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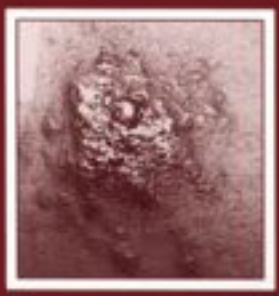

DERMATOLOGIC CLINICS

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Cutaneous lupus erythematosus: a review

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This article reviews and updates information about the pathogenesis, clinical presentation, diagnosis, and treatment of cutaneous lupus erythematosus (LE). LE can present as a skin eruption, with or without systemic disease. Cutaneous LE (CLE) is subdivided into chronic CLE (CCLE), subacute CLE (SCLE), and acute CLE (ACLE). The prevalence of systemic LE (SLE) is 17 to 48 per 100,000 population worldwide [1]. Skin disease is one of the most frequent clinical complaints of patients suffering from SLE. It has been found to occur in up to 70% of patients during the course of the disease [1]. The most frequent mucocutaneous manifestations of SLE are malar rash (40%), alopecia (24%), and oral ulcers (19%) [2]. Tebbe et al [3] found that risk factors that are more likely to signal transition of CLE into SLE are high antinuclear antibody (ANA) titers (> 1:320) and the presence of arthralgias. CLE patients who exhibit these symptoms should be monitored closely, because they may be at increased risk to develop SLE.

Pathogenesis

Genetic associations

Genetic predisposition is probably the greatest risk factor of SLE [4]. The genes or loci for SLE susceptibility are mainly located on the long arm of chromosome 1 [5]. Linkage studies used in human SLE have identified high logarithm of odds scores for such regions as FcγRIIA at chromosome 1q23; the major histocompatability complex (MHC) at 6p21.3; and chromosome 1q31, which includes genes encoding interleukin (IL)-10 and Ro-60 [6–9]. Most autoimmune disorders are associated with certain HLA subtypes. ACLE usually occurs in the context of SLE and both are associated with HLA-DR2 and HLA-DR3 [10]. SCLE is associated with HLA-B8, HLA-DR3, HLA-DRw52, HLA-DQ1, and HLA-DQ2 [11].

The SLE murine models show that a single susceptibility gene may contribute to a particular phenotype [12]. The class III region of the MHC includes genes for complement components [7]. Genetic deficiencies in the complement components C2 and C4 have been strongly linked to SCLE [13–16]. C1q, C3, and C5 deficiencies have also been associated with discoid lupus erythematosus (DLE) and LE panniculitis [15,17–19]. Deficiencies in these complement components may cause failure to clear immune complexes and apoptotic cells [7,20]. Increased numbers of apoptotic cells, whether caused by increased formation or decreased clearance, are likely to cause increased immunologic stimulation including increased anti-Ro (SSA) antibody formation [15,16,21]. C1q, the first component of the classic complement pathway, binds directly and specifically to apoptotic keratinocytes [22]. There is evidence that C1q on apoptotic cells can bind to CD91 C1q receptor on macrophages, potentially playing a role in the clearance of apoptotic cells [23]. A C1q-deficient human is nearly guaranteed to develop SLE [22]. These patients tend to develop SLE at a younger age and there is no

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female predominance [22]. Mice with homozygous C1q deficiency have been found spontaneously to develop high titers of ANA and glomerulonephritis coupled with the accumulation of apoptotic bodies in the glomeruli [24]. Mice with homozygous deficiency in C2 and factor B are unable to activate C3 by either the classic or alternative complement pathway, and do not develop spontaneous autoimmunity unless coupled with homozygous C1q deficiency [25].

Tumor necrosis factor (TNF)-α and β are also encoded by MHC class III genes and the −308A form of the TNF-α promoter has been shown to have an increased incidence in patients with SCLE and SLE [26,168]. There is increased production of TNF-α in mitogen-activated peripheral blood lymphocytes or enriched monocyte cells with the −308A allele [27–30] and there is higher TNF-α in sera of whites and individuals homozygous for −308A have higher serum TNF-α levels than −308G homozygotes [31]. In addition, ultraviolet (UV) B activates the −308A TNF-α promoter significantly more than the wildtype −308G, suggesting a role for TNF-α in the UV-induced flares seen in photosensitive forms of LE [32]. The role of TNF-α in apoptosis of keratinocytes and exposure of translocated intracellular and intranuclear antigens to the immune system, a likely mechanism relevant to induction of SCLE, is discussed later. Heat shock protein (Hsp70) genes are located within the class III MHC region and increased expression has been shown to increase binding of anti-Ro antibodies to keratinocytes and exacerbate CLE [33,34].

Environment

It has been found that 69% of LE patients [35], 63% to 100% of SCLE patients, 70% of SLE patients, and 64% of DLE patients have a pathologic photoprovocation reaction when exposed to UVA and UVB light [36]. Because reactions to photoprovocation may be delayed, patients may not associate cutaneous flares with sun exposure. The presence of Ro/SSA or La/SSB antibodies is associated with photosensitivity [36,37]. Irradiation of human keratinocytes with UVB induces the apoptosis of keratinocytes, resulting in translocation of nuclear antigens (SSA/Ro, SSB/La, snRNP, and Sm) to the cell membrane [38]. TNF-α plays a role in induction of apoptosis [39], and patients with the −308A polymorphism are likely to have enhanced sensitivity to light. This apoptosis is associated with increased expression of p53 and proliferating cell nuclear antigen [40]. During the apoptotic process and through oxidative modification, autoantigens may become altered and this could result in immunocryptic epitopes and provide a challenge for immune tolerance [41]. It has been found that autoantigens are cleaved by intracellular proteases, which are activated during the apoptotic process [42–44]. Autoantigens also can be selectively phosphorylated during the apoptotic process by stress-activated protein kinases, and these kinases are recognized by autoantibodies from SLE patients [45]. The localized concentration of these antigens is speculated to challenge immune tolerance [11]. When stained, these autoantigens appear as apoptotic blebs on the surface of the keratinocytes [38]. In skin these blebs appear as a particulate staining over both the nuclei and cytoplasm of keratinocytes, with most intense staining in the lower levels of the epidermis [46].

It is hypothesized that keratinocyte-induced apoptosis of the nuclear proteins causes autoantibody production. The production of autoantibodies is time dependant after exposure to UV light, with antinucleosome antibodies produced in high titers before the appearance of anti-DNA and antihistone antibodies [47]. Anti-Ro/SSA, anti-La/SSB, and U1RNP antibodies have been found to appear 20 to 24 hours after keratinocyte UVB irradiation both in vivo and in vitro [48]. It is thought that following UV exposure and then cytokine release by cells, a transient increase in antibody binding to the surface may occur, making the keratinocyte more susceptible to killing by complement or antibody-dependant cellular cytotoxicity [49].

Drugs that induce CLE tend to be photosensitizers. They include angiotensin-converting enzyme inhibitors (cilazapril [50] and captopril [51]); calcium channel blockers (diltiazem, verapamil, and nifedipine) [52]; aldactone [53]; procainamide [54]; hydrochlorothiazide [55–57]; d-penicillamine [58]; beta-interferon 1a [59]; sulfonylureas [58]; oxyprenolol [60]; terbinafine [61]; griseofulvin [62]; cinnarizine and thiethylperazine [62]; naproxen [63]; COL-3 [64]; and piroxicam [65]. Uracil-tegafur [66] is reported to cause DLE. Long-term exposure to quartz (silica) is thought to induce CLE [67], and smoking has been found to be a risk factor for the development of DLE [68]. Laser-induced thermal injury has been reported to result in the onset of cutaneous lupus [69].

Cellular immune mechanisms

Different peripheral lymphocyte numbers are seen between the subtypes of CLE, and this suggests that there may be unique immune mechanisms causing the different manifestations of CLE [70]. Most of the infiltrating T cells seen in SLE lesions are CD28+, B7-1, and B7-2 [71].

Studies looking at chronic inflammation and dermal fibroblasts have found that on long-term TNF-α stimulation, membrane-bound IL-15 is involved in stimulating proliferation of accumulated, activated T cells [72]. Cytokine profiles performed on DLE lesions have shown that DLE is associated with type 1 cytokines characterized by the expression of IL-2 and interferon-γ [73]. The prevailing inflammatory cell population in DLE has been found to be CD45RA+ cells [74].

Humoral immune mechanisms

The Ro/SSA system contains a 60-kd RNA-binding protein with a possible role in transcription regulation, and a 52-kd peptide that is a T-cell regulator [75]. La/SSB is a 48-kd peptide that serves as a transcription termination factor of RNA polymerase III [75]. In particular anti-SSA/Ro antibodies that recognize 60 kd (and to a lesser extent 52 kd [37]) in sera are the best indicator of photosensitive cutaneous lupus, such as SCLE, SLE, and neonatle (LE) [76]. NLE is the best example of how important anti-Ro/SSA antibodies are in pathogenesis of CLE. NLE is the neonatal equivalent of SCLE. Anti-Ro/SSA antibodies are produced in the mother and cross the placenta during pregnancy. The infant manifests cutaneous disease for the first few months of life only, while maternal anti-Ro/SSA antibodies are still present. This is a strong indicator that anti-Ro/SSA antibodies are causing or contributing to the disease.

Calreticulin is a calcium-binding autoantigen that can also be found on the surface blebs of epidermal keratinocytes following UVB-induced apoptosis [11]. It has been shown that calreticulin is able to bind to the 52-kd Ro/SSA protein and hYRNA, the RNA backbone of Ro/SSA ribonuclear particles [11,77]. This work also suggests that calreticulin plays a facilitating role in the binding of 60-kd Ro/SSA polypeptide to hYRNA [77]. Epitope spreading resulting in an antibody response to calreticulin has been found with peptide immunization using the antigens 60-kd Ro, 52-kd Ro, and La [78,79]. These data plus other work suggest that a subpopulation of calreticulin molecules could play a role in the formation of Ro/SSA ribonuclear particles through the ability to link the 52-kd Ro/SSA protein to hYRNA by calreticulin bridging and the ability to promote the binding of 60-kd Ro/SSA protein with hYRNA molecules [11]. It has been found that there is a far greater immunity to Epstein-Barr virus in the lupus population when compared with a control population, and the epitope of the virus is similar to that of the lupus autoantigen Sm [80]. One hypothesis for the development of these autoantibodies is through a primary exposure with an antigen with a similar epitope.

Other mechanisms in LE induction

Fas is a transmembrane glycoprotein receptor that has an intracellular death domain that initiates apoptosis when *Fas* ligand (*Fas*L belongs to the TNF family) binds to it. Bcl-2 and Bax are proteins associated with apoptosis whose genes are regulated by the tumor suppressor gene TP3 [81]. Increased *Fas* expression and decreased Bcl expression have been found in LE lesions when compared with healthy skin [82]. Increased expression of *Fas* and ICAM-1 (adhesion molecule 1) on keratinocytes has been found to be caused by interferon-γ [83].

Adhesion molecule expression in CLE lesions is significantly affected by the wavelength of light the lesions are exposed to [84]. UV radiation also induces delayed proinflammatory cytokine-mediated up-regulation of ICAM-1 in exposed human keratinocytes [85,86]. VCAM-1 staining intensity has been seen to be increased on endothelium from lesions in LE compared with lesions in systemic sclerosis and it is thought that endothelial events including VCAM-1 may also be important in sustaining chronic inflammation in CLE [87]. E-selectin is seen in significantly elevated levels in DLE patients with widespread lesions [88]. Lymphocytes interacting with the up-regulated adhesion molecules, ICAM-1, VCAM-1, and E-selectin, on keratinocytes could further enhance the cell-mediated death pathway.

Summary

There are many mechanisms involved in the induction of CLE. New advances in the understanding of genetic variations that contribute to the susceptibility and different disease manifestations will continue to enhance our understanding about this disease.

Diagnosis

The CLE is mainly diagnosed using clinical, serologic, and histologic criteria. Gilliam's classification scheme is used in the diagnosis of CLE. In this scheme cutaneous findings of LE are classified as ACLE, SCLE, CCLE, and LE nonspecific skin disease.

Serologic diagnosis of SLE is performed by testing patient sera for the presence of increased ANA and anti-dsDNA (native double-stranded DNA) titers. The frequency of finding positive ANA titers

in SLE patient is between 95% and 100% [89]. Anti-Smith antibody, although not present in a high frequency of SLE patients, is very specific for the disease [90]. The frequency of positive antinative DNA is 60% [89]. Serologic tests that are found in CLE are rheumatoid factor (positive frequency of 20% [89]); anti-Sm (positive frequency between 10% and 25% [89]); anti-Ro/SSA (positive frequency of 15% to 20% in SLE patients [89]); and anti-La/SSB (positive frequency between 5% and 20% [89]). Anti-ds DNA and anti-Sm antibodies are disease specific for SLE, anti-Ro/SSA antibodies are more prevalent in SCLE and NLE, and high titers of anti-U1RNP antibodies are more prevalent in mixed connective tissue disease [90]. Complement studies are also useful [10]. Approximately 40% of LE patients have antiphospholipid antibodies, which have the propensity to cause thrombosis and spontaneous abortion [90].

CCLE

The CCLE is thought to be two to three times more frequent than SLE, with the common age of onset being 20 to 40 years of age [1]. CLE is considered to have a less severe course and a better prognosis than SLE. Both disease entities, however, can result in limited patient quality of life and disability from work. CLE is considered to be the third most common cause of industrial disability from dermatologic disease, after atopic dermatitis and contact dermatitis [91]. It has been found that 45% of patients with CLE experience some form of vocational handicap [1,91]. Early diagnosis, treatment, and patient education are imperative in improving patient standard of living and socioeconomic outcome.

Although CLE is considered to carry a better prognosis than SLE, 67% to 70% of SCLE patients and 14% to 27% of DLE patients have extracutaneous signs of disease [1]. Patients who have more generalized skin involvement tend to have more systemic symptoms than those with lesions localized to the head and neck [1].

The CCLE most commonly occurs in patients who have long-term low-grade illness. It can, however, also occur in patients who are suffering from acute episodes of life-threatening SLE [93]. CCLE includes multiple manifestations, such as discoid LE (localized and generalized); hypertrophic DLE; lupus panniculitis; mucosal DLE; lupus tumidus; and chilblains LE.

The DLE usually occurs in the third to fourth decade of life [1,46,94]. Fifteen percent of patients with DLE have been found to have a history of Raynaud's phenomenon [1]. Up to 25% to 40% of these patients remit spontaneously with only 5% to 10% going on to develop SLE [95]. Twenty percent of patients with generalized DLE and 5% with localized DLE go on to develop SLE. DLE clinically appears as one or more sharply demarcated scaly erythematous papules or plaques with an adherent scale extending into the follicular orifices [46]. Involvement is usually on the head and neck region (up to 80% [1]) with a predilection for the scalp and the ears [46]. Scalp lesions tend to result in a scarring alopecia. There is an increased incidence if alopecia areata with LE [96]. There can also be mucosal involvement. Lesions tend to heal with atrophy and scar formation [1]. Generalized DLE, especially when involving the trunk, is associated with progression to systemic LE. Squamous cell carcinoma (SCC) can develop in DLE lesions [97]. Serologically, patients with DLE have a lower tendency to be positive for ANA, double-stranded DNA, Sm, U1RNP, and Ro/SSA antibodies [10].

The lupus band test can be a useful criterion to distinguish patients with LE from those without LE [98]. A positive lupus band test is found in 80% to 90% of erythematous lesions in SLE and in 50% of nonlesional skin of SLE [4]. Immune deposits are more commonly composed of IgM [98,99] and IgG [4,98]. A positive lupus band test on nonlesional, non–sun-exposed skin has been found to correlate with a worse prognosis [98,100] and disease activity [101,102], elevated anti-DNA titers [100,103], leukopenia [104], hypocomplementemia [103], and a rim pattern ANA [101,103]. False-positive lupus band tests may occur with lichen planus [105], polymorphous light eruption [106], rosacea [107], drug-induced lupus [102,108], and facial telangiectasia [107]. The lupus band test is rarely used in clinical practice today if the histopathology already establishes the diagnosis. When there is a positive lupus band test with DLE (greater than 90% of the time [98]), the most common immune deposits are reported to be C3 and IgM [94]. C1q deposits have been found in 88% of DLE patients who have concurrent SLE [94]. Serologically, patients with DLE have been found to have less ANA positivity than SCLE and ACLE [94].

Hypertrophic CCLE represents 2% of the lesions seen in CLE [109]. Lesions mainly occur on the face, extensor extremities, palms, and soles [109]. Lesions are papulonodular and hyperkeratotic in nature. They can present as scaly plaques covered by adherent horny white material or regionally diffuse hyperkeratosis that looks like a chalky dust applied over the skin [109]. This variant of CCLE

may show pseudocarcinomatous hyperplasia on biopsy and can be confused with SCC [109]. Fortunately, patients with hypertrophic CCLE usually have classic DLE lesions elsewhere on their bodies, aiding in diagnosis [110].

Lupus panniculitis (lupus profundus) can occur alone or in the setting of SLE (10% [111]), DLE (33% [111]), and other autoimmune diseases. It is a lobular panniculitis that tends to occur most commonly in middle-aged women [111]. Plaque or nodular lesions are seen 97% of the time, often accompanied with scarring, pain, erythema, and sometimes ulceration [111]. Most lesions are found in areas of increased fat deposition, such as the trunk, breasts, buttocks, and proximal arms and legs [111]. Serologically, ANAs may be found to be low in titer or nonexistent. Hypergammaglobulinemia has been found to be present (42% [111]) along with low total complement (7% [111]) and C4 levels (22% [111]). The major morbidity in this disease is usually disfigurement and disability related to pain [111]. There is seldom death from lupus panniculitis, and the course of disease is characterized by periods of remission and exacerbation [111]. It is important to obtain ample biopsy material to confirm the diagnosis, because a number of cases of subcutaneous lymphoma have given a clinical appearance of lupus panniculitis [112].

Tumid CCLE is characterized by smooth, nonscarring, erythematous to violaceous, single or multiple plaques with no surface changes, such as follicular plugging [113]. Lesions are photodistributed [114] and are easily photoinduced [113]. Lesions can coalesce to produce gyrate configurations and tend to resolve spontaneously with no scarring or dyspigmentation [113]. Tumid CCLE lesions can coexist with DLE lesions [114] and have been reported to mimic alopecia areata when present in the scalp [96]. Histologically, there is perivascular and periadnexal superficial and deep lymphocytic infiltration with distinct subepidermal edema and mucin deposition between collagen bundles [113]. Direct immunoflourescene findings (DIF) are commonly negative [113].

Chilblain CCLE is a rare manifestation of CLE. It acquired its name because it looks like frostbite. Lesions are located on fingers, toes, calves, heels, knees, elbows, nose, or ears and are aggravated with cold exposure [109]. They can be violaceous, infiltrated, pruritic, or painful when exposed to cold. Ulceration is common in digital pulp lesions and lesions on the soles easily become necrotic [109]. As chilblain lesions evolve, they may take on the clinical appearance of DLE lesions [10]. Serologic findings have included increased serum immunoglobulin levels and positive rheumatoid factor [115]. DIF may show speckled staining of ANA [115]. There are usually no detectable cold agglutinins, cryoglobulins, or circulating anticoagulants [115].

SCLE

The SCLE is the more photosensitive subset of CLE. It usually presents in the third or fourth decade of life (mean age of onset in one study was found to be 30.6 [94]), although children and elderly individuals are also affected. Women are three to four times more affected than men [116]. It presents as a photodistributed, nonscarring papulosquamous or annular, polycyclic eruption that can be isolated or can involve mild extracutaneous manifestations [46]. Lesions are easily photoprovoked and can persist for long periods of time. One study found 42% of the patients studied exhibit annular SCLE, 39% have psoriasiform-type SCLE, and 16% to have both manifestations [116]. Twenty-seven percent of the patients had nonspecific LE lesions, such as malar eruption, livedo reticularis, and periungual telangiectasia [116]. SCLE has been reported to present as pityriasis-like [117], and to be associated with generalized poikiloderma [118]. Approximately 20% of patients with SCLE have DLE lesions that appeared before the onset of the SCLE lesions [58,119].

The neck was affected in 83% of patients with 66% of patients exhibiting lesions on the face, 39% on the extensor arms, 21% on dorsal hands, 16% on the lower limbs, and 12% on the scalp [116]. Lesions tend to heal without scar formation. Histologically, patients with SCLE have an interface lichenoid dermatitis with suprabasilar exocytosis of lymphocytes showing satellitosis to necrotic spinous layer keratinocytes [58]. The use of antibody to C5b-9, although not specific, has been found to help subclassify SCLE [120].

Patients with SCLE often have circulating antibodies to Ro/SSA directed to two antigenically distinct ribonuclearprotein antibodies of 60 kd and 52 kd [121]. ELISA has been found to be the most sensitive and specific method to detect these antibodies for serologic diagnosis [121]. ANA is positive in 70% to 80% of SCLE patients [10]. Approximately 50% [122] to 71% [116] of SCLE patients are Ro/SSA positive (especially the annular variant [123]). Parodi et al [116] found that 86% of SCLE patients studied exhibited reactants at the dermal-epidermal junction. In this study they also found 71% of SCLE patients had anti-Ro/SSA antibodies and only 5% of the patients had anti-dsDNA [116]. The presence of

"dust-like particles" of IgG deposition on DIF is a specific but not sensitive pattern in SCLE [124] that is associated with the presence of Ro/SSA autoantibodies [125].

ACLE

Patients with ACLE have a 100% chance of developing SLE during the course of their disease [122]. ACLE usually presents rather abruptly in the context of a systemic illness [126]. This type of CLE is seldom examined with routine histology. These patients are on average in their third decade of life [94], and have signs and symptoms of SLE, along with the confirmatory serologic findings [127]. In one study women were found to be six times more affected than men [94]. There are localized and generalized forms. Localized ACLE is commonly manifested as the classic malar or butterfly rash seen in LE. The generalized form is commonly seen as photosensitive lupus dermatitis or a maculopapular lupus rash. Patients may have diffuse thinning or a receding frontal hairline with broken hairs (lupus hair); telangiectasias and erythema of the proximal nail fold; cuticular abnormalities; and nail-fold changes [119].

An ACLE presenting as bullous [126] and toxic epidural necrolysis (TEN)-like lesions has also been described. Bullae are most common on sun-exposed skin and neutrophils, not lymphocytes, are seen histologically [126]. Lesions have been found to occur more on the face (87%) and upper limbs (73%) than on the trunk (36%) [94]. Serologically, 95% of ACLE patients are ANA positive and often have anti-dsDNA and anti-Sm antibodies [10].

Typical lesions exhibit vacuolar alteration at the dermal-epidermal junction with an interface, perivascular, and periadnexal infiltrate that is composed of lymphocytes [127]. Examination of ACLE skin using DIF shows granular deposition of multiple immunoreactants at the dermal-epidermal junction and around the superficial dermal vasculature [127] with the most common immune deposit being C1q [94].

Treatment

The goals of managing CLE are to prevent lesion progression and to improve patient appearance. Standard therapy consists of patient education on heat, sun, and drug avoidance, along with the use of sunscreens. Giving patients agents, such as Dermablend (Johnson Products, Chicago, IL) or Cover Mark (Cosmetic Essence Inc, Monarchy, NJ), to camouflage dyspigmentation [10,11,128] can be helpful. Lesions should not be manipulated because new lesions may appear at the site of surgical manipulation [128]. Patients should be educated about sun-protective clothing with Food and Drug Administration sun-protective factors [11,129], and use a broad-spectrum sunscreen with a sun-protection factor above 15. Sunscreens found to be most effective contain parsol 1789, mexoryl SX, and mexoryl XL as UVA protectants (not available in the United States) and octocrylene as UVB protectant [130]. Patients who notice lesion induction through glass windows should use a sunscreen that also contains a UVA screen, such as Durascreen, Ombrelle, PresunUltra, and Shade UVA [128], or apply UV blocking films to home and automobile windows (Solis films, Southwall Technologies Dallas, TX). Opaque physical blockers, such as zinc oxide or those containing microparticles of titanium dioxide, provide excellent broad-spectrum coverage [11].

Localized CCLE is sometimes effectively treated with topical corticosteroids. Low-potency agents (hydrocortisone, aclomethasone, desonide, or hydrocortisone valerate) should be used on the face with mid-potency agents (fluorinated corticosteroids, such as betamethasone valerate or triamcinolone acetonide) on the trunk and arms, and high-potency agents (halobetasol, clobetasol, or betamethasone disproportionate) on the soles and palms [128]. For lesions on the scalp a steroid lotion or foam should be prescribed [128]. Patients can also be taught to self-taper after a short period of time so stronger steroids can be used on new areas. For localized lesions, intralesional corticosteroids can be effective.

Lasers are being used in increasing frequency to treat superficial localized lesions of CLE. The pulse dye laser has been found to be efficacious in the treatment of vascular lesions of CLE [131] and has been used in treatment of SCLE [132]. There is a clearance rate of 70% reported, with few side effects and no scarring [131]. The argon laser has also been found to be effective in treatment of vascular lesions seen in DLE [133]. There has, however, been a case reported of CLE induced by thermal injury from laser treatment [69]. Scarring secondary to CCLE can be treated using the carbon-dioxide laser [134]. Risks associated with laser treatment are pigmentary changes with the 532-nm laser and temporary hyperpigmentation in 25% to 30% of patients. This usually resolves in 2 to 3 months [135]. The risk of scarring associated with laser treatment is low, with a higher incidence seen on the chest or neck [135]. Textural changes are more common following treatment with one of the continuous-wave

lasers [136]. Possible contraindications to laser treatment include isotretinoin intake in the past 2 years and a history of keloid or hypertrophic scars [135]. Localized DLE lesions have been treated with cryosurgery [137].

Disseminated CLE with no systemic symptoms and lesions refractory to intralesional and topical corticosteroids are treated with antimalarials. Hydroxychloroquine sulfate is usually the first-line antimalarial drug of choice [2]. In oral doses of 400 mg/d or less than 6.5 mg/kg/d it is safer to use than its sometimes more effective counterpart, chloroquine phosphate. Patients should be informed that onset of response may take 6 to 8 weeks, so they continue to comply with treatment. If this regimen is ineffective it is often useful to add quinacrine (100 mg/d) to the hydroxychloroquine regimen. Quinacrine can be bought at compounding pharmacies [92]. If patients fail the combination hydroxychloroquine and quinacrine, then switching from hydroxychloroquine to chloroquine phosphate can be beneficial at times. The use of chloroquine phosphate results in a slightly greater incidence of eye toxicity and should be dosed at less than 3.5 mg/kg/d [138]. Therapy adding quinacrine (100 mg/d) to chloroquine ($<$305 mg/kg/d) has also been found to be effective in treatment of refractory CLE [128]. Hydroxychloroquine and chloroquine should not be used in combination because there is an additive risk of retinopathy [92]. Patients should be monitored by an ophthalmologist every 6 months for hydroxychloroquine and every 4 months after a baseline examination for chloroquine [92]. The eye examination should include a funduscopic examination; visual field testing (including central fields with a red object); and visual acuity testing [10].

Other adverse side effects of antimalarials are blue-gray hyperpigmentation; urticarial eruption; bleaching of lightly pigmented hair; gastrointestinal upset (distention, nausea, diarrhea, and heartburn); myopathy; cardiomyopathy; and rare central nervous system effects (headache, insomnia, nervousness, seizures, and psychosis) [10,92,130]. Hydroxychloroquine may lower the seizure threshold [92]. Desirable effects of hydroxychloroquine are lowering of cholesterol levels and antithrombotic effects [92]. Antimalarials also improve fatigue, fever, headache, arthralgias, arthritis, pleuritis, and pericardial inflammation [92]. Quinacrine can cause headache, dizziness, gastrointestinal distress, yellow discoloration of skin, sclera and bodily secretions [10], blue-black skin discoloration [92], and hematologic toxicity [130]. Eczematous, lichenoid, and exfoliative skin eruptions are also associated with quinacrine [92].

It has been shown that patients who smoke are less responsive to antimalarial treatment [139], so patients should be encouraged to discontinue smoking to avoid potentially more toxic drug regimens. Low-dose systemic corticosteroids have been found to be ineffective in treating CCLE, but may be useful when treating severe DLE or SCLE patients short-term while the antimalarials are being started. Because patients with LE are more prone to develop avascular necrosis, use of systemic steroids should be minimized [92].

Severe CLE can be treated with immunosuppressives. Azathioprine has been found to work particularly well with nonscarring lesions of SCLE [128] and acral DLE [140]. Very low doses of azathioprine (25 to 50 mg/d) can also be effective in patients with acral DLE [92]. Methotrexate (10 to 20 mg/wk) [141–144], cyclophosphamide, cytarabine [145], cyclosporine [146], and mycophenolate mofetil [147] have all been reported to be effective treatments. High-dose intravenous immunoglobulin (1 g/kg/d for 2 consecutive days) has also been reported to be effective with minimal side effects [148,149], and the use of extracorporeal photochemotherapy [150].

Thalidomide when started at 100 mg/d and decreased to 50 to 25 mg/d for maintenance therapy after remission, has been shown to produce excellent results in patients refractory to antimalarial therapy [151,152]. Patients have been found to note improvement within 2 weeks after starting treatment and maximum benefit is achieved within 3 months [152]. It is thought to work by reducing the activity of TNF-α and inhibiting angiogenesis [153]. Administration may result in an increase in the lymphocyte count and a decrease in the C-reactive protein [154]. The most common adverse effects reported are sedation, constipation, and weight gain [153,155]. Amenorrhea has also been found to be a side effect of therapy [152,156]. Lesions tend to recur on cessation of treatment [152], but may be easier to control with other therapies after thalidomide. Peripheral neuropathy is a serious side effect that should be monitored in patients on long-term therapy [153,155]. There has been a case of pustuloderma reported associated with thalidomide treatment of CLE [157]. Because thalidomide is a potent teratogen, pregnancy must be avoided in women [128].

Dapsone (25 to 150 mg/d) is found to be effective in patients with vasculitic LE lesions, nonscarring CLE, bullous LE, and oral ulcerations [128]. Combined with hydroxychloroquine, dapsone has been found to be effective in the treatment of DLE [158]. Clofazimine is also good for treating CLE. It has been found that two thirds of patients with DLE who

received 100 mg/d oral clofazimine for 3 to 6 months benefited from treatment [159]. The most notable side effect reported was a pink-to-reddish discoloration of the skin [159] that is slowly reversible with discontinuation of the drug [10].

Retinoids used both topically and orally can be effective in the treatment of hypertrophic DLE and acral CLE [92,119,130,160]. Good results using retinoid etretinate are seen in men with DLE [160]. One study compared the efficacy of oral acetretin (50 mg/d) with hydroxychloroquine (400 mg/d) in the treatment of CLE and found overall improvement in 46% of the patients on acetretin and 50% of the patients taking hydroxychloroquine [161]. Both drugs where found to provide effective treatment in 50% of cases of CLE [161]. There was a higher incidence of side effects in the acetretin group [161]. Retinoids are teratogenic and frequent laboratory evaluation should be carried out to avoid drug-induced hepatitis and hypertriglyceridemia [10]. Bony changes consistent with diffuse idiopathic skeletal hyperostosis syndrome, headaches, pseudotumor cerebri, xerosis, visual disturbances, sun sensitivity, and alopecia have been associated with long-term retinoid therapy [10]. Laboratory parameters, including β-human chorionic gonadotropin in women, lipid profile, liver function tests, and complete blood count, should be measured every month of therapy [162].

Auranofin when used in the same manner as in patients with rheumatoid arthritis is reported to work best in nonscarring forms of CLE [128]. Chimeric CD4 monoclonal antibody infusions [163] have been found to be more effective than the use of interferon-α, which can exacerbate lupus and rarely causes long-term remission [164]. The use of cefuroxime, a second-generation cephalosporin, at 500 mg/d, was reported to resolve SCLE lesions in three patients [165]. Vitamin E, dosed at 1000 IU/d and increased as tolerated, has been given to treat SCLE and DLE, with marked improvement in superficial disease of recent onset [166]. Low-dose aspirin therapy is recommended in patients with antiphospholipid antibodies [92]. Patients with a history of thrombotic events should be treated with long-term warfarin [92]. The newer TNF inhibitors may play a role in future treatment of CLE, but have not been studied well enough at this time to make recommendations as to their use. There is concern that these inhibitors have induced autoimmune disease and are associated with production of anti-dsDNA antibodies [167].

The diagnosis of CLE requires a good history and physical examination, serologic analysis, and histologic evaluation. Thorough characterization of the type of CLE can aid prognostically and therapeutically. Patients should be educated that CLE may persist for decades and should be aware of symptoms that may mark progression to more serious disease.

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Dermatomyositis: an overview of recent progress with emphasis on dermatologic aspects

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It is not difficult to find recent, comprehensive reviews on the general subject of the idiopathic inflammatory myopathies (IIM) (ie, dermatomyositis [DM] and polymyositis [PM]) as expressed in children and adults [1–10]. Much of this information, however, is not of practical relevance to practicing American dermatologists for several reasons.

First, dermatologists in the United States today tend to be involved only in the management of patients having the cutaneous manifestation of DM. It is quite unlikely that dermatologists are involved in the care of patients with PM and inclusion body myositis. Second, modern American dermatologists usually co-manage DM patients with other medical specialists with dermatologists providing care for the cutaneous manifestations of DM, whereas internists, rheumatologists, neurologists, and pulmonary medicine specialists are primarily involved with the management of the muscular, pulmonary, and other systemic manifestations of the disease. Third, general discussions of the IIM often underemphasize the importance of (1) the hallmark cutaneous manifestations of DM in the diagnosis of major disease subsets of IIM (eg, classic DM); (2) the profound clinical impact that cutaneous inflammation can have on the quality of life of DM patients whether or not they have myositis or other systemic disease manifestations; and (3) the existence of DM subsets that have clinical expression only or predominately in the skin (eg, clinically amyopathic DM [C-ADM]). Definition of terms used in this article that may not be familiar, such as "clinically amyopathic DM," can be found in Table 1.

Because the readers of this article are predominantly dermatologists, the author has chosen to focus primarily on issues relating to the cutaneous manifestations of DM. Because of space limitations, special attention is given to data pertaining to DM skin involvement that has been published over the past 5 years. The reader is referred to other more comprehensive reviews of all aspects of DM by the author [10, 11–14] and others [1–10]. Because relatively little attention has been paid to patients with C-ADM, a subject that is highly relevant to the dermatologist, this aspect is also emphasized in this article. By seasoning the article with one or more of the current general reviews of the IIM, it is hoped that the reader will be in a better position to gain the broadest possible perspective on patients who present with one or more of the cutaneous manifestations of DM.

History

A historical perspective of the cutaneous manifestations of DM with special emphasis on C-ADM has recently been presented elsewhere by the author [14]. Keil [15] was among the first to accept the concept that patients can express the classic cutaneous manifestations of DM for years without the appearance of symptomatic muscle disease. The term *amyopathic dermatomyositis* seems to have been initially coined in 1979, not by a dermatologist but

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Table 1
Definitions of unfamiliar and unconventional terms

Terms (abbreviation)	Definitions
Amyopathic DM[a] (ADM)	A subset of DM patients characterized by biopsy-confirmed hallmark cutaneous manifestations of classic DM occurring for 6 months or longer with no clinical evidence of proximal muscle weakness and no serum muscle enzyme abnormalities. If more extensive muscle testing is carried out, the results should be within normal limits (if such results are positive or abnormal, the patient could be classified as having hypomyopathic dermatomyositis). For the purpose of improved communication and future clinical studies, an approach to defining the minimal set of skin findings necessary to qualifying as "hallmark cutaneous manifestations of DM" is defined in Table 2. Exclusion criteria for amyopathic DM include: Treatment with systemic immunosuppressive therapy for 2 consecutive months or longer within the first 6 months after skin disease onset (such therapy could prevent the development of clinically significant myositis). Use of drugs known to be capable of producing isolated DM-like skin changes (eg, hydroxyurea, statin cholesterol lowering agents) at the onset of cutaneous DM changes.
Classic DM (CDM)	Patients having the hallmark cutaneous manifestations of DM, proximal muscle weakness, and objective evidence of muscle inflammation characteristic of DM.
Clinically amyopathic DM (C-ADM)	A functional designation that can be used to refer either to amyopathic DM or hypomyopathic DM patients as defined here (ie, clinically amyopathic DM = amyopathic DM + hypomyopathic DM). This designation has been coined to emphasize the fact that the predominant clinical problem is skin disease in patients so affected.
DM siné myositis	A term now of predominately historic significance that is synonymous with amyopathic DM.
DM-specific skin disease (DSSD)	A clinicopathologic pattern of skin change seen only in DM (analogous to the LE-specific skin disease concept coined by Gilliam, in 1975).
Hallmark cutaneous lesions and changes of DM	Skin lesions that alone or in combination are seen only in patients with some form of DM (synonymous with DM-specific skin disease).
Hypomyopathic DM	Patients with DM-specific skin disease and no clinical evidence of muscle disease who are found to have subclinical evidence of myositis on laboratory, electrophysiologic, or radiologic evaluation.
Idiopathic inflammatory dermatomyopathies (IIDM)	A more inclusive disease group designation for the spectrum of illness that has conventionally been referred to as *idiopathic inflammatory myopathies*.

[a] For the purposes of clinical studies, amyopathic DM and hypomyopathic DM can be qualified as provisional (skin disease duration for 6–23 months) or confirmed (skin disease duration for 24 months or longer).

rather by a highly regarded rheumatologist and clinical investigator, Pearson [16]. Before 1990, virtually nothing had been published in English under the designation "dermatomyositis siné myositis," the informal term by which C-ADM had previously been referred. Further discussion of the history of DM skin disease is beyond the scope of this article.

Definitions and nomenclature

The IIM are a heterogeneous group of genetically determined autoimmune disorders that predominately target the skin and skeletal musculature resulting in widespread, highly symptomatic cutaneous inflammatory disease and limb girdle muscle weakness. In a relatively small percentage of patients, other organ systems, such as the lungs (eg, interstitial lung disease), joints (arthritis), and heart (eg, cardiomyopathy and conduction defects) can also be the target of inflammatory injury. On very rare occasion, some patients can display IIM-related internal organ involvement (eg, interstitial lung disease with antisynthetase autoantibodies) without clinical evidence of myositis or skin disease [17]. Significant clinical differences exist between adult-onset and juvenile-onset DM, with juvenile DM displaying higher rates of the hallmark skin lesions of DM and vasculopathy-

vasculitis with the resulting complication of dystrophic calcification. DM and PM represent the most common clinical presentation of the IIM.

The diagnostic criteria for DM under the traditional IIM classification system have not allowed for the inclusion of cutaneous-only or cutaneous-predominantly subsets of DM, such as amyopathic DM and hypomyopathic DM, respectively. The more inclusive disease category designation idiopathic inflammatory dermatomyopathies recently has been proposed as an alternative to the IIM designation because it allows for the inclusion of these cutaneous subsets of DM [10,14].

Table 2 contains a provisional minimal set of hallmark cutaneous manifestations of DM being proposed by the author that needs to be present for the purpose of defining amyopathic DM for future clinical studies. This proposal is presented here only to stimulate discussion and consensus development in this area. Obviously, formal studies designed to determine systematically such a minimal set of skin findings is preferred.

It should be noted that some workers continue to prefer the historic term *DM siné myositis* [9,18,19] even though most data reported on such patients over the past decade have been reported under the designation amyopathic DM [14]. As of November 28, 2001, there were 60 citations in the PubMed database containing the word *amyopathic*, a term that has been used in the PubMed cited medical literature so far only to characterize a subset of DM patients. The first of these publications appeared in 1991. On the same date there were only 15 citations in the PubMed database under the search term *dermatomyositis siné*

Table 2
Proposed minimal set of hallmark cutaneous manifestations of DM for the purpose of defining amyopathic DM for future clinical studies*

For this purpose, the hallmark cutaneous manifestations of DM are presumed to be present if the following conditions are met: presence of two major criteria or one major criterion and two minor criteria (biopsy of at least one skin lesion should show changes consistent with cutaneous DM)

Major cutaneous criteria

Heliotrope rash
- Macular violaceous erythema with our without associated scale of the eyelids or periorbital skin. Secondary or associated cutaneous findings, such as scale, pigmentary change, telangiectasia, or edema also can be present.

Gottron's papules
- Violaceous papules or small plaques overlying the dorsal or dorsal-lateral aspects of interphalangeal or metacarpophalangeal joints. When fully formed, these papules become slightly depressed at the center, which can assume a white, lacy appearance. Associated scale-hyperkeratosis, pigmentary change, or telangiectasia may be present.

Gottron's sign
- Macular violaceous erythema with or without associated scale-hyperkeratosis, pigmentary change, or telangiectasia involving extensor aspects of the knuckles, elbows, knees, or medial malleoli.

