL.⁶⁶⁷

Several morphologic variations on the theme of follicular lymphoma have been described. They include the following:

1. Presence of fine or coarse bands of fibrosis that accentuate even more the nodular character of the lesion but, in so doing, may induce confusion with carcinoma. This feature is more commonly seen in grade 3 tumors;⁶⁶⁸ it is particularly frequent in the retroperitoneum, but it also occurs in the cervical region, mediastinum, and other locations.
2. Presence of monocyteoid B cell/marginal zone differentiation. In about 10% of follicular lymphomas, discrete foci of monocyteoid B cells are seen, typically appearing on low-power examination as a pale rim around the neoplastic follicles.^{669,670} Molecular studies have shown a common clonal origin of the monocyteoid B cells from follicle center cells.^{671,672} Clinically, this feature is said to be associated with a shorter survival time.⁶⁷³
3. Deposition of proteinaceous material in the center of the nodules, similar to that seen in some reactive conditions, particularly the plasma cell variant of Castleman disease (Fig. 37.75). The material is amorphous, acellular, brightly eosinophilic, and PAS

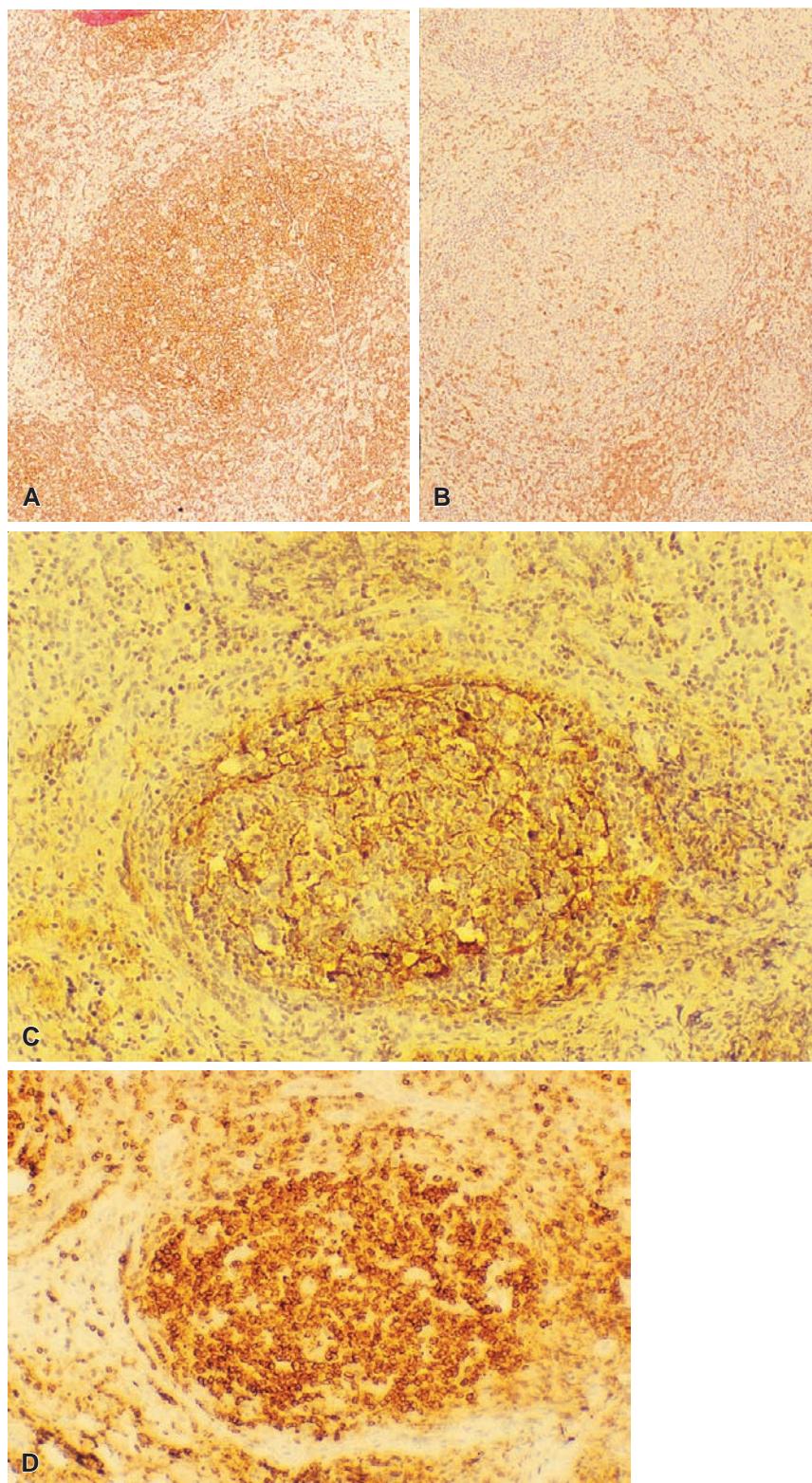


Figure 37.73 Follicular Lymphoma. **A**, CD20 stain decorates the neoplastic nodule and identifies the cells as of B-cell nature. **B**, CD3 stain shows a rim of non-neoplastic T cells around the follicles. **C**, CD21 stain shows a large number of dendritic follicular cells within the neoplastic follicle. **D**, BCL2 stains the B cells within the germinal centers. (Courtesy of Dr. Glauco Frizzera, New York, NY, USA.)

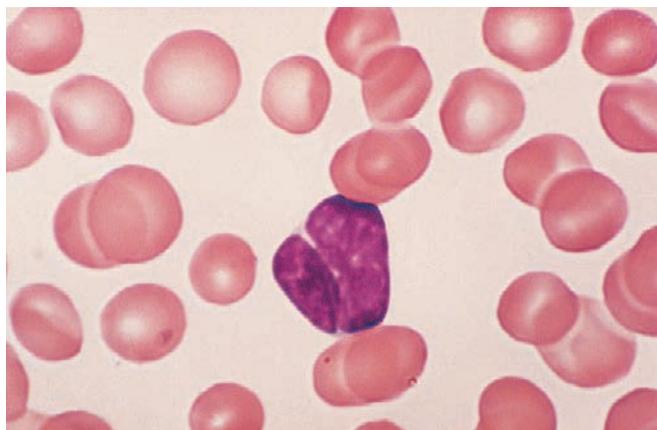


Figure 37.74 Blood smear from a patient with follicular lymphoma showing a so-called notched nucleus cell or buttock cell.

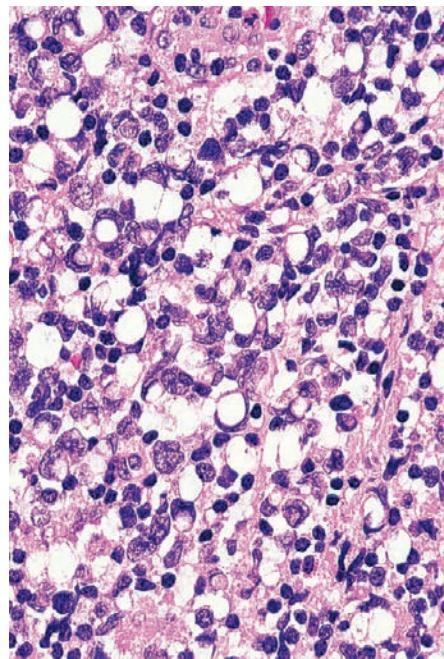


Figure 37.76 Follicular lymphoma featuring signet ring changes in some of the tumor cells.

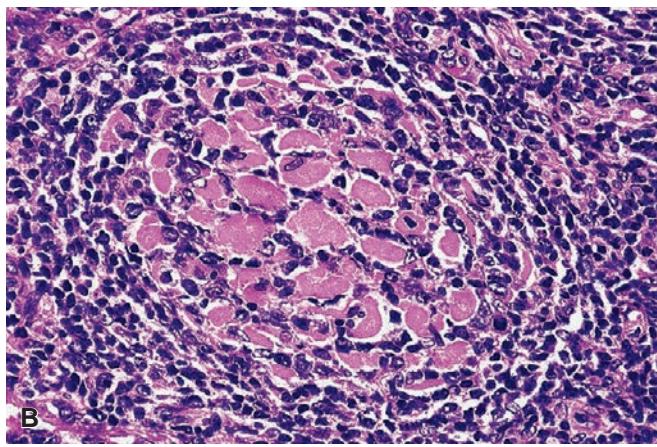
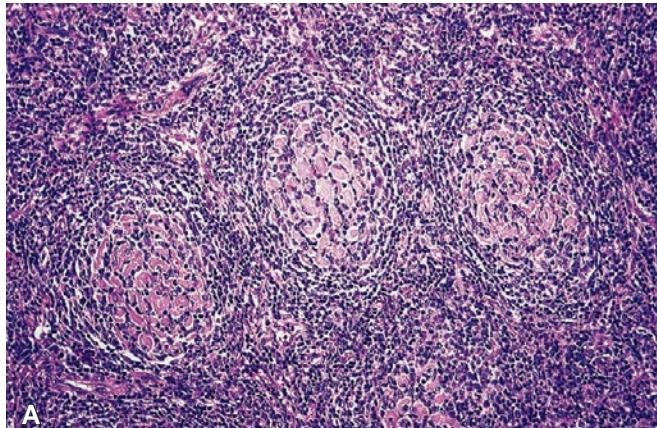


Figure 37.75 A and B. Follicular lymphoma with deposition of proteinaceous material among the tumor cells. Ultrastructurally, some of this material was found to be within the cytoplasm of dendritic follicular cells.

- positive.^{654,674} Ultrastructurally, it is composed of membranous structures, membrane-bound vesicles, and electron-dense bodies.⁶⁵⁴ It is described in grade 1/2 follicular lymphomas.⁶⁷⁵
- Presence of large cytoplasmic eosinophilic globules—presumably immunoglobulins—or a single vacuole that push the nucleus laterally and result in a signet ring effect (Fig. 37.76).⁶⁷⁶
 - Clear-cut plasmacytic differentiation in some or many of the neoplastic follicular center cells.^{669,677}

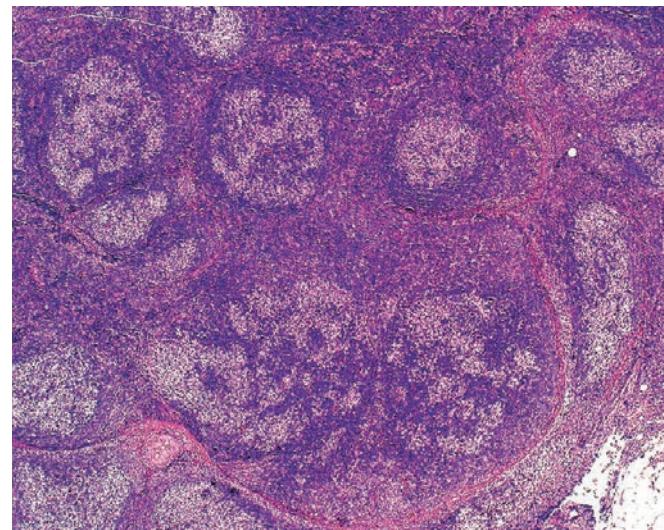


Figure 37.77 So-called floral variant of follicular lymphoma which refers to the flower-like pattern of the expanded, disrupted neoplastic follicles.

- Presence of cells with cerebriform nuclei (similar to those of T-cell lymphoma)⁶⁷⁸ or multilobated nuclei.⁶⁷⁹
- Permeation of the tumor follicles by small round lymphocytes of presumably mantle zone origin, the appearance simulating that of progressively transformed germinal centers ("floral" variant) (Fig. 37.77).^{63,680}
- Presence of rosettes made up of cytoplasm and cytoplasmic processes of the lymphoid tumor cells and simulating the appearance of a neuroendocrine neoplasm (Fig. 37.78).²⁷⁰
- Presence of hyaline vascular follicles similar to those seen in the hyaline-vascular type of Castleman disease.
- Inversion of the usual staining pattern as seen on low-power examination so that the neoplastic follicles appear darker than

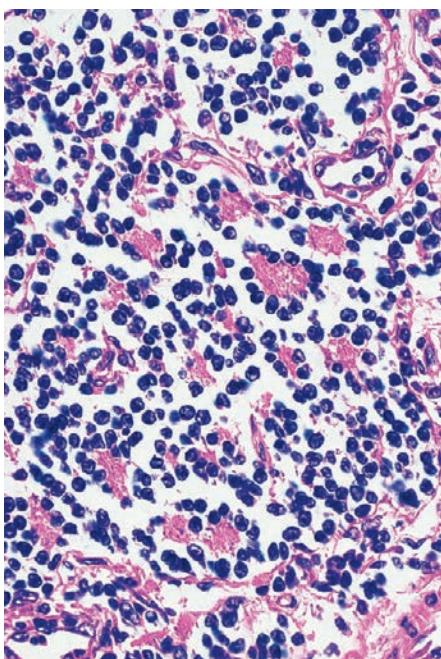


Figure 37.78 Follicular lymphoma showing rosette formation by some of the lymphoid cells.

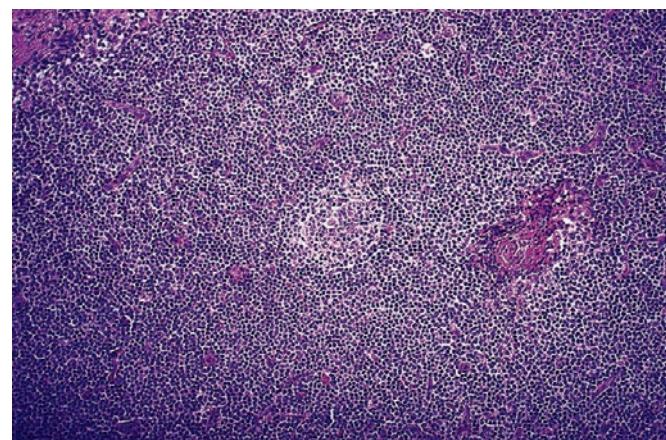


Figure 37.79 Mantle cell lymphoma surrounding a small residual germinal center.

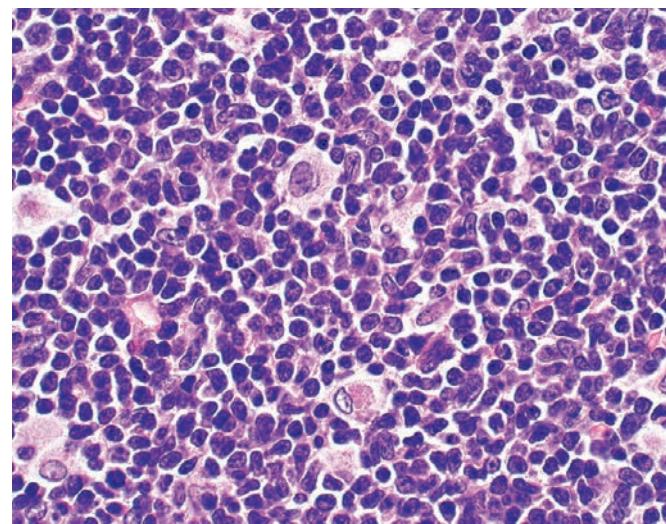


Figure 37.80 High-Power View of Mantle Cell Lymphoma. There are subtle abnormalities of the nuclear contours, the appearance being intermediate between that seen in small cleaved follicular lymphoma and that of small lymphocytic lymphoma. Note the individual epithelioid histiocytes that are characteristically associated with this disorder.

the surrounding lymphoid tissue. This pattern, which is referred to as the “reverse” or “inverse” variant of follicular lymphoma, carries no prognostic significance.⁶⁸¹

11. Prominent epithelioid granulomatous response.⁶⁸²
12. Preserved reactive germinal centers in some foci of the involved lymph node. This feature is said to be a strong indicator of limited disease stage,⁶⁸³ and such reported cases may have represented *in situ* follicular neoplasia (see later).

In some reactive lymph nodes, BCL2-positive germinal centers can be detected in the absence of infiltration beyond the germinal center or other evidence of follicular lymphoma. Such cases may occur in patient with follicular lymphoma or another lymphoma type elsewhere but may also occur in otherwise healthy individuals. Their presence does not consistently predict development of frank lymphoma and such lesions should diagnosed *in situ* follicular neoplasia rather than follicular lymphoma.^{407,684,685}

Pediatric-type follicular lymphoma is a distinct entity in the 2016 WHO classification.^{407,686,687} It is a localized disease that usually occurs in children but is reported in adults. It usually shows grade 3b features with a blastoid, large cell predominance. These cases often do not express BCL2 and should not demonstrate a t(14;18). They have an indolent course and should only be diagnosed in the setting of localized disease and in the absence of diffuse areas.

Large B-cell lymphoma with *IRF4* rearrangement is a provisional entity in the 2016 WHO classification that also tends to occur in children and young adults, is negative for t(14;18), and is usually localized to cervical lymph nodes or Waldeyer’s ring.^{686,688} These may have a follicular or diffuse pattern, show strong expression of BCL6 and *IRF4* (MUM1), and usually demonstrate a translocation involving *IRF4*. Although more aggressive than pediatric-type follicular lymphoma, these patients usually respond well to lymphoma therapy.

Finally, duodenal-type follicular lymphoma is a distinct category in the WHO classification that tends to present at a low stage with a more indolent course when compared to traditional follicular lymphoma or even follicular lymphoma involving other gastrointestinal sites.⁶⁸⁹

Mantle Cell Lymphoma

Mantle cell lymphoma is a relatively aggressive neoplasm of small B-lymphocytes that includes cases previously known as intermediate lymphocytic, mantle zone, centrocytic, and diffuse small cleaved cell lymphoma.^{690–692} It comprises from 3% to 10% of all cases of non-Hodgkin lymphoma. Like follicular lymphoma, it usually occurs in middle-aged and elderly individuals.^{693,694} The low-power appearance is largely that of a diffuse lymphoma, although nodular and mantle zone patterns also occur (Fig. 37.79).⁶⁹⁵ The neoplastic cells are small and often show irregular and indented nuclear contours similar to those seen in small cleaved cell follicular lymphoma without an admixed large cell component (Fig. 37.80).⁶⁹⁶ On occasion, some of the tumor cells show plasma cell differentiation.⁶⁹⁷ In some cases, the tumor cells have larger nuclei with more dispersed chromatin and a higher proliferative fraction (“blastoid” or “pleomorphic” variant)⁶⁹⁸ (Fig. 37.81), but the lymphoma cells retain a homogeneous pattern of cell size in contrast to CLL/SLL and follicular lymphoma. Admixed epithelioid histiocytes are common but do not form clusters

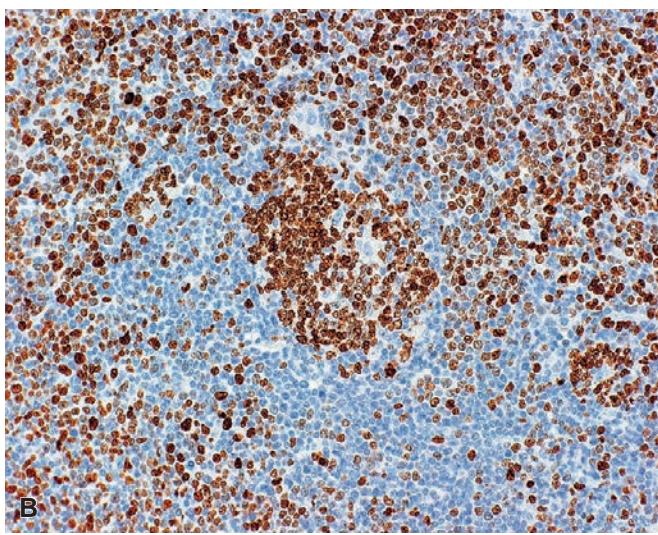
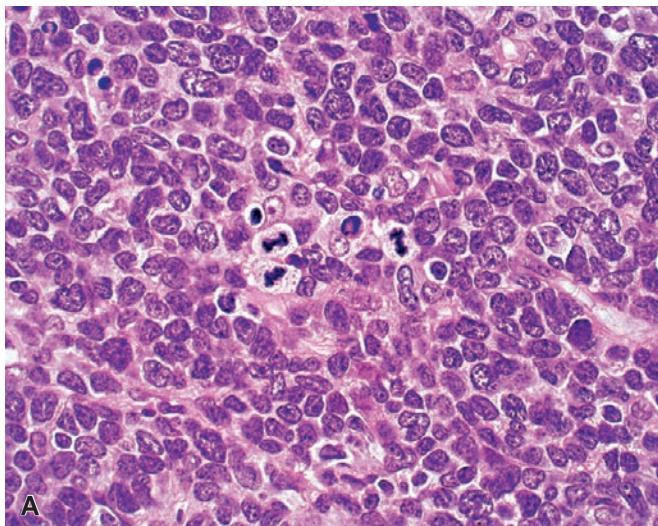


Figure 37.81 So-Called Blastoid Variant of Mantle Cell Lymphoma. **A**, Hematoxylin-eosin-stained section showing high mitotic activity. **B**, A high percentage of the tumor cells show nuclear immunoreactivity for MIB-1.

or granulomas and do not contain cellular debris. The blastoid form of mantle cell lymphoma (and sometimes also the classic form) may be accompanied by blood, bone marrow, and spleen involvement ("mantle cell leukemia").⁶⁹⁹⁻⁷⁰²

The tumor cells are mature B cells, positive for immunoglobulins (IgM and often also IgD), and immunoglobulin light chain restricted; express B cell-associated antigens such as CD19, CD20, CD79A, and PAX5; and demonstrate aberrant expression of CD43 and CD5.^{703,704} The general absence of CD23 is useful in distinguishing mantle cell lymphoma from SLL,^{572,705} and the presence of CD5 is useful in the differential diagnosis with follicular and marginal zone lymphomas. It should be remarked, however, that CD5 expression is not always present in mantle cell lymphoma⁷⁰⁶ and can be present in some DLBCLs apparently unrelated to mantle cell lymphoma.⁷⁰⁷ Most cases demonstrate nuclear expression of cyclin D1, correlating with the presence of a t(11;14)(q13;q32) (Fig. 37.82).^{708,709} Rare cases are cyclin D1 negative, and SOX11 is usually expressed in such cases.⁵⁷⁵

The immunoglobulin genes are clonally rearranged, and the variable regions are usually nonmutated, suggesting a naive B-cell

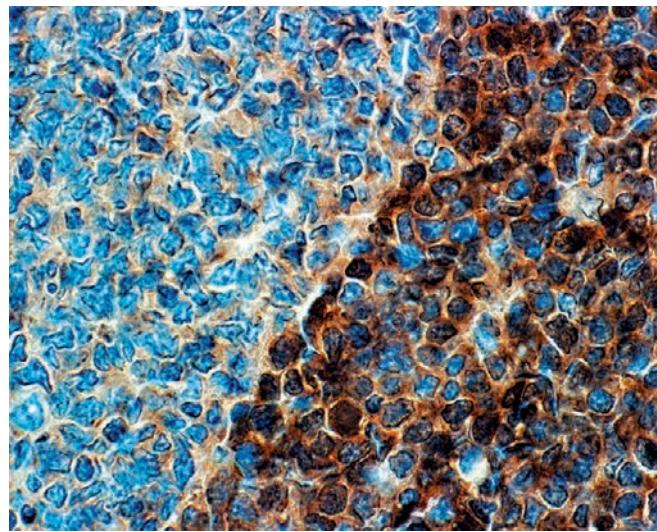


Figure 37.82 Immunoreactivity for cyclin D1 in mantle zone lymphoma.

stage of differentiation.^{710,711} Nearly all cases show fusion of CCND1 (cyclin D1) with the IGH gene, which results from t(11;14)(q13;q32) (in approximately 70% of cases by karyotype and almost 100% with molecular methods).^{692,712} As a consequence, cyclin D1, a cell cycle protein, is overexpressed, promoting cell proliferation. CCND1 translocation is practically specific for mantle cell lymphoma, except that it also occurs in some cases of plasma cell myeloma, and thus its demonstration may help confirm a diagnosis of mantle cell lymphoma.^{713,714} FISH gives the highest sensitivity (>95%) and is superior to conventional cytogenetics, Southern blot, or PCR.^{712,715} Additional genetic changes are common in mantle cell lymphoma, such as inactivating mutation of ATM (11q22–23), homozygous deletions of INK4a/ARF (p16), and TP53 mutation.^{710,716,717} The blastoid/pleomorphic variant is correlated with presence of TP53 mutation, MYC abnormalities, and tetraploidy.⁷¹⁸⁻⁷²¹

Microarray studies have shown that mantle cell lymphoma exhibits a unique gene expression signature distinct from other lymphoma types, and furthermore confirm the existence of a cyclin D1-negative subset of mantle cell lymphoma (up to 7% of cases).^{722,723} At least some cases of the latter subset express cyclin D2 or cyclin D3 instead of cyclin D1,⁷²³⁻⁷²⁵ and most express SOX11.⁵⁷⁵ Mantle cell lymphoma may be difficult to distinguish from follicular hyperplasia with a prominence of mantle zone cells ("mantle zone hyperplasia") and Castleman disease.⁷⁰ Determination of clonality of the infiltrate by immunohistochemical techniques is of importance in this regard as is demonstration of cyclin D1 in mantle cell lymphoma. The differential diagnosis also includes grade 1 follicular lymphoma. The fact that centroblasts and immunoblast-like cells are totally absent in mantle cell lymphoma is an important differential feature. Expression of cyclin D1, while very useful in the diagnosis, is not specific for mantle cell lymphoma and may also occur in hairy cell leukemia, multiple myeloma, and proliferation centers of CLL/SLL.

