distinctly uncommon. The white blood cell count is usually within the normal range, but approximately 30% of patients will have leukocytosis or leukopenia during the course of this infection. Another laboratory abnormality is a transient increase in the serum alkaline phosphatase level. Pulmonary function studies, performed in only a few patients, have demonstrated reversible restrictive defects, impaired diffusing capacity of lung for carbon monoxide (DL_{CO}), and obstructive defects.[47]

Pericarditis

At least 6% of patients who acquire histoplasmosis develop acute pericarditis.[48] This figure may underestimate the true incidence because only those most seriously affected seek medical attention. Precordial chest pain and fever are frequent. A high proportion of patients report a respiratory illness approximately 6 weeks before the onset of the pericarditis. A pericardial friction rub is auscultated in more than 75% of patients with pericarditis, and pulsus paradoxus is also present in more than 75%. An enlarged cardiac silhouette is usually seen on chest radiographs. Electrocardiographic abnormalities indicative of pericarditis—for example, ST segment elevation—are often observed. Only a small percentage of individuals develop cardiac tamponade. The likely cause of the pericarditis is not direct invasion of the organism because it is rarely found in tissue specimens or in pericardial fluid, but rather the granulomatous inflammatory response that is mounted in mediastinal lymph nodes adjacent to the pericardium.

Differential Diagnosis

Acute pulmonary histoplasmosis must be distinguished from influenza and other forms of community-acquired pneumonia.[49] This task is difficult unless a thorough exposure history is obtained. Of greater concern, however, are patients who present with mediastinal lymphadenopathy. This finding is often considered to be caused by a hematologic malignancy rather than histoplasmosis. In such cases, patients may undergo unnecessary surgical procedures in an attempt to establish a diagnosis. Sarcoidosis also should be considered, and distinguishing between these conditions can be difficult. Both may have similar histopathologic features, and serum angiotensin-converting enzyme levels are elevated in each disease.[50] Thus, in all patients who present with mediastinal or hilar lymphadenopathy, it is critically important that histoplasmosis be considered in the differential diagnosis in patients who reside or have recently been in an endemic region.

A Ghon complex and pulmonary calcifications are common in healed pulmonary histoplasmosis. Another characteristic feature of resolved primary infection is the presence of splenic or liver calcifications. In fact, the presence of these on a routine radiograph should be considered evidence of resolved histoplasmosis if the patient has been in an endemic area. Although splenic and liver calcifications are also noted in healed tuberculosis, the most likely cause of these findings remains histoplasmosis because the incidence of tuberculosis in the United States is much lower than that of histoplasmosis. Positron-emission tomography studies performed to diagnose malignant pulmonary nodules are reported to be falsely positive in healed histoplasmosis lesions, especially if there is active inflammation. One assessment that distinguishes cancer from histoplasmosis is that in the latter, the fluorodeoxyglucose signal intensity is often higher in lymph nodes than in the lung lesion[51]

Acute Reinfection

It is not uncommon for those who reside in endemic areas to be exposed more than once to *H. capsulatum*. Those who are reexposed to a large inoculum in heavily endemic areas present with a milder influenza-like illness. The onset can begin within 3 days, which is shorter than in primary infection. The characteristic chest radiograph is one of numerous small nodules that are diffusely scattered throughout both lung fields. This feature has been referred to as *miliary granulomatosis*. Hilar or mediastinal lymphadenopathy is absent. The duration of illness is often briefer than in primary infection.[43,44,52]

Complications of Primary Histoplasmosis

Histoplasmoma

An infrequent complication of primary histoplasmosis is the development of a mass lesion that resembles a fibroma.[53] When it arises, it is found most often in the lung. Instead of resolving, a nidus of infection gradually enlarges over years to form a concentric mass. Presumably, the growth is caused by persistent antigenic stimulus from the yeasts. It is composed of active inflammation at the periphery and fibrous tissue within the inner sphere, and eventually the central portion calcifies. Radiographically, the histoplasmoma may have a central core of calcium or rings of calcium, and these findings are useful in distinguishing it from a neoplastic growth.

Mediastinal Granuloma and Fibrosis

Another complication of primary infection is a massive enlargement of the mediastinal lymph nodes that is caused by the granulomatous inflammation mounted in response to the fungus.[54] The diameter of these nodes can reach 8 to 10 cm. The nodes are caseous and contain a fibrotic shell that may be up to 5 mm thick. Often, this process is asymptomatic. Occasionally, however, the nodes may impinge on major airways and impair gas exchange. During the healing process, the fibrotic tissue can cause retraction of the airways, leading to postobstructive pneumonias, hypoxemia, and bronchiectasis. The fibrosis also may constrict the esophagus or the superior vena cava, resulting in dysphagia, superior vena cava syndrome, or both.[53,54]

Calcific deposits that originate within the lungs occasionally produce lithoptysis. More common, however, is the penetration of enlarged, calcified nodes into the airways and the generation of particles of calcium that can be expectorated. If the calcified mass is large, airway obstruction may ensue. Another consequence of enlarged nodes is the creation of sinuses or fistulas between the airways and pericardium or esophagus.[53]

A rare but dire consequence of mediastinal involvement is mediastinal fibrosis.[55] This syndrome is similar to that observed with tuberculosis, in which the infection leads to a massive deposition of fibrotic tissue within the mediastinum (Fig. 263.6). The mechanism underlying this exuberant immune response is unknown. However, it appears not to be triggered by massive numbers of yeast because they are observed infrequently in lesions. The reaction to the antigen or antigens from *H. capsulatum* must be host specific, based on its infrequent development. Genetic susceptibility loci for this entity have not been identified. The fibrosis encroaches on all the structures of the mediastinum, including the major airways, superior vena cava, and esophagus. The symptoms that arise from the fibrotic process are attributable to the narrowing of the patency of these structures. Hypoxemia, shortness of breath, superior vena cava syndrome, and dysphagia may ensue as the fibrotic process progresses.

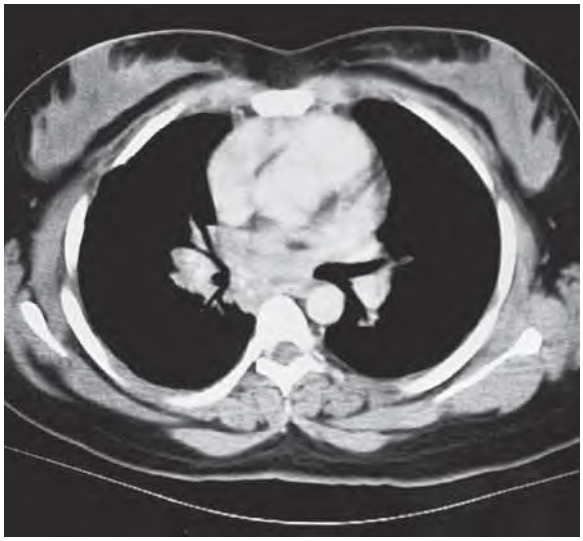

FIG. 263.6 Computed tomography scan of the mediastinum in a patient with mediastinal fibrosis.

CHRONIC PULMONARY HISTOPLASMOSIS

Cavitary pulmonary histoplasmosis and chronic pulmonary histoplasmosis have been considered for many years to be synonymous terms. However, one review called for reconsideration of this usage. Although the precise incidence was not known because of the sporadic nature of the disease, approximately 8% of individuals developed fibrocavitary disease following two large epidemics in Indianapolis.[56] Cavitary lesions were found in the upper lobes in more than 90% of cases (Fig. 263.7). Men older than 50 years with preexisting chronic lung disease, usually emphysema, were reported to constitute the highest proportion of patients, and it was quite unusual in those younger than age 40 (<5% of all cases).[56,57] However, a recent review has called this association into question. Among a group of patients with pulmonary symptoms that extended for at least 6 weeks, nearly 50% were women and 20% had chronic obstructive pulmonary disease (COPD). Cavities were detected in less than 40%.[58] The causes for the changing face of this illness are not clearly defined, but the decrease in tobacco use is certainly a contributing factor. It also suggests that there are at least two forms of chronically active lung disease, cavitary and noncavitary.

Symptoms

In the classic form of cavitary disease, the most frequent symptoms are low-grade fever, productive cough, dyspnea, and weight loss of insidious onset. Night sweats, chest pain, hemoptysis, and malaise are less common. Hemoptysis is rare. Completely asymptomatic intervals with radiologic stability are interspersed with periods of recurrent symptoms and radiologic progression. Both an early and a late stage have been described. The major difference between the two forms is the symptoms. In the early stage, the illness, characterized by chest pain, productive cough, fever, and weakness, begins abruptly and persists for several weeks before medical attention is sought. In the late stage, the proportion of patients experiencing productive cough and hemoptysis is much higher, whereas chest pain and fever are much less frequent. Bronchogenic transmission from one segment of the lung to another may occur during cough or aspiration.[57]

Laboratory Findings

Radiographically, patchy infiltrates appear and develop areas of dense consolidation that progress to cavitation. Over months or years, extensive fibrosis, retraction, and areas of compensatory emphysema appear unless effective treatment is given. The most common location is the upper lobes. Almost all patients have a history of heavy cigarette use or exhibit evidence of emphysema coexisting with COPD, and therefore the cavities must be distinguished from preexisting bullae. Thin-walled or thick-walled cavities may form in response to *H. capsulatum.* Enlarged hilar or mediastinal lymph nodes are notably absent, and distinctive laboratory features are not present. Leukocytosis and elevated alkaline phosphatase levels are detected in about one-third of symptomatic patients, and anemia is present in half.[56,57]

FIG. 263.7 Chest radiograph of a patient with cavitary histoplasmosis.

Pathology

The earliest lesion that appears at histopathologic assessment is an interstitial pneumonitis. The inflammatory infiltrate is composed primarily of lymphocytes and macrophages and is often found adjacent to bullae. The alveolar walls are thickened, and the peribronchial lymphatics contain a similar type of inflammatory infiltrate. Subsequently, necrosis develops, and it resembles that caused by infarction. Vascular compromise, as denoted by subintimal thickening and vessel obliteration, is present in inflamed regions. Proteinaceous exudate can be found in bullae, and yeasts are present in the necrotic lining of a cavity or in small encapsulated necrotic lesions. Areas of infarction are slowly replaced by scarring of the involved parenchyma. The healing phase is characterized by fibrosis and retraction, some leaving central areas of caseous necrosis surrounded by epithelioid cells, lymphocytes, and giant cells. Neighboring bullae may enlarge from compensatory emphysema. After healing, recurrence of cavitary lesions will develop in approximately 20% of patients, but the prognosis of recurrence is no different from that of the initial infection.[57]

Spontaneous resolution of thin-walled and thick-walled cavities ranges from 10% to 60%, and thin-walled cavities have a higher healing rate. Despite shrinking and fibrosis of individual lesions, new lesions continue to appear and radiologic progression occurs in an estimated 79%. In individuals with COPD, cavitary histoplasmosis can exacerbate the existing pulmonary dysfunction, and the destructive nature of the inflammation irreversibly compromises pulmonary function. Death caused by cavitary histoplasmosis is distinctly unusual but is attributable to respiratory failure, cor pulmonale, or secondary bacterial pneumonia.

The association between the presence of COPD and chronic cavitary histoplasmosis suggests that the anatomic defect present in these lungs predisposes patients to this clinical form of infection and promotes the formation of cavities. This intriguing postulate has been proposed and is most likely correct, although no experimental data exist to support it.[57] The difficulty in testing this hypothesis is that a suitable animal model has not been developed. In addition, it does not explain the development of cavities in other patients. At present, *H. capsulatum* is not known to elaborate any elastinolytic or proteolytic enzymes that digest collagen.

Noncavitary Chronic Pulmonary Disease

The most common symptoms of those with the redefined chronic pulmonary histoplasmosis who did not necessarily have cavitary lesions are cough, weight loss, and fever and chills. Radiographic changes commonly include nodules, infiltrates, and lymphadenopathy. Less common are fibrosis, thickened pleura, and volume loss. Arthralgias, dyspnea, fatigue, and chest pain are observed in less than 50% of patients. The most striking difference is that in those without cavities, positive cultures are highly unusual. Most patients in a series were treated with antifungal therapy, and infection resolved in 70% of those. Of the remaining patients who received therapy, 10% manifested a protracted illness, 15% had a recurrence, and in 5% the infection did not resolve. Among the group that did not receive antifungal therapy (13 of 46), 2 manifested progressive infection and 1 did not clear the infiltrate.[58]

PROGRESSIVE DISSEMINATED HISTOPLASMOSIS

Incidence

Although all primary infections can be considered disseminated because yeast cells migrate from the lungs to organs rich in mononuclear phagocytes, the term *progressive disseminated histoplasmosis* refers to the relentless growth of the organism in multiple organ systems. The estimated incidence is 1 in 2000 cases of histoplasmosis. After the two Indianapolis epidemics, 8% of clinically recognized cases of histoplasmosis were PDH.[59] The major risk factors in those two epidemics for this manifestation of histoplasmosis were age older than 54 years and immunosuppression. In the pre–antiretroviral therapy era, the incidence approached 25% in AIDS patients from endemic regions. The outcome

of infection with *H. capsulatum* was poor among HIV-infected individuals, including the presence of a chronic medical condition and a history of herpes simplex virus infection. Conversely, the use of antiretrovirals and triazoles was associated with a decreased risk. In an analysis of 1074 renal allograft recipients, 0.4% developed clinically recognized PDH over a 25-year span.[60] This value is moderately different from the one reported during the Indianapolis epidemic, in which 2.1% of renal allograft recipients exhibited PDH.[61] Others have reported an incidence of 0.1%. Another risk factor for acquiring PDH is the use of TNF-α antagonists.[34] Disseminated histoplasmosis in hematopoietic stem cell transplant recipients appears to be infrequent. This finding seems unusual given the severity of immunosuppression but may support the concept that many cases of disseminated disease are reinfections.

Reactivation Versus New Exposure

The exposure leading to PDH is inapparent, without an antecedent episode of acute pulmonary histoplasmosis. PDH can develop by reexposure to the fungus or by reactivation of dormant endogenous foci. The precise distribution of cases that arise from endogenous reactivation is unknown. In endemic areas, it is impossible to distinguish reactivation versus reinfection. Autopsy studies in the 1950s revealed that the fungus could be detected in lymph nodes by means of silver stain, yet the tissues were sterile. This finding certainly suggests that reinfection is more important in endemic areas. Reactivation of latent infection can develop from transplanted organs.[62] In one such case, kidney transplantation from one donor was associated with infection in recipients who were not residents of an endemic area. These types of cases are difficult to discern in endemic areas. Most cases of PDH are now observed in immunosuppressed individuals.[59,63] However, there still exist cases in previously normal individuals, often at the extremes of age, who were not known to exhibit preexisting immunologic dysfunction. The perturbations that cause a breach in the integrity of the immune system and therefore lead to reactivation of quiescent infected foci have not been delineated.

Pathology

Although infection with *H. capsulatum* produces a broad range of disease, PDH also can be categorized according to clinical and pathologic manifestations. There is an acute form associated with a fulminant course. Histopathologically, massive macrophage infiltration and scattered lymphocytes are apparent. Tissue macrophages are engorged with yeast cells, and tests of cellular immunity often reveal poor to absent responses. At the other extreme is the chronic form, characterized by an indolent course and the presence of well-circumscribed granulomas in involved tissues. In tissues, few numbers of yeast are seen, and delayed-type hypersensitivity responses are intact in a high proportion of individuals.

Acute Progressive Disseminated Histoplasmosis

In the era before aggressive immunosuppressive or cytotoxic therapy, this entity was principally seen in infants—hence its moniker, the infantile form. To date, however, it is most often observed in those who are severely immunosuppressed, especially those with AIDS and hematologic malignancies such as Hodgkin and non-Hodgkin lymphoma. When it occurs in infants and young children, it is believed that this form of histoplasmosis is a progression of a primary exposure or reinfection because pulmonary symptoms dominate the early phases of illness. The onset is usually abrupt, extending over just a few days. Fever and malaise are the two most common manifestations, followed by weight loss, cough, and diarrhea. Physical findings include hepatosplenomegaly in almost all patients, lymphadenopathy, especially of the cervical chain, in about 30%, and crackles. Jaundice is observed in a minority, and oropharyngeal ulcers develop in less than 20%.[63]

Laboratory Abnormalities

Hematologic disturbances are frequent. Anemia is present in more than 90% of cases, and most have a hematocrit lower than 20%. Leukopenia and thrombocytopenia are observed in more than 80% of children. Serum levels of the liver enzymes alanine aminotransferase and alkaline phosphatase are elevated in a high proportion. Chest radiographs most often reveal a patchy pneumonitis with mediastinal and hilar node enlargement. This finding supports the contention that acute PDH in children represents an extension of an exogenous exposure. Untreated, the mortality is 100%; before the introduction of effective antifungal agents, most children died within 5 to 6 weeks after onset of symptoms. Terminal events include disseminated intravascular coagulation; gastrointestinal hemorrhage, probably resulting from severe thrombocytopenia; and secondary bacterial sepsis associated with profound granulocytopenia.