Minor cutaneous criteria

Macular violaceous erythema (with or without associated scale-hyperkeratosis, pigmentary change, or telangiectasia) involving:
- Scalp or anterior hairline
- Malar eminences of face, or forehead, or chin
- V-area of neck or upper chest (open collar area; V-sign)
- Nape of the neck or posterior aspect of shoulders (shawl sign)
- Extensor surfaces of the arms or forearms
- Linear streaking overlying extensor tendons on the dorsal aspects of the hands
- Periungual areas
- Lateral surface of thighs or hips (holster sign)
- Medial malleoli

(involvement of each above anatomic region qualifies as a single minor criterion)

Periungual nailfold telangiectasia or cuticular hemorrhage-infart with or without dystrophic cuticles

Poikiloderma (concurrence of hyperpigmentation, hypopigmentation, telangiectasia, and superficial atrophy)

Mechanic's hand lesions

Cutaneous calcinosis

Cutaneous ulcers

Pruritus

* These criteria were originally presented and discussed at the Third Annual Meeting of the Medical Dermatology Society in San Francisco on March 20th, 1997.

myositis. Between 1965 and 1991 the author could find only nine publications concerning the entity *dermatomyositis siné myositis* (not all of which were cited on the PubMed or Medline databases) [16,10–26]. Only two PubMed citations were listed under the search term *dermatomyositis siné myositis* before 1991 and neither of these related directly to patients who one would refer to as qualifying for the diagnosis of amyopathic DM. In addition, on the same date there were 113 web pages identified by the Google search engine in which the term *amyopathic* was present, whereas there were 56 web pages identified containing the term *dermatomyositis siné myositis*. The term *amyopathic DM* seems to be the default designation that most modern investigators are using to refer to this subset of DM patients.

It is also unfortunate that some investigators are using the term *amyopathic DM* to describe patients who have just been recognized to have hallmark DM skin changes but who lack clinical evidence of muscle involvement [27]. The dilemma of a physician who is desperately searching for a firm diagnosis when caring for a patient displaying the hallmark cutaneous manifestations of DM without muscle weakness but who is concurrently suffering from potentially fatal interstitial lung disease can certainly be appreciated. It should be remembered, however, that it is not at all unusual for classic DM to present initially with only cutaneous disease that is then followed in a short period of time (few weeks to several months) by the clinical appearance of myositis.

In addition, it is also unfortunate that some workers have used in the term *amyopathic DM* to describe the stage of classic DM in which persistent or recurrent cutaneous involvement is the predominant clinical problem following therapy-induced remission of muscle weakness. Perhaps the designation *post-myopathic DM skin disease activity* might best be used to describe this phase of such a patient's illness. It is strongly recommended that for the purposes of various forms of clinical investigation, the term *amyopathic DM* should be reserved for those individuals displaying the hallmark cutaneous manifestations of DM for at least 6 months or longer without the appearance of clinical evidence of myositis. Other diagnostic criteria for amyopathic DM are presented in Table 1.

The term *premyopathic* has been offered to describe C-ADM patients with the implication that all such patients eventually develop clinically significant muscle involvement [28]. There is increasing evidence, however, that some patients who present with C-ADM go for 10 to 20 years or longer without developing clinical evidence of muscle disease [10, 29,30]. Perhaps the term *premyopathic* might be used to describe those patients displaying the hallmark cutaneous manifestations of DM without muscle weakness for less than 6 months.

The term *DM-specific skin disease* has also been proposed as an alternative designation for the biopsy-confirmed hallmark cutaneous manifestations of DM whether or not accompanying clinically significant myositis [14]. If adopted, perhaps this term could focus more interest and emphasis on the skin manifestations of DM for their own sake whether or not they are accompanied by clinically significant or insignificant abnormalities in other organ systems. The analogy between DM-specific skin disease and lupus erythematosus (LE)–specific skin disease is discussed elsewhere [14]. The term *DM-specific skin disease* is likely preferred by many dermatologists over such terms the *heliotrope rash* or the *rash of dermatomyositis* that have often been used in the literature to refer to the cutaneous manifestations of DM. In several reports, the term *amyotrophic DM* seems to have been used mistakenly in referring to C-ADM patients [31,32].

Classification

Because of the large differential diagnosis of proximal muscle weakness, modern rheumatologists, influenced by the earlier work of Bohan et al [33,34], are very reticent to make a diagnosis of IIM in an adult without there being very firm evidence that this inflammatory myositis exists as the cause of weakness. This approach, however, often results in undervaluing the clinical specificity of the hallmark cutaneous manifestations of DM. Because of this specificity, the only significant differential diagnostic consideration is cutaneous LE having overlapping features with myositis. Those who care predominately for juvenile-onset DM patients, a form of the disease in which the hallmark cutaneous manifestations are virtually always present at the outset of the disease process, have a greater appreciation of the diagnostic specificity of the cutaneous changes of DM. In one recent survey, a large percentage of pediatric rheumatologists indicated that they found EMG and muscle biopsy to be of little incremental value when the hallmark cutaneous manifestations of DM are present along with a typical pattern of muscle weakness [35].

The most widely accepted classification scheme for this category of disease is the IIM scheme that was originally presented in the early 1990s [36,37]. The older Bohan et al [33,34] classification criteria that

require some indication of the presence of myositis continue to be applied by most authorities to patients having DM skin disease. This approach does not allow patients with C-ADM to be included as a form of DM under the IIM classification scheme. There has been a need to develop a classification approach that recognizes and includes C-ADM patients.

Stonecipher et al [38] in 1993 proposed a classification scheme for patients having cutaneous manifestations of DM that included three groups: (1) patients with cutaneous changes only (amyopathic DM); (2) patients with cutaneous changes at baseline and subsequent evolution to myositis; and (3) patients with cutaneous changes and normal muscle enzymes but in whom diagnostic evaluations showed subclinical myositis (hypomyopathic DM). This classification approach has been advocated by others [4,30].

The author has also recently summarized his personal perspective on disease classification in this area and has proposed a more inclusive classification scheme under the designation *idiopathic inflammatory dermatomyopathies* [10,14]. This classification scheme is presented in Table 3. Until very recently, the general medical community has not felt obligated to account for patients with C-ADM in the classification approach to clinical disorders that have traditionally been referred to as DM-PM [2,3,9,39–41]. To continue to do so, however, further (1) orphans patients having exclusively or predominately cutaneous subsets of DM, (2) delays the design and completion of clinical studies needed to ascertain the overall clinical significance of skin-only patterns of disease presentation, (3) delays the development of optimal management strategies for C-ADM patients, and (4) inhibits a more complete understanding of the immunopathogenetic relationships that exist within the myositis spectrum of clinical illness. Fig. 1 and Table 4 consolidate and illustrate the ideas and concepts concerning C-ADM that are discussed in this article.

Table 3
Classification of the idiopathic inflammatory dermatomyopathies

Dermatomyositis (DM)
Adult-onset
Classic DM
Classic DM alone
Classic DM with malignancy
Classic DM as part of an overlap connective tissue disorder
Clinically amyopathic DM[a]
Amyopathic DM
Hypomyopathic DM
Juvenile-onset
Classic DM
Clinically amyopathic DM
Amyopathic DM
Hypomyopathic DM
Polymyositis (PM)
PM alone
PM as part of an overlap connective tissue disorder
PM associated with internal malignancy (?)[b]
Inclusion Body Myositis
Other Clinical-Pathological Subgroups of Myositis
Focal myositis
Proliferative myositis
Orbital myositis
Eosinophilic myositis
Granulomatous myositis

[a] Both adult-onset and juvenile-onset amyopathic DM and hypomyopathic DM patients can be further subcategorized as "provisional" and "confirmed" when patients have biopsy-confirmed hallmark cutaneous manifestations of DM without muscle weakness and with normal muscle enzymes for greater than or equal to 6 months (provisional) or 24 months (confirmed) [136]. This table has been adapted from an earlier published version [108] and is included here with the publisher's permission.

[b] While recent population-based European studies have clearly confirmed that adult-onset classical DM is associated with a significant risk for internal malignancy, if such a relationship exists for PM it is much weaker.

Epidemiology

Classic DM

Several recent reports address the rare familial occurrence of adult and juvenile DM-IIM [8,42–44]. HLA-DQA1 homozygosity has been suggested to be a genetic risk factor for familial IIM. A single nucleotide polymorphism in the tumor necrosis factor–alpha promoter (TNF-α–308A) has been associated with disease chronicity, calcinosis, and high levels of TNF-α in a cohort of white juvenile-onset classic DM patients [45]. In addition, there has been a single case report of adult-onset DM occurring in a young Japanese woman who was subsequently shown to be genetically deficient in the C5 component of complement [46]. Recent reports from Singapore, Hong Kong, and Taiwan have indicated that DM patients of those ethnic backgrounds are more likely to be male as opposed to female (females are affected more often than males in white populations). DM-associated interstitial lung disease seems to occur more commonly in Japanese DM patients compared with other ethnic groups.

Clinicians appreciate that DM-specific skin disease can be provoked or aggravated by exposure to

Table 4
Examples of subsets of patients falling within the various categories presented in Fig. 1

Disease category	A	B	C	D	E
IIDM	ADM	HDM	CDM with mild DM-specific skin disease	PM, inclusion body myositis	CDM with significant DM skin disease and muscle disease
LE	Localized DLE[a] lesions occurring as an isolated clinical phenomenon	Generalized DLE lesions or SCLE lesions occurring as the predominant clinical manifestation	SLE with localized ACLE lesions	SLE without skin disease	SLE with generalized ACLE lesions or generalized DLE lesions or SCLE lesions
Localized scleroderma/SSc	Plaque-type morphea	Generalized morphea	SSc with localized cutaneous scleroderma	SSc siné scleroderma	SSc with generalized cutaneous scleroderma

[a] In this context, localized refers to lesions occurring only on the head or neck and generalized refers to lesions occurring both above and below the neck.

ultraviolet radiation, although there are little published data documenting this. Photoinduction of polymyositis had not been reported until recently, however, in the form of an adult black man with vitiligo who developed isolated myositis while undergoing psoralen ultraviolet A therapy [47].

Certain drugs, such as the statin lipid lowering agents (atrovostatin, pravastatin, simvastatin [48,49], alfuzosin [50], and phenytoin [51]), seem to be capable of inducing both the cutaneous and muscle manifestations of DM. Further discussion of drug-induced cutaneous DM changes can be found later.

The role of infectious agents, such as viruses, in the induction of DM has long been debated. Further anecdotal evidence has been presented arguing in favor of a relationship between DM and parvovirus B19 [52,53] and Epstein-Barr virus [54].

C-ADM

The incidence and prevalence of C-ADM in the United States is unknown but assumed to be extremely low. Most such data relating to classic DM have been collected from hospitalized patient populations fulfilling the Bohan and Peter [33,34] diagnostic criteria, thereby excluding C-ADM patients. Information related to the incidence of C-ADM in the United States derives predominately from the outpatient practices of academic dermatologists, where C-ADM has been estimated to occur with approximately 10% of the incidence of classic DM. In Europe, a similar incidence has been observed [55], whereas in Asia, C-ADM seems to be relatively more common. A retrospective analysis of 28 DM patients at the National Skin Center in Singapore between 1996 and 1998 revealed that 13 (46%) had C-ADM [39]. In another cohort of 143 Taiwanese DM-PM patients seen in a veterans' hospital system, C-ADM was the second-most commonly encountered subgroup (14%) following classic adult-onset DM

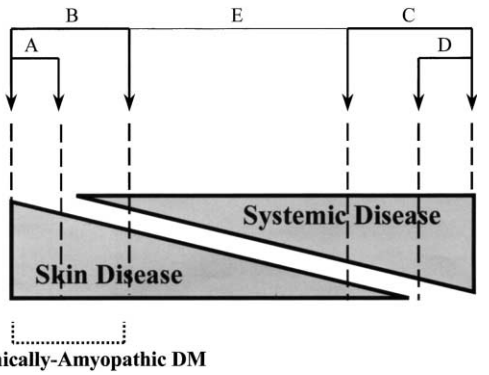

Fig. 1. Conceptualization of the relationship between the cutaneous and systemic manifestations of the three major categories of rheumatic skin disease: (1) the idiopathic inflammatory dermatomyopathies (IIDM), (2) lupus erythematosus (LE), and (3) systemic sclerosis (SSc). These three groups of polygenic autoimmune disorders represent spectra of clinical illness in which some patients are affected clinically only by skin disease (A); others are affected by skin disease and trivial amounts of systemic disease (B); some are affected only by systemic disease (D); others are affected by systemic disease and lesser degrees of skin involvement (C); and the remainder are affected equally by systemic disease and skin involvement (E). Examples of distinctive clinical subsets of patients that fall within these various categories are presented in Table 3.

(64%). C-ADM was somewhat more common than juvenile DM-PM (13%) and PM (10%) in this study [56]. Very little data currently exist concerning the incidence of juvenile C-ADM. In a retrospective analysis of all juvenile DM patients seen at an academic medical center in Pennsylvania between 1968 and 1998, 2 (12%) of 16 patients were categorized as having C-ADM [57].

Indirect evidence has suggested that C-ADM shares HLA associations similar to those found in classic DM patients (ie, HLA-DQA1) [58]. In Asian patients, C-ADM seems to be more common in males [56].

It is being increasingly recognized that certain drugs can induce the cutaneous or systemic manifestations of DM-PM [10,59]. Recent reports have further emphasized that chronic hydroxyurea therapy in the setting of chronic myelogenous leukemia can produce a DM-like cutaneous eruption that is clinically and histopathologically quite similar to idiopathic DM-specific skin disease [60,61]. Muscle weakness and other systemic symptoms have been characteristically absent, however, raising the possibility that this might be a C-ADM–like cutaneous eruption rather than a classic DM-like cutaneous eruption. Painful leg ulcers are often seen in association as is xerosis and cutaneous atrophy. This symptom complex usually occurs only after the patient has been on hydroxyurea for several years (2 to 10 years). Other drugs that have been implicated in inducing DM-like skin disease include nonsteroidal anti-inflammatory drugs (eg, diclofenac) and d-penicillamine.

Clinical features

Cutaneous manifestations

It is often not emphasized that the hallmark cutaneous manifestations of DM often undergo sequential change over time. DM-specific skin disease often initially presents clinically in a nonspecific fashion, frequently being understandably confused with seborrheic dermatitis, rosacea, psoriasis, atopic dermatitis, contact dermatitis, photodermatitis, or LE. As the cutaneous changes progress and evolve to assume the typical anatomic distribution, however, a more recognizable pattern becomes apparent.

The primary skin change is a macular violaceous erythema that can be confluent or patchy. Pruritus is often present early in the course helping to distinguish DM skin change from all clinical forms of cutaneous LE, which usually lack pruritus. Secondary changes of DM skin disease can include scale, follicular hyperkeratosis, pigmentary change, subepidermal bullous change, and ulceration. Chronic skin involvement from DM, especially in certain parts of the body, such as the V-area of anterior neck and upper chest, back, and buttocks, can assume the appearance of poikiloderma indistinguishable from other causes of this multicomponent skin change (eg, mycosis fungoides). A number of less common cutaneous and mucosal manifestations of DM injury have been described or outlined elsewhere [11].

There have been no documented differences in the clinical and histopathologic expression of skin disease in patients having classic DM or C-ADM except for a difference in the anatomic distribution of skin lesions. A number of reports now indicate that macular violaceous erythema overlying the extensor aspect of the upper extremities with or without fully formed Gottron's papules is present more frequently in both classic DM and C-ADM than is periorbital heliotrope erythema [30,56,57,62]. As more information is published concerning C-ADM, skin changes thought previously to be seen only in classic DM patients (eg, mechanic's hand lesion) are being recognized also to occur in the context of C-ADM. Also, further attention has been focused recently on the highly-pruritic scaling scalp involvement seen in classic adult-onset classic DM and C-ADM patients that can be associated with nonscarring alopecia. This feature was recently pointed out to occur also in approximately 25% of juvenile-onset DM patients [57].

The mechanic's hand skin lesion has been suggested to be associated with Jo-1 autoantibody production and other elements of the antisynthetase syndrome, such as arthritis, Raynaud's phenomenon, and interstitial pneumonitis [37]. Further study of this skin change, however, has failed to support such associations [63]. In addition, the author has personally observed the mechanic's hand lesion in several patients having C-ADM without arthritis, Raynaud's phenomenon, interstitial pneumonia, or myositis-specific autoantibodies (personal unpublished observations).

The author has been impressed by another cutaneous sign of a DM-specific skin disease that has attracted little attention in the published literature. Patients having hallmark cutaneous manifestations of DM in the more typical locations (knuckles; elbows; knees; extensor arms; V-area of anterior neck and upper chest; and posterior aspect of neck and shoulders [ie, shawl sign]) not infrequently can be found also to have a bilaterally symmetric, patchy, macular violaceous erythema often displaying a reticulated or livedoid array over the lateral aspects of the upper thighs and hips (Fig. 2). These skin changes are

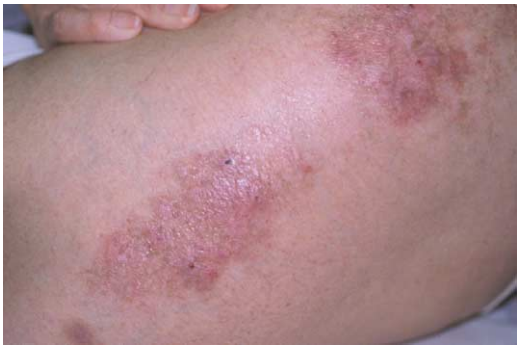

Fig. 2. The holster sign of cutaneous DM. Patchy, macular, violaceous erythema often displaying a reticulated or livedo array over the lateral aspects of the hips and upper thighs. These skin changes are typically seen over and around the greater trochanter of the femur and as such have some similarity to the localization of DM skin lesions elsewhere over bony prominences. Such changes are usually bilaterally symmetric and can be associated with scale and hyperkeratosis, pigmentary change, or poikilodermatosus change. This cutaneous change has been designated as the holster sign because the area of skin affected roughly simulates the outline of a leather pistol holster worn from a belt on the waist.

centered over and inferior to the greater trochanter of the femur and as such have some similarity to the localization of DM skin lesions elsewhere over bony prominences. For the sake of convenience, this cutaneous change is referred to as the *holster sign,* because the area of skin affected roughly simulates the outline of a leather pistol holster worn from a belt on the waist. As with DM-specific skin changes noted on other parts the body, these lesions can be extremely pruritic.

A rather unusual cutaneous finding in DM is the presence of mucinous papules and plaques centered over the creases of the palms and palmar creases of the fingers [11,64]. This seems to be an extremely rare cutaneous finding in DM; however, when present it is quite striking clinically. Other clinical forms of cutaneous mucinosis have been noted to occur in association with classic DM including plaque-like mucinosis [65] and scleromyxedema (lichen myxedematosus) [66].

Recently, attention has been refocused on another unusual cutaneous finding of DM: pityriasis rubra pilaris–like lesions (ie, type Wong DM) [67]. This variant usually presents as perifollicular keratosis over the extensor aspects of the upper extremities in adult-onset classic DM [68]. This can simulate the appearance of florid keratosis pilaris and some such patients have had atopic dermatitis and DM. More widespread patterns of involvement better simulating pityriasis rubra pilaris have also been described, however, although such patients have not had other classic features of pityriasis rubra pilaris, such as desquamative palmar plantar hyperkeratosis.

Acquired lipodystrophy has been increasingly recognized in juvenile classic DM patients. One report of 20 patients indicated that 25% had evidence of lipodystrophy, whereas 50% demonstrated hypertriglyceridemia and insulin resistance [69]. In another preliminary report lipodystrophy was associated with calcinosis [70].

Gingival telangiectasia has recently been noted as an oral mucosal manifestation of juvenile-onset classic DM [71]. These mucosal changes are not specific for DM, however, having also been observed in LE and systemic sclerosis patients. Anasarca as the presenting manifestation of classic juvenile DM has again been noted to be an ominous prognostic sign [72]. It has also recently been suggested that high-dose corticosteroid therapy may exacerbate the cutaneous vasculopathy that can occur in juvenile classic DM patients, thereby potentiating cutaneous ulceration [73]. This is in distinction to the thought by others that early aggressive therapy with corticosteroids can lessen the risk of vasculopathy-vasculitis with resultant dystrophic calcification [74].

Rider and colleagues at the National Institute of Environmental Health Sciences are preparing a comprehensive photoessay of the full range of cutaneous changes that can be observed in both juvenile-onset and adult-onset DM patients (Lisa Rider, personal communication, 2001). Once published and made universally available through the Internet without charge, as is planned, this set of expert clinical photographs will serve as a tremendous resource for those involved in both the management and study of DM patients.

Muscle manifestations

Magnetic resonance imaging has now become the method of choice for diagnostic imaging of muscle abnormalities in myositis patients [75]. In addition, MRI and P-31 magnetic resonance spectroscopy (MRS) have also been shown to be useful in assessing the status of muscle disease activity during treatment with systemic corticosteroids and other immunosuppressive drugs. Unfortunately, these procedures are quite expensive and cannot be used in some individuals having metallic implants. Less costly approaches to monitoring muscle disease activity, such as power Doppler and gray-scale ultrasonography, are being examined for this purpose [76].

The use of MRI and MRS in documenting subclinical muscle changes in C-ADM patients has recently been reviewed [75]. Functional metabolic changes in muscles identified by MRS have been especially evident on exercise in some ADM patients (such patients are better classified as having hypomyopathic DM by the nomenclature and classification proposed previously in this article). Artificial neural networks have been proposed as an effective way to analyze the multichannel functional data that result from P-31 MRS examination [77]. A central issue in this area is whether the subtle muscular abnormalities that can be identified with these sensitive imaging systems have real clinical value (ie, can they predict with significant clinical utility the subsequent appearance of weakness occurring as a result of clinically significant myositis).

A retrospective analysis of all DM patients seen at the Mayo Clinic between 1976 and 1994 revealed that 32 (4%) of 746 DM patients conformed to the definition of C-ADM [30]. Twenty-seven of these patients had amyopathic DM and 5 had hypomyopathic DM (an additional group of five patients having subjective muscle weakness but no demonstrable muscle abnormalities was included in the analysis by el-Azhary and Pakzad [30]; however, these five patients are not included in the analysis here because they do not conform to the definition of C-ADM presented in Table 1). Follow-up information was available on 16 of the Mayo clinic amyopathic DM patients. Ten patients (67%) had no muscle weakness after 2 to 10 years of follow-up; 4 (25%) had no weakness at 1 year; and 2 (13%) developed weakness within 5 years after diagnosis. None of the three hypomyopathic DM patients who were followed-up showed evidence of muscle weakness 8 to 17 years after diagnosis. Of the 19 C-ADM patients who were followed-up (16 ADM and 3 hypomyopathic DM), only 2 (11%) had developed clinical evidence of myositis after prolonged follow-up periods. These results suggest that presence of subclinical muscle abnormalities at the time of diagnosis of ADM does not necessarily portend the subsequent development of clinically significant muscle disease.

Fibromyalgia is a well-known symptomatic accompaniment of classic DM. Although fatigue or myalgia without objective evidence of muscle inflammation have been described in a number of C-ADM case descriptions, a single case report of documented fibromyalgia occurring in ADM has now appeared [78]. The symptoms of fatigue, muscle pain, and muscle tenderness associated with fibromyalgia could falsely imply the development of myositis in a patient with C-ADM. Park and Olsen [75] have proposed dividing amyopathic DM into three subsets: (1) pure amyopathic with skin disease only, (2) skin disease with subjective myalgias, and (3) skin disease with normal muscle strength but some abnormal laboratory abnormalities. Perhaps subgroup II is synonymous with amyopathic DM with fibromyalgia, and subgroup III with hypomyopathic DM.

There continues to be debate concerning the risk for juvenile-onset C-ADM patients of ultimately developing clinically significant myositis, with some groups seeing a relatively low risk [79] and others a relatively high risk [80].

To fulfill the definition of C-ADM, clinical evidence of muscle weakness should not be present. It is important that dermatologists who deal with such patients be fully aware of how to do an adequate muscle physical examination to detect weakness resulting from inflammatory myositis. Muscle strength testing is graded on a 1 to 5 scale: 0 is no muscle action, 1 is trace contraction, 2 is visible contraction but unable to overcome gravity, 3 is fair contraction but can overcome gravity, 4 is contraction able to offer some resistance, and 5 is evaluator cannot overcome contracted muscle. The focus of the examination should be on the proximal muscle groups that control the neck, shoulders, and hips. It should be realized that manual muscle testing is reproducible; however, such variables as pain, contractures, voluntary effort, and motivation may influence the ability of an individual to exert maximal muscle effort (eg, concurrent arthritis might give one the impression that a patient has distal muscle weakness because of guarding).

Risk of other systemic disease manifestations

DM can impact a number of organ systems beyond the skeletal muscles and skin, including lungs, joints, heart, gastrointestinal tract, and eyes. The most recent focus of interest in this area within the literature has been on pulmonary and joint disease.

Pulmonary disease

Lung function can be compromised in a number of ways in patients with classic DM: restrictive lung defect caused by respiratory muscle weakness, aspiration pneumonia secondary to gastrointestinal reflux and impaired esophageal muscle function, opportunistic infections, and interstitial pneumonitis related to the underlying autoimmune disease process. In addition, systemic drug therapy, such as methotrexate,

used to treat DM can also produce pulmonary complications (ie, hypersensitivity pneumonitis).

There has been increasing interest in interstitial pneumonitis resulting from both classic DM and C-ADM. This subject recently has been reviewed comprehensively [81,82]. Between 5% and 40% of patients with classic DM develop interstitial lung disease (chest CT scan can identify earlier lung involvement than routine chest radiograph). This complication presents clinically with symptoms of nonproductive cough and exertional dyspnea that are accompanied by bibasilar fine crackling rales. Pulmonary function tests show a restrictive pattern with reduced diffusion capacity. Several clinical patterns of interstitial lung disease have been described: bronchiolitis obliterans with organizing pneumonia, diffuse alveolar damage, desquamative interstitial pneumonia, nonspecific interstitial pneumonia, and respiratory bronchiolitis interstitial lung disease.

Interstitial lung disease can present with two clinical patterns: an acute-subacute type and chronic type. In the acute-subacute type, patients present with severe, rapidly progressive dyspnea and progressive hypoxemia within a month from onset of lung involvement. Such a patient is often treatment-resistant and at risk for death. The chronic type presents with a much slower pace of progressive dyspnea. Interstitial lung disease can also be identified by chest radiograph or pulmonary function tests in the complete absence of symptoms. It has also been suggested that interstitial lung disease associated with the myositis-specific autoantibodies (antisynthetases) can occur occasionally in the absence of skin and muscle disease [16]. In some individuals, interstitial lung disease presents before the clinical appearance of myositis. In addition, interstitial lung disease can occur in patients having only the cutaneous manifestations of DM for prolonged periods of time.

Classic DM patients who have the antisynthetase syndrome (Jo-1, PL-7, PL-12, or other synthetase autoantibodies; arthritis; Raynaud's phenomenon) have increased risk of developing interstitial lung disease. The antisynthetase syndrome and interstitial pneumonitis can also be seen in children with classic DM. Interstitial pneumonitis and air leakage were recently observed in a 4-year-old girl with classic juvenile DM [83].

Interstitial pneumonitis and pulmonary fibrosis can complicate C-ADM and classic DM [21,29, 31,81,84–92]. Also, five C-ADM patients reported by el-Azahry and Pakzad [30] were said to have radiologic evidence of pulmonary fibrosis that was asymptomatic. A number of the reports of interstitial lung disease occurring in C-ADM patients have been published in languages other than English; however, by virtue of the English titles and abstracts of these articles, each of these reports seems to describe one or more patients who have developed interstitial lung disease in the context of the hallmark cutaneous manifestations of DM without accompanying muscle weakness. In some of these reports, however, DM-specific skin disease has been present less than 6 months [91]. Perhaps such cases might be referred to as *premyopathic DM* or as individuals expressing DM-specific skin disease without myositis. Clearly, some type of convention needs to be agreed on to describe previously healthy individuals who present with DM-specific skin lesions and then die from interstitial lung disease within a matter of several weeks or several months.

Based on the author's review of the published and pending publication medical literature in this area, it seems that there has been at least 34 published C-ADM patients who have developed symptomatic interstitial lung disease. In many cases, interstitial pneumonitis has occurred in C-ADM patients in the absence of antisynthetase autoantibodies, such as Jo-1, which are considered to be markers for interstitial lung disease risk in patients with classic DM. The prevalence of interstitial pneumonitis in C-ADM has not yet been determined; however, it may approach 5% to 10% based on an estimate made from the current published literature. A disproportionately high percentage of C-ADM patients with interstitial lung disease have been reported from Japan, perhaps related to the fact that interstitial pneumonitis seems to be an especially common complication of classic DM in the Japanese. In addition, the acute-subacute pattern of disease presentation with rapidly progressive dyspnea, progressive hypoxemia, treatment-resistance, and fatal outcome has been observed in a disturbingly high percentage of C-ADM patients developing pulmonary disease. Cyclosporine and cyclophosphamide have each been reported to be of value in severe complications of interstitial lung disease in C-ADM patients, especially when started before frank respiratory failure has developed [86,88].

In addition to the formally published literature, there are several anecdotal descriptions of fatal cases of interstitial pneumonitis in C-ADM patients present on several Internet sites including two men in their 40s, one a Canadian academic physician (http://www.cma.ca/cmaj/vol-164/issue-8/1263.htm; http://www.napanet.net/~segall/joe1.html). One of these cases is currently being prepared for formal publication (Kari Connolly, MD, personal communication, 2002). It seems that pulmonary disease must be added

to malignancy as a potentially life-threatening complication of the C-ADM pattern of disease presentation.

Arthritis

Arthritis has been noted to occur in 20% to 65% of juvenile-onset DM classic DM [93]. Typically, this is a nonerosive arthritis involving knees, wrists, elbows, and fingers and is seen early in the course of the disease. For some patients this can be a major symptomatic problem. Arthritis has also been observed in some juvenile-onset C-ADM patients. In one recent study, three (60%) of five juvenile C-ADM patients followed over an average period of 4.9 years were reported to have arthritis, whereas 49 (61%) of 80 children with classic DM in the same study were observed to experience arthritis [93].

Laboratory features

Autoantibodies

Antinuclear antibodies identified on human tumor cell substrates are present in 40% to 60% of classic DM patients. Autoantibodies of known molecular specificity in DM are now categorized into two groups: myositis-specific autoantibodies and myositis-associated autoantibodies [94]. Myositis-specific autoantibodies include the antisynthetases (Jo-1, PL-7, PL-12, and OJ); Mi-2; and SRP. PM/Scl, Ro/SS-A (Ro52, Ro60), and U1RNP represent the major myositis-associated autoantibodies. The prevalence of these various autoantibody specificities in a cohort of 181 unselected European classic DM patients was recently reported [95] and the results are illustrated in Table 5. These results are quite similar to those previously reported for separate cohorts of DM patients from the United States and Japan. This study also identified a very strong relationship between Ro52 and Jo-1 antibodies. The fact that none of the myositis-specific autoantibodies occur with a prevalence greater than one in five of DM patients makes routine clinical testing for these autoantibodies of very little clinical use.

The DM patients who produce Jo-1 or other synthetase autoantibodies have an increased risk of having arthritis, Raynaud's phenomenon, and interstitial lung disease. This constellation has been described as the antisynthetase syndrome.

The initial report of a new autoantibody reactive by immunoblot with a 56-kd autoantigen [96] seems to have been confirmed [97]. Approximately 60% of juvenile classic DM patients produce this autoantibody. In addition, this autoantibody specificity seems to correlate positively with the presence of the HLA-DQA * 0501 allele. This association has been proposed to be circumstantial evidence for a viral-induced cause of this particular autoimmune response.

Table 5
Prevalence of autoantibodies in 181 European classic DM patients

Autoantibody Specificity	Number of Patients (%)
Myositis-Specific Autoantibodies	
Antisynthetase autoantibodies	
Jo-1	28 (16)
Other antisynthetases	5 (3)
SRP (signal recognition particle)	5 (3)
Mi-2 (antinuclear helicase and ATPase)	38 (21)
Myositis-Associated Autoantibodies	
PM/Scl (antiexosome complex)	10 (6)
Anticytoplasmic Ro/SS-A ribonucleoproteins (RNPs)	
Ro60	8 (4)
Ro52	44 (24)
La/SS-B	6 (3)
U1RNP (splicesome)	7 (4)

Data from Brouwer R, Hengstman OJ, Vree EW, et al. Autoantibody profiles in the sera of European patients with myositis. Ann Rheum Dis 2001;60:116–23.

Preliminary studies using immunoprecipitation have identified a new autoantibody, named "MJ," in juvenile classic DM patients (data reviewed in [94]). This autoantibody reacts with a 140-kd protein of unknown molecular specificity. In addition, another new myositis-specific autoantibody, PMS1, has been described, which reacts with a DNA repair enzyme [98].

Most of the published cases of C-ADM are antinuclear antibody–positive (an even larger majority in those studies specifying human tumor cells as the antinuclear antibodies substrate). Such patients, however, do not seem to produce myositis-specific or myositis-associated antibodies. The molecular specificities of the autoantibodies seen in C-ADM have been unknown. Preliminary studies have indicated that a unique pair of new autoantibody specificities (155 kd and Se) might serve as serologic markers for this subset of DM patients [99,100]. Combining the results of immunoblot and immunoprecipitation studies using HeLa cell extracts, 16 (89%) of 18 white adult C-ADM patients showed autoantibodies to the 155-kd autoantigen or the Se autoantigen. The molecular identities of these autoantigens have not yet been identified, but neither seems to be associated

with RNA. If these preliminary results can be confirmed, they could provide a very useful clinical tool for confirming a diagnosis of C-ADM. A different group of investigators has reported finding autoantibodies reactive with a 140-kd polypeptide in five Japanese adult-onset C-ADM patients having interstitial pneumonia [101]. It is currently not clear whether a relationship exists between this autoantibody and the 155-kd autoantibody described by Targoff et al [100].

Other indicators of disease activity

Because enzymatic indicators of muscle inflammation can normalize rather quickly after onset of systemic therapy, other surrogate markers of DM disease activity are used by some to guide therapy. Such indicators have been used more in the management of juvenile-onset classic DM patients to make certain that all systemic disease activity outside the muscles, such as vasculopathy-vasculitis, is fully quenched before tapering and discontinuing therapy. Such markers include the vWF:Ag, CD19+ B cells, and neopterin (data reviewed in [45]). Elevated levels of other markers of vascular activation including soluble forms of VCAM-1 and E-selectin have also been reported to occur in the circulation of patients with classic DM.

KL-6 is a human MUV-1 class mucin that is preferentially expressed on type II pneumocytes. KL-6 has been proposed to be a sensitive serum marker for the presence of interstitial pneumonia in the setting of classic DM (data reviewed in [81]). This molecule, however, is not specific for DM and interstitial lung disease in that elevated levels are also found in the serum of patients with various malignancies, serving as a tumor marker in this setting [102]. Serum levels of KL-6 have also been suggested to be correlated with the activity of interstitial pneumonia in C-ADM patients [103,104]; however, as previously noted elevated serum KL-6 is not specific for C-ADM or classic DM.

Patients with classic DM express VCAM-1 and E-selectin in the microvessels of inflamed muscular and cutaneous tissue. In addition, patients with classic DM have recently been reported to display elevated blood levels of VCAM-1 and E-selectin [105]. Whether these soluble vascular adhesion molecules reflect activation of the muscular or dermal microvasculature (or both) has not been determined. A preliminary study involving C-ADM patients was carried out to address this issue [106]. This study found similar rates of elevation of soluble VCAM-1 in classic DM and C-ADM patient serum specimens suggesting that circulating levels of this vascular adhesion molecule could reflect activation of the muscular or dermal microvasculature (or both). Much higher levels of soluble E-selectin levels were observed in C-ADM patients, suggesting that circulating levels of this vascular adhesion molecule might better reflect (or be limited to) activation of the dermal microvasculature.

Complications

Internal malignancy

Considerable controversy existed in the past concerning the question of an association between classic DM-PM and occult malignancy [56,107–109]. Several population-based epidemiologic studies of this issue over the past decade, however, have clearly confirmed the existence of such a relationship in European whites having classic DM [109–113]. Curiously, these studies indicate marginal to no increased risk of malignancy in PM patients. Increasing age, skin disease extent and severity (ie, blistering, ulceration), and creatine kinase levels seem to enhance the risk of malignancy in patients with classic DM. It has been suggested that the presence of other systemic manifestations of DM, such as interstitial lung disease, is negatively correlated with risk for internal malignancy [56]. Many different types of malignancy, usually carcinoma rather than sarcoma, can occur in patients with classic DM. White women, however, seem to have an especially high risk of ovarian carcinoma, whereas Asian men most frequently develop nasopharyngeal carcinoma [110,112].

The starting point for an occult malignancy evaluation in patients presenting with classic DM is a comprehensive medical history; review of systems; physical examination; and baseline laboratory screen (eg, chest radiograph, mammography, sigmoidoscopy and colonoscopy, complete blood count, serum chemistries, stool occult blood examination, and prostate specific antigen) with careful follow-up of any leads detected. All routine age- and sex-directed malignancy surveillance guidelines should be followed. It is recommended that every effort be taken to identify early evidence of ovarian carcinoma in an adult woman presenting with any form of DM. It has been recommended that transvaginal ultrasonography and serum levels of tumor markers, such as CA-125, be obtained in this regard. After that, different physicians have different approaches [114]. Some pursue aggressive blind radiologic imaging studies of the

entire body, whereas others advocate watchful waiting with aggressive follow-up of new signs and symptoms. Repeat malignancy surveillance measures need to be carried out regularly (every 6 to 12 months) for the first 3 to 5 years following the diagnosis of DM. After this period of time, the risk of malignancy seems to fall back to that of the age- and sex-matched population in general.

There is a broad consensus that serum tumor markers (eg, CEA, CA-125, CA 15-3, MUC-1, and TPS) are not sufficiently sensitive or specific enough for malignancy screening purposes in the general population. It has been pointed out, however, that in a patient population (ie, classic DM) having a higher incidence of a disease (ie, malignancy), Bayes' theorem argues that the usefulness of tumor markers should increase [115]. Tumor markers, such as those indicated previously, might be of greater value in monitoring for malignancy in classic DM, especially if a trend of changing values is noted in multiple assays obtained sequentially over time in the same patient [115]. Considering the now-confirmed association of ovarian cancer and classic DM, it is curious that there have been no reports examining the role that screening for mutations in familial and sporadic cancer-associated genes, such as BRCA-1 and 2, might have in stratifying risk of malignancy in women with classic DM.

Although there have been a number of case reports of internal malignancy occurring in C-ADM patients, whether there is a statistically significant increased relative risk of internal malignancy in patients with C-ADM is not known for certain (the published data and author's personal experience concerning this question have been reviewed [10]). In a recent systematic review of the world literature, only approximately 300 cases of C-ADM were found (Lewis and Sontheimer, unpublished data). Ten percent of these cases were associated with internal malignancy (that figure drops to 11% if one excludes two reports from Singapore). Unfortunately, there are no population-based data on the risk of internal malignancy in patients with C-ADM.

A retrospective analysis of all DM patients seen at the Mayo Clinic between 1976 and 1994 revealed that 32 (4%) of a total of 746 DM patients conformed to the definition of C-ADM [30]. Twenty-seven of these patients had amyopathic DM and five had hypomyopathic DM. An additional group of five patients having subjective muscle weakness but no demonstrable muscle abnormalities was included in the analysis by el-Azhary and Pakzad [30]; however, these five patients are not included in the analysis here because they do not conform to the definition of C-ADM presented in Table 1. Four (25%) of the 16 ADM patients who were followed up after 2 to 10 years were found to have an internal malignancy (all four were women, one each with lung cancer, ovarian carcinoma, both breast and endometrial carcinoma, and one with metastatic adenocarcinoma of unknown primary). None of the three hypomyopathic DM patients who were available for follow-up had associated malignancy. Overall, a minimum of 4 (15%) of 27 of the C-ADM patients reported in this series had an associated internal malignancy, with two patients succumbing from this complication.

In a recent 3-year retrospective review of DM patients seen at the National Skin Centre of Singapore, it was conclude that C-ADM is a common presentation in that ethnic population and that C-ADM presentation might carry a lower risk of associated malignancy than classic DM [39]. In a retrospective analysis of 143 Taiwan DM patients, no malignancies were observed in the 20 ADM patients [56]. Six of 10 ADM patients identified in a retrospective study in Hong Kong, however, were found to have associated malignancy, especially nasopharyngeal carcinoma [116].

When discussing the possibility of using systemic immunosuppressive therapy to control the clinical symptoms in patients with either classic DM or C-ADM, some physicians feel obligated to discuss with the patient the small but finite increased risk of malignancy that can accompany such therapy.

Dystrophic calcification

Approximately 25% of juvenile-onset classic DM patients have dystrophic calcification at the time of diagnosis and 40% to 50% develop calcinosis sometime during the course of their illness. Some individuals can die from septic complication of ulcerating dystrophic calcification long after complete resolution of their myositis disease activity.

The TNF-α–308A promoter polymorphism might represent a risk factor for developing calcinosis [45]. This treatment-resistant complication can be a major contributor to morbidity and occasionally mortality in such patients. The higher rate of vasculopathy-vasculitis that occurs in juvenile DM is thought to be a forerunner of dystrophic calcification. MRI has recently been suggested to be capable of identifying edema and inflammation in skin, subcutaneous tissue, and fascia resulting from vasculopathy-vasculitis in classic juvenile DM patients [117]. In approximately 80% of the 26 children studied, MRI abnormalities indicating skin, subcutaneous, or fascial edema were observed. Clinical skin disease

activity scores correlated positively with MRI skin edema scores. Five children were shown to develop soft tissue calcification in areas previously found to be edematous by MRI after 4- to 9-month follow-up intervals. These observations suggest the intriguing possibility that MRI soft tissue assessment can be of value in predicting risk for developing this most difficult complication of juvenile DM and in monitoring disease treatment so as to prevent or minimize this complication.