Finally, the blastoid form of mantle cell lymphoma needs to be distinguished from either T- or B-cell lineage lymphoblastic lymphoma.⁵⁵⁶

The median survival of mantle cell lymphoma is approximately 3–5 years. As a group, it is characterized by more widespread disease and a much lower response rate to chemotherapy than follicular lymphoma.^{709,726} The blastic variant has a more aggressive clinical course.^{690,727} A rare indolent type of mantle cell lymphoma has also

been described.⁷²⁸ Proliferation rate is a strong predictor of survival for all types of mantle cell lymphoma, with rates of 30% or higher associated with a worse prognosis.⁷²⁹ For this reason, Ki-67 staining should be performed on all new diagnosis specimens.

Some clonal mantle cell proliferations have a more indolent clinical course. *Leukemic nonnodal mantle cell lymphoma* is one such example.⁷³⁰ In addition to lack of lymph node involvement, it tends to involve the spleen and be negative for SOX11. Cases with cyclin D1-positive cells restricted to the mantle zones without infiltration to surrounding structures or diffuse nodal involvement are now termed *in situ mantle cell neoplasia* to reflect the low rate of progression of such lesions.⁷³¹

Diffuse Large B-Cell Lymphoma and Related Disorders
DLBCL encompasses a heterogeneous group of disorders. The term replaces the old histiocytic lymphoma, which in turn replaced the older reticulum cell sarcoma. It is characterized morphologically by large size of the cells, vesicular nuclei with prominent nucleoli, and relatively abundant cytoplasm, and immunophenotypically by expression of B-lineage markers. In general, DLBCLs can be diagnosed based on a limited panel of markers that confirm that the diffuse, large cell proliferation is of B-cell lineage, but there are now numerous subtypes of DLBCL that require additional studies and there are numerous prognostic markers that must now be performed on individual cases.

As a group, DLBCL occurs in both children and adults but mostly in the latter.⁷³² In comparison with most other types of lymphoma, it has a greater tendency for extranodal presentation and for being localized at the time of presentation. The progression is rapid, and the prognosis is poor if untreated. Indeed, it constitutes a high percentage of so-called aggressive lymphomas.^{733,734} However, excellent responses have been obtained with multidrug chemotherapy, in particular in combination with rituximab (anti-CD20 therapy),⁷³⁵⁻⁷³⁷ and new therapies are being developed for some subtypes.⁷³⁸ In many cases, the tumor is limited to one side of the diaphragm (40%, as opposed to 90% for follicular lymphoma).⁷³⁹ Involvement of the bone marrow or liver is less common than in follicular or SLs.⁷⁴⁰ Approximately 40% of the cases present in extranodal sites, such as the digestive system, skin, and skeletal system.⁷³⁹ When the liver or spleen is involved, it is usually in the form of scattered large tumor masses instead of the multiple smaller nodules or miliary type seen with the group of lymphomas composed of small lymphocytes. The involved nodes are usually markedly enlarged, homogeneous, individualized, and with little or no necrosis (Fig. 37.83).

Microscopically, the pattern of nodal involvement is by definition diffuse. However, it may be complete or partial, and on occasion it may be interfollicular or show a sinus pattern (see later). There is commonly extranodal extension, sometimes with accompanying sclerosis. Mitoses are numerous, and a starry sky pattern may be present.

In the past, a separation based on cytologic features was made between tumors composed of germinal center (large cleaved and noncleaved; centroblastic) cells (Fig. 37.84) and immunoblastic cells with a large vesicular nucleus with prominent central nucleolus and thick nuclear membrane, and a deeply staining amphophilic and pyroninophilic cytoplasm with a distinct nuclear hof (Fig. 37.85). Such distinctions, however, have shown poor intraobserver and interobserver reproducibility and are no longer recommended.

The majority of cases of DLBCL fall into the “not otherwise specified”, or NOS group, but even within this group there is great morphologic variability. Most of these variations do not have an impact on therapy or prognosis and for this reason are not formally



Figure 37.83 Gross appearance of lymph nodes involved by non-Hodgkin lymphoma of diffuse large B-cell type. The nodes are enlarged and show a homogeneous tan cut surface.

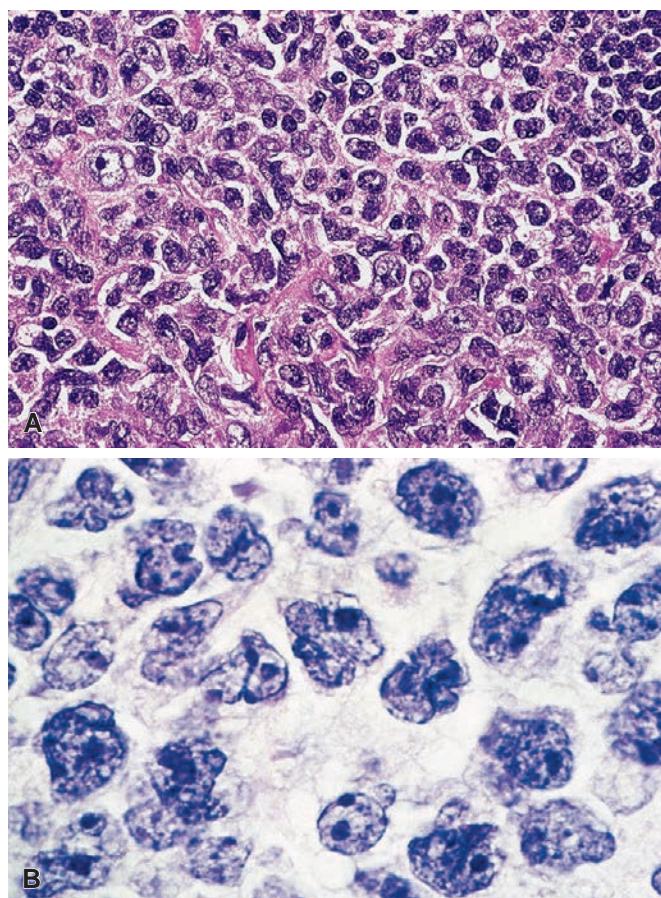


Figure 37.84 Medium- (A) and high-power (B) views of diffuse large B-cell lymphoma with large cleaved cells.

subclassified, but they are important because they may result in a mistaken diagnosis. They include the following:

1. **Sclerosis.** Diffuse large cell lymphomas can undergo marked sclerosing changes, similar to those seen in follicular lymphomas (Fig. 37.86).^{668,674,741,742} This material is mainly composed of types I, III, and V collagen and fibronectin.⁷⁴³ Sclerosis is a

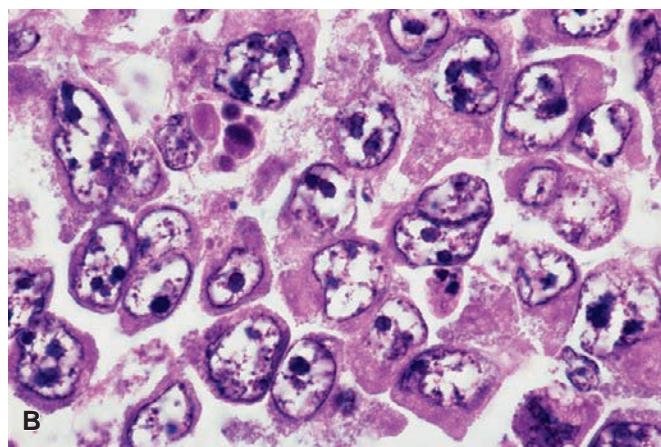
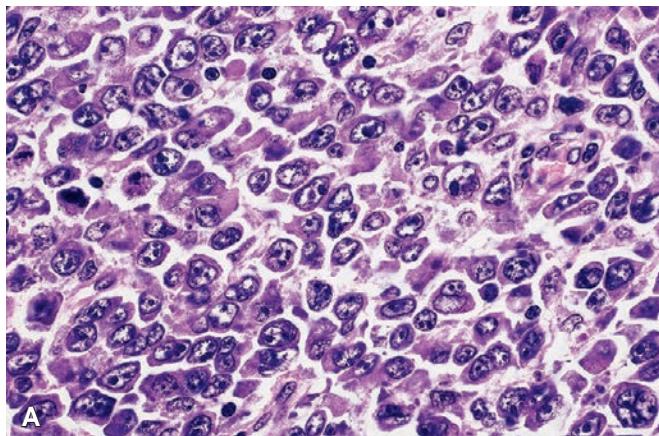


Figure 37.85 Medium- (A) and high-power (B) views of diffuse large B-cell lymphoma with immunoblastic features.

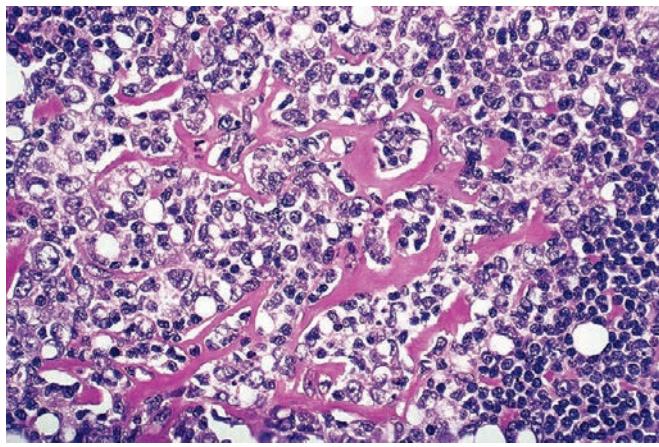


Figure 37.86 Marked sclerosis and hyalinization in diffuse large B-cell lymphoma.

particularly common feature in mediastinal (thymic) large B-cell lymphomas.

2. *Spindling of tumor cells*. This phenomenon, which is probably related to the aforementioned fibrosis, seems to be more common in large cell lymphomas of mediastinum and bone but it can be seen in any location, including lymph nodes.⁷⁴⁴ It is thought to be related to the presence of markers characteristic of a germinal center B-cell origin.⁷⁴⁵

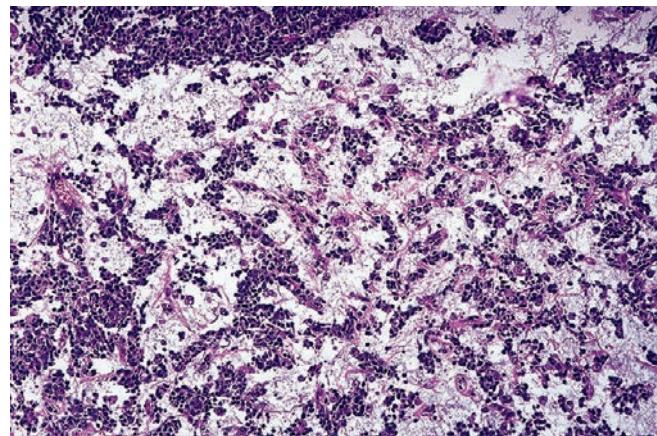


Figure 37.87 Myxoid stromal change in diffuse large B-cell lymphoma. This is an exceptional occurrence.

3. Presence of a *myxoid stroma* that can simulate the appearance of myxoid malignant fibrous histiocytoma or myxoid chondrosarcoma (Fig. 37.87).^{746,747}
4. *Rosette formation*. This peculiar change, originally described in follicular lymphoma, has also been seen in large cell lymphoma. Ultrastructural studies have shown that the material in the center of the rosettes is made up of complex cell prolongations.⁷⁴⁸
5. *Filiform cell prolongations*. This phenomenon, which is probably related to that described in the previous paragraph, is appreciable in ultrastructural preparations and is similar to that sometimes seen in carcinomas, mesotheliomas, and other neoplasms. Large cell lymphomas exhibiting this spectacular feature have been designated anemone cell, microvillous, filiform cell, villiform cell, and porcupine lymphomas.^{749,750}
6. *Signet ring features*. This alteration, which is more common in follicular lymphoma, is rarely seen in large cell lymphoma and may simulate metastatic adenocarcinoma.⁷⁵¹
7. *Sinus pattern of spread*, in which the tumor cells are predominantly or entirely confined to the lymph node sinuses, resulting in an appearance closely simulating that of metastatic carcinoma, malignant melanoma, or ALCL (Fig. 37.88).^{737,752} Such cases may also demonstrate anaplastic morphology and even expression of CD30, but should not be diagnosed as ALCLs, which is a distinct entity of T- or null-cell lineage.
8. *Interfollicular pattern of growth*. This is more common in T-cell tumors but has also been described in B-cell neoplasms.
9. *Nuclear multilobation*. Although originally thought to be a feature of T-cell tumors, this alteration is now known to occur in B-cell neoplasms.^{753,754}

Immunophenotypically, DLBCL is by definition a monotypic B-cell neoplasm positive for B-lineage markers (most importantly CD20 but also CD19, CD79A, and PAX5) and variably immunoglobulin (surface or cytoplasmic).⁷⁵⁵ The follicle center cell markers CD10 and BCL6 are expressed in 40% and 60% of cases, respectively. A proportion of cases express postgerminal center cell or plasma cell-associated markers such as CD38, VS38, and MUM1. About 50% of cases express BCL2 protein. A minority of DLBCLs express CD30, usually in a heterogeneous pattern. CD5 is expressed in 10% of cases and a pleomorphic variant of mantle cell lymphoma must be excluded in such cases. Ki-67 staining usually shows a variable, but usually high proliferation index, with some cases showing an index approaching 100%. An exceptionally rare occurrence is immunoreactivity for cytokeratin, which may lead the unwary to a misdiagnosis of carcinoma.⁷⁵⁶

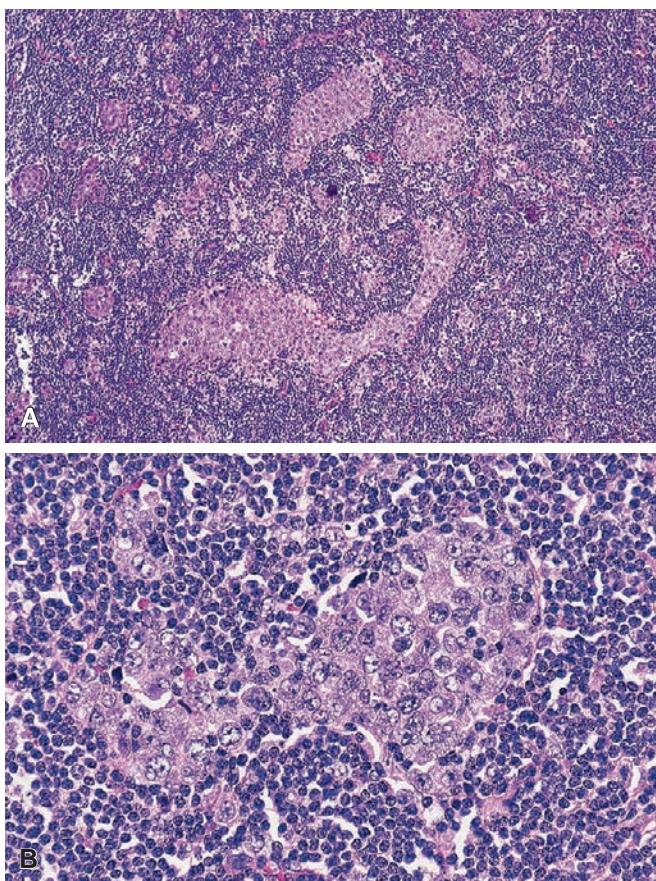


Figure 37.88 **A** and **B**, Large B-cell lymphoma with a sinus pattern of growth that simulates a metastatic tumor.

DLBCLs show rearrangements of the immunoglobulin genes as expected for a B-lineage neoplasm. The variable region of the IGH is usually hypermutated, with some cases also showing ongoing somatic mutations, indicating a germinal center or postgerminal center stage of B-cell differentiation.⁷⁵⁷

Approximately 20% of cases of DLBCLs show *BCL2* rearrangement due to t(14;18)(q32;q21), a hallmark of follicular lymphoma.⁷⁵⁸⁻⁷⁶⁰ Such cases may have transformed from a known or occult follicular lymphoma, or may have even directly evolved to DLBCL without a precursor phase of follicular lymphoma. However, additional genetic alterations are required for the development of DLBCL, such as *TP53* mutation. The *BCL6* gene encodes a transcription factor essential for formation of secondary lymphoid follicles and T-cell-dependent antibody responses, and its aberrant expression plays an important role in the *de novo* pathway of DLBCL formation. In about 35% of cases of DLBCLs, translocation of *BCL6* (3q27) with a variety of partner genes (with IGH gene located on 14q32 being the commonest) results in constitutive overexpression of *BCL6* protein, causing a sustained proliferative setting in which additional mutations can occur.⁷⁶¹⁻⁷⁶⁴ This translocation is not specific for DLBCL but is also found in a subset of follicular lymphomas.^{648,765} In addition, about 75% of cases of DLBCLs show somatic mutations in the 5' noncoding regions of the *BCL6* gene, a phenomenon also commonly observed in other germinal center and postgerminal center B-cell lymphomas.^{766,767} At least some of the mutations result in deregulation of *BCL6* expression.⁷⁶⁸ These mutations, occurring independent of *BCL6* translocation, are generated by the same somatic hypermutation mechanism that targets the variable regions of immunoglobulin

genes.^{769,770} *MYC* (8q24) translocation is found in up to 10% of DLBCLs.⁷⁷¹⁻⁷⁷⁴ In contrast to Burkitt lymphoma, the *MYC* gene may be fused with a non-immunoglobulin gene, and the karyotype is complex. *MYC* translocation is associated with a highly aggressive behavior.⁷⁷⁵ *MYC* translocations in DLBCL are often associated with translocations of *BCL2* or *BCL6* and these "double-hit" lymphomas have a particularly aggressive clinical behavior.⁷⁷⁶ A *MYC* translocation alone in a case with morphologic features of DLBCL does not alter the diagnosis of DLBCL, NOS; however, the finding of double hit would now change the diagnosis to *high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements* (see later). For this reason, routine testing for translocations of these three genes by FISH is recommended for many patients with DLBCL, NOS. Expression of *MYC*, *BCL2*, and/or *BCL6*, detected by immunohistochemistry, does not directly correlate with translocations detected by FISH, but so-called double expressors are also associated with a worse prognosis,⁷⁷⁷ and some centers routinely perform immunohistochemistry for *MYC* to identify this group.

Gene expression profiling studies can identify three major groups of DLBCLs^{33,34,38,778,779}: (1) germinal center B cell-like (GCB) DLBCL that expresses genes characteristic of germinal center B cells, and is correlated with presence of t(14;18) and *C-REL* amplification; (2) activated B cell-like (ABC) DLBCL that expresses genes normally induced during in vitro activation of peripheral blood B cells, and is correlated with presence of *BCL6* translocation, *PRDM1/BLIMP1* inactivation, and constitutive activation of NF κ B due to somatic mutations in genes encoding the NF κ B pathway components, such as *A20/TNFAIP3* and *CARD11*; and (3) a type 3 that did not correlate with either of the first two groups.³⁴ The GCB group is associated with a better prognosis than the ABC group, with 5-year overall survival of 60% versus 35% with CHOP or CHOP-like therapy.³⁹ Although gene expression profiling for these subtypes is not available in most diagnostic laboratories, several immunohistochemical algorithms have been proposed to distinguish the GCB group from the non-GCB lymphomas. The Hans algorithm is most commonly used and is now recommended for all cases of DLBCL, NOS.⁴⁰ This approach uses three immunohistochemical markers: CD10, *BCL6*, and MUM1. Cases are defined as GCB if CD10 positive (without regard to *BCL6* or MUM1 status) or if CD10-/BCL6+/MUM1-. All others (CD10-/BCL6+/MUM1+ or CD10-/BCL6-/MUM1+/-) are considered as non-GCB type. While this approach does not perfectly match CGH studies, it still identifies prognostically significant disease groups and some novel DLBCL therapies are recommended for the non-GCB type.^{738,780} The WHO classification now includes *germinal center B-cell type* and *activated B-cell type* as subgroups of DLBCL, NOS.⁴⁰⁷

Although most cases of DLBCL fall into the NOS category of the 2016 WHO classification, this classification also defines a number of specific types of DLBCL.⁴⁰⁷ Some do not primarily involve the lymph node and are discussed elsewhere in this text, including *primary mediastinal (thymic) large B-cell lymphoma*, *primary cutaneous DLBCL, leg type*, *primary DLBCL of the central nervous system*, *EBV+ mucocutaneous ulcer*, and *lymphomatoid granulomatosis*. *Intravascular large B-cell lymphoma* (angiotropic lymphoma)⁷⁸¹ is a systemic malignant disease that may present in lymph nodes or any organ. It was originally regarded as a multicentric malignant transformation of endothelial cells and designated as malignant angioendotheliomatosis but is now known to be a type of large B-cell lymphoma with a remarkable tropism for blood vessels.⁷⁸²

T-cell/histiocyte-rich large B-cell lymphoma is a large B cell overshadowed by a reactive population of T cells (Fig. 37.89).^{783,784} The tumor cells may represent less than 10% of the entire cell population. The pattern of growth is diffuse, and there may be a fine interstitial fibrosis. The main differential diagnosis is with NLPHL,

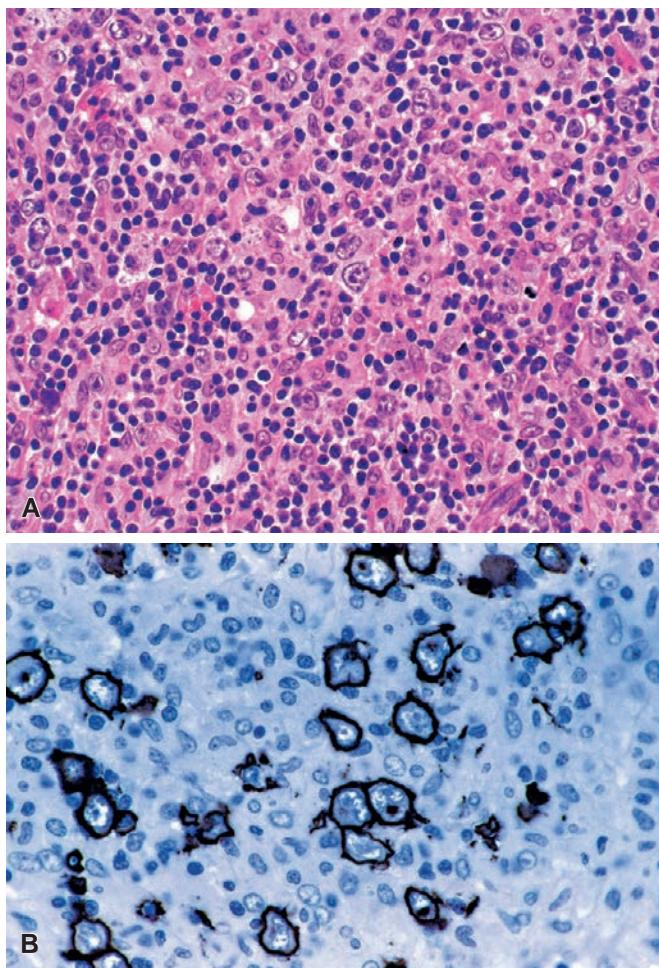


Figure 37.89 T-Cell/Histiocyte-Rich Large B-Cell Lymphoma. **A**, hematoxylin–eosin; **B**, membrane and Golgi-type immunoreactivity for CD20 in the large tumor cells.

with which it shares many phenotypic features,⁷⁸⁵ but NLPHL should demonstrate a nodular growth pattern, usually with admixed small B lymphocytes. Some authors have questioned the validity of separating the two entities.⁷⁸⁶ It would seem, though, that there are enough clinical, morphologic, and molecular genetic differences to keep them distinct. T-cell/histiocyte-rich large B-cell lymphoma is clinically more aggressive,⁷⁸⁷ has a different pattern of follicular dendritic cell staining,⁷⁸⁸ and has a different genetic pattern on comparative genomic hybridization.⁷⁸⁹

DLBCL associated with chronic inflammation. This variant occurs in the context of long-standing chronic inflammation, and shows consistent association with EBV.⁷⁵⁵ Most cases involve body cavities or narrow spaces, with the prototype being pyothorax-associated lymphoma, which involves the pleural cavity of patients with longstanding pyothorax.⁷⁹⁰ Occasional cases are discovered incidentally in surgical specimens, such as splenic cyst, hydrocele sac, and atrial myxoma.⁷⁹¹

EBV-positive DLBCL, NOS was previously termed EBV-positive DLBCL of the elderly or senile EBV-positive lymphoproliferative disorder.⁷⁹² This is a type of DLBCL that may occur at any age but is most common in adults aged over 50 years, without overt underlying immunodeficiency.^{793–796} It is, by definition, EBV positive by *in situ* hybridization. It frequently shows associated necrosis but has no specific or distinctive morphologic features. This is a diagnosis of

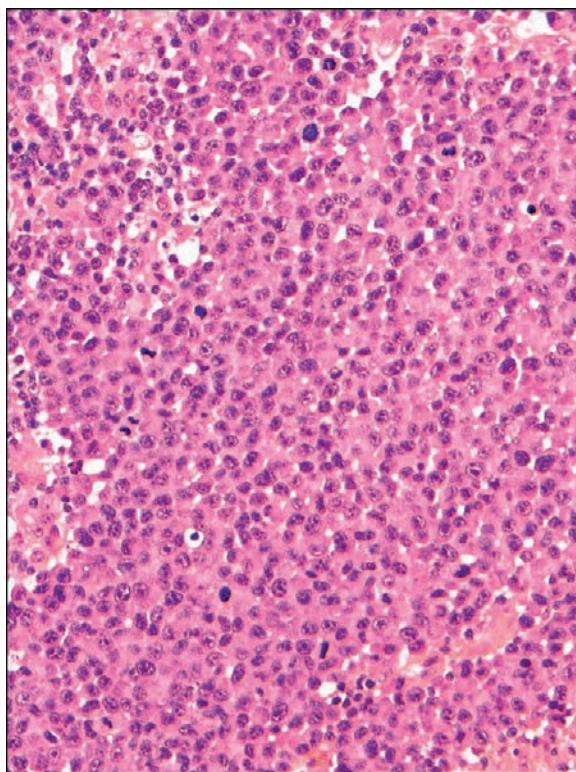


Figure 37.90 The neoplastic cells of this case of plasmablastic lymphoma have fairly fine nuclear chromatin with abundant eosinophilic cytoplasm and a high mitotic rate.

exclusion, in the sense that a case will not be classified as such if it fits other defined DLBCL entities (such as DLBCL associated with chronic inflammation, EBV+ mucocutaneous ulcer, or plasmablastic lymphoma).