Progressive Disseminated Histoplasmosis and HIV

In HIV-infected individuals, the risk factors for the development of histoplasmosis are a $CD4^+$ cell count lower than 200 cells/mL, history of exposure to chicken coops, and a known positive serologic finding of complement-fixing (CF) antibodies before illness.[64] In the era of antiretroviral therapy, the incidence of disease in HIV-infected individuals has dropped substantially. Most AIDS patients who develop PDH have had at least one opportunistic infection. On seeking medical attention, almost all patients manifest evidence of a systemic illness. Fever and weight loss are found in more than 90% of those with AIDS and PDH. The most common physical findings include rales, hepatosplenomegaly, and lymphadenopathy. Mucosal ulcers are distinctly uncommon, but as many as 10% of patients will exhibit cutaneous lesions.[65] The common cutaneous findings are a maculopapular eruption, petechiae, or ecchymosis. The maculopapular rash does not display any unique pattern of distribution. The finding of skin lesions is much more common in those infected with the South American strains of *H. capsulatum.* In a small study, up to 66% of South American AIDS patients with disseminated histoplasmosis manifested skin lesions. The most common appearance is a papular eruption with crusting. Less frequent are nodular or purely pustular lesions. Histopathologic evaluation of skin lesions reveals necrosis circumscribing the superficial dermal vessels. There is perivascular cuffing with lymphocytes and neutrophils, but the number of cells is few. Yeasts are present both intracellularly and extracellularly. In addition to the skin findings, a number of other unusual manifestations have been reported, including colonic masses, perianal ulcers, chorioretinitis, meningitis, and encephalitis. It is estimated from results of one series that up to 20% of patients with PDH will have central nervous system (CNS) involvement.[66] The more aggressive forms include encephalitis, acute meningitis, and encephalopathy in acute PDH. Histoplasmoma of the CNS and chronic meningitis are manifestations of a more indolent form of PDH.

Laboratory Abnormalities in Coinfection

Anemia, thrombocytopenia, and leukopenia are common laboratory features of PDH in the immunosuppressed population. In AIDS patients, the alteration in the peripheral blood counts may be attributable in part to the disease or to the drugs that they are receiving. Elevated serum levels of hepatic enzymes are frequently detected. Again, concomitant drugs may obscure the laboratory abnormalities caused strictly by *H. capsulatum.* Chest radiographs typically demonstrate widely scattered nodular opacities or a diffuse reticular pattern (Fig. 263.8). However, a substantial percentage of patients (30%) may present with a normal radiograph.[67]

The fatality rate of acute PDH in the immunocompromised patient is 100% if untreated. With therapy, survival rates of the acute episode exceed 80%. Infrequently, patients exhibit a sepsis-like syndrome characterized by disseminated intravascular coagulation, encephalopathy, acute respiratory distress syndrome, vascular collapse, and, subsequently, multiorgan failure. In some patients, bone marrow biopsy has demonstrated the presence of histiocytes phagocytosing erythrocytes. This form of PDH has been termed the *reactive hemophagocytic syndrome* and, despite aggressive management and therapy, the outcome is usually catastrophic.

Subacute Progressive Disseminated Histoplasmosis

Subacute PDH is distinguished from the acute form primarily by the more prolonged nature of the symptoms before the patient seeks medical attention. Fever and weight loss are common at some time during the

FIG. 263.8 **Diffuse infiltrates in patients with progressive disseminated histoplasmosis and acquired immunodeficiency syndrome.**

FIG. 263.9 **Tongue ulcer in a patient with chronic disseminated histoplasmosis.**

course of infection, but fever is a presenting complaint in only about 50%. Physical findings include hepatosplenomegaly and oropharyngeal ulcers. In contrast to the ulcers observed in acute PDH, these are deeper and more likely to be confused with malignancy. Laboratory abnormalities are much less striking than in acute PDH. Although anemia and leukopenia are noted in up to 40%, the percentage of patients with severe depression of the hematocrit or leukocyte count is low. Thrombocytopenia is evident in about 20% and is usually mild. Rarely is the platelet count lower than 20,000/μL.[63]

Clinical Features

One of the notable features of subacute PDH is the presence of focal lesions in various organ systems, including the gastrointestinal tract, endovascular structures, CNS, and adrenal glands.[63,68] Aside from the liver and spleen, the gastrointestinal tract is one of the most common organs affected in subacute PDH. Yeast cells can be found in the bowel mucosa in up to 70% of autopsy cases. Macroscopic ulcerations of the small and large bowel are present in about 40%, and perforation from a penetrating ulcer has been reported. The terminal ileum and cecum are the sites most frequently involved. Symptoms referable to the bowel are not frequent, but if present, diarrhea and crampy abdominal pain are typical complaints. Intestinal obstruction of the ileum has also been reported.

Endovascular Infection

Endocarditis and infection of other vascular structures may be a manifestation of subacute PDH.[69] The aortic and mitral valves are affected more commonly than right-sided valves, and the aortic valve is the single most common valve involved. In about 50% of cases, there is prior evidence of valvular disease, such as a bicuspid aortic valve. Echocardiography shows that the lesions tend to be extensive, and large-vessel embolization can be the presenting symptom. Clumps of yeasts embedded in a fibrin mesh are the characteristic histopathologic feature. Occasionally, allomorphs as large as 20 μm in diameter have been observed. In addition, hyphal forms of *H. capsulatum* have been detected in valvular lesions. If untreated, death usually ensues. Other endovascular manifestations include prosthetic valve endocarditis, infection of abdominal aortic aneurysms, and prosthetic vascular grafts. Previous reports have indicated that blood cultures are rarely positive. However, those reports preceded improved methods for isolating *H. capsulatum* from blood.

Central Nervous System Involvement

CNS infection involves all age groups and causes a number of manifestations, including chronic meningitis, mass lesion, and cerebritis. Among these, chronic meningitis is the most frequent.[66] Symptoms of CNS histoplasmosis may antedate medical attention for several weeks, and they include headache, altered sensorium, and cranial nerve deficits. Seizures, ataxia, meningismus, and other focal deficits constitute much of the remaining symptoms. It must be emphasized that only half of patients may complain of symptoms localized to the CNS. Associated physical findings consist of hepatosplenomegaly in about one-third, lymphadenopathy, and mucocutaneous lesions.

Pleocytosis of the cerebrospinal fluid (CSF) is present in all patients. Cell counts usually range from 10 to 100/μL with a preponderance of lymphocytes. Hypoglycorrhachia and elevated protein levels are detected in 80%. Histopathology of the brain parenchyma and meninges characteristically reveals granulomatous inflammation. A perivenous granulomatosis in which parasitized macrophages are observed beneath the intima of parenchymal and meningeal veins is commonly seen. The basilar meninges are the most severely affected area of the CNS. Hydrocephalus may contribute to the symptoms.

An intracerebral granulomatous mass, or histoplasmoma, causes a mass effect and may be mistaken for a malignancy or abscess on computed tomography (CT) images because it exhibits ring enhancement with the administration of contrast. Dense fibrotic tissue surrounds a caseous center in which yeasts are detected. Histoplasmomas may be associated with meningitis but often are independently present. CSF pleocytosis is common, but hypoglycorrhachia is not.

Although symptoms arising from involvement of adrenal glands are not frequent, autopsy series indicate that yeasts invade this organ system in approximately 80% of cases.[70] Macrophages containing yeasts are found scattered throughout the parenchyma of the adrenal gland. There is no particular predilection for the cortex or the medulla. The severity of infection ranges from focal areas containing parasitized macrophages to diffuse involvement of the adrenal parenchyma. The former is most commonly detected. Tissue necrosis is seen but usually involves only a small portion of the gland. Grossly, the adrenal glands are enlarged. This postmortem discovery has been supported by findings on CT in which a high percentage of patients with subacute PDH display enlarged adrenals. Overt Addison disease is uncommon, occurring in less than 10%.

Chronic Progressive Disseminated Histoplasmosis

Clinical Findings

Chronic PDH can be distinguished from subacute PDH by the prolonged chronicity of symptoms that are often mild. This form is seen almost exclusively in previously normal adults. Malaise and lethargy stand out as the most frequent complaints. Fever is much less frequent (<30%) and is often low grade. The most common physical finding (50%) is an oropharyngeal ulcer that is well circumscribed, indurated, and usually deep and painless (Fig. 263.9).[63] The tongue, buccal mucosa, larynx, gums, and lip are the most affected structures. Occasionally the lesion is on the labia or glans penis. These lesions are often confused with

squamous carcinoma oral malignancy. Hence, it is incumbent on the clinician to consider the diagnosis of histoplasmosis; otherwise, tissue will be sent only for histologic evaluation. Histopathologically, the center of the lesion contains macrophages with many yeasts, but the number of such macrophages decreases in the periphery of the lesion. Unlike the histologic reaction in other viscera, the response in the mucosa is an admixture of acute and chronic inflammation. Thus, plasma cells, lymphocytes, eosinophils, and granulocytes are found infiltrating the ulcer, and fibrosis is a characteristic feature. Areas of intact mucosa may show hyperplasia that can be confused with squamous carcinoma on superficial biopsy. Well-circumscribed granulomas are typically found, usually at the periphery.

Other symptoms include hepatosplenomegaly in about one-third of patients. Chronic meningitis or chronic granulomatous hepatitis may be the only manifestation of infection. Unlike subacute PDH, there is a notable absence of disease involvement of other organ systems, including CNS, heart, and adrenals. Bone infection, Addison disease, and endocarditis all have been described, but these entities are uncommon. Hematologic abnormalities are distinctly uncommon and often not significant. This illness may persist for years, with periods of spontaneous improvement in symptoms, without being recognized. On occasion, there may be an abrupt worsening caused by involvement of a particular organ such as the CNS, adrenals, or heart.[63] Usually, however, the illness remains undiagnosed until symptoms arising from a single organ are observed. Without appropriate therapy, infection progresses to death.

OCULAR HISTOPLASMOSIS

Two different syndromes of ocular involvement are described. The less common is a uveitis or panophthalmitis in association with active PDH. Granulomas are present in the uvea, and yeasts are recovered from lesions. Much more frequent is the presumed ocular histoplasmosis syndrome (POHS), which consists of a posterior uveitis or choroiditis in individuals who manifest skin test positivity to histoplasmin and intrathoracic calcifications.[71] However, it must be stressed that a skin test and the presence of intrathoracic calcifications do not prove cause and effect.

Typically, in POHS there are peripheral atrophic scars and a lack of vitreous or anterior segment inflammation. The scars or "histospots" are located posterior to the equator of the eye. They range in size from 0.2 to 0.7 disk diameters and can vary in number from 1 to 70 in a single eye. Involvement of both eyes is uncommon (<10%). Most individuals are between 20 and 50 years of age when this syndrome is diagnosed, and the prevalence may be as high as 10% in endemic regions. The major destructive consequence of this lesion is macular hemorrhage, which develops 10 to 20 years after the appearance of scars. Neovascularization and scarring can lead to loss of vision in up to 60% of patients.[71] Because neovascularization can exert such devastating effects, efforts have been made to understand its cause. It has been shown that the integrin is expressed on blood vessels from patients with POHS.

The histopathology of POHS reveals a lymphocytic infiltration in the scarred areas. Yeasts are rarely observed in the eye or elsewhere. A model for this syndrome has been developed in primates to define the cellular immunopathology. Chronic lesions contain a preponderance of B and $CD4^+$ cells. As in affected human eyes, yeasts are not found in the lesions. Within the choroidal lesions, there is an increase in the percentage of $CD4^+$ cells and macrophages. There is no definitive proof that *H. capsulatum* causes the scars that are observed in humans, although the primate model establishes that this fungus can produce choroidal scars. The pathogenesis appears to be an exuberant cellular immune reaction to inert fungal antigens, thus somewhat resembling the tissue response in mediastinal fibrosis. Corticosteroid treatment of POHS does not activate latent histoplasmosis.

AFRICAN HISTOPLASMOSIS

In Africa, the classic *H. capsulatum* var. *capsulatum* coexists with *H. capsulatum* var. *duboisii*. The yeast form of the latter is typically much larger, with a diameter of up to 15 µm, and has a thicker wall. The mycelial form of both is indistinguishable. The pathogenesis of this fungus is presumed to be inhalation from the soil, although a primary pulmonary infection has not been demonstrated. Cutaneous inoculation is certainly an alternative mode of acquisition of the infection. Spontaneous disease has been reported in baboons and cynocephalus monkeys. Only a few hundred cases have been reported, but most cases have been reported from Uganda, Nigeria, Zaire, and Senegal. Cases in other African countries and a case in India have also been reported.[72,73]

The clinical picture associated with infection by *H. capsulatum* var. *duboisii* is distinctly different from that caused by *H. capsulatum* var. *capsulatum*.[74] Skin and skeleton are the most frequent organs affected by this pathogen. In the skin, the usual findings are ulcers, nodules, or psoriatic-like lesions that may spontaneously resolve. Involvement of the subcutaneous tissue may present with tender nodules ("cold" abscesses) in which the typical manifestations of inflammation are absent. Osteolytic bone lesions are fairly common and are noted in up to 50% of cases. The skull and ribs are the bones affected most frequently, followed by vertebrae. The organism produces granulomatous inflammation within the bone. This type of inflammation can lead to sinus formation and cystic bone lesions. In a high proportion of patients, multiple bones may be infected. Even in the presence of overt skin or bone lesions, chest radiographs are often free of evidence of previous exposure to *H. capsulatum*. Draining lymph nodes also may become inflamed.

A progressive disseminated disease has been recognized. Patients are febrile, with hematologic abnormalities. There is multiorgan involvement, including liver, spleen, kidney, and lung, and miliary lesions are observed in the lungs. The histopathology resembles that induced by *Blastomyces dermatitidis* or *Coccidioides immitis*—that is, a pyogranulomatous reaction in which there is a combination of granulomas and suppuration. One likely reason for this pathologic reaction is the large size of *H. capsulatum* var. *duboisii,* which prevents avid ingestion by macrophages. Thus, neutrophils may ingress to assist in the clearance of the fungus.

Reports of African histoplasmosis in HIV-infected individuals are emerging. A variety of manifestations in individual patients has been observed. Disseminated infection with fever, cutaneous infection, and bone infection have been recognized.[75] The outcome has been favorable in only a minority of patients.

DIAGNOSIS

Fungal Culture

The use of diagnostics for histoplasmosis is encapsulated in Table 263.2. Histoplasmosis can be definitively established only by means of isolation from body fluids or tissues. The typical medium that is used to recover the fungus from sterile fluids includes brain heart infusion agar, with the addition of antibiotics and cycloheximide when nonsterile fluids such as sputum are cultured. Cultures are incubated at 30°C for up to 6 weeks. Often, growth is noted within 3 weeks, and more than 90% of cultures exhibit fungus within 7 days. Previously, confirmation that the fungus was *H. capsulatum* required exoantigen testing or conversion of the mycelial form to the yeast form, but this step is no longer necessary. All mycelial isolates are confirmed with a DNA probe that recognizes ribosomal RNA. Manipulation of the mycelial phase in the laboratory is a potential biohazard and requires Biosafety Level 3 precautions.

The incidence of positive cultures varies considerably and often is correlated with the number of specimens collected, source of the specimen, and burden of infection. Recovery of *H. capsulatum* from sputa of patients with acute pulmonary histoplasmosis ranges from 10% to 15%, whereas in cavitary histoplasmosis, cultures are positive in up to 60% of patients.[76] The yield of positive cultures increases with the number of specimens collected. Three or more specimens are more likely to be positive for *H. capsulatum.* In AIDS patients with pulmonary manifestations, up to 90% of cultures from the lungs obtained from bronchoscopic samples will grow *H. capsulatum.* Bone marrow and blood cultures are positive in up to 50%.[76] Yields for blood cultures are considerably higher if the lysis centrifugation technique is used. The organism can be frequently isolated from oropharyngeal ulcers in patients with chronic PDH. In endocarditis, valve cultures are positive in a high percentage but blood cultures often are negative. However, much of the evidence concerning blood cultures used the biphasic medium, which may not be as sensitive as lysis centrifugation. In meningitis, the organism is recovered from CSF in 25% to 65% of patients,[66] and the yield is improved

TABLE 263.2 Diagnostics for Histoplasmosis

INFECTION SITE	DISEASE SEVERITY	DIAGNOSTIC
Lung		
Acute	Mild-moderate	H and M bands and complement fixation.
	Moderate to severe	As above. Serum or urine antigen, or both, also may be positive in up to 70%. Bronchoalveolar fluid antigen may be useful. Culture of bronchoalveolar lavage fluid and silver stain of concentrated lavage fluid. Sputum culture.
Chronic cavitary		H and M bands and complement fixation. Culture of bronchoalveolar lavage fluid and silver stain of concentrated lavage fluid. Sputum cultures.
Disseminated		
	Acute	Serum or urine antigen, or both. H and M bands and complement fixation. These are not useful in AIDS patients. Examination of the buffy coat for yeast cells in phagocytes. Biopsy of bone marrow or liver with silver stain and culture. Blood culture.
	Chronic	Serum or urine antigen, or both. H and M bands and complement fixation. Biopsy of tissue with silver stain and culture.
Central nervous system		Serum or urine antigen, or both. CSF antigen. Culture of CSF. H and M bands and complement fixation are not as useful.
Mediastinal		
	Lymphadenitis	H and M bands and complement fixation.
	Granuloma	H and M bands and complement fixation.
	Fibrosis	H and M bands and complement fixation.
Rheumatologic	Arthralgias	H and M bands and complement fixation.
Pericarditis		H and M bands and complement fixation.
Endocarditis or endovascular		H and M bands and complement fixation. Serum or urine antigen, or both. Culture and silver stain of valve.

AIDS, Acquired immunodeficiency syndrome; *CSF,* cerebrospinal fluid.

if a large volume (20 mL or more) is cultured. The organism is unlikely to be isolated from pericardial or pleural fluid, but more likely from their respective serosal tissues. Similarly, *H. capsulatum* rarely is isolated from mediastinal tissues in patients with mediastinal fibrosis.