Treatment of dystrophic calcification in DM has been extremely challenging. Aluminum hydroxide antacids and diltiazem are currently used for this problem with less than ideal results [118–120]. A recent report has suggested that the bisphosphonates, such as alendronate, might be of value [121].

Dystrophic calcification seems to be quite uncommon in both adult- and juvenile-onset C-ADM. It is of interest in this regard that there was little relationship found between MRI indices of edema and inflammation in the superficial (skin and subcutaneous tissue) and deep (fascial and muscle) tissue compartments of juvenile-onset classic DM patients [117].

Differential diagnosis

The contrasting features of the classic cutaneous manifestations of LE and DM have recently been emphasized with outstanding color illustrations [122]. In addition, the broad differential diagnosis of proximal muscle weakness has also been reviewed [7]. One curious report indicated that skin metastasis from breast cancer appeared clinically undistinguished from the skin involvement of amyopathic dermatomyositis [123].

Treatment

Oral or intravenous pulse corticosteroids remain the treatment of choice for suppressing all manifestations of newly diagnosed adult- and juvenile-onset classic DM patients. Methotrexate, cyclosporine, and high-dose intravenous immunoglobulin (IVIG) have traditionally been used as steroid-sparing agents. Similar benefit from mycophenolate mofetil has also been reported [124]. Cyclophosphamide is often used for difficult problems related to vasculitis-vasculopathy in childhood-onset disease. Chlorambucil has also been used in desperate attempts to control skin and muscle disease activity. Because enzymatic indicators of muscle inflammation tend to normalize quite quickly after onset of systemic therapy, other surrogate markers of DM systemic disease activity are used by some to guide therapy. Such markers include the vWF:Ag, CD19+ B cells, and neopterin (data reviewed in [45]). As previously mentioned, serum levels of KL-6 have also been suggested to reflect DM interstitial lung disease activity.

To mitigate DM skin disease activity, advice concerning avoidance of unnecessary ultraviolet light exposure should be given. Information concerning the use of broad-spectrum chemical or physical sunscreens should be provided. Local therapy with potent or super-potent topical corticosteroid creams and ointments can be of some value for often-pruritic cutaneous DM. When using superpotent topical corticosteroids, it is advisable to use cyclical therapy (daily use for 2 weeks followed by a 2-week rest period off the medication with repetition of this 4 week cycle as needed). Topical corticosteroids in solution, gel, foam, or spray vehicles can be used after shampooing to lessen the severe pruritus and hair loss that can accompany scalp DM involvement. Other forms of topical and systemic antipruritic therapy should also be provided as needed. Nonsedating oral antihistamines during the day combined with long-acting, sedating antihistamines at bedtime (eg, low-dose doxepin) should also be considered. In addition, use of topical antipruritic formulations (5% doxepin cream [Zonalon Cream], pramoxine, camphor, menthol, and phenol) also can be of value.

Although they are generally less effective than in cutaneous LE, aminoquinoline antimalarial drugs can provide some degree of moderating effect on cutaneous inflammation for many DM patients. When single-agent therapy with either hydroxychloroquine or chloroquine fails, consideration should be given to combination antimalarial therapy (hydroxychloroquine plus quinacrine or chloroquine plus quinacrine [hydroxychloroquine should not be combined with chloroquine because of enhanced risk of retinopathy]). If extrapolation from the experience gained from cutaneous LE patients is valid, DM patients who smoke cigarettes might be less responsive to antimalarial therapy than those who do not. It should be remembered that on rare occasion antimalarials can contribute to muscular weakness by causing a vacuolar myopathy as a drug side effect.

Dapsone has again been suggested anecdotally to be of value in patients with limited to moderately active forms of cutaneous DM [29]. Mycophenolate mofetil has also been suggested to have steroid-sparing value for the cutaneous manifestations of DM [124].

Based on experimental evidence indicating a role for TNF-α in the pathogenesis of the classic DM

muscle inflammation, anti–TNF-α therapy been used on an anecdotal basis for both the muscular and cutaneous manifestations of DM. Thalidomide, a TNF-α production inhibitor, has been observed anecdotally to be of value for cutaneous DM inflammation (Warren Piette, MD, personal communication, 2001). In addition, five cases of severe, treatment-resistant DM that were treated successfully with etanercept (Enbrel) have been published informally [125,126]. In addition, three similar cases were managed successfully with infliximab (Remicade) [127,128]. More systematic study in this area is needed to define the value of such treatment. Such therapy has to be used with caution concerning the possibility of its uncovering other patterns of systemic autoimmunity (eg, SLE).

There are no systematically ascertained data to guide one in the treatment of either adults or children with C-ADM. All current approaches are based on anecdotal observations of individual cases or relatively small case series and are open to question. It is now clear, however, that the following considerations require vigilance in the management of such individuals: the recent realization that C-ADM patients are at risk for potentially fatal interstitial lung disease, the possibility that C-ADM patients may have a statistically significant increased risk of internal malignancy, and the fact that some C-ADM patients have developed symptomatic myositis greater than 2 years after disease onset. Added to these concerns is the inherently refractory nature of DM skin inflammation. These aspects together can present the dermatologist with a formidable task when faced with a new C-ADM patient.

One approach has been to treat C-ADM patients aggressively from the outset with systemic corticosteroids with the hope that progression to systemic involvement might be delayed or prevented [62]. This approach is supported by studies of both juvenile- and adult-onset classic DM patients that indicate that early systemic immunosuppressive treatment can lessen long-term disability from muscle dysfunction and complications, such as calcification. In most published reports to date concerning C-ADM, however, a more conservative treatment approach has been taken, an approach that is supported by reports of C-ADM patients going 10 to 20 years and longer without any sign of disease activity outside the skin [10,30,78,129]. More work is needed to identify risk factors for systemic disease or malignancy development in C-ADM patients.

Until it is confirmed that adult C-ADM patients do not have an increased risk of internal malignancy, they should be evaluated for this potential complication in a manner similar to classic DM patients. Because internal malignancy has not yet been reported in juvenile C-ADM, it can be assumed that, as in juvenile classic DM patients, routine evaluation for internal malignancy is not indicated.

Because the cutaneous manifestations of C-ADM and classic DM are indistinguishable, the management of skin disease activity in both clinical settings is similar. Systemic immunosuppressive therapy is used from the outset in classic DM patients, however, and as a result symptomatic skin disease activity is generally less of a problem.

Prognosis

A recent examination of prognosis in 77 consecutive patients with DM-PM having a minimum of 18 months follow-up revealed a 22% mortality rate resulting predominately from malignancy and lung disease [130]. As has been previously observed in both juvenile- and adult-onset classic DM, a better prognosis was seen in this study in individuals who received early systemic treatment for their disease. Poor outcome was associated with older age, pulmonary and esophageal involvement, and malignancy.

Antisynthetase antibodies and TNF-α–308A allele may represent risk factors for disease chronicity and severity in juvenile-onset classic DM [45]. Black children with DM tend to have more aggressive disease than white or Hispanic children. Calcinosis remains a primary cause of both disease morbidity and mortality in juvenile classic DM patients.

One study has suggested that juvenile DM patients who have only cutaneous manifestations and no muscle weakness are usually not treated aggressively and frequently develop pathologic calcifications [80]. This report is contrary to other studies of C-ADM in both children [79] and adults [30,55] that have indicated that this mode of presentation is usually not associated with a high rate of subsequent dystrophic calcification. One study indicates that both rheumatologists and dermatologists tend to be quite conservative in treating C-ADM patients [79]. Interestingly, this report indicates that a high percentage of juvenile-onset C-ADM patients enjoy spontaneous remission without systemic immunosuppressive treatment.

Etiology and pathogenesis

Fig. 3 presents a summary overview of current thinking concerning the etiology and pathogenesis of

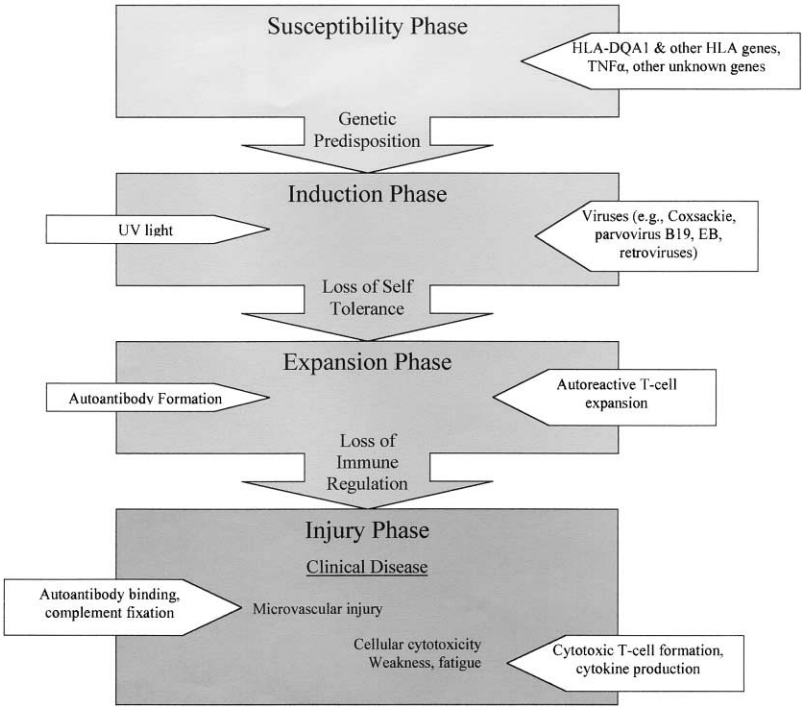

Fig. 3. Summary of current thought concerning the etiology and pathogenesis of DM. TNF = tumor necrosis factor; UV = ultraviolet; EB = Epstein-Barr. (Figure concept courtesy of Melissa Costner, MD, Dallas, TX).

tissue injury (skin, muscle, lung, and so forth) in idiopathic inflammatory dermatomyopathies. Like other systemic autoimmune diseases involving autoantibody production, such as SLE, DM-PM is thought to evolve through multiple sequential phases: the susceptibility phase, the induction phase, the expansion phase, and the injury phase. A comprehensive discussion of this sequence of susceptibilities and events is beyond the scope of this article.

Evidence is accumulating that TNF-α could play a role in the pathogenesis of muscle injury in myositis. A single nucleotide polymorphism in the TNF-α promoter (TNF-α−308A) has recently been associated with high levels of TNF-α production, disease chronicity, and calcinosis in a cohort of white juvenile-onset classic DM patients [45]. This genetic trait could be related causally to DM or could represent only an association through linkage disequilibrium with the autoimmune haplotype, HL-A1,B8,DR3,DQ2, that is known to be present with increased frequency in DM patients.

The TNF-α promoter polymorphism could potentially play a role in the photosensitivity experienced by many DM patients. TNF-α−308A promoter polymorphism has also been linked to the photosensitive LE-specific skin disease subset, subacute cutaneous LE [131]. In these studies, epidermal keratinocytes containing this TNF-α allele have been shown to produce exaggerated levels of TNF-α in the presence of interleukin-1α following exposure to ultraviolet B radiation. These observations raise the possibility that TNF-α inhibiting therapy, such as thalidomide or monoclonal antibodies (infliximab, etanercept), might be of value in selected patients with photosensitive DM or subacute cutaneous LE.

In addition, a single case report of young adult Japanese woman who presented with C-ADM that evolved into classic DM over a 3-year period was shown to be genetically deficient in the C5 component of complement [46]. If confirmed, this case could call into question the hypothesis that skin and muscle disease activity in classic DM is causally related to the deposition of complement membrane attack complex in cutaneous and muscular microvessels.

Further evidence has been presented recently supporting the concept that cell-mediated myocytotoxicity plays a role in the pathogenesis of myositis. Both myocytotoxic CD3+ T-cell clones and non-HLA restricted myocytotoxic cells of other lineages

have been shown to be present in the peripheral blood of patients with inflammatory myopathies [132]. Unfortunately, very little has been done experimentally to probe for cytotoxic epidermal or dermal cell injury in patients having DM skin disease activity.

There is not always good agreement between the degree of muscle weakness or fatigue experienced by classic DM patients and the degree of inflammation noted on muscle biopsy and elevation of serum muscle enzymes. This has led to the idea that inflammatory cytokines might be capable of mediating metabolic disturbances within muscle that can exacerbate muscle weakness and fatigue (data reviewed in [133]).

As with other rheumatic diseases, such as systemic sclerosis, maternal microchimerism has been observed in juvenile classic DM patients [134]. The pathogenetic significance of alloreactive maternal lymphoid cells being present in the circulation and muscle and skin tissue of juvenile DM patients is not yet known.

Recently work has indicated that factor XIIIa+ dermal perivascular dendritic cells may be the source of abnormal mucin production in conditions, such as the reticular erythematous mucinosis syndrome [135]. It is tempting to extrapolate these observations to autoimmune conditions that involve abnormal dermal mucin accumulation, such as cutaneous LE and DM.

Unfortunately, virtually nothing has been done recently to address directly the pathogenesis of cutaneous inflammation seen in C-ADM or classic DM. The preliminary observation that C-ADM patients might preferentially produce a pair of autoantibodies (155 kd, Se) [99,100] could yield a new experimental approach to addressing this issue. It is not yet known whether these two autoantigens might be aberrantly expressed in the skin of C-ADM patients endogenously or as a result of environmental stimuli (eg, ultraviolet light), thereby targeting cutaneous tissue for autoantibody-mediated inflammatory injury.[1]

[1] The author apologizes to those readers who might be offended by the rather subjective, sermon-like tone of this discussion with respect to the subject of C-ADM. This approach has resulted from career-long frustration on the author's part from observing the unnecessary pain, suffering, and possibly preventable death that has and continues to be caused by lack of attention and focus on clinical issues related to this subgroup of DM patients by both the dermatologic, rheumatologic, and general medical communities.

Summary

Important points regarding DM and C-ADM are as follows:

- C-ADM is a working functional designation for patients having the skin-only and skin-predominant subsets of DM, amyopathic DM, and hypomyopathic DM.
- C-ADM seems to have approximately 10% the incidence of classic DM in whites and possibly a higher incidence in Asians.
- Some patients who present with C-ADM, with or without subclinical laboratory abnormalities, can slowly progress to develop symptomatic muscle weakness over a period of years, whereas others go for 10 to 20 years and longer without the appearance of muscle weakness.
- C-ADM patients are at risk for potentially life-threatening complications of classic DM, such as interstitial lung disease, which may occur in up to 10% of C-ADM patients. This risk seems to be even greater in some ethnic subgroups (eg, Japanese).
- C-ADM patients may also be at increased risk for internal malignancy and until further studies are carried out to confirm the statistical significance of this association, all such patients should have a thorough evaluation for internal malignancy, identical to the approach currently used in classic DM patients.
- Dermatologists are in the best position initially to diagnose C-ADM patients and can contribute greatly to their overall management and quality of life. Ongoing vigilance is required, however, for complications that can arise in C-ADM patients including potentially fatal interstitial lung disease, internal malignancy, delayed onset of muscle weakness from myositis, and complications of systemic drug therapy.
- Topical therapy with broad-spectrum sunscreens, anti-inflammatories, and antipruritics should be maximized during the initial management of the cutaneous manifestations of either classic DM or C-ADM.
- Single-agent or combined aminoquinoline antimalarial therapy represents the safest initial form of systemic therapy for DM-specific skin disease occurring in any clinical setting; however, this approach tends to be less effective in general than for cutaneous LE.
- There is a theoretical rationale for and limited preliminary successful anecdotal experience

with the use of anti–TNF-α therapy in refractory cases of classic DM and C-ADM. Cautious systematic clinical trials in this area should be considered.

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DERMATOLOGIC CLINICS

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Neutrophilic dermatoses

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The neutrophilic dermatoses are a group of noninfectious disorders characterized by the presence of an angiocentric, vessel-based primary neutrophilic inflammatory cell infiltrate (Table 1) [1]. These disorders can be further divided into those that lead to destruction of vessel walls (vasculitis) and those that do not destroy the vessels. The disorders discussed in this chapter are those in which the vessel wall is not destroyed. The remaining disorders are linked by the presence of similar associated processes, massive cutaneous neutrophilic infiltrates, occasionally overlapping clinical features, and similar approaches to therapy.

Sweet's syndrome (acute febrile neutrophilic dermatosis)

In 1964, R.D. Sweet described a group of patients with one or more attacks of painful, erythematous plaques accompanied by fever, arthralgias, and leukocytosis [2]. These lesions are characterized histopathologically by a massive neutrophilic infiltration in the dermis which generally lacks vessel wall destruction (vasculitis). Sweet termed the process acute febrile neutrophilic dermatosis, but it has become known as Sweet's syndrome, as summarized in an excellent review by Cohen and Kurzrock [3].

This syndrome is more frequent in women (3.7:1) between the ages of 30 and 70 years (mean age 52.6 years), but incidence among men and children has also been reported [4]. The disease is often preceded by symptoms suggestive of an upper respiratory tract infection. The skin lesions appear to be distinctive but may simulate several other processes. The characteristic lesion is a well-defined erythematous plaque with a mammillated surface that may give the clinical impression of vesiculation (Fig. 1). Classically, there is an absence of ulceration, and the lesions usually heal without a resultant scar. Pustules may stud the surface or may be a major feature of the process. Another clinical variant is a tender erythematous dermal or subcutaneous nodule that clinically resembles erythema nodosum [5]. Genital lesions have been reported but are rare [6]. The lesions occur in crops and may be initiated by a variety of traumatic injuries (pathergy) such as a needle stick, wound debridement, or burn (Fig. 2). Fever and malaise are present in many patients, and myalgias and/or arthralgias occur in about half of the patients. Headache, nausea, vomiting, diarrhea, and/or conjunctivitis may also occur in some patients. Untreated lesions resolve over 6 to 8 weeks; however, many patients continue to produce new lesions chronically or recurrently, particularly those with an associated hematologic disorder.

The laboratory findings include a leukocytosis that is composed of mature neutrophils. White blood cell counts generally range from 10 to 20,000 cells/mm^3. The remainder of the blood count is within normal limits, except in patients who have leukemia-associated Sweet's syndrome. The erythrocyte sedimentation rate is frequently elevated. On rare occasions, a patient may have proteinuria. In addition, patients will frequently have a positive p-ANCA antibody.

The histopathologic features are characterized by a dense dermal infiltrate of mature polymorphonuclear leukocytes. In patients with leukemia-associated disease, the infiltrate is composed primarily of benign neutrophils, but some patients with atypical infiltrates have been reported [7]. The infiltrate may be more pronounced in perivascular areas and leukocytoclasia is frequent, but the vessel walls are classically spared. In a recent study, however, Malone et al [8] demonstrated that vascular inflammation is frequent and

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Table 1
Noninfectious neutrophilic dermatoses

Nonangiocentric
Psoriasis
Reiter's syndrome
Subcorneal pustular dermatosis
Acne fulminans
Blastomycosis-like pyoderma (pyoderma vegetans)
Neutrophilic eccrine hidradentitis
Angiocentric
Vessel wall destruction
Leukocytoclastic vasculitis
Polyarteritis nodosa
No vessel wall destruction
Acute febrile neutrophilic dermatosis (Sweet's syndrome)
Typical
Atypical
Pyoderma gangrenosum
Typical
Atypical
"Pustular vasculitis"
Behçet's disease
Bowel-associated dermatosis-arthritis syndrome
Rheumatoid neutrophilic dermatosis
Pyostomatitis vegetans
Pustular eruption of ulcerative colitis
Familial Mediterranean fever

correlates with the age of the lesion. Edema in the papillary dermis may be intense and coincide with the microvesicular lesions observed clinically.

Immunofluorescence microscopy has been negative in a small number of cases in which it has been reported.

Sweet's syndrome has been reported in association with a variety of diseases (Table 2). Von den Driesch et al [9] have suggested that Sweet's syndrome can be subdivided into four groups: (1) classic or idiopathic, (2) parainflammatory (either infectious or disorders of the immune system), (3) paraneoplastic, and (4) pregnancy associated [3]. While idiopathic cases are the most frequent, paraneoplastic Sweet's syndrome is the most frequently identified association, and myelogenous leukemia or preleukemic states such as a myelodysplastic syndrome account for most of the paraneoplastic conditions [3]. Sweet's syndrome is not clinically or histopathologically different among the four groups; however, in the presence of leukemia or myelodsyplasia, the patients tend to be anemic or thrombocytopenic and may have hemorrhagic lesions (Fig. 3). Other associated processes in paraneoplastic Sweet's syndrome include benign monoclonal gammopathy, lymphoma, and various solid tumors (most commonly including breast, stomach, genitourinary, and colon). Parainflammatory Sweet's syndrome has also been reported primarily in conjunction with inflammatory bowel disease (Crohn's disease and ulcerative colitis), but rheumatoid arthritis, Behçet's disease, sarcoidosis thyroiditis, and erythema nodosum have also been reported [3]. The linkage seems to be strong for inflammatory bowel disease and less strong for the other entities. The strongest links for infections are those of the upper respiratory tract, but HIV, hepatitis, mycobacteria, cytomegalovirus, and salmonella have all been reported. There are several drug hypersensitivities that present as Sweet's syndrome. Granulocyte colony–stimulating factor is the most often reported and has the strongest link, but minocycline, nitrofurantoin, trimethoprim-sulfamethoxazole, carbamazepine, hydralazine, and all-trans-retinoic acid have also been linked to the development of Sweet's syndrome in individual cases. It is not known how frequently paraneoplastic Sweet's syndrome occurs, but most authorities quote a figure ranging from 10% to 20%, with ~40% to 50% of these patients having a hematological malignancy.

Recent reports have focused on extracutaneous disease that may occur in patients with Sweet's syndrome and other neutrophilic dermatoses. Neutrophilic infiltration of the lungs, myocardium, muscles, central nervous system, eyes, and bone has been reported in multiple patients. Pulmonary infiltrates

Table 2
Acute febrile neutrophilic dermatosis (Sweet's syndrome): associated diseases and phenomena

Myeloproliferative disorders
Myelodysplasia (agnogenic myeloid metaplasia)
Acute myelocytic leukemia
Hematologic disorders
Acute myelogenous leukemia
Chronic myelogenous leukemia
Myelodysplasia
Multiple myeloma
Other malignancies (variety of individual reports)
Sarcoidosis
Inflammatory bowel disease
Crohn's disease
Ulcerative colitis
Rheumatoid arthritis
Lupus erythematosus
Immunizations
Pregnancy
Postinfectious—bacterial, fungal, parasitic
Behçet's disease
Drug induced
Administration of leukocyte colony–stimulating factors
Hashimoto's thyroiditis

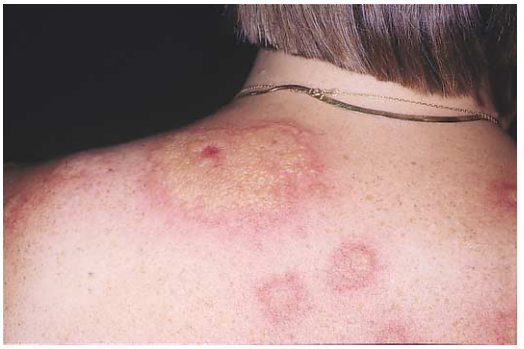

Fig. 1. Sweet's syndrome. This patient developed erythematous plaques with a central mammillated "microvesicular" surface.

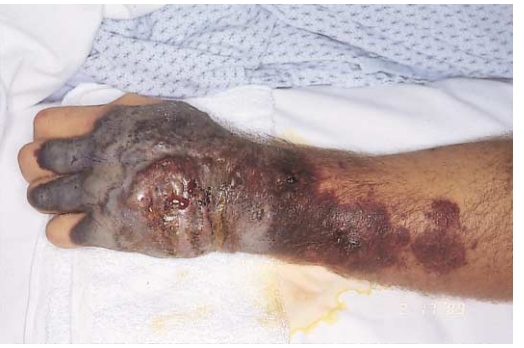

Fig. 3. Sweet's syndrome in a patient with acute myelogenous leukaemia. The purpura is caused by bleeding into the lesions associated with thrombocytopenia.

that might even cavitate have been reported [10]. The eye disease that seems to be frequently reported is known as peripheral ulcerative keratitis [11]. This disorder is said to be a "vasculitis" of the eyes and tends to be associated with vasculitic syndromes such as Wegener's granulomatosis and with rheumatoid arthritis. This condition can cause a loss of vision if left untreated. The bony lesion that occurs is known as multifocal sterile osteomyelitis [12]. This condition is characterized by bone pain and defects that reveal a culture-negative neutrophilic infiltrate on biopsy.

The pathogenesis of Sweet's syndrome is not known. Although the infiltrate is neutrophilic, the disease may well be driven by T lymphocytes or cytokines because therapies such as cyclosporin and infliximab are regularly effective. Tests for circulating immune complexes, tissue-bound immunoglobulins, or complement have generally been negative. Kemmett and Hunter [13] reported perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) in six patients with Sweet's syndrome, but believed this to be an epiphenomenon. Von den Driesch [14] was unable to demonstrate p- or c-ANCA in any of his 10 patients who were tested. Studies of neutrophil function have not shown a consistent abnormality. Furthermore, abnormalities of T cells and proinflammatory cytokines such as γ-interferon or interleukin 8 have not been reproducibly reported.

Fig. 2. This patient's pustular lesion on an erythematous base was initiated after a kitchen accident in which boiling water splattered on her hand.

The diagnosis of Sweet's syndrome is one of exclusion. Infections, neoplasia, vasculitis, and factitial disease must be excluded. The lesion at times is difficult to differentiate from erythema nodosum, erythema elevatum diutinum, and small vessel vasculitis. Also, it is this doctor's opinion there is overlap with several other neutrophilic dermatoses such as pustular eruption of ulcerative colitis, bowel bypass syndrome, and rheumatoid neutrophilic dermatosis. Finally, patients with Behcet's disease or inflammatory bowel disease may have Sweet-like lesions, and there may be confusion regarding nomenclature and classification of such patients.

Sweet's syndrome is classically an acute, corticosteroid-responsive, self-limited disease. A 2-week tapering course of oral prednisone (40 to 60 mg/d) is generally effective. One or more exacerbations requiring brief reinstitution of corticosteroids are common. From Sweet's initial report and many later ones, it appears that the process can follow a chronic course, and the use of steroid-sparing agents should be considered. In reports of individual or small groups of patients, dapsone, potassium iodide, indomethacin, doxycycline, clofazimine, colchicine, metronidazole, isotretinoin, methotrexate, chlorambucil, cyclosporin, and pulse dosage of methylprednisolone have been used successfully [6,14–19]. This doctor's choice of therapy for these patients depends on their course. On initial presentation, oral corticosteroids are the treat-

ment of choice. In patients with recurrent or chronic disease, however, this doctor attempts to use "steroid-sparing" agents, most often an antibiotic such as dapsone or metronidazole first, and then an immunosuppressive such as cyclosporin.

Pyoderma gangrenosum

Pyoderma gangrenosum is an uncommon, ulcerative, cutaneous condition with distinctive clinical characteristics. There frequently is an associated systemic disease. The diagnosis is made by exclusion of other processes that may cause cutaneous ulcers.

There are two variants that account for most of the cases of PG: the typical (classical) form and the atypical more superficial form [20]. These two differ in their clinical manifestations, their associations with systemic diseases, and their responsiveness to corticosteroids.

The ulcerations of typical (classical) pyoderma gangrenosum are frequently clinically characteristic. The border is well defined,with a deep erythematous to violaceous color (Fig. 4). The lesion extends peripherally, and often the border overhangs the ulceration (undermined) as the inflammatory process spreads within the dermis, only secondarily causing necrosis of the epidermis. The lesions may be single or may occur in crops, often beginning as a discrete pustule with a surrounding inflammatory erythema. Like patients with Sweet's syndrome, patients with pyoderma gangrenosum are often pathergic, with lesions sometimes developing after minor trauma (Fig. 5). The lesions may occur on any surface but are most common on the legs. Pain is a prominent feature and is sometimes so severe that narcotics are required for symptomatic relief. As the lesion heals, scar formation occurs and the resulting scar is often described as cribriform (Fig. 6). These patients frequently have an association with inflammatory bowel disease or a polyarthritis.

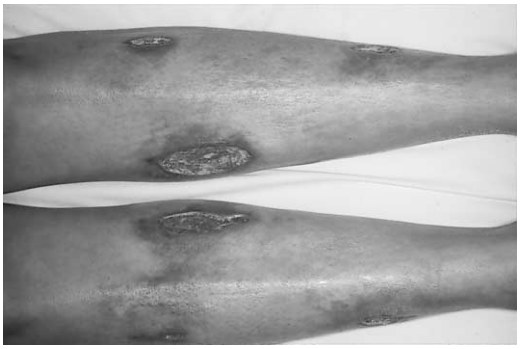

Fig. 5. Multiple lesions of pyoderma gangrenosum that followed a fasciotomy for compartment syndrome in this young woman.

Several variants of pyoderma gangrenosum have been described. The pustular eruption of ulcerative colitis was first reported by O'Loughlin and Perry [21]. In this process, the patient is acutely ill with fever and develops multiple sterile pustules [22,23]. The lesions may regress without scarring, or some may progress into a typical lesion of pyoderma gangrenosum. Biopsy of the early lesion reveals sheets of mature polymorphonuclear leukocytes.

Peristomal pyoderma gangrenosum is a recently recognized variant that occurs primarily in patients with inflammatory bowel disease, either ulcerative colitis or Crohn's disease, but may also occur in patients who have had abdominal surgery for cancer with the creation of an ileostomy, colostomy, or urostomy [24–26]. The ulceration may occur as an early or late phenomenon (Fig. 7). Irritation from the ileostomy or colostomy appliance may be involved in

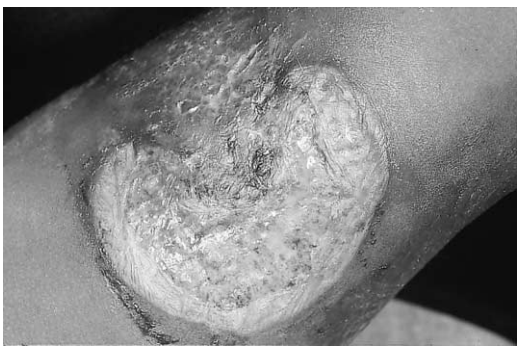

Fig. 4. Pyoderma gangrenosum. Typical large ulceration with an undermined violaceous border.

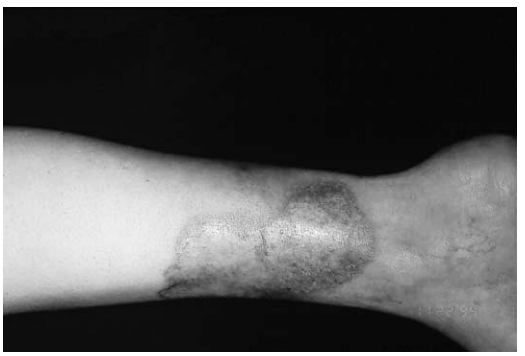

Fig. 6. Healed lesion of pyoderma gangrenosum.

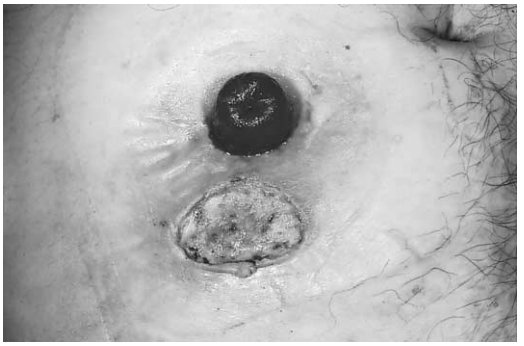

Fig. 7. Peristomal pyoderma gangrenosum in a patient with an ileostomy after bowel surgery for ulcerative colitis.

the induction of this process (pathergy). These ulcerations must be differentiated from infections, dermatitis, or extension of the underlying bowel disease (Crohn's only). Patients with this variant may be discovered to have active inflammation of the bowel. Even patients with a history of ulcerative colitis whose entire large colon has been resected or those who develop the process after cancer surgery should be studied for the presence of Crohn's disease. These patients may respond to excision of actively inflamed bowel [26], to antibiotics such as dapsone or metronidazole, to topical agents such as superpotent corticosteroids or tacrolimus [25], to infliximab as used for Crohn's disease [24], or may require more aggressive therapies.

Vulvar pyoderma gangrenosum is another variant [27]. Except for its location, the ulceration is otherwise typical of pyoderma gangrenosum (Fig. 8). This variant should be differentiated from Behçet's disease.

Another variant is pyostomatitis vegetans. This process is one in which chronic, pustular, eventually vegetative erosions develop on the mucous membranes, most notably in the oral cavity [28]. Most of these patients have had inflammatory bowel disease, and some have had ulcerative skin lesions similar to pyoderma gangrenosum [29].

A condition known as malignant pyoderma is distinguished from pyoderma gangrenosum by three features: (1) lesions predominantly on the head and neck (atypical for pyoderma gangrenosum), (2) lack of associated systemic diseases, and (3) the absence of undermined borders and surrounding erythema [30]. The distinctiveness of this variant has been questioned [31,32].

Finally, there is a variant known as atypical or bullous pyoderma gangrenosum. In this variant, the ulceration is more superficial, there is often a bullous, blue-gray margin (Fig. 9), and the upper extremities and face are more commonly affected [33]. In rare instances, patients may have typical PG on the legs and atypical PG on the arms/hands. In this doctor's view, an entity termed pustular vasculitis of the dorsal hands (later termed neutrophilic dermatosis of the dorsal hands) is a variant of atypical PG [34]. Atypical pyoderma gangrenosum has been reported primarily with hematological disease, primarily myelodysplastic conditions [20] or acute myelogenous leukemia. At times, the separation of atypical pyoderma gangrenosum from leukemia-associated Sweet's syndrome is difficult.

The histopathological features of pyoderma gangrenosum are not specific but are useful in ruling out other causes of cutaneous ulceration. There is controversy over what is the initial histopathological change, with some classifying the process as a neutrophilic dermatosis [1], and others believing that the initial changes involve lymphocytic infiltrate, endothelial cell swelling, and fibrinoid necrosis of the vessel wall (a lymphocytic vasculitis) [35]. Regardless, the lesion does not involve a leukocytoclastic vasculitis, nor is

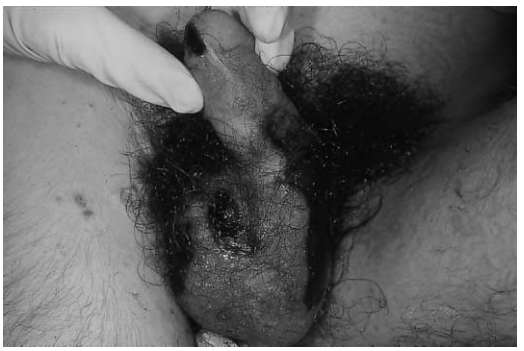

Fig. 8. Penile pyoderma gangrenosum.

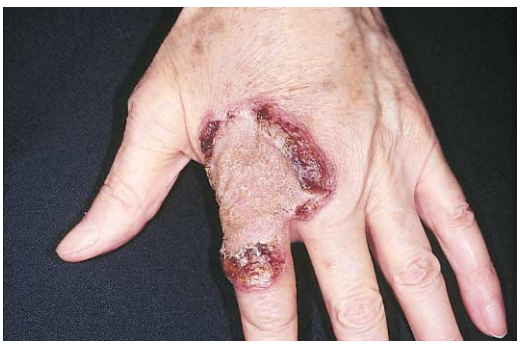

Fig. 9. Atypical pyoderma gangrenosum in a patient with a preleukemic state. The lesion is a shallow ulcer with a bullous, blue-gray border.

granuloma formation compatible with a diagnosis of pyoderma gangrenosum.

The etiology and pathogenesis of pyoderma gangrenosum are not understood, but a variety of abnormalities of the immune system have been described. Although associated conditions are common (Table 3), perhaps one quarter to one half of the patients have "idiopathic" disease. The most commonly associated conditions are inflammatory bowel disease, arthritis, paraproteinemia, and hematological malignancy, and their frequency varies with the clinical variant of PG.

Initial reports of pyoderma gangrenosum emphasized the association with ulcerative colitis [36]. It has eventually become recognized that regional enteritis and Crohn's disease (granulomatous colitis) are found with pyoderma gangrenosum as often as ulcerative colitis [37,38]. In the most recent accounts, inflammatory bowel disease constitutes about 15% to 20% of the associated phenomena. In addition, early reports stressed the relationship between pyoderma gangrenosum and the activity of the bowel disease, and even suggested that some patients' pyoderma gangrenosum lesions may benefit from surgical resection of the inflamed bowel (ulcerative colitis only). Callen et al [39] have reported pyoderma gangrenosum in association with inactive terminal ileitis, and Talansky et al [40] also have reported lack of effectiveness of bowel resection in some patients with pyoderma gangrenosum and ulcerative colitis.

Table 3
Diseases associated with pyoderma gangrenosum

Common associations
Inflammatory bowel disease (IBD)
Chronic ulcerative colitis (CUC)
Regional enteritis, granulomatous colitis (Crohn's disease)
Arthritis
Seronegative with IBD
Seronegative without IBD
Rheumatoid arthritis
Spondylitis
Osteoarthritis
Hematologic diseases
Myelocytic leukemias
Hairy cell leukemia
Myelofibrosis, agnogenic myeloid metaplasia
Monoclonal gammopathy (IgA)
Rarely reported associations
Chronic active hepatitis
Myeloma
Polycythemia rubra vera
Paroxysmal nocturnal hemoglobinuria
Takayasu's arteritis
Primary biliary cirrhosis
Systemic lupus erythematosus
Wegener's granulomatosis
Hidradenitis suppurativa
Acne conglobata
Malignancy—various sites and cell types
Thyroid disease
Pulmonary disease
Sarcoidosis
Diabetes mellitus
HIV infection
Other pustular dermatosis—particularly Behçet's disease

Arthritis is a frequent finding with pyoderma gangrenosum. In some of the later reports, arthritis has been the most frequently associated condition [37,38]. Five of the nine patients with arthritis reported by Prystowsky et al [38] had inflammatory bowel disease associated arthritis. In general, the arthritis associated with pyoderma gangrenosum is a symmetrical polyarthritis that may be seronegative or seropositive. Although spondylitis may occur in conjunction with inflammatory bowel disease associated with pyoderma gangrenosum, it has not been reported independently with pyoderma gangrenosum.

A variety of malignancies have been reported with pyoderma gangrenosum, most commonly myelogenous leukemia or preleukemia. This association may be more common with the atypical variants of pyoderma gangrenosum. Although a variety of solid tumors have been reported, their presence is probably coincidental.

Paraproteinemia, a generally benign variety, has been reported with pyoderma gangrenosum. With newer techniques of protein separation, it appears that 15% of patients with pyoderma gangrenosum may have a benign monoclonal gammopathy, most often of IgA variety [38,41]. The development of myeloma in patients with pyoderma gangrenosum has been reported [42] but is very rare.

The diagnostic evaluation (Table 4) of the patient presumed to have pyoderma gangrenosum has two objectives: (1) to rule out other causes of cutaneous ulceration and (2) to determine whether there is a treatable, systemic-associated disorder. There is no specific laboratory or histopathological test that is diagnostic. Moreover, some of the associated disease processes may be clinically silent.

The differential diagnoses of ulcerative cutaneous lesions include: (1) infectious diseases, (2) halogenodermas, (3) vasculitis, (4) insect bites, (5) venous or arterial insufficiency (including occlusive disease associated with antiphospolipid antibodies), and (6) factitial ulcerations. Cultures should be taken from both exudates and tissues.

Table 4
Diagnostic evaluation of the patient with pyoderma gangrenosum

Careful history and thorough physical examination
Skin biopsy with tissue taken for cultures (bacterial, viral and fungal, etc)
Studies of the gastrointestinal tract
Studies for possible abnormal serum proteins
Complete blood count, examination of the peripheral smear, and possibly a bone marrow examination

To test for the presence of an associated disorder, another series of examinations should be made. A thorough historical evaluation and examination of the gastrointestinal tract should be undertaken in conjunction with a gastroenterologist. Radiographic procedures may include an upper gastrointestinal series with a small bowel follow-through and a barium enema. Flexible sigmoidoscopy, colonoscopy, or both may also be done, with appropriate biopsies being taken. A complete blood count, careful evaluation of the peripheral smear, and possibly a bone marrow aspirate or biopsy will help rule out the presence of an associated hematological malignant process. Serum protein electrophoresis, serum immunodiffusion studies, and possibly serum and urine immunoelectrophoresis will help to eliminate a diagnosis of an associated monoclonal gammopathy or myeloma. Multiple reports of pyoderma gangrenosum–like leg ulcers in patients with antiphospholipid antibodies have appeared, and tests such as VDRL, anticardiolipin antibody, lupus anticoagulant, and partial thromboplastin time are now standard in the evaluation of a patient with pyoderma gangrenosum [43].