Plasmablastic lymphoma was originally described as neoplastic proliferation of the oral cavity associated with HIV infection, but it may occur in any site, including lymph nodes, and in association with other causes of immunodeficiency or with aging.^{797–799} Two morphologic types of plasmablastic lymphoma have been described. The monomorphic variant has features more typical of DLBCL, with large cells with vesicular nuclei, a single centrally located prominent nucleolus, or multiple peripheral nucleoli and abundant basophilic cytoplasm (Fig. 37.90), while the plasmacytic variant may mimic an anaplastic plasmacytoma with multinucleation and paranuclear hofs. The immunophenotype usually mirrors that of plasma cells, being CD45–, CD20–, CD79a+–, PAX5–, CD38+, VS38c+, CD138+, and MUM1+. There is variable expression of cytoplasmic immunoglobulin. EBV is positive in 60%–75% of cases, and HHV8 is, by definition, negative. B lineage can be confirmed by demonstrating rearrangement of IGH, and translocations of MYC are present in approximately half of cases.^{800,801}

The diagnosis of plasmablastic lymphoma should be considered in cases with morphologic features of DLBCL that lack the common B cell markers, such as CD20, CD79A, or PAX5, and for cases with features of anaplastic myeloma but are EBV positive. Other disorders have morphologic features similar to plasmablastic lymphoma. These include ALK+ large B-cell lymphoma, tissue infiltrates of primary effusion lymphoma, and HHV8+ DLBCL that may be associated with Castleman disease (see later). These are all distinct entities that take diagnostic precedence over plasmablastic lymphoma.

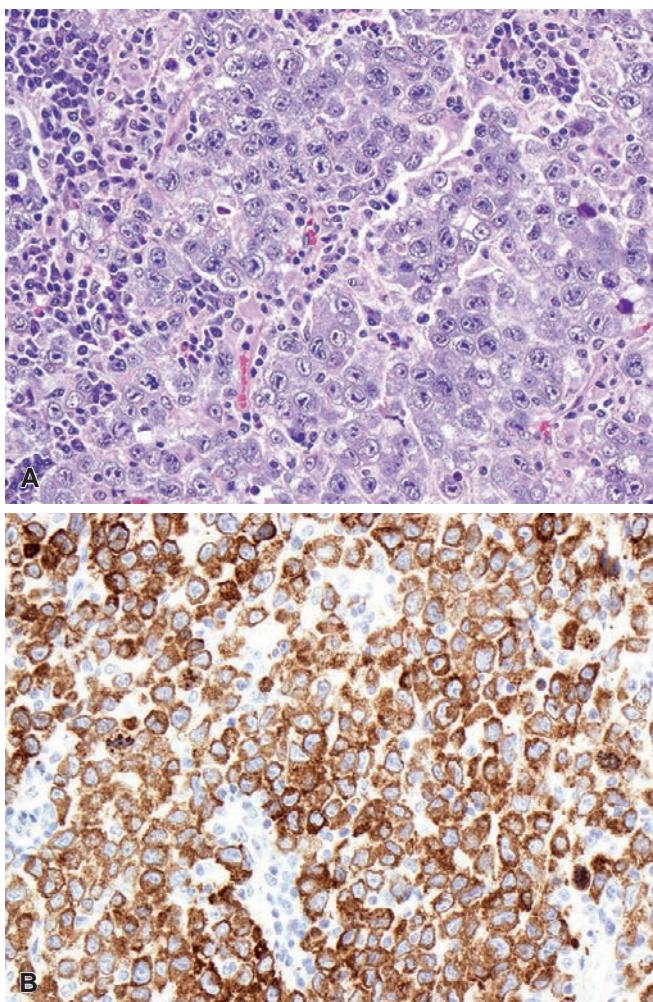


Figure 37.91 ALK-Positive Large B Cell Lymphoma. **A**, The large atypical cells cluster and may mimic metastatic carcinoma. **B**, the neoplastic cells demonstrate ALK expression.

ALK+ large B-cell lymphoma is an uncommon form of DLBCL with plasmablastic differentiation and a poor prognosis. The tumor cells have an immunoblastic or plasmablastic appearance, and sinusoidal infiltration is common.^{802,803} Since they can appear deceptively cohesive, they may be misinterpreted as carcinoma cells (Fig. 37.91). The immunophenotype is similar to plasmablastic lymphoma, CD30 is negative and IgA is commonly positive. The commonest molecular alteration is $t(2;17)(p23;q23)$, which fuses the *ALK* gene with the *CLTC* gene.^{804,805} Since *CLTC* encodes a granule-associated protein, immunostaining for ALK is typically in the form of cytoplasmic granules. These tumors are negative for EBV and HHV8 and lack *MYC* translocations.⁸⁰⁶

Primary effusion lymphoma does not usually involve lymph nodes but is briefly mentioned here due to its potential overlap with plasmablastic lymphoma. This is a large B-cell lymphoma with plasmablastic differentiation, occurring predominantly as a pleural or pericardial effusion in patients with AIDS.⁸⁰⁷ These effusions contain markedly pleomorphic cells that may suggest carcinoma or mesothelioma. Similar to plasmablastic lymphoma, the cells tend to lack B-cell antigen expression and are associated with both HIV and EBV. They also show a strong association with HHV8, which does not occur with plasmablastic lymphoma. A solid tissue counterpart also exists.⁸⁰⁸ The tumor differs from plasmablastic lymphoma

by the presence of HHV8, its clinical presentation in body fluids, and by the absence of *MYC* translocations.

HHV8-positive DLBCL, NOS is an aggressive lymphoma type that was previously termed *large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease*.^{809,810} While the association with Castleman disease remains, cases arising outside of this disorder may occur. These lymphomas have plasmablastic morphologic features (Fig. 37.92), similar to plasmablastic lymphoma, but are more likely to express CD20, are EBV-negative, and are positive for HHV8, which can be detected with LANA-1 antibodies by immunohistochemistry; all features that do not occur in plasmablastic lymphoma. The neoplastic cells only express lambda light chains, a feature of HHV8 infection even in non-neoplastic settings. In contrast to individual atypical lambda positive plasmablastic cells in multicentric Castleman disease, these lymphomas form sheets of neoplastic cells. Some cases are associated with Kaposi sarcoma in the same lymph node.

Current Testing in Diffuse Large B-Cell Lymphoma

While demonstrating sheets of large B-cells with a CD20 stain may be sufficient for an overall diagnosis of DLBCL, the above discussion highlights the need for a variety of other tests to be performed currently in the routine evaluation of these cases. As mentioned, testing for CD10, BCL6, and MUM1 are now necessary to subclassify cases of DLBCL, NOS into germinal center versus non-germinal center types. FISH testing for translocations involving *MYC*, *BCL2*, and *BCL6* are also now routinely done to identify the high-risk "double-hit" group. Most centers also perform Ki-67 staining for prognosis and CD30 staining may be performed since new anti-CD30 antibodies make this a potential therapeutic target. *In situ* hybridization is necessary to identify the EBV-associated NOS group. CD5 staining, which when present would warrant further evaluation (cyclin D1 staining, etc) to exclude a pleomorphic mantle cell lymphoma, may also be useful. *MYC* and *BCL2* immunohistochemistry to identify so-called high risk "double expressors" is not currently routine but will probably be more commonly performed in the near future.

Burkitt Lymphoma

Burkitt lymphoma is a high-grade malignant lymphoma composed of germinal center B cells, which can present in three clinical settings:

1. **Endemic.** This occurs in the equatorial strip of Africa and is the most common form of childhood malignancy in that area. The patients characteristically present with jaw and orbital lesions. Involvement of the gastrointestinal tract, ovaries, kidney, and breast are also common.
2. **Sporadic.** This is seen throughout the world. It affects mainly children and adolescents and has a greater tendency for involvement of the abdominal cavity than the endemic form.⁸¹¹
3. **Immunodeficiency associated.** This is seen primarily in association with HIV infection and often occurs as the initial manifestation of the disease.^{812,813}

In all three forms peripheral lymphadenopathy is rare and, when present, usually limited to a single group.^{814,815} Bone marrow involvement is common in the late stage of the disease, but leukemic manifestations are less common.^{811,816}

Microscopically, the pattern of growth of Burkitt lymphoma is usually diffuse, although early cases may show preferential involvement of germinal centers.⁸¹⁷ The tumor cells are medium sized (10–25 μ m) and round. The nuclei are round or oval and have several prominent basophilic nucleoli. The chromatin is coarse and the nuclear membrane is rather thick. The cytoplasm is easily identifiable; it is amphophilic in hematoxylin–eosin-stained preparations

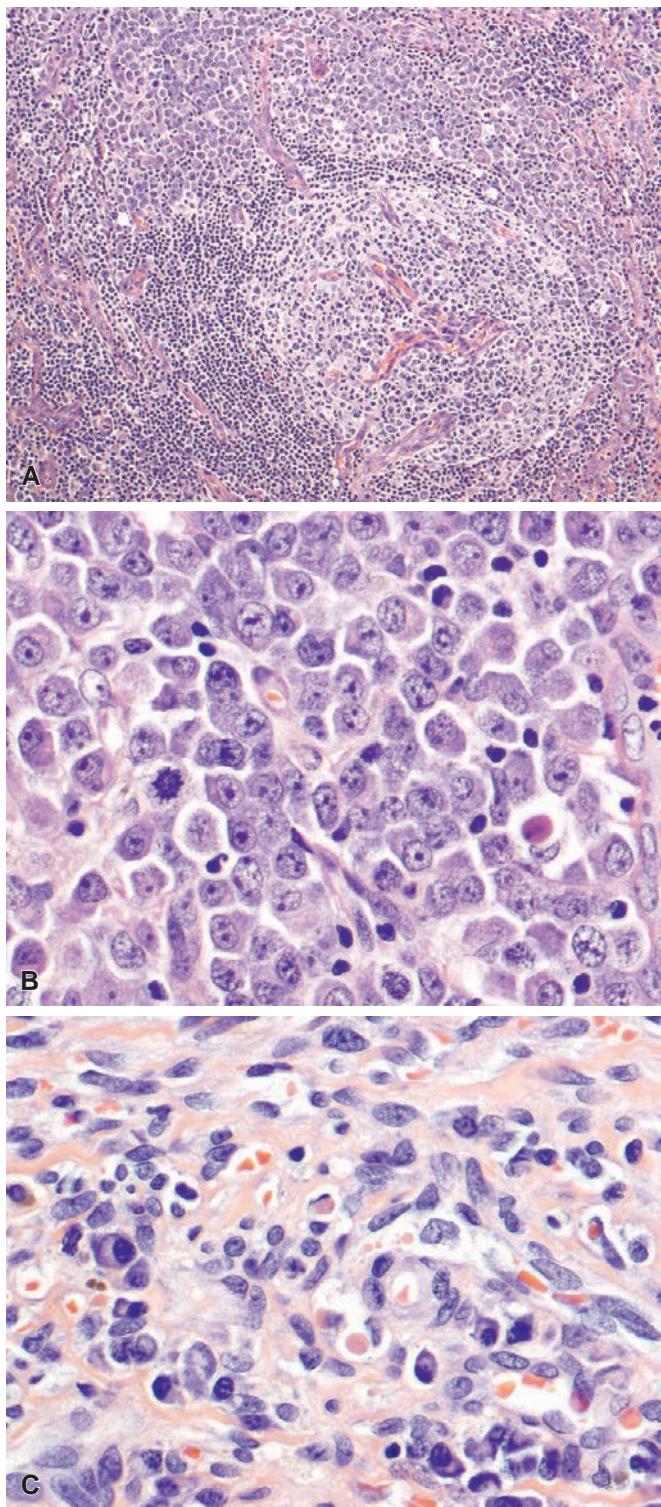


Figure 37.92 HHV+ DLBCL, NOS Arising in a Patient With Castleman Disease. **A**, The lymphoma cells surround the upper left portion of the typical Castleman germinal center. **B**, The cells have morphologic features similar to plasmablastic lymphoma but were HHV8 positive and EBV negative. **C**, The lymph node capsule also showed a focus of Kaposi sarcoma.

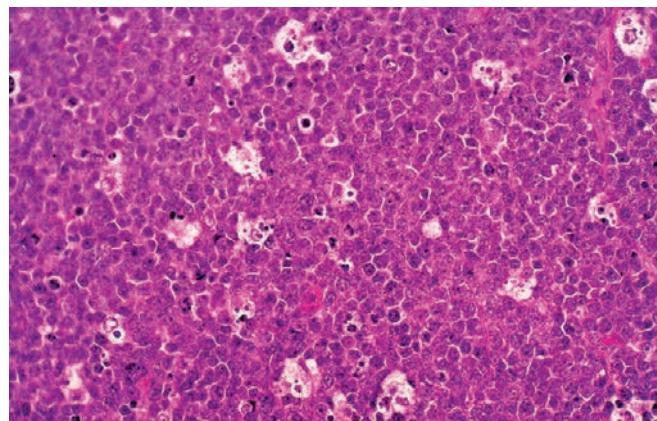


Figure 37.93 Burkitt lymphoma with characteristic starry sky appearance.

and strongly pyroninophilic. Fat-containing small vacuoles are present; these are particularly well appreciated in touch preparations. Mitoses are numerous, and a prominent starry sky pattern is the rule, although by no means pathognomonic (Fig. 37.93).⁸¹⁸ There are also many admixed apoptotic bodies. In well-fixed material, the cytoplasm of individual cells "squares off," forming acute angles in which the membranes of adjacent cells abut on each other. Occasionally, the tumor is accompanied by a florid granulomatous reaction.⁸¹⁹ Ultrastructurally, the main features are abundant ribosomes, frequent lipid inclusions, lack of glycogen particles, and presence of nuclear pockets or projections.⁸²⁰

Burkitt lymphomas are of mature B-cell lineage. They express immunoglobulins (predominantly IgM), invariably associated with heavy and light chain restriction.⁸²¹ B cell-specific antigens (such as CD19, CD20, and CD22) as well as the germinal center cell markers CD10 and BCL6 are expressed.⁸²² They are negative for the activation markers CD25 and CD30 and are BCL2 negative. In contrast to lymphoblastic lymphoma, they do not express TdT. The most helpful immunohistochemical profile to aid in diagnosis of Burkitt lymphoma includes CD20+, CD10+, BCL2-, and a Ki-67 index over 95%.

As expected of a B-lineage neoplasm, Burkitt lymphoma shows clonal rearrangements of the immunoglobulin genes. The hallmark genetic change is t(8;14), t(2;8), or t(8;22), which fuses the *MYC* gene with an *IGH*, kappa light chain, or lambda light chain gene.⁸²³ As a result, the *MYC* gene is overexpressed, promoting cell cycle progression and inhibiting differentiation.⁸²⁴ However, *MYC* translocation is not entirely specific for Burkitt lymphoma; it can also be observed in transformed follicular lymphomas, rare cases of DLBCL, and the highly lethal "double-hit" lymphomas (with presence of both *MYC* and *BCL2* translocation).^{775,825-828} In Burkitt lymphoma, as currently defined, the *MYC* translocation should be the sole abnormality.⁷⁷⁵

FISH studies are now necessary to support a diagnosis of Burkitt lymphoma by demonstrating the presence of a *MYC* translocation together with absence of *BCL2* and *BCL6* translocations.⁸¹⁹

There is an association of Burkitt lymphoma with EBV, with frequencies of approximately 100% for the endemic type, 20%-30% for the sporadic type, and 25%-40% for the immunodeficiency-associated type (Fig. 37.94).⁸²³ The EBV shows type I latency, that is EBER and EBNA1 are expressed, while LMP1 and EBNA2 are negative.

In the past, some cases resembling Burkitt lymphoma but having atypical morphologic and/or immunophenotypic features were diagnosed as *atypical Burkitt lymphoma*, *Burkitt-like lymphoma*, *small non-cleaved, non-Burkitt lymphoma*, *gray-zone lymphoma*, or *B-cell*

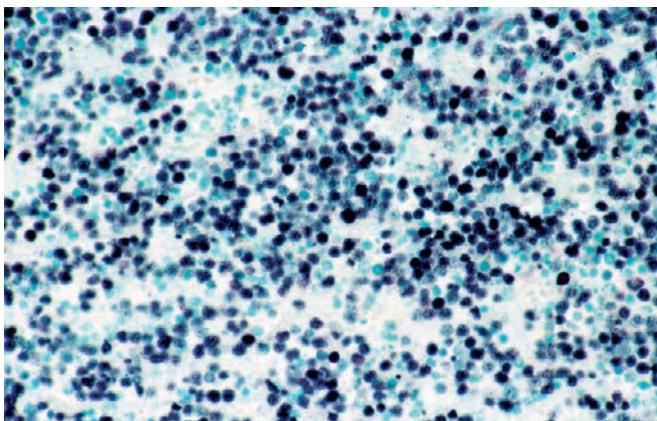


Figure 37.94 Presence of EBV genome in Burkitt lymphoma, as demonstrated with *in situ* hybridization for EBER.

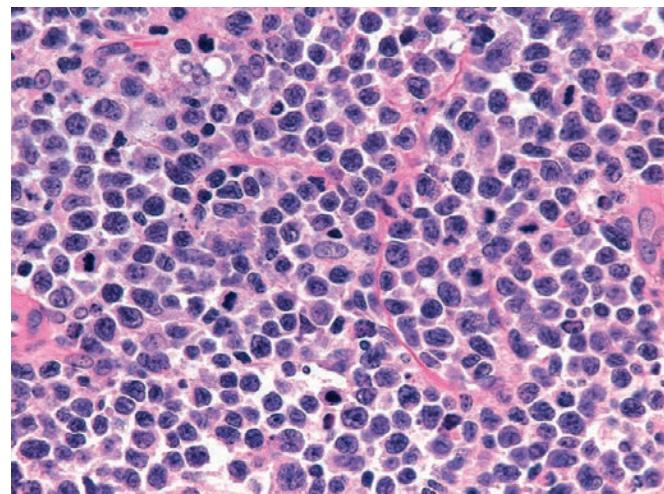


Figure 37.95 High-Grade B-Cell Lymphoma With *MYC* and *BCL2* Rearrangements. The morphologic features are intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma. The presence of a so-called double hit of the two translocations confirms this diagnosis.

lymphoma, unclassifiable with features intermediate between DLBCL and Burkitt lymphoma. These terms are no longer used and have been replaced with several new categories/names in the 2016 WHO classification.⁴⁰⁷

Burkitt-like lymphoma with 11q aberration is a provisional entity in the 2016 WHO classification. It has morphologic and immunophenotypic features similar to Burkitt lymphoma described previously except it may have more nuclear pleomorphism than usual type Burkitt lymphoma.^{829,830} In contrast to Burkitt lymphoma, which has *MYC* translocations without other complex cytogenetic abnormalities, Burkitt-like lymphoma with 11q aberration has gains or losses at 11q and may have an associated complex karyotype. Some cases of this type are reported post-transplantation or in association with immunodeficiency. Since testing for these 11q aberrations is not routinely available, most cases currently would be classified as high-grade B-cell lymphoma, NOS (described next).

High-Grade B-Cell Lymphomas

Some lymphomas, particularly those with features similar to Burkitt lymphoma, either lack *MYC* translocations or have *MYC* translocations as well as additional cytogenetic abnormalities, particularly translocations of *BCL2* or *BCL6*.^{776,831} Cases with a *MYC* translocation with either a *BCL2* or *BCL6* translocation are now termed **high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements**. These cases may have morphologic features of DLBCL or Burkitt lymphoma and often express CD10 and *BCL2* and demonstrate a very high proliferation rate (Fig. 37.95). No single finding, however, is predictive of these combined cytogenetic abnormalities. Many cases also have other cytogenetic abnormalities. Some prognostic variation is reported based on the second “hit” and for “triple-hit” cases that have all three translocations,^{832–834} but any combination of two or more translocations would qualify a case for this category. Cases with a morphologic appearance similar to Burkitt lymphoma or intermediate between DLBCL and Burkitt lymphoma, but lack a *MYC* translocation or an 11q aberration are now termed **high-grade B-cell lymphoma, NOS**.

Lymphoma in Immunodeficiency States

An increase in the incidence of malignant lymphoma has been documented in most types of congenital and acquired immunodeficiency.^{835–837} Chronic antigenic stimulation—possibly by oncogenic viruses—and perhaps loss of antibody feedback inhibition of the lymphoid proliferation may account for the high rate of

lymphoid malignancies.⁸³⁸ EBV in particular has been repeatedly implicated.⁸³⁹

1. **Primary immunodeficiencies.** Patients with genetically determined immune deficiencies have an increased incidence of malignant tumors, especially lymphomas.^{835,840,841} This includes ataxiatelangiectasia, Wiskott–Aldrich syndrome, X-linked lymphoproliferative syndrome, common variable immunodeficiency, and severe combined immunodeficiency syndrome.⁸⁴²
2. **Post-transplant lymphoproliferative disorders (PTLDs).** The incidence of lymphoma is increased in recipients of all types of solid organ transplant as a direct or indirect result of the induced immunosuppression.^{843–847} In renal transplant recipients, this incidence is in the order of 4%–6%.⁸⁴⁸ Skin tumors, malignant lymphomas, Kaposi sarcoma, and cervical carcinoma are the most common neoplasms. The frequency of lymphoma has been estimated to be 350 times higher than in the age-matched general population.^{848–850} The incidence has been found to be particularly high in adult cardiac transplant patients treated with OKT-3-containing regimens.^{851,852} In approximately half of the reported cases, the central nervous system is involved, compared with less than 1% in lymphoma patients in general. In 30% of the cases, the allograft is also involved.

A number of microscopic patterns of PTLD occur. More indolent cases involve lymph nodes or tonsils without a destructive architectural pattern. These include *plasmacytic hyperplasia*, *infectious mononucleosis*, and *florid follicular hyperplasia* types of PTLD. While these may progress to destructive and frankly neoplastic proliferations, many do not, and it is controversial whether these types all actually represent PTLDs or are unrelated hyperplastic lesions. This is particularly true for plasmacytic hyperplasia and florid follicular hyperplasia types that may have only rare EBV-positive cells and are similar to reactive lesions seen in patients with no transplant history. The infectious mononucleosis type of PTLDs is morphologically identical to what is seen in infectious mononucleosis in immunocompetent individuals but may at times be difficult to differentiate from polymorphic PTLDs (see later). Reactive-appearing proliferations without EBV should probably not be considered as a PTLD.

There is better agreement that destructive lesions, often similar to other lymphoma types, represent true PTLDs. These include

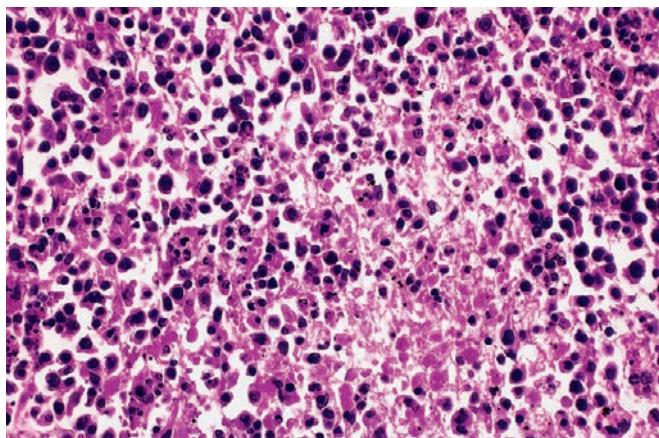


Figure 37.96 Polymorphic lymphoproliferative process associated with necrosis in lymph node of a renal transplant patient. There was evidence of active EBV infection.