Antigen Detection

The antigen assay, which detects polysaccharide antigen in serum or urine by means of enzyme-linked immunosorbent assay (ELISA), is the mainstay of diagnosis, especially in those with PDH. Several laboratories now offer the test. Antigen is detected in up to 90% of patients with acute PDH and 40% with cavitary disease.[75] In patients with moderate-to-severe acute pulmonary histoplasmosis, antigen testing of urine and serum yielded a detection rate of approximately 80%. If only single specimens were obtained, the values approximated 65% to 70%.[77] The test is also useful for monitoring relapses of acute PDH, especially in immunosuppressed patients. Failure of antigenemia to fall after a month of therapy should raise concern. Antigen detection is much more sensitive than serology for identifying relapsing cases, and it has been applied successfully to CSF in patients with meningitis. The test was positive in 12 of 14 cases. Thus, it has a high degree of sensitivity. Cross-reactivity in the urine test has been found for patients infected with *B. dermatitidis, C. immitis, Paracoccidioides brasiliensis,* or *Talaromyces (Penicillium) marneffei,* but with improvements in the test, cross-reactions are becoming less frequent. The galactomannan test, often used for detection of invasive aspergillosis, has been reported to be positive in patients with histoplasmosis. The 1,3 β-D-glucan assay also can be positive in histoplasmosis, especially disseminated disease. In a small study, serum IL-2 receptor levels have been reported to be elevated.

Several reports of the usefulness of the polymerase chain reaction have been published, and although such assays are not in clinical use yet, they show promise.

Serology

Since the late 1940s, serology has been a vital instrument in the diagnosis of infection with *H. capsulatum.* CF antibodies and precipitin bands have been the most common tests used in the clinical laboratory. The greatest usefulness has been in the retrospective diagnosis of acute histoplasmosis, using a fourfold or greater rise in CF titer between acute and convalescent serum. This has been particularly helpful in outbreaks that are recognized in time to collect acute sera, but the antibody titer rise occurs too late to be of value in patient management. For chronic pulmonary histoplasmosis or PDH, fourfold rises are not observed and antibody tests have insufficient sensitivity and specificity to be of clinical value. For CF antibodies, a titer of 1:8 to yeast or mycelial antigen is considered positive, and a titer of 1:32 indicates the need to pursue a possible diagnosis of histoplasmosis. Titers that fall between these two values neither exclude nor suggest the diagnosis. On occasion, a result is returned that states that the test is anticomplementary. This result signifies that the serum contained a substance or substances that interfered with the CF test. Repeat of the test with a new serum specimen frequently yields a result.

Low levels of CF antibodies are detected in approximately 10% of healthy individuals who reside in an endemic region. A low percentage of individuals with acute pulmonary histoplasmosis will develop CF antibodies within the first 3 weeks of infection, but by 6 weeks at least 75% of patients manifest a positive CF antibody titer or a fourfold rise. Over the course of months, the antibody titer will decline, although it may remain serofast for years, especially in those with cavitary pulmonary disease or with chronic PDH. The false-positive rate is estimated to be 15% and is most commonly observed in those with coccidioidomycosis or with blastomycosis.[78] The reason for the cross-reactivity is the presence of a carbohydrate antigen common to the three fungi.

Another test is the detection of H and M bands during the illness. On the agar gel precipitin test, these bands are identified by lines of identity with bands formed by control sera known to have precipitating antibody to H or M antigens. These two precipitin bands were originally identified using immunodiffusion as specific to sera from patients with histoplasmosis. The H and M antigens are glycoproteins released by mycelial and yeast phase cultures. The H antigen has been cloned and sequenced, and it demonstrates homology to β-glucosidases. Antibody to H antigen is infrequently detected (<10%) in the sera of patients but, when present, signifies active infection. The M antigen has also been cloned and sequenced, and it has a high degree of homology to catalase. Unlike the H antigen, antibody to M antigen is detected in up to 80% of individuals after exposure to the fungus. However, it is present in patients who have recovered from infection or who have active disease; therefore it is not useful in discriminating remote from current infection. A major limitation of the serologic tests is that even in the presence of active infection, their results are negative in up to 50% of immunosuppressed patients, especially those with AIDS. One explanation for the poor anti-*Histoplasma* antibody response is that the immunosuppressive agents or HIV induces dysfunctional B cells or $CD4^+$ T cells, or both, thus rendering serologic assays almost useless.

Histochemical Identification

Stains for the presence of *H. capsulatum* can be extremely useful for rapid identification of the fungus in various tissues or body fluids. The yeast is visualized poorly with hematoxylin-eosin stain but is more apparent with the periodic acid–Schiff (PAS) stain. The most useful stain is either the Gomori methenamine silver (GMS) or Grocott silver stain. The organism can be detected in peripheral blood smears stained

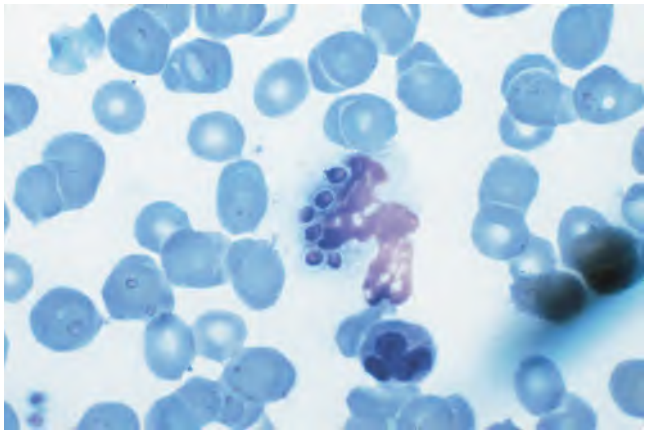

FIG. 263.10 Circulating neutrophil with intracellular yeast cells. (Wright-Giemsa stain, ×400.)

with Wright-Giemsa in up to 40% of cases of acute PDH (Fig. 263.10). This percentage is much lower if the reader of the blood smear is scrutinizing the slide only to determine a differential, but it is useful if the clinician suspects PDH as a cause of a patient's illness. The yeast must be discriminated from *Pneumocystis jirovecii* in the lung. The latter is larger, nonbudding, and usually extracellular. Moreover, it is exceedingly rare to find *P. jirovecii* outside the lung or in an area of caseous necrosis. Although *Leishmania* spp. and *Toxoplasma gondii* may on occasion be confused morphologically with *H. capsulatum,* neither stains with silver.

Miscellaneous Laboratory Tests

One retrospective study has suggested that patients with AIDS who are admitted to the hospital with pulmonary infiltrates and fever higher than 38°C and serum lactate dehydrogenase (LDH) levels higher than 600 IU/mL are highly likely to have disseminated histoplasmosis.[79] Other studies have suggested that elevated serum ferritin levels are strongly suggestive of histoplasmosis.[80]

THERAPY

The introduction of azoles has moved much of the treatment of histoplasmosis from an inpatient to outpatient setting. Several azoles and polyenes are now available for the treatment of this fungal disease. Updated practice guidelines for the treatment of various forms of histoplasmosis have been published.[81] Table 263.3 summarizes the treatment options.

Acute Pulmonary Histoplasmosis

The vast majority of cases of acute pulmonary histoplasmosis do not require therapeutic intervention. Bed rest and antipyretics suffice for these individuals. Treatment should be instituted for those who have not improved after 1 month of illness or who exhibit hypoxemia. In those in whom illness has not spontaneously resolved after 1 month, oral itraconazole, 200 mg three times daily for 3 days, followed by 200 mg once or twice daily for 6 to 12 weeks will be sufficient. Fluconazole is not as active as itraconazole and should be avoided. If the patient cannot ingest an oral medication or tolerate an azole, liposomal amphotericin B is the preferred agent. A dose of 3 to 5 mg/kg IV can be given every day until the symptoms subside, often within 2 weeks. The dose for the lipid complex formulations of amphotericin B (ABLC) is 5 mg/kg. The deoxycholate formulation can be used at 0.7 to 1 mg/kg daily if there is a low risk of serious nephrotoxicity. No comparative trials of amphotericin B and azoles have been performed, but clinical experience suggests that resolution of symptoms is faster with the former.

If the patient is hypoxemic and requires mechanical ventilation, liposomal amphotericin B, 3 to 5 mg/kg/day, is recommended until improvement is achieved. When patients improve to the point that they can ingest food and medications, itraconazole, 200 mg three times daily for 3 days, followed by once or twice daily should be used to complete 12 weeks of therapy. If the patient is at low risk for renal dysfunction, the deoxycholate preparation of amphotericin B may be substituted at a dose of 0.7 to 1 mg/kg/day. The inflammatory response may be responsible in part for the respiratory compromise. Although ample evidence does not exist, corticosteroids may be used to mitigate inflammation. Intravenous methylprednisolone can be used at a dosage of 0.5 to 1 mg/kg/day for up to 14 days.

TABLE 263.3 Treatment of Histoplasmosis

INFECTION SITE	DISEASE SEVERITY	TREATMENT
Lung		
Acute	Mild-moderate	None or itraconazole 200 mg 3 times daily for 3 days followed by 200 mg twice a day for 6–12 wk.
	Moderate-severe	Lipid-formulated amphotericin B, 3–5 mg/kg, or deoxycholate amphotericin B, 0.7–1 mg/kg, daily for 1–2 wk followed by itraconazole 200 mg 3 times a day for 3 days followed by 200 mg twice a day for a total duration of 12 wk. For children, itraconazole 5–10 mg/kg or deoxycholate amphotericin B, 1 mg/kg daily.
Chronic cavitary		Itraconazole 200 mg 3 times a day for 3 days followed by twice daily for at least 1 yr and as long as 2 yr.
Disseminated[a]		
	Acute	Lipid-formulated amphotericin B, 3–5 mg/kg, or deoxycholate amphotericin B, 0.7–1 mg/kg, daily for 1–2 wk followed by itraconazole 200 mg 3 times a day for 3 days followed by 200 mg twice a day for at least 12 mo. For children, deoxycholate amphotericin B (1 mg/kg) daily for 4–6 wk or 2–4 wk followed by itraconazole 5–10 mg/kg daily. Total duration = 3 mo.
	Chronic	Itraconazole 200 mg 3 times a day for 3 days followed by 200 mg twice a day for at least 1 yr. Serum levels should be monitored to ensure adequate concentrations.
Central nervous system		Liposomal amphotericin B, 5 mg/kg daily for 4–6 wk followed by itraconazole administered as above for at least 1 yr and resolution of symptoms and negative cerebrospinal fluid antigen.
Mediastinal		
	Lymphadenitis	No treatment. If symptomatic (e.g., dysphagia), itraconazole 200 mg twice daily for 12 wk. Corticosteroids (60 mg with a rapid taper) may be used to diminish lymph node size.
	Granuloma	Same as lymphadenitis. Corticosteroids are not necessary.
	Fibrosis	Surgical intervention with stents. Antifungals are not useful.
Rheumatologic	Arthralgias, etc.	Nonsteroidals
Pericarditis		Nonsteroidals or corticosteroids. If the latter, treat with itraconazole (200 mg × 3 for 3 days and then once a day) until corticosteroids have been discontinued.
Endocarditis/ Endovascular		Surgical removal of the valve combined with lipid-formulated amphotericin B, 5 mg/kg daily for 6 wk. Lifelong suppression may be considered in some who are not surgical candidates with itraconazole 200 mg once or twice a day.

[a]See text for duration of treatment in acquired immunodeficiency syndrome (AIDS) patients.

Data from Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. *2007;45:807–825.*

Itraconazole is a lipophilic agent that inhibits the cytochrome P-450 system (see drug interactions listed in Chapter 39). The cyclodextrin oral liquid formulation of itraconazole increases absorption by 50% and makes administration to young children much easier.

Mediastinal Granuloma, Mediastinal Fibrosis, and Histoplasmoma

Hilar and mediastinal lymphadenopathy from acute pulmonary histoplasmosis is usually asymptomatic but can cause a brassy cough or compress the middle lobe bronchus, leading to temporary atelectasis. Although no therapy is usually necessary, persistent symptoms could be treated with itraconazole, 200 mg three times daily for 3 days, followed by 200 mg once or twice daily for 6 to 12 weeks. Rarely, large caseous mediastinal nodes will compress the esophagus or erode into both the esophagus and bronchus, causing a bronchoesophageal fistula. Surgical resection of the nodes may be indicated, although the nodes may be densely adherent to the pulmonary veins and other surrounding structures. Corticosteroids may be used if the enlarged nodes cause significant compression of surrounding structures. Prednisone at a dose not to exceed 80 mg may be tried, with a rapid taper over 1 to 2 weeks.

Mediastinal fibrosis is an exceptionally difficult clinical problem for which there is no consensus on optimal management. Surgery, corticosteroids, and antifungal agents have been used in the treatment of this condition, with minimal success. Surgery to remove the fibrosis area and placement of intravascular stents can alleviate the life-threatening situation, but the fibrosis often progresses. Moreover, the surgery may jeopardize essential venous collaterals, such as the hemiazygos or azygos veins. Addition of azoles after surgery has been proposed, but the usefulness of this approach is debatable.[81]

A histoplasmoma of the lung, which is a fibrocaseous nodule resulting from healed acute pulmonary histoplasmosis, does not require any therapy. Surgical resection or biopsy may be needed to exclude malignancy in a solitary pulmonary nodule if no central calcification is evident. Serology is of no value in proving the nodule is a histoplasmoma.

Cavitary Pulmonary Histoplasmosis

Although in some patients fibrocavitary disease will eventually stabilize without treatment, the inability to predict which patients will eventually develop disease progression has led to the recommendation that all patients should be treated, even those who are currently asymptomatic. Treatment does not improve pulmonary function already lost and, in fact, healing may lead to some further loss of function because of fibrosis. Discontinuing cigarette smoking is an important adjunct in preventing further loss of pulmonary capacity. Many patients with only thin-walled cavities spontaneously resolve infection without therapeutic intervention. Such patients, if untreated, should be followed with serial chest radiographs every 2 to 3 months. Those who have thick-walled cavities, progressive pulmonary infiltrates, or persistent cavities associated with declining respiratory function should be treated. Oral itraconazole, 200 mg three times daily for 3 days, followed by once or twice daily, should be given for 12 to 24 months.[81] This regimen will arrest progression in 75% to 85% of patients. Relapse may be difficult to detect radiologically in patients with extensive prior lung damage. Sputum culture is the best means for detecting relapse, although *Aspergillus* and other rapidly growing molds may overgrow the culture plate. Fluconazole is not recommended. Itraconazole levels should be determined after 2 weeks of therapy to determine if adequate levels have been achieved. A trough blood level of 2 μg/mL by bioassay or the sum of native itraconazole and its hydroxymetabolite by high-performance liquid chromatography (HPLC) has been proposed (see Chapter 39). If there is progression of infection while the patient is on azoles or if relapse has occurred after azole therapy, amphotericin B is preferable. If deoxycholate amphotericin B is used, the total dose is 30 to 35 mg/kg and can be given as 0.7 mg/kg/day or approximately 50 mg daily.[81] If renal dysfunction is a consideration, the liposomal formulation may be used at 3 to 5 mg/kg/day.

The relapse rates for cavitary pulmonary histoplasmosis are as high as 20%, with the highest relapse rates seen in patients with thick-walled cavities. If there is a failure of antifungal therapy, surgical resection may be indicated if the patient has sufficient pulmonary reserve.

Acute Progressive Disseminated Histoplasmosis

Prompt institution of amphotericin B therapy is necessary for treatment of patients with acute, life-threatening PDH. Patients should be begun on liposomal amphotericin B at a dose of 3 mg/kg/day. If ABLC is used, the dose should be 5 mg/kg/day. Within 1 to 2 weeks, most patients are symptomatically improved, and laboratory abnormalities begin to return to baseline values. If deoxycholate amphotericin B is used, the starting dose should be 25 mg followed by a rapid escalation to 1 mg/kg. Once the patient has become afebrile and clinically stable, amphotericin B can be administered at a lower dose of 0.4 to 0.5 mg/kg daily. Patients who demonstrate resolution of symptoms while on amphotericin B may be switched to itraconazole 200 mg three times daily for 3 days, followed by 200 mg twice daily for a total duration of 12 months. In acute PDH that is not associated with hemodynamic instability or severe illness, itraconazole may be used initially. Therapy should begin with 200 mg three times daily for 3 days, followed by 200 mg twice daily for at least 12 months. Itraconazole interacts with many antiretrovirals, including elevating serum concentrations of several protease inhibitors.

In patients with AIDS, lifelong suppressive therapy with itraconazole 200 mg daily is recommended for most patients. Although there are no reliable data to make this decision, it may be reasonable to discontinue maintenance therapy in patients receiving highly active antiretroviral therapy who have a CD4 count higher than 150 cells/μL for 6 months, a nondetectable viral load, at least 12 months of antifungal therapy, and a negative test for *Histoplasma* antigen in urine. If relapse occurs while the patient is receiving azole maintenance therapy, amphotericin B should be given.[81] After treatment for the relapse, the patient should receive amphotericin B as maintenance therapy with 0.7 to 1 mg/kg once or twice weekly. A self-limiting immune reconstitution syndrome (IRS) has been recognized occasionally in HIV patients being treated for PDH who have had an effective response to highly active antiretroviral therapy. The syndrome manifests as fever, with or without an elevated alkaline phosphatase level. Management is supportive. Relapse of PDH is common in other persistently immunosuppressed patients and may be difficult to detect until far advanced. Indefinite suppressive therapy with itraconazole may be a useful option.

Subacute and Chronic Progressive Disseminated Histoplasmosis

Because many of these cases develop in patients whose immune system is intact, itraconazole 200 mg three times daily, followed by 200 mg twice daily is highly efficacious. The success rate in these individuals approaches 90%. If the patient requires hospitalization, does not improve on azole therapy, is immunosuppressed, or demonstrates intolerance to azoles, lipid-based preparations of amphotericin B, 3 to 5 mg/kg/day, should be given. When the infection is controlled with this drug, it is possible to switch to itraconazole to complete a total of 12 months of therapy.