There is no specific uniformly effective treatment for pyoderma gangrenosum. Although systemic treatment may affect the underlying disease process in some patients with chronic ulcerative colitis [44], it sometimes becomes necessary to consider colectomy. Some patients' skin lesions will respond to bowel resection or therapies aimed at control of the bowel disease (eg, infliximab for Crohn's disease), but there are patients with presumed ulcerative colitis in whom total colectomy, including removal of the rectosigmoid colon, does not lead to a remission [40]. It is possible that in retrospect the more appropriate diagnosis for the inflammatory bowel disease was Crohn's colitis rather than ulcerative colitis.

In mild cases of pyoderma gangrenosum, local measures such as dressings, elevation, rest, topical agents, or intralesional injections may be sufficient to control the disease process. Compresses, wet to dry dressings, or the newer bio-occlusive semipermeable dressings may be useful. Cleansing or therapies with antibacterial agents such as hydrogen peroxide or benzoyl peroxide have been reported to be beneficial in an occasional patient. In a small number of cases, hyperbaric oxygen has also been reported to be effective. Superpotent topical corticosteroids or topical tacrolimus might be beneficial, particularly in those patients with peristomal pyoderma gangrenosum [25]. Intralesional injections of corticosteroids [45] may be beneficial in some patients, but care must be taken to avoid introducing an infection and to limit the potential systemic effects of corticosteroids that arise from injecting large doses. Other topical approaches include the use of sodium cromoglycate, nitrogen mustard, and 5-aminosalicyclic acid [46,47].

In patients who do not respond to topical or local therapies, or in whom a severe, rapid course warrants the use of a systemic agent, sulfonamides, sulfones, or corticosteroids have been the most commonly used agents. Perry [36] reported that oral sulfasalazine is effective in patients both with and without inflammatory bowel disease. Dapsone in doses of up to 100 mg/d has often been used as a monotherapy or as an adjunctive steroid-sparing agent. The drug is usually administered in lower doses (100 to 150 mg/d), and the usual precautions and pretherapy evaluation are necessary. The mechanism of action of the sulfanomides and sulfones in this process is not understood, but effects on the polymorphonuclear leukocyte may be a factor. Another antileprosy agent, clofazimine, has also been reported to be successful in some patients with pyoderma gangrenosum. Finally, several other antibiotics have been used successfully in individual cases; these include minocycline and rifampicin.

Systemic corticosteroids have been used extensively in patients with pyoderma gangrenosum and its variants and are generally believed to be very effective. Large doses (40 to 120 mg/d) are usually necessary to induce a remission of the disease. These doses, used over the long term, will frequently result in steroid-related side effects. In the studies by Holt et al [48], 6 of their 12 patients treated with corticosteroids developed serious steroid complications, and 4 of these 6 died as a result of the therapy. To avoid the complications of long-term steroid use, Johnson and Lazarus [49] and subsequently others have used pulse therapy with 1 g of methylprednisolone given intravenously each day for a period of 5 days. Maintenance of the remission was accomplished with oral corticosteroids every other day. Prystowsky et al [38] have reported the same experience as Lazarus with an additional eight patients. They found that remissions occurred in five of the patients, and that they were usually able to

remove oral corticosteroid therapy and often lower the dose of other therapies. Pulse therapy is not without side effects, including sudden death. In the hands of Prystowsky et al and this doctor's own experience with three patients, this therapy has primarily resulted in transient hyperglycemia; however, it should only be used with great caution and proper monitoring.

Immunosuppressive agents have been suggested for use in patients who fail to respond to other therapies, particularly systemic corticosteroids, or who develop steroid-related side effects. Individual reports using oral azathioprine, cyclophosphamide [50], chlorambucil [51], cyclosporin [52], tacrolimus (FK 506) [53], or methotrexate [54] have suggested that, at least in some patients, these agents may be successful. Intravenous pulses of cyclophosphamide [55] or immunoglobulin [56] have also been successful in individual patients. The mode of action of the immunosuppressive agents is not understood.

With the introduction of biologic therapies for inflammatory bowel disease and rheumatoid arthritis, there are now reports of the effectiveness of the anti–tumor necrosis factor α monoclonal antibody (infliximab) for patients with pyoderma gangrenosum [57]. Thalidomide may also be useful for individual patients [58]. Finally, although it is generally recommended that surgery be avoided, some patients have successfully been grafted with bioengineered skin when pretreated with an immunosuppressive agent [59].

Rheumatoid neutrophilic dermatitis

Ackerman [60] described a neutrophilic dermatosis in patients with rheumatoid arthritis. Most patients have seropositive rheumatoid arthritis, but recent reports by Gay-Crosier et al [61] and Brown et al [10] suggest that the process may occur in seronegative patients. This is apparently a rare manifestation of rheumatoid arthritis, and has only been reported in a small number of patients [62–64]. The patients are described as having symmetric, erythematous nodules and plaques on the extensor surfaces of the joints (Fig. 10). There is an apparent predilection for the dorsa of the hands and arms. It is not clear whether this condition is clinically or histopathologically distinct, specifically whether it can be differentiated from Sweet's syndrome or the atypical variant of pyoderma gangrenosum. An effective therapy includes corticosteroids, dapsone, and colchicine.

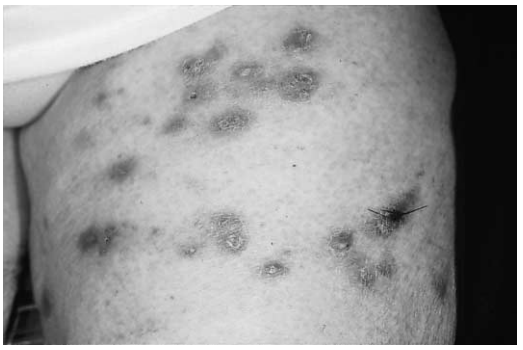

Fig. 10. Rheumatoid neutrophilic dermatosis. This patient developed multiple vesiculopustular plaques and nodules on the thighs.

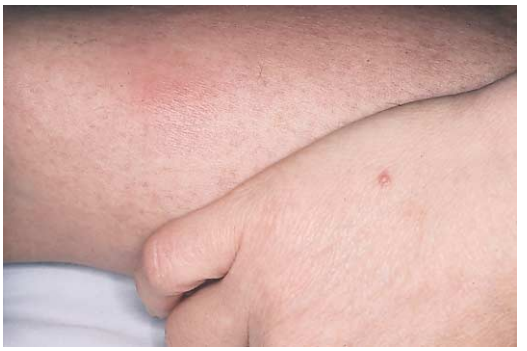

Fig. 11. Scattered pustules on an erythematous base in a patient with a bowel bypass for morbid obesity.

Bowel-associated dermatosis–arthritis syndrome

Patients who had undergone bowel bypass surgery for morbid obesity have occasionally developed scat-

Fig. 12. Vesiculopustular eruption in a patient with previous ulcer surgery (Billroth II) and a blind loop—the so-called "bowel bypass syndrome without a bowel bypass."

tered pustular lesions (Fig. 11) and arthritis. This became known as the bowel bypass syndrome, and was felt to be an immune-complex disease caused by bacterial overgrowth in the blind loop. Treatment with antibiotics was often effective in clearing the cutaneous lesions and improving the joint symptoms. Jorizzo et al [65] later coined the term "bowel-bypass syndrome without bowel bypass" or "bowel-associated dermatosis–arthritis syndrome." They reported on four patients with this syndrome; two had blind loops as a result of Billroth II procedures, one had ulcerative colitis, and one had Crohn's disease. Dicken [66] reported two similar patients who had had Roux-en Y procedures with resultant blind loops. These patients presented with a widespread eruption characterized by pustules on an erythematous or necrotic base. The lesions may be few in number or extensive. Ulceration is rare. The appearance of the lesions is often accompanied by fever, arthralgias or a true inflammatory arthropathy, and myalgias. The arthritis accompanying this process is generally symmetrical, nondeforming, and most frequently involves the small joints such as the wrists, ankles, metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints. The disease bears a histopathologic resemblance to Sweet's syndrome. In fact, only after the report by Jorizzo et al [65] did we recognize that a patient reported by our group [67] probably would have been more correctly diagnosed as having the bowel-associated dermatosis–arthritis syndrome rather than Sweet's syndrome because of his previous Billroth II procedure (Fig. 12). This disease is presumed to be caused by immune complexes [68], and while anti-inflammatory therapy is helpful at times, antibiotics frequently control the process, or bowel surgery (to remove 'blind' loops) will reverse it.

Neutrophilic eccrine hidradenitis

Neutrophilic eccrine hidradenitis is a recently described entity characterized by erythematous papules, plaques, or nodules, most often on acral skin [69]. The clinical presentation may be varied, however, and includes periorbital inflammation, pustular presentations, and disseminated disease. The histopathologic examination of the lesion reveals neutrophilic infiltration that surrounds necrotic eccrine glands. The process is primarily linked to acute myelogenous leukemia and usually occurs during chemotherapy with cytarabine or an anthracyclin; however, there are instances in which the presence of neutrophilic eccrine hidradenitis heralds the onset of the leukemia. The process is self-limiting.

Summary

The neutrophilic dermatoses are a group of related cutaneous disorders that frequently have systemic manifestations or associations. While there are distinct clinical differences in the classical lesions of these disorders, there are many patients who have overlapping features. In addition, the associated systemic manifestations or associated diseases are often similar among these disorders. Finally, the management of these disorders with the frequent use of corticosteroids and nonsteroidal immunosuppressive or immunomodulatory agents is common.

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DERMATOLOGIC CLINICS

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Panniculitis

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The classification of inflammatory disorders of the subcutaneous tissue has mystified dermatologists for decades. Lack of specific treatments and overlapping clinical and histologic features have added to the confusion [1,2]. This article first classifies the various panniculititides by their primary histopathologic pattern: (1) septal panniculitis without vasculitis, (2) septal panniculitis with vasculitis, (3) lobular panniculitis without vasculitis, and (4) lobular panniculitis with vasculitis [3,4]. We then describe the key clinical findings in the most important forms of panniculitis. We begin with the most common form of panniculitis, erythema nodosum. Before engaging in an elaborate (and expensive) exercise in differential diagnosis for suspected cases of panniculitis, a worthwhile question to consider initially might be, "Is this erythema nodosum, or is it not?"

Septal panniculitis without vasculitis (Table 1)

Erythema nodosum

Erythema nodosum is the most common of the panniculitides. It is best considered a reactive process to a variety of possible inciting causes and is manifested as an inflammatory reaction in the subcutaneous tissue. The most common identifiable cause of erythema nodosum is a beta-streptococcal upper respiratory tract infection, although other infections, drugs, inflammatory bowel disease, pregnancy, autoimmune diseases, and malignant diseases have also been recognized [5]. The condition may also typically occur in association with sarcoidosis.

Exquisitely tender, deeply seated erythematous nodules occur primarily on the extensor surfaces of the distal lower extremities (Fig. 1). Involvement of the thighs, forearms, and face has been reported occasionally. The eruption lasts 4 to 6 weeks, after which spontaneous resolution is the rule. Recurrence or persistence beyond this time is not unusual, however, especially in patients with identifiable inciting factors that are significant and persistent. As the individual lesion resolves, the skin takes on the appearance of a bruise (erythema contusiformis). Scarring does not result because there is no breakdown of fat.

Systemic symptoms may accompany the cutaneous eruption, especially fever, chills, malaise, arthralgias, and myalgias. A prodrome of sore throat may suggest the possibility of an upper respiratory tract infection.

Histopathologically, the condition is primarily a septal panniculitis (Fig. 2). Early inflammatory cells, including neutrophils and occasionally eosinophils, are replaced by a more chronic infiltrate including lymphocytes, histiocytes, and giant cells, whose presence in the edematous fibrous septae may evoke a frankly granulomatous picture. Vasculitis and ulceration do not occur.

The laboratory work-up of patients with erythema nodosum should generally be guided by the associated signs and symptoms. Nevertheless, throat cultures should be done even in the absence of upper respiratory tract symptoms. Serological studies may be indicated in patients with severe joint symptoms. In persistent cases, a chest radiograph should be performed to rule out sarcoidosis.

The disease may persist over several weeks, with the appearance of new nodules as older ones

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Table 1
Panniculitis

Septal without vasculitis						
Type	General	Clinical	Pathology	Ulcer	Therapy	Other
Erythema nodosum	F > M, 20–30 y Etiologies = sarcoid, CVD, infxn, pregnancy, bowel, drugs (sulfa, OCP), Behçets, lymphoma/ leukemia	Red, tender nodules Ant shins b/l +/– arms, face, neck, thighs	Meischer's radial granulomas	No	Spontaneous bedrest SSKI, NSAIDS stop offenders	Arthropathy EN migrans = unilateral chronic type E. contusiformis = resolving form Infxn = strep, yersinia, TB, leprosy, Lyme
Scleroderma	Localized morphea, progressive SS	Indurated plaques	New collagen deposition leads to fat necrosis			
Lipodermato-sclerosis	Chronic venous stasis	LE edema, varicosities, indurated nodules on LE (inverted champagne glass)	Sclerosis, dermal fibrosis	No	Compression stockings, stanozolol	
Eosinophilic fasciitis		Indurated, fixed skin extremities	Dermal thickening, eosinophilic, hyalinized collagen, deep to fascia	No		Trauma ? *Borrelia burgdorferi*
Eosinophilia myalgia syndrome	Ingestion of L-tryptophan – contaminant "peak K"					Myopathy, eosinophilia, pulm dz

resolve. Bed rest and support stockings may aid especially symptomatic patients, as may treatment with potassium iodide or nonsteroidal anti-inflammatory agents [6]. Systemic steroids may also be used if not contraindicated by any underlying disease. Full recovery is the rule. Recurrences are most common in patients with significant underlying disease.

Scleroderma panniculitis

Scleroderma panniculitis, manifested as subcutaneous morphea, appears as discrete indurated plaques on the shoulders and upper arms that usually resolve leaving subcutaneous atrophy with residual hyperpigmentation [7,8]. Histologically, fibrous septal thickening leads to new collagen deposition and possible fat necrosis. Treatment with intralesional steroids or D-penicillamine may be effective, although most lesions tend to slowly progress [9].

Lipodermatosclerosis

Lipodermatosclerosis is seen most often in women with chronic venous stasis [10]. Recent etiologic theories focus on microvascular leakage of serous fluid, which causes localized edema. The resulting vessel fibrosis decreases the oxygenation and nutrient supply to the overlying skin, thereby causing abnormal collagen cross-linking and uncontrolled release of plasminogen and free radicals [11]. Over time, unchecked proteolytic enzyme activation may lead to ulceration [12]. Clinically, indurated areas that eventually become confluent (inverted champagne glass appearance) develop over the shins (Fig. 3).

Histologically, dermal fibrosis and septal sclerosis are striking. Prognosis for resolution is poor, yet aggressive compression therapy (30 to 40 mm/Hg) can be extremely beneficial in controlling active disease [13]. Systemic anabolic steroids (ie, stanozolol and oxandrolone) may benefit some patients,

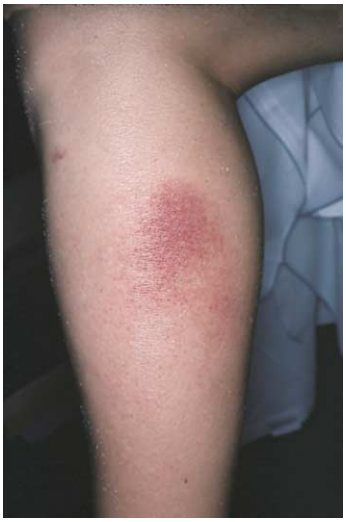

Fig. 1. Erythema nodosum. Tender erythematous nodule on the lateral leg.

presumably by decreasing the degree of capillary fibrosis [14]. End-stage ulceration may respond to excision and split-thickness skin grafting [15].

Eosinophilic fasciitis

Eosinophilic fasciitis (Shulman's syndrome) has been classified as a variant of localized scleroderma that usually occurs in otherwise healthy young individuals. The disease process has rarely been noted (5% of cases) to occur sporadically in patients with malignant lymphoma [16]. Other proposed infrequent associations include initiation of dialysis [17], chronic asthma [18], carpel tunnel syndrome [19], and various medications. Clinically, the lesions may present after intense physical exertion as symmetric,

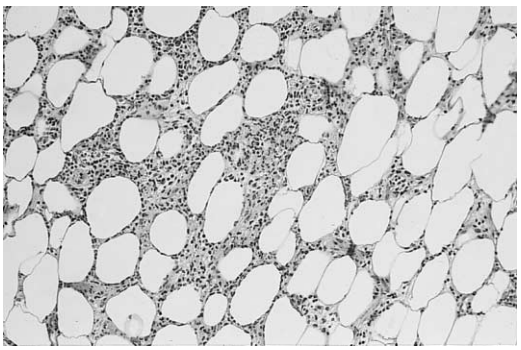

Fig. 2. Septal panniculitis. Hematoxylin and eosin (×100).

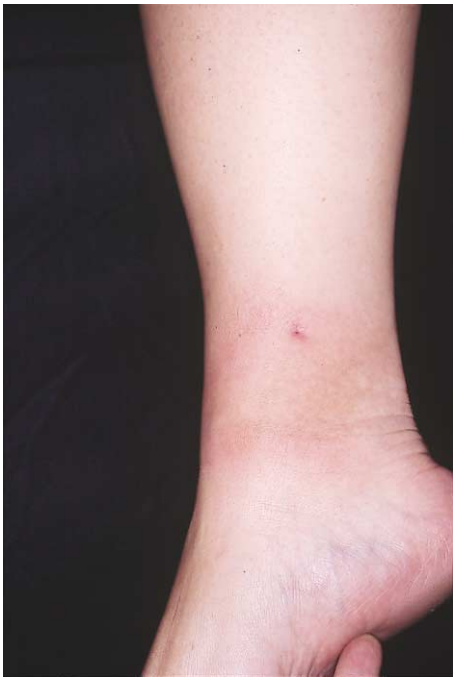

Fig. 3. Sclerosing panniculitis. The induration often overlies the medial malleolus.

fixed sleeve-like induration of the extremities or pitting edema of the extremities [20]. Peripheral eosinophilia and an elevated sedimentation rate may be found. Histologically, changes similar to scleroderma occur with septal thickening and dermal deposition of collagen; however, the fascia is also involved, with edema, thickening, and infiltration of eosinophils. The lesions often slowly resolve spontaneously. More recalcitrant cases have anecdotally been reported to respond to cyclosporine [21], methotrexate, bath PUVA [22], systemic steroids, and allogeneic bone marrow transplantation [23].

Eosinophilia myalgia syndrome

Eosinophilia myalgia syndrome (EMS) was first observed in 1989 after ingestion of selected batches of L-tryptophan [24]. Some recent research hypothesizes that EMS may be a drug-induced allergic disease in certain susceptible individuals suffering from functional somatic syndromes such as fibromyalgia syndrome [25]. EMS often has identical clinical manifestations to eosinophilic fasciitis; however, these patients also manifest systemic myopathy, eosinophilia, and pulmonary disease. The majority of patients have recently been shown to demonstrate

cortical white matter damage that manifests clinically as deficiencies in complex visual memory, verbal memory, motor slowing, and attention span [26]. Eosinophilic cholecystitis has also been documented as a late manifestation of EMS [27]. Most patients improve with systemic steroid therapy, although severe systemic involvement might require the use of immunosuppressive drugs. No specific treatment has been singularly beneficial. To date, many clinicians question whether EMS is a distinct disease entity because of the small number of diagnosed patients (23 total) and the continued clinical diagnosis of the disease despite the removal of the contaminated L-tryptophan from the market.

Septal panniculitis with vasculitis (Table 2)

Superficial migratory thrombophlebitis

Superficial thrombophlebitis is seen most often in patients with venous insufficiency; however, a hypercoagulable state should be excluded [28,29]. Behçet syndrome may present with superficial thrombophlebitis and organ thrombosis [30]. Historical literature describes superficial thrombophlebitis as a paraneoplastic syndrome (Trousseau's sign) associated with pancreatic, stomach, lung, prostate, colon, and bladder carcinoma [31]. The disease is characterized by multiple tender erythematous nodules distributed in a linear fashion, often on the lower extremities but rarely on the upper extremities, that can change location over time because of varying segments of vein involvement. No ulceration is seen. Histologically, there is thrombosis of the superficial veins with a dense inflammatory infiltrate within the vessel wall. It is remarkable that neither inflammation nor necrosis is seen within the lobules.

Treatment is conservative, with emphasis on elevation and compression. Patients with venous insufficiency should seek surgical intervention. Chronic or periodic therapy with anticoagulants may be helpful.

Polyarteritis nodosa

Cutaneous involvement has been reported in $\sim$10% to 15% of patients with systemic polyarteritis nodosa. The purpuric papules and nodules result from leukocytoclastic vasculitis and are most common on the distal lower extremities [32]. There may be an associated livedo vascular pattern. Systemic lesions of vasculitis may be detected in other organs including the kidneys, liver, and brain [33]. Histology shows a necrotizing arteritis; mortality is high.

Cutaneous polyarteritis nodosa

Cutaneous polyarteritis nodosa defines a vasculitis of the arteries and arterioles of the fibrous septae in the absence of systemic involvement. The lesions present as tender, bilateral erythematous nodules that may ulcerate, mostly on the lower extremities. Livedo reticularis may be noted. There may be mild consti-

Table 2
Panniculitis

Septal with vasculitis						
Type	General	Clinical	Pathology	Ulcer	Therapy	Other
Superficial migratory thrombophlebitis	Complication of varicosities/ hypercoaguable states/ Ca (Trousseau's: lung, breast)	Multiple tender nodules in linear configuration Legs, +/− arms	Thrombosis superficial veins, no inflammation, no necrosis	No		
Polyarteritis nodosa		5–10 mm nodules along superficial arteries, distal legs and feet, +/− livedo, urticaria, redness, vesicles, pustules	Necrotic vasculitis of lg arteries with neuts	Yes	High mortality	Renal, cardiac ? Hep B/C
Cutaneous polyarteritis nodosa	Benign cutaneous variant associated with strep, hepatitis, enteritis	Crops of red 5–20 tender nodules, LE +/− head/neck/shoulders/ buttocks + livedo, "starburst," purpura	Necrosis of small/med arteries	Yes		Nodules do not follow vessels; arthralgias, myalgias, fever

tutional symptoms although systemic involvement is absent. Although the course may be chronic, the prognosis is good. Histologically, the lesions of cutaneous polyarteritis nodosa show vasculitis of the medium-sized arteries and arterioles in the septae of the upper subcutaneous tissue. The inflammatory infiltrate is initially mostly neutrophilic, although a greater proportion of mononuclear cells can be found in later-stage lesions. The etiology is unknown, although a few cases have been reported to be associated with bacterial or viral (hepatitis B or C) infection [34,35]. Steroidal or nonsteroidal inflammatory drugs are usually effective, although antibiotics may be used in patients with a documented underlying bacterial infection.

Lobular panniculitis without vasculitis (Table 3)

Idiopathic lobular panniculitis (Weber-Christian disease)

Also called acute febrile nonsuppurative nodular panniculitis, this condition is probably not a single disease entity but represents various entities presenting as a lobular panniculitis that cannot be more specifically classified. As originally described, Weber-Christian disease was said to be caused by three broad groups of etiologic factors: physical and chemical agents, infectious agents, and immunologic factors. Many of these conditions should be given more specific diagnoses related to their precipitating factor(s), and thus the term Weber-Christian disease is best reserved for those idiopathic panniculitides for which an inciting agent cannot be identified [36].

Clinically, variable numbers of subcutaneous nodules occur symmetrically, most often on the legs and thighs, although the trunk and extremities can be affected (Fig. 4). The individual lesions range from 1 to 2 cm or larger in diameter, and are dull red, edematous, and often somewhat tender and painful. The nodules occasionally break down and discharge an oily material through the skin (liquefying panniculitis). Because of the underlying fat necrosis, atrophic scarring often ensues. The eruption may be accompanied by fever, fatigue, nausea and vomiting, anorexia, arthralgias, and myalgias. The disease is chronic and recurrent and has characteristic remissions and exacerbations. Involvement of the visceral fat may cause a variety of systemic symptoms (systemic Weber-Christian disease) [37,38].

Histologically, Weber-Christian disease is a lobular panniculitis in which three stages can be identified. In the first (or acute inflammatory) stage, degeneration of fat cells is associated with a dense inflammatory infiltrate of neutrophils, lymphocytes, and histiocytes. In the second (or macrophagic) stage, macrophages invade and digest the degenerated fat, leading to the formation of foam cells. The foam cells may be large, multinucleated, and completely replace the fat lobule. In the third (or fibrotic) stage, the foam cells are replaced by fibroblasts and a few mononuclear cells, with subsequent collagen formation and fibrosis.

A variety of therapeutic measures have been suggested. Systemic corticosteroids are most reliable, but recurrences are common as the dose is reduced. Nonsteroidal anti-inflammatory agents, immunosuppressive agents, thalidomide, and iodides are of variable effectiveness. Tetracycline (because of its antilipase activity) and heparin (because of its ability to liberate lipoprotein lipase) are anecdotally reported to be beneficial. Surgery may be necessary for large, liquefying lesions.

Cytophagic histiocytic panniculitis

Cytophagic histiocytic panniculitis (CHP) is a lobular, nonvasculitic panniculitis of unknown etiology that affects both children and adults. Two distinct entities have been characterized as CHP: one is a primary panniculitis and the other an infiltrative neoplasia [39]. CHP in some cases appears to be a benign histiocytic response resulting in a lobular panniculitis. In other cases perhaps more appropriately referred to as subcutaneous panniculitis-like T-cell lymphoma (SPTL), a malignant T-cell infiltration clinically presents as a panniculitis [40–42]. There appears to be no association of either entity with Epstein-Barr virus, as once hypothesized [43]. Some investigators have suggested a natural disease progression of CHP to SPTL.

Clinically, the large inflammatory subcutaneous nodules and plaques are primarily seen on upper and lower extremities (Fig. 5), rarely on the trunk and face, with overlying ecchymosis and ulceration. Fever, weight loss, hepatosplenomegaly, lymphadenopathy, and pancytopenia may develop over time. Fatal hemorrhage can result from aggressive bone marrow involvement; this has been characterized as terminal hemophagocytic syndrome.

Histologically, CHP demonstrates a mostly lobular infiltrate of large, benign histiocytes (beanbag cells) that engulf lymphocytes, erythrocytes, and platelets, along with fat necrosis and hemorrhage. If detected, a clonal proliferation of atypical T- or B-cell lymphocytes supports the progression of CHP into SPTL.

In vitro measurement of phagocytic activity may have diagnostic value and help to monitor the

Table 3

Lobular without vasculitis

Type	General		Clinical	Pathology	Ulcer	Therapy	Other
Idiopathic lobular panniculitis (Weber-Christian)	F>M, age 30–60 y Waves of lesions over weeks to months		Symm thighs/LE	Foam cells + neuts	Yes (oily)		+ scar + systemic sx
Histiocytic cytophagic panniculitis	? CTCL		Lg nodules UE/LE +/− bruising oral/ genital ulcers	Bean bag cells with atypical lymphs and benign histiocytes	Yes	Chemo, prednisone	+ systemic sx death from hemorrhage not always fatal
Physical	Cold	Neonates in winter	Face/extremities Violet-blue		No	Spont resolution	− scar
	Traumatic		Breast "peau de orange"		No		+ scar
	Chemical	Injected oils		Swiss-cheese	Yes		
	Factitial	Unusual sites		+ polarize			Paint, acid, alkali, feces
Neonatal	Scleroderma neonatorum	Debilitated infants	1–3 d old diffuse thick +/− inflammation thighs/back	Needle-like radial clefts (TG)		Death common	Toxic
	Neonatal subcutaneous fat necrosis	Full-term infant	1–2 wk old localized over pressure sites	Granulomas + calcification			Hypercalcemia

Systemic	Pancreatic	Pancr. CA Etoh pancr	M>F pretibial	Ghost cells + calcification	Yes	Tx pancreat	Circul pancr enzymes
	Lupus panniculitis "lupus profundus"	2% LE pts + ANA	Medium-sized nodules on face and proximal extremities	Hylanization Fat necrosis with plasma cells	Yes	Antimalarials IL steroids	+ scar/atrophy
	Sarcoidosis "Darier-Roussy"			Epithelioid tubercles in fat lobules	Yes		
	Renal failure (calcifying)	"Calciphylaxis" hyperparathyroid	Nodules, plaques, ectopic calcification LE, abdomen	Mural calcification	Yes with eschar	Amphogel, parathyroidectomy	
	Lymphoma/ leukemia		Red nodules		Yes		
	Infectious	Fungal/bacterial immunosuppressed				Tx infxn	Staph/strep, kleb, pseudo, nocardia, sporo, crypto
	α-1 antitrypsin deficiency	Trauma induced	Recurrent tender red nodules; trunk, prox extrem; drain serum		Yes	Avoid trauma dapsone Stop tobacco/Etoh	Emphysema, hepatitis, cirrhosis, vasculitis, angioedema
Post-steroid	1–2 wks after therapy		Cheeks, arms, and trunk +/− pruritus	Foam cells needle-like clefting		Spont resolution	Can restart steroids

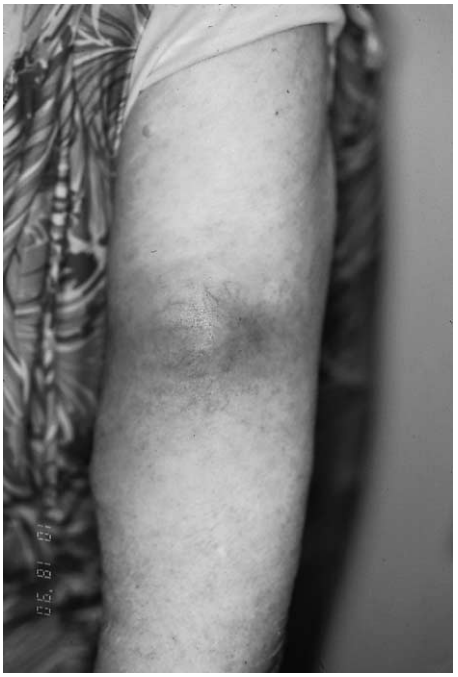

Fig. 4. Weber-Christian panniculitis.

response to treatment [44]. Pleural effusion cytology has aided in diagnosis with the detection of hemophagocytic histiocytes in the exudate [45].

No definitive treatment exists for CHP, although both spontaneous and therapeutically induced remissions have occurred. When involvement of the bone marrow or liver occurs, aggressive treatment is indicated because of the high risk of fatal hemorrhage. Case reports support different combinations of prednisone, cyclosporine, bleomycin, chlorambucil, vincristine, or doxorubicin as chemotherapeutic options [45,46]. The value of bone marrow transplantation is under investigation.

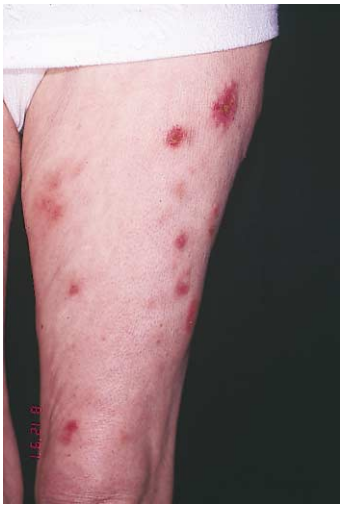

Fig. 5. Subcutaneous T-cell lymphoma–like panniculitis.

Physical panniculitis

Four types of panniculitis induced by physical agents have been reported: cold, traumatic, chemical, and factitial. Mainly supportive treatment is indicated as these entities spontaneously resolve. Cold-induced panniculitis occurs most often in infants and young children. Etiologic factors have included popsicles [47], ice packs (eg, applied to the faces of infants to control supraventricular tachycardia [48] or to the lower extremities after vaccination [49]), and cold exposure (eg, scrotal panniculitis in infants [50] or equestrian women wearing tight clothing in winter climate [51]). Mildly violaceous-blue, firm, nontender subcutaneous nodules occur within a few days after exposure. Histologically, nonspecific lobular adipocyte necrosis is observed at the dermal-epidermal junction, with a surrounding mixed inflammatory infiltrate. Plaques slowly soften and gradually resolve without scarring.

Acute blunt trauma to the skin can elicit panniculitis. Traumatic panniculitis usually occurs on the trunk, especially on the breasts of women [52]. Patients often cannot recall the inciting event. Firm, mobile, tender subcutaneous nodules are covered by normal skin, sometimes with a peau de orange appearance [53]. Important differential diagnosis includes an underlying breast carcinoma. The histologic findings include a granulomatous lobular panniculitis with foamy histiocytes, necrosis, and microcysts caused by confluent necrosis. Lesions heal with fibrosis of the septae. Clinical lipoatrophy often results.

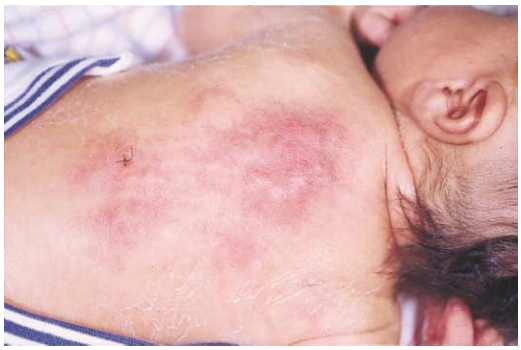

Fig. 6. Subcutaneous fat necrosis of the newborn.

Chemical fat necrosis occurs from materials injected into the subcutis for therapeutic or cosmetic purposes. Reported substances include povidone, pentazocine, vitamin K, paraffin, silicone, or synthetic microspheres [54]. Clinically, injection of these substances produces subcutaneous nodules, often with overlying erythema and induration, sometimes mimicking cellulitis. Ulceration has also been documented [55]. Many patients also experience systemic symptoms (ie, arthralgias, Raynaud's phenomenon, and Sjogren's syndrome). Histologically, a lobular panniculitis that resembles Swiss cheese is observed from paraffin injection. Foamy histiocytes and multinucleated giant cells surrounding translucent impurities occur from silicone injection [56]. Fibrosis is often a prominent feature.

Factitial panniculitis is a result of self-injection of various materials (eg, paint, acids, feces). This disease is most commonly seen among health-care professionals who have access to syringes, needles, and tubing supplies [57]. Underlying psychiatric or personality disorders are not uncommon [58]. Clues of uncommon site, distribution, and healing can be obtained upon clinical examination. Histologically, foreign material may be detected using polarization, incineration, or mass spectroscopy.

Neonatal panniculitis

Two types of panniculitis may occur in the newborn [59,60]. Sclerema neonatorum is characterized by diffuse hardening of the skin and occurs in premature or seriously ill and debilitated infants, usually during the first week of life. The skin hardening begins on the buttocks, thighs, or legs and spreads elsewhere. The palms, soles, and genitalia are usually spared. The skin is firm and bound to underlying structures; it appears pale and mottled. The disease is felt to represent a sign of peripheral circulatory failure and a lowered peripheral temperature.

In contrast, subcutaneous fat necrosis affects otherwise healthy, usually full-term infants, generally during the first 6 weeks of life. As with sclerema, hypothermia may play a role in its pathogenesis [61]. Localized, sharply circumscribed nodules and plaques are present, most often on the cheeks, buttocks, back (Fig. 6), arms, and thighs. The individual nodules are slightly movable, hard, and often have an uneven, mammilated, violaceous surface. Over weeks to months, they become softer, more fluctuant, and resolve without sequelae, although scarring may occur from lesions that break down. Resolution of large, calcified plaques may be accompanied by hypercalcemia. Very rarely, internal adipose tissue may be involved.

The histopathology of the two conditions differs but includes some overlapping features. In sclerema neonatorum, the adipose cells contain needle-shaped crystals and are diffusely distributed throughout the lobules. Edema and thickening of the fibrous septae may be conspicuous and calcification may be noted in older lesions. In subcutaneous fat necrosis, a granulomatous lobular panniculitis is observed with infiltration of lymphocytes, histiocytes, and foreign body giant cells, many of which may contain needle-shaped crystals. Fat necrosis may be noted. Calcium deposits may be observed, especially in patients with hypercalcemia. A few fibroblasts may be seen, and the fibrous septae may be thickened and edematous with increased vascularity.

Infants with sclerema have a poor prognosis and the condition is often considered to be a premorbid sign. New nodules of subcutaneous fat necrosis may continue to develop for 1 to 2 weeks, but resolution is the rule and the overall prognosis is generally good. No treatment is required, although dietary restriction of calcium and vitamin D may be necessary for patients with hypercalcemia.

Poststeroid panniculitis

Poststeroid panniculitis occurs primarily in children receiving brief courses of high doses of systemic steroids. Shortly after the steroid therapy is discontinued, small, painful, occasionally pruritic nodules appear, mainly on the cheeks, arms, and trunk, areas prone to the greatest accumulation of fat during steroid treatment [62]. Visceral lesions are rare. The nodules resolve slowly over weeks to months. The histological features resemble subcutaneous fat necrosis of the newborn, with a patchy lobular panniculitis associated with cleft-containing fat cells and histiocytic giant cells. No treatment is necessary, although the nodules may regress if the steroid therapy is reinstituted.

Panniculitis associated with systemic disease

Pancreatic panniculitis

Pancreatic panniculitis occurs in patients with either neoplastic or inflammatory disease of the pancreas [63,64]. The disease likely results from the breakdown of subcutaneous fat caused by the release of pancreatic enzymes into the circulation. Variably inflammatory nodules occur in areas of highest fat density, in a pattern somewhat reminiscent of Weber-Christian disease. Microscopic examination reveals a

lobular panniculitis with focal areas of coagulation necrosis of lipocytes with formation of ghost cells and calcification. A sparse infiltrate of inflammatory cells may be present. Treatment is directed at the underlying pancreatic disorder.

Lupus panniculitis (lupus profundus)

Lupus panniculitis differs from most other forms of panniculitis because of the tendency of lesions to occur on the upper part of the body. Involvement of the face and upper arms is common. Lesions may occur under plaques of discoid lupus erythematosus or with overlying normal skin. They are sharply defined nodules that are one to several centimeters in size, asymptomatic, firm, and may persist unchanged for years. Considerable atrophy (Fig. 7), scarring, and cosmetic deformity may ensue as the nodules resolve. Despite the condition's name, it often occurs in patients without other stigmata of lupus erythematosus [65].

Histologically, a lobular panniculitis usually predominates, but septal involvement may also be noted. There is a dense infiltrate of lymphocytes, plasma cells, and histiocytes; although small vessels may be obliterated by sclerosis, there is no true vasculitis. Hyalinization and sclerosis occur as the nodules resolve. Similar microscopic changes may be seen in the adjacent deep reticular dermis, and microscopic features of discoid lupus erythematosus may be found in the skin overlying the nodules.

Subcutaneous sarcoidosis (Darier-Roussy sarcoid)

Subcutaneous sarcoidosis is not a true panniculitis, but simply involvement of the subcutaneous fat with sarcoidal granulomas [66]. The nodules appear principally on the extremities and have the histopathologic appearance of sarcoidosis localized to the subcutaneous tissue. Treatment is directed at the underlying disorder.

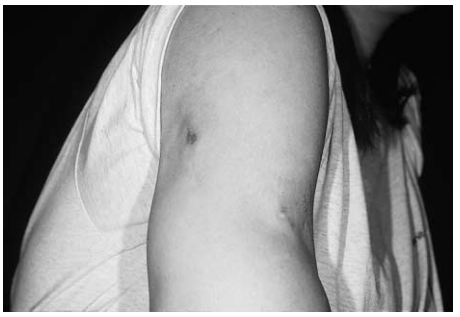

Fig. 7. Atrophy caused by lupus panniculitis.

Calciphylaxis

This disorder is almost exclusively associated with end-stage chronic renal failure. It is characterized by calcification of cutaneous vessel walls and results in necrosis and ulceration. Abnormalities in calcium-phosphorous metabolism with associated secondary hyperparathyroidism are thought to play a role in its pathogenesis. Skin lesions consist of mottled, reticulated, violaceous patches and plaques that may evolve to necrotic, indurated plaques and nodules. Histologically, calcium deposition involves small and medium-sized blood vessels in the reticular dermis and subcutaneous fat with associated lobular fat necrosis, inflammation, and calcification. The condition carries a poor prognosis and high mortality.

Leukemia and lymphoma

Infiltration of the subcutaneous fat with the malignant cells in leukemia and lymphoma does not represent a true panniculitis, although there may be associated inflammation. Lesions may be present in any location, but often predominate on the trunk. The red-purple nodules are sometimes initially mistaken for insect bites. The diagnosis is usually made by biopsy, although it is often suspected in patients already known to have an underlying lymphoproliferative disorder.

Infectious panniculitis

A lobular panniculitis may be an important clinical manifestation of infection with a variety of bacteria and fungi. Such deep infections usually occur in immunosuppressed patients. The diagnosis should be suspected when there is a significant neutrophilic infiltrate in the nodules, although infectious panniculitis caused by atypical mycobacteria shows suppurative granulomas. These infections may occur either from direct physical inoculation into the skin or as a result of direct or hematogenous spread from another focus of infection. Appropriate histochemical staining and cultures should be performed on biopsy specimens. Treatment is directed at the offending organism.