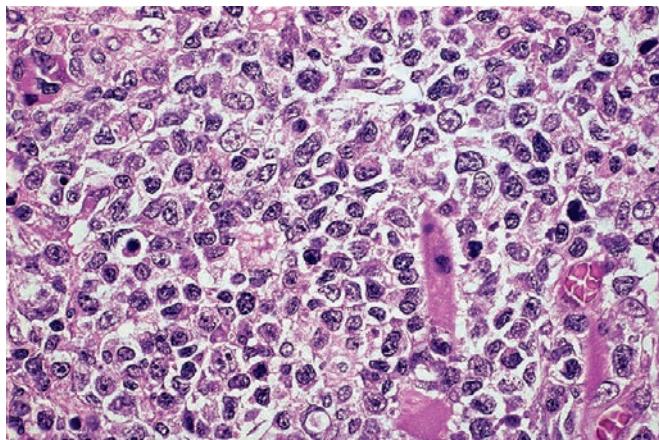


Figure 37.97 Monomorphic posttransplant lymphoproliferative disorder (diffuse large B-cell lymphoma) in a recipient of a renal transplant.

polymorphic, monomorphic, and classical Hodgkin lymphoma types. **Polymorphic PTLD** distorts the normal lymph node architecture with a heterogeneous mix of B cells and plasma cells (Fig. 37.96).⁸⁵³ Large, admixed immunoblasts and cells with Hodgkin-like features are often present. The B-cell and plasma cell component may be monotypic or polytypic in these proliferations. The large atypical cells are frequently CD30 positive and EBV is present in most cells of the majority of cases. **Monomorphic PTLD** has histologic features similar to well-established non-Hodgkin lymphoma types of non-immunocompromised patients (Fig. 37.97). These most commonly are DLBCL, Burkitt lymphoma, or plasmacytoma and are usually EBV positive.⁸⁵⁴ T- or NK-cell lineage cases of monomorphic PTLD are also described.⁸⁵⁵ Rare cases of monomorphic PTLD of marginal zone lymphoma type are reported and are EBV positive,⁸⁵⁶ a feature that is otherwise uncommon in marginal zone lymphoma. In general, however, most lymphomas of small B cells arising in the post-transplant setting are not considered to be PTLD. The **classical Hodgkin lymphoma PTLDs** have morphologic and immunophenotypic features of classical Hodgkin and are usually EBV positive. Cases with Hodgkin-like cells admixed with a polymorphous background, not typical of classical Hodgkin lymphoma, are considered polymorphic PTLD and not the classical Hodgkin lymphoma type.

Molecular studies have confirmed the recipient origin of the lymphoma following solid organ transplantation, with donor origin more common after hematopoietic cell transplantation.^{857–859}

The clinical course of post-transplant lymphoma/lymphoproliferative disease is usually very rapid.^{860,861} Treatment of PTLDs consists of a combination of immunosuppression reduction and standard lymphoma therapy (chemotherapy and radiation).⁸⁶²

3. **HIV.** Patients with HIV infection are at a high risk for developing malignant tumors, principally Kaposi sarcoma and malignant lymphoma,^{863–869} sometimes in combination.⁸⁰⁹ It has been estimated that approximately 3% of AIDS patients develop non-Hodgkin lymphoma, and that the risk of developing a lymphoma in this population is 60-fold greater than in the normal population. The majority of the cases present with multiple sites of extranodal involvement, with a high incidence of involvement of the gastrointestinal tract, central nervous system, bone marrow, liver, oral cavity, body cavities, and heart.^{866,870} Practically all cases are of B-cell lineage and—as such—show clonal immunoglobulin gene rearrangements.^{864,871,872} Distinct morphologic subtypes of lymphoma associated with HIV have already been described, but many patients have DLBCL or Burkitt lymphoma, with similarities to non-HIV cases.^{812,813,873,874} Cases have also been reported of peripheral T-cell lymphomas with a peculiar component of Touton-like giant cells,⁸⁷⁵ and others having the features of the polymorphic lymphoproliferative disorders seen more often in solid organ transplant recipients.⁸⁷⁶ HIV-associated lymphomas, especially the unique types of plasmablastic lymphoma, primary effusion lymphoma, and HHV8+ DLBCL (see earlier), have an increased association with HHV8 and/or EBV infection.^{877–880}
4. **Others.** Acquired diseases of the immune system in which an increased incidence of lymphoma has been recorded include rheumatoid arthritis,^{881,882} Sjögren syndrome,⁸⁸³ Hashimoto thyroiditis, and other autoimmune diseases.⁸⁸⁴

Peripheral (Post-Thymic) T-Cell and Natural Killer-Cell Lymphomas

Peripheral (post-thymic) T-cell and NK-cell lymphoma is the generic term given to a family of tumors composed of neoplastic lymphocytes with phenotypic and genotypic features of mature T cells or NK cells.^{885,886} This is an extremely heterogeneous group of lesions, many of them occurring primarily at extranodal sites, and which have received a myriad of designations. Most of them were identified as entities long before their peripheral T-cell or NK-cell nature was ascertained.

Peripheral T-cell and NK-cell lymphomas in general are highly aggressive. Their morphologic features are variable depending on the type, but immunohistochemical studies are always required to confirm their T-cell or NK-cell nature. They commonly express CD3, CD45RO, CD2, CD5, and CD7, although expression of one or more of these pan-T-cell markers may be lost (so-called aberrant immunophenotype, which is sometimes utilized to support the neoplastic nature of a T-cell proliferation). NK-cell lymphomas are commonly CD2+, cytoplasmic CD3+, surface CD3–, CD5–, and CD56+ and are EBV-positive by *in situ* hybridization. Most cases of peripheral T-cell lymphoma express a CD4+/CD8– mature helper phenotype; approximately 20% express a CD4-/CD8+ cytotoxic/suppressor phenotype, with rare cases having CD4-/CD8- or CD4+/CD8+ phenotypes.

At the molecular level, peripheral T-cell lymphomas exhibit clonal rearrangements of the γ and β T-cell receptor genes, although about 10% of cases may show simultaneous clonal rearrangements of IGH.⁸⁸⁷

The T/NK neoplasms of the 2016 WHO classification are listed in **Box 37.1**. Many do not primarily involve lymph nodes and are discussed in other chapters. The major lymph node disease categories are AITL, ALCL, and peripheral T-cell lymphoma, NOS.

Angioimmunoblastic T-Cell Lymphoma

AITL includes cases originally described as angioimmunoblastic lymphadenopathy (AILD) and immunoblastic lymphadenopathy. AILD was originally considered a premalignant proliferation with a high risk for transformation to T-cell lymphoma but is not considered neoplastic from its origin.⁸⁸⁸ AILD was originally described as occurring almost exclusively in adults and elderly individuals and is characterized clinically by fever, anemia (usually hemolytic), polyclonal hypergammaglobulinemia, and generalized lymphadenopathy.⁸⁸⁹⁻⁸⁹¹ Other common manifestations include hepatomegaly, splenomegaly, constitutional symptoms, and skin rash.⁸⁹²⁻⁸⁹⁴ In 27% of the patients studied in the classic series by Lukes and Tindle,⁸⁹¹ the disease occurred abruptly after administration of drugs, particularly penicillin. Some of these cases, however, might now be considered as mimics of AITL rather than lymphoma based on more extensive testing now performed.

Microscopically, the disease is systemic, with lesions in the lymph nodes, spleen, liver, bone marrow, and skin. The lymph node changes are characterized by obliteration of the nodal architecture (with focal preservation of sinuses) by a polymorphic cellular infiltrate and by an extensive proliferation of finely arborizing vessels of the caliber of postcapillary venules (Fig. 37.98). The cellular infiltrate is composed of small lymphocytes, plasma cells, numerous immunoblasts, frequent and sometimes abundant eosinophils, and, occasionally, multinucleated giant cells. Normal germinal centers are usually absent; what one may find instead are germinal centers composed of loose aggregates of pale histiocytes, rare immunoblasts, or large epithelioid cells; these are referred to as "burnt-out germinal centers" and can closely resemble the appearance of granulomas. Only occasionally one finds hyperplastic germinal centers.⁸⁹⁵ There is also a component of proliferating cells of dendritic/reticulum nature⁸⁹⁶ that extends beyond the residual germinal centers and is highlighted by CD21 or CD23 staining. An amorphous, eosinophilic PAS-positive intercellular material may be found scattered throughout the node. Extension of the infiltrate in the capsule and pericapsular tissue is common. Although subtle in many cases, some cases demonstrate clusters of large, often clear cells that represent the clonal T-cell proliferation in most cases (Fig. 37.99). These T cells are now believed to arise from the germinal center and are termed TFH cells. Immunohistochemical studies for CD21 or CD23 are useful to identify the expanded follicular dendritic cell networks characteristic of this disorder. The identification of TFH cells outside of follicles is also a helpful feature. These T cells express CD10, CXCL13, BCL6, and PD1. Lymphoid cells positive for EBV are found in over 75% of the cases, but these cells may be infrequent and do not correlate with the neoplastic T cell population.⁸⁹⁷ Additionally, admixed atypical large B cells and/or increased plasma cells may be present, and these may be monotypic. Hodgkin-like cells may also occur in AITL. The increase in large B cells may create diagnostic difficulties,⁸⁹⁸ with the T-cell component missed in some cases at presentation or the lymphoma correctly identified as AITL relapsing with features of DLBCL.

While AITL expectedly shows clonal rearrangements of the T-cell receptor genes in most cases, up to 40% of cases show simultaneous clonal rearrangements of the immunoglobulin genes supportive of an underlying B cell clone. This finding has been attributed to EBV infection of B cells in the past but is also seen in EBV-negative cases.^{17,899,900} Chromosomal alterations in AITL are common but

nondistinctive, such as +3, +5, +18, +19, +21, +X, -6q, and -7.^{505,899,901,902} The gene expression profile shows a strong contribution by the admixed follicular dendritic cells, B cells, and stromal components, as well as overexpression of genes characteristic of normal TFH cells.⁹⁰³⁻⁹⁰⁵ A variety of mutations have now been described in AITL, including mutations in myeloid-associated genes *TET2*, *DNMT3A*, and *IDH2*.⁹⁰⁶⁻⁹⁰⁸ Mutations in *RHOA*, however, appear to be most common reported in approximately 60% of cases.⁹⁰⁹ A subset of cases demonstrate t(5;9)(q33;q22) involving *ITK* and *SYK*.

Two rare lymphoma types are now considered provisional entities in the 2016 WHO classification and both are closely related to AITL.^{407,910} Both are neoplasms of TFH cells with expression of CD10, BCL6, CXCL13, and/or PD1 on the neoplastic T cells. **Follicular T-cell lymphoma** shows a prominent follicular pattern with extensive follicular dendritic cell networks. **Nodal peripheral T-cell lymphoma with TFH phenotype** does not show all typical features of AITL but has a similar lymphoma cell immunophenotype.

Anaplastic Large Cell Lymphoma

ALCL in its most typical form is characterized by highly atypical and pleomorphic neoplastic cells with expression of the activation marker CD30.⁹¹¹⁻⁹¹⁴ ALCL is distinguished from CD30-positive transformation of other lymphomas, especially mycosis fungoides, and only includes cases of T-cell or null lineage. Primary cutaneous ALCL is also a distinct entity that is part of the spectrum of primary cutaneous CD30+ T-cell lymphoproliferative disorders and is not discussed here.

The systemic form of ALCL can involve lymph nodes or extranodal sites, such as the bone marrow, bone, respiratory tract, skin, and gastrointestinal tract.⁹¹⁵⁻⁹¹⁷ It can occur in children or adults.⁹¹⁸⁻⁹²¹ Exceptionally, it is accompanied by leukemic manifestations.⁹²² Systemic symptoms such as fever can be present. Currently two types are segregated based on ALK expression, owing to differences in clinical features and prognosis. ALK+ ALCL tends to occur in children and young adults, and the outcome is good if appropriate treatment is given. ALK- ALCL tends to occur over a wider age range, especially older adults, and is associated with a poor outcome similar to peripheral T-cell lymphoma, NOS.

Microscopically, the infiltrate has a polymorphic appearance, often with a variable admixture of neutrophils, lymphocytes, and histiocytes, with the highly atypical large lymphoma cells showing marked pleomorphism.⁹²³ The nuclei of these cells are often horseshoe shaped or multilobed, and nucleoli are prominent. Cells indistinguishable from Reed-Sternberg cells may be seen. The cytoplasm is abundant and eosinophilic. Cohesive growth and preferential sinus involvement are common (Fig. 37.100). The undue prominence of the latter feature in some cases was one of the reasons for this lesion to be mistakenly placed in the category of malignant histiocytosis. ALCL can also simulate malignant melanoma, undifferentiated carcinoma, and various types of soft tissue sarcoma.⁹²⁴

Several morphologic variants of ALCL (usually ALK+) have been described.

1. **Small cell.** As the name indicates, this shows a predominant population of small- to medium-sized cells. A very important clue is the presence of the characteristic large anaplastic cells around blood vessels.^{923,925} Cases of the small cell variant have been seen to transform into the classic anaplastic large cell form.⁹²⁶
2. **Lymphohistiocytic.** The distinctiveness of this variant results from the presence of a large number of admixed reactive (nonepithelioid) histiocytes (Fig. 37.101).⁹²⁷⁻⁹²⁹ As for the previous variant, an important diagnostic clue is the clustering of anaplastic tumor cells around vessels.

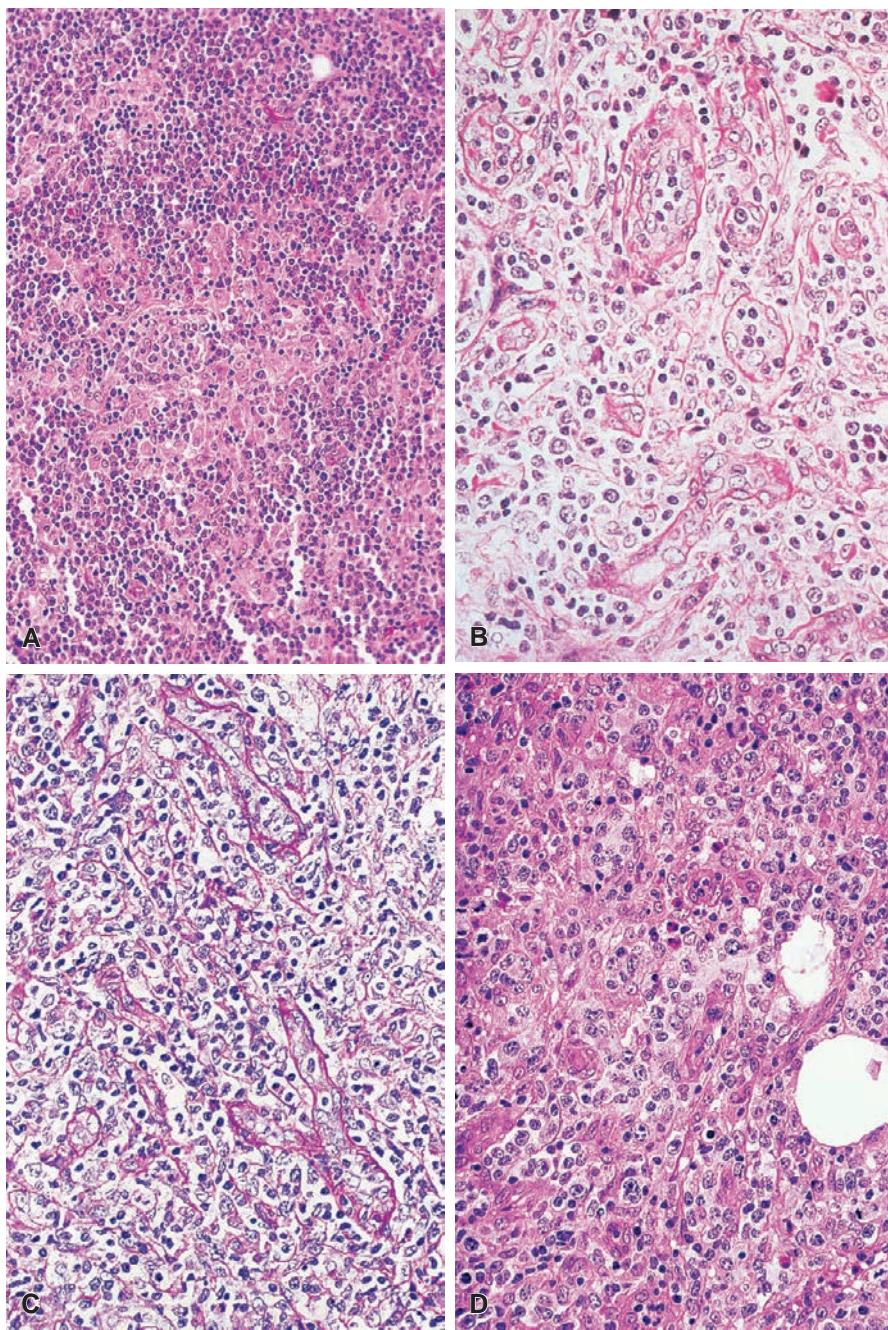


Figure 37.98 Lymph Node Involvement by Angioimmunoblastic T-Cell Lymphoma. **A**, Low-power view showing a moderate effacement of the architecture by a polymorphic infiltrate composed of lymphocytes, plasma cells, and histiocytes. There is also marked vascular proliferation. **B** and **C**, The PAS stain highlights the prominence of the postcapillary venules. **D**, Atypical lymphoid cells are present in this polymorphic infiltrate, often with clusters of cells with clear cytoplasm. There are also scattered eosinophils.

3. Other morphologic variations of ALCL that do not qualify as bona fide tumor variants are the neutrophil—and/or eosinophil-rich,^{930,931} sarcomatoid,⁹²⁴ giant cell,⁹³² signet ring-like,⁹³³ and hypocellular.⁹³⁴

Immunohistochemically, the tumor cells of ALCL are by definition CD30+ (Ki-1) positive (Fig. 37.102).⁹³⁵ There is also consistent positivity for EMA, interleukin-2 receptor,⁹³⁶ clusterin (in a Golgi pattern),⁹³⁷ cadherins,^{938,937} and galectin-3 (a β -galactoside-binding animal lectin).^{939,940} There is occasional reactivity for keratin.⁹⁴⁰

There is variable expression of T-lineage markers, and application of a wide panel may be required to have one or two markers staining. In the so-called null-cell cases, T-lineage markers cannot be demonstrated. B-cell markers are, by definition, absent. The B-cell transcription factor PAX5 is usually not expressed, and this marker is extremely helpful for distinction of ALCL from classic Hodgkin lymphoma (PAX5+). ALK, by definition, is expressed in ALK+ ALCL, but not in ALK- ALCL (Fig. 37.103). EBV is generally negative.⁹⁴¹

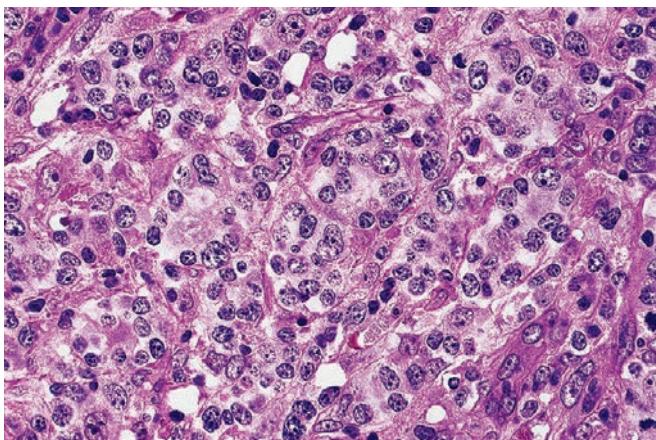


Figure 37.99 Angioimmunoblastic T-cell lymphoma with a uniform proliferation of large neoplastic lymphoid cells.

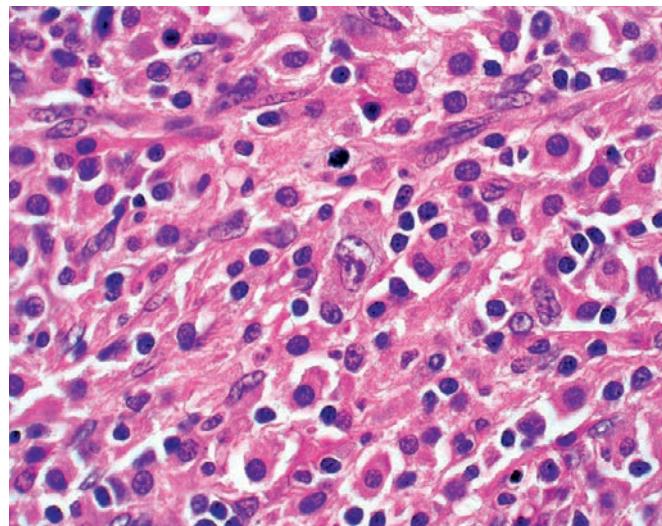
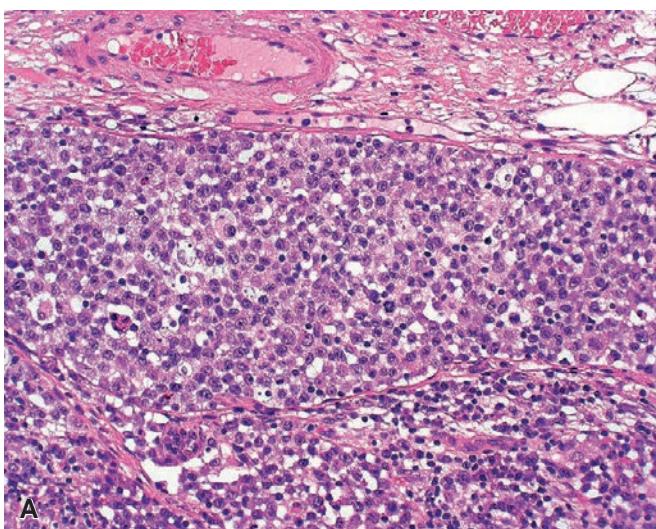
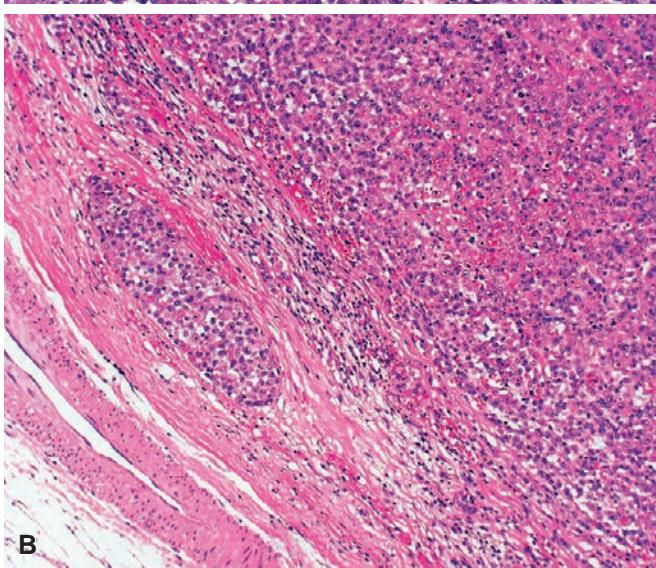


Figure 37.101 So-called lymphohistiocytic variant of anaplastic large cell lymphoma with only scattered, large neoplastic cells.



A



B

Figure 37.100 Anaplastic Large Cell Lymphoma. **A**, Packing of the peripheral sinus. **B**, Vascular involvement.

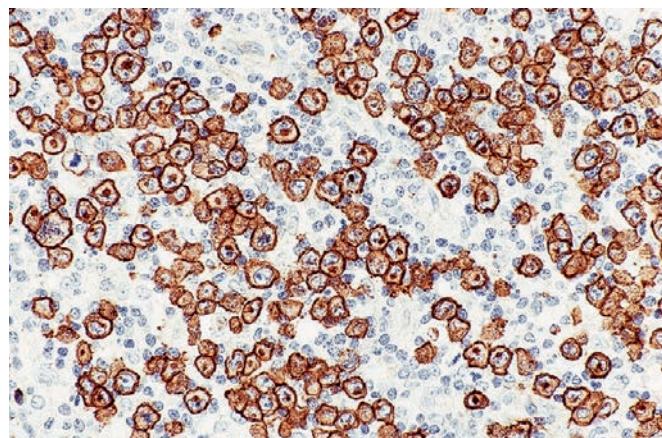


Figure 37.102 Strong membranous and Golgi-type immunoreactivity for CD30 in anaplastic large cell lymphoma.

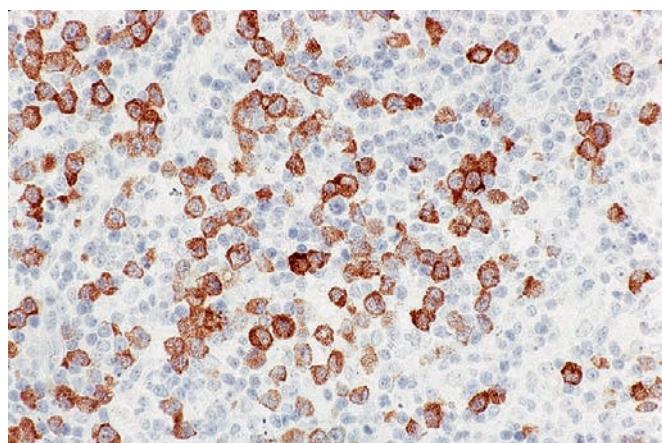


Figure 37.103 ALK immunoreactivity in anaplastic large cell lymphoma.