Meningitis

Patients with meningitis should be given liposomal amphotericin B, 3 to 5 mg/kg/day for 4 to 6 weeks, followed by itraconazole, 200 mg two or three times daily, for at least 1 year. Blood levels of itraconazole should be determined. CSF should have a normal glucose level and no detectable CSF *Histoplasma* antigen at the end of therapy. Repeat lumbar punctures should be performed approximately every week for the first 6 weeks and every 2 weeks thereafter to assess therapy. Although a high percentage of patients may respond initially to therapy, relapse frequently occurs. Overall cure rates are no better than 50%, and immunocompetent patients respond much better to treatment than immunosuppressed persons.

Endocarditis

As with bacterial causes of endocarditis, a microbicidal agent should be used. Therefore, liposomal amphotericin B, 3 to 5 mg/kg/day, should be given. If ABLC is used, 5 mg/kg should be administered. Alternatively, if there is a low risk of nephrotoxicity, deoxycholate amphotericin B, 0.7 to 1 mg/kg, may be used. Administration of an antifungal agent alone is not sufficient and must be used in combination with surgical

removal of the affected valve(s). One issue is how long to treat after the valve has been removed. If there are other foci of active histoplasmosis, then treatment guidelines for PDH should be used. However, if the valve was the only site involved, treatment with a lipid formulation or the deoxycholate preparation for 2 weeks after surgical extraction may be sufficient. If the patient cannot undergo surgery, an amphotericin B preparation in the highest tolerated dose should be given daily.[81]

Pericarditis

Pericarditis following acute pulmonary histoplasmosis does not require antifungal therapy. Most patients can be treated symptomatically with nonsteroidal antiinflammatory drugs (NSAIDs) for 2 to 12 weeks.[74] If patients do not respond to these agents, or if the patient manifests hemodynamic instability, corticosteroids are indicated for 1 to 2 weeks, followed by nonsteroidal agents. One must be cautious because if there are active lesions of histoplasmosis, the infection may become more aggressive during corticosteroid therapy. Itraconazole, 200 mg three times daily for 3 days, followed by 200 mg once or twice daily for 6 to 12 weeks, should be included if corticosteroids are necessary. The rationale for the antifungal is to prevent reactivation, although there is little information regarding the frequency with which this occurs in short-term use of corticosteroids. Cardiac tamponade associated with *H. capsulatum* pericarditis is uncommon, but when it occurs, it must be treated as a medical emergency with pericardiocentesis. Despite the severity of illness, antifungal therapy is not indicated. Unlike tuberculous pericarditis, constrictive pericarditis rarely develops, but patients should be monitored for several years after the acute attack. In the uncommon situation in which the pericardium is infected as a manifestation of PDH, antifungal therapy with amphotericin B or azoles is indicated, depending on the severity of illness.

Arthropathies

Nonsteroidals should be continued until resolution of symptoms. If corticosteroids are used to alleviate symptoms, itraconazole should be used concomitantly, as noted earlier.

Presumed Ocular Histoplasmosis

Presumed ocular histoplasmosis does not require antifungal therapy. Laser therapy is used to prevent additional neovascularization within the choroid, but lesions that abut the fovea cannot be subjected to this treatment.[71] Photodynamic therapy for this region of the eye appears promising, as does the implementation of intravitreous antiangiogenic agents. The role of retrobulbar local injection of corticosteroids is unclear.

Other Considerations

Histoplasmosis in pregnancy should be treated with amphotericin B, preferably a lipid formulation, but the deoxycholate preparation can be used if nephrotoxicity is of low concern. The dose of liposomal preparation should be 3 to 5 mg/kg/day for 4 to 6 weeks, and that of the deoxycholate formulation 0.7 to 1 mg/kg/day. If ABLC is used, 5 mg/kg is the preferred dose.

No clear guidelines exist for patients receiving TNF-α antagonists. Those from the endemic area are at the highest risk for reactivation or reinfection. If a patient develops histoplasmosis while on therapy, the biologic agent should be stopped and therapy for disseminated histoplasmosis completed. A study of 98 cases provided a guide to managing these patients.[82] In the vast majority of patients, the TNF-α antagonist was discontinued, and the duration of therapy was approximately 12 months on cessation of the biologic agent. The TNF-α antagonist may be restarted after cessation of antifungal therapy based on results in a small number of cases. Candidates for resumption are those in whom there is no evidence of disease and the antigen is undetectable. However, patients should be monitored closely for clinical symptoms and an antigen every 3 months. Prophylaxis with an antifungal in those who are resuming therapy appears to be unnecessary.

Immune Reconstitution Syndrome and *Histoplasma*

IRS after initiation of treatment for *H. capsulatum* and many other pathogens has been reported. The constellation of symptoms poses a conundrum for clinicians because they have to discriminate between inadequately treated infection and exaggerated host response. The development of IRS is not restricted to those who start antiretroviral therapy; it also has been observed in those in whom biologics have been discontinued or even when corticosteroids have been tapered or discontinued. If the diagnosis of IRS is established, the use of corticosteroids should be considered. TNF-α antagonists have also been recommended because of their ability to enhance the numbers of regulatory T cells. However, one must be cautious in using these agents for histoplasmosis because they are known to exacerbate disease.[83]

PREVENTION

Prophylaxis of Immunocompromised Persons

For immunosuppressed patients who have a high risk of acquiring histoplasmosis from the environment because of their work or their residence, itraconazole, 200 mg/day, is useful. Such patients would include those with AIDS whose CD4 cell count is less than 150/μL or those who require potent immunosuppressive therapy. In the former group, prophylaxis with itraconazole reduced the incidence of infection by more than twofold. Another indication for prophylaxis in immunosuppressed patients would be residence in an area that has a high incidence of infection, as defined by at least 10 cases per 100 patient-years.[84]

Other Considerations

Educational efforts must be ongoing to alert those who work in areas in which a substantial risk of infection exists. Dust control and the use of N95 masks should be considered. For example, construction workers who are restoring buildings that have served as homes for starlings and bats must be warned about the possibility of exposure, and steps taken to remove the guano safely. Spraying 3% formalin on guano deposits will kill the fungus within several days, and the material can then be removed. However, formaldehyde decontamination is rarely used because the vapor is toxic, it can seep into groundwater (thus posing an environmental hazard), and it does not penetrate dried guano uniformly.

There is a continuing effort to develop a vaccine preventive against *H. capsulatum* pathogenic fungi because of their escalating incidence. Among those in which animal studies have defined a vaccine is *H. capsulatum*. Vaccine candidates containing heat shock protein 60 and H antigen from *H. capsulatum* have been demonstrated to confer protection to mice given a pulmonary challenge. A region of heat shock protein 60 that spans amino acids 174 to 445 appears to contain the protective activity of the entire protein. In mice, a monoclonal antibody to the cell surface has been shown to augment the efficacy of antifungal therapy.[85]

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264 Blastomycosis

Gregory M. Gauthier and Bruce S. Klein

SHORT VIEW SUMMARY

Definition
- Infection by *Blastomyces* species, most commonly *B. dermatitidis* and *B. gilchristii*

Microbiology
- Thermal dimorphism with growth as hyphae at ambient temperature and yeast at 37°C
- Morphologic switch from hyphae and conidia to yeast form is essential for virulence
- *Blastomyces* yeast actively subverts and evades host immune defenses

Epidemiology
- Primarily found in North America—Midwest, Central, and Southeastern United States as well as regions along the Great Lakes and St. Lawrence River
- Outbreaks and sporadic disease
- Infection often associated with recreational or occupational activities that disrupt soil
- Most patients have intact immune defenses; however, *Blastomyces* can infect people with impaired immunity
- Cell-mediated immunity required to control infection

Clinical Manifestations
- Blastomycosis can mimic other entities such as community-acquired pneumonia, tuberculosis, and malignancy
- Pneumonia is most common clinical manifestation
- Dissemination to other organs such as skin and bone is common; however, any organ can become infected

Diagnosis
- Fungal staining of clinical specimens provides rapid, presumptive diagnosis
- Broad-based budding yeast with doubly refractile cell wall
- Culture provides definitive diagnosis
- Complement fixation and immunodiffusion serologic tests have poor sensitivity
- Antigen testing of urine useful for diagnosis, but cross-reactions can occur with other dimorphic fungi

Treatment
- Itraconazole: drug of choice for mild-to-moderate pulmonary or non–central nervous system disseminated disease
- Amphotericin B (AmB; deoxycholate or lipid): for patients with moderately severe to severe blastomycosis and immunocompromised patients until improvement and then itraconazole
- Lipid AmB: for initial treatment of central nervous system blastomycosis, followed by azole antifungal therapy for at least 12 months
- Lipid AmB: for blastomycosis in pregnancy

The etiologic agents of blastomycosis belong to a group of fungi that are characterized by thermal dimorphism.[1] Advances in genomics and phylogenetics have expanded the number of *Blastomyces* species to include *B. dermatitidis, B. gilchristii, B. percursus, B. helicus, B. parvus,* and *B. silverae*.[2–6] Infection is primarily acquired through the inhalation of infectious conidia and hyphal fragments following the disruption of soil. Once inside the lungs, the infectious particles convert into pathogenic yeast, which causes pneumonia and can disseminate to other organs. Blastomycosis can mimic other diseases, which often delays diagnosis and initiation of therapy. Thus diagnosis requires a high degree of clinical suspicion. Antifungals with activity against *Blastomyces* yeast include polyenes and azoles.

HISTORY

Blastomycosis was first described in 1894 by Gilchrist[7] as a protozoan infection. Subsequent research by Gilchrist and Stokes[8–10] at Johns Hopkins University correctly identified the organism as a fungus, which they named *Blastomyces dermatitidis*. In 1907 Hamburger[11] at Rush Medical College described thermal dimorphism in *B. dermatitidis* with budding yeast at 37°C and hyphal growth at ambient temperature. Colloquial names for blastomycosis coined early in the 20th century included *Gilchrist disease, Chicago disease,* and *North American blastomycosis.*

In 1951 Schwarz and Baum[12] at the Jewish and General Hospitals in Cincinnati determined that the lung was the primary portal of entry, and involvement of other organs such as the skin was due to lympho-hematogenous dissemination. In 1955 Smith and colleagues[13] at Duke Hospital described the first recognized outbreak of blastomycosis (1953–1954) in Grifton, North Carolina. During the 1960s and 1970s the epidemiology and geographic distribution of blastomycosis were refined. In the mid-1980s *B. dermatitidis* was successfully cultured from soil at the site of an outbreak in Eagle River, Wisconsin.[14] In the 1990s clinical trials under the auspices of the National Institutes of Allergy and Infectious Diseases Mycoses Study Group were conducted to assess the efficacy of fluconazole and itraconazole.[15–17] The first practice guideline for treatment of blastomycosis was published by the Infectious Diseases Society of America (IDSA) in 2000 and updated in 2008.[18,19] The American Thoracic Society (ATS) Fungal Working Group published their guidelines in 2011.[20]

There have been substantial advances in the past 2 decades in understanding the molecular pathogenesis including identification and characterization of genes critical for immune evasion and morphogenesis. In addition, the *Blastomyces* genus has undergone taxonomic revision. In 2013 Brown and colleagues[2,21] discovered a new species in North America, which they named *Blastomyces gilchristii* in honor of Dr. Gilchrist. *B. dermatitidis* and *B. gilchristii* are estimated to have diverged 1.9 million years ago during the Pleistocene epoch.[21] In 2017 Dukik and colleagues[4] identified another new species, *Blastomyces percursus,* when analyzing human clinical isolates from South Africa and Israel. Several *Emmonsia* species have been reclassified into the *Blastomyces* genus including *Blastomyces helicus* (formerly *E. helicus*) and *Blastomyces parvus* (formerly *E. parvus*).[5,6] *B. helicus* causes blastomycosis in North America, but outside the traditional endemic region. This species chiefly infects patients with impaired immunity, and results in fungemia and high mortality.[5] *B. parvus* predominantly causes infection in rodents.[6] *Blastomyces silverae* is a new species named after Eleanor Silver Keeping who was a distinguished mycologist at the University of Alberta.[6] *B. silverae* has been misidentified as *E. parvus* and can cause infection in humans.[6] The genomic sequences of *B. dermatitidis, B. gilchristii,* and *B. percursus* are publicly available.[22]

MYCOLOGY

Blastomyces spp. belong to the Ascomycota phylum, which includes other dimorphic fungi such as *Histoplasma, Coccidioides, Sporothrix,*

Paracoccidioides, Emmonsia, and *Talaromyces marneffei* (formerly *Penicillium marneffei*).[23] The biology of these fungi is characterized by the ability to reversibly convert between hyphal and yeast forms in response to temperature.[23]

At environmental temperature (22°C–25°C), *Blastomyces* grows as septated hyphae (1–2 µm in diameter) that produce small conidia (4–5 µm) attached to a short conidiophore, which resembles a lollipop (Fig. 264.1A).[24,25] *B. percursus* has a slightly different morphologic appearance than *B. dermatitidis* or *B. gilchristii* at ambient temperature, with conidiophores bearing single or multiple conidia.[4] The appearance of *B. helicus* is unique because the hyphae can coil into a helical morphology and fail to produce conidia under most in vitro conditions.[5] In the laboratory, *Blastomyces* conidia are difficult to liberate from hyphae and require wetting the culture plate with water or phosphate-buffered saline solution followed by mechanical disruption.[26] The morphologic appearance of mycelia is not distinctive, and definitive identification requires conversion to yeast or molecular methods.[27]

FIG. 264.1 ***Blastomyces*** **hyphae and yeast.** (A) Yeast growth at 37°C characterized by broad-based budding. (B) Hyphae with conidia at 22°C. Scale bar = 10 µm.

At 37°C, *B. dermatitidis, B. gilchristii,* and *B. percursus* yeast (8–20 µm) is characterized by a doubly refractile cell wall, multiple nuclei (typically three or four per cell), and a broad-based budding pattern between mother and daughter cells (Fig. 264.1B).[4,24,27,28,35] *B. dermatitidis* and *B. gilchristii* have similar morphology and cannot be distinguished using microscopy. Differentiation requires DNA sequencing to assess for a single nucleotide polymorphism (C for *B. gilchristii* and T for *B. dermatitidis*) at base-pair 19 in the untranslated region of *ITS2*.[2,29] *B. helicus* yeast (4–9 µm) also exhibit broad-based budding but can form short chains of yeast cells.[5] Definitive identification of *B. helicus* requires sequencing of the ITS (internal transcribed spacer) or D1/D2 domains of the long subunit of ribosomal RNA.[5]

Blastomyces refers to the asexual form, whereas the sexual form is known as *Ajellomyces*.[30,31] Asexual (or clonal) reproduction involves the production of conidia by hyphae or yeast cell division by budding. In contrast, sexual reproduction occurs only in the hyphal phase. *Ajellomyces* undergoes heterothallic mating in which the hyphae of opposite mating types (+ and −) join together to form special structures known as cleistothecia that exchange genetic material to produce ascospores.[30,32] The + mating type contains the α-box gene, whereas the − mating type contains the *HMG* gene.[30] The mating type ratio (+:−) for *B. dermatitidis* is 1:1, whereas it ranges from 1:1 to 1:2 for *B. gilchristii*.[21] Mating typically occurs within a single species (e.g., *B. dermatitidis* mating with *B. dermatitidis*); however, genotyping has suggested the potential for recombination between *B. dermatitidis* and *B. gilchristii*.[29] Sexual ascospores and asexual conidia can germinate as hyphae at 22°C to 25°C or yeast at 37°C.[30,33]

The genomes of *B. dermatitidis* and *B. gilchristii* range from 66.6 to 75.4 MB and contain 9180 to 10,187 genes.[3] Although *B. dermatitidis* and *B. gilchristii* contain a similar number of genes as other thermally dimorphic fungi, the genome size is twofold larger than other closely related fungi such as *Histoplasma capsulatum* and, surprisingly, *B. percursus* (32.3 MB).[3,4]

GEOGRAPHIC DISTRIBUTION AND ECOLOGY

Blastomycosis is a disease primarily localized to the United States and Canada. The endemic region for *Blastomyces* includes the Midwest, South Central, and Southeastern United States and Canadian providences including Quebec, Ontario, Manitoba, and Saskatchewan (Fig. 264.2A). *Blastomyces* is not uniformly distributed throughout the endemic region.