α_1-antitrypsin deficiency panniculitis

This disorder occurs in patients who are homozygous for the defective allele. Although multiple clinical manifestations are associated with α_1-antitrypsin deficiency, including emphysema, hepatitis, cirrhosis, vasculitis, and angioedema, panniculitis may be an early sign. Multiple subcutaneous nodules are noted; these predominate on the lower extremities but may be found at any location. Biopsy specimens show a severe lobular panniculitis. Although dapsone

Table 4
Lobular with vasculitis

Type	General	Clinical	Pathology	Ulcer	Therapy	Other
Nodular vasculitis "erythema induratum of Bazin"	Females, painful chronic, recurrent, + livedo backgrd EIB = + Myobacterium tuberculosis	Posterior calves vasculitis → necrosis "paucity of lesions"	Caseative granulomatous necrosis + necrosis	Yes	+ TB: tx antiTB - TB: bedrest, steroids	+ scar ? hepatits role

may be effective, supplemental infusion of exogenous α_1-antitrypsin concentrate is indicated in severely affected patients.

Lobular panniculitis with vasculitis (Table 4)

Nodular vasculitis

Panniculitis caused by nodular vasculitis is thought to represent a hypersensitivity reaction to an underlying antigenic stimulus. Bacterial infections, including streptococcal infection, have been implicated, as have drugs and, occasionally, mycobacterial infections. In the latter case, the histology characteristically includes tuberculoid granulomas, and the condition has been referred to as erythema induratum of Bazin [67].

The disease can occur at any age although middle age women are most often affected. A circulatory disturbance may predispose to the condition. Tender or painful nodules or plaques are noted on the posterolateral aspects of the lower legs and may be asymmetric or unilaterally distributed. The nodules are hot, inflamed, and heal slowly, occasionally with atrophy or scarring. Ulceration may occur. In erythema induratum of Bazin, dusky, tender nodules develop along the ankles and calves, with a relatively high incidence of ulceration. Patients with this disorder may have a history of previous tuberculosis and show signs of old pulmonary disease on chest radiographs. The tuberculin test is positive although mycobacteria cannot be detected in the skin. Thus, erythema induratum of Bazin is often characterized as a tuberculid.

The histopathology of nodular vasculitis includes a lobular panniculitis with an associated vasculitis. The muscular arteries of the fibrous septae and the smaller vessels within the lobules may be involved. Tuberculoid granulomas within the lobule are characteristic of erythema induratum of Bazin; however, histochemical stains and cultures for mycobacteria are negative.

The disease runs a chronic course with remissions and exacerbations. Systemic steroids or nonsteroidal anti-inflammatory agents may be effective for nontuberculous nodular vasculitis, whereas anti-tuberculous therapy should be administered to patients with erythema induratum, especially those with suspected active underlying tuberculous disease.

Acknowledgments

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DERMATOLOGIC CLINICS

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Sarcoidosis

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Sarcoidosis is a systemic disorder of unknown origin characterized histologically by noncaseating granulomas that can occur in any organ of the body. It most commonly involves the lungs, lymph nodes, skin, liver, spleen, eyes, bone, and glandular tissue. There is no consistent diagnostic laboratory test for sarcoidosis, although several laboratory abnormalities may be found. These include hypercalcemia, hypercalcuria, hypergammaglobulinemia, an elevated angiotensin-converting enzyme level, and in vitro evidence of depressed cellular immunity. When the diagnosis is suspected, characteristic histopathologic findings, although nonspecific, must be demonstrated and other granuloma-forming processes such as tuberculosis, fungal infection, and various foreign bodies must be excluded. Sarcoidosis has a highly variable course ranging from an acute self-limiting process to a chronic, debilitating systemic disease [1,2].

Clinical manifestations

Cutaneous manifestations

Cutaneous involvement occurs in ~25% of sarcoidosis and most often appears simultaneously with systemic disease [3–5]. Screening for systemic sarcoidosis is indicated in any granulomatous skin lesion without an apparent diagnosis [3,6]. Skin lesions may be classified as specific, which reveal granulomas on histology, or nonspecific, which are typically a reactive process [5]. The lesions generally have no prognostic significance or correlation with disease severity or systemic involvement [2,3,6,7]. Exceptions to this include erythema nodosum and lupus pernio. Erythema nodosum, although nonspecific, is the hallmark of acute sarcoidosis and tends to have a good prognosis because of its association with spontaneously resolving disease [8–10]. Lupus pernio, which is sarcoid specific, has been associated with bone cysts, sarcoidosis of the upper respiratory tract, and pulmonary fibrosis [1,2,11].

Many morphologic skin lesion types have been described for sarcoidosis and, like syphilis, it is a great mimic of other diseases. Common specific or granulomatous skin lesions in sarcoidosis include macules, papules, nodules, plaques, subcutaneous nodules, lupus pernio, and infiltrative scars [5,6,12]. Papules are the most common of the specific cutaneous lesions (Fig. 1) [6,12]. These may be localized or generalized and are typically firm, red-brown to violaceous in color, and less than 1 cm in size. Diascopy (examination under a glass slide) of the lesions may give a characteristic "apple-jelly" color [13]. They are commonly found on the head, neck, and extremities but rarely in the oral cavity. The periorbital area and lips are frequently involved [5,6,12].

Plaques of sarcoidosis indicate deeper granulomatous involvement and can be found on any area of the body [1]. They are typically indurated, with prominent borders and a red-brown color [6,12]. When the lesions have large telangectasias they are called angiolupoid [1,3]. Plaque lesions have been associated with chronic sarcoidosis. The lesions tend to resolve with scarring, and alopecia has been reported [6,14].

Lupus pernio (Fig. 2) is a chronic plaque-type lesion of sarcoidosis that progresses slowly, often causing significant disfigurement resulting from fibrosis and scarring [11]. Lesions are indurated, brown to purple, and appear on the nose, lips, cheeks, and

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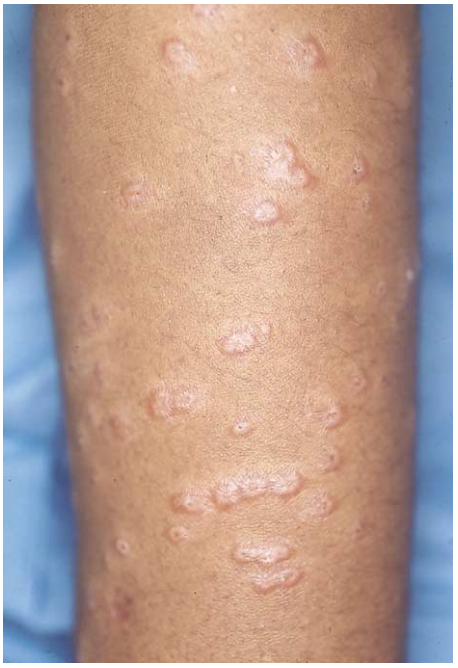

Fig. 1. Papular sarcoidosis on the arm.

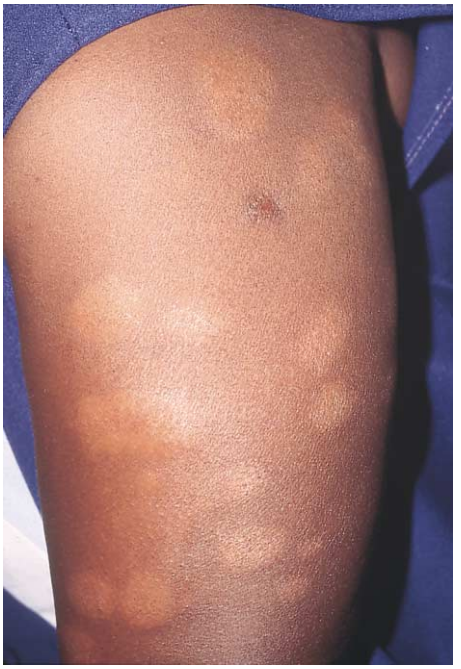

Fig. 3. Hypopigmented lesions in a patient with sarcoidosis.

ears [5,12,15]. The nose lesion can involve the nasal mucosa and underlying bone, leading to perforation [16]. It is the most characteristic skin lesion of sarcoidosis and is most common in African-American women [3,5,6,15]. The association of lupus pernio with upper respiratory tract involvement is well recognized, and includes the nasal and oral mucosa [17], larynx and pharynx [18], salivary glands [19], tonsil, and tongue [20]. It is often accompanied with pulmonary infiltration and fibrosis, chronic uveitis, and bone cysts [2,11]. Spontaneous remission of skin and systemic lesions is extremely rare [2].

Subcutaneous nodules, or Darier-Roussy sarcoidosis, are typically painless, firm, oval lesions that exhibit no signs of inflammation on the skin surface. They are typically found on the trunk and extremities [3,6,12,21]. This is a form of panniculitis that exclusively involves the subcutaneous tissue and does not extend into the dermis [22].

Scars or areas of skin chronically damaged by infection, radiation, or mechanical trauma may become infiltrated with sarcoidosis [2]. These lesions

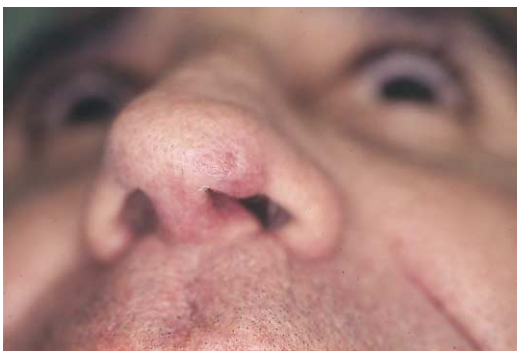

Fig. 2. Lupus pernio with a violaceous lesion on the nose.

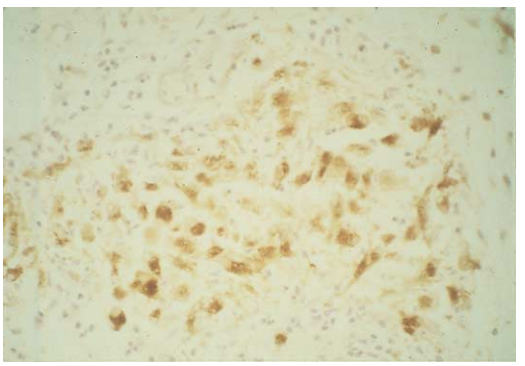

Fig. 4. Naked granuloma with macrophages stained for lysozyme from a patient with a positive Kviem test.

develop a red or purple discoloration with induration and can appear early in the disease, parallel chronic disease, or indicate possible reactivation of the disease [3,6,12,23].

Other less common specific presentations of sarcoidosis that have been reported include erythroderma [2,24], ulcerative [25,26], verrucous [25], ichthyosiform [24,27], psoriaform [25], hypopigmented (Fig. 3) [28], faint erythema [29], folliculitis [2], lichenoid [3], eruptive [3], red plaques of palm and soles [2], lower extremity edema [30], nodules of finger tips [31], penile and vulvar papules and plaques [32–34], chelitis [35], erythema annulare centrifugum [36], annular elastolytic [37], palmar erythema [38], rosacea-like [39], morpheaform [40], perforating [3], lupus erythematous–like [11], umbilicated [41], and scarring and nonscarring alopecia [42]. Specific and nonspecific nail changes may also occur [12,43–46].

Erythema nodosum is a hypersensitivity reaction that can be caused by many different infections, inflammatory bowel disease, and medications. It is the most common nonspecific cutaneous lesion of sarcoidosis and has been reported to occur in up to 25% of cases [11,47]. Lesions are typically erythematous, firm, subcutaneous nodules most commonly found on the anterior shins. Young women are most frequently affected and lesions occur commonly in Caucasians and uncommonly in American blacks. Erythema nodosum is the hallmark of acute sarcoidosis and is accompanied by a good prognosis because of the associated high rate of spontaneous resolution [8–10]. In a review by Neville, Walker, and James of 251 cases of sarcoidosis presenting with erythema nodosum, 83% of patients had remission of their disease within 2 years [10]. Other reviews have also found that the absence of erythema nodosum is a risk for persistent disease [9]. Skin lesions of sarcoidosis other than erythema nodosum were more commonly associated with lymphadenopathy and hepatosplenomegaly [47]. Lofgren's syndrome is the combination of erythema nodosum with fever, polyarthralgias or polyarthritis, uveitis, and bilateral hilar lymphadenopathy [2]. It is an acute form of sarcoidosis and typically resolves without treatment. Other nonspecific cutaneous lesions of sarcoidosis reported include erythema multiforme, erythroderma, pruritus, and calcifications [12]. Sarcoidosis presenting with leonine facies has also been reported [48].

Pulmonary manifestations

Pulmonary disease is the most common clinical manifestation of sarcoidosis [1]. Lung manifestations are found in 90% of cases of sarcoidosis and patients may be asymptomatic or present with dyspnea, cough, chest pain, and in rare cases hemoptysis [3,15]. Sarcoidosis of the lung can be staged radiographically with prognostic implications [49]. Stage 0 shows no changes on radiograph; stage I consists of bilateral hilar and/or paratracheal adenopathy without parenchymal disease; stage II is bilateral hilar adenopathy with pulmonary infiltrates; stage III is pulmonary infiltrates without adenopathy; stage IV is irreversible fibrosis and bullae formation. Bilateral hilar adenopathy is the earliest and most common intrathoracic manifestation of sarcoidosis [11]. The majority of patients with stage I disease have spontaneous resolution and patients may not need histologic confirmation by biopsy if asymptomatic or displaying signs of Lofgren's syndrome [11]. Chronic pulmonary disease is much more common with stages II and III [11]. Up to 15% of patients with sarcoidosis have irreversible fibrosis and severe disability [21]. Less common intrathoracic findings include bronchial stenosis with obstruction, pleural thickening, pleural effusion, and calcification [2].

Ocular manifestations

Ocular disease occurs in 25% to 50% of patients with sarcoidosis and is the second most common manifestation of sarcoidosis [11]. Sarcoidosis can affect any structure of the eye but most commonly presents as acute anterior uveitis [50]. Other forms of ocular disease include iris nodules, conjunctival granulomas, corneal and lacrimal gland involvement, scleral plaques, and posterior uveitis [2,11,50]. Conjunctival granulomas are present in up to one third of patients, and positive biopsy results are often obtained in this area even if they are not clinically suspected [2]. Involvement of the posterior chamber of the eye most commonly presents as chorioretinitis [2,11].

Lymphadenopathy, splenomegaly, and bone marrow involvement

When hilar nodes are included, lymphadenopathy has an incidence of 90% in patients with sarcoidosis [2,11] and is associated with both acute and chronic disease. Enlarged nodes are usually asymptomatic and nontender when palpated. Splenic involvement is present in up to 25% of patients [2] and is associated with diffuse fibrotic changes in other organs [51].

Bone marrow and hematologic changes of sarcoidosis such as leukopenia, lymphocytopenia, and an ele-

vated erythrocyte sedimentation rate can be seen in up to 40% of patients [3].

Endocrine manifestations

The incidence of endocrine gland disease is typically low in sarcoidosis. When involved, the hypothalamic and pituitary areas are the most frequently affected, and can manifest as diabetes insipidus and panhypopituitarism [2]. Sarcoidosis has also been reported to involve the thyroid, parathyroid, adrenal glands, and pancreas. Mikulicz's syndrome is bilateral sarcoidal involvement of the parotid, submandibular, sublingual, and lacrimal glands [3]. Lacrimal and salivary gland involvement may clinically produce a Sjogrens's-like syndrome [11].

Hypercalcemia can be seen in sarcoidosis and is caused by alveolar macrophage secretion of 1,25 dihydroxyvitamin D3 that is independent of feedback mechanisms [52]. Granuloma production of vitamin D3 is not suppressed with supplemental oral calcium [53].

Hepatic manifestations

Sarcoidal involvement of the liver is not uncommon and blind liver biopsy can give a positive result in up to 60% of patients [2,11]. Obstructive jaundice can be a manifestation of hepatic granulomas [54], and liver function tests, such as alkaline phosphatase, may be abnormally elevated [21].

Cardiac manifestations

Autopsy studies have shown 10% to 20% of sarcoidosis cases in the United States and 67% in Japan to have cardiac muscle granulomas [55]. Clinically, however, only 5% of cases have cardiac manifestations [56]. Roberts et al found conduction defects and ventricular arrhythmias to be the most common manifestations in symptomatic patients [2]. Cardiac findings include electrocardiographic abnormalities such as complete heart block and arrhythmias, papillary muscle dysfunction, infiltrative cardiomyopathy with congestive heart failure, and pericarditis. In 5% to 10% of cases of cardiac sarcoidosis, sudden cardiac death can be the initial manifestation. Roberts et al found that symptomatic disease was associated with sudden death in 60 of 89 patients [2]. Cardiac disease should be evaluated using myocardial scintigraphy with thallium 201, echocardiography, 24-hour Holter monitor, and gallium 67 scan [3,15].

Musculoskeletal manifestations

Up to 39% of patients with sarcoidosis have musculoskeletal involvement [57]. Muscle disease is typically asymptomatic [2], but random tissue biopsy often gives a positive result [2]. Muscle disease, though rare, can present as acute and chronic myositis, secondary atrophy, hypertrophy, contracture [11], myopathy [58], muscle nodules [59], and tumor-like lesions [60]. Clinical presentations include weakness, pain, tenderness, and erythema and warmth of the overlying skin [49].

Bone lesions occur in up to 20% of sarcoidosis patients and are usually asymptomatic [11]. Lesions tend to be cystic and favor the terminal phalanges of the hands and feet [11]. Bone involvement often indicates chronic, progressive disease and is seen with pulmonary changes and lupus pernio [11].

Acute and chronic arthralgias and arthritis have been reported in sarcoidosis [61,62]. Acute lesions are often seen in Lofgren's syndrome, while chronic lesions are rare [11]. The wrists, knees, and ankles are the most commonly affected joints.

Neurologic manifestations

Neurosarcoidosis affects 5% to 10% of sarcoid patients [4,63,64]. Half of these patients have central nervous system involvement [11]. All cranial nerves may be involved, with the most common presentation being cranial nerve VII as a self-limited palsy [63,64]. Other manifestations of neurologic sarcoidosis include peripheral nerve involvement [65], psychiatric changes [63,64], aseptic meningitis [66], space-occupying masses [65], sudden hearing loss [67], seizures [63,64], stroke [68], and arachnoiditis/perivasculitis [69]. Heerfordt's syndrome or uveoparotid fever consists of uveitis, facial nerve palsy, fever, and parotid gland enlargement, and is frequently associated with central nervous system involvement [11].

Other clinical manifestations

Sarcoidal granulomas can affect almost any body organ. Renal involvement may present as nephritis, with or without identifiable renal granulomas [49], and nephrolithiasis and nephrocalcinosis [70]. Urethral obstruction [71] and hydronephrosis [72] have also been reported.

In uncommon cases, sarcoidosis affects the gastrointestinal system. Presentations include a stomach ulcer or mass [73], dysphagia [74], pancreatitis [75], appendicitis [76], and small bowel obstruction [77].

Other sites of sarcoidosis involvement reported include the breasts, uterus, fallopian tubes, ovaries, testicles, epididymis, and prostate gland [3,33,78–81].

Childhood sarcoidosis

There are two types of sarcoidosis in children: late onset (ages 8 to 15) and early onset (age 4 or less). Late onset disease has similar clinical manifestations to adult sarcoidosis. Arthritis, uveitis, and skin lesions without bilateral hilar lymphadenopathy are the classic triad of early onset childhood sarcoidosis and this can mimic juvenile rheumatoid arthritis [82]. Skin lesions are usually macular and papular, with erythema nodosum being unusual [83]. The typical lung disease of sarcoidosis is not usually present initially [84]. Almost all children have complaints of fever, weight loss, and fatigue [85]. Peripheral adenopathy is present in approximately two thirds of patients [83], and when skin lesions are not present, lymph nodes are the best site for biopsy [84]. There is a significant morbidity in childhood sarcoidosis even though most patients have spontaneous resolution [84]. Glucocorticoids are the treatment of choice [85].

Blau syndrome, a rare autosomal dominant granulomatous disease, is similar to childhood sarcoidosis in that it presents with arthritis, uveitis, and skin lesions [86]. It has been linked to chromosome 16p12-q21 and, unlike sarcoidosis, lacks pulmonary involvement [87]. Skin lesions have similar histology to sarcoidosis and can appear as red macules [86].

Incidence and epidemiology

Sarcoidosis primarily affects young adults between 25 and 35 years of age. It also affects women between the ages of 45 and 65 years [3,88]. In the United States, sarcoidosis affects women approximately 10 times more frequently than men [11]. African Americans are also more frequently affected than whites, have more severe and prolonged disease, and have more atypical cutaneous expressions [11,49,89].

The incidence of sarcoidosis is recorded as follows [3]: Sweden, 64/100,000; United Kingdom, 20/100,000; France 10/100,000; Germany, 9/100,000; Greece 7/100,000; Spain, 1.4/100,000; and Japan 1.4/100,000 [21,90,91]. In the United States, the incidence in the white population is 10/ to 14/100,000 and 35.5/ to 64/100,000 for African Americans [92].

Etiology

The cause of sarcoidosis is unknown. Immunologic mechanisms, genetic susceptibility, and infectious and environmental agents have all been implicated as possible factors. There is much speculation as to whether the cause is multifactorial or caused by an antigen(s) that has not yet been identified [3].

Immunology

Immunologic abnormalities found in sarcoidosis include polyclonal hyperglobulinemia [11,21], circulating immune complexes, a depressed cell-mediated immunity often manifested by skin anergy, and decreased peripheral lymphocytic blastogenesis [11]. Noncaseating granulomas are thought to form through antigenic stimulation of CD4 T lymphoctyes/TH1 phenotype through macrophage presentation [93,94]. The T cells in sarcoidosis predominantly express α/βT-cell receptors, are major histocompatibility complex (HLA) class II restricted [4,95], and depend on the B7:CD28/CTLA-4 costimulatory pathway for activation [96].

There is a highly focused, antigen-driven immune response within tissue affected by sarcoidosis [97]. The CD4 T cells redistribute from the peripheral blood, manifesting as anergy [98], and localize in tissues involved in the inflammatory process [3,99]. Once localized, lymphocytes proliferate and induce granuloma formation through production of cytokines (interleukin 2, interferon-γ, IL-8, and tumor necrosis factor-α). Other immunomodulatory cells including macrophages, natual killer cells, and mast cells are believed to be involved [100]; subsequently, there is shift in the cytokine profile to that of TH2 CD4 T cells which has been demonstrated during the fibroproliferative phase of the granuloma and is believed to result in tissue scarring [100].

T-helper lymphoctyes of sarcoid alveolitis have been shown to stimulate B-lymphocytes in vitro to produce immunoglobulin [11]. This may account for the presence of a polyclonal hyperglobulinemia and immune complex formation.

Genetics

No consistent inheritance pattern has been established for sarcoidosis, but support for a certain genetic makeup is evident by the presence of positive familial clusters [101,102]. Certain HLA typing has been associated with sarcoidosis. A positive association with sarcoidosis has been reported with HLA-A1, -B8, and -DR3, and a negative association

has been reported with HLA-B12 and DR-4. Other HLA associations include disease limited to the lungs and HLA-B21; early disease onset and HLA-B13 and -B35; and good outcome of disease and HLA-DR3 [103]. The HLA-DRB1 locus has also been used to determine susceptibility to sarcoidosis [104]. Possible evidence for genetics playing a role in sarcoidosis has been found involving angiotensin-converting enzyme (ACE) polymorphism [105], the presence of GLU residue at position 69 of HLA-DPB1 [106], and the increased expression of the acute-phase reactant genes ORM1 (orosomucoid) and HP1 (haptoglobin) [107]. Erythema nodosum associated with sarcoidosis may be pathogenically linked to altered tumor necrosis factor-α (TNF-α) production caused by a genetic promoter polymorphism [108].

Infectious and environmental agents

Fungal, viral, and bacterial agents have all been implicated as possible causative factors in sarcoidosis despite lack of definitive identification or proof. The association of tuberculosis and sarcoidosis is controversial. Despite being inconclusive, polymerase chain reaction (PCR) studies have caused mycobacterium tuberculosis to re-emerge as a possible causative agent in sarcoidosis [3]. Many studies support this association [109], while numerous others give evidence against any relationship [110]. Unfortunately, PCR does not discriminate between living or dead mycobacteria and is fragile and easily contaminated, therefore rendering it a poor method of evaluation for the etiology of sarcoidosis [111,112]. Further evidence against a mycobacterial cause includes studies in which these organisms have not been demonstrated in the lesions or successfully grown in appropriate culture media, a lack of fulminant mycobacterial disease with the use of immunosuppressives in patients with sarcoidosis, the fact that Bacille Calmette Guerin vaccination does not reduce the incidence of sarcoidosis, and the fact that antituberculosis medications are ineffective in treating sarcoidosis [111,113,114]. Occasional elevation of fungal and viral antibody titers in patients with sarcoidosis is likely caused by a nonspecific polyclonal elevation of immunoglobulins [11].

Environmental antigens implicated but not proven in the etiology of sarcoidosis include clay, talc, pine pollen, oxalosis, beryllium, and zirconium [115,116]. Nonsmokers have been found to have sarcoidosis more often than smokers [3]. Seasonal clustering of sarcoidosis lesions also suggests an environmental factor [117].

Associated disorders

Autoimmune disease, neoplasia, and medications have all been associated in sarcoidosis, and this may be related to the overall immune system disturbance of this condition. Many autoimmune diseases have been reported to occur with sarcoidosis, which may result from the immunologic dysfunction and polyclonal gammopathy [3]. Lymphoproliferative disease, most commonly Hodgkin's lymphoma, has been reported with sarcoidosis [118]. Medications reported to induce sarcoidosis include interferon-α, particularly in the treatment of hepatitis C [119,120] and chronic myelogenous leudemia [3], and interferon-β treatment for multiple myeloma [121]. Ulcerative sarcoidosis has been induced in previous cutaneous lesions with therapy using the flashlamp-pumped pulsed dye laser [122].

Histopathology

The classic histologic finding in sarcoidosis is that of a noncaseating granuloma composed of epithelioid cells and occasional Langhans giant cells. Inclusion bodies (asteroid bodies/entrapped collagen or Schaumann bodies/altered lysosomes [13]) are frequently observed in giant cells but are nonspecific. Lymphocytes, macrophages, and fibroblasts may surround the granulomas, but there are typically few inflammatory cells, the so-called "naked" tubercles [11]. Similar histologic findings are present in other conditions. It is therefore important to perform special stains and cultures to rule out an infectious granuloma, polarize the specimen to examine for foreign bodies, and to rule out an underlying neoplasm exhibiting an associated sarcoidal reaction [11]. Marcoval et al [123] concluded that foreign body material is not uncommon in cutaneous lesions of sarcoidosis patients after finding polarizable foreign particles in 14 of 65 cutaneous biopsy specimens from patients with sarcoidosis.

Diagnosis and evaluation

Evaluation of a patient with suspected sarcoidosis involves a combination of clinical, radiologic, and laboratory findings along with histologic examination of affected tissue. A diagnostic test for sarcoidosis does not exist, and physical examination should focus on the skin, lungs, eyes, nerves, and the heart [3]. Tissue biopsy of any abnormalities

should show evidence of noncaseating granulomas, while polarization for foreign bodies and cultures and stains for infectious causes should be negative. Several satisfactory biopsy sites exist to confirm a diagnosis of sarcoidosis. The skin is very accessible and any suspicious skin lesions should be biopsied [2,124]. Other valuable biopsy sites include the conjunctiva, which is positive in one third of patients even when ocular lesions are not present [2]; peripheral nodes, which may be positive in up to 75% of patients [11]; minor salivary glands of the lower lip, which are positive in greater than half of the patients [2]; and muscle biopsy, which shows positive results in ~50% of patients [2]. Lung biopsy with a fiberoptic bronchoscope is sometimes indicated [21]. Bronchoscopy with transbronchial lymph node biopsy can be performed, at which time bronchoalveolar lavage may also be evaluated for leukocyte differential counts. A diagnosis is suggested when the CD4/CD8 ratio is greater than 3.5 [125]. Mediastinoscopy and biopsies of the liver, spleen, and bone marrow are less commonly performed because of low yield or high incidence of morbidity.

Chest radiography is helpful in the diagnosis and evaluation of sarcoidosis; however, this cannot be used as the sole diagnostic procedure. Gallium scans can be helpful when used as a complement to other diagnostic tools [126], while computed tomography of the chest is often overused and does not affect therapeutic treatment [49]. Ga gallium scans may demonstrate panda and/or lambda appearance, which are gallium uptake by parotid and lacrimal gland sarcoidosis (panda) and by the bilateral hilar lymph node (lambda) [126,127]. Gallium scanning may identify lesions of nodular cutaneous sarcoidosis [128]. Technetium-74m-tetrofosmin scintigraphy and somatostatin analogue scintigraphy may also be useful in suspected sarcoidosis evaluation [129,130].

Laboratory evaluation for sarcoidosis includes complete blood count, liver and renal function tests, protein electrophoresis, serum and urine Ca, ACE level, and erythrocyte sedimentation rate [3,11]. Additional evaluation should include ophthalmologic evaluation including slit lamp examination and electrocardiography, tuberculin/anergy testing, and pulmonary function tests [4,6,21,131]. The Kviem test involves intradermal injection of spleen or lymph node homogenate from a patient with sarcoidosis into another patient with suspected sarcoidosis, whose skin is later biopsied for evidence of sarcoid granuloma (Fig. 4) [114,132]. This test may be an interesting immunologic phenomenon but is of very limited practical use and is not approved by the Food and Drug Administration [1,3].

Measurement of disease progression

Pulmonary function tests are useful for monitoring the respiratory status of a patient but may not correlate with disease progression or activity [11,21]. Gallium scans and bronchoalveolar lavage are also not typically used to monitor disease progression [21].

The angiotensin-converting enzyme (ACE) level is elevated in about 60% of patients with sarcoidosis [5]. This enzyme is derived from the epithelioid cells of the granuloma and reflects the granuloma load in the body, but is not specific for sarcoidosis and can be elevated in other conditions [49,133]. ACE levels may be used as an adjunct for diagnosis of sarcoidosis but not for the specific diagnosis because of the high false-negative (10%) and false-positive (40%) rates when used for diagnosis [3,88]. It is generally not a useful method for determining disease progression or response to therapy [2,3,88,114].

Numerous experimental methods have been reported to evaluate disease progression in sarcoidosis. These include TNF-α and serum IL-2 [134]; serum IL-2 receptors [135]; serum TNF-receptor II levels [136]; serum IL-8 [137]; locally derived IL-6 and IL-8 [138]; serum procollagen I and III [139]; serum vitamin D3, IL-10, and CD23 [98]; CD26 [140]; T-cell receptor γ/δ expression in the peripheral circulation [141]; circulation E-selectin [99]; serum intercellular adhesion molecule-1 [142]; and serum copper [143].

Treatment

Cutaneous involvement of sarcoidosis is typically asymptomatic and is not life threatening. The major indication for treating these lesions is disfigurement [49]. Glucocorticoids are the mainstay of treatment and lesions can be treated with oral, intralesional, or topical therapy. Limited cutaneous disease may respond to superpotent topical corticosteroids [144], topical steroid with occlusive dressing [145], hydrocortisone 5% powder in hydrophilic ointment with phonophoresis [146], and intralesional triamcinolone repeated monthly [147]. Other effective nonoral therapies reported include intralesional choroquine [148], carbon dioxide or pulsed dye laser for lupus pernio [149,150], dermabrasion, surgical excision with grafting, and plastic surgery [3].

Lesions resistant to topical therapy and large or diffuse lesions may require systemic therapy. Many

therapies have been reported to have some success, including prednisone [21,25,147,153], hydroxychloroquine [147,154,155], chloroquine [151], methotrexate [152,153,156], allopurinol [158,159], thalidomide [160–162], isotretinoin [3,163], PUVA [3,153], UVA 1 [164], tranilast [165], melatonin [166], prospidine [167], and minocin [168]. Prednisone therapy has been used successfully both as a tapered daily dose [3] and alternate-day dose [147]. Hydroxychloroquine is administered with a daily or alternate-day dose of 200 to 400 mg [147,154,155]. Chloroquine is typically given at 250 mg/d for long-term suppression; Zic et al [151] recommend an initial 14-day course of 500 mg. Methotrexate has been effective in both chronic cutaneous disease and lung disease [152, 153,156]. Typical dosage is 15 to 25 mg/wk in three divided doses at 11-hour intervals [147]. Baughman and Lower noted 94% of 17 patients noted improvement in cutaneous lesions treated with methotrexate [169]. Allopurinol has been effective for cutaneous sarcoidosis at doses of 100 to 300 mg/d for several months [157–159]. Thalidomide works by inhibiting cytokines, especially TNF-α, and has been reported to be effective in doses up to 200 mg/d [160–162,170]. PUVA has been reported to be successful in erythrodermic and hypopigmented lesions [3,153]. Isotretinoin, usually in doses of 0.5 to 1.0 mg/kg/d, has shown resolution of lesions after six or more weeks [3,163]. Eight of eleven patients showed complete remission of their skin lesions after treatment with minocin (200 mg/d) for a median of 11 months [168].

Determining when to treat systemic sarcoidosis depends on the extent and activity of the inflammatory lesions and the organs at greatest risk. Evaluation of the lungs, eyes, heart, and central nervous system are essential. Glucocorticoids are the therapy of choice [4], and the suggested dosage of prednisone for systemic sarcoidosis is 1 mg/kg for 4 to 6 weeks and then a slow taper over 2 to 3 months [21]. The action mechanism of steroids in sarcoidosis is unknown, but it has been reported that a normal TH1/TH2 balance is re-established between the locally produced cytokines and immunoglobulin isotypes in the sarcoid lung [171]. To avoid long-term steroid–induced morbidity in chronic disease, nonsteroidal immunosuppressive medications are used despite only anecdotal data for efficacy [4,121,154]. Some of the more common agents used are antimalarials, methotrexate, azathioprine, chlorambucil, cyclophosphamide, and cyclosporine [15,154,169]. Infliximab, an anti–human TNF-α monoclonal antibody, recently has been reported to have promising results in complicated sarcoidosis [172,173].

Prognosis/mortality

Sarcoidosis has spontaneous remission in up to 60% of cases. Corticosteroids increase this rate by 10 to 20% [89]. Acute sarcoidosis consisting of bilateral hilar adenopathy alone or in combination with erythema nodosum and other inflammatory manifestations is typically self-limited and may resolve spontaneously in more than 80% of the cases [9,10]. Ten percent to twenty percent of patients have chronic, progressive disease and mortality is $\sim$1% to 5% [15]. Causes of death are most commonly caused by cardiac and pulmonary complications and include pneumonia, pulmonary fibrosis, chronic obstructive pulmonary disease, cardiac arrhythmias, and sudden cardiac death [133,174,175]. Mortality rates have been found to be higher in age-adjusted African American patients compared to white patients and in females compared to males within racial strata [176].

Morbidity of sarcoidosis includes ocular disease causing scarring and blindness, pulmonary disease causing shortness of breath and fatigue, and cutaneous disfigurement. Granulomatous involvement of the kidneys, calcium deposits, and kidney stones can cause renal failure.

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Hepatitis C and the skin

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The hepatitis C virus (HCV) is a single-stranded RNA flavivirus that replicates in hepatocytes and peripheral blood mononuclear cells [1–7]. There are six main genotypes, each with a different worldwide prevalence:

Type 1a: United States and developed western countries
Type 1b: United States, Japan, and Europe
Type 2: Most developed countries, not very common
Type 3: Rising in prevalence among injection-drug users
Type 4: Confined to the Middle East and North Africa
Type 5: South Africa
Type 6: Asia

Types 1a and b account for approximately 75% of infections in the United States. Four million or 1.8% of the US population is infected with HCV, and approximately 35,000 new cases are reported each year. An estimated 2.7 million patients have chronic active infection and 8000 to 10,000 deaths occur per year secondary to HCV infection. Transmission of HCV is primarily by blood or blood products. Aerosolization and casual contact do not seem to cause infection [8,9].

Etiology

Table 1 lists the major and minor risk factors for HCV infection. The two most common causes are blood or blood product transfusions (particularly before 1989) and illicit intravenous drug use. Since the development of screening techniques for HCV, intravenous drug use is now the most common risk factor accounting for two thirds of new infections [8]. Nosocomial transmission through blood product exposure has been reported in dialysis units, from hollow-bore and solid-bore needlesticks, from blood splashing into conjunctivae, and from infected surgeons to patients during surgery [10–12]. Other risk factors include intranasal cocaine use; multiple sexual partners; ear piercing (in men); and tattooing [13]. Patients with tattoos, and especially those containing white, yellow, orange, and red pigments from commercial tattoo parlors, were at increased risk [14]. The most predictive risk factors are intravenous drug use for more than 1 year, male ancillary health care worker, commercial tattoos, and three or more six packs of beer consumed per month. Other possible risk factors include animal bites, bone marrow transplants before 1991, and patients on long-term hemodialysis. Education less than 12 years, single status, poverty, and nonwhite race are other less documented risk factors [15–17].

Vertical transmission is rare, and recent studies on amniotic fluid transmission show no increased risk of infection from mother to fetus [18,19,100]. Transmission from breast-feeding is also rare [20].

Sexual transmission of HCV in a monogamous relationship is uncommon. The Centers for Disease Control and Prevention does not recommend a change in sexual practices among stable monogamous couples, although partners of HCV-positive individuals should be tested at least once for evidence of infection and should avoid sharing personal items that might transmit blood products (eg, razors and toothbrushes). One study determined that intramuscular immune globulin aided in prevention of transmission of HCV to partners of infected individuals

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Table 1
Risk factors for hepatitis C virus infection

Major risk factors	Minor risk factors
Blood/blood product transfusion (especially prior to 1989)	Intranasal cocaine use
Intravenous drug use	Multiple sexual partners
Tattoos	Ancillary health care workers
	Long-term hemodialysis
	Blood product exposure

[21]. Co-infection with HIV increases the risk of sexual and vertical transmission of HCV. One study suggests that the more severe the infection the higher the rate of transmission to sexual partners and casual household contacts [22,23].

Pathogenesis

The hepatic damage from HCV occurs by viral replication within liver hepatocytes. The mechanism of the extrahepatic effects is uncertain. The virus replicates within lymphoid cells potentially resulting in the extrahepatic manifestations. Another theory suggests that circulating immune complexes composed of HCVag and antibodies deposit in tissues and cause initiation of the inflammatory cascade. Other proposed mechanisms are that viral antigens induce local immune complex formation, or that induced autoantibodies react with tissue antigens causing local tissue inflammation.

The cutaneous manifestations are thought to be caused by viral antigens or viral-laden lymphocytes depositing in the skin, because skin biopsies have shown viral antigens in skin lesions of palpable purpura and patients with cryoglobulinemia [24,25]. HCV establishes chronicity by an immune escape mechanism. The virus has two hypervariable regions, which results in heterogeneity and the ability to escape host responses [26,27]. It circulates in low titers that allow for it to resist therapy and recur soon after therapy is withdrawn.

Conversion to infection occurs 6 to 8 weeks after exposure. Twenty-five percent of patients develop symptomatic hepatitis and a positive polymerase chain reaction (PCR) in 2 weeks during acute infection; however, most patients are asymptomatic with initial infection. The course of HCV infection is chronic in 50% to 70% of patients, with cirrhosis developing in 20% to 30%. Hepatocellular carcinoma has been reported to develop in 4% to 11% of patients with HCV infection. Hepatocellular carcinoma occurs more rapidly in patients with high alanine aminotransferase levels and cirrhosis [28].

The average time from infection to symptomatic hepatitis is 10 to 18 years and to cirrhosis 20 to 21 years [29,30]. There are factors that are thought to affect the risk for chronic infection, cirrhosis, and hepatocellular carcinoma. Viral genotype 1b is more commonly seen in severe infections [31]. Children and patients with high host response who develop HCV have a better prognosis for clearing the virus and overall fare better [32,33]. Excessive alcohol intake and concurrent hepatitis B virus infection increase the severity of infections [34].