The T-cell receptor genes are clonally rearranged in approximately 90% of cases of ALK+ ALCL, including cases lacking expression of T-lineage markers.^{936,941} The hallmark of this lymphoma type is translocation of anaplastic lymphoma kinase gene (*ALK* on 2p23), although this molecular alteration is also found in an uncommon subtype of DLBCL (ALK+ large B-cell lymphoma), ALK+ histiocytosis, inflammatory myofibroblastic tumor and an uncommon subset of pulmonary adenocarcinoma.^{802,942-947} The *ALK* gene can be fused with a variety of partner genes, most of which are housekeeping genes.⁹⁴⁸ The translocation results in production of a chimeric protein, in which the *ALK* domain (a tyrosine kinase receptor) is constitutively activated due to presence of an oligomerization domain at the N-terminus. The commonest partner gene is *NPM* (nucleophosmin gene on 5q35), accounting for 80% of cases. Other partner genes include *TPM3* (tropomyosin-III), *TPM4* (tropomyosin-IV), *TFG* (*TRK* fused gene), *ATIC*, *CLTL* (clathrin), *MSN* (moesin), *CARS*, and *MYH9*. Interestingly, the subcellular localization of *ALK* on immunostaining correlates well with the normal distribution of the protein encoded by the partner gene, for example, nuclear-cytoplasmic staining for nucleophosmin, cytoplasmic staining with subplasmalemmal accentuation for tropomyosin, cell membrane staining for moesin, and cytoplasmic granular staining for clathrin. The partner gene fused with the *ALK* gene does not influence the prognosis of ALK+ ALCL.⁹⁴⁹

ALCLs with *ALK* translocation have a much more favorable prognosis than ALK- ALCLs.⁹⁴⁹⁻⁹⁵² Gene expression profiling studies have also confirmed that these two types of ALCL represent distinct entities.⁹⁵³ Recent studies, however, have identified two additional recurring genetic abnormalities in ALCL that are exclusive of *ALK* translocations.^{954,955} Translocations involving *DUSP22*, usually as a t(6;7)(p25.3;q32.3), are found in approximately 30% of cases and abnormalities of *TP63*, usually as in inv(3)(q26q28), occur in approximately 8% of cases. *DUSP22* translocations appear to be associated with a more favorable prognosis, similar to ALK+ ALCL, while *TP63* abnormalities are associated with a worse prognosis, possibly worse than peripheral T-cell lymphoma, NOS. Patients with ALCL lacking *ALK*, *DUSP22*, and *TP63* abnormalities have an intermediate prognosis.

The differential diagnosis for ALCL is broad due to the large number of CD30-positive tumors now known. Classical Hodgkin lymphoma with high numbers of Hodgkin cells usually lacks T-cell antigen expression and is PAX5 positive. CD30 positive lymphoma cells are relatively common in peripheral T-cell lymphoma, NOS, but the expression is not strong and uniform in most cases. Cases of DLBCL with pleomorphic, CD30 positive lymphoma cells are excluded by the expression of B-lineage markers. Primary cutaneous ALCL is biologically distinct from systemic ALCL and should be ALK negative and localized to skin. Identification of ALK-positive cutaneous disease should result in a thorough systemic evaluation. Finally, an ALK-negative ALCL is now recognized in association with serous fluid accumulations in women with breast implants. Such cases are considered biologically distinct from systemic ALCL, do not infiltrate the breast stroma, and are often clinically indolent.⁹⁵⁶

Peripheral T-Cell Lymphoma, Not Otherwise Specified

Peripheral T-cell lymphoma, NOS is a fairly common "waste basket" group of peripheral T-cell neoplasms that do not meet criteria for other T- or NK-cell lymphoma types. They show a gene expression profile distinct from that of AITL and ALCL with diverse profiles, indicating that it represents a heterogeneous category.^{904,905,957} Morphologic features are quite variable with infiltration by virtually

any combination of cell sizes. A proportion of cases (5%-11%) show association with EBV^{958,959}; they may show variable expression of CD30 and may have an associated B-cell proliferations similar to AITL. Similar to DLBCL, NOS, this category will continue to shrink over time as specific biologic entities are identified.

Current Testing in Peripheral T- and Natural Killer-Cell Lymphomas

Because of the large number of disease categories associated with these rare disorders, a fairly extensive work-up is needed to diagnose peripheral T- and NK-cell neoplasms. Multiple T-cell associated antigens, such as CD2, CD3, CD5, CD7, CD4, and CD8, should be performed on each case due to the high frequency of loss of one or more antigen as well as the lack of specificity of some markers (such as CD5 on some B-cell neoplasms). Markers such as CD10, CXCL13, BCL6, and PD1 are useful to evaluate TFH cells and CD21 and/or CD23 are useful to evaluate follicular dendritic cell networks that are characteristically disrupted in AITL. Additionally, *in situ* hybridization for EBV and CD56 immunohistochemistry are necessary to identify the nasal-type NK/T cell lymphoma (discussed elsewhere) and CD30 staining (with ALK staining when positive) should be performed to evaluate for ALCL. T-cell receptor gene rearrangement studies are helpful when the differential diagnosis is with reactive conditions, but care must be taken to not overinterpret such studies since oligoclonal reactive proliferations may result in false positive clonality results in some cases.

Tumors of the Accessory Immune System

The accessory immune system includes two major categories of cells: antigen-presenting cells (dendritic cells) and antigen-processing cells (macrophages).⁹⁶⁰⁻⁹⁶⁵ The dendritic cells belong to the group of nonlymphoid elements traditionally designated by histologists and pathologists as reticulum cells, which have been divided into more or less well-defined subtypes on the basis of location, enzyme histochemical, ultrastructural, and immunohistochemical features. Tumors of most, if not all, of these cell types are now described, and both the WHO and the Histiocyte Society offer recently revised classifications of these neoplasms.^{407,966}

Follicular dendritic cell tumor (follicular dendritic cell sarcoma; dendritic reticulum cell sarcoma) often presents as a solitary mass in a cervical lymph node (Fig. 37.104)⁹⁶⁷ but can involve other lymph node groups and a large variety of extranodal sites,⁹⁶⁸ including stomach,⁹⁶⁹ small bowel,⁹⁷⁰ large bowel,⁹⁷¹ omentum,⁹⁷² mesentery,⁹⁷³ liver,⁹⁷⁴ nasopharynx,⁹⁷⁵ oral cavity,⁹⁷⁶ tonsil,⁹⁷⁶ soft tissues of head and neck region,⁹⁷⁷ mediastinum,⁹⁷⁸ spleen,⁹⁷⁹ lung,⁹⁸⁰ and breast.^{981,982} Some cases of follicular dendritic cell tumor have occurred as a complication of the hyaline vascular type of Castleman disease,^{983,984} and others in connection with inflammatory pseudotumor of the liver and spleen,⁹⁸⁵ although the latter instance has been a constant association with EBV that is not seen in other sites.^{974,986,987}

Microscopically, follicular dendritic cell tumor is characterized by a proliferation of oval to spindle cells that form fascicles and whorls (Fig. 37.105).⁹⁸⁸ Sometimes there is a suggestion of a storiform or palisading pattern.^{967,989} In other instances the stroma has a myxoid quality.⁹⁸¹ The appearance at low power may simulate that of meningioma. The nuclei are generally oval, with a vesicular chromatin pattern, small nucleoli, and scanty mitotic activity. Pseudonuclear inclusions and multinucleated giant cells may be present. A characteristic feature is the presence of small lymphocytes scattered throughout the tumor cells, resulting in a thymoma-like appearance.⁹⁹⁰ The ultrastructural and immunohistochemical features correspond

to those of follicular dendritic cells (Fig. 37.106). Markers that are particularly useful for their identification are CD21, CD35, clusterin, Ki-M4P, and Ki-FDRC1p.^{991,992}

The tumor cells are negative or equivocal for CD45RB and erratically positive for S100 protein. Although it was thought previously that these tumors do not exhibit clonal rearrangements of the immunoglobulin or the T-cell receptor genes, it has been shown recently that a proportion of cases indeed exhibit clonal rearrangements of immunoglobulin genes.⁹⁹³

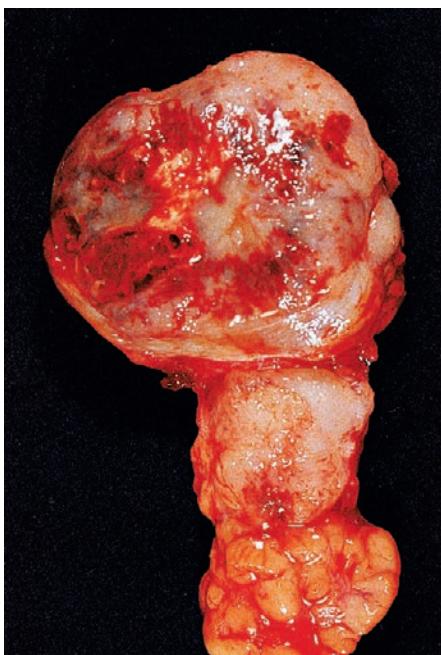


Figure 37.104 Gross appearance of follicular dendritic cell tumor.

The behavior is that of a malignant tumor, with local recurrence and distant metastases to sites such as the liver and lung.^{994,992} The pattern of spread resembles that of a soft tissue sarcoma more than that of a malignant lymphoma. Intra-abdominal neoplasms tend to be particularly aggressive.⁹⁹⁵ Recurrent and metastatic lesions may show increased atypia and pleomorphism.⁹⁹²

Interdigitating dendritic cell tumor (interdigitating reticulum cell sarcoma) is even more uncommon or perhaps not as easily recognized.⁹⁹⁶ Most patients are adults, but it can also occur in the pediatric population.⁹⁹⁷ Most of the reported cases have arisen in lymph nodes,^{998,999} but instances of extranodal involvement in sites such as skin, bowel, spleen, and testis have been recorded.^{979,1000–1002} The microscopic appearance can be indistinguishable from that of follicular dendritic cell tumor, but there is more tendency to spindling



Figure 37.106 Electron Microscopic Appearance of Follicular Dendritic Cell Tumor. A characteristic feature is the presence of well-developed cytoplasmic prolongations joined by desmosomes.

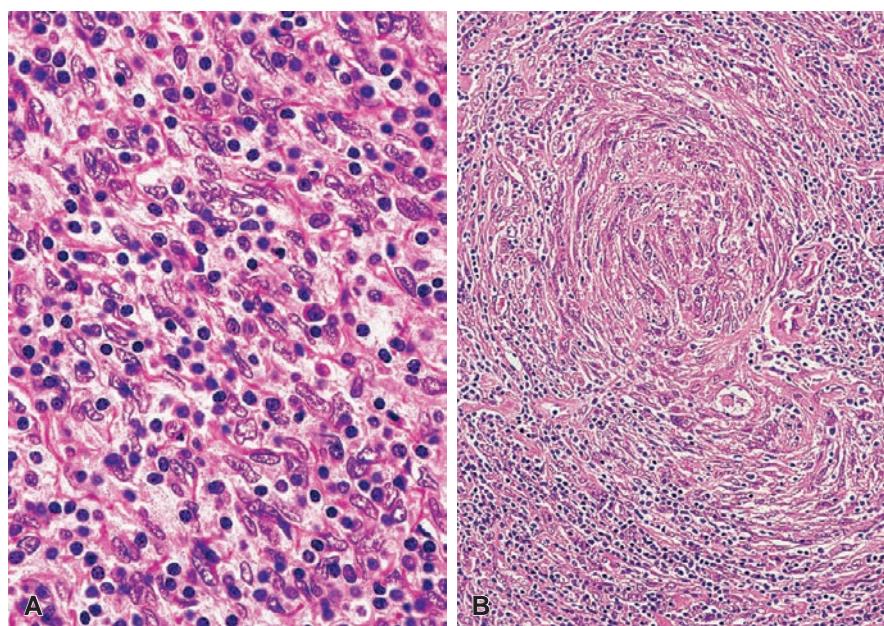


Figure 37.105 Follicular Dendritic Cell Tumor of Lymph Node. **A**, The admixture of neoplastic cells with predominantly oval vesicular nuclei and non-neoplastic small lymphocytes results in an appearance reminiscent of thymoma. **B**, Prominent whorling in a case of follicular dendritic cell tumor, engrafted upon Castleman disease.

and pleomorphism.^{1003,1004} The diagnosis is dependent on the immunohistochemical profile, which unfortunately is not entirely specific. The tumor cells are positive for S100 protein but are negative for CD21 and CD35. The behavior seems more aggressive than for follicular dendritic cell tumor. Contrary to earlier belief, a proportion of cases are shown to exhibit clonal rearrangements of the immunoglobulin genes.^{993,400}

Langerhans cell histiocytosis (LCH), also known as Langerhans cell granulomatosis, histiocytosis X, differentiated histiocytosis, and eosinophilic granuloma, is applied to a specific, although remarkably variable, clinicopathologic entity characterized and defined by the proliferation of Langerhans cells.^{1005–1007} These cells are regarded as a distinct type of immune “accessory” cells that are involved in the capturing of some antigens and their presentation to the lymphoid cells. Contrary to a formerly held belief, these cells are not primarily phagocytic in nature. Their nuclei are highly characteristic: irregular, usually elongated, with prominent grooves and folds that traverse them in all directions. The cytoplasm is abundant and acidophilic, sometimes to the point that an embryonal rhabdomyosarcoma or ALCL is simulated. Most Langerhans cells are mononuclear, but occasional ones contain several nuclei while still maintaining the aforementioned nuclear and cytoplasmic features. An extensive eosinophil infiltrate usually accompanies LCH. Histochemically, they show weak acid phosphatase and nonspecific esterase activity but considerable leucyl-β-naphthylamidase activity and membrane-bound ATPase activity.¹⁰⁰⁸ They are believed to develop from a lymphoid-committed precursor,¹⁰⁰⁹ a hypothesis supported by the presence of an identical rearrangement of the IGH in cases with B-cell lymphoma and in cases without an associated lymphoma.^{1010,1011}

In paraffin sections, both Langerhans cells and the cells of LCH are reactive for S100 protein, vimentin, langerin (CD207), fascin (a dendritic cell marker), CD1a, CD74, and HLA-DR in most cases (Fig. 37.107).^{1012–1014} They also tend to be positive for peanut agglutinin lectin and the macrophage-associated antigens CD68, cathepsin D, and cathepsin E.^{1015–1017} They generally do not express CD45RA, CD45RB, CDw75, α1-antitrypsin, EMA, or CD15. The most useful of these formalin-resistant epitopes are S100, CD1a,¹⁰¹⁸ and langerin, the latter having a great degree of specificity and sensitivity.^{1019,1020}

By electron microscopy, they contain a highly characteristic and apparently diagnostic organelle: the Birbeck or Langerhans granule,

which correlates with langerin immunohistochemistry. This is an elongated, zipperlike cytoplasmic structure of unknown function, sometimes continuous with the cell membrane.¹⁰²¹

Scattered Langerhans cells are present in the skin, lymph node, thymus, and other organs in normal conditions and may be slightly increased in some disorders, such as interstitial lung diseases and dermatopathic lymphadenitis. Therefore the identification of a few cells with these features in one of these sites is not necessarily indicative that the patient has LCH.¹⁰²² Rather, the infiltrate should have a sizable number of these cells before such a diagnosis is entertained.¹⁰²⁰ Conversely, the identification of Langerhans cells is necessary for the diagnosis of LCH. There is already too much confusion in the literature stemming from the fact that cases have been given this label only because a widespread proliferation of histiocytes was associated with a compatible clinical picture.

LCH can present as solitary or multiple lesions in one organ system (bone being the most common) or as a disseminated disease.¹⁰²³ Most patients are children or adolescents, but the disease can affect any age group, including the elderly.¹⁰²⁴ The treatment, prognosis, and terminology used largely depend on the extent (staging) of the disease rather than the microscopic features or the pattern of DNA ploidy.^{1025–1028} The term **Letterer–Siwe disease** was used in the past for the systemic form occurring in infants, and **Hand–Schüller–Christian disease** for the less widespread and more indolent type seen in older children and adults.¹⁰²⁹ A self-healing, congenital form is known as **Hashimoto–Pritzker disease**.¹⁰³⁰

Lymph node involvement can be seen as a component of the systemic form, or it may represent the initial and sometimes exclusive manifestation of the disease.^{1031–1033} The microscopic appearance is characteristic. There is distention of the sinuses by an infiltrate of mononuclear and multinuclear Langerhans cells, admixed with a variable number of eosinophils (Fig. 37.108); foci of necrosis are common, often surrounded by a rim of eosinophils (so-called “eosinophilic microabscesses”), and always confined to the sinuses. The nodal architecture may be preserved or variably effaced.¹⁰³⁴

Sometimes, incidental foci of LCH are seen in lymph nodes involved by non-Hodgkin lymphoma or Hodgkin lymphoma, a sharp segregation existing between the two processes.^{1035,1036} In most of these cases, the Langerhans cell proliferation is limited to the node and may represent a reaction to the lymphoma,¹⁰³⁷ but in others it is an expression of generalized LCH.¹⁰³⁸ Follow-up studies have shown a broad spectrum of involvement, embracing all those syndromes that have been associated with LCH. However, the prognosis is usually excellent.

In addition to bone and lymph nodes, solitary LCH has been described in the lung, thymus, skin, central nervous system, and many other sites, including stomach, liver, anus, female genital tract, and thyroid.^{1039–1044} (see respective chapters). Changes morphologically consistent with LCH have been seen in coexistence with RDD, with Erdheim–Chester disease, and in lymph nodes draining malignant melanoma or papillary thyroid carcinoma.^{1045,1046}

The differential diagnosis of LCH is wide and to some extent influenced by the site of involvement. It includes RDD, parasitic infections, Kimura disease, hypersensitivity reactions, cat-scratch disease, Erdheim–Chester disease, and some types of malignant lymphoma, such as Hodgkin lymphoma and peripheral T-cell lymphoma.¹⁰⁴⁷

The etiology of LCH remains unknown. A viral cause has been suggested but not substantiated.^{1048,1049} Molecular studies have shown evidence of clonality in most cases, but some cases of localized pulmonary belch may be nonclonal.^{359,1050,1051} Approximately 60% of cases have mutations of *BRAF* or associated pathways^{1052–1054} and most *BRAF* V600E mutations can be identified by immunohistochemistry.¹⁰⁵¹ The Langerhans cells are affected by recurrent cytogenetic

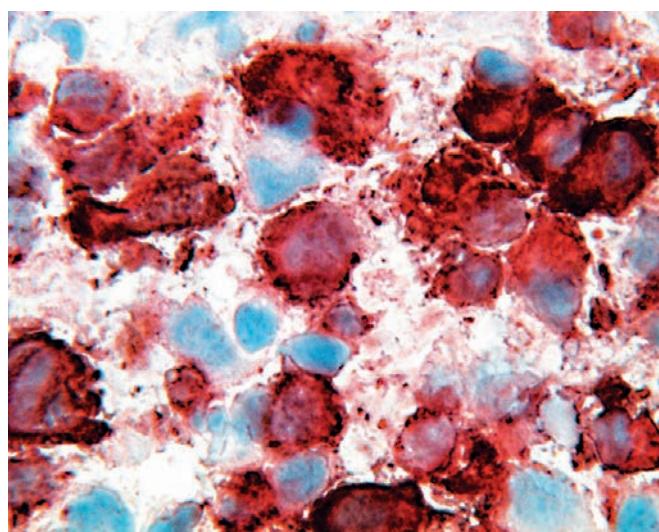


Figure 37.107 Immunoreactivity of the cells of Langerhans cell histiocytosis for langerin.

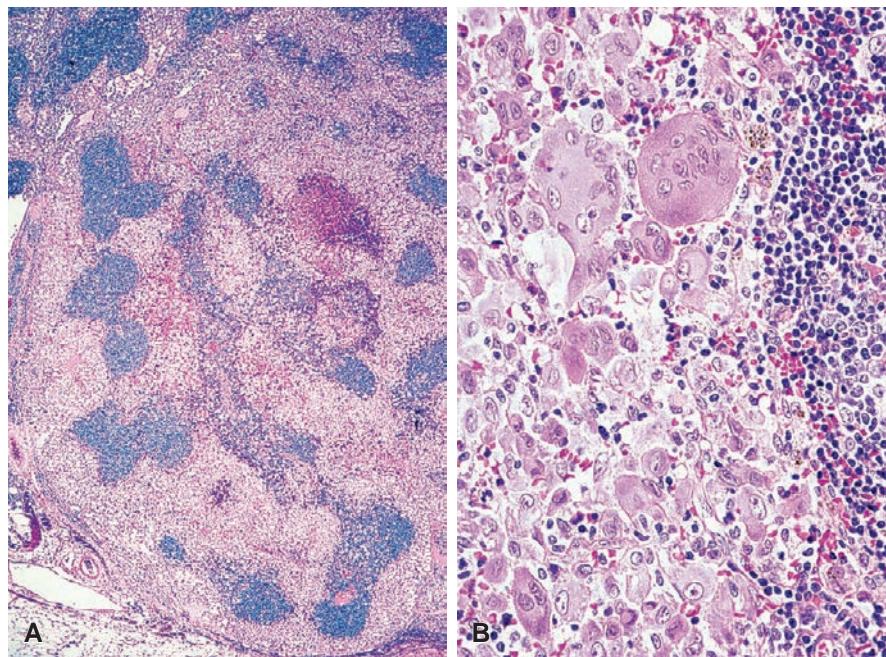


Figure 37.108 Lymph Node Involvement by Langerhans Cell Histiocytosis. **A**, The infiltrate has a predominantly sinus distribution. **B**, High-power view showing mononuclear and multinucleated Langerhans cells. There are also numerous eosinophils.

alterations¹⁰⁵⁵ and do not appear to be a particularly proliferative cell population.¹⁰⁵⁶

Exceptionally, a morphologically malignant process is seen in which the tumor cells have the ultrastructural and immunohistochemical features of Langerhans cells.^{1057–1059} This is to be regarded as Langerhans cell sarcoma.¹⁰⁶⁰

Indeterminate dendritic cell tumor is a rare neoplasm that more commonly involves skin but has been reported in lymph nodes.^{1061,1062} It has features of LCH, with expression of S100 and CD1A, but lacks Birbeck granules by electron microscopy and langerin by immunohistochemistry. Recently, a fusion of *ETV3-NCOA2* has been reported as unique to this tumor.¹⁰⁶³

Erdheim–Chester disease is another “histiocytosis” of unknown etiology involving mainly the central nervous system, bones, and lung. The histiocytes in this condition are only focally S100 positive, are negative for CD1a and langerin, and lack Birbeck granules.¹⁰⁶⁴

Histiocytic sarcomas (malignant histiocytosis) are malignant neoplasms of histiocytic lineage that do not meet criteria for other accessory cell neoplasms. Their presentation is highly variable, with a high proportion of extranodal involvement in sites such as the spleen, skin, bone, and particularly the gastrointestinal tract.^{1065–1069} As in the case of the dendritic cell tumors, some “true histiocytic sarcomas” have been seen in combination with bona fide malignant lymphoma,¹⁰⁷⁰ and some subdivide these tumors into primary and secondary disease.⁹⁶⁶ Microscopically, the tumor cells are large, with irregularly shaped nuclei and abundant, generally acidophilic cytoplasm. Immunohistochemically, the tumor cells lack by definition B cell- and T cell-related markers and show reactivity for histiocytic markers, such as CD68, CD163, lysozyme, and CD4.^{1071–1073}

Although the presence of immunoglobulin or T-cell receptor gene rearrangement was previously considered to be incompatible with a diagnosis of histiocytic sarcoma, recent studies have shown that clonal immunoglobulin gene rearrangement, and

rarely T-cell receptor gene rearrangement, can occur in up to 50% of cases.^{401,993} This phenomenon is observed in sporadic cases as well as cases that occur subsequent to or concurrent with B- or T-lymphoblastic leukemia/lymphoma or low-grade B-cell lymphoma (especially follicular lymphoma).^{401,993,1074–1076} In the latter scenario, the histiocytic sarcoma often shares the clonal markers of the previous leukemia/lymphoma, such as immunoglobulin gene rearrangement, *BCL2* rearrangement, and clonal cytogenetic aberrations.^{401,1074}

Vascular Tumors and Tumorlike Conditions

Hemangioma and **lymphangioma** involving nodes usually represent extension by contiguity of primary soft tissue lesions. However, rare cases of primary nodal hemangioma and lymphangioma have been described (Fig. 37.109).^{1077,1078}

Epithelioid vascular neoplasms of lymph nodes include epithelioid hemangioma, epithelioid hemangioendothelioma, spindle and epithelioid hemangioendothelioma, and polymorphous hemangioendothelioma, which are discussed in more detail elsewhere.^{1079–1082}

Bacillary angiomatosis, which occurs almost exclusively in the setting of immunodeficiency (especially in patients with HIV infection), presents as multiple coalescent intranodal clusters of proliferating vessels. These vessels are lined by plump, somewhat epithelioid endothelial cells (hence the original term epithelioid angiomatosis for this condition). A feature of great diagnostic importance is the presence of abundant eosinophilic to amphophilic, amorphous, or granular material in the interstitium. Another helpful feature is the presence of neutrophils, sometimes forming microabscesses.^{1083–1085} When stained with the Warthin–Starry technique, this material is shown to be composed of aggregated bacillary organisms, now known to represent *Bartonella henselae* and *Bartonella quintana*, that are indistinguishable from those of cat-scratch disease (also