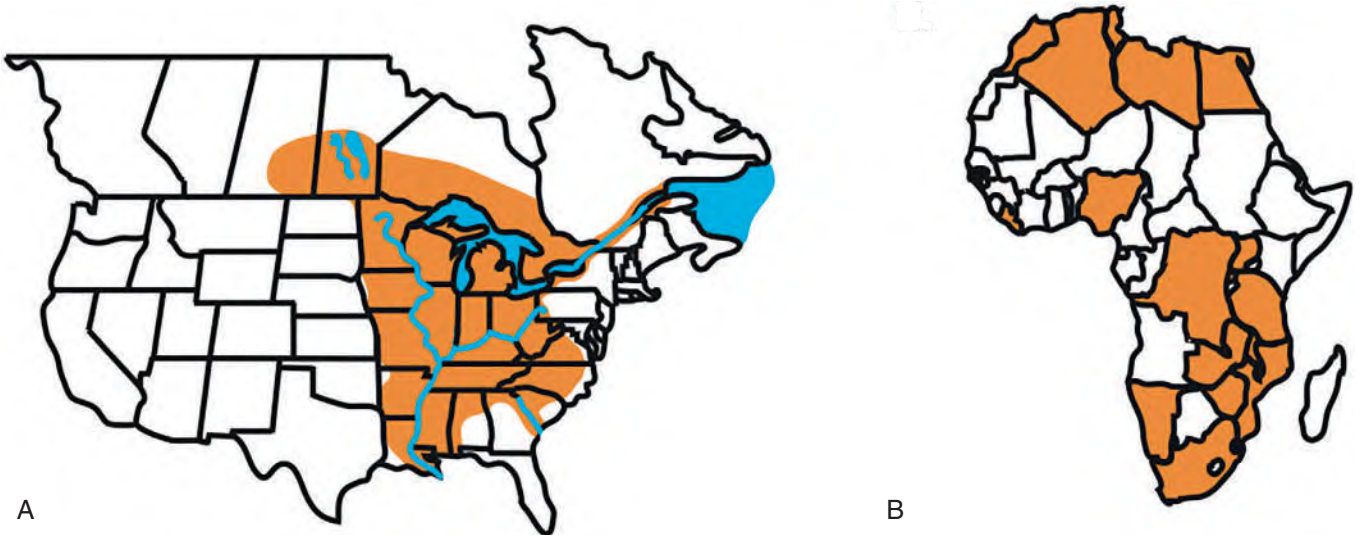

FIG. 264.2 (A) Endemic region of blastomycosis in North America. (B) African countries with case reports of blastomycosis. *(From Gauthier GM, Klein BS. Blastomycosis. In: Cherry JD, Harrison GJ, Kaplan SL, Steinbach WJ, Hotez PJ, eds.* Feigin and Cherry's Textbook of Pediatric Infectious Diseases. 7th ed. *Philadelphia: Saunders; 2014.)*

Rather, it is found in a specific ecologic niche characterized by sandy soil with an acidic pH and decaying vegetation that is located in forested areas near fresh water.[14,21,34,35] This includes watershed areas for Mississippi, Ohio, Savannah, Saint Lawrence, and Nelson rivers as well as areas adjacent to the Great Lakes. Ecologic niche modeling incorporating vegetation indices, soil characteristics, hydrologic features, and geocoded cases of blastomycosis in Wisconsin suggests that land near waterways is favorable for *Blastomyces*.[36]

Within the ecologic niche, *B. dermatitidis* and *B. gilchristii* exhibit geographic restriction and overlap.[21] On the basis of phylogeographic mapping of soil and species determination of clinical isolates, *B. gilchristii* appears to be restricted to Canada, Minnesota, Wisconsin, and New York.[21] In contrast, *B. dermatitidis* has a wider geographic distribution including Canada and Midwest, South Central, and Southeastern United States along with states along the St. Lawrence River.[21] *B. dermatitidis* and *B. gilchristii* overlap in Canada, Minnesota, and Wisconsin.[21] Genetic diversity within *B. dermatitidis* and *B. gilchristii* is influenced by geography that corresponds to freshwater drainage basins (e.g., Nelson River, Mississippi River).[21] McTaggart and colleagues[21] hypothesized that glaciation during the Pleistocene epoch, when *B. dermatitidis* and *B. gilchristii* diverged 1.9 million years ago, may have influenced the geographic distribution of *B. gilchristii* because it is restricted to formerly glaciated areas.

Human and veterinary cases of *B. helicus* infection occur outside the endemic region of *B. dermatitidis* and *B. gilchristii* in North America.[5] All clinical cases occurred in the western United States and Canada.[5] The majority of *B. silverae* isolates have been from the United States or Canada; however, the geographic range of this species has yet to be fully elucidated.[6] Outside of North America, blastomycosis is a rare cause of invasive fungal infection. Autochthonous culture-proven cases of blastomycosis have been reported from Africa and India (Fig. 264.2B).[37–39] African *Blastomyces* strains have a decreased ability to convert to yeast at 37°C in vitro, unique media requirements for growth in the laboratory, and a cell surface that is less antigenically complex.[40] *B. percursus* has been isolated from patients living in Israel and South Africa.[4]

EPIDEMIOLOGY

The epidemiology of blastomycosis is largely based on passive surveillance data, small-scale retrospective studies, and analysis of outbreaks. Mandatory reporting of blastomycosis is required in Minnesota, Wisconsin, Michigan, Arkansas, Louisiana, and Manitoba. In Ontario, laboratory-confirmed cases are tracked by the Northwestern Health Unit jurisdiction. The lack of reliable skin and serologic tests for assessing exposure to *Blastomyces* has hindered the epidemiologic understanding of blastomycosis. Thus epidemiologic data are limited to reports of patients with clinically apparent infection. However, an estimated 50% of patients with blastomycosis may have asymptomatic or subclinical infection.[14] Collectively, these limitations result in underestimation of the true incidence of blastomycosis.

Within the endemic region, the annual incidence of blastomycosis ranges from 0.11 to 1.94 cases per 100,000 persons (Table 264.1), and the overall mortality rate is 0.21 per 1 million person-years.[41–61] A study analyzing a sample of Medicare beneficiaries (1999–2008) reported a nationwide incidence of 0.7 per 100,000 with the highest rates in the Midwest and Southern United States.[62] Within the endemic region, certain areas are considered hyperendemic including Kenora (Ontario), Eagle River (Wisconsin), Vilas County (Wisconsin), and south-central Mississippi (see Table 264.1).[43,53,59] In the mid-1980s, Washington Parish in Louisiana was recognized as a hyperendemic area with 6.8 cases per 100,000 persons (vs. a statewide incidence of 0.23/100,000).[63] Subsequent analyses demonstrated that the incidence in Washington Parish is lower at 1.29 per 100,000 but remains higher than the statewide incidence of 0.11 per 100,000.[55]

Although most cases of blastomycosis are sporadic, outbreaks have been reported from seven states, with multiple outbreaks occurring in Wisconsin, North Carolina, and Minnesota (Table 264.2).[13,14,34,63–79] These outbreaks have often been associated with activities that disrupt soil, such as construction or recreation along riverbanks (see Table 264.2). Although exposure to *Blastomyces* most commonly occurs in rural areas, soil disruption in urban areas can lead to infection (sporadic cases and outbreaks) (see Table 264.2). Similar to rural areas, urban blastomycosis

TABLE 264.1 Epidemiology of Blastomycosis in North America

STATE OR PROVINCE	YEARS	INCIDENCE PER 100,000 PERSONS	AGE (Y)	MALE:FEMALE	REFERENCE
Wisconsin	1973–1982	0.5 (0.32–0.72)	43.7[a]	1.8:1	41
	1986–1995	1.4	46[b]	1.5:1	42
	1984–1990	40.4 (Vilas County); 101.3 (Eagle River)	42[b]	1.6:1	43
	2002–2006	2.0	—	—	44
	2011–2015	1.61 (sporadic only)	48[b]	2.1:1	45
Minnesota	2002–2006	0.5	—	—	44
	2012–2016	0.6	46[b]	2.9:1	46
Illinois	1981–1989	1.94 (Rockford)	40[b]	2.2:1	47
	2001–2007	0.4–1.1[c]	41–47[b]	1.4–2.4:1	48
Michigan	2012–2016	0.14 (0.11–0.20)	—	4.4:1	49
Arkansas	2007–2016	0.39 (0.2–0.74)	—	1.97:1	49, 50
Missouri	1992–1999	0.2[d]	46.7[a]	2.1:1	51
Alabama	1992–1994	0.6	—	—	52
Mississippi	1979–1988	1.3[e]	46[a]	1.7:1	53
Louisiana	1987–2016	0.11	48[b]	1.4:1	54, 55
Tennessee	1988–1995	1.23[f]	52[a]	2.3:1	56, 57
	1996–2005	1.29[f]	59[a]	2.5:1	56, 57
Northwest Ontario	1989–2005	17.0	—	—	58
Kenora, Ontario	1997–1999	117.2	41.9[a]	1.1:1	59
Manitoba	1988–1999	0.62	38[a]	1.9:1	60
Ontario, Quebec, Manitoba, Saskatchewan	—	0.62	—	—	58

[a]Mean age.
[b]Median age.
[c]Highest incidence of infection occurred in northeastern Illinois (Cook, Lake, Kane, and Will counties).
[d]Highest incidence was in southeastern Missouri with the highest incidence in Mississippi County (12/100,000).
[e]Highest incidence was in central and south-central Mississippi (>5/100,000) and accounted for 63% of blastomycosis from 1979–1988.
[f]For Carter, Cocke, Greene, Hawkins, Johnson, Sullivan, Unicoi, and Washington counties, which are located in northeastern Tennessee.

TABLE 264.2 Outbreaks of Blastomycosis in the United States

YEAR	STATE	LOCATION	NO. CASES	RURAL OR URBAN	SOURCE OF OUTBREAK	REFERENCE
1953–1954	North Carolina	Pitt County	11	Rural	Not identified	13
1972	Minnesota	Big Fork	12	Rural	Cabin construction	64
1975–1976	North Carolina	Enfield	5	Rural	Peanut harvest	65
1974–1975	Illinois	Westmont	5	Urban	Construction	66
1979	Wisconsin	Namekegon River	8	Rural	Canoeing	67
1984	Wisconsin	Eagle River	48	Rural	Beaver lodge	14
1984	Virginia	Southampton County	4	Rural	Raccoon hunting	68
1985	Wisconsin	Tomorrow River	7	Rural	Fishing on river bank	34
1985	Wisconsin	Crystal River	7	Rural	Underground fort	34
1988	Wisconsin	Watersmeet Lake	32[a]	Rural	Hotel construction	69
1989	Tennessee	Elizabethton	3	Urban	Factory construction	70
1989–1990	Wisconsin	Oconto County	8	Rural	Not identified	71
1998	Colorado	Boulder	2	Rural	Prairie dog relocation	72
1998–2000	Wisconsin	Indian reservation	9	Rural	Likely excavation	73
1999	Minnesota	Mountain Iron	18	Urban	Excavation	74
2001–2002	North Carolina	Duplin County	8	Rural	Likely construction or excavation	75
2005–2008	Indiana	Indianapolis and surrounding counties	59	Urban	Highway construction	76
2006	Wisconsin	Lincoln County	21	Urban	Pine needle yard waste	77
2009–2010	Wisconsin	Marathon County	55	Urban	Not identified	78
2015	Wisconsin	Little Wolf River	90	Rural	Tubing on the river	79

[a]3 confirmed, 18 suspected, and 11 probable cases.

has been associated with waterways such as lakes, rivers, and streams; use of a community compost pile; and highway construction.[76,77,80,81]

Outbreak investigations have advanced the clinical understanding of blastomycosis and uncovered novel areas for further study. Analysis of outbreaks along the Eagle River, Tomorrow River, and Crystal River in Wisconsin helped define the ecologic niche and established that the incubation period of blastomycosis ranges from 3 weeks to 3 months.[14,34] Moreover, these investigations demonstrated that approximately 50% of people exposed to blastomycosis develop symptomatic disease, whereas the remaining 50% have asymptomatic or subclinical disease.[14] Analysis of blastomycosis outbreaks in Marathon County, Wisconsin, in 2006 and 2009–2010 found a high rate of blastomycosis in people of Hmong ethnicity (adjusted odds ratio of 12.1 [95% confidence interval 1.3–611.9; $P = .019$] by multivariable logistic regression).[78] The high rate of blastomycosis did not appear to be related to environmental exposure.[78] This led to the hypothesis that increased susceptibility to blastomycosis in people of Hmong ethnicity may be related to genetic predisposition.[78] In Ontario and Manitoba, people of Aboriginal ethnicity have an increased incidence of blastomycosis.[60,82,83]

PATHOGENESIS, VIRULENCE, AND HOST DEFENSE

Fungal traits that contribute to invasive disease include thermotolerance (e.g., growth at 37°C), intracellular survival, and upregulation of yeast phase–specific virulence factors that subvert host defenses.[84] Hyphal growth at ambient temperature promotes environment survival, genetic diversity through mating, and transmission to mammalian hosts via spores and hyphal fragments.[1,84] Temperature is the major stimulus that drives the reversible conversion between hyphae (22°C–25°C) and yeast (37°C).[84] The uptake of exogenous cysteine, which restarts mitochondrial respiration during the morphologic switch, is required to complete the conversion to yeast.[85,86] Compared with *Coccidioides* and *Paracoccidioides*, carbon dioxide tension and estradiol do not appear to affect the morphologic switch or growth of *Blastomyces*.[87–89] Following inhalation of conidia into the lungs, resident pulmonary macrophages engulf these infectious particles, of which a subpopulation will survive and convert to yeast. Within macrophage, the morphologic switch from conidia to yeast is accelerated.[90] The capacity for intracellular survival as well as extracellular replication is a shared biologic feature among the endemic dimorphic fungi.[84]

Once in the yeast phase, *B. dermatitidis* and *B. gilchristii* upregulate *Blastomyces*-adhesin-1 (BAD1, formerly known as WI-1), an essential virulence factor that is specific to the yeast phase.[91–96] In a murine model of pulmonary infection, *BAD1* was the most upregulated gene in the *Blastomyces* transcriptome.[3,97] BAD1 is secreted by yeast and can either bind back to the yeast cell surface via interactions with chitin in the cell wall or remain soluble in the extracellular environment.[92–94] BAD1 functions as an adhesin and an immune evasin.[91–96] It facilitates binding of yeast cells to host tissue via interactions with heparan sulfate and adherence to host immune cells via interactions with complement receptors (CR3) and CD14.[92,95,96] BAD1 on the yeast cell wall inhibits the production of tumor necrosis factor-α (TNF-α) by macrophages and neutrophils in a transforming growth factor-β–dependent manner.[95,96] Soluble BAD1 also inhibits TNF-α production, but independent of transforming growth factor-β.[95] In addition to blocking TNF-α, BAD1 inhibits $CD4^+$ T-lymphocyte activation, which results in reduced production of interleukin-17 (IL-17) and interferon-γ.[92] Importantly, deletion of *BAD1* severely attenuated the pathogenicity of *Blastomyces* yeast in a murine model of pulmonary infection, which indicates that this gene is essential for virulence.[91]

Other mechanisms that contribute to virulence include secretion of dipeptidyl peptidase IVA (DppIVA), relative resistance to oxidative and nitrosative killing, and alteration of yeast cell wall carbohydrates. DppIVA is a serine protease that inactivates granulocyte-macrophage colony-stimulating factor, which in turn impairs recruitment of innate immune cells into the lungs and inhibits macrophage and neutrophil activation.[98] Silencing of DppIVA using RNA interference results in yeast cells with attenuated virulence in vivo and reduced survival when cocultivated with activated immune cells.[98] Compared with conidia, yeast is more difficult for macrophages to kill and is less susceptible to reactive oxygen species.[99] The resistance to oxidative damage may be due to upregulation of superoxide dismutases and catalase in yeast during infection.[3,97]

Blastomyces yeast suppresses the production of nitric oxide by macrophages; however, the mechanism underlying this defense strategy remains to be elucidated.[100] During the temperature-dependent morphologic switch, the amount of β-(1,3)-glucan in the cell wall decreases from 40% in hyphae to less than 5% in yeast.[101] This reduction has the potential to limit recognition of yeast by the dectin-1 and mannose receptors on host immune cells.[102] In addition, the reduction of β-(1,3)-glucan impairs the ability of echinocandin antifungals to effectively kill *Blastomyces* yeast.[103]

To uncover novel virulence factors, in vivo transcriptional profiling using RNA sequencing has been performed on RNA isolated from *Blastomyces* yeast during murine pulmonary infection.[3,97] Compared with controls (yeast and mycelia grown in medium alone or yeast cocultivated with macrophages in vitro), 72 genes were significantly upregulated more than twofold during pulmonary infection, independent of temperature, culture media, and interaction with macrophages.[3] A subset of these 72 genes contributed metal uptake (zinc, nickel) and amino acid metabolism (tyrosine, tryptophan, cysteine).[3] Exogenous uptake of zinc and nickel contributes to the virulence of *Candida albicans* and *Cryptococcus neoformans,* respectively.[104,105] The catabolism of L-cysteine influenced virulence of *C. albicans* in a murine model of infection, and sulfite, a breakdown product of L-cysteine, promoted keratin breakdown by dermatophytes such as *Arthroderma benhamiae*.[106,107] Ongoing research is deciphering the role of these processes in the pathogenesis of *Blastomyces* infection.