Cutaneous manifestations

Common associations

Many cutaneous findings and diseases are associated with HCV. These may be arbitrarily divided into commonly associated, associated, and uncommonly associated conditions (Table 2). Cryoglobulinemia is commonly seen in patients with HCV. It is an immunologic disorder characterized by the presence of serum immune complexes, which precipitate at cold temperatures. These generally include rheumatoid factor, complement, HCV particles, HCV antibodies, and other immunoglobulins. There are three main types of cryoglobulinemia. Type I is a monoclonal proliferation of B lymphocytes and is usually seen in plasma cell disorders (eg, multiple myeloma). Types II and III

Table 2
Cutaneous manifestations and associations with hepatitis C virus infection

Common associations	Associations	Uncommon associations
Cryoglobulinemia	Lichen planus	Erythema nodosum
Porphyria cutanea tarda	Sjögren's syndrome	Erythema multiforme
Leukocytoclastic vasculitis (palpable purpura)	Urticaria	Unilateral nevoid telangiectasia
Livedo reticularis	Pruritus	Pyoderma gangrenosum
	Polyarteritis nodosa	Vitiligo
		Psoriasis
		Behçet's syndrome
		Mooren corneal ulcer
		Granuloma annulare
		Disseminated superficial actinic porokeratosis

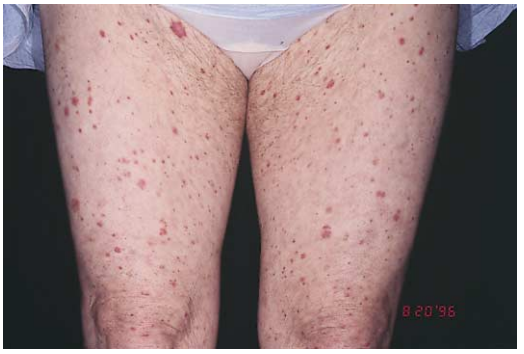

Fig. 1. Leukocytoclastic vasculitis (palpable purpura) in a patient with cryoglobulinemia and hepatitis C virus (HCV) infection.

are called *mixed cryoglobulinemias*. Type II has a polyclonal IgG component and a monoclonal IgM component. Type III has polyclonal IgG and IgM components. Mixed cryoglobulinemia (type II or III) occurs in patients with HCV. Thirty-three percent to 50% of patients with HCV infection have circulating cryoglobulins. Cutaneous findings are present in 60% to 100% of patients and include palpable purpura (leukocytoclastic vasculitis) (Fig. 1), livedo reticularis (Fig. 2), acrocyanosis, hemorrhagic bullae, urticaria plaques, and ulcerations (Fig. 3). The cutaneous manifestations are secondary to immune complex deposition. Glomerulonephritis and nephropathy may also occur from the deposition of these immune complexes.

Testing for cryoglobulinemia is difficult. The serum must be kept at a constant temperature immediately after it is drawn and then placed in an ice bath of

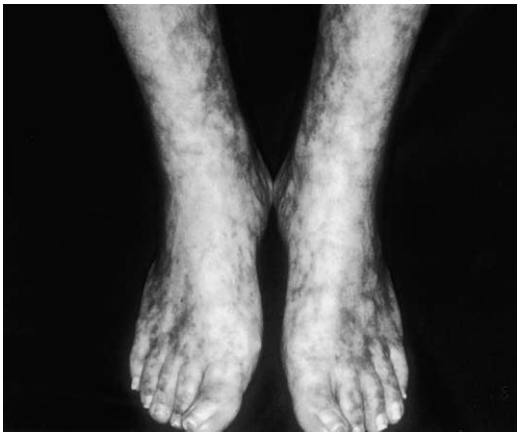

Fig. 2. Livedo reticularis in a patient with mixed cryoglobulinemia and HCV infection.

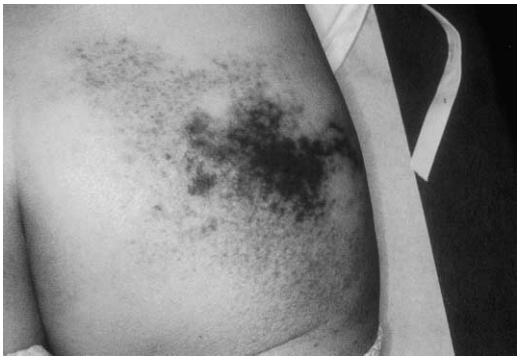

Fig. 3. Hemorrhagic plaques and ulceration in a patient with cryoglobulinemia and HCV infection.

constant temperature for 30 minutes to precipitate any cryoglobulins. Rheumatoid factor is usually present in the mixed cryoglobulins and is a good screen for cryoglobulinemia without the requirements of temperature regulation. Rheumatoid factor is positive in 5% of the general population as a nonspecific marker of inflammation; false-positives do occur [35–38].

Porphyria cutanea tarda (PCT) is seen in 62% to 82% of patients with HCV infection. It presents as tense bullae, vesicles, and erosions that heal with scarring and milia. These findings are seen on sun-exposed skin and patients complain of skin fragility rather than sensitivity to sunlight (Fig. 4). There are two primary types of PCT: acquired and familial. The familial type is inherited and the acquired type results from depletion of one of the enzymes in the porphyrin pathway, usually uroporphyrinogen decarboxylase. Clinically there is no difference between acquired and familial PCT. The mechanism of hepatitis C–induced PCT is unknown, but there are four proposed mechanisms: (1) decreased intracellular glutathione concentration and

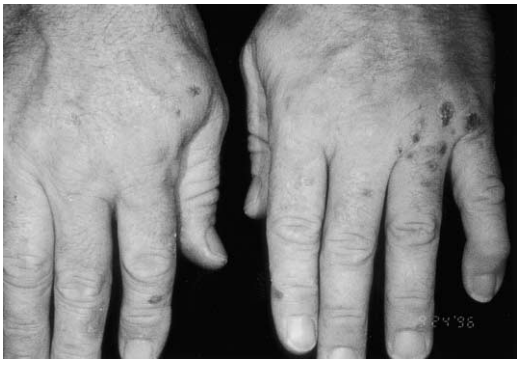

Fig. 4. Porphyria cutanea tarda changes in a patient with HCV infection.

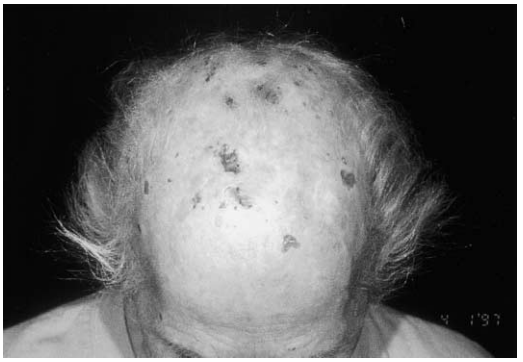

Fig. 5. Vesicles, bulla, and erosions with some sclerodermoid features in a patient with HCV, PCT, and cutaneous features of polyarteritis nodosa.

increased oxidatative stresses; (2) decreased uroporphyrinogen decarboxylase activity; (3) elevated hepatocellular iron; and (4) damaged production of an uroporphyrinogen decarboxylase inhibitor. Increased uroporphyrin type I in the skin stimulates collagen synthesis, which may result in sclerodermoid features in some patients (Fig. 5) [39–41].

Associations

Lichen planus occurs frequently in patients with hepatitis C infection. The mechanism of HCV-induced lichen planus is unknown but possibly related to the viral replication in lymphocytes. The incidence of HCV in patients with lichen planus varies from 0.1% to 35%. HCV is found more frequently in patients with generalized lichen planus; mucosal lichen planus, particularly the erosive variant (Fig. 6); or lichen planus of chronic duration. Treatment with interferon (IFN) is controversial. Some patients note improvement of their lichen planus with IFN therapy, whereas others experience exacerbation of their lichen planus after IFN therapy [42–45].

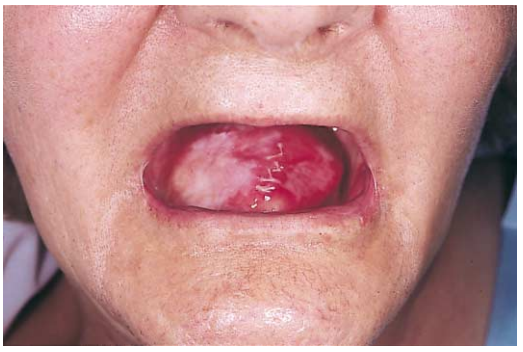

Fig. 6. Oral erosive lichen planus in a patient with HCV infection and cirrhosis.

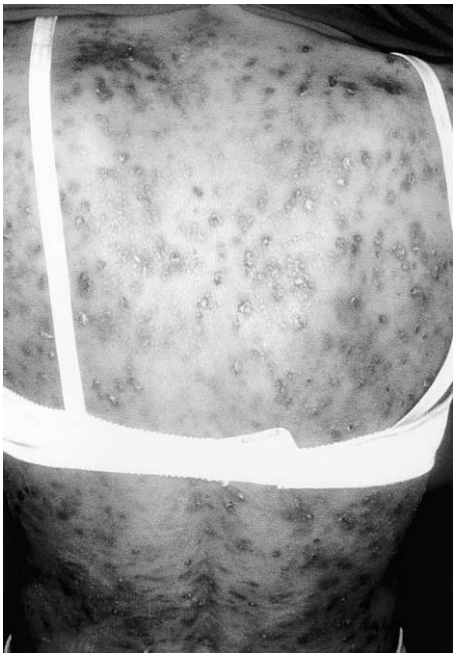

Fig. 7. Prurigo nodules in a patient with HCV infection and pruritus.

Sjögren's syndrome is seen in some patients with HCV infection. It results when HCV viral particles are shed in the saliva and then recruit lymphocytes. In a recent study, 10 of 28 patients with HCV had symptoms consistent with Sjögren's syndrome, and 16 of 28 patients revealed histologic changes of Sjögren's syndrome [46].

Urticaria is seen in varying amounts in patients with HCV infection. In one study, 19 (24%) of 79 patients with urticaria were HCV positive. Patients

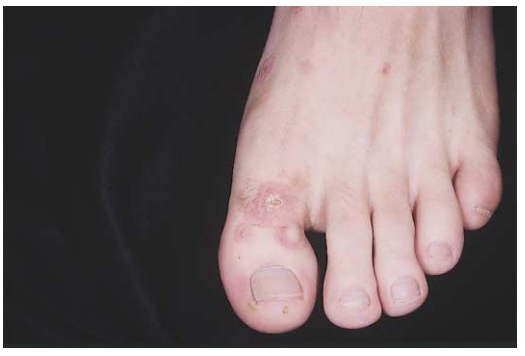

Fig. 8. Erythema multiforme and lichen planus in a patient with HCV infection.

with HCV and urticaria were older with a more chronic course. They also have a tendency toward more post-inflammatory hyperpigmentation after lesion resolution than those without HCV [47]. It is important to watch for urticarial vasculitis because this may mimic urticaria and is really a clinical variant of leukocytoclastic vasculitis (LCV). The two conditions are distinguished by time course and by histopathology. Lesions of urticarial vasculitis last longer than 24 hours and show small vessel vasculitis on biopsy, whereas lesions of urticaria last less than 24 hours and show no vasculitis on biopsy [48].

Pruritus may be a clinical manifestation of HCV infection. Patients may present with severe pruritus that precedes a rash or an uncontrollable itch. The skin may have excoriations, areas of healing, and old scars, but usually no primary lesions; however, prurigo nodules may be seen and some consider these primary lesions (Fig. 7) . It is the same type of pruritus as in patients with any liver disease. It is thought to be related to an increase in bile salts that occurs with hepatic damage. Another theory is that HCV may act as an opioid agonist [49–51].

Polyarteritis nodosa (PAN) is an immune complex–mediated condition that is associated with HCV. Most patients with HCV and PAN have more systemic complaints than patients with PAN not associated with HCV. HCV-associated PAN patients have more neuropathies, hypertension, cerebral angiitis, ischemic abdominal pain, and kidney and liver disease. Most patients also are genotype 1b [41,52–54].

Uncommon associations

Many other conditions have been reported in association with HCV; however, these are less common. Erythema nodosum-panniculitis [18] and erythema multiforme [55] have been reported. There is a report of lichen planus, erythema nodosom, and erythema multiforme in a patient with hepatitis C [56] (Fig. 8). Pyoderma gangrenosum has been reported in a patient with HCV in association with cryoglobulinemia [57]. This is debatable because pyoderma gangrenosum is a diagnosis of exclusion and if cryoglobulins are present the diagnosis of pyoderma gangrenosum is in doubt, because an ulcer of cryoglobulinemia may mimic that of pyoderma gangrenosum. It is possible to have both conditions concurrently, but they are both so uncommon it seems unlikely.

Unilateral nevoid telangiectasia has been seen in some patients with HCV infection. It is possibly related to HCV damage to the liver decreasing estrogen metabolism and increasing circulating estrogen levels [58].

Vitiligo is seen in some patients with HCV and is possibly related to HCV particles depositing at the dermoepidermal junction causing a lymphocytic infiltrate that destroys melanocytes. This theory has not been proved and because both HCV and vitiligo are common the association may be by chance.

Psoriasis has also been noted in patients with HCV infection. HCV RNA has been detected in the skin of some patients with psoriasis and might play a role in the disease process [59,60].

Other rare associations include Behçet's syndrome [61]; Mooren's corneal ulcers (chronic painful progressive ulcerations of the peripheral cornea) [62,63]; and disseminated superficial actinic porokeratosis. Three patients developed disseminated superficial actinic porokeratosis concurrently with the development of hepatocellular carcinoma and cirrhosis from HCV infection [64]. Granuloma annulare was reported in a patient with HCV, and both conditions resolved with IFN-α therapy [65]. HCV infection was also reported in seven patients with necrolytic acral erythema [66].

There are reports of patients with systemic lupus erythematosus also having HCV. The patients with both systemic lupus erythematosus and HCV tended to have higher levels of hepatic involvement, a higher frequency of cryoglobulinemia, lower C4 and CH50 levels, lower dsDNA levels, and a lower frequency of cutaneous lupus erythematosus features than patients with systemic lupus erythematosus alone [67].

Other extrahepatic manifestations

Other extrahepatic manifestations in some patients with HCV include the following:

Autoimmune thyroiditis
Pulmonary fibrosis
Aplastic anemia
Autoimmune thrombocytopenic purpura
Peripheral neuropathy
Lymphoproliferative diseases
Arthralgias
Systemic sclerosis

Thyroid autoantibodies are frequently seen in patients with HCV and autoimmune thyroiditis is common in these patients. The thyroiditis may or may not be affected by therapy with IFN-α.

Autoimmune thrombocytopenic purpura is seen at increased rates in patients with HCV secondary to antiplatelet antibodies. This suggests that therapy with IFN-α may be helpful rather than harmful in these patients [68].

There is an increase risk of lymphoproliferative disorders in patients with HCV secondary to clonal proliferation of lymphocytes by the viral antigens or the antigen and antibody complexes. B-cell non-Hodgkin's lymphoma and lymphoproliferative disorders are the most common [69–72]. Others include multiple myeloma and lymphoblastic leukemia. The presence of both serologic and molecular markers of HCV infection in a high percentage of certain types of B-cell non-Hodgkin's lymphoma, not associated with cryoglobulinemia, help confirm this association.

Arthralgias are a common symptom seen in patients with HCV infection. These may be associated with circulating cryoglobulins and a positive rheumatoid factor. This is not rheumatoid arthritis, because the destructive changes of rheumatoid arthritis are not present. If they are, the arthralgias may be secondary to rheumatoid arthritis and not HCV.

Recently reports of patients with HCV and systemic sclerosis suggest a possible association. The proposed mechanism is by the clonal proliferation of lymphocytes [73].

Diagnosis

There are three main laboratory evaluations used in diagnosing hepatitis C infection: (1) ELISA, (2) recombinant immunoblot assay, and (3) HCV proliferation by PCR. The ELISA test is good for general screening but has a high false-positive rate. It detects 95% of all patients with HCV infection.

The recombinant immunoblot assay test is more specific but less sensitive; if a patient has a positive recombinant immunoblot assay it is indicative of active HCV infection. If the recombinant immunoblot assay is negative it means there is no past or present active infection regardless of the ELISA results.

The PCR is used to amplify small amounts of DNA for detection of specific agents (eg, HCV particles). There are two types of PCR: quantitative and qualitative. The qualitative PCR detects fewer viral particles less than 50 mRNA/mL versus the quantitative PCR, which detects more than 500 mRNA/mL. The qualitative PCR is used for confirmation and the quantitative test is used to monitor disease activity and response to therapy [74].

Treatment

The treatment of HCV is difficult and extensive research and studies are underway to develop better therapy for the infection. Currently IFN alfa-2a, ribavirin, or amantadine are the suggested treatments. Viral serotypes are important in determining treatment response, with HCV type I being less responsive.

IFN alfa-2a

Currently, the only Food and Drug Administration approved treatment of HCV is with IFN alfa-2a [75,76]. There are significant risks and side effects associated with this treatment. The side effects occur early and late. The early side effects are a flulike illness during the first 1 to 2 weeks of therapy. This occurs along with the inconvenience of subcutaneous administration of the medicine three times a week. The later side effects are less predictable and variable. They include autoimmune hypothyroidism, vitiligo [77,78], alopecia [79], myelosuppression, psoriasis and psoriatic flares, autoimmune hemolytic anemia, and major depressive episodes [80,81]. The other problem with IFN is the high relapse rate, which is as high as 50% [82].

Most of the side effects associated with IFN are caused by autoimmunity. IFN causes an increase in major histocompatibility types I and II, which increases autoantibody formation. It is suggested that all patients under consideration for IFN therapy be prescreened for autoantibodies because there is an increased risk of autoimmune hepatitis.

Contraindications for IFN alfa-2a therapy include thrombocytopenia (< 100,000); neutropenia (3000); end-stage cirrhosis; autoimmune disorders; drug or alcohol abuse; and major psychiatric disorders. Factors predicting a favorable response to IFN include short disease duration; young age; absence of cirrhosis; low serum HCV RNA titer (< 100,000); genotype 2 to 6; and female gender.

The benefits of therapy are variable, with some patients having excellent responses. The benefits of IFN therapy are related to the decrease in viral load. This is monitored with quantitative PCR assays. Patients with cutaneous manifestations of HCV related to immune complex deposition or viral antigen deposition tend to improve with IFN if viral titers diminish. Patients with mixed cryoglobulinemia treated with IFN have fewer arthralgias and cutaneous findings secondary to the decreased viral load [83,84].

Pegylated IFN or peg-IFN is a new IFN with a pegylated side chain attached, which allows for better absorption, slower clearance, and longer half-life than IFN. The benefit is once-a-week dosing with peg-IFN versus three times a week with IFN alfa-2. There is a greater tendency for neutropenia with peg-IFN compared with IFN alfa-2a. The other side effects and risks are comparable [85].

Ribavirin

Ribavirin is another antiviral agent used in the treatment of HCV. It is usually used in combination with IFN. It is the treatment of choice for patients treated with IFN alone who have relapsed. Many recommend combined therapy with IFN alfa-2a and ribavirin from the outset. The risk of cutaneous reactions seen with ribavirin is greater than those seen with IFN alfa-2a [86–91]. One study suggests that triple antiviral therapy with IFN, ribavirin, and amantadine may be better than each alone or two combined [92].

Hepatitis G virus

The hepatitis G virus is a newly discovered virus seen in some patients with posttransfusion hepatitis. It does not seem to be a major cause of posttransfusion hepatitis, and rarely runs a chronic course. It is seen in 10% to 25% of patients with HCV [93,94].

Miscellaneous

Co-infection with HCV and HIV is common, occurring in 50% to 80% of people who acquired HIV through parenteral exposure. Antiretroviral with ritonavir therapy has shown to increase the risk of severe hepatotoxicity [95].

Treatment of HCV-infected patients with cyclosporin A at low doses (3 mg/kg) is safe in patients with low viral titers [96]. Corticosteroids have shown a tendency to increase viral load and should be used cautiously in patients with HCV [97].

Occult hepatitis B is commonly seen in patients with chronic hepatitis C liver disease and may correlate with a worse prognosis and a decreased response to IFN [98].

Patients with hepatitis C who developed hepatitis A infection had a much higher incidence of fulminant hepatitis than those with hepatitis B. Patients with HCV should be vaccinated against hepatitis A [99].

Summary

Hepatitis C is an important and common cause of chronic hepatitis and cirrhosis. Cutaneous manifestations are often the first signs of infection. Dermatologists must be aware of these manifestations, because early diagnosis is the best treatment. HCV Ab by ELISA should be ordered in patients with LCV-urticarial vasculitis, cryoglobulinemia, lichen planus, Sjögren's syndrome, unexplained pruritus, PCT, PAN, chronic urticaria, patients starting methotrexate, unexplained pruritus, and any patient initiating therapy with a potentially hepatotoxic drug.

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Pruritus in systemic disease: mechanisms and management

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Pruritus or itch is the most common symptom of skin disease. Even in the absence of primary cutaneous findings, severe and extensive pruritus is often associated with systemic disease [1]. This review proposes to consider briefly the physiology of pruritus and to discuss the various systemic diseases often accompanied by this troublesome symptom. In addition to exploring the possible mechanisms and potential therapies of itching in selected disorders, this review presents general recommendations for evaluating patients with unexplained pruritus as well as management guidelines for alleviating their discomfort.

Pathophysiology of pruritus

Itch represents an unpleasant sensation which arises in the superficial layers of skin, mucous membranes, upper respiratory tract, and conjunctivae [2]. The nerve endings responsible for pruritus have abundant terminal branches located at the junction of the dermis and epidermis, superficial to those responsible for pain [3,4]. These unmyelinated C fibers, which are distinct from but similar to the slow-conducting fibers that conduct pain, transmit itch impulses to the ipsilateral dorsal root ganglia, where they synapse with itch-specific secondary neurons [5]. These secondary neurons immediately cross over to the opposite anterolateral spinothalamic tract and continue through the thalamus to end in the somatosensory cortex of the postcentral gyrus [3]. Recent research using positron emission tomography (PET) suggests that histamine-induced itch activates both the anterior cingulate cortex, which processes the sensorial and emotional aspects of itch, and the supplemental motor area, which is thought to participate in the preparation of scratching behavior [6]. This evidence supports the traditional definition of itch as a sensation inextricably connected with the urge to scratch [7].

Mediators of itching

The specialized unmyelinated C fiber nerve endings may be stimulated by a vast array of chemical mediators, termed pruritogens. Though many pruritogens have been identified, researchers continue to explore other potential mediators of itch (see Table 1).

The main peripheral mediator of pruritus is *histamine*, which is produced by mast cells and circulating basophils. Histamine causes vasodilation and edema by interacting with H_1 receptors and generates itch by directly acting upon epidermal nerve endings [1]. Interestingly, histamine is not thought to be the main mediator in most cases of pruritus caused by systemic disease, and antihistamines are rarely effective in those situations [8].

Serotonin, which is contained in platelets and is released when they aggregate, is a weaker pruritogen than histamine; however, the experimental combination of serotonin and prostaglandin E_2 (PGE_2)—itself a weak pruritogen—causes more intense pruritus than either substance alone [9]. This laboratory finding has clinical relevance in the management of polycythemia vera, in which antihistamines have no effect. On the other hand, serotonin antagonists [10] and aspirin, which inhibits both prostaglandin synthesis and platelet aggregation, do relieve the itch

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Table 1
Potential chemical mediators of pruritus

Amines	Histamine, serotonin, dopamine, adrenaline, noradrenaline, melatonin
Neuropeptides	Substance P, neurotensin, vasoactive intestinal peptide (VIP), somatostatin, α- and β-melanocyte-stimulating hormone (MSH), calcitonin gene-related peptide (CGRP), bradykinin, endothelin, neurokinin A and B, cholecystokinin (CCK), bombesin
Eicosanoids	PGE_1, PGE_2, PGH_2, LTB_4
Cytokines	IL-2, TNF-α and TNF-β, eosinophil products
Opioids	Met-enkephalin, leu-enkephalin, β-endorphin, morphine
Proteolytic enzymes	Tryptases, chymases, kallikrein, papain, carboxypeptidases

Adapted from Krajnik M, Zylicz Z. Pruritus in advanced internal diseases: pathogenesis and treatment. Netherlands J Med 2001; 58:27–40; with permission.

associated with polycythemia vera [9]. These data implicate both serotonin and PGE_2 in the pathogenesis of certain types of pruritus. Furthermore, plasma serotonin levels are increased in patients with uremic pruritus, and the use of ondansetron, a potent and selective 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) receptor inhibitor, has demonstrated efficacy in relieving this pruritus and concomitantly lowering plasma serotonin levels [11].

A variety of *neuropeptides* found in cutaneous sensory neurons have also been implicated as pruritogens. These neurogenic peptides, including substance P, neurotensin, vasoactive intestinal peptide (VIP), somatostatin, and melanocyte-stimulating hormone, to name a few, are thought to mediate pruritus by liberating histamine from dermal mast cells [12,13]. For example, the intradermal injection of substance P causes flare, wheal, and itching, a reaction inhibited by antihistamines [14].

Prostaglandins E_1, E_2, and H_2 do not seem to cause pruritus by themselves, but they have been shown to potentiate itching caused by histamine [15–18]. In contrast, other eicosanoids, such as leukotrienes B_4, C_4, and D_4, have not caused pruritus when injected intradermally [19] and do not seem to sensitize histamine-induced itch [13].

Research of the pruritogenic potential of *cytokines* has produced mixed results. One group of scientists has found that interleukin-2 (IL-2) induces weak but significant pruritus unrelated to histamine release. In contrast, tumor necrosis factor-α (TNF-α) does not generate itching or histamine liberation [20].

Endogenous *opioids*, such as enkephalin and β-endorphin, also cause pruritus by releasing histamine after intradermal injection [21]. Furthermore, opioids potentiate the action of histamine by a still-uncharacterized mechanism [13]. In addition to these peripheral effects, opioids commonly cause pruritus after epidural or spinal administration and less often after systemic administration [22]. The mechanism of opioid-induced itching is not completely understood but is thought to involve the mu receptor [23].

Finally, proteolytic enzymes such as trypsin, chymase, and kallikrein also produce itch when injected intradermally [24–26]. Because their pruritogenic action is not inhibited by antihistamines, they are not thought to release histamine from cutaneous mast cells [25]. Other potential pruritogens are listed in Table 1.

Evaluating patients with pruritus

Most patients with pruritus present with primary skin manifestations. Itch is frequently encountered as a symptom of common dermatologic conditions such as atopic dermatitis, psoriasis, contact dermatitis, bullous pemphigoid, dermatitis herpetiformis, miliaria, urticaria, xerosis, and infestations [27]. Evaluating an itchy patient without primary skin findings, however, requires a different approach, one directed at detecting any underlying systemic disorder. A thorough history should include specific details about the pruritus, such as the duration, quality, and distribution of itching and any exacerbating or ameliorating factors. In addition, the patient should be questioned about medications and recreational drugs, personal or family history of atopy or skin disease, sexual habits, travel history, bathing habits, occupation and hobbies, domestic pets, and other environmental exposures. Furthermore, a meticulous review of systems may provide clues to underlying systemic disease [28,29].

Physical examination of the patient should initially be geared toward ruling out a primary cutaneous condition and should include palpation of lymph nodes, liver, and spleen to evaluate for lymphadenopathy and organomegaly as well as inspection of finger webs, axillae, and genitals to evaluate for scabies or other infestations. Secondary skin findings such as

excoriations, dyspigmentation, or lichenification are common in generalized pruritus [29].

If no specific dermatologic disorder can be identified after thorough history and physical examination, practitioners are encouraged to order laboratory tests aimed at diagnosing the most common of the systemic diseases responsible for generalized pruritus (see Table 2).

Systemic disorders associated with pruritus

Among patients being evaluated for pruritus, the prevalence of underlying systemic disease has been reported to range from 10% to 50% [27,30]. These systemic disorders include chronic renal failure, hepatobiliary disease, polycythemia vera and other hematopoietic diseases, metabolic and endocrine disorders, neurologic derangements, malignancy, and a variety of miscellaneous conditions (see Table 3). The following sections review the most common systemic disorders associated with generalized pruritus, the potential pathogenesis of the pruritus in selected conditions, and the recommended treatments for patients in each category.

Renal disease: chronic renal failure

Pruritus is frequently seen in patients with chronic, but not acute, renal failure. So-called ''renal itch'' can be paroxysmal or constant, localized or generalized [31,32]. The prevalence of uremic pruritus varies widely, affecting 25% to 86% of patients with chronic renal failure [31–33]. Up to one third of uremic patients who are managed without dialysis suffer from renal itch, and the prevalence is increased in patients on maintenance hemodialysis and on continuous ambulatory peritoneal dialysis (CAPD) [11,34].

The pathogenesis of renal itch is not completely understood, though several mechanisms have been suggested. Among these hypotheses are associations with xerosis, cutaneous mast cell proliferation, secondary hyperparathyroidism, cutaneous nerve proliferation or dysfunction, increased elaboration of pruritogenic cytokines or other toxic metabolites, aberrant divalent ion metabolism, elevated vitamin A levels, increased levels of endogenous opioids, and impaired sweating [34–41]. Despite these proposed mechanisms, neither the cause nor the most effective treatment of uremic pruritus has been clearly established.

Renal transplantation is thought to be the most definitive therapy of uremic itch [32]. For those

Table 2
Diagnostic laboratory tests in generalized pruritus

Complete blood count with differential
Liver function tests including plasma albumin
Renal function tests including urinalysis
Thyroid function tests
Plasma glucose
HIV antibody (if risk factors are present)
Chest radiograph
Stool for occult blood and parasites

Adapted from Krajnik M, Zylicz Z. Pruritus in advanced internal diseases: pathogenesis and treatment. Netherlands J Med 2001;58:27–40; with permission.

Table 3
Systemic diseases associated with pruritus

Renal disease
Chronic renal failure
Hepatobiliary disease
Intrahepatic cholestasis
Primary biliary cirrhosis
Pruritus gravidarum
Sclerosing cholangitis
Infectious hepatitis
Drug-induced cholestasis
Extrahepatic biliary obstruction
Hematopoietic diseases
Polycythemia vera
Iron-deficiency anemia
Hodgkin's disease
Leukemias and lymphomas
Plasma cell dyscrasias
Mycosis fungoides
Mastocytosis
Metabolic and endocrine disorders
Hyperthyroidism
Hypothyroidism
Diabetes mellitus
Multiple endocrine neoplasia II (Sipple's syndrome)
Carcinoid syndrome
Neurologic disorders
Multiple sclerosis
Cerebral tumor
Cerebral abscess
Stroke
Malignancy
Miscellaneous conditions
Acquired immunodeficiency syndrome (AIDS)
Parasitosis
Anorexia nervosa
Advanced age
Psychogenic disorders

Adapted from Krajnik M, Zylicz Z. Pruritus in advanced internal diseases: pathogenesis and treatment. Netherlands J Med 2001;58:27–40, and Yosipovitch G, David M. The diagnostic and therapeutic approach to idiopathic generalized pruritus. Int J Dermatol 1999;38:881–887; with permission.

patients awaiting transplantation, optimizing dialysate concentrations of magnesium and other divalent ions has demonstrated relief of pruritus [38,42]. Though plasma levels of histamine are increased in uremic patients [11,43], conventional antihistamines are notoriously ineffective in ameliorating renal itch; however, because approximately 50% of patients on dialysis have xerosis, emollients and moisturizers are recommended and may provide some relief [1,32]. In addition to these measures, several specific therapeutic modalities have demonstrated relief of uremic pruritus (see Table 4).

Ultraviolet light, particularly ultraviolet B (UVB), has shown remarkable efficacy in relieving pruritus in hemodialysis patients, with 70% to 90% of patients responding to as few as eight twice-weekly sessions [44]. In addition to diminishing uremic itch, UVB also reduces vitamin A levels in the epidermis, leading researchers to suggest that increased epidermal vitamin A, as seen in hemodialysis patients, may be causally related to uremic pruritus [35]. *Oral activated charcoal* seems to be a safe, effective, and inexpensive treatment of uremic pruritus, and its therapeutic efficacy has been found to last up to 21 weeks after its discontinuation [45,46]. Researchers posit that the mechanism of charcoal, which nonspecifically absorbs organic and inorganic compounds, may be the removal of pruritogenic chemicals from body fluids [45,46]. Thought to act by a similar mechanism, *cholestyramine*, a nonabsorbable ion-exchange resin, has also demonstrated effective reduction of pruritus in patients on chronic hemodialysis [47].

Administration of *naltrexone*, an oral opioid antagonist, has also achieved reduction in severe intractable pruritus in hemodialysis patients. Because the higher-than-normal plasma histamine levels seen in patients with renal itch were decreased after naltrexone, its mechanism is thought to involve the inhibition of histamine release rather than an antiopioid effect [40].

In a recent study, *ondansetron*, a potent and selective inhibitor of 5-HT_3 receptors, significantly reduced the pruritus of patients on CAPD. Furthermore, ondansetron reduced the plasma levels of both histamine and serotonin in these patients, suggesting a prominent role for these two mediators of itching in the pathogenesis of renal itch [11].

Table 4
Management of pruritus associated with chronic renal failure

Ultraviolet B (UVB) phototherapy twice weekly
Oral-activated charcoal 6 g daily
Cholestyramine 5 g twice daily
Naltrexone 50 mg daily
Ondansetron 4 mg twice daily
Topical capsaicin (if localized)
Encourage renal transplantation program enrollment

Adapted from Murphy M, Carmichael A. Renal itch. Clin Exp Dermatol 2000;25:103–106; with permission.

Frequent application of *topical capsaicin*, which depletes substance P from peripheral sensory neurons, has proven effective in ameliorating localized pruritus in hemodialysis patients [31,48]. Though local irritation is common, burning and erythema usually resolve within 72 hours of repeated application [31].

Reports of successful treatments for uremic pruritus also include *azelastin*, an antiallergy medication, which significantly reduced pruritus in an open study of patients on hemodialysis, though it had no effect on the elevated plasma histamine concentrations seen in these patients [43]. In addition, *thalidomide* has been shown to alleviate uremic pruritus after less than a week of therapy and is thought to act by interfering with inflammatory mediators such as tumor necrosis factor-α [49]. Furthermore, intravenous *lidocaine* slowly infused during hemodialysis relieved uremic itch for 48 hours in a series of 20 patients [33].

Some researchers have found that *erythropoietin* therapy decreases pruritus in uremic patients on hemodialysis. They also documented concomitant decline in plasma histamine levels, leading to the suggestion that the hormone diminishes pruritus by directly or indirectly lowering histamine concentrations [50]. Other investigators, however, have failed to document any antipruritic effect of erythropoietin [51].

Subtotal parathyroidectomy has resolved the uremic pruritus of some patients with secondary hyperparathyroidism, encouraging researchers to implicate derangements in calcium and phosphorous metabolism as pathogenetic factors in renal itch [39]. Other workers, however, have not found a relationship between intensity of uremic pruritus and levels of parathyroid hormone [48].

A less-traditional therapeutic modality has also shown some efficacy in relieving uremic pruritus. *Electrical needle stimulation*, a modified acupuncture technique, decreased pruritus and improved the sleeping habits of six dialysis patients with intractable pruritus [52].

Hepatobiliary disease: cholestasis

Pruritus affects 20% to 25% of patients with jaundice but is rare in those without cholestasis, the impaired hepatic secretion of bile [1]. Although cholestatic pruritus is generalized, it most markedly affects the palms of the hands and the soles of the feet [1,53]. On physical examination, patients may have

postinflammatory hyperpigmentation sparing the midback and producing a characteristic, hypopigmented butterfly sign [54].

Intrahepatic cholestatic pruritus occurs in patients with primary biliary cirrhosis, pruritus gravidarum, sclerosing cholangitis, viral or syphilitic hepatitis, and drug-induced cholestasis [27,53,55]. Pruritus occurs in virtually 100% of patients with primary biliary cirrhosis and is the presenting symptom in 50% [1]. Pruritus gravidarum, or cholestasis of pregnancy, occurs in 0.5% to 2% of pregnancies and typically appears in the third trimester [56,57]. Pruritus gravidarum usually resolves soon after delivery, but recurrences may develop with subsequent pregnancies or with oral contraceptive ingestion [53]. Medications associated with cholestasis include phenothiazines, estrogens, tolbutamide, and other drugs [27,58]. In addition, both malignant and benign extrahepatic biliary obstructions are frequently associated with pruritus [53].

Though pruritus is common in patients with cholestasis, the cause of cholestatic pruritus has not been well elucidated. Part of the difficulty in characterizing its pathogenesis is the lack of correlation of the severity of cholestasis with either the presence or the intensity of pruritus in these patients [59]. Most proposed mechanisms of cholestatic pruritus involve the liver's involvement in producing or in failing to detoxify pruritogens.

Cholestasis is associated with high plasma concentrations of bile salts, and their presence in the skin was initially thought to be responsible for cholestatic pruritus [60]. Subsequent research, however, has failed to correlate plasma or tissue concentrations of bile acids with the presence or intensity of pruritus [61,62]. Nevertheless, it is possible that bile salts are indirectly involved in cholestatic pruritus, possibly by inducing the release of pruritogenic factors [61]. The impaired excretion of bile acids in pruritus gravidarum has been attributed to an exaggerated hepatic response to estrogens and their metabolites [1,57]. Another proposed mechanism of cholestatic pruritus involves the accumulation of endogenous opioids, which may act centrally to produce pruritus. Serotonin has also been suggested as a mediator of cholestatic pruritus, possibly by modulating central opioidergic action [59].

Definitive treatment of cholestatic pruritus can be achieved with liver transplantation, and for patients with severe, intractable pruritus, transplantation should be considered regardless of the degree of hepatic decompensation. Other therapies that reverse or diminish cholestasis, such as S-adenosylmethionine and ursodeoxycholic acid, have not repeatedly demonstrated relief of pruritus. Alternatively, if the extrahepatic biliary obstruction is surgically reversed, cholestatic pruritus typically subsides within 24 hours [59].

Because of the uncertain mechanism of pruritus in patients with cholestasis, most symptomatic therapies for this bothersome condition are theoretically and empirically based. Emollients, topical corticosteroids and anesthetics, antihistamines, and sedatives have demonstrated little efficacy in treating cholestatic pruritus [53]. On the other hand, several therapeutic modalities have shown experimental success (see Table 5).

In spite of the lack of evidence for a direct causative role for bile acids or their intermediaries in the pruritus of cholestasis [61,62], an etiologic association of bile acids with cholestatic pruritus is appealing because of the occasional relief provided by orally administered *cholestyramine*, an anion exchange resin [60,63,64]. By binding and sequestering bile acids in the intestine and thus partially interrupting the enterohepatic circulation, cholestyramine lowers bile acid levels and other potential pruritogenic factors in plasma and tissues [53,60]. *Extracorporeal plasmapheresis*, or plasma perfusion through charcoal-coated glass beads, also removes bile acids and other possible pruritogens from the plasma of patients with cholestasis and has demonstrated efficacy in the temporary resolution of cholestatic pruritus [65]. For women with pruritus gravidarum, some relief has been associated with the administration of *oral guar gum*, a dietary fiber that binds bile acids in the intestinal lumen and increases their fecal elimination [66].

Other therapies that are thought to reduce levels of putative pruritogens include medications that induce hepatic microsomal enzymes involved with steroid and bilirubin metabolism. *Rifampin*, an antibiotic that inhibits hepatic bile acid uptake and stimulates mixed-function oxidases, has been shown to alleviate cholestatic pruritus [67–69]. Thought also to act by enhancing hepatic microsomal function, *phenobarbital* has similarly demonstrated antipruritic effects in patients with cholestasis [67,70].

Table 5
Management of pruritus associated with intrahepatic cholestasis

Cholestyramine 4 g once to three times daily
Rifampin 300–450 mg daily
Ultraviolet B (UVB) phototherapy twice weekly
Naltrexone 50 mg daily
Ondansetron 8 mg twice daily
Encourage liver transplantation program enrollment

Phototherapy has also been successful in alleviating cholestatic itch through an unknown mechanism. In particular, twice weekly *UVB* treatments have demonstrated reduction in the pruritus of cholestasis [63,71]. More recent research indicates that *bright-light therapy* directed toward the eyes of patients with cholestasis ameliorates pruritus and reduces scratching activity. The investigators proposed that cholestatic pruritus is partially mediated by centrally acting opioids that display a circadian rhythm which is altered by bright-light therapy [72].

Several other medications for cholestatic pruritus are also based on theories of endogenous opioid effects on the central nervous system. According to the hypotheses, poor hepatic function results in the retention of endogenous opioids, which act as central pruritogens. Several opioid antagonists have been used successfully to relieve the pruritus of cholestasis [73]. In well-controlled trials, parenterally administered *naloxone* has demonstrated reduction of pruritus and scratching activity in cholestatic patients [74,75]. Similarly, oral *nalmefene*, another opiate receptor antagonist, has been associated with amelioration of cholestatic pruritus and reduction in scratching activity [76]. In the United States, however, nalmefene is available only in parenteral form [73]. Alternatively, oral *naltrexone*, an opiate antagonist used to treat opiate addiction, has been shown to alleviate the pruritus of chronic liver disease with fewer side effects than nalmefene [77]. Considering the occasional occurrence of opiate withdrawal symptoms with the use of opiate receptor antagonists such as naloxone, nalmefene, and naltrexone [74,75,77], one group of researchers recently explored the use of *codeine*, a nonantagonistic opioid, and reported relief of cholestatic pruritus without opiate withdrawal symptoms in a patient with primary biliary cirrhosis [78]. Though impractical in an outpatient setting, subhypnotic doses of *propofol*, an intravenously administered agent used in anesthesiology, reduced cholestatic pruritus in a small but well-controlled crossover study. The investigators posited that propofol depresses spinal excitation by endogenous opioids or by postulated opioid-like pruritogens [79].

Finally, a potential role for serotonin in cholestatic pruritus has been suggested by the effectiveness of intravenous and oral *ondansetron*, a 5-HT_3 receptor antagonist widely used as an antiemetic agent [80–82].

Hematopoietic diseases

Generalized pruritus has been associated with several apparently unrelated hematopoietic disorders, including polycythemia vera, iron-deficiency anemia, Hodgkin's disease, leukemias and lymphomas, plasma cell dyscrasias, mycosis fungoides, mastocytosis, and others [27].