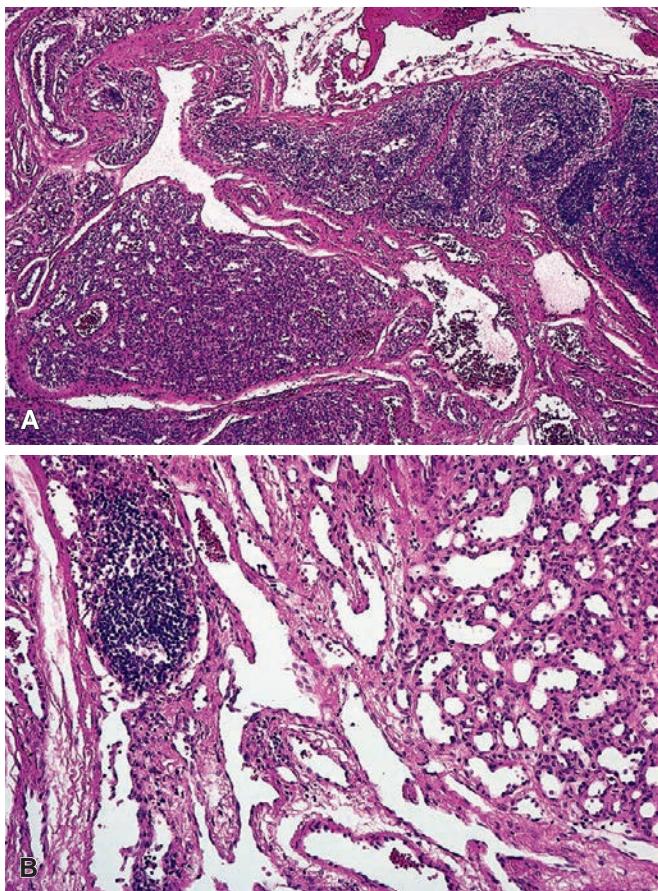


Figure 37.109 Low-power (A) and medium-power (B) views of nodal hemangioma.

caused by *B. henselae*). These organisms may be more precisely detected by immunohistochemistry or PCR. A recent study of the lymph nodes changes associated with *B. henselae*, however, found that infection was usually not associated with features of bacillary angiomatosis.¹⁰⁸⁶

Vascular transformation of sinuses is characterized by a conversion of lymph node sinuses into a complex network of anastomosing endothelial-lined channels (Fig. 37.110).¹⁰⁸⁷ Fibrosis and reactive stromal changes are commonly present.¹⁰⁸⁸ *Nodal angiomyomatosis* probably refers to a more cellular form of the same condition (Fig. 37.111).^{1089,1090} In the *nodular spindle-cell variant*, spindle-cell nodules composed of interlacing fascicles alternate with the vascular clefts.¹⁰⁹¹ This variant is particularly likely to be misdiagnosed as Kaposi sarcoma. It is distinguished from the latter because it is HHV8-negative, is confined to the sinuses (with sparing of the capsule and parenchyma), shows no cellular atypia, contains fascicles that blend with well-formed vascular channels, commonly is associated with fibrosis, and almost invariably lacks the PAS-positive hyaline globules of Kaposi sarcoma (Fig. 37.112).^{1092,1093} Other cases of vascular transformation may result from proximal obstruction of the efferent vessels; indeed, the process has been reproduced experimentally by complete occlusion of these vessels.¹⁰⁹⁴

Angiolipoma (including its cellular variant) is usually located in the soft tissue, but exceptionally it may be centered in a lymph node.¹⁰⁹⁵

Kaposi sarcoma of the lymph nodes may be associated with typical skin lesions or develop in their absence.¹⁰⁹⁶ The latter occurrence is seen mainly in African children, but it also occurs in adults

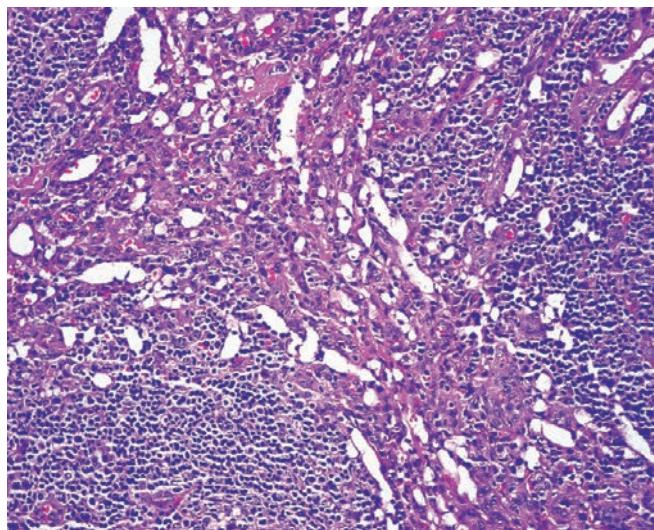


Figure 37.110 Lymph Node Involvement by Bacillary Angiomatosis. An intense vascular proliferation featuring epithelioid endothelial cells is seen in the interfollicular region, accompanied by neutrophils and other inflammatory cells.

(usually but not always HIV infected). Microscopically, the involved nodes show proliferation of spindle cells separated by slitlike spaces containing red blood cells (Fig. 37.113).¹⁰⁹⁷ The earliest changes are seen in the nodal capsule, but eventually there is involvement of the entire node and extension into the perinodal tissues. Cytoplasmic and extracellular hyaline globules that are positive for PAS and PTAH are almost always present.¹⁰⁹⁸ Recognition of early nodal involvement by Kaposi sarcoma is an extremely difficult task; although a definitive diagnosis can be made if immunostaining for HHV8 is positive in the proliferating spindle cells. In well-developed cases, the tumor may grow in a diffuse fashion or as discrete deposits. The spindle-cell lesion is often accompanied by a lymphoid proliferation with a prominent component of plasma cells and immunoblasts. Kaposi sarcoma is also associated with HHV8+ multicentric Castleman disease, usually of the plasma cell type.²⁶⁹ In other instances, nodal Kaposi sarcoma coexists with malignant lymphoma or leukemia.¹⁰⁹⁹

If a lymph node is involved by a malignant tumor with the morphologic features of **angiosarcoma**, there is a high probability that the tumor is metastatic (Fig. 37.114).

Other Primary Tumors and Tumorlike Conditions

Systemic mastocytosis often involves lymph nodes, resulting in partial (usually interfollicular) or complete effacement of the architecture by a monotonous proliferation of round, spindled or polygonal cells (Fig. 37.115).^{1100,1101} Clues as to the nature of the proliferation include the regular contours of the round or oval nucleus, the clear or granular cytoplasm, the well-defined cell outlines, admixture of eosinophils, and accompanying sclerosis. Special techniques that confirm mast cell lineage, especially immunohistochemical stains for CD117 and tryptase, are required for diagnosis.^{1102–1108}

Acute myeloid leukemia can first be seen in a lymph node biopsy and misdiagnosed as malignant lymphoma.¹¹⁰⁹ Traditionally, the disease has been referred to as granulocytic sarcoma, myeloid sarcoma, or chloroma when appearing as a tumor mass in a lymph node or

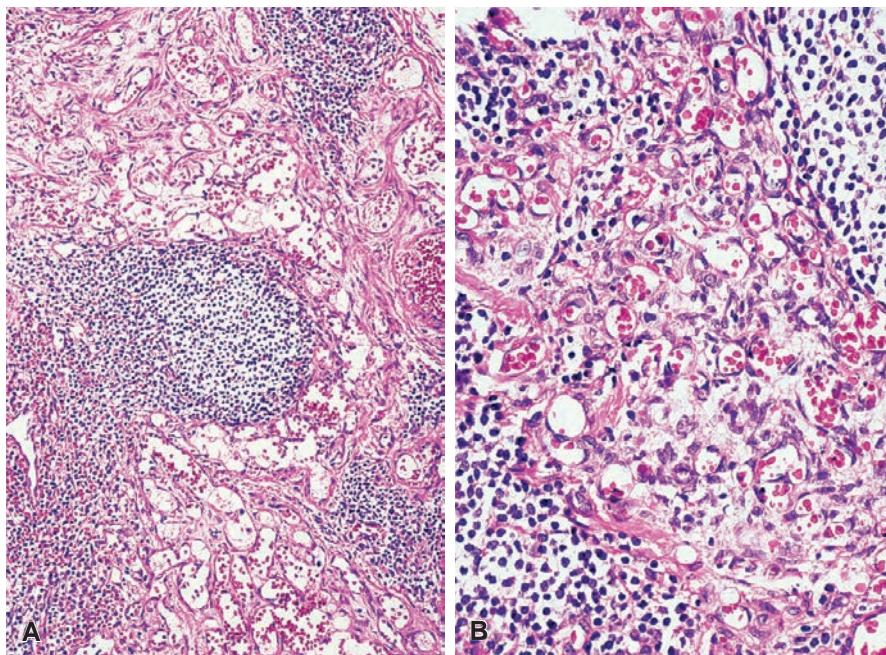


Figure 37.111 **A** and **B**, Vascular transformation of lymph nodes. The process involves the sinuses, and it has a reactive appearance.

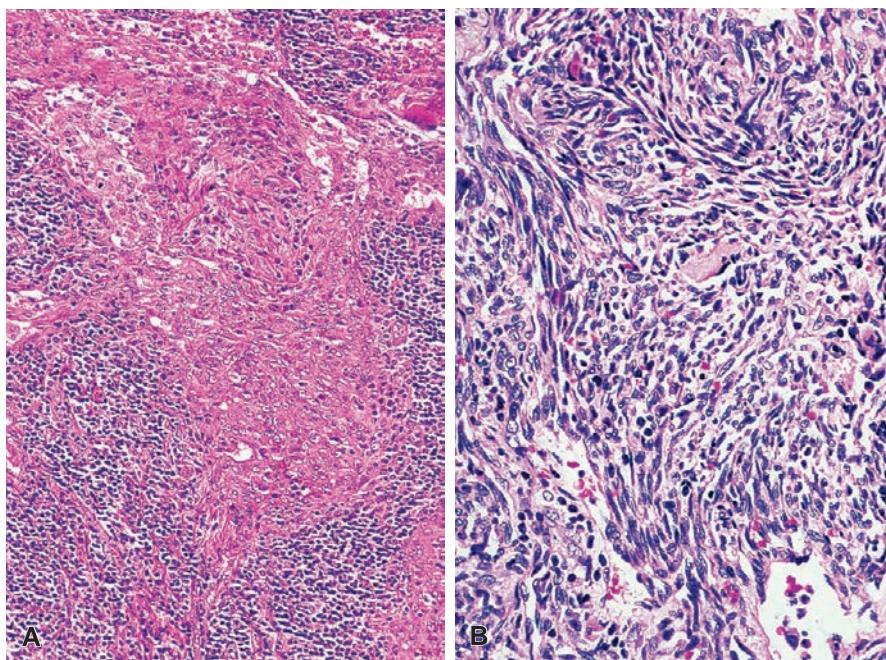


Figure 37.112 Solid Form of Vascular Transformation of Lymph Nodes. This process has also been designated as nodal angiomatosis. **A**, Predominantly sinus distribution of the lesions. **B**, Example in a retroperitoneal lymph node in a patient with renal cell carcinoma.

some other location outside the bone marrow (Fig. 37.116). Clues to the diagnosis include a patchy or sinus type of nodal involvement, sometimes associated with a single-file pattern of infiltration in the capsule; fine granularity of the cytoplasm; fine nuclear chromatin without the typical chromatin clearing of DLBCL; and presence of eosinophilic myelocytes. Immunohistochemically, there is reactivity for CD43, lysozyme, myeloperoxidase, CD99, and CD117.^{110,111}

Identification of a myeloid sarcoma should trigger a bone marrow evaluation. If negative, additional material from lymph nodes, even if by fine-needle aspiration, should be obtained to perform complete immunophenotyping, karyotype analysis, and molecular studies necessary to completely classify the acute myeloid leukemia (see Chapter 39). *Extramedullary hematopoiesis*, either reactive or secondary to a myeloproliferative neoplasm, accompanied by megakaryocytes can

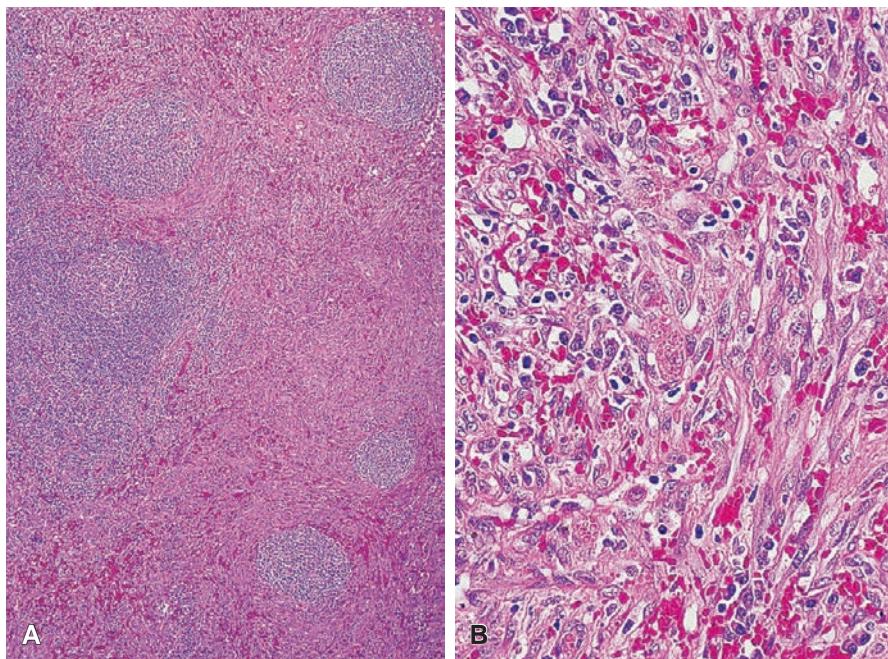


Figure 37.113 **A** and **B**, Lymph node involvement by Kaposi sarcoma. The infiltrate is predominantly in sinuses and is characterized by a proliferation of spindle cells forming slits containing red blood cells.

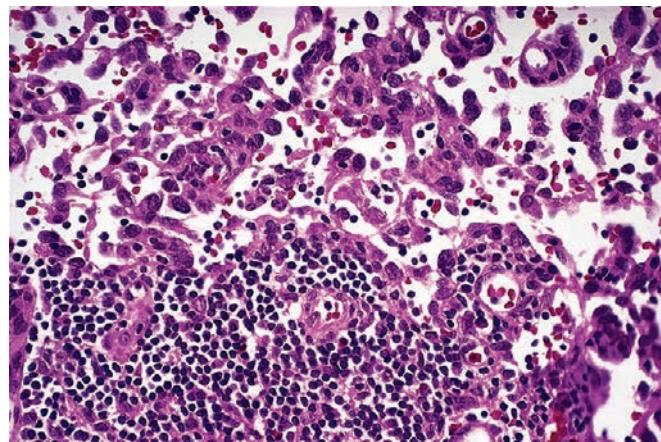


Figure 37.114 Angiosarcoma of Skin of Scalp Metastatic to a Posterior Cervical Lymph Node. The nodal lesion was the first manifestation of the disease.

be confused with Hodgkin lymphoma and other malignancies (Fig. 37.117). A Leder chloroacetate or myeloperoxidase stain will reveal the maturing myeloid forms.

Smooth muscle proliferations of a primary nature can be seen within lymph nodes in the following situations:

1. *Smooth muscle proliferation in the hilum.* This is often accompanied by fibrosis and prominent vascularity.¹¹¹² It is most common in the inguinal region and is of no clinical significance.
2. *Angiomyolipoma.* The most common location is the retroperitoneal region, usually in conjunction with a renal tumor of the same type.¹¹¹³ Immunoreactivity for HMB45 and other melanocyte-related markers is a constant feature of this entity.
3. *Lymphangiomyomatosis.* This is seen exclusively in women, often in association with pulmonary involvement, but sometimes showing pelvic lymph node involvement alone as an incidental

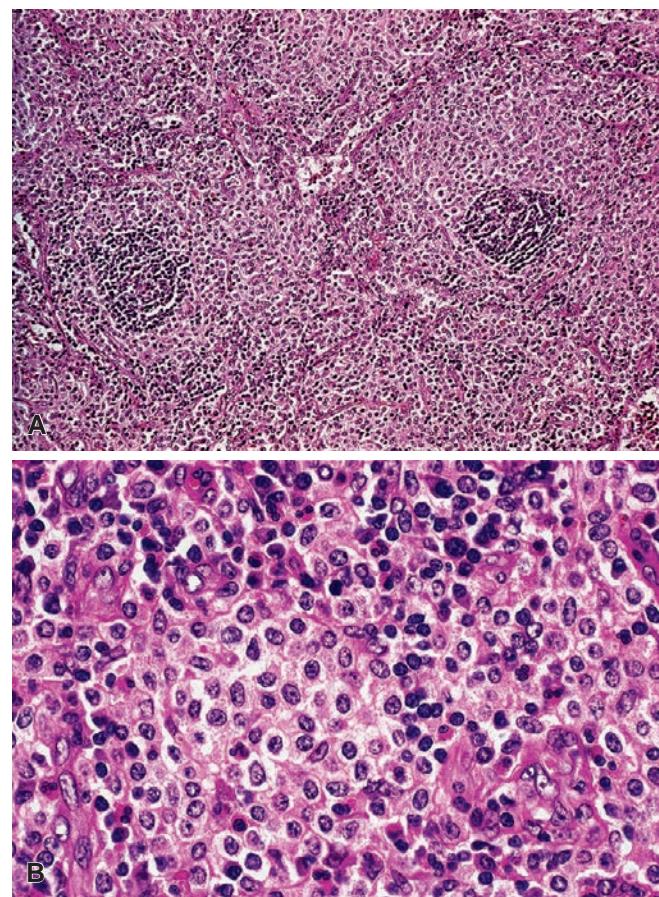


Figure 37.115 Medium-power (**A**) and high-power (**B**) views of lymph node involvement in systemic mastocytosis. Note the perfectly round shape of the centrally located nuclei, the finely granular cytoplasm, and the well-defined cell membranes.

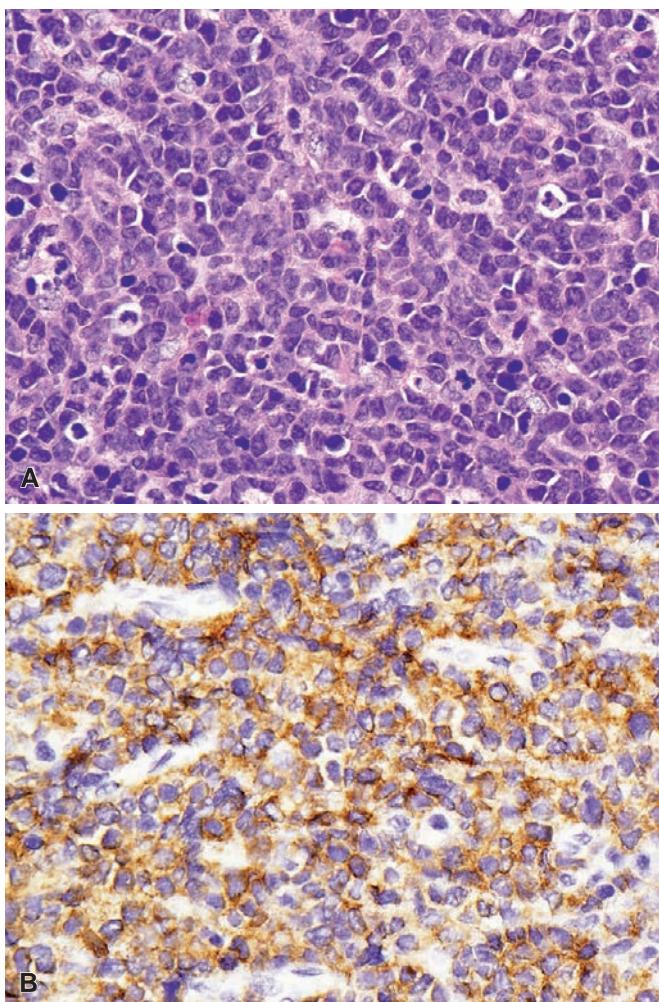


Figure 37.116 Lymph Node Involved by Acute Myeloid Leukemia (Myeloid Sarcoma). **A**, The infiltrate is medium in size with irregular nuclear contours but fine nuclear chromatin. **B**, The cells express the myeloid-associated antigen CD33.

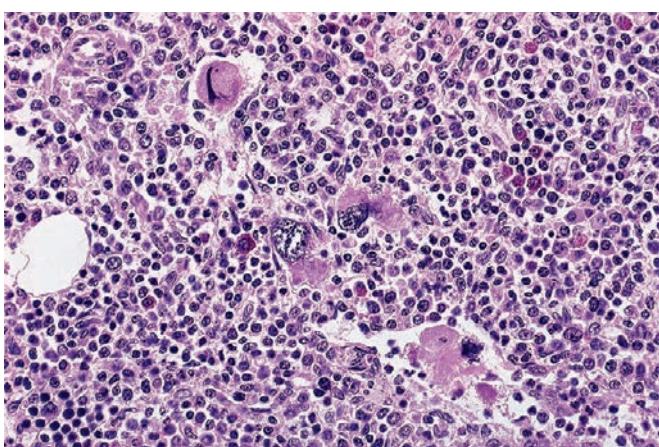


Figure 37.117 Scattered Megakaryocytes in Lymph Node Involved by Extramedullary Hematopoiesis. These elements should not be confused with Reed–Sternberg cells or carcinoma cells.

finding.¹¹¹⁴ Like the previous entity, to which it is histogenetically related, it exhibits immunoreactivity for HMB45.

4. *Leiomyomatosis*. This has been reported mainly in intra-abdominal nodes, sometimes in association with uterine leiomyomas or leiomyomatosis peritonealis disseminata.^{1115,1116}
5. *Angiomatous hamartoma*. This is a distinctive form of smooth muscle proliferation that seems to occur only in the inguinal region. It is characterized by a proliferation of thick-walled hilar blood vessels that sometimes extends into the nodal parenchyma.¹⁰⁷⁹
6. *Intranodal leiomyoma*. Some of the reported cases have occurred in the setting of HIV infection.¹¹¹⁷

Hemorrhagic spindle-cell tumor with amianthoid fibers (also known as palisaded myofibroblastoma) is a distinctive benign neoplasm that occurs preferentially in inguinal lymph nodes but that can involve nodes of other sites, such as the neck and mediastinum.^{1117–1123} The main microscopic features are the proliferation of bland-looking spindle cells, sometimes in a palisading fashion; extensive foci of recent and old hemorrhage; and giant rosettelike collections of collagen fibers (so-called “amianthoid fibers”) (Fig. 37.118).^{1124–1126} The differential diagnosis includes Kaposi sarcoma and intranodal schwannoma. Immunohistochemically, the spindle cells are reactive for vimentin and actin, particularly around the rosettelike formations, and are negative for LANA-1 (HHV8) and S100 protein. The staining qualities and ultrastructural features are more in favor of a smooth muscle than a myofibroblastic derivation.¹¹²⁷ The behavior has been benign in all reported cases, but there has been an isolated instance of recurrence.¹¹²⁸

Inflammatory pseudotumor-like change of lymph nodes may be localized or affect several lymph node groups and may be accompanied by fever, anemia, elevated erythrocyte sedimentation rate, and hypergammaglobulinemia.^{1129–1133} Microscopically, the process involves primarily the fibrous stroma of the node, with secondary spread into the lymphoid tissue and perinodal tissues. It is characterized by a storiform pattern of growth, vascular proliferation, and a polymorphic infiltrate composed of fibroblasts, plasma cells, immunoblasts, small lymphocytes, histiocytes, dendritic cells, and neutrophils (Fig. 37.119). Morphologic variations on this basic theme exist, which have been attributed to the stage of the disease at which the biopsy has been taken.¹¹³⁴ In contrast to morphologically similar, but neoplastic, lesions in the spleen and liver, EBV is not usually present in lymph node cases.¹¹³⁵ A diagnosis of inflammatory pseudotumor in lymph nodes is not a specific diagnosis and often represents a chronic response to infection or other damage. The cause is unknown in most patients, but some are responses to infectious organisms, including syphilitic infection¹⁵¹ and *Mycobacterium avium-intracellulare* infection.¹²⁰ The latter occurs in immunocompromised individuals (mycobacterial spindle cell pseudotumor) (Fig. 37.120).

Anthracosis and **anthracosilicosis** can result in a pseudoneoplastic appearance because of the presence of a sometimes intense histiocytic proliferation with a focally storiform pattern of growth (Fig. 37.121).¹¹³⁶

Solar elasticotic material can be found in the subcapsular sinus and parenchyma of lymph nodes, presumably as a result of mechanical transport from the skin.¹¹³⁷

Lymph Node Inclusions

Inclusions of various types of benign tissue can occur within lymph nodes.¹¹³⁸ Lack of awareness of this phenomenon can lead to a mistaken diagnosis of metastatic carcinoma. These include the following:

1. *Salivary gland tissue*. This is an extremely common finding in high cervical nodes, to be regarded as a normal event related to

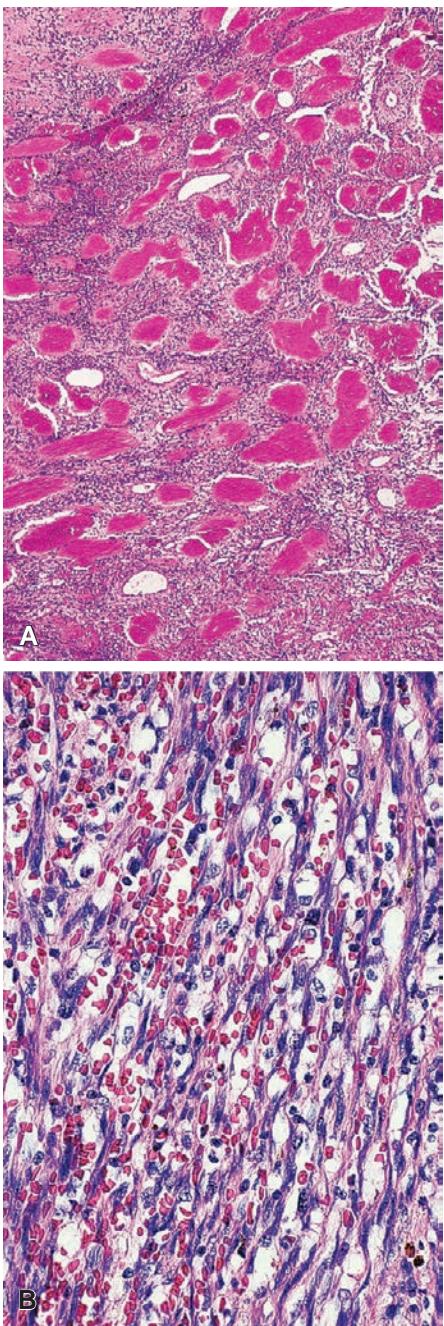


Figure 37.118 Hemorrhagic Spindle Cell Tumor With Amianthoid Fibers. **A**, Prominent deposition of “amianthoid” collagen throughout the tumor. **B**, The admixture of neoplastic spindle cells and extravasated red blood cells results in a Kaposi sarcoma-like appearance.

the embryology of the region (Fig. 37.122).¹¹³⁹ Both ducts and acini are usually present. These inclusions may undergo neoplastic changes. Warthin tumor is the most common type, but many other types have been reported, including benign mixed tumor, monomorphic adenoma, mucoepidermoid carcinoma, and acinic cell carcinoma.