The application of molecular techniques to genetically manipulate fungi has led to the identification of genes that govern the temperature-dependent morphologic switch. The discovery of *DRK1* (dimorphism regulating kinase-1), which encodes a group III hybrid histidine kinase, provided the first genetic proof that the temperature-dependent morphologic switch from hyphae or conidia to yeast is essential for virulence.[108,109] Homologues of *DRK1* participate in the high-osmolarity glycerol signaling pathway, which promotes adaptation to osmotic stress, oxidative stress, and temperature. Silencing or deleting *DRK1* in *Blastomyces* or *Histoplasma* prevents the conversion of mycelia to yeast in response to an increase in temperature.[108] Thus *Blastomyces* and *Histoplasma* cells remain locked in the mold form at 22°C and 37°C, respectively.[108] Moreover, they are unable to upregulate yeast phase–specific virulence genes (*BAD1* in *Blastomyces, CBP1* in *Histoplasma*) and exhibit defects in the cell wall.[108] *DRK1*-silenced strains of *Blastomyces* and *Histoplasma* are avirulent in murine models of pulmonary infection.[108] Subsequent work in *T. marneffei* highlighted the conserved nature of *DRK1* on the phase transition. Deletion of the *DRK1* homologue in *T. marneffei* hindered the ability of conidia to germinate to yeast in macrophages.[110]

The phase transition in the other direction, from yeast to hyphae, following a drop in temperature is regulated in part by a GATA transcription factor encoded by *SREB* (siderophore biosynthesis repressor in *Blastomyces*).[111,112] Deletion of *SREB* results in (1) the failure of yeast to convert to hyphae at ambient temperature without affecting viability and (2) the inability to suppress the biosynthesis and uptake of iron-gathering molecules known as siderophores.[111,112] The defect in the morphologic switch is associated with a quantitative reduction in lipid droplets and decreased neutral lipid biosynthesis (triacylglycerol, ergosterol).[112] The addition of exogenous saturated fatty acids to *SREB* null mutants partially corrects the defect in lipid droplets and hyphal development.[112] The function of *SREB* appears to be conserved in other endemic dimorphic fungi. Targeted gene knockdown of *SRE1,* an *SREB* homologue in *H. capsulatum,* impairs hyphal conversion and siderophore biosynthesis.[113] In addition to *SREB* and *SRE1, N*-acetylglucosamine (GlcNAc) transporters NGT1 and NGT2 promote hyphal development in *Blastomyces* and *Histoplasma* spp.[114]

Although *Blastomyces* uses multiple strategies to subvert and evade the immune system, the host can mount a successful defense with innate and adaptive immune cells. Macrophages and neutrophils are capable of killing a large percentage of conidia inhaled into the lungs.[115] T lymphocytes coordinate the adaptive immune response to control infection by activating macrophages to become fungicidal against yeast.[116,117] This requires Th1 cytokines such as TNF-α and interferon-γ as well as the production of IL-17 by Th17 T lymphocytes.[116,117] Cell-mediated immunity following recovery from blastomycosis can last for at least 2 years.[118]

Cell-mediated immune defenses have the potential to be exploited to prevent invasive fungal infections. When injected subcutaneously, *BAD1* null (*BAD1*Δ) yeast induces sterilizing immunity in mice, which provides 100% protection against experimental pulmonary infection.[119] Thus *BAD1*Δ yeast can serve as a live, attenuated fungal vaccine. Following subcutaneous injection, *BAD1*Δ yeast is transported intracellularly by inflammatory monocytes to draining lymph nodes for antigen presentation to lymph node resident dendritic cells.[120] This results in priming of naïve $CD4^+$ T lymphocytes to differentiate into Th17 cells via dectin-2/FcRγ/Syk/Card9, dectin-3 (also known as MCL), and mannan receptor signaling pathways.[120–123] Once differentiated, Th17 cells migrate to the lungs in response to infection to mediate vaccine immunity by secreting IL-17 to recruit and activate phagocytes (neutrophils, macrophages).[117] In the absence of $CD4^+$ T cells, *BAD1*Δ-vaccinated mice use IL-17 $CD8^+$ T lymphocytes (Tc17 cells) to mediate protective vaccine immunity against lethal pulmonary infection.[124,125] Proliferation and activation of IL-17 $CD8^+$ T cells occurs through Myd88-Akt1-mTOR signaling.[126] The antigenic component of the *BAD1*Δ vaccine that induces T cell–based immunity is a 13–amino acid sequence in calnexin that is conserved among ascomycetes including *H. capsulatum, Coccidioides posadasii, Aspergillus fumigatus, Fonsecaea pedrosoi* (chromoblastomycosis), and *Pseudogymnoascus destructans* (white nose syndrome in bats).[127] This has led to the development of a calnexin-based vaccine. The addition of endoglucanase II as an adjuvant enhances the immunogenicity of the calnexin vaccine and protects mice against pneumonia.[128]

CLINICAL MANIFESTATIONS

Clinical recognition and diagnosis of blastomycosis are often delayed because the clinical manifestations are wide-ranging and often resemble other diseases.[129] Thus blastomycosis has been referred to as a "great pretender."[129] Pulmonary blastomycosis can mimic bacterial pneumonia, tuberculosis, and lung cancer with respect to symptoms and radiographic findings. Extrapulmonary dissemination, which can occur with or without pulmonary symptoms, can result in misdiagnosis. Skin lesions can clinically and histologically appear similar to pyoderma gangrenosum, sarcoidosis, basal cell carcinoma, and squamous cell carcinoma in the absence of fungal staining.[130,131] Similarly, laryngeal lesions can resemble malignancy.[130] Moreover, the incubation period of blastomycosis, which lasts 3 weeks to 3 months, results in clinical presentation throughout the year including winter. Many studies have demonstrated no seasonal peak with respect to onset of symptoms and diagnosis; however, one study suggested that localized pneumonia was more common in the autumn and winter, whereas diffuse pulmonary and extrapulmonary disease was more common in the spring.[43,53,132,133]

Blastomyces infection is most commonly acquired through inhalation of aerosolized conidia or mycelial fragments following disruption of soil related to recreational or occupational activities. Following evasion of host immune defenses, *Blastomyces* can remain in the lung or disseminate to other organs such as the skin, bone, brain, or prostate. Although the lung is the primary portal of entry, uncommon mechanisms of acquisition include direct inoculation of the skin from environmental trauma or laboratory accident (e.g., needlestick, injury during autopsy).[134,135] Rarely, cutaneous blastomycosis can develop through direct inoculation from infected oral secretions following the bite of an animal with severe pulmonary blastomycosis (e.g., dog, kinkajou)[134,136,137]; however, *Blastomyces* yeast is *not* transmitted from animal to human via the respiratory route. Direct cutaneous inoculation results in a localized cutaneous lesion with or without regional lymphadenopathy or lymphangitis.[134] Blastomycosis during pregnancy has the potential to result in transmission to the newborn, possibly via aspiration of infected secretions during birth or transplacentally.[138]

Pulmonary Blastomycosis

In patients with symptomatic blastomycosis, pulmonary infection is the most common clinical manifestation, occurring in 69% to 93% of patients.[a] The spectrum of pulmonary blastomycosis is heterogeneous

[a]References 53, 56, 57, 60, 82, 129, 133, 139, 140.

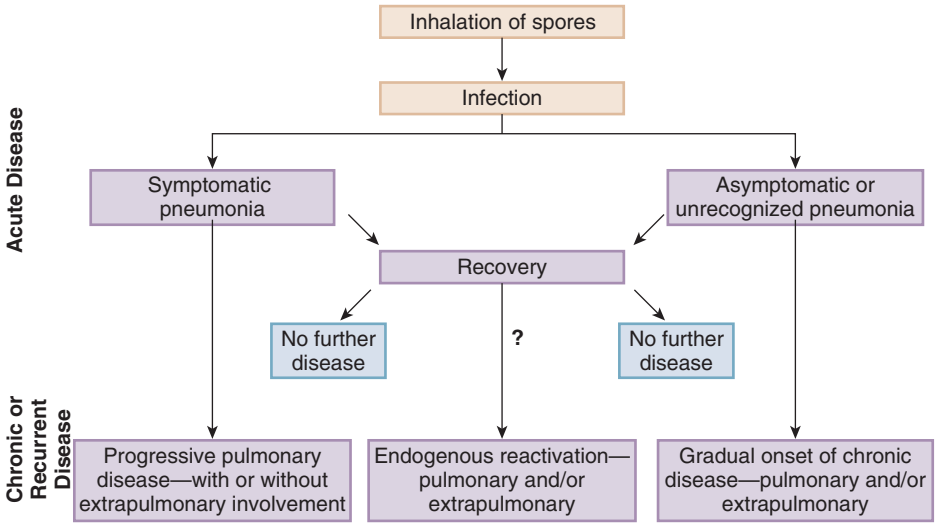

FIG. 264.3 Clinical classification of blastomycosis. *(Modified from Sarosi GA, Davies SF. Blastomycosis.* Am Rev Respir Dis. *1979;120:911–938.)*

FIG. 264.4 Left lung pneumonia. This patient had symptoms resembling acute bacterial pneumonia. Fungal smear of sputum using potassium hydroxide preparation demonstrated broad-based budding yeast. Sputum culture confirmed the diagnosis.

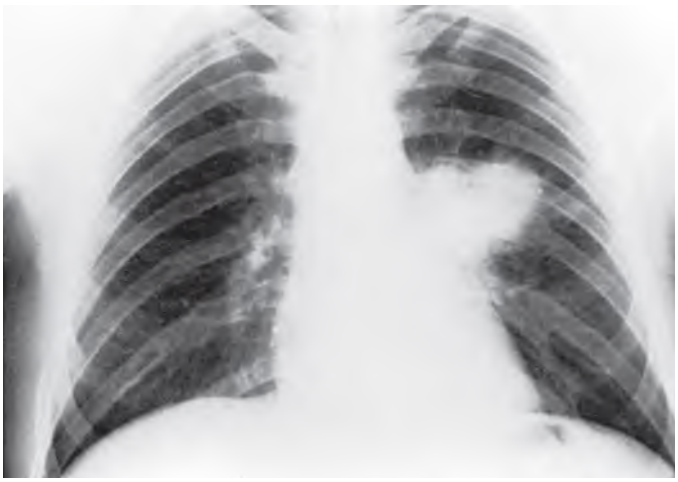

FIG. 264.5 Left lung mass. Radiographic appearance mimics that of carcinoma of the lung. *(Courtesy Dr. Stan Chapman, Jackson, MS.)*

and includes asymptomatic infection, brief influenza-like illness, acute pneumonia with or without respiratory failure, acute respiratory distress syndrome (ARDS), and chronic pneumonia (Fig. 264.3).[141] Acute pulmonary blastomycosis results in symptoms similar to community-acquired pneumonia (CAP) such as fevers, chills, cough, chest pain, malaise, decreased appetite, and hemoptysis.[b] There are no pathognomonic features on chest imaging to distinguish blastomycosis from other pulmonary diseases. Lobar consolidation, either unilobar or multilobar, is the most common finding and is indistinguishable from CAP (Fig. 264.4).[142] The next most frequent radiographic manifestations are masses, interstitial infiltrates, and nodules (Fig. 264.5).[142] Pleural effusion and hilar adenopathy are relatively uncommon.[142] Empyema is a rare manifestation.[143] Miliary blastomycosis is uncommon but is associated with severe infection and disseminated disease.[142] The clinical and radiographic features of acute pulmonary blastomycosis often result in an initial misdiagnosis of bacterial CAP and initiation of antibiotics, which fails to achieve clinical improvement.[129,144] In one study, a median of 2.5 antibiotic courses was administered before the diagnosis of blastomycosis was established.[144]

Patients with unrecognized or untreated pulmonary blastomycosis are at risk for progressive infection resulting in respiratory failure, ARDS, chronic infection, and extrapulmonary dissemination. Risk factors for severe pulmonary blastomycosis requiring admission to the intensive care unit include multilobar pneumonia, diabetes, and immunosuppression.[82,140,145] Retrospective studies from Tennessee, Indiana, Mississippi, Ontario, and Manitoba found that 4% to 15% of patients with blastomycosis met clinical criteria for ARDS.[c] Blastomycosis-induced ARDS is characterized by a fulminant clinical course and high mortality (40%–89%).[56,140,145–147] Patients with chronic pulmonary blastomycosis typically experience progressive symptoms of fever, chills, night sweats, weight loss, and hemoptysis over of a period of several months. Consolidation and cavitary lesions are usually associated with chronic infection.[142] Other manifestations include masslike lesions that resemble malignancy (see Fig. 264.5).[142]

Disseminated Blastomycosis

Once pulmonary infection is established, *Blastomyces* yeast can disseminate to nearly every organ in the body. On the basis of retrospective case studies, extrapulmonary spread occurs in 15% to 48% of sporadic cases.[d] An increased risk for extrapulmonary disease has been associated with prolonged duration of pulmonary symptoms and some forms of immunosuppression (e.g., increased risk of central nervous system [CNS] disease in human immunodeficiency virus (HIV)–seropositive patients with $CD4^+$ T-cell count <200 cells/mm^3).[60,149] In solid-organ transplant

[b]References 43, 53, 56, 60, 82, 139, 140.

[c]References 56, 57, 60, 76, 82, 140, 146.
[d]References 43, 53, 56, 57, 60, 76, 82, 133, 140, 148.

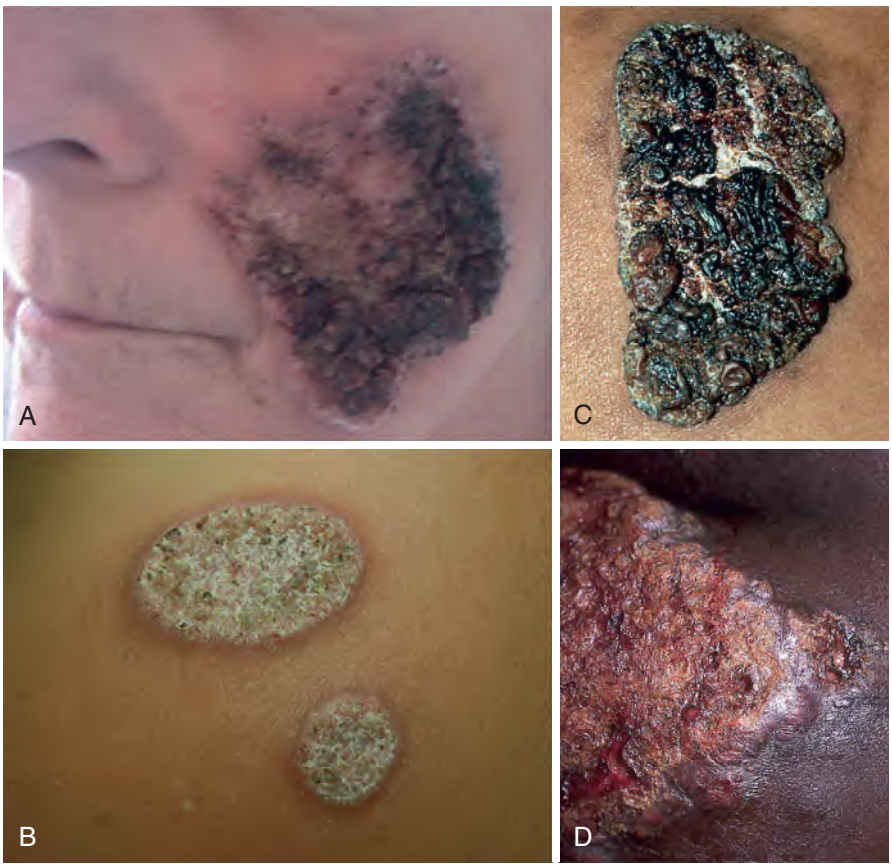

FIG. 264.6 Verrucous lesions secondary to blastomycosis. (A) Facial lesion. (B) Verrucous lesions with heaped-up margin with a satellite lesion on the shoulder. (C) Verrucous lesion on the back. (D) Verrucous lesions with beginning of ulcerations on the back. *(A courtesy Dr. Ryan Bariola, Little Rock, AR; B courtesy Dr. Dan Young, Rogers, AR, and Dr. Chris Schach, Fayetteville, AR.)*

(SOT) recipients, the rate of dissemination is 33% to 50%.[150,151] Evidence suggests that the infecting *Blastomyces* spp. may influence dissemination. An analysis of 240 human clinical isolates found that individuals infected with *B. dermatitidis* were more likely to develop disseminated disease (34.8%; 31 of 89 patients) than individuals infected with *B. gilchristii* (9.3%; 14 of 151 patients).[29] The mechanism for the differences in dissemination between *B. dermatitidis* and *B. gilchristii* is unknown.

The skin is the most common site for extrapulmonary infection, occurring in 40% to 80% of patients with disseminated disease.[19] Classically, cutaneous blastomycosis manifests as a papule that enlarges to form a verrucous or ulcerative lesion, which can involve the scalp, face, trunk, or extremities. Verrucous lesions are characterized by a raised, well-demarcated border with crusting (Fig. 264.6). Ulcerative lesions typically have an exudative base and heaped-up edges (Fig. 264.7). Ulcers can also develop from an underlying subcutaneous abscess or osteomyelitis.[130] Less common manifestations include widespread pustular lesions and subcutaneous nodules mimicking panniculitis.[152,153] Erythema nodosum, which is associated with histoplasmosis and coccidioidomycosis, is rare in blastomycosis. The severity of cutaneous involvement ranges from subtle, solitary lesions to large, destructive lesions that heal by scarring (see Fig. 264.7).[154] Skin biopsy usually demonstrates epidermal hyperplasia, papillomatosis, microabscess formation, neutrophilic infiltration, and noncaseating granulomas.[154,155] Because *Blastomyces* yeast can be difficult to visualize under light microscopy with hematoxylin and eosin staining, special fungal stains are required for optimal identification.

The bone is the second most common site of extrapulmonary blastomycosis, occurring in 15% to 44% of patients with disseminated infection.[e] Concomitant pulmonary or cutaneous disease is common.[156] However, the absence of lung infection does not exclude the diagnosis; slightly more than one-third of patients with a presumed pulmonary portal of entry for osteoarticular blastomycosis had no evidence of pulmonary blastomycosis at the time of diagnosis.[156] Bone involvement is characterized by pain, localized swelling, and sinus tract formation.[156] Soft tissue abscess and deep cutaneous ulceration can be associated with underlying osteomyelitis.[156] Most patients have a single site of bone involvement; however, a subset can have multifocal osteomyelitis or extension into the joint resulting in septic arthritis.[156,157] The most common bones affected include vertebral bodies, long bones (e.g., femur, tibia, humerus), and ribs; however, any bone can be involved including the sternum, scapula, pelvis, skull, and small bones of the hands or feet.[156–158] Vertebral osteomyelitis manifests with back pain and can be complicated by diskitis, epidural abscess, paraspinal abscess, psoas abscess, and vertebral body collapse (Fig. 264.8).[158,159] There are no radiographic features that can accurately distinguish blastomycosis from bacterial osteomyelitis, tuberculosis, or tumor. Imaging findings include periosteal reaction, sclerosis, lytic destruction, and skip lesions involving the vertebral bodies.[158] Bone biopsy with fungal culture and stains is needed for diagnosis. Histopathologic features include granulomatous inflammation, neutrophilic infiltrate, microabscesses, and necrosis.[157]

Genitourinary (GU) blastomycosis is considered the third most frequent site of dissemination. Early literature estimated that GU involvement occurred in 20% to 30% of cases; however, more recent case series suggest a lower rate (<10%).[f] Concomitant pulmonary or cutaneous blastomycosis is common.[160] The vast majority of GU blastomycosis affects men and results in prostatitis or epididymo-orchitis. Symptoms of prostatitis include dysuria, nocturia, suprapubic or perineal discomfort, and obstruction.[161,162] Urinalysis can show sterile pyuria or hematuria.[160–162] On examination, the prostate can be tender, enlarged, or indurated.[160] Epididymo-orchitis is characterized by pain, scrotal or testicular swelling, and, rarely, a draining sinus.[161] Diagnosis of GU blastomycosis can be facilitated by urine culture, collection of prostatic

[e]References 53, 56, 57, 82, 133, 140, 148.