Pruritus occurs in 25% to 70% of patients with polycythemia vera [9,10]. The pruritus is typically generalized, has a pricking quality, and occurs most frequently after hot baths or showers [9]. In some cases, the pruritus precedes the development of disease by years [83].

Reducing the red cell mass through phlebotomy occasionally ameliorates the pruritus associated with polycythemia vera [84]; however, other writers claim that effective management of the underlying disorder with venesection or chemotherapy does not commonly control the pruritus [85]. Because its pathogenesis is unknown, conventional therapies for the pruritus associated with polycythemia vera lack a sound scientific basis, and multiple agents are used on an empirical rather than on a rational basis (see Table 6).

Despite elevated levels of histamine in both blood and urine of patients with myeloproliferative diseases and a correlation between blood histamine levels and pruritus [86], conventional antihistamines are not usually effective in treating polycythemia vera [3]; however, *cyproheptadine*, a medication with both antihistamine and antiserotonin effects, has controlled the pruritus associated with polycythemia vera and other myeloproliferative disorders [86]. Notwithstanding the relief from itching provided by cyproheptadine, patients did not experience a concomitant diminishment in blood or urine levels of histamine, lending support to an indirect role of histamine in these disorders [86]. The success of *cimetidine*, an H_2 receptor antagonist, has led researchers to posit that the pruritus associated with polycythemia vera is caused by a derangement of histamine metabolism [83,87]. Alternatively, cimetidine's effectiveness has been attributed to its inhibition of hepatic cytochrome enzymes [58]. Other investigators have reported success with *pizotifen*, a medication with potent antihistamine and antiserotonin effects usually prescribed for migraine prophylaxis [10].

Table 6
Management of pruritus associated with polycythemia vera

Phlebotomy or chemotherapy to reduce red cell mass
Cyproheptadine 4 mg three times daily
Cimetidine 300 three times daily
Pizotifen 0.5 mg three times daily
Cholestyramine 4 g three times daily
Aspirin 500 mg three times daily

Though *cholestyramine* administration has resulted in relief from pruritus in polycythemia vera [9], investigators have been unable to document a clear association between elevated bile acids and the pruritus of polycythemia vera [10].

One controlled study of patients with polycythemia vera demonstrated the alleviation of pruritus with *aspirin*, leading researchers to postulate an etiologic role for platelets and their production and release of PGE_2 and serotonin [9].

In several reports, subcutaneous administration of *interferon-α2b* three times per week has markedly diminished the pruritus of patients with polycythemia vera and has also improved hematological control of the underlying disease [85,88,89]. Investigators speculate that clinically inapparent angiogenesis in the skin may be responsible for the itching experienced by these patients and that the effectiveness of interferon-α2b in polycythemia vera may result from its ability to inhibit angiogenesis [85].

The iron-deficiency anemia that results from repeated phlebotomies may occasionally intensify pruritus in patients with polycythemia vera. In one study, *iron supplementation* relieved the pruritus of such patients within a period of 2 to 3 weeks, though the authors cautioned against indiscriminate use of iron in patients whose underlying disease may be exacerbated by its administration [90].

Iron deficiency, with or without an accompanying anemia, may rarely be a cause of generalized pruritus, and patients often respond to oral ferrous sulfate [91].

Pruritus develops in approximately 30% of patients with Hodgkin's disease [92] and may precede the clinical development of lymphoma by up to five years [93]. Usually described as burning in quality [58], pruritus most commonly occurs on the lower half of the body, particularly on the legs, where it is often associated with ichthyotic changes [1]. Some research has suggested that severe pruritus is a negative prognostic indicator in Hodgkin's disease [92].

Management of the pruritus associated with Hodgkin's disease is best achieved by treating the lymphoma itself [58]. As symptomatic therapy, only *cimetidine* has shown efficacy in anecdotal reports [94]. The success of cimetidine has led investigators to suggest that histamine is the mediator of pruritus associated with lymphoproliferative diseases [1], though other researchers propose that an autoimmune response to lymphoma cells may induce the liberation of pruritogens such as bradykinins and leukopeptidases [95].

Generalized pruritus in the absence of cutaneous findings has very rarely been described in patients with leukemia, most commonly in chronic lymphocytic leukemia [1,93,96]. Generalized pruritus has also been reported as a presenting symptom or a complication of multiple myeloma, and management of the underlying disorder has resulted in the diminution of itch. Pruritus is rarely the presenting symptom in patients with Waldenstrom's macroglobulinemia or in those with benign gammopathies [97].

Pruritus in the premycotic phase of mycosis fungoides (cutaneous T-cell lymphoma) is usually not present in the absence of cutaneous findings, but it has been reported to precede the disease by up to 10 years [1,58]. Treatments of the underlying tumor, including topical corticosteroids, radiation therapy, topical nitrogen mustard, psoralen combined with ultraviolet A phototherapy (PUVA), photopheresis, and cyclosporin A, should relieve any pruritus associated with mycosis fungoides [58,95].

Systemic mastocytosis may also be rarely associated with generalized pruritus in the absence of cutaneous lesions [98]. As the pruritus is presumed to be mediated by histamine liberation from dermal mast cells, symptomatic relief may be accomplished with the use of antihistamines, both H_1 and H_2 antagonists, and with medications such as cyproheptadine, which has antiserotonin action as well [98–100]. First-line management includes the avoidance of specific mast cell degranulators, such as temperature extremes and narcotics [100]. The administration of nifedipine has also had positive results and is thought to act by blocking calcium channels on mast cells, thus inhibiting their degranulation [101]. Finally, oral PUVA therapy has also demonstrated successful alleviation of pruritus associated with systemic mastocytosis [99].

Metabolic and endocrine disorders

Pruritus has been described in patients with a variety of systemic metabolic derangements, including hyperthyroidism, hypothyroidism, diabetes mellitus, Sipple's syndrome, and carcinoid syndrome [1].

Generalized pruritus develops in 4% to 11% of patients with thyrotoxicosis, especially in those with untreated Graves' disease [102]. Hypotheses of the pathogenesis of pruritus in patients with hyperthyroidism include reduction of the itch threshold as a result of increased body temperature and vasodilation as well as the activation of kinins secondary to increased tissue metabolism [3]. Pruritus typically responds to correction of the patient's hyperthyroidism [18].

Similarly, pruritus occurs in patients with hypothyroidism and is thought to be caused by xerosis, which is present in 80% to 90% of patients. Xerosis, and therefore pruritus, seem responsive to emollients

and to treatment of the underlying disorder with thyroid hormone [3].

Although 30% of diabetic patients manifest cutaneous signs of the disease, generalized pruritus without skin findings occurs in only 3% of patients with diabetes mellitus [103–105]. Proposed mechanisms include diabetic neuropathy, metabolic derangements secondary to renal failure, and autonomic dysfunction with resultant anhidrosis [1,3]. Xerosis, on the other hand, is often seen in diabetics and should be treated with emollients [105]. Furthermore, pruritus ani and pruritus vulvae caused by *Candida albicans*, dermatophytes, or β-hemolytic Streptococcus can presage the development of diabetes [104,105]. Pruritus vulvae in particular has been significantly associated with poor control of diabetes, and investigators recommend treatment of the underlying infection and optimal management of diabetes in these patients [104].

Pruritus occasionally occurs in patients with multiple endocrine neoplasia II (MEN-II), also known as Sipple's syndrome, in which parathyroid hyperplasia and increased levels of histaminase have been described [1]. Pruritus has also been described in patients with carcinoid syndrome and has been attributed to the liberation of histamine or kallikrein and the subsequent release of bradykinin from tumor cells [1,27] In addition, peripheral vasodilation may lower the itch threshold in patients with carcinoid syndrome, and management of pruritus should center on correction of the underlying disorder [27].

Neurologic disorders

Pruritus is occasionally seen in patients with neurologic disorders such as multiple sclerosis and in patients with focal neurologic lesions including tumors, abscesses, and strokes.

Patients with multiple sclerosis may rarely experience brief, recurrent, and severe bouts of generalized itching, attributed to the activation of artificial synapses between axons in partially demyelinated areas of the central nervous system. These paroxysmal attacks of pruritus in patients with multiple sclerosis have been effectively relieved with carbamazepine [106,107].

Advanced brain tumors, especially those invading the fourth ventricle, have been characterized by severe and persistent pruritus restricted to the nostrils. The pruritus may resolve with successful treatment of the underlying cancer [108]. Unilateral cerebral lesions, such as those occurring in smaller tumors, abscesses, and strokes, are occasionally associated with localized or generalized pruritus, particularly on the contralateral side of the body [108–111]. Although its exact pathogenesis has not been clarified, the itching has been attributed to lesional effects on pathways that modulate pruritus [111].

Poststroke pruritus syndrome is characterized by severe localized or generalized itching, especially prominent on the side of the body contralateral to the cerebral insult, and typically develops days to weeks after the cerebrovascular accident [110]. Treatments such as amitriptyline, doxepin, and carbamazepine have been effective in treating poststroke pruritus [109,110].

Malignancy

In rare cases, pruritus heralds the emergence of internal malignancy [58]. As a paraneoplastic phenomenon, pruritus has been reported in patients with malignant tumors of the nasopharynx, prostate, stomach, breast, uterus, and colon, to name but a few [112,113]. Malignancy-associated pruritus typically affects the upper trunk, legs, and extensor surfaces of the upper extremities, but it may be generalized [112]. In some patients, however, localization of the pruritus correlates with the site of primary tumor; for example, in instances of cervical carcinoma, women may develop pruritus vulvae, and patients with rectal or sigmoid cancer may report symptoms of pruritus ani. The etiology of malignancy-associated itching is unknown, and suggested mechanisms include the release of toxic products of necrotic tumor cells or a local inflammatory reaction to microscopic implants of tumor in the skin [3]. Various symptomatic therapies may slightly reduce the pruritus, and the rapid antipruritic effect of paroxetine has recently been reported [114]. The only definitive treatment, however, is removal or ablation of the underlying cancer [112,113].

Miscellaneous conditions

A host of other systemic diseases have also been associated with generalized pruritus in the absence of skin findings. Pruritus may be the presenting sign of human immunodeficiency virus infection [115]. Pulmonary, intestinal, and systemic parasitic infestations are occasionally accompanied by generalized pruritus, and the mechanism is presumed to involve allergic sensitization of the host to the parasitic organisms [27]. An association between low body mass index and itching has been demonstrated recently, and the pruritus of patients with anorexia nervosa seems to diminish with the restoration of weight. In these patients, investigators have proposed several potential mechanisms: zinc or other

nutritional deficiency, deranged thresholds of thermoregulation, and altered activity of opioids and serotonin in the central nervous system [116]. At least 50% of elderly people seem to suffer from generalized pruritus [3]. Xerosis is occasionally present, but more often no evidence of any underlying disorder can be discovered. So-called "senile pruritus" has been attributed to age-associated skin atrophy and degeneration of cutaneous nerve endings [27]. Finally, some cases of generalized pruritus have a psychogenic origin, whether caused by nonspecific states such as anxiety or fatigue, by depression, or by outright psychosis [1], but all potential organic causes should be excluded and a full psychological assessment should be performed before diagnosing psychogenic pruritus [117].

Treatment of pruritus

Management of generalized pruritus centers on treatment of the underlying systemic disorder [58]. Specific recommendations for pruritus associated with particular systemic diseases have already been mentioned. The following section briefly explores the symptomatic management of pruritus in patients who are not responsive to disease-specific treatment or in whom no underlying disorder can be clearly diagnosed (see Table 7).

Initial nonspecific measures include the use of emollients on dry skin and topical corticosteroids on inflamed skin [58]. Even without clinically apparent xerosis, moisturizers may be helpful, since minimal or sporadic dryness may worsen pruritus [27]. As warm and moist conditions also tend to exacerbate itching, patients should keep their environment cool and avoid overexposure to hot water and to heat. Furthermore, patients should avoid irritating textiles, such as woolen garments [29].

Topical preparations

Topical application of emollients or shake lotions containing menthol, camphor, and/or phenol may offer temporary relief by cooling the skin and by acting as counterirritants to pruritic sensations [113, 118,119]. Topical anesthetic agents have demonstrated some success with pruritus relief. The eutectic mixture of the local anesthetics lignocaine and prilocaine (EMLA cream) relieves experimentally induced pruritus [120]. Thought to interfere with sensory nerve fiber transmission, topical anesthetic agents such as pramoxine reduce both the magnitude and duration of histamine-induced itch [121]. The clinical usefulness of topical anesthetics in generalized pruritus remains to be seen, however.

Table 7
Symptomatic treatment of pruritus

General measures
Use emollients
Maintain cool environment
Avoid hot water, alkaline soaps, irritating clothing
Topical preparations
Shake lotions with menthol, phenol, and/or camphor
Topical anesthetics: EMLA, pramoxine
Doxepin cream
Capsaicin cream
Tar compounds: crude coal tar, liquor carbonis detergens
Physical modalities
Ultraviolet B (UVB) phototherapy
Psoralen and ultraviolet A (PUVA) photochemotherapy
Transcutaneous electrical nerve stimulation (TENS)
Cutaneous field stimulation (CFS)
Systemic therapies
Antihistamines: hydroxyzine, diphenhydramine, cyproheptadine, cetirizine
Antidepressants: doxepin
Opiate antagonists: naltrexone
Serotonin antagonists: ondansetron, paroxetine

Adapted from Kantor G. Pruritus. In: Sams W, Lynch P, editors. Principles and practice of dermatology. New York: Churchill Livingstone, 1996; p. 881–885; with permission.

In general, topical antihistamines should be avoided because they frequently cause contact sensitization [58]. Though topical doxepin, a potent H_1 and H_2 antihistamine and tricyclic antidepressant, has proven effective in reducing the pruritus of eczema [122], it may cause an allergic contact dermatitis in some patients [123,124]. The efficacy of topical doxepin in generalized pruritus has yet to be studied.

Based on its success in hemodialysis patients, topical capsaicin may have beneficial antipruritic effects in localized pruritus of any type [31,48,125]. Furthermore, pretreatment with topical anesthetics such as EMLA seems to prevent or reduce the burning often induced by capsaicin [137]. However, the usefulness of capsaicin cream in generalized pruritus remains to be determined.

Finally, tar compounds, including crude coal tar and liquor carbonis detergens, have demonstrated efficacy in relieving pruritus, though their precise mechanism of action remains unknown [127,128].

Physical modalities

Several physical modalities have been successfully used in managing pruritus. Ultraviolet B (UVB) phototherapy as well as psoralen and ultraviolet A

(PUVA) photochemotherapy are well suited to the treatment of generalized pruritus, and their effectiveness in reducing the itch associated with renal or cholestatic pruritus has been demonstrated persuasively [35,44,63,71]. Usually administered two to five times each week, UV doses are progressively increased until the development of erythema, at which point therapy is tailored to accommodate each patient's photosensitivity. Up to 30 treatments may be required to attain relief from pruritus, and once weekly maintenance therapy is often continued [113]. The exact mechanism by which ultraviolet light ameliorates pruritus remains uncertain.

Transcutaneous electrical nerve stimulation (TENS) uses high-frequency electric current and hypothetically acts to inhibit the central perception of itch. Frequently used in pain management, TENS has also produced symptomatic relief in patients with generalized pruritus [129,130]. Cutaneous field stimulation (CFS) is similarly thought to interrupt the scratch-itch cycle by mimicking the beneficial aspects of scratching without damaging the skin. In this way, CFS may activate central inhibitory pathways and thus relieve pruritus [131]. Although the efficacy of CFS currently seems limited to localized pruritus, further research on patients with generalized pruritus may expand its therapeutic applications [131,132].

Systemic therapies

In the management of itch, antihistamines are prescribed frequently, but their usefulness is limited in treating the pruritus that accompanies most systemic disorders. The marginal benefits of certain antihistamines—hydroxyzine, diphenhydramine, cyproheptadine, and cetirizine—are usually attributed to their sedating side effects [133,134].

Doxepin, a tricyclic antidepressant with antihistamine activity, is strongly recommended [28,109]. In addition to ameliorating itch and causing sedation, the antidepressant effects of doxepin are also important in managing patients with intractable generalized pruritus [58].

The opiate antagonist naltrexone has significantly reduced the severity of uremic and cholestatic pruritus [40,77]. Other research has demonstrated naltrexone's effectiveness in treating pruritus caused by a variety of other internal disorders [126,135].

Serotonin antagonists have also shown antipruritic efficacy. Ondansetron, a selective 5-HT_3 receptor antagonist, relieves renal itch and cholestatic pruritus [11,80–82] and may also be effective in other systemic conditions associated with generalized pruritus [136]. Furthermore, the selective serotonin reuptake inhibitor paroxetine has been shown to alleviate pruritus in patients with a variety of advanced cancers as well as in a patient with psychogenic pruritus [114, 117]; these successes suggest that it may also be useful in treating pruritus associated with other systemic disorders.

Conclusion

Generalized pruritus caused by systemic disease presents a formidable therapeutic challenge. Though many disease-specific therapies exist, treatment of pruritus is frequently inadequate, especially in patients without detectable underlying disorders. The paucity of definitive data regarding the pathogenesis of itch prevents more effective relief of this common and distressing symptom.

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Thyroid disease and the skin

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Cutaneous manifestations of thyroid disease are protean in nature and can be divided into specific lesions such as the thyroglossal duct cyst and cutaneous metastases from thyroid malignancy, nonspecific signs secondary to thyroid hormone imbalance, and associated dermatologic and systemic disorders.

This review constitutes a summary and update of the cutaneous manifestations of thyroid disease, as previously reviewed by Heymann [1,2]. Details regarding the physiology of the thyroid may be found in Werner and Ingbar's *The thyroid: A fundamental and clinical text* [3].

Specific thyroid lesions

Thyroglossal duct cysts

The thyroglossal duct cyst is the most common congenital cystic abnormality of the neck, accounting for 70% of such lesions. Though most present in the first decade of life, they may be encountered throughout adulthood. The majority (65%) are located inferior to the hyoid bone and the remaining are found either juxtahyoid or superior to the hyoid bone.

The thyroglossal duct originates from the endodermal thyroid anlage on the pharyngeal floor at the base of the tongue. Ectopic thyroid tissue may be present anywhere along the route of development and may extend from the larynx to the diaphragm [3]. When attachment to the base of the tongue persists, movement of the thyroglossal duct cyst may be seen with protrusion of the tongue. If retrosternal placement of the thyroid occurs in the setting of goiter development, the superior vena cava syndrome may ensue. Signs of caval compromise include vertical, palpable, dilated, and tortuous cutaneous vessels on the trunk, above the lower margin of the rib cage. Subsequent sequelae include development of facial edema, erythema, cyanosis, neck vein distension, proptosis, conjunctival injection, and swelling of the nasal mucosa [4,5]. Sinus tracts are present in 35% of cases and are secondary to the rupture of an infected cyst or a consequence of surgery [6].

Malignancies develop in less than 1% of thyroglossal duct cysts and are most commonly encountered in elderly women. Rapid growth often portends a worse prognosis [7]. The majority of carcinoma is comprised of papillary adenocarcinoma (75% to 85%) and is found during routine excision of thyroglossal duct cysts [8]. Other variants include mixed papillary and follicular carcinoma, squamous cell carcinoma, and anaplastic carcinoma. Squamous cell carcinoma derived from the thyroglossal duct has a better prognosis than the rare squamous cell carcinoma originating in the thyroid gland [9]. Cases of Hürthle cell carcinoma have also been reported [10]. Excision of the thyroglossal duct, cyst, and a portion of the hyoid bone (the Sistrunk procedure) is the treatment of choice for most of these lesions [7].

Before the removal of a thyroglossal duct cyst, ectopic thyroid tissue must be differentiated from cyst tissue because 75% of patients with an ectopic thyroid gland have no other functioning thyroid tissue present. The incidence of ectopic thyroid tissue has been reported to be as frequent as 1:4000 to 1:8000 in

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patients with thyroid disease [11]. Radionuclide scans are recommended preoperatively for prevention of iatrogenic hypothyroidism from the removal of the thyroglossal duct cyst. Ultrasonography may be an acceptable alternative for preoperative evaluation, with the exclusion of patients who are either hypothyroid or do not demonstrate a normal thyroid gland on ultrasound.

Cutaneous metastases from thyroid malignancies

To date, fewer than 50 cases of cutaneous metastasis from primary thyroid cancer have been reported in the literature [12]. Lesions may present as solitary or multiple, flesh-colored, violaceous, or blue-colored papules or nodules. Cutaneous metastases are accompanied by thyromegaly or internal metastases in the majority of cases [13]. The scalp appears to be a favored site for follicular and papillary thyroid carcinoma metastases [12]. Virtually all histologic types of thyroid carcinoma have been reported with cutaneous metastases, including follicular, papillary, and mixed follicular-papillary. Immunohistochemical staining with markers for thyroglobulin and calcitonin is helpful in confirming thyroid origination.

Medullary carcinoma of the thyroid with metastases to the skin has been reported and may be associated with one of the autosomal dominant transmitted multiple endocrine neoplasia (MEN) syndromes. MEN-2a (Sipple syndrome) is comprised of medullary thyroid carcinoma, pheochromocytoma, and parathyroid adenoma. MEN-2b (multiple mucosal neuroma syndrome) is comprised of medullary thyroid carcinoma, pheochromocytoma, mucosal ganglioneuroma, and a marfanoid habitus. MEN-2a is secondary to a missense mutation of the RET protooncogene in chromosome 10, which encodes for the transmembrane receptor tyrosine kinase, while MEN-2b is secondary to a mutation of the intracellular tyrosine kinase domain [1]. Penetrance of medullary carcinoma approaches 100% in these kindreds, and prophylactic thyroidectomy has been suggested [14]. Reports of notalgia paresthetica, macular amyloidosis, or biphasic amyloidosis have been reported in patients with MEN-2a kindreds. Within the families, 50% of patients presented with a pruritic eruption of the interscapular area; of these, all had medullary thyroid cancer [15].

Dermatologists should keep a high index of suspicion for dermal nodules or unusual lesions along the track of a fine needle aspiration of the thyroid gland. Cases have been reported of implantation of both papillary and follicular thyroid cancer along needle tracts [16].

Nonspecific thyroid-related lesions

A variety of cutaneous findings may present in the setting of either a hyperthyroid or hypothyroid state. Elucidation of the specific etiology depends on the assistance of history, physical examination, and laboratory confirmation.

Cutaneous manifestations of hyperthyroidism

A hyperthyroid state may arise as the result of numerous causes. Excessive thyroxine intake, thyroiditis (including Graves' disease), a single toxic nodule, a toxic multinodular goiter, or less commonly, a thyrotropin-secreting pituitary adenoma, molar pregnancy, struma ovarii, or metastatic follicular cancer may all result in hyperthyroidism. The specific pathophysiology linking hyperthyroidism to classic cutaneous findings remains to be well explained.

Thyroid hormone appears to play a pivotal role in the growth and formation of hair and sebum production. Thyroid hormone stimulates epidermal oxygen consumption, protein synthesis, mitosis, and determination of epidermal thickness, while effects on the dermis are less well defined [17]. The epidermis is usually found to be thin but not atrophic. The skin in hyperthyroidism is warm, moist, and smooth, bearing a resemblance to infantile skin. Warmth can be attributed to increased cutaneous blood flow and peripheral vasodilatation, which may also lead to the commonly noticed facial flushing and palmar erythema seen in hyperthyroid patients. Generalized hyperhidrosis may be noted with a predilection for the palms and soles. Scalp hair is soft and fine and sometimes accompanied by diffuse, nonscarring alopecia. Approximately 5% of patients may present with nail findings. Characteristic, though not pathognomonic, is the "Plummer's nail" with a concave contour and distal onycholysis. This finding may also be seen in hypothyroidism, psoriasis, after traumatic injury, or allergic contact dermatitis [17]. Hyperpigmentation may be seen in a distribution resembling that seen in Addison's disease (creases of the palms and soles, gingiva, and buccal mucosa), and is particularly pronounced in darker skin types.

Scleromyxedema has been reported in the setting of hyperthyroidism. This rare entity is comprised of numerous firm, white, yellow, or pink papules scattered on the face, trunk, axillae, and extremities. It is commonly accompanied by weight loss, monoclonal gammopathy, esophageal dysmotility, vascular disease, Raynaud's phenomenon, telangiectasia, decreased pulmonary diffusion capacity, neurologic manifestations, joint disease, and myopathy. Cuta-

neous lesions are the result of accumulation of acid mucopolysaccharides, mostly hyaluronic acid, in the dermis, accompanied by large fibrocytes [18]. The palms and soles are typically spared, though swelling of the fingers and calcinosis cutis may occur. Treatment of the hyperthyroid state with radioactive iodine does not improve cutaneous findings [19].

Graves' disease

Graves' disease is characterized by the aforementioned cutaneous findings of hyperthyroidism in addition to distinctive cutaneous features including pretibial myxedema (dermopathy; 0.5% to 4% of patients) and acropachy (1%). Pretibial myxedema is a misnomer because lesions may appear anywhere, including the preradial aspect of the arms, shoulders, thigh, head, and neck. Clinical presentation may vary from a "peau d'orange" appearance to the extensive infiltration resembling elephantiasis vurrucosa nostra. Most often, lesions appear as bilateral, asymmetric, raised, firm plaques or nodules varying in color from pink to purple-brown and sometimes accompanied by woody induration. In rare cases, overlying hyperhidrosis or hypertrichosis may be present [20].

Graves' dermopathy occurs less frequently than ophthalmopathy, and although it is usually seen with ocular pathology, it may occur alone. The vast majority of patients with dermopathy have Graves' disease; however it has also been reported in the setting of Hashimoto's thyroiditis [21]. The status of thyroid function is independent of dermopathy development, and lesions can occur in the setting of a hyperthyroid, hypothyroid, or euthyroid patient. Histologically, the process appears as an accumulation of hyaluronic acid in the dermis more so than in the subcutis. In clinically verrucous lesions, marked hyperkeratosis may also be seen.

The precise pathogenesis of pretibial myxedema remains to be defined. One leading theory is that pretibial fibroblasts are the target for antithyroid antibodies. After stimulation by thyroid autoantibodies, fibroblasts may produce excess glycosaminoglycans. In support of this theory, Chang et al. reported the presence of thyrotropin (TSH) and TSH receptor antibody binding in fibroblasts as well as the presence of RNA encoding the extracellular domain of the TSH receptor [19]. Other theories have implicated T cells as the primary effector of Graves' dermopathy. T cells may interact with an autoantigen that is either identical or cross-reactive with a thyroid autoantigen in the dermis. In turn, this may induce secretion of cytokines such as glycosaminoglycan-stimulatory lymphokine, interleukin 1, tumor necrosis factor, and gamma interferon, which activate fibroblasts to secrete hyaluronic acid and chondroitin sulfate [22,23]. Anther theory suggests that Graves' dermopathy is not exclusively caused by site-specific cell properties, but rather by the superimposition of local physical and anatomical factors (trauma and edema) within a subclinical, systemic, connective tissue inflammation. Therefore, the autoimmune state alone may not be enough to elicit the extrathyroidal manifestations of Graves' disease [24].

Management of dermopathy continues to pose a challenge to physicians. Though there have been reports of successful local excision, overall success remains equivocal and surgery should probably be avoided. A 20-year study of 150 patients with pretibial myxedema demonstrated the value of using topical triamcinolone [25]. It would not be unreasonable to assume that newer ultrapotent steroid or intralesional steroids may show even greater benefit. Other therapies may include octreotide, intravenous immunoglobulin, and intravenous pulse steroids followed by oral steroids [1]. Ultrasonography may be a useful modality in measuring skin thickness and response to therapy or in detecting subclinical dermopathy [26].

Thyroid acropachy is a triad consisting of digital clubbing, soft tissue swelling of the hands and feet, and periosteal new bone formation. The first, second, and fifth metacarpals, the proximal phalanges of the hand, and the first metatarsal and proximal phalanges of the feet are most commonly affected. Pathognomic radiographic osseous changes are comprised of periosteal reaction of a lamellar type paralleling the diaphyses and has been described as "feathery." New bone spicules may be arranged perpendicularly to the long axis of the bone. Fewer than 100 cases have been reported, and the cause is unknown. When seen, it is usually accompanied by either exophthalmos and/or pretibial myxedema. Similarly to dermopathy, the majority of patients reported developed acropachy after the diagnosis and treatment of thyrotoxicosis [27]. Patients may be euthyroid or hypothyroid. The vast majority of cases are associated with Graves' disease. Thyroid acropachy has also been reported to occur in Hashimoto's thyroiditis and Hürthle cell adenocarcinoma [28,29]. A bone scan may be the most sensitive and objective diagnostic test because it reflects the linear increase in osteoblastic activity in the diaphyseal region of small bones [30].

Most cases of acropachy are asymptomatic and require no therapy. In rare cases, complete remission may occur with time. Therapeutic assessment is difficult because the natural history is variable. Excisional therapy, administration of hyaluronidase, and

local radiotherapy have yielded equivocal results [2]. Successful therapy with topical fluorinated steroids under occlusion has been reported [30].

Hypothyroidism

Hypothyroidism may result from either inadequate circulating levels of thyroid hormone or target cell resistance to hormonal action. Primary hypothyroidism as a result of glandular failure is the most common cause and most frequently results from autoimmune disease. Other potential causes of primary hypothyroidism include previous therapy with I^{131}, thyroid surgery, antithyroid medication, or infiltrative diseases. Secondary hypothyroidism is the result of pituitary dysfunction with resulting inadequate release of thyrotropin (TSH). Possible causes for secondary hypothyroidism include tumor, infarction, trauma, radiation, or surgical treatment of the pituitary gland. Secondary hypothyroidism is commonly accompanied by other pituitary-related endocrinopathies. Tertiary hypothyroidism caused by hypothalamic failure shares similar etiologies with secondary hypothyroidism; however, primary idiopathic hypothalamic hypothyroidism has been reported. In the rare event of isolated thyroid-releasing hormone (TRH) deficiency, other pituitary functions remain normal and the resulting hypothyroidism may be transient [31].

Congenital hypothyroidism

Congenital hypothyroidism (cretinism, congenital athyrosis) occurs when insufficient quantities of thyroid hormone are produced either in utero or during the early perinatal period from primary, secondary, or tertiary hypothyroidism. If unrecognized, a distinctive syndrome of dwarfism, cutaneous and systemic features of hypothyroidism, and mental retardation may occur. Myxedema is classically present with characteristic periorbital puffiness, thick lips, acral swelling, macroglossia, and/or a smooth, red tongue. Yellowing of the skin may be present secondary to carotenemia (from diminished hepatic conversion of β-carotene to vitamin A), prolonged physiologic jaundice, anemia, and myxedema. A pronounced clavicular fat pad may be present. Hypothermia is common secondary to a decreased metabolic rate with resultant reflexive peripheral vasoconstriction and cool, dry, pale skin. Cutis marmorata may be accentuated in this setting. Hair tends to be coarse, dry, and brittle. Patchy alopecia and/or persistent lanugo hairs may be present. A collodion baby with congenital hypothyroidism has been reported. Other anomalies reported in association with congenital hypothyroidism include cardiovascular abnormalities (ventricular septal defect, patent ductus arteriosus, and pulmonary stenosis), gastrointestinal abnormalities (colic duplication with hypertrophic pyloric stenosis), and musculoskeletal abnormalities (unilateral clubfoot and congenital dislocation of the hip) [32].

The incidence of congenital hypothyroidism is 1 case per 4000 live births. Ninety-five percent of all cases are sporadic and five percent are genetic, most often secondary to dyshormonogenesis [33]. Endemic cretinism, secondary to iodine deficiency in utero, still exists in some regions of the world. Fetal hypothyroidism may also be caused by the transplacental passage of goitrogens [2].

Newborn screening for congenital hypothyroidism is now mandatory in the United States because 33% of infants with the condition present with no abnormal symptoms or signs. The best time to collect blood between 3 and 6 days after birth to avoid the transient physiologic hyperthyroidism noted shortly after delivery.

Adult hypothyroidism

Adult-onset hypothyroidism may be insidious in onset and occur over the course of many years. Symptoms commonly associated with onset include fatigue, muscle cramps, weakness, inability to concentrate, and cold intolerance, which patients sometimes falsely attribute to aging [34].

The skin in hypothyroidism is a reflection of the resultant hypometabolic state and subsequent reduced core body temperature and reflex cutaneous vasoconstriction. The skin becomes cool, dry, and pale. Xerosis may present with severity mimicking acquired icthyosis. Xerosis in hypothyroidism has been reviewed, raising the speculation that topical thyroid hormone could be of potential use in treating xerosis, even in euthyroid patients [35]. Hypohidrosis, possibly accompanied by diminished epidermal sterol biosynthesis, may lead to acquired palmoplantar keratoderma. Skin pallor is the result of cutaneous vasoconstriction and increased deposition of water and mucopolysaccharides in the dermis, which alter the refraction of light. A yellowish hue may be imparted on the skin, particularly on the palms, soles, and nasolabial folds, as the result of carotenemia observed in hypothyroidism [2].

Hair changes may be dramatic and classically manifest as dry, coarse, brittle head and body hair with a tendency to fall out, resulting in diffuse, partial alopecia. Loss of hair from the lateral third of the eyebrow is a common finding. Patients with hypo-

thyroidism have an increased percentage of telogen hairs, which is reversed with normalization of thyroid hormone levels [36].

The most characteristic clinical sign of hypothyroidism is generalized myxedema, which occurs as a result of deposition of dermal acid mucopolysaccharides, particularly hyaluronic acid and chondroitin sulfate. Skin may appear swollen, dry, pale, waxy, and firm to the touch. Despite its edematous appearance, the skin is nonpitting. The face assumes a typical appearance with swollen lips, a broad nose, macroglossia, and puffy eyelids. Drooping of the eyelids may occur and is attributed to decreased sympathetic stimulation of the superior palpebral muscle. Entrapment syndromes such as carpal tunnel syndrome and facial nerve palsy have been reported [37]. Wound healing is impaired, and purpura may be noted as a result of diminished levels of clotting factors and/ or loss of vascular support secondary to dermal mucin [2].

Associated cutaneous and systemic diseases

Disorders of the thyroid, particularly autoimmune thyroid disease, have been associated with a number of different cutaneous and/or systemic diseases (Table 1). In some cases, the presence of a particular disease state warrants investigation for thyroid abnormalities (T4 and TSH) or carries an increased risk for development of autoimmune thyroid disease.

Table 1
Associated cutaneous and systemic diseases

- Alopecia areata
- Anemia
  - Pernicious anemia [40]
  - Pure red blood cell aplasia [41]
- Bullous disorders
  - Bullous pemphigoid [44,45]
  - Dermatitis herpetiformis [47]
  - Herpes gestationis [46]
  - Pemphigus foliaceus [42]
  - Pemphigus vulgaris [42]
- Connective tissue diseases
  - Dermatomyositis [49]
  - Discoid lupus erythematosus [51]
  - Scleroderma [53]
  - Sjögren's syndrome [54]
  - Systemic lupus erythematosus [52]
  - Polymyositis [50]
- Endocrinopathies
  - Acanthosis nigricans [58]
  - Chronic mucocutaneous candidiasis [57]
  - MEN 2a, 2b [15]
  - Schmidt syndrome [56]
- McCune-Albright syndrome [69]
- Pustulosis palmoplantaris [65,66]
- Sweet's syndrome [67]
- Urticaria [59–62]
- Vitiligo [63,64]
- Other
  - AIDS-Kaposi's sarcoma [74]
  - Cowden's syndrome [71]
  - Erythema annulare centrifugum [72]
  - Generalized granuloma annulare [73]
  - Melasma [75]
  - Multicentric reticulohistiocytosis [76]
- Pseudoxanthoma elasticum [77]
- Reticular erythematous mucinosis [78]

Alopecia areata

Thyroid function test abnormalities have been reported to occur in as many as 24% of children with alopecia areata [38]. Despite this seemingly high prevalence, most patients in this same study did not manifest clinically evident thyroid dysfunction. Another study of 143 children demonstrated an incidence of 20% of children with alopecia areata also with clinically evident thyroid disease, antithyroid antibodies, or raised T3 levels [39].

Anemia

Autoimmune thyroid disease has been reported in association with atrophic gastritis (and resultant pernicious anemia). Up to 10% of patients with hypothyroidism may demonstrate pernicious anemia [40]. Pure red blood cell aplasia with severe normochromic normocytic anemia and absent red blood cell precursors in otherwise normal bone marrow has been reported in association with numerous autoimmune disorders (systemic lupus erythematosus, thymoma, and multiple endocrine gland insufficiency). Three patients have been reported to manifest pure red blood cell aplasia with primary autoimmune hypothyroidism. All three patients also demonstrated concordant systemic lupus erythematosus (SLE) [41].

Bullous disorders

Autoimmune thyroid disease (specifically, Graves' disease) has been reported to occur simultaneously with pemphigus foliaceus and pemphigus vulgaris [42]. One report of a patient with Graves' disease and pemphigus vulgaris also demonstrated the presence of HLA-DR3 and -DR4, raising the question of genetic susceptibility [43]. Bullous pemphigoid has been observed in patients with Hashimoto's thyroiditis

and Graves' disease [44,45]. Herpes gestationis has been reported to occur with Graves' disease (with one patient also demonstrating alopecia totalis and ulcerative colitis) [46]. Dermatitis herpetiformis has been reported to have concomitant thyroid disease in as many as 52% of patients [47]. The atrophic variant of Hashimoto's thyroiditis has been associated specifically with dermatitis herpetiformis and with antigens HLA-B8 and HLA-DRw3 [48].

Connective tissue diseases

Autoimmune thyroiditis has been reported in association with dermatomyositis, polymyositis, discoid lupus erythematosus, systemic lupus erythematosus, scleroderma, and Sjögren's syndrome [49–54]. Genetic susceptibility and common immunopathogenesis have been explored in a number of cases, and histocompatibility antigens HLA-B8 and DR3 have been noted to appear with increased frequency in autoimmune thyroiditis and adult dermatomyositis, while HLA-DR3 has been noted to be associated with thyroiditis and SLE [55].

Endocrinopathies

Autoimmune thyroiditis has been noted as part of the Schmidt syndrome, which consists of idiopathic adrenal insufficiency, chronic lymphocytic thyroiditis, insulin-dependent diabetes mellitus, hypoparathyroidism, gonadal failure, pernicious anemia, mucocutaneous candidiasis, and sometimes thyrotoxicosis [56]. Chronic mucocutaneous candidiasis in association with hypothyroidism has been proposed as a distinct entity and possibly transmitted as an autosomal dominant trait. Unlike the polyglandular association with mucocutaneous candidiasis, where patients demonstrate high-titer antimicrosomal or antithyroglobulin thyroid antibodies, those with hypothyroidism alone did not demonstrate detectable autoantibodies, which raises the question regarding the presence of an unidentified, undetectable thyroid autoantigen [57].

Thyroid carcinoma may occur as part of an endocrine-related syndrome. Multiple endocrine neoplasia type 2a (MEN2a), a rare, autosomal dominant genetic syndrome, is comprised of hyperplasia or carcinoma of thyroid C cells (medullary carcinoma), adrenal medullary hyperplasia, pheochromocytoma, and parathyroid hyperplasia. Multiple endocrine neoplasia type 2b (MEN 2b) is comprised of medullary thyroid carcinoma, pheochromocytoma, mucosal and gastrointestinal ganglioneuromatosis, and marfanoid features.

Acanthosis nigricans (AN), a cutaneous manifestation of a number of systemic diseases including endocrine and malignant neoplasms, has been reported in association with hypothyroidism. The relationship has been examined, and it has been suggested that AN is not directly related to thyroid dysfunction, but rather to the resulting effects of hypothyroidism, including obesity and subsequent insulin resistance [58].

Urticaria

Since 1983, reports have surfaced regarding the association of thyroid autoimmunity with urticaria. A statistically significant increase in the incidence of urticaria, chronic urticaria, and angioedema when compared to similar control groups has been demonstrated in the literature on several occasions [59]. Urticarial vasculitis has been reported with thyroid autoimmunity [60]. The mechanism by which this association occurs is poorly understood. Thyroid hormone has been used to treat chronic urticaria and/or angioedema in patients with evidence of thyroid autoimmunity with significant success [61,62]. In patients with idiopathic chronic urticaria and/ or angioedema, it is warranted to screen for thyroid autoimmunity; if this is demonstrated and the patient is unresponsive to standard therapies, use of levothyroxine in hypothyroid or euthyroid patients should be considered [59].

Vitiligo

Vitiligo has been associated with autoimmune thyroid disease presenting as either hyperthyroidism or hypothyroidism, and with Addison's disease, pernicious anemia, diabetes mellitus, idiopathic heart block, uveitis, melanoma, and ovarian and testicular failure [63]. Kumar et al studied 22 clinically euthyroid patients with vitiligo and demonstrated a lower than normal radioactive iodine uptake (RAIU) in 90% of patients [64].

Other associations

Patients with pustulosis palmoplantaris have been demonstrated to have one or more signs of thyroid disease, such as a goiter or abnormal thyroid function tests in up to 53% of patients and the presence of antimicrosomal antibodies, antithyroglobulin antibodies, or both in 40% of patients [65,66].

Sweet's syndrome (acute febrile neutrophilic dermatosis) has been reported in association with thyroid disease. Nakamura et al reported the case of a patient in whom Graves' disease was diagnosed three years before the development of Sweet's syndrome [67].