2. *Squamous epithelium*. Microscopic cystic structures lined by well-differentiated squamous epithelium are sometimes seen in the upper cervical lesion. They are thought to represent an anomaly related to the aforementioned one, in the sense of being composed of branchial pouch derivatives. The term “benign lymphoepithelial

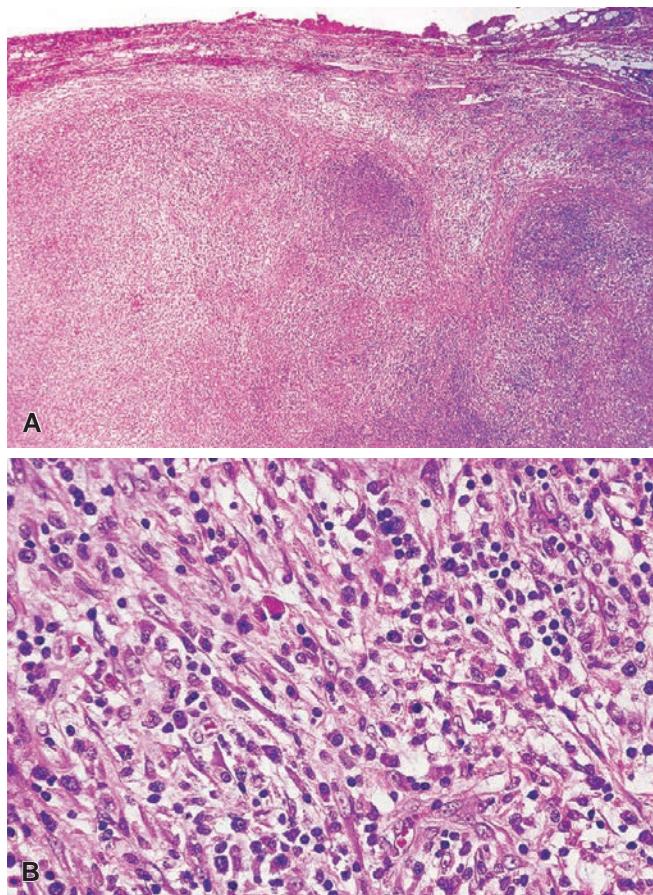
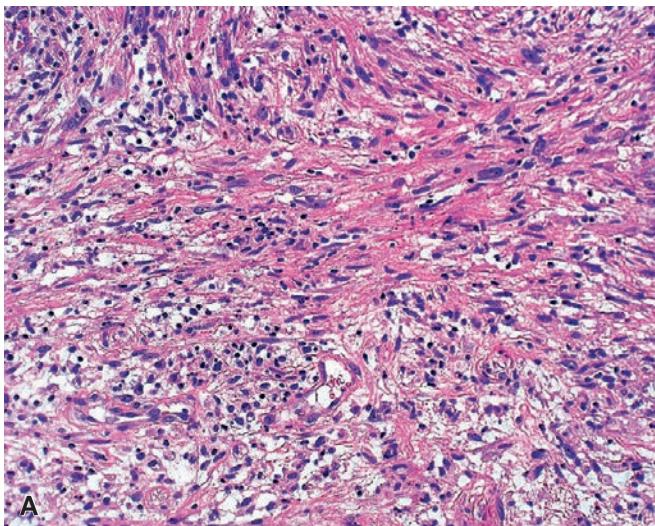


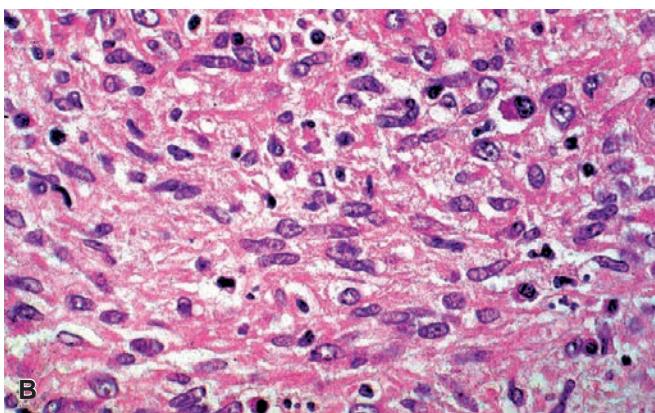
Figure 37.119 Inflammatory Pseudotumor of Lymph Node. **A**, Low-power appearance showing partial effacement of architecture and expansion of the sinusal and perinodal regions by a reactive proliferation. **B**, High-power view showing a polymorphic infiltrate composed of lymphocytes, plasma cells, and myofibroblasts.

cyst” is sometimes applied to them. We have hypothesized that these formations result from cystic dilation of preexisting epithelial inclusions as the result of their stimulation by the lymphoid component that surrounds them, a pathogenesis that also applies to multilocular thymic cysts, other cystic structures of the head and neck region, and possibly to Warthin tumor itself (see Chapter 6). Similar formations have been described in peripancreatic lymph nodes.¹¹⁴⁰ The obvious differential diagnosis is metastatic well-differentiated squamous cell carcinoma, which in the cervical region is notorious for its tendency to undergo marked cystic changes.¹¹⁴¹

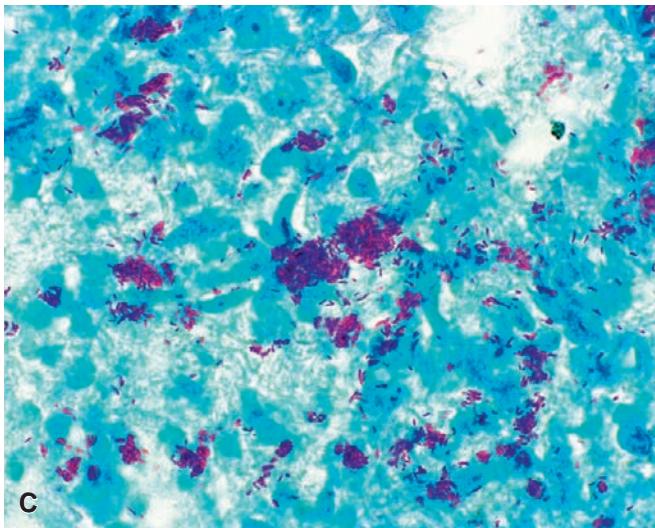
3. *Thyroid follicles*. These can be found in the capsular or subcapsular region of midcervical nodes in the absence of pathologic changes of the thyroid gland. The differential diagnosis with metastatic thyroid carcinoma can be very difficult.
4. *Decidual reaction*. During pregnancy, decidual reaction may occur within pelvic nodes and mimic metastatic carcinoma.¹¹⁴² The decidual reaction can occur in the stromal cells of endometriosis or in hormonally receptive cells of the region, in a fashion similar to that seen in peritoneal decidual reaction.
5. *Müllerian-type epithelium*. Glandular inclusions lined by cuboidal cells with a müllerian or coelomic appearance are commonly found in the capsule of the pelvic lymph nodes of females and sometimes within the node itself.^{1143,1144} Their appearance and pathogenesis are similar to those of the peritoneal lesions generally known as endosalpingiosis (Fig. 37.123). Like the latter, these



A



B



C

Figure 37.120 Inflammatory Pseudotumor of Lymph Node Due to *Mycobacterium avium-Intracellulare* Infection in an HIV-Infected Patient. **A**, Low-power view, showing spindle cell admixed with lymphocytes. **B**, High-power view. **C**, Acid-fast stain.

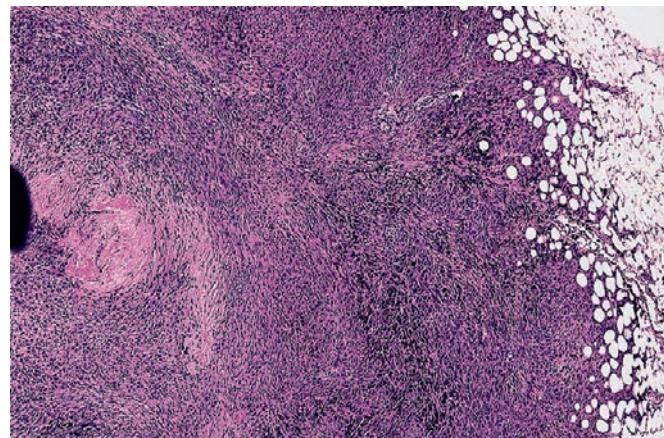


Figure 37.121 Anthracosilicotic Nodules in Mediastinal Lymph Node. When florid, these changes may acquire pseudoneoplastic features.

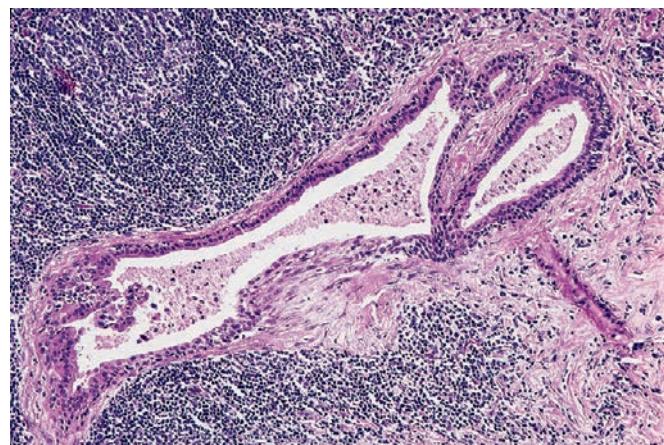


Figure 37.122 Salivary Gland Inclusion Composed of Ductal Structures in a High Cervical Lymph Node. This is a very common occurrence.

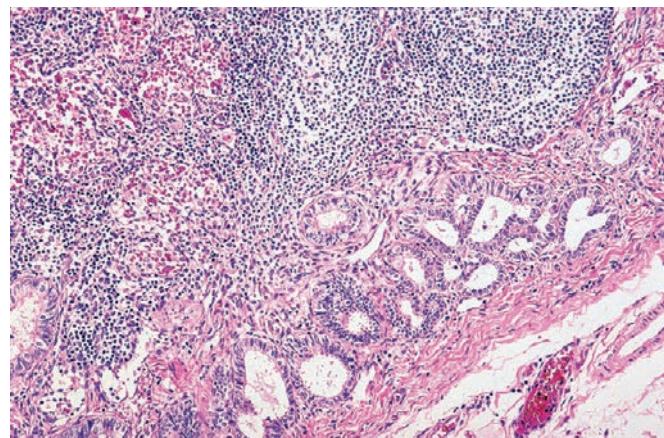


Figure 37.123 Pelvic Lymph Node Involved by Endosalpingiosis. Glands lined by cuboidal cells with a müllerian appearance and lacking atypical figures are present in the capsule of the node.

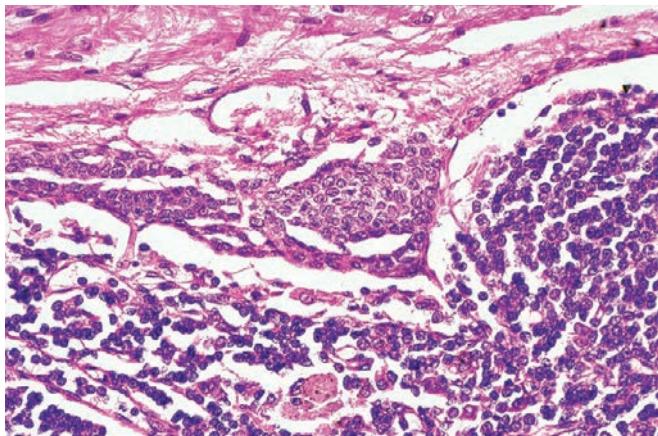


Figure 37.124 Nevus Cells in the Capsule of an Axillary Lymph Node. These inconsequential formations should not be mistaken for metastatic melanoma or metastatic carcinoma.

lymph node inclusions may be difficult to distinguish from metastases originating in low-grade ovarian neoplasms, since they may grow into the peripheral sinuses, form papillae, be accompanied by psammoma bodies, and even proliferate as small sheets of cells.¹¹⁴⁵ Some authors have suggested that some of these "inclusions" are actually metastases from ovarian serous borderline tumors.¹¹⁴⁶ Morphologically similar inclusions have been seen in the mediastinal nodes of males¹¹³⁸ and axillary nodes of females. Nodal glandular inclusions of similar appearance but surrounded by endometrial-type stroma occur less frequently and represent *nodal endometriosis*.

6. **Nevus cells.** Clusters of normal-appearing nevus cells are occasionally found in the capsule of lymph nodes, without involvement of the nodal parenchyma (Fig. 37.124). Most of the reported cases have occurred in axillary lymph nodes.¹¹⁴⁷ A related lesion is the *blue nevus* that has been reported in the lymph node capsule (Fig. 37.125).¹¹⁴⁸ The morphologic features of these formations and their differential diagnosis with metastatic malignant melanoma are discussed in Chapter 3.
7. **Mesothelial cells.** Occasionally, mesothelial cells are found within lymph nodes in the apparent absence of a malignant mesothelioma.^{1149–1151} The obvious differential diagnosis is with metastatic malignant mesothelioma from an occult primary in the peritoneal cavity or pleura.¹¹⁵²
8. **Breast tissue.** One of the most unusual forms of ectopia is represented by normal mammary lobules within axillary lymph nodes.^{1153–1155} A slightly more common occurrence is the presence in axillary nodes of tubules lined by a single layer of cuboidal cells (sometimes with a hobnail appearance), located in the nodal capsule or immediately beneath. These formations are similar to the müllerian-type epithelial inclusions in pelvic lymph nodes previously described. Since some of these cases occur in patients with breast carcinoma, the distinct possibility exists of mistaking them for metastatic tumor.^{1156,1157} Epithelial inclusions in axillary lymph nodes of females can be classified into three major groups: those composed exclusively of glandular structures, those made up only of squamous cysts, and those containing both glandular and squamous epithelium.¹¹⁵⁸

Other Non-Neoplastic Lesions

Adipose metaplasia of lymph nodes is very common. When extensive, it may lead to the formation of large masses, up to 10 cm or more

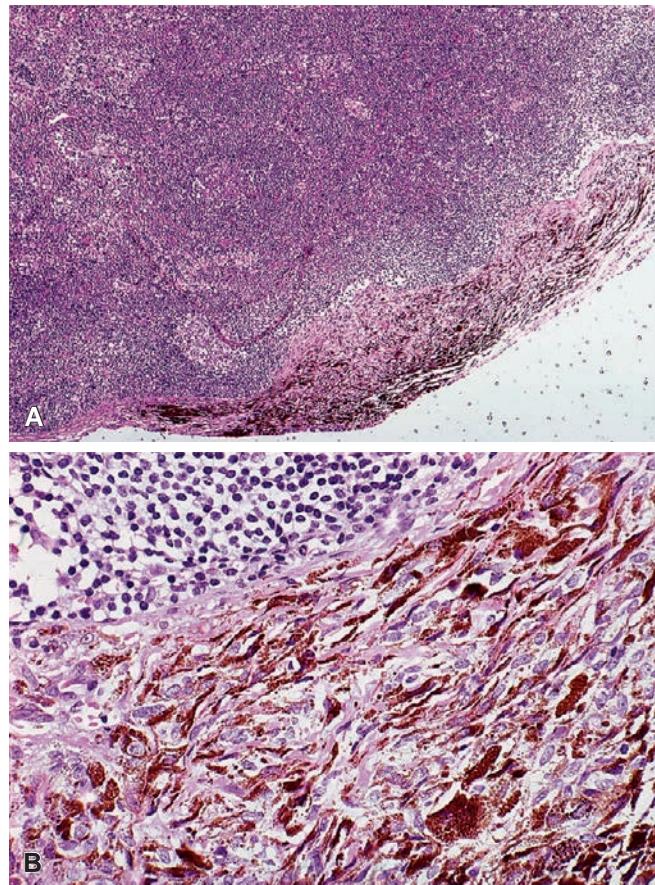


Figure 37.125 **A** and **B**, Blue nevus involving lymph node capsule.

in diameter. These nodes are sometimes referred to as *lipolymph nodes*; the external iliac and obturator groups are the sites most commonly involved.¹¹⁵⁹

Ectopic thymus sometimes seen in supraclavicular lymph node biopsies should be mentioned here for the sake of differential diagnosis even if it is not a lymph node lesion. The pathologist unaware of this occurrence might easily misinterpret the Hassall corpuscles as islands of metastatic squamous cell carcinoma.

Vasculitis involving lymph nodes may be seen in a large number of disorders: polyarteritis nodosa (having necrotizing qualities and only rarely biopsied), Henoch–Schönlein purpura (leukocytoclastic, also rarely biopsied), Wegener granulomatosis (sometimes accompanied by extensive infarct), systemic lupus erythematosus, drug hypersensitivity, and mucocutaneous lymph node syndrome. One should also mention the obliterative vasculitis often seen in syphilitic lymphadenitis.

Infarction of the lymph nodes presents with painful swelling, usually located in a superficial lymph node chain. Microscopically, there is extensive necrosis of medullary and cortical lymphoid cells, with marked reactive perinodal inflammation and a layer of granulation tissue. A thin rim of viable subcapsular lymphoid tissue may be present.¹¹⁶⁰ Thrombosis of veins within the substance and the hilum of the nodes has been suggested as the pathogenesis.¹¹⁶⁰ Similar changes can be seen in mesenteric lymph nodes in patients with intestinal volvulus.¹¹⁶¹ Other cases are the result of embolism, arterial occlusion in cases of polyarteritis nodosa and related disorders, or fine-needle aspiration.^{1162,1163} In these instances, the nodal infarct tends to have a segmental quality. The differential diagnosis of lymph node infarction includes necrotizing lymphadenitis, mucocutaneous

lymph node syndrome, infectious mononucleosis,¹¹⁶⁴ necrotizing granulomatous inflammation, and necrotic malignant tumors. Two types of malignancy that have been occasionally found to undergo extensive and sometimes massive infarct-type necrosis when involving lymph nodes are malignant lymphoma^{1165,1166} and metastatic malignant melanoma. Therefore thorough examination of the infarcted node, the extranodal region, and other nodes submitted is mandatory in order to exclude a concomitant or underlying malignancy (Fig. 37.126A and B).¹¹⁶⁶ A thorough immunohistochemical study

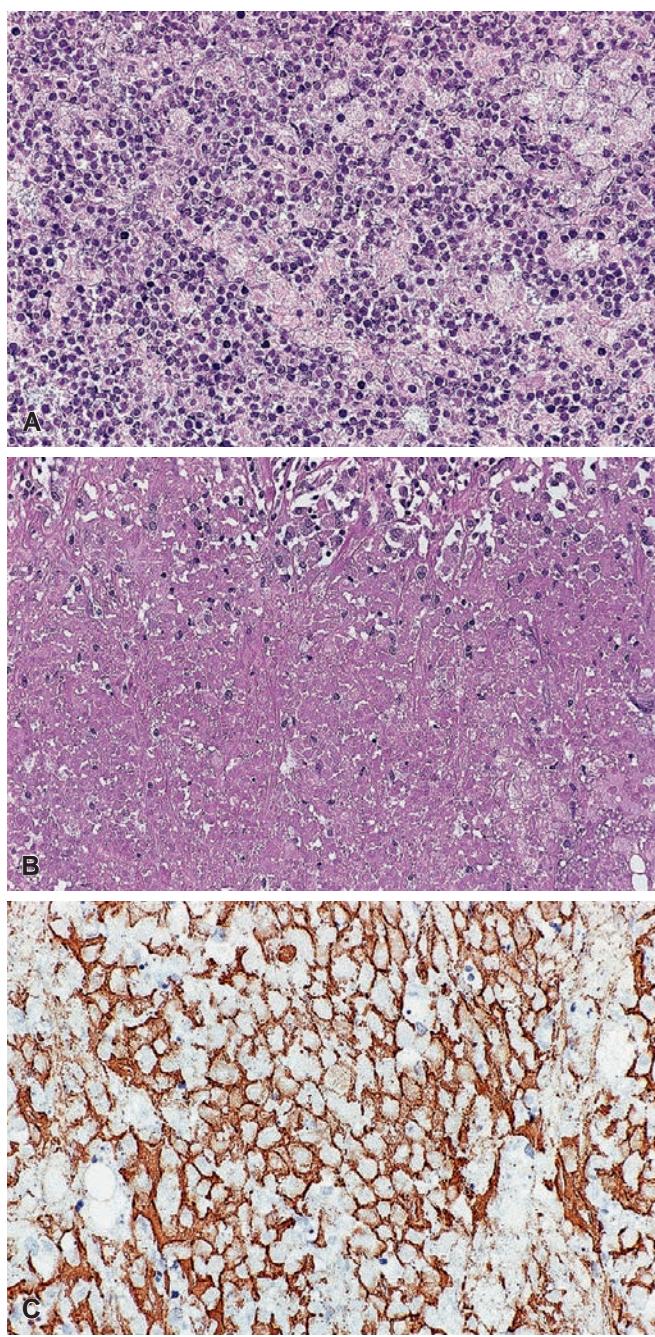


Figure 37.126 A–C, Large B-cell lymphoma that has undergone massive infarct-type necrosis. **A**, The outlines of the tumor cells can still be discerned. **B**, A totally necrotic area, indistinguishable from that of a “benign” infarct. **C**, There is a remarkable degree of retained immunoreactivity for CD20 in the necrotic area.

is also in order. Tumor cells reactivity for CD20 in the face of extensive necrotic changes is retained (see Fig. 37.126C).^{1167,1168} As a general rule, the possibility of an underlying malignancy should be suspected if the infarcted node is markedly enlarged.

Hyaline material sometimes accumulates in the stroma of lymph nodes. This finding is very frequent in those situated in the aorto-iliac region (Fig. 37.127). The material can undergo secondary calcification. Because of its homogeneous eosinophilic appearance, it can be confused with amyloid and has been referred to in the past as *para-amyloid*. It should also be distinguished from the hyaline material deposited in nodes in cases of hemorrhagic spindle cell tumor with amianthoid fibers. The presence of this hyaline material, which is probably an abnormal type of collagen, has no clinical significance.

Proteinaceous lymphadenopathy is the name given to a lymph node abnormality in which an eosinophilic extracellular material of proteinaceous nature is deposited in lymph nodes. This material simulates the appearance of amyloid but is histochemically and ultrastructurally distinct from it. The few patients who have been described with this obscure abnormality had hypergammaglobulinemia, and the hyaline material itself has been shown to contain precipitated immunoglobulin.¹¹⁶⁹

Foreign material of various types can accumulate in lymph nodes. One example is the *silicone lymphadenopathy* developing as a side effect of mammary augmentation produced by injection of liquid silicone or by placement of a bag-gel prosthesis. Microscopically, a nonbirefringent refractive material is present in the sinuses, together with variously sized vacuoles and multinucleated giant cells (Fig. 37.128).¹¹⁷⁰

Another example is the already mentioned sinus histiocytosis of pelvic lymph nodes, which is induced by the cobalt-chromium and titanium contained in hip prostheses (Fig. 37.129).¹¹⁷¹

Metastatic Tumors

Lymph nodes are the most common site of metastatic malignancy and sometimes constitute the first clinical manifestation of the disease.^{1172–1174} The task of the pathologist is to identify the presence of a malignant process in the node, to establish whether it is metastatic or not, and—if metastatic—to provide an estimate of its amount, microscopic type, and possible source. If malignant cells are identified within the efferent lymph vessels and/or extranodal adipose tissue, this should also be noted in the report because of the possible prognostic significance of these findings.

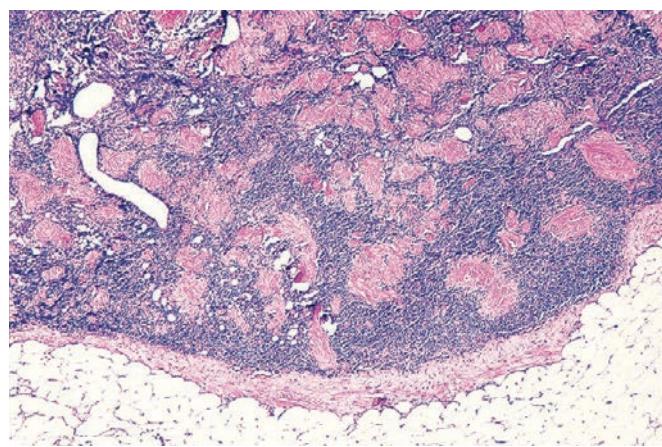


Figure 37.127 Hyaline Deposits in Pelvic Lymph Node. This change is of no clinical significance.