[f]References 56, 57, 60, 82, 133, 140, 148.

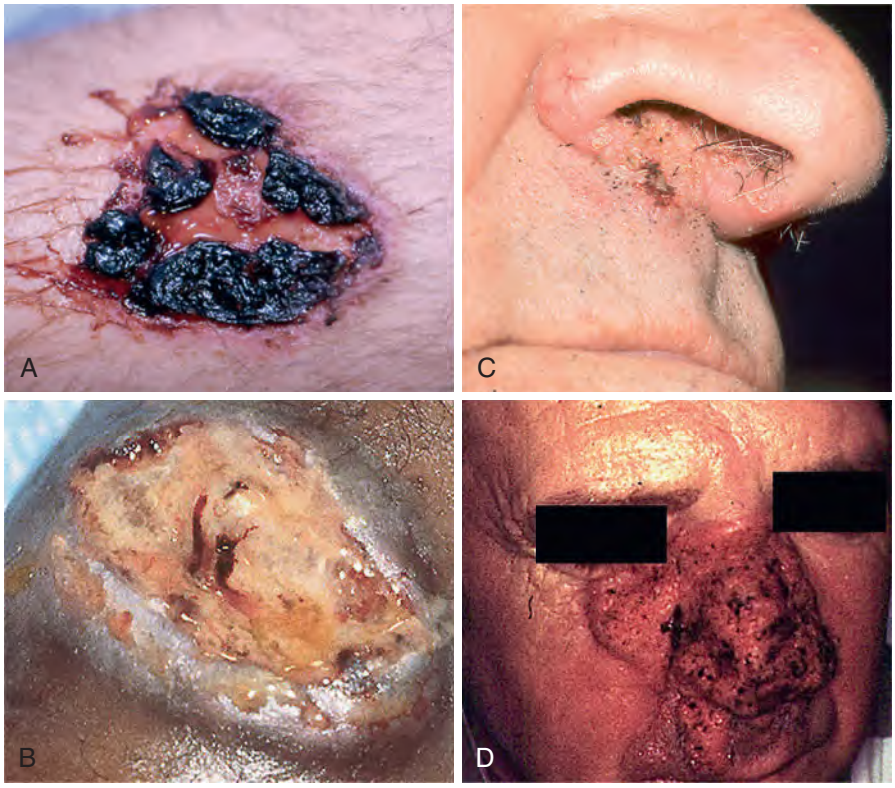

FIG. 264.7 Heterogeneity of cutaneous blastomycosis. (A) Ulcerative lesion on the leg in a patient with acquired immunodeficiency syndrome. (B) Large ulcer on the leg. (C) Small verrucous lesion on nares in a patient without other symptoms. (D) Extensive ulceration and cutaneous destruction from blastomycosis initially misdiagnosed as keratoacanthoma. When a new lesion appeared on the thigh, biopsy of both sites demonstrated *Blastomyces dermatitidis*.

secretions after massage, or needle biopsy.[161,162] Prostatic secretions and semen are potentially infectious with one reported case of male-to-female sexual transmission resulting in endometritis, salpingitis, and peritonitis.[163] GU involvement in women is rare and can include tubo-ovarian abscess with or without peritoneal involvement.[164]

Dissemination of *Blastomyces* to the CNS, which occurs in ≤10% of patients, can result in meningitis, brain abscess, or intracranial mass.[148,165] A subset of patients can have abscess or mass with concomitant meningitis.[165,166] Blastomycosis of the spinal cord (e.g., epidural abscess or granuloma) is rare.[166] Most cases of CNS blastomycosis are due to dissemination from the lungs; however, direct extension from overlying cranial osteomyelitis has been reported.[167] Most patients with CNS involvement (77%–81%) have evidence of extracranial blastomycosis involving organs such as the lung, skin, or bone.[165–168] Isolated CNS blastomycosis is uncommon.[165–168] Clinical features include headache, alteration in mental status, focal neurologic deficit, and seizures.[165–168] Symptoms are often progressive and are present for weeks to months before diagnosis is established.[165–168] Abscesses and mass lesions can involve the brainstem, cerebellum, or cerebrum.[167]

CNS blastomycosis can easily be misdiagnosed as tuberculosis or malignancy.[166,168,169] In patients with meningitis, cerebrospinal fluid (CSF) can have a neutrophilic or lymphocytic pleocytosis, elevated protein, and hypoglycorrhachia.[165] CSF cultures are positive in ≤45%.[165,166] In patients with brain masses, histopathology demonstrates granulomatous inflammation and necrosis.[167] In one study, cultures from biopsied tissue were positive in 71%.[167] Magnetic resonance imaging is the most sensitive imaging modality for CNS blastomycosis and can show meningeal or parenchymal enhancement.[167] Complications of CNS infection include mass effect from edema, cerebral herniation, and hydrocephalus.

Unusual manifestations of blastomycosis include ocular invasion, otitis media, sinusitis, lesions of the oral cavity (papular, verrucous, ulcerative) with extension to the mandible, endocarditis, splenic abscess, biliary obstruction leading to cholangitis, pancreatic mass, adrenal insufficiency from granulomatous destruction, thyroid mass, breast mass or abscess, renal abscess, and lymphadenopathy.[130,164,170,171] Laryngeal blastomycosis is uncommon but well described. Patients typically present with progressive hoarseness with variable degrees of cough, dyspnea, sore throat, and dysphagia.[171–173] Laryngoscopic examination can demonstrate polypoid masses and vocal cord paralysis.[171–173] Histopathology of vocal cord lesions is characterized by pseudoepitheliomatous hyperplasia, which can mimic malignancy if fungal staining is not performed.[171–173] Misdiagnosis as laryngeal cancer has led to patients undergoing laryngectomy and radiation therapy.[171–173] Dissemination of *Blastomyces* to the peritoneum is rare and associated with underlying tubo-ovarian abscess or abdominal organ infection.[164] Symptoms include fever, night sweats, weight loss, and abdominal discomfort related to new-onset ascites resulting in increased abdominal girth.[164] Most patients have antecedent or concomitant pulmonary blastomycosis.[164] During laparoscopy or laparotomy, nodular studding of the peritoneum, omentum, and bowel is frequently observed.[164] Ascitic fluid is characterized by pleocytosis with a lymphocytic (or rarely neutrophilic) predominance.[164] In patients with peritoneal blastomycosis, tuberculosis has been initially misdiagnosed.

Blastomycosis in Immunocompromised Patients

Although most patients with blastomycosis have intact immune defenses, *Blastomyces* is capable of infecting individuals immunocompromised by SOT, acquired immunodeficiency syndrome (AIDS), TNF-α antagonists, high-dose steroids, and malignancy.

The incidence of blastomycosis in SOT recipients in the endemic region is 0.13% to 0.14%, which is lower than the incidence of posttransplant histoplasmosis or coccidioidomycosis.[150,151,174] The onset of blastomycosis is highly variable, ranging from 0.4 to 250 months, which likely reflects the variability in disease acquisition including primary infection after transplant, reactivation of latent disease related to immunosuppression, and conversion of subclinical pretransplant infection to symptomatic posttransplant disease.[150] Donor-derived blastomycosis has not yet been reported. There is near-equal distribution of patients who develop blastomycosis before or after the first year of SOT.[150,151]

FIG. 264.8 **CT imaging demonstrating vertebral osteomyelitis.**

The most common manifestation is pneumonia, which is frequently complicated by respiratory failure or ARDS.[150,151] Symptomatic coinfection with opportunistic pathogens such as cytomegalovirus, varicella-zoster virus, and *Aspergillus* can occur in a subset of patients.[150] Extrapulmonary dissemination occurs in 33% to 50%, which is a rate similar to the general population analyzed in large case series (15%–44%).[150,151,174] Mortality ranges from 33% to 38% but increases to 67% in patients with ARDS.[150,151,175]

Within the endemic area, blastomycosis in patients with HIV is relatively rare. In the largest case series, which was published before the implementation of highly active antiretroviral therapy, the majority of patients had pulmonary disease (87%) with dissemination to other organs (53%) and $CD4^+$ T-cell counts <200/mm^3.[149] Multiple organ involvement was common with 33% having three or more sites of infection. Surprisingly, 40% of patients developed CNS blastomycosis, which is uncommon in other forms of immunosuppression including SOT.[149–151] A review of clinical cases published before 1994 had similar findings with 85% of patients having $CD4^+$ T-cell counts <200/mm^3 and high rates of extrapulmonary (67%) and CNS (46%) blastomycosis.[176] Since the mid-1990s, there has been a paucity of published clinical data regarding blastomycosis in patients with HIV infection.

In 2008, the US Food and Drug Administration issued a warning regarding TNF-α inhibitors increasing the risk for blastomycosis, histoplasmosis, and coccidioidomycosis.[177] A retrospective study analyzing patient health claims data from the years 2007–2009 identified 158 patients with mycobacterial or fungal infection in the setting of TNF-α inhibitor therapy.[178] *Mycobacterium tuberculosis* (61%) and *H. capsulatum* (60%) were the two most common infections (28.5% of persons had more than one infection; range, 2–8 infections per patient).[178] Less common infections were coccidioidomycosis (10%), blastomycosis (4%), *Cryptococcus* (3%) and *Pneumocystis* (2%).[178] There is very limited clinical information regarding clinical presentation and risk for dissemination of blastomycosis in individuals receiving TNF-α antagonists.[177–179]

Blastomycosis has been reported in patients with malignancies including head and neck cancer, breast cancer, gastrointestinal cancer, acute myelogenous leukemia, chronic lymphocytic leukemia, multiple myeloma, and Hodgkin disease.[175,180] Most patients have pneumonia, and extrapulmonary dissemination is common (50%).[175]

Blastomycosis is rare in patients with primary immunodeficiency disorders. Case reports include disseminated blastomycosis in a 59-year-old man with idiopathic $CD4^+$ lymphocytopenia and a 12-year-old girl with necrotizing pulmonary blastomycosis complicated by lung abscess in the setting of GATA2 deficiency.[181,182] In contrast, histoplasmosis and coccidioidomycosis has been described in individuals with CD40 ligand deficiency, interferon-γ deficiency, *STAT1* defect, and hyperimmunoglobulinemia E syndrome (Job syndrome).[183] Dimorphic fungal infections have not been associated with lymphocyte adhesion disorders or chronic granulomatous disease.[183]

Pregnancy

Blastomycosis in pregnancy is uncommon with clinical descriptions limited to 23 well-reported cases.[138] The majority of patients (91%) present during the second or third trimester with pneumonia (74%) or disseminated infection (48%).[138] Despite the high rate of disseminated disease, placental involvement appears to be uncommon.[138] Most newborns were delivered vaginally and were healthy; however, two neonates died of pulmonary blastomycosis at 18 and 21 days of life.[138,184,185] There is potential for mother-to-infant transmission; however, the route is undefined. Hypotheses include intrauterine transmission and aspiration of infected vaginal secretions during birth.[184,185] The optimal timing and route of delivery in pregnant patients with untreated blastomycosis in the third trimester is unknown.[138] Blastomycosis during pregnancy does not appear to increase the risk for congenital malformations.

DIAGNOSIS

The diagnosis of blastomycosis can be challenging; it requires a high degree of suspicion because the diverse clinical and radiographic presentations mimic more common entities such as CAP, tuberculosis, and malignancy. Even within the endemic area, the diagnosis of blastomycosis is frequently delayed longer than 1 to 2 months.[133,144] For individuals who reside in or visit endemic areas, clinical manifestations that should prompt evaluation for blastomycosis include pneumonia with cutaneous lesions; CNS disease (abscess, mass, meningitis) with concomitant pneumonia or skin lesions; new-onset ascites with antecedent or concomitant pneumonia; and the failure of lung, bone, or skin infections to respond to antibiotic therapy. A detailed exposure history has the potential to facilitate a timely diagnosis. Occupational and recreational activities associated with blastomycosis include construction (road, home, commercial), canoeing, tubing, hiking, fishing by riverbanks, logging, beaver dam exploration, and use of a community compost pile. Workers in microbiology laboratories or the veterinary field are at risk for primary cutaneous blastomycosis from direct inoculation by laboratory or medical instruments. The concurrent diagnosis of blastomycosis in a companion animal such as a dog or cat suggests a common exposure. The incidence of canine blastomycosis is 10- to 13-fold higher than human blastomycosis.[186] Thus canine blastomycosis can be a harbinger for human blastomycosis.[187]

Once suspected, establishing the diagnosis of blastomycosis is usually straightforward. Staining of clinical specimens is the most expeditious method to identify *Blastomyces* yeast but is often underused.[188] Calcofluor, 10% potassium hydroxide, or Papanicolaou is used to stain respiratory specimens (sputum, tracheal aspirate, bronchoalveolar fluid) or purulent drainage (Fig. 264.9). Sensitivity of these stains is 50% to 90% for respiratory secretions.[27] For tissue specimens, Gomori methenamine silver or periodic acid–Schiff are used because *Blastomyces* yeast is poorly visualized by Gram or hematoxylin and eosin stains (see Fig. 264.9).[27] Moreover, if *Blastomyces* is in the differential diagnosis, the microbiology laboratorian or pathologist should be notified to perform fungal stains. A presumptive diagnosis is established when broad-based budding yeast (8–20 μm) with a doubly refractile cell wall is visualized.[27,141] Delayed

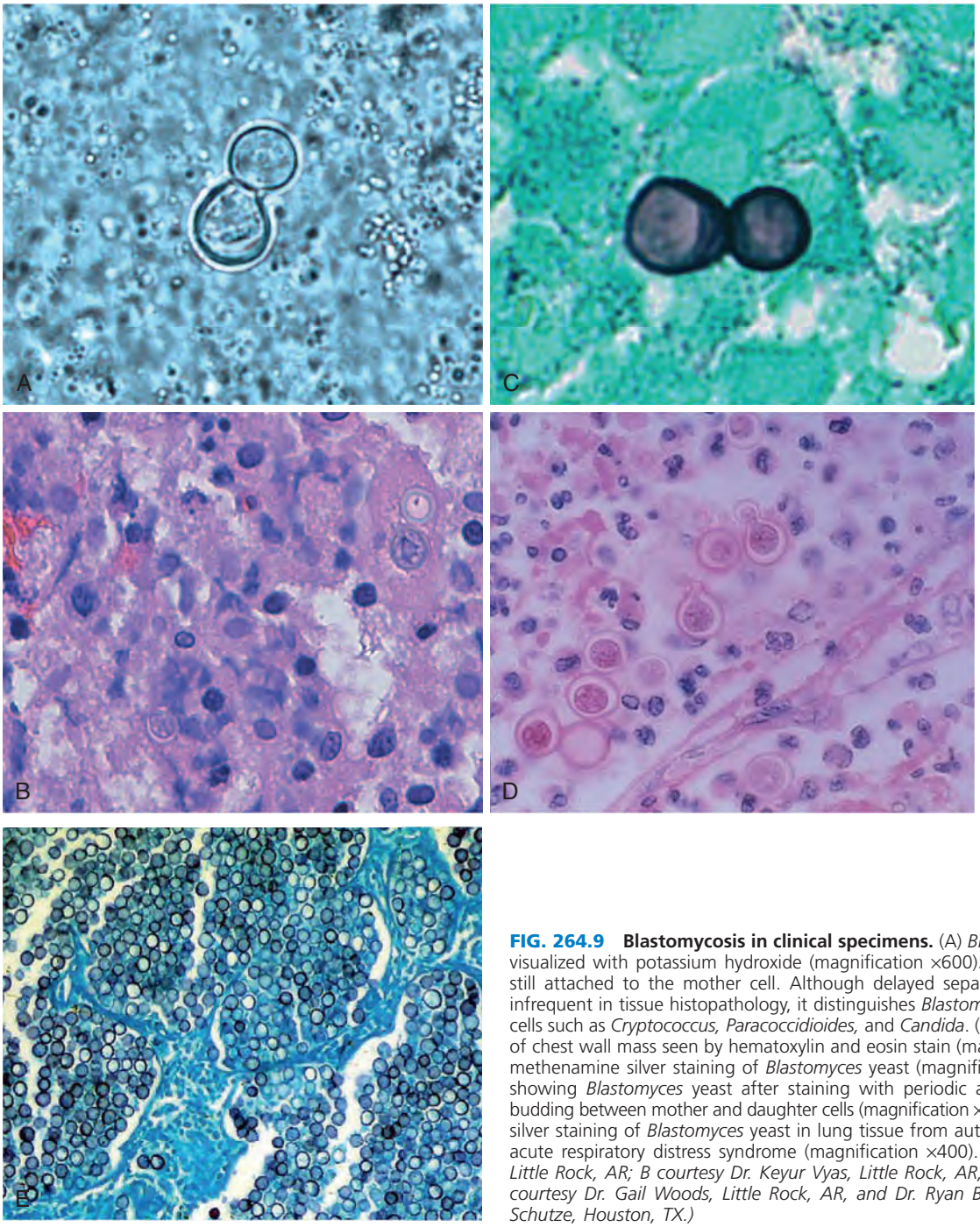

FIG. 264.9 Blastomycosis in clinical specimens. (A) *Blastomyces* yeast from exudate visualized with potassium hydroxide (magnification ×600). Note the large daughter cell still attached to the mother cell. Although delayed separation of the daughter cell is infrequent in tissue histopathology, it distinguishes *Blastomyces* from similarly sized yeast cells such as *Cryptococcus, Paracoccidioides,* and *Candida*. (B) *Blastomyces* yeast on biopsy of chest wall mass seen by hematoxylin and eosin stain (magnification ×600). (C) Gomori methenamine silver staining of *Blastomyces* yeast (magnification ×600). (D) Lung biopsy showing *Blastomyces* yeast after staining with periodic acid–Schiff. Note broad-based budding between mother and daughter cells (magnification ×400). (E) Gomori methenamine silver staining of *Blastomyces* yeast in lung tissue from autopsy of a patient who died of acute respiratory distress syndrome (magnification ×400). *(A courtesy Dr. Ryan Bariola, Little Rock, AR; B courtesy Dr. Keyur Vyas, Little Rock, AR; C courtesy Dr. Keyur Vyas; D courtesy Dr. Gail Woods, Little Rock, AR, and Dr. Ryan Bariola; E courtesy Dr. Gordon Schutze, Houston, TX.)*

detachment of the daughter cell is also a useful sign. The size of the yeast and budding pattern allow *Blastomyces* to be distinguished from other endemic fungi including *H. capsulatum* (small, narrow-based budding), *Coccidioides* spp. (spherules with endospores), *Paracoccidioides* ("pilot wheel" multiple budding yeast), *Sporothrix schenckii* (round or cigar-shaped with a narrow bud), and *T. marneffei* (oblong with central septum between mother and daughter cell). The presence of granulomatous inflammation with neutrophils (e.g., pyogranulomas) on a tissue biopsy specimen should prompt examination for yeast using special stains such as Gomori methenamine silver (see Fig. 264.9). Morphologic identification of *Blastomyces* yeast correlates well with culture results.[189] Moreover, the results of stained clinical specimens are known within 24 to 48 hours, which is often before culture and nonculture diagnostic tests results are available.