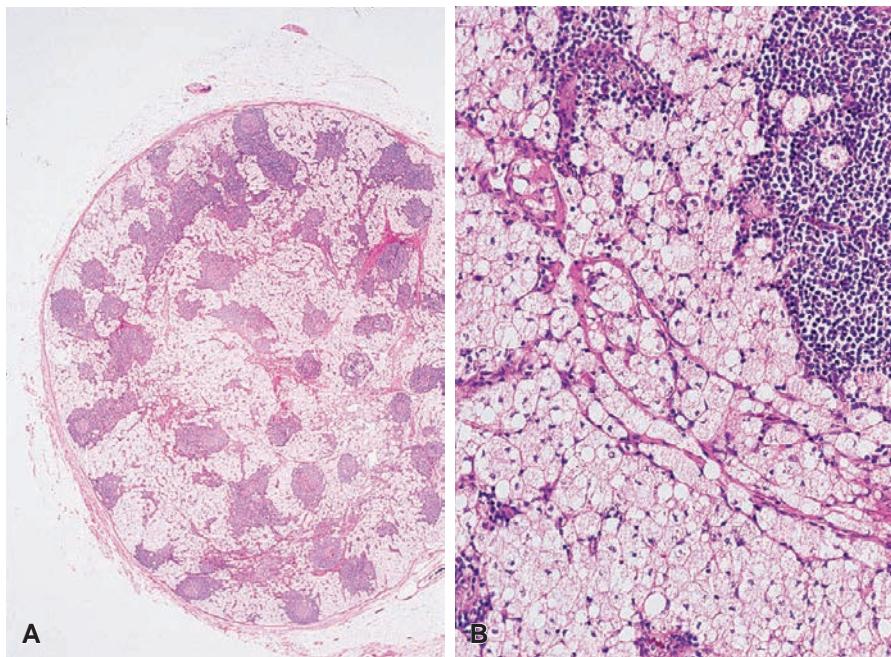


Figure 37.128 Low-power (A) and medium-power (B) appearances of silicone lymphadenitis. The sinuses are massively expanded by a histiocytic infiltrate, which simulates the appearance of Rosai–Dorfman disease.

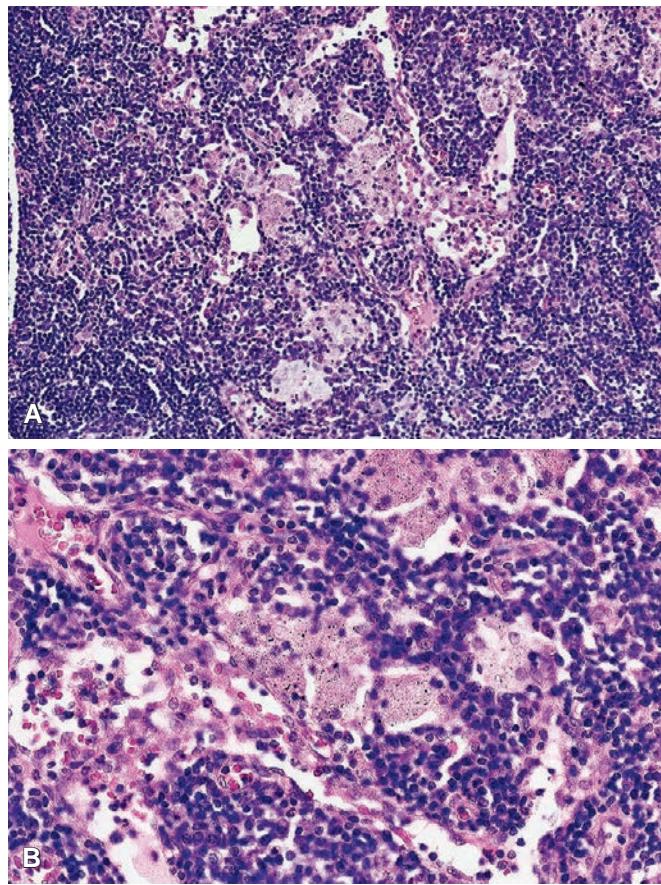


Figure 37.129 A and B, Lymph node changes in a patient who had a prosthesis implanted in the joint drained by this node. A fine particulate black material can be appreciated in the high-power view. It is easy to dismiss this material as “dirt.”

Any malignant tumor can give rise to lymph node metastases, but the incidence varies greatly depending on the tumor type. It is common with carcinomas, malignant melanomas, and germ cell tumors, and rare with sarcomas and central nervous system tumors. It should also be noted that large cell lymphomas primary in an organ (such as stomach or thyroid) sometimes involve the regional nodes in a pattern consistent with metastatic spread and the pattern of lymph node infiltration of ALCL may mimic a metastasis.

An additional diagnosis to consider in a lymph node involvement by metastatic tumor is that of malignant mesothelioma (Fig. 37.130). Examples of this tumor type presenting initially with lymphadenopathy in the cervical or inguinal region are reported; most of the primary tumors were located in the peritoneum rather than the pleura, regardless of the location of the nodes.¹¹⁵² The differential diagnosis includes reactive benign mesothelial cells in lymph nodes (see later) (Fig. 37.131).

It is very rare for soft tissue sarcomas to present initially as a lymph node metastasis. The outstanding exception is alveolar rhabdomyosarcoma (particularly the solid variant), which can be confused with malignant lymphoma not only on morphologic grounds but also because it may involve several lymph node groups (so-called “lymphadenopathic form”) (Fig. 37.132). Other sarcomas that have a greater than average tendency to metastasize to regional nodes are embryonal rhabdomyosarcoma, angiosarcoma, epithelioid sarcoma, and synovial sarcoma.

The differential diagnosis between metastatic undifferentiated carcinoma and diffuse large cell lymphoma in routine sections may be difficult or even impossible without ancillary studies in some cases. Features favoring lymphoma are presence of focal nodularity within the tumor not induced by fibrosis, and diffuse permeation of walls of veins (as opposed to tumor thrombi) and adipose tissue if an extranodal component is present. Features favoring metastatic tumor are focal nodal involvement, definite nesting, extensive necrosis, predominantly sinus distribution, and solid tumor plugs in lymphatic vessels. The types of malignant lymphoma most likely to be misdiagnosed as metastatic carcinoma are ALCL, large B-cell lymphoma

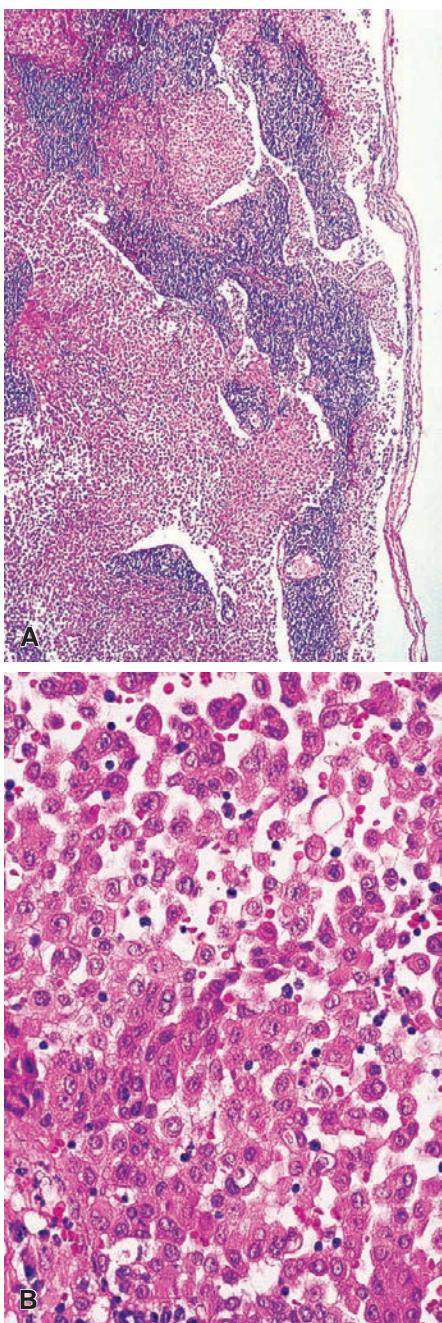


Figure 37.130 **A** and **B**, Lymph node involved by metastatic mesothelioma. The tumor massively expands the sinuses and is composed of cuboidal cells with a central nucleus and acidophilic cytoplasm. The primary tumor was located in the peritoneal cavity.

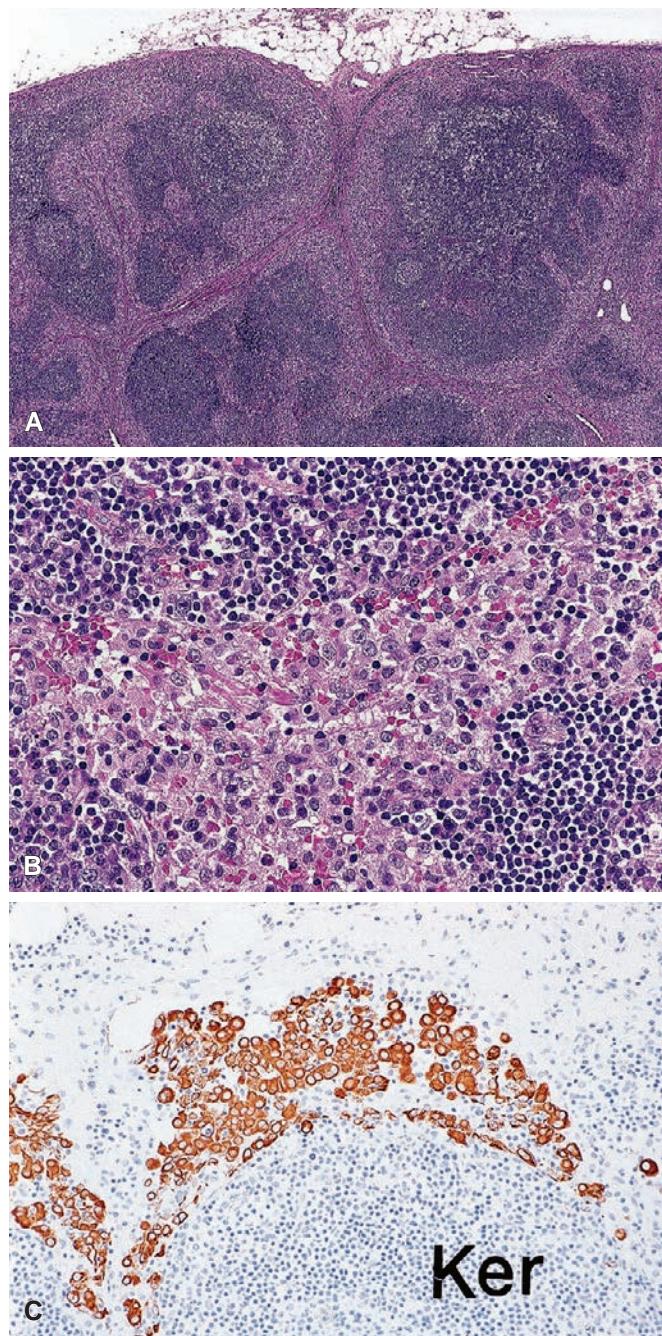


Figure 37.131 Hyperplastic Mesothelial Cells in Lymph Node. **A**, Sinusal distribution. **B**, Bland cytologic appearance. **C**, Strong immunoreactivity for keratin. *Ker*, Keratin.

with sclerosis resulting in prominent nesting, large B-cell lymphoma with a predominantly sinus pattern of growth, nodular sclerosis Hodgkin lymphoma with concentration of large mononuclear variants of Reed-Sternberg cells around areas of necrosis, and signet ring cell lymphoma. Yet another type is the composite lymphoma made up of follicular small cleaved and diffuse large cell components, the double error consisting in diagnosing the latter component as metastatic carcinoma and the former as follicular hyperplasia.

The metastatic carcinomas that most closely simulate a malignant lymphoid process are nasopharyngeal lymphoepithelial carcinoma

and lobular carcinoma of the breast (Figs. 37.133 and 37.134). The first may masquerade clinically and pathologically as Hodgkin lymphoma because of its common presentation in a young adult with painless unilateral cervical lymphadenopathy, EBV positivity, and the presence of a polymorphic population (including eosinophils) on microscopic examination.¹¹⁷⁵ The second may be confused with malignant lymphomas of one type or another, including signet ring lymphoma (Fig. 37.135), or the carcinoma cells may be mistaken for histiocytes. Metastatic small cell neuroendocrine carcinoma from the lung or other sites can be difficult to distinguish from lymphoma;

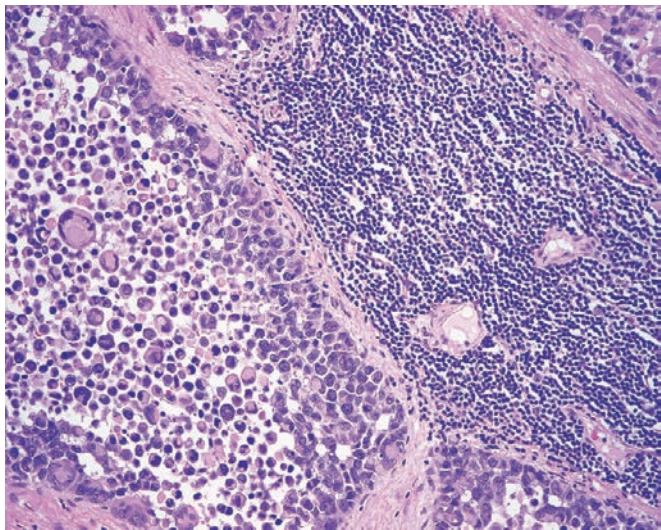


Figure 37.132 Alveolar Rhabdomyosarcoma Metastatic to a Lymph Node. This is a relatively common occurrence in this tumor type, and it may be the first clinical manifestation of the disease.

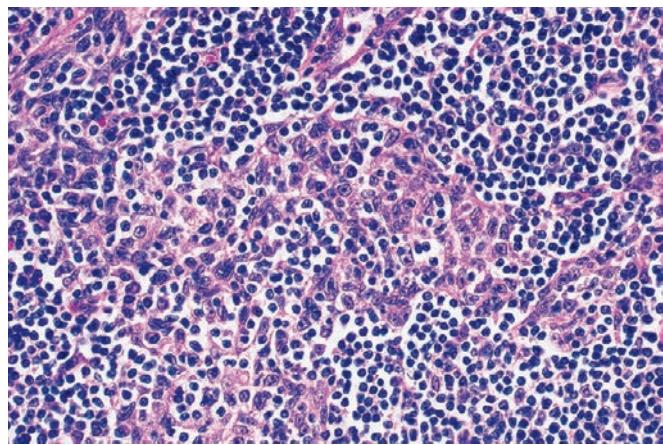


Figure 37.133 Lymph Node Involved by Metastatic Lymphoepithelioma From the Nasopharynx. The relatively diffuse pattern of the proliferation may result in a mistaken diagnosis of malignant lymphoma.

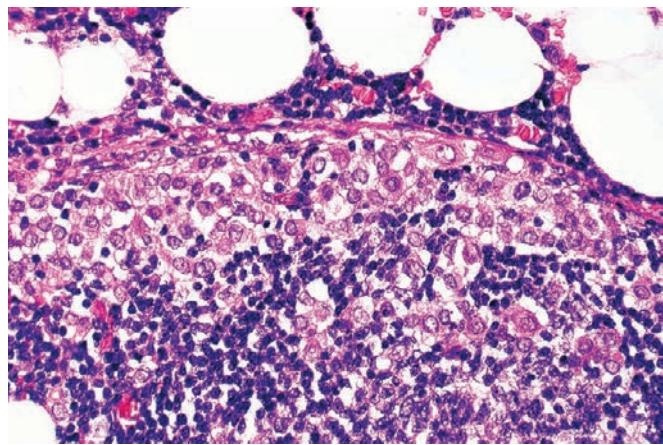


Figure 37.134 Breast Carcinoma of Lobular Type Metastatic to the Sinuses of a Lymph Node. The cytologic appearance may be confused with that of a malignant lymphoma or a benign histiocytic proliferation.

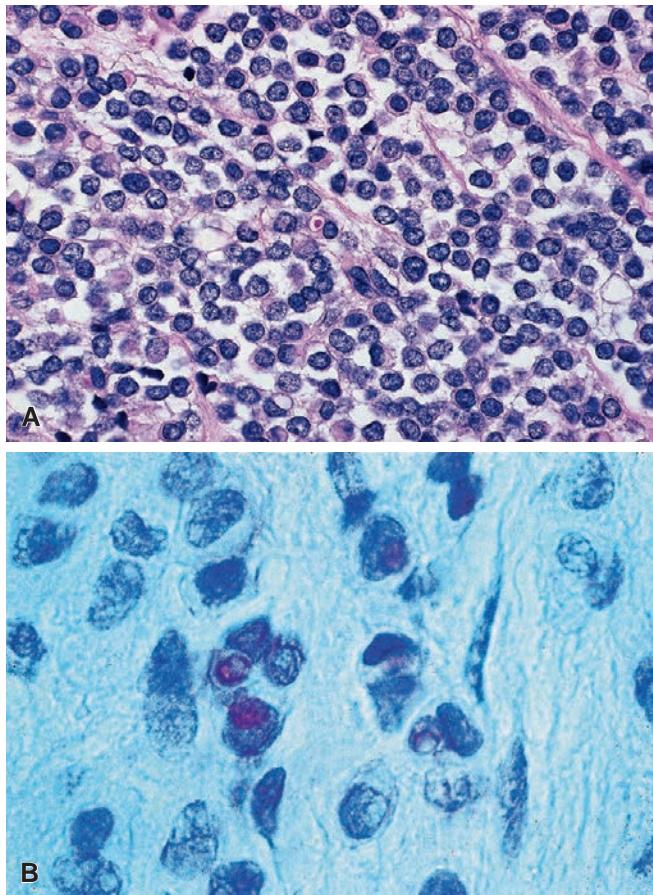


Figure 37.135 Poorly Differentiated Adenocarcinoma With Signet Ring Features Initially Misinterpreted as a Malignant Lymphoma. The mistake may have been partially induced by the fact that the tumor developed in a renal transplant recipient. **A**, Hematoxylin–eosin. **B**, Mucicarmine stain, showing a few droplets of intracytoplasmic mucin.

dense nuclear chromatin pattern, nuclear molding, focal areas of necrosis, and hematoxyphilic staining of vessel walls favor a diagnosis of small cell carcinoma. Somewhat similar considerations pertain to the diagnosis of metastatic Merkel cell carcinoma. Metastatic melanoma can closely simulate on cytologic grounds the appearance of large cell lymphoma and plasmacytoma. The balloon cell variety can closely mimic RDD (Fig. 37.136). One should also not forget that metastases can develop in a node already involved by lymphoma or leukemia.

Nodal metastases of squamous cell carcinoma have a particular tendency to undergo cystic changes. When these are prominent in a node located in the neck, a mistaken diagnosis of branchial cleft cyst may ensue (Figs. 37.137 and 37.138).

The location of a node involved by metastatic carcinoma gives important clues about the possible site of the primary. The large majority of tumors metastatic to *upper cervical* lymph nodes originate from the upper aerodigestive tract. Sites well known for harboring small, clinically undetectable primaries in the presence of cervical adenopathy are the nasopharynx and retrotonsillar pillar.^{1176–1178} *Midcervical* nodes containing papillary carcinoma are usually examples of metastatic thyroid carcinoma, a possibility that becomes a virtual certainty in the presence of psammoma bodies. However, these papillary tumors may also originate from salivary gland, female genital tract, or thymus (see respective chapters). Squamous cell

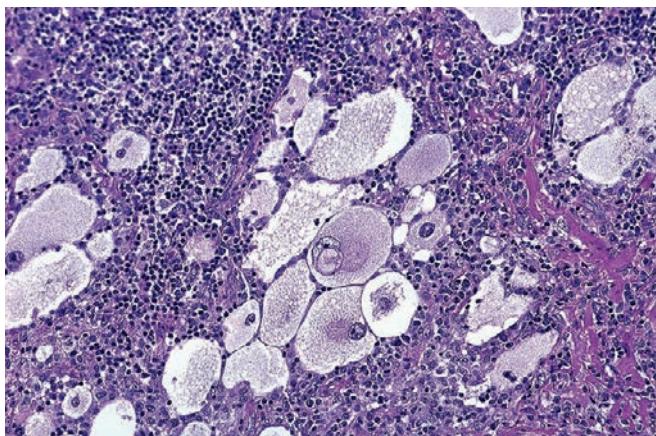
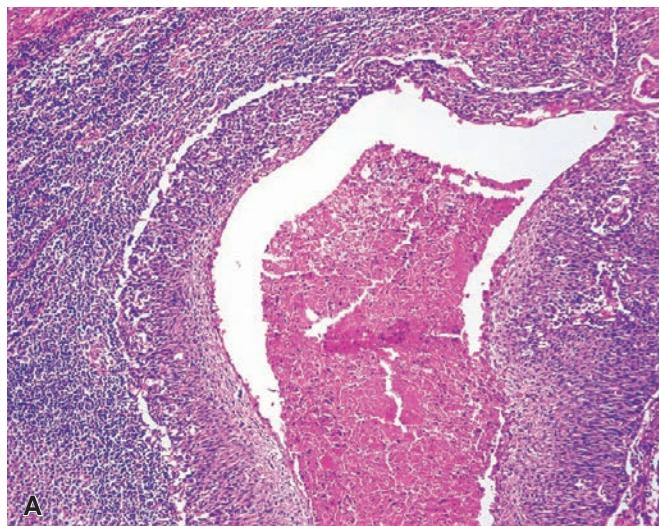


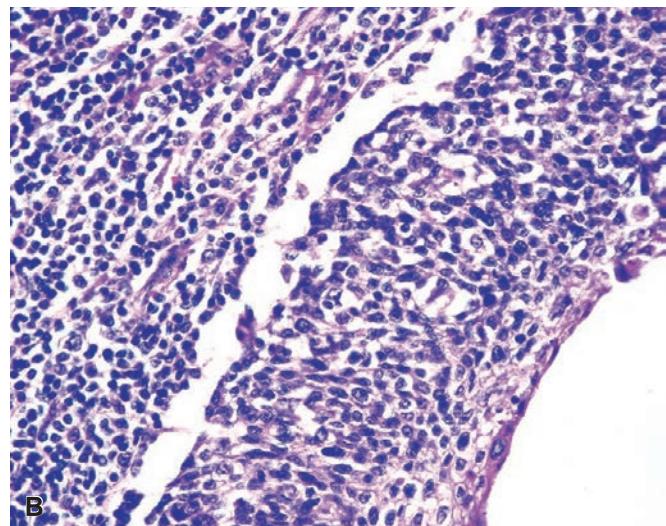
Figure 37.136 Balloon cell melanoma metastatic to a lymph node and simulating a histiocytic disorder.



Figure 37.137 Squamous Cell Carcinoma Metastatic to Lymph Node. The tumor has undergone partial cystic transformation.



A



B

Figure 37.138 Squamous Cell Carcinoma Metastatic to Cervical Lymph Node. **A**, Medium-power view, showing marked cystic change that may result in a mistaken diagnosis of branchial cleft cyst. **B**, High-power view showing malignant cytologic features involving the entire thickness of the epithelial strip.

carcinomas in lymph nodes of this region usually arise in the upper aerodigestive tract, particularly pharynx and larynx.¹¹⁷⁹ Most carcinomas metastatic to *supraclavicular* lymph nodes originate in the lung or breast. Other sources of metastases to this nodal group, particularly if located on the left side, are carcinoma of stomach, pancreas, prostate, and testis.^{1177,1180} These reach the node through the terminal collecting lymphatic trunks. Supraclavicular nodes involved by intra-abdominal carcinomas are sometimes referred to as Virchow or Troisier nodes.¹¹⁸¹ The large majority of metastatic tumors in *axillary* nodes of adult females are breast carcinoma and malignant melanoma.^{1182,1183} Lung carcinoma should also be considered, especially in older patients with a smoking history.¹¹⁸⁴ *Inguinal* nodes are often the recipients of carcinomas from the external genital organs (usually evident on clinical examination) or malignant melanomas of the lower extremities, but only rarely from the internal abdominal organs (ovary, uterine cervix, anal canal) and even less commonly from the testis, unless direct extension to the scrotal skin has occurred.¹¹⁸⁵

The immunohistochemical approach to an obviously malignant tumor involving a lymph node is CD45, keratin, and S100 protein, as markers for lymphoid, epithelial, and melanocytic cells, respectively. A second line of reagents could include EMA, CEA, CD20, CD3, CD30, and—depending on the circumstances—GCDFP-15 and lactalbumin (for breast), chromogranin (for endocrine tumors), PSA/PAP (for prostate), and keratin subsets. The specific immunoprofiles of various tumor types are discussed in more detail in other chapters. When properly applied and interpreted, the performance of these studies should solve all but a very small minority of cases.

It is just as important to mention some of the benign conditions of lymph nodes that can mistakenly be interpreted as metastatic carcinoma. They include hyperplastic mesothelial cells,¹¹⁴⁹ megakaryocytes,¹¹⁸⁶ signet ring sinus histiocytosis,¹¹⁸⁷ the related nodal muciphages and mucicarmophilic histiocytes,^{1188,1189} florid anthracosis/anthracosilicosis,¹¹³⁶ and the various lymph node epithelial inclusions listed above, without forgetting the banal germinal centers of hyperplastic follicles cut tangentially.

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