Identification of *Blastomyces* on specialized culture media such as brain-heart infusion, potato dextrose agar, or Sabouraud dextrose agar provides definitive diagnosis. Growth in culture is slow and requires 5 days to 4 weeks of incubation.[27,141] Most laboratories use 25°C to 30°C incubator temperatures, which promotes mycelial growth.[27] Because the mycelial form can appear similar to other fungal species, confirmation is required. This can include chemiluminescent DNA probes, polymerase chain reaction (PCR) amplification of specific target sequences, and conversion to yeast.[27] In several case series, 72% to 87% of patients with blastomycosis had positive cultures[53,56,76,82,140]; however, in one study the rate was only 64%.[148] The diagnostic yield for sputum cultures obtained by noninvasive means is 75% and for bronchoscopy is 92%.[188]

Nonculture diagnostics include serologic and antigen testing. Most studies have demonstrated that serologic methods such as complement fixation (CF) and immunodiffusion (ID) have poor sensitivity (≤25% for CF and ≤40% for ID).[14,56,188,190–192] Moreover, the sensitivity of ID appears to be influenced by burden of infection with reduced sensitivity in patients with localized infection.[190] An enzyme immunoassay that

detects immunoglobulin G antibodies against the *Blastomyces* A antigen has demonstrated improved sensitivity of 77% to 83%.[191,193]

Serologic testing has largely been supplanted by a quantitative antigen assay that detects a galactomannan component shed from the *Blastomyces* cell wall.[194–197] Specimens collected for antigen analysis can include urine, blood, bronchoalveolar lavage (BAL), and CSF. In patients with culture-proven blastomycosis, the sensitivity of the urine assay is 76.3% to 92.9%.[195–197] Similar to serologic testing, the sensitivity of the antigen assay can be influenced by the burden of infection.[195] Although the *Blastomyces* antigen test can be performed on BAL samples, robust data exist only for *H. capsulatum*.[198,199] In one study, five of eight patients (62.5%) with pulmonary blastomycosis had a positive BAL antigen.[197] Data regarding sensitivity of the assay in CSF for patients with CNS blastomycosis are limited.[195,200,201] The antigen assay cross reacts with other endemic dimorphic fungi including *H. capsulatum* (96%–100%), *Paracoccidioides* (100%), and *T. marneffei* (70%).[194] This cross-reactivity lowers the specificity to 76.9% to 79%.[194,195] The impact of a false-positive result is limited because histoplasmosis and blastomycosis are treated similarly, and the geographic distribution of *Paracoccidioides* spp. (Southern Mexico, Central America, South America) and *T. marneffei* (southeast Asia and China) does not overlap with *Blastomyces*. Rarely, the antigen assay cross-reacts with *Cryptococcus* (2.9%) or *Aspergillus* (1.1%).[194] The mechanism underlying these cross-reactions is likely related to varying degrees of similarity of the galactofuranose side chains in galactomannan among these different fungal species.[202] Moreover, cross-reaction of the Platelia *Aspergillus* galactomannan assay from BAL samples has been reported in patients with pulmonary blastomycosis.[202] Serial measurement of the urine antigen can be used to monitor response to antifungal therapy where a decline in antigen levels is associated with successful treatment.[197]

The serum β-(1,3)-glucan test is unreliable for diagnosis of blastomycosis because the yeast cell wall contains very little of this carbohydrate.[101,203] In the hyphal phase, β-(1,3)-glucan accounts for 40% to 50% of cell wall glucan, but in the yeast phase, it represents less than 5%.[101,203] In contrast, the serum β-(1,3)-glucan test can be positive in patients with histoplasmosis and coccidioidomycosis.[203,204]

Discoveries in the laboratory are beginning to influence the clinical diagnosis of blastomycosis. A serologic assay that detects antibodies against BAD1 rather than the A antigen has been developed. Compared with CF and ID, the BAD1 antibody assay has a sensitivity of 87% and specificity of 94% to 99%.[192] When this assay is combined with the *Blastomyces* antigen test, the sensitivity increases to 97%.[192] Moreover, this assay does not cross-react with other thermally dimorphic fungi because BAD1 is unique to *Blastomyces*. A real-time PCR assay that amplifies the *BAD1* promoter from *Blastomyces* in culture or paraffin-embedded tissues has been developed.[205] Similarly, a PCR assay that uses primers against *BAD1* has been developed to identify *Blastomyces* in the soil.[206] This assay has been used in epidemiologic investigations of human and canine outbreaks of blastomycosis.[77,206]

TREATMENT

The IDSA and ATS have published similar guidelines for the treatment of blastomycosis.[19,20] Antifungal therapy for blastomycosis is based on the severity of infection, presence or absence of CNS involvement, underlying immunodeficiency, and pregnancy status. All patients with a diagnosis of blastomycosis should be offered antifungal therapy. Although there are scattered reports of self-limited, acute pulmonary blastomycosis, most experts agree that antifungal therapy should be initiated to minimize the risk of relapse or dissemination. Moreover, there are no clinical or laboratory features that can accurately determine if blastomycosis will be self-limited and not disseminate. If a patient is not treated, careful follow-up for several years is required.

Before initiation of antifungal therapy, baseline evaluation of hematologic, hepatic, and renal function should be performed. A detailed review of all medications is required to avoid harmful drug-drug interactions. Fluconazole, voriconazole, and posaconazole can lengthen the QT interval, which can lead to fatal cardiac arrhythmias. In contrast, isavuconazonium sulfate shortens the QT interval and is contraindicated in patients with congenital short QT syndrome.[207] Azole antifungals elevate serum concentrations of statins metabolized by cytochrome P-450 3A4, which can increase the risk for rhabdomyolysis. Pravastatin is metabolized through a different pathway and can be safely used. Azole antifungals can also interact with immunosuppressive medications, sulfonylureas, antiarrhythmics, and anticonvulsants. Itraconazole has negative inotropic effects that can precipitate congestive heart failure and should be used with caution in patients with ventricular dysfunction.[208] The negative inotropic effect is unique to itraconazole and has not been observed with other azoles. For women of childbearing age, a pregnancy test must be performed because azole antifungals increase the risk for spontaneous abortion and are teratogenic.[209,210] Periodic laboratory monitoring is recommended in patients on azole therapy.[19]

Recommendations for antifungal therapy are based on prospective trials, case series, and expert opinion. Similar to other uncommon fungi, large clinical trials are challenging to conduct due to relatively low numbers of patients with a diagnosis of blastomycosis. The first clinical trials involving azole antifungals assessed the efficacy of ketoconazole 400 mg daily, which cured 79% to 81% of patients.[211,212] However, owing to endocrine side effects and increased risk of relapse (10%–14%), ketoconazole is no longer recommended.[19] An open-label, multicenter randomized controlled trial found that fluconazole 400 to 800 mg daily for a median of 8 months (range, 2–24 months) resulted in cure in 64% and improvement in 23% of patients with pulmonary and non-CNS disseminated blastomycosis.[16] The most common side effects were gastrointestinal effects, alopecia, and chapped lips.[16] The role of fluconazole is limited because it is not as efficacious as itraconazole. In addition, fluconazole minimal inhibitory concentrations (MICs) are higher than MICs of other azoles.[213] A prospective, open-label, nonrandomized trial demonstrated that itraconazole 200 to 400 mg daily for a median of 6 months (range, 3–24.4 months) cured 95% of patients with pulmonary or non-CNS extrapulmonary blastomycosis.[17] At the present time, itraconazole is considered the drug of choice for patients with mild-to-moderate non-CNS blastomycosis.[19,20] Voriconazole, posaconazole, and isavuconazonium sulfate have in vitro activity against *Blastomyces,* and case reports suggest that these agents can be effective.[150,167,213–215]

Among polyene antifungals, amphotericin B (AmB) deoxycholate results in cure in 77% to 91% when total cumulative dosage exceeds 1 g and in 97% when cumulative dosage is >2 g.[19] A cumulative dose of 2 g is recommended by the IDSA, and 1.5 to 2.5 g is recommended by the ATS if azole step-down therapy is not done.[19,20] Although no clinical trials have compared lipid and deoxycholate formulations for blastomycosis, animal studies and clinical experience suggest they should be equally efficacious.[19] In adults, lipid formulations are preferred over AmB deoxycholate because the former have lower rates of nephrotoxicity and infusion reactions.

For patients with pulmonary or disseminated blastomycosis that is mild to moderate in severity, itraconazole is considered the drug of choice for initial treatment (Table 264.3).[19,20] In general, diagnosis and treatment of patients with mild-to-moderate blastomycosis occur in the outpatient setting. Duration of itraconazole treatment is 6 to 12 months, with osteoarticular infection requiring at least 12 months of therapy.[19,20] For patients with pulmonary or disseminated disease that is moderately severe or severe, AmB (deoxycholate or lipid) is recommended for induction therapy of 1 to 2 weeks (or until clinical improvement) followed by a 6- to 12-month course of itraconazole (see Table 264.3).[19] Patients with moderately severe or severe blastomycosis usually require admission to the hospital (general ward, intermediate care unit, or intensive care unit).

All immunosuppressed patients (e.g., SOT recipients) should be treated with 1 to 2 weeks of AmB followed by 1 year of itraconazole (see Table 264.3).[19,20] To minimize nephrotoxicity, lipid AmB is preferred over AmB deoxycholate. The IDSA guidelines state that for patients with irreversible immunosuppression, lifelong suppressive therapy may be required, but specific criteria for selection of these patients is not provided due to the heterogeneity of this patient population.[19] For SOT recipients who have received the recommended duration of therapy, relapse is uncommon, and lifelong therapy is usually not required.[150] However, in patients with profound cell-mediated immunosuppression that is anticipated to be prolonged, suppressive antifungal therapy may need to be considered. For AIDS-associated blastomycosis, itraconazole suppression is recommended and should be continued until the patient

TABLE 264.3 Treatment of Blastomycosis in Adults

INDICATION	THERAPY
Mild-to-moderate blastomycosis	Itraconazole 200 mg once or twice a day for 6–12 months[a]
Moderately severe–to–severe blastomycosis	Liposomal AmB 3–5 mg/kg daily for 1–2 weeks,[b] then itraconazole 200 mg PO once or twice daily for 6–12 months[a]
Immunocompromised state	Liposomal AmB 3–5 mg/kg daily for 1–2 weeks, then itraconazole 200 mg PO once or twice daily for 12 months[a]
CNS blastomycosis	Liposomal AmB 5 mg/kg daily for 4–6 weeks, then fluconazole 800 mg daily, itraconazole 200 mg bid to tid, or voriconazole 200–400 mg bid for at least 12 months
Pregnancy	Liposomal AmB 3–5 mg/kg daily for 6–8 weeks[c]

[a]Itraconazole should be loaded as 200 mg PO tid for 3 days, then 200 mg PO daily once or twice a day with dosing frequency based on serum itraconazole levels (itraconazole plus hydroxyitraconazole).
[b]Can substitute with AmB deoxycholate 0.7–1 mg/kg.
[c]Azoles should be avoided in pregnancy.
AmB, Amphotericin B; *bid,* twice daily; *CNS,* central nervous system; *PO,* per os (orally); *tid,* three times a day.

is on antiretroviral therapy, has received ≥1 year of antifungal therapy, and has a $CD4^+$ T-cell count that is >150 cells/μL.[19,20]

For CNS blastomycosis, liposomal AmB 5 mg/kg/day is recommended for 4 to 6 weeks followed by itraconazole 200 mg two to three times a day, fluconazole 800 mg daily, or voriconazole 200 to 400 mg twice a day for at least 12 months of therapy (see Table 264.3).[19] Liposomal AmB is the preferred formulation because it penetrates the CSF better than amphotericin B lipid complex or AmB deoxycholate.[19,20,216] Although fluconazole has higher MICs than other azoles against *Blastomyces,* it has excellent CSF penetration.[217] The ATS guidelines state that high-dose fluconazole can be used as add-on therapy to liposomal AmB in patients who have severe or refractory CNS disease or are immunocompromised.[20] However, clinical data regarding combination antifungal therapy for blastomycosis are very sparse. Despite limited penetration into the CSF (<10% of serum), itraconazole has been used to successfully treat CNS blastomycosis.[167] Voriconazole has very good penetration into the CSF and has been used to successfully treat CNS blastomycosis.[167,217]

For pregnant women, liposomal AmB 3 to 5 mg/kg/day is considered the antifungal of choice because it is not teratogenic and is better tolerated than AmB deoxycholate.[19] Azole antifungal therapy is not recommended. Fluconazole during pregnancy in animals and probably in humans is associated with an Antley-Bixler–like syndrome, which is characterized by craniofacial, skeletal, and cardiac deficits.[209] Itraconazole increases the risk for spontaneous abortion.[210] Voriconazole and posaconazole cause skeletal abnormalities in animal models.[210] Echinocandins are not an option for treatment of blastomycosis because these agents have poor activity against *Blastomyces* yeast and are teratogenic in animal models.[19,20,210]

Effective management of blastomycosis requires minimizing drug toxicities, optimizing bioavailability of oral azole antifungals, and therapeutic drug monitoring. AmB deoxycholate and lipid formations require frequent monitoring of serum creatinine, potassium, magnesium, and bicarbonate. Salt loading using intravenous normal saline before and after amphotericin infusion can reduce nephrotoxicity.[218] Most patients receiving AmB require potassium and magnesium supplementation to prevent or treat hypokalemia and hypomagnesemia from urinary wasting of these electrolytes. In contrast, bicarbonate replacement is rarely required. Itraconazole can be administered as a capsule or oral solution (100 mg/10 mL). Initial therapy with either formulation should be administered as 200 mg three times a day for 3 days followed by 200 mg once or twice a day thereafter with dosing based on serum drug levels.[19] To optimize the bioavailability of itraconazole capsules, they need to be taken with an acidic beverage and food. In contrast, itraconazole solution is better absorbed and should be administered without food. Moreover, gastric acidity is not required for absorption of the liquid solution, and it can be used in patients on H2 blockers or proton pump inhibitors. The capsule formulation should not be used in individuals taking medications that reduce gastric acidity. If SUBA-itraconazole is used, the dose is 130 to 260 mg daily. With any itraconazole formulation, serum itraconazole levels should be measured at 14 days of therapy, and due to its long half-life, drug levels can be obtained independent of when the drug was administered. Goal serum itraconazole level is 1 to 5 μg/mL when itraconazole and hydroxyitraconazole concentrations are added together.[219] Serum concentrations >10 μg/mL are not needed and can be associated with significant side effects.[19] In addition to its negative inotropic effects, itraconazole can result in hypokalemia. Fluconazole has excellent bioavailability, it can be administered regardless of gastric acidity or food, and therapeutic drug monitoring is not required. Oral voriconazole should be taken without food, and goal serum trough concentrations are 1 to 5.5 μg/mL.[219] Delayed-release posaconazole tablets and isavuconazonium sulfate capsules are well absorbed and can be administered regardless of food or gastric acidity. Therapeutic drug monitoring is currently recommended for posaconazole. Voriconazole, posaconazole, and isavuconazonium sulfate can also be administered intravenously.

Despite aggressive antifungal therapy with AmB, mortality due to blastomycosis-induced ARDS remains high. The role of adjunctive steroids to decrease pulmonary inflammation remains unclear. A few case reports have suggested that intravenous steroids can result in improved survival.[220,221] A retrospective review of 43 patients with blastomycosis-induced ARDS did not find a survival benefit among patients who received steroids (odds ratio, 0.52; 95% confidence interval, 0.11–2.34).[145] In this study, patients with severe ARDS (Pao_2:Fio_2 ≤100) were more likely to receive steroids than patients with less severe ARDS.[145] Nevertheless, the authors of the study stated that definitive conclusions could not be drawn to recommend for or against adjuvant steroids, and administration should be based on clinical judgment.[145] If adjuvant steroids are used, the ATS guidelines recommend prednisone 40 to 60 mg daily (or equivalent) for 1 to 2 weeks.[20] Although combination therapy is not well studied, the ATS guidelines suggest considering AmB plus itraconazole in patients with severe pulmonary blastomycosis.[18]

Surgical intervention should be considered in patients with osteomyelitis, intracranial abscess or mass, epidural abscess, and vertebral osteomyelitis with spinal instability. Surgical débridement is not curative, and antifungal therapy is still required.

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