Another case was described of the simultaneous onset of Sweet's syndrome and subacute thyroiditis with spontaneous resolution of the thyroiditis [68].

Thyroid disease represents the second most common endocrinopathy in association with McCune-Albright Syndrome (MAS), with reported cases of hyperthyroidism with and without goiter development, TSH-producing pituitary adenomas, and non-autoimmune hyperthyroidism [69]. MAS-associated thyroidopathies have been linked to G-protein mutations with resultant cAMP overproduction, growth of thyrocytes, and/or hormone hypersecretion [70].

Other associated findings/disease states reported in association with thyroid abnormalities include Cowden's syndrome (thyroid goiter, adenoma, and carcinoma); erythema annulare centrifugum (Graves' disease); generalized granuloma annulare (autoimmune thyroiditis); AIDS-Kaposi's sarcoma (thyroid nodules); melasma (increased rate of thyroid disorders); multicentric reticulohistiocytosis (thyromegaly); reticular erythematous mucinosis (hypo-and hyperthyroid states); and pseudoxanthoma elasticum (hypothyroidism and autoimmune thyroiditis) [71–78].

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DERMATOLOGIC CLINICS

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Cutaneous manifestations of diabetes mellitus

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Diabetes mellitus (DM), the most common endocrine disorder, affects an estimated 11 million in the United States. Ninety percent have type II, non–insulin-dependent (NIDDM), whereas 10% have insulin-dependent type I (IDDM) [1]. At least 30% of diabetics have some cutaneous involvement during the course of their disease [1]. Although the overall prevalence of cutaneous disorders does not seem to differ between type I and type II diabetes patients [2], type II patients do develop more frequent cutaneous infections, whereas type I patients develop more autoimmune-type cutaneous lesions [2,3]. Cutaneous manifestations generally appear subsequent to the development of the diabetes, but may be the first presenting sign or even precede the diagnosis by many years. The cutaneous findings can be classified into four major groups: (1) skin diseases associated with diabetes, such as necrobiosis lipoidica (NL), diabetic dermopathy, and diabetic bullae; (2) cutaneous infections; (3) cutaneous manifestations of diabetic complications, such as neuropathic foot ulcers; and (4) skin reactions to diabetic treatment. This article outlines the major skin findings in DM and summarizes recent studies and reports.

Cutaneous conditions associated with DM

Necrobiosis lipoidica

Necrobiosis lipoidica (NL) appears in 0.3% to 1.6% of diabetics [2]. Only 11% to 65% of patients with NL have DM at the time of cutaneous diagnosis [4,5]. Of those without diabetes, approximately 90% eventually develop diabetes, have abnormal glucose tolerance, or report one or both parents with diabetes [2]. Consequently, nondiabetic patients with NL should be evaluated and followed for development of diabetes. The general consensus is that diabetic control has no effect on the course of NL. Cohen et al [6], however, believe that the pathogenesis of NL differs in diabetics versus nondiabetic patients and tighter glucose control could reduce the incidence of NL in diabetics.

Necrobiosis lipoidica is three times more common in women. IDDM patients develop NL considerably earlier at a mean age of 22 years, whereas NL appears in NIDDM and nondiabetic patients at a mean age of 49 years [7].

Initially, an erythematous, slowly enlarging irregular plaque with an elevated border, NL becomes more brownish yellow, telangiectatic, porcelain-like, and depressed. NL may present as single or multiple plaques that often coalesce. Classically, NL occurs bilaterally on the pretibial or medial malleolar areas [7]. NL involving the hands, forearms, abdomen, face, and scalp is less consistently associated with diabetes [8,9]. Although not painful and often insensate to pinprick and fine touch, NL may ulcerate spontaneously or from trauma, resulting in pain, especially if secondarily infected [10]. Spontaneous gradual resolution is noted in 13% to 19% after 6 to 12 years, but residual atrophic scarring persists [1,8].

Etiologically, NL may be associated with microangiopathic changes consisting of thickened basement membranes and capillary walls, particularly in pretibial lesions. These changes are less common in NL sites elsewhere on the body, however, indicating that microangiopathy may not be necessary for development of lesions [8]. If microangiopathy is responsible for NL, other microvascular complications, such as retinopathy and nephropathy, should correlate with NL. A few studies have supported these associations.

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One noted such a direct correlation in adolescents with NL and IDDM [11]. Other proposed causative factors include obliterative endarteritis, immune-mediated vasculitis, other immune factors, delayed hypersensitivity, nonenzymatic glycosylation and other defects in collagen, trauma, platelet aggregation, defective mobility of neutrophils, and vascular insufficiency [7].

Histologically, the dermis shows degenerated collagen surrounded by a horizontal palisade of histiocytes with minimal mucin and interspersed lymphocytes, plasma cells, and foreign body giant cells. Treatment includes potent topical steroids with or without occlusion, intralesional steroids at the active border, or rarely systemic steroids. Topical psoralen plus ultraviolet A (PUVA), cyclosporine, high-dose nicotinamide, clofazimine, pentoxifylline, aspirin, and dipyridamole have been tried with varying success [12–15]. Attempts at local excision and grafting are usually complicated by recurrences at the borders [16]. Based on the collagen destruction in NL, topical retinoids have been used to enhance collagen formation [12]. Laser treatment of the telangiectases may improve the appearance and reduce trauma-related bleeding [17]. Benzoyl peroxides have been reported to be useful in ulcerated lesions [8].

Granuloma annulare

The association of localized granuloma annulare (GA) with diabetes has not been clearly established. Four patients with nodular GA and DM were reported from one facility [18]. Several studies, which used glucose or prednisone-glucose tolerance provocative testing for diabetes, support the view that generalized GA, especially in older patients, is associated with diabetes [19]. Other studies have not been confirmatory. Despite the controversy, it is reasonable to screen all patients who present with generalized GA for abnormal glucose tolerance.

No universally accepted theory explains the cause of the usually asymptomatic, occasionally pruritic lesions of generalized GA [2,20]. Histologic features include focal degeneration of collagen in the upper and mid-dermis, palisaded histiocytes around collagen bundles, and abundant dermal mucin.

Although localized GA frequently resolves spontaneously without scarring, the generalized variant has a more protracted course with rare spontaneous resolution. Sporadic therapeutic success has been reported with topical, systemic, and intralesional steroids; isotretinoin; chlorambucil; freezing; chloroquine; potassium iodide; niacinamide; chlorpropamide; dapsone; antimalarials; and PUVA [7,20].

Diabetic dermopathy

Affecting 7% to 70% of diabetics, predominantly men over the age of 50, diabetic dermopathy, also known as *shin spots* and *pigmented pretibial papules*, is considered the most common cutaneous manifestation of DM [8,21,22]. Diabetic dermopathy, however, is not pathognomonic of diabetes because 20% of nondiabetics show similar lesions. Although a correlation with higher hemoglobin A_{1c} values has been noted in one study, most believe diabetic dermopathy is not related to blood glucose control [2]. Similar to NL, shin spots may precede abnormal glucose metabolism [19].

Shin spots appear as multiple, bilateral, asymmetric, annular, or irregular red papules or plaques on the extensor surface of the lower legs with gradual evolution into atrophic hyperpigmented finely scaled macules. Lesions may also be observed on the forearms, thighs, and the lateral malleoli [10]. Older lesions may persist or disappear while new lesions appear.

Histologically, the epidermis is thin with thickened vessels in the papillary dermis, showing increased periodic acid–Schiff–positive (PAS) diastase-resistant material. There is often a mild perivascular lymphohistiocytic infiltrate with scattered hemosiderin deposits associated with hemorrhage. Unlike NL, the collagen change is much less marked and necrobiosis is absent [16].

The genesis of shin spots is unclear. The frequency of changes over bony prominences suggests that trauma may be a modifying factor, especially in diabetics with neuropathy. Blunt trauma did not elicit lesions in one study but another investigator induced lesions with heat and cold injury [23,24]. Evidence also exists for and against the role of microangiopathy. The thick-walled capillaries are present in lesions and in adjacent noninvolved skin. Several investigators have reported a correlation of microangiopathic changes of diabetic dermopathy with the presence of retinopathy, neuropathy, and nephropathy, whereas others have been unable to substantiate these findings [21,22,24–26]. Capillary changes may predispose to, but are not likely to be the sole cause of shin spots.

The differential diagnosis includes NL, stasis dermatitis, pigmented purpuric eruption, or posttraumatic scarring. No treatment is effective for these generally asymptomatic, nonulcerated lesions [27,28].

Diabetic bullae

Approximately 0.5% of diabetics develop diabetic bullae or bullosis diabeticorum, a clinically distinct

diabetic marker [2]. These bullae have only been reported in adults (40 to 77 years old), more commonly in men, with long-standing diabetes and neuropathy [2,29]. There have been a few reports of diabetic bullae leading to the diagnosis of DM [30,31]. These painless bullae on a noninflamed base suddenly appear most commonly on the dorsa and sides of the lower legs and feet, sometimes in association with similar lesions on the hands and forearms or on the hands alone. Ranging in size from a few millimeters to several centimeters the bullae contain clear, sterile fluid.

Two different types of bullae have been described: the more frequent nonscarring lesions with a histologic intraepidermal split without acantholysis [32,33]; and the occasionally hemorrhagic bullae that heal with scarring, slight atrophy, and have a histologic subepidermal split [34]. Histologic differences may be explained by different pathogeneses or by biopsies taken at different stages of development [7].

Although the pathogenesis of these blisters is not well understood, some evidence supports trauma with a reduced threshold to suction blister-induced formation in type 1 diabetics [35]. Multiple bullae at widely separated sites, however, argue against trauma as a pathogenic factor [7]. Other suggested causes include immunologic factors; disturbed metabolism of calcium, magnesium, or carbohydrates; microangiopathy; vascular insufficiency; or ultraviolet light in conjunction with nephropathy [13,16,29,30,36,37].

The differential diagnosis includes bullous pemphigoid, epidermolysis bullosa acquisita, porphyria cutanea tarda, bullous impetigo, erythema multiforme, and coma blisters. Bullosis diabeticorum remains a diagnosis of exclusion with negative immunofluorescent studies, porphyrin levels, and cultures.

The bullae heal spontaneously in 2 to 5 weeks but may recur in the same or new anatomic locations [38]. If large and symptomatic, the bullae can be aspirated with an intact blister roof providing a physiologic wound covering.

Acanthosis nigricans

Acanthosis nigricans (AN) presents clinically as hyperpigmented velvety plaques in body folds, mostly the axillae and neck [4]. Other locations include the groin, umbilicus, areolae, submammary regions, and hands (tripe hands) [2].

Acanthosis nigricans is seen in situations of insulin resistance, including type II DM, obesity, and total lipodystrophy. In these cases the pathogenesis may be related to insulin binding insulin-like growth factor receptors on keratinocytes and dermal fibroblasts, stimulating growth [39]. In a study of 223 patients with AN, nearly 50% of patients in their fifth decade had NIDDM, whereas only 4 of the 99 patients under age 20 had documented NIDDM. Impaired glucose tolerance without a diagnosis of DM, however, was present in a larger proportion of the younger patients [4]. Because AN can also be seen as a complication of carcinoma (particularly of the stomach), secondary to medications, such as nicotinic acid or corticosteroids, and in various other endocrinopathies, work-up becomes necessary in the diabetic patient to rule out other underlying disorders [16].

Histopathologically, the lesions reveal papillomatosis, hyperkeratosis, and mild acanthosis. The dark color is related to the thickness of the keratin-containing superficial epithelium, not to any change in melanocyte number or melanin content [4].

Although generally asymptomatic, retinoic acid and salicylic acid may be effective for cosmetic improvement [8]. Weight control is clearly of benefit. Clinical improvement with dietary fish oil supplementation has been reported [40].

Acquired perforating dermatosis

The cutaneous perforating disorders, characterized by the transepidermal elimination of some component of the dermis, have classically been divided into four types: (1) elastosis perforans serpiginosa, (2) reactive perforating collagenosis, (3) Kyrle's disease, and (4) perforating folliculitis. All four of these major perforating disorders have been reported in patients with chronic renal failure, diabetes, or both. In 1989, Rapini et al [41] helped to clarify the issue of perforating disorders in patients with systemic disease, such as chronic renal failure or DM, by proposing the term *acquired perforating dermatosis*. Acquired perforating dermatosis consists of pruritic, 2- to 10-mm, hyperkeratotic, dome-shaped, often umbilicated papules and nodules usually on the extensor limbs, trunk, dorsal hands, and less so the face [19]. A linear configuration suggests koebnerization. Histologically, transepidermal channels filled with keratin, pyknotic nuclear debris, inflammatory cells, elastin, and collagen traverse an acanthotic epidermis. With maturity, elastin disappears and collagen acquires a more basophilic staining in a cup-shaped plug [42]. Elements of both elastic material and collagen may represent different stages or different types of lesions of a single pathologic process.

Although acquired perforating dermatosis is often associated with hemodialysis, some cases have occurred before initiation of dialysis [43]. The dermal theory of pathogenesis proposes that the metabolic derangements associated with chronic renal failure

and diabetes induce superficial dermal connective tissue changes and trigger transepidermal elimination. Because ultrastructurally the eliminated collagen fibers show normal periodicity, the collagen might be biochemically but not morphologically altered [42,44]. Another theory proposes that the primary defect resides in the epidermis. Pruritus caused by uremia or diabetes may result in epidermal injury secondary to scratching, whereas the altered blood supply of diabetic vasculopathy results in localized dermal necrosis and extrusion of dead tissue through the epidermis [42,44]. Lesions can often be reproduced by superficial scratching and tend to be distributed on trauma-prone areas [44,45]. One study of eight diabetics reported thickened (PAS) positive vessel walls in the surrounding dermis suggesting an etiologic role of microangiopathy [44].

These lesions are chronic but may heal after months if scratching and trauma are avoided. Reported treatments include topical keratolytics, topical and systemic retinoids, PUVA, UVB, topical and intralesional steroids, oral antihistamines, and cryotherapy [42,44,46]. Dialysis does not have therapeutic value. Renal transplantation has resulted in clearance of the dermatosis [43].

Lichen planus

Numerous reports have studied the association of diabetes and lichen planus, especially oral lichen planus. The prevalence of decreased glucose tolerance in patients with oral lichen planus varies widely between 1.6% and 85% [47,48,99]. In two of these studies, the prevalence of diabetes in patients with oral lichen planus did not differ from that of diabetes in the general population [47,49]. This wide variation may be explained by the different methods and criteria used. Some studies diagnose DM at lower values than those recommended by the World Health Organization [50]. Also, 12% to 14% of the general population has abnormal glucose tolerance tests [51]. Lundstrom [51] did not support the observation that erosive lichen planus occurs in a higher percentage of diabetics with oral lichen planus than in nondiabetics [52,53]. One report found a higher frequency of lichen planus on the tongue in diabetics [52].

Fewer studies have examined the frequency of lichen planus in known diabetics. Although most reports do not differentiate the types of diabetes, the reported rates vary from 0.55% to 5.76% of diabetics having clinical and less often histologic evidence of oral lichen planus. Petrou-Amerikanou et al [50] reported a prevalence of oral lichen planus in type I diabetics of 5.76%, significantly higher than the control population. The difference in prevalence between type II diabetics and controls did not meet statistical significance. Some authors argue that what seems clinically to be oral lichen planus may actually be lichenoid reactions to drugs, such as nonsteroidal anti-inflammatory drugs, antihypertensives, and oral hypoglycemic agents [54]. Withdrawal and rechallenge of these medications in those affected have not been studied. Two studies, however, did not find a statistical association between oral lichen planus and medications known to cause lichenoid mucosal reactions [50,55].

Diabetic thick skin

Three forms of diabetic thick skin have been identified. First, diabetics in general have an asymptomatic, often unnoticed, but measurable increase in skin thickness. Second, the diabetic hand syndrome (syndrome of limited joint mobility, cheiroarthropathy, waxy skin and stiff joints, scleroderma-like syndrome, and diabetic sclerodactyly) consists of scleroderma-like skin changes in the fingers with limited joint mobility. Third, diabetic scleredema is distinct from the self-resolving scleredema adultorum of Buschke seen in children after a streptococcal infection. The abnormality in diabetic thick skin consists of abnormal collagen, which may be caused by hyperglycemic accelerated nonenzymatic glycosylation. These glycosylation end products lead to increased cross-linking rendering the collagen fibers resistant to degradation by collagenase, which in turn leads to excessive accumulation of abnormal collagen [56]. Other theories abound: insulin acting as a growth factor can cause overproduction of collagen [57]; decreased local oxygen pressure secondary to microangiopathy may increase collagen and glycosaminoglycan synthesis by fibroblasts [58]; and polyol accumulation caused collagen hydration [9].

Quantitative estimations of skin thickness have been determined by microscopic measurement, caliper measurement, ultrasonography, and radiologic investigation [9]. Normally, skin thickness varies based on body site, age, and sex. Typically, the skin thickens until adulthood then decreases in thickness after age 20. Several groups have found an increase in skin thickness of the forearm in insulin-dependent diabetics in comparison with age and sex-matched nondiabetic controls [59,60].

Originally described in insulin-dependent adolescent diabetics, the diabetic hand syndrome has been subsequently reported in non–insulin-dependent diabetic patients. With an 8% to 50% prevalence variation [56] the syndrome begins with stiffness of the

metacarpophalangeal and proximal interphalangeal joints, generally the fifth digit, and then progresses to the other fingers [7]. The limitation of movement initially involves active and later passive extension. Flexion limitations may occur in the end stage. Limited joint mobility can be demonstrated by inability to flatten the hand on a tabletop and by failure of palmar approximation (the prayer sign). Although the joints are not directly involved, the abnormal stiffening of the collagen in the periarticular tissue [7] leads to joint limitations in one third to one half of patients. The thickening of the skin can also be manifested by pebbling of the fingers (Huntley's papules or finger pebbles), which are multiple grouped minute papules on the extensor surfaces of the fingers, on or near the knuckles or periungual areas [61]. Palmar fascia thickening (Dupuytren's contracture) further complicates the diabetic hand syndrome [16,62].

Most authors have been unable to find a correlation between the development of the diabetic hand syndrome and long-term glycemic control [21,56, 63,64]. Studies vary in support of the relationship between the diabetic hand syndrome and the duration of diabetes [21,56,62]. The literature suggests that this disorder is a marker for other diabetes-related microvascular complications, such as retinopathy, neuropathy, and nephropathy [9,56,62,63,65].

Diabetic scleredema is characterized by diffuse nonpitting induration of the skin with loss of skin markings over the upper back, neck, and shoulders with occasional extension to the face, arms, chest, and abdomen [8]. Although usually asymptomatic, neck discomfort and back pain may accompany severe cases of this chronic disorder, most common in poorly controlled non–insulin-dependent diabetic obese men. Although diabetic scleredema occurs in 2.5% to 14% of diabetics [66,67], 94% of adult patients with scleredema have diabetes [10]. Histologic findings include markedly thickened dermis, increased numbers of mast cells, fenestration of collagen, accumulation of hyaluronic acid, and the absence of edema and sclerosis. Potent topical and intralesional steroids, strict glucose control with an insulin infusion pump, penicillamine, intralesional insulin, bath-PUVA, low-dose methotrexate, prostaglandin E_1, and pentoxifylline provided limited therapeutic success [58,68,69].

Xanthoma

Eruptive xanthomas present as sudden crops of small, discrete, yellow, erythematous-based papules over the buttocks, elbows, and knees [2]. Often presenting as a Koebner phenomenon, the lesions may be pruritic or tender [7]. Multiple xanthomas may coalesce and form tuberous xanthomas [28]. Eruptive xanthomas appear in association with elevated levels of triglyceride-rich lipoproteins, including chylomicrons and very low-density lipoprotein. The lipid changes appear in association with familial hypertriglyceridemia or insulin deficiency with uncontrolled IDDM resulting in lack of adequate lipoprotein lipase activity and impaired clearance of chylomicrons and very low-density lipoprotein [19]. Polyphagia in uncontrolled diabetes accelerates formation of very low-density lipoprotein and chylomicrons [37]. Histologically, foamy, lipid-laden histiocytes with a mixed lymphocytic and neutrophilic infiltrate accumulate in the dermis [70]. Control of the diabetes or underlying hyperlipidemia leads to xanthoma resolution.

Rubeosis facei

Although difficult to quantify, flushed face or rubeosis facei has been reported in 3% to 59% of diabetics [2]. Blond and red-haired persons appear more erythematous because of reduced cutaneous melanin to obscure the erythema. The red color may be caused by microangiopathy, increased solar sensitivity, or dehydration [27]. Tighter glucose control might improve the appearance [2].

Yellow skin

In carotenemia, the yellow pigment concentrates in areas of prominent sebaceous activity and in areas with a thick stratum corneum, such as the palms, soles, and face. Unlike jaundice the sclerae are not discolored [28]. Earlier studies reported carotenemia in more than half of diabetics and yellow skin in 10% of this population. The reports may have been due to of a diabetic diet high in yellow fruits, vegetables, and butter; impaired conversion of carotene to vitamin A in the diabetic liver; or hyperlipidemia accompanying diabetes [16,37]. A recent study has found normal carotene levels in diabetic patients with yellow skin [19]. Perhaps the carotene may have disproportionate accumulation in the skin despite normal blood levels or the skin color may not be caused by carotene but by dermal collagen glycosylation with yellow end-stage glycosylation products [9].

Other

Vitiligo, Werner's syndrome, pseudoxanthoma elasticum, lipoid proteinosis, Kaposi's sarcoma

[19], pigmented purpuric dermatosis, clear cell syringoma [1], and dermatitis herpetiformis [16] may be associated with diabetes. Various disease processes with cutaneous manifestations may involve secondary diabetes including hemochromatosis; hepatic porphyrias, especially porphyria cutanea tarda; and lipodystrophies, such as Lawrence-Seip syndrome and partial lipoatrophy.

Cutaneous infections associated with diabetes mellitus

Skin infections occur in 20% to 50% of poorly controlled diabetics, most commonly type II diabetics [2,3]. Poor diabetic control might be the cause or the consequence of the concurrent infection. The infectious disorders can be of fungal or less commonly bacterial origin [3] and may be related to abnormal microcirculation, hypohidrosis, peripheral vascular disease, diabetic neuropathy, decreased phagocytosis and killing activity, impaired leukocyte adherence, and delayed chemotaxis seen in diabetics [7,8,13].

Bacterial infections

Pyodermic infections, such as impetigo, folliculitis, furunculosis, carbuncles, ecthyma, and erysipelas, can be more severe and widespread in diabetic patients. Leg ulcer infection can rapidly progress to gangrene and amputation.

Fatal in over 50% of patients [19], malignant otitis externa caused by *Pseudomonas aeruginosa,* especially in elderly diabetic men, can progress to chondritis, osteomyelitis, and bacterial meningitis. Green fluorescence on Wood's lamp examination identifies *Pseudomonas* toe web infection clinically similar to dermatophytosis [9].

Erythrasma, caused by gram-positive *Corynebacterium minutissimum*, identified with Wood's light coral fluorescence, presents as reddish tan scaling patches of the upper inner thighs, axillae, toe web spaces, and submammary creases in obese patients. Extensive erythrasma occurs with increased frequency in diabetes [1,19].

Fungal infections

Little controversy exists about the increased frequency and severity of *Candida* infections in poorly controlled diabetics. A classic cutaneous complication in childhood diabetics and occasionally in diabetic adults, presenting as white, curdlike material adherent to an erythematous, fissured oral commissure, angular stomatitis may be caused by increased concentrations of salivary glucose [9].

Frequently recurrent, candidal paronychia presents as painful nail fold erythema, swelling, and separation from the nail margin with subsequent nail dystrophy. Pseudohyphae and spores on potassium hydroxide preparation support a candidal diagnosis. Purulent drainage may indicate secondary bacterial involvement. Treatment involves drainage of abscess, control of the blood sugar, keeping the digits dry, and topical antifungal solutions. Less common than paronychia, occlusion and retention of moisture lead to interdigital infections most commonly between the third and fourth fingers (erosio interdigitale blastomycetica) or between the fourth and fifth toes.

In women, Candida commonly infects the inframammary area and the genitalia with severe pruritus vulvae. Genital infections in elderly uncircumcised men with diabetes include balanitis and phimosis.

Authors sustain [71–73] and negate [74–76] the correlation between the prevalence of dermatophytosis and blood levels of glucose. Because maceration and skin breaks can serve as portals of entry for bacteria leading to cellulitis and potentially serious limb-threatening infections, tinea pedis should be aggressively managed in diabetics.

Cutaneous manifestations of diabetic complications

Diabetic foot

Foot ulcerations account for significant morbidity and mortality in the diabetic population and are responsible for 70% of annual US lower limb amputations. The economic impact of medical and surgical therapy, rehabilitation, loss of work, and mortality is staggering [77–79]. An understanding of the pathophysiology of diabetic foot complications results in appropriate therapy, healing, and the avoidance of many amputations. Adequate blood supply should preclude amputation. Proper evaluation of diabetic feet identifies peripheral neuropathy (60% to 70%), peripheral ischemic vascular disease (15% to 20%), and combined clinically significant neuropathy and vascular disease (15% to 20%) as the cause of ulcerations [80,81]. If a surgical revascularization procedure can correct the ischemic state, adherence to principles of wound therapy effect healing. In a setting of diminished or absent sensation, foot deformity, and adequate blood supply, neuropathic ulcers usually heal within weeks if treated with aggressive debridement [82] and offloading with

various devices, or most effectively with a total contact cast [83,84]. Any use of topical growth factors or bioengineered skin grafts cannot replace a needed revascularization procedure, debridement, and ulcer offloading [85,86]. Because of the prevalence of bacterial colonization of foot ulcerations, the need for antibiotic therapy rests on clinical evaluation and judgment [70]. Osteomyelitis can often be cured surgically with rongeur and excision of infected small foot bones [87,88]. Prevention of foot complications remains paramount through daily foot inspection; foot care guidelines; and prevention of pressure, friction, and callus formation with appropriate footwear [89–91].

Diabetic gustatory sweating

In response to eating certain foods, long-standing diabetics with neuropathy and nephropathy experience gustatory sweating in areas supplied by the superior cervical ganglion on the face and neck. This may be caused by axonal degeneration and aberrant sprouting of nerve fibers [92]. Gustatory sweating may resolve postrenal transplant suggesting an etiologic role of nephropathy. Effective treatment consists of oral anticholinergics, clonidine, and topical glycopyrrolate [92].

Cutaneous reactions to diabetic treatment

Insulin

Insulin allergy may be local or systemic and usually occurs within the first month of insulin therapy. Erythematous or urticarial pruritic nodules at the site of the injection, may appear immediately, within 15 minutes to 2 hours of injection, or delayed with onset 4 or more hours after injection [19]. Allergic reactions may be caused by impurities in the insulin preparation; to beef or pork proteins; to the insulin molecule itself; to additional polypeptides (proinsulin); to preservatives (parabens); or to additives (zinc) [19,93]. A local reaction has also been reported in a patient allergic to latex caused by small amounts of latex rubber antigens in the insulin injection materials (insulin vial and syringe) [94]. The highly purified or recombinant insulins have reduced allergy prevalence to 0.1% to 0.2% [2]. Treatment may be unnecessary because of spontaneous resolution. The patient's technique should be observed to ensure that the injection is not intradermal. Substitution of a more purified insulin is the treatment of choice. Systemic allergic reactions to insulin manifested as generalized urticaria and rarely anaphylaxis may necessitate discontinuation of insulin for other forms of therapy or may require desensitization.

Lipoatrophy and lipohypertrophy (lipodystrophy) can coexist in the same patient. Lipoatrophy presenting as circumscribed depressed areas of skin at the insulin injection site 6 to 24 months after starting insulin and occasionally at distant sites [8,16] seems to occur more in children and women in areas of substantial fat deposits, such as the thighs [16]. The cause may be related to lipolytic components of the insulin preparation or an immune complex–mediated inflammatory process with release of lysosomal enzymes [1]. Other theories include cryotrauma from refrigerated insulin; mechanical trauma caused by angle of injection; contamination with surface alcohol [95]; and local hyperproduction of tumor necrosis factor-α from macrophages induced by injected insulin [96]. Because duration of injected insulin deposition may also be a complicating factor, Murao et al [96] suggest substituting rapidly acting insulin to avoid lipoatrophy. Spontaneous improvement after rotating injection sites is rare but has been reported. Use of purified and recombinant human insulin has resulted in decreased lipoatrophy [8]. Lipohypertrophy presenting as soft dermal nodules, clinically resembling lipomas, at the site of frequent injections may be a response to the lipogenic action of insulin [2]. Chronically injected sites become hypoesthetic; however, absorption from these areas is very erratic [10]. Lipohypertrophy can be treated and prevented by injection site rotation. Other local cutaneous complications of insulin injection include keloids, hyperkeratotic papules, purpura, and localized pigmentation [27].

Oral hypoglycemic agents

Most cutaneous reactions to oral antidiabetic medications have been reported with the first-generation sulfonylureas, such as chlorpropamide and tolbutamide. One percent to 5% of patients taking sulfonylureas develop cutaneous reactions [2] within the first 2 months of treatment, most commonly maculopapular eruptions that often disappear despite continuation of the drug [2]. Other reported cutaneous reactions include generalized erythema, urticaria, photosensitivity, lichenoid eruptions, erythema multiforme, exfoliative dermatitis, and erythema nodosum [97]. In 10% to 30% chlorpropamide may cause a disulfiram-like reaction consisting of marked flushing, headache, tachycardia, and shortness of breath beginning 15 minutes after alcohol consumption and gradually resolving over the following hour [16].

This reaction pattern seems to be inherited in an autosomal-dominant pattern [1]. With increasing use, second-generation sulfonylureas, such as glyburide, glipizide, and glimepiride, have also been reported in association with cutaneous reactions. The most frequent reactions associated with glyburide include erythema, exanthems, photosensitivity, pruritus, and urticaria [97]. Similar reactions have also been reported with metformin. Reports of cutaneous reactions are still limited with the newer classes of antidiabetics including acarbose and rosiglitazone [97]. One case of erythema multiforme caused by acarbose has been reported [98].

Summary

Diabetes is a common disease with many cutaneous manifestations encountered by dermatologists. Diabetes and the skin may be linked by association (eg, necrobiosis lipoidica); infection; diabetic complication (eg, neuropathic ulcer); or treatment reaction. Review of recent studies and reports focuses on pathogenesis and treatment of these many diabetic cutaneous changes.

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Diffuse cutaneous mucinoses

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Cutaneous mucinoses are a heterogenous group of disorders so named because of the variable amount of mucin deposition in the dermis. Mucin, an acid mucopolysaccharide produced by fibroblasts, is composed of hyaluronic acid bound to heparin and chondroitin sulphate [1]. All of these diseases are marked by variable amounts of mucin deposition, some accompanied by fibroblast proliferation. Cutaneous mucinoses are classified as focal, follicular, or diffuse:

- Focal
  - Cutaneous mucinosis of infancy
  - Cutaneous focal mucinosis
  - Myxoid cyst
  - Self-healing juvenile cutaneous mucinosis
  - Papular mucinosis (lichen myxedematosus)
  - Acral persistent papular mucinosis
  - Papular and nodular mucinoses of lupus erythematosus
- Follicular
  - Follicular mucinosis
- Diffuse
  - Scleredema
  - Scleromyxedema
  - Reticular erythematosus mucinoses
  - Generalized myxedema
  - Pretibial myxedema

These disorders differ from local mucinoses by greater cutaneous involvement, systemic-organ dysfunction from mucin deposition, and associated extracutaneous disease not related to mucin deposition. This article reviews the diffuse cutaneous mucinoses.

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Scleredema

Clinical manifestations

Scleredema is marked by mucin deposition leading to chronic diffuse induration of the subcutaneous tissue. The skin has a wood-like, nonpitting hardening and only the epidermis may be wrinkled by pinching on palpation (Fig. 1) [2]. The disease usually arises abruptly over a period of weeks, symmetrically involving the neck, face, upper trunk, arms, and occasionally lower trunk and proximal thighs [3,4]. The affected areas are erythematous, indurated but painless, and nonpruritic, and patients usually present with a complaint of firmness of the skin or restricted range of motion of the head and neck.

The first subgroup of scleredema occurs days to months after a viral or bacterial infection [2,5]. Patients may exhibit nonspecific findings, such as myalgias, malaise, and arthralgias, between the antecedent infection and the onset of skin thickening, but most are asymptomatic. This group accounts for most pediatric patients, and has a 2:1 female preponderance [2].

The second definitive subgroup of scleredema is that associated with monoclonal gammopathy. Several cases of scleredema have been reported with monoclonal gammopathy, multiple myeloma, and other diseases on the continuum of plasma cell dyscrasia, such as smoldering myeloma and Waldenström's macroglobulinemia [6–8]. In most cases the associated paraprotein is IgG kappa [6,8–10]. Daoud et al [10] outlined several dermatologic disorders associated with monoclonal gammopathy (multiple myeloma or monoclonal gammopathy of undetermined significance), and categorize diseases into four groups: group I—diseases that are a consequence of the monoclonal gammopathy, such as heavy chain

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disease and amyloidosis; group II—cutaneous diseases that have a high association (> 50%) with paraproteinemia (scleredema and scleromyxedema fall into this category); group III—anecdotal reports associating diseases with paraproteinemias; and group IV—symptoms and complications related but not specific to monoclonal gammopathy, such as purpura and pruritus. The etiologic relationship of monoclonal gammopathy and skin disease is unknown [3]. Because of the strong association of scleredema with monoclonal gammopathy, it is recommended that all patients with scleredema have a serum protein electrophoresis performed to exclude coexisting monoclonal gammopathy, particularly multiple myeloma. Monoclonal gammopathy of undetermined significance is considered a premalignant condition and a risk factor for multiple myeloma. Studies have shown that up to 29% of the patients with a monoclonal gammopathy of undetermined significance may progress to multiple myeloma [11]. Patients who are found to have monoclonal gammopathy of undetermined significance, a monoclonal gammopathy not meeting the criteria for multiple myeloma, should be followed on a routine basis to watch for the progression of their disease.

The third subgroup of scleredema occurs in association with long-standing diabetes mellitus. Patients who are obese, more than 40 years old, male, and have severe vascular complications of their diabetes are more likely to be affected [12]. This form of the disease is chronic but not progressive, with variable systemic involvement.

Systemic scleredema is much less common [13]. Multiple systemic findings in patients with scleredema have included electrocardiographic abnormalities; pleural, pericardial, and peritoneal effusions; hepatomegaly; and parotid gland, tongue, and eye involvement [14]. Further reported systemic manifestations include the bone marrow, peripheral nerves, salivary glands, and skeletal and cardiac muscle [4,9]. Cardiac involvement can be severe and cause tachycardias; diastolic murmurs; prolonged QT intervals, ST segment, and T-wave changes; and even heart failure [2]. These changes are presumably caused by end-organ mucin deposition because they resolve with resolution of skin findings [2].

Histology

In scleredema, the epidermis is unaffected, whereas the dermis is thickened and displays hallmark swelling and separation of collagen bundles, with variable amounts of mucin deposited between bundles [3,4]. There is no increase in fibroblastic proliferation within the collagen hyperplasia [3,4]. Additionally, whereas transient erythema or hyperemia [3,4] and generalized hyperpigmentation have been reported, [15] there has not yet been demonstrated involvement of inflammatory cells or melanocytes [15–17].

Etiology

The etiology for the cutaneous mucinoses is not well established. This holds true for scleredema, in which the cause is unknown. Several researches have concluded that a biosynthetically activated phenotype of fibroblast was likely involved in the cutaneous changes seen with scleredema [3,17,18]. Overall, because paraproteinemia may or may not be present at the initial assessment of scleredema, it has been concluded that the paraproteinemia does not initiate the dermal changes found with the disease, but reflects chronic immunostimulation that may be a factor in the development of such skin pathology [2,19].

Treatment and prognosis

Numerous treatments have been evaluated for scleredema including systemic corticosteroids, nonsteroidal immunosuppressants, antibiotics, thyroid hormones, pituitary extract, antifibrotics, physiotherapy, and hyaluronidase [2,16,20]. Unfortunately, these therapies have met little success, are anecdotal, and are not confirmed by controlled randomized clinical trials. Treatment is usually limited to management of disease complications, including antibiotics for precedent infections, particularly those caused by β-hemolytic streptococcal organisms; physical or occupational therapy to limit development of contractures; maintenance of adequate nutrition; and cardiology referral for those with cardiac manifestations [2]. A review of the literature noted new potential treatments to include cyclosporine, electron-beam therapy, extracorporeal photophoresis, and psoralen plus ultraviolet A (PUVA) [16,21–23].

The prognosis of scleredema depends largely on the associated disease. Scleredema associated with infection has the most benign disease course, with spontaneous resolution occurring in most patients within 6 months to 2 years [2]. Cases associated with diabetes have a poorer prognosis, but this is directly related to glucose control and vascular complications of diabetes mellitus. Morbidity and mortality in this group are correlated more with the extent of other factors, such as obesity, cardiac events, and renal insufficiency [4]. Cases associated with a monoclonal

gammopathy tend to have a chronic and sometimes progressive course. If multiple myeloma develops in these patients, however, their course is shifted to parallel that of this malignancy with usually poor outcome. The median survival for patients with multiple myeloma is 3 years [24].

Scleromyxedema

Clinical manifestations

Scleromyxedema, also known as *generalized lichen myxedematosus*, should not be confused with localized lichen myxedematosus or papular mucinosis. It is characterized by marked mucin deposition, similar to scleredema, but also by significant fibroblast proliferation [25,26]. Rongioletti and Rebora [27] divided lichen myxedematosus into two clinical subsets: generalized (scleromyxedema) and localized (papular mucinosis). Scleromyxedema includes the following: (1) generalized papular and sclerodermoid eruption; (2) mucin deposition, fibrosis, and fibroblast proliferation; (3) monoclonal gammopathy; and (4) absence of thyroid disease. Papular mucinosis is defined as a papular, nodular, or confluent plaque-like eruption with mucin deposition with variable fibroblast proliferation, and the absence of both monoclonal gammopathy and thyroid disease [27].

Scleromyxedema usually affects middle-aged adults without sex predilection as a widespread eruption of small waxy and firm papules, closely spaced and often arranged in a linear fashion (Fig. 2) [27]. The 2- to 3-mm papules occur most commonly on the face, neck, distal forearms, hands with sparing of the palms, the scalp, and mucous membranes [26,27]. Nearby skin may be shiny like that seen with scleroderma, but telangiectasias and calcinosis are absent [27]. The affected areas may exhibit erythema, edema, and brownish discoloration, and often there is an associated sparseness of eyebrow, pubic, and axillary hair [26]. Like scleredema, affected areas are usually not pruritic, although intense pruritus has been reported, and presenting symptoms are more likely to be related to skin stiffness and decreased range of motion, particularly around joints and the mouth [27]. A common yet unique complaint of patients with scleromyxedema is inability to remove their dentures secondary to perioral and manual stiffness [26]. Other findings particularly notable of scleromyxedema include the leonine facies secondary to diffuse facial mucin deposition and marked involvement of the glabella producing deep longitudinal furrows [26,27]. The doughnut sign has been used to describe the skin thickening of the proximal interphalangeal joints with a central depression, creating the appearance of a doughnut [27,28].

The paraproteinemia associated with scleromyxedema occurs in 83.2% of patients [27], and is predominantly an IgG lambda gammopathy [26,27]. Like scleredema, there are associated cases of multiple myeloma and Waldenström's macroglobulinemia, but other hematologic malignancies may occur, including Hodgkin's and non-Hodgkin's lymphoma and leukemia [26,27].

Although the association of scleromyxedema with monoclonal gammopathy is stronger than that of scleredema, the monoclonal gammopathy is usually of undetermined significance, with few cases of associated multiple myeloma. As noted for scleredema, however, it is recommended that patients with scleromyxedema have periodic assessment of their paraproteinemia to look for evidence of conversion to multiple myeloma [10].

Systemic manifestations are vast. Head and neck problems include dysphagia, nasal regurgitation, and often restriction of mastication [27,29]. Laryngeal involvement has been reported with altered morphology and decreased mobility of the epiglottis and vocal cords, leading to hoarseness, and increasing the risk for aspiration and resultant pneumonia [29]. Communication can be limited secondary to both the decreased oral aperture and laryngeal involvement [30]. Thickening of the eyelids leads to ectropion and lagophthalmos [31].

Approximately a third of patients develop proximal muscle weakness with elevations of muscle enzymes and electromyogram findings consistent with an inflammatory myopathy. But only 2% of patients have been found to have mucin deposition in their muscles [26,27]. Several joint manifestations are also seen, including arthralgias, migratory arthritis, seronegative polyarthritis, and carpal tunnel syndrome [26,27].

Involvement of the peripheral nervous system in the form of peripheral neuropathies may follow or antedate cutaneous findings. More seriously, various central nervous system findings have been reported, including memory loss, vertigo, gait problems, transient aphasia, dysarthria, hallucinations, seizures, confusion, and coma [26,32,33]. Scleromyxedematous encephalopathy and coma usually follow a flu-like prodrome of weakness and malaise, with variable cutaneous exacerbation, frequently are associated with acute psychosis, and can be fatal [26,30,34]. River et al [32] describe this phenomenon as a triad of high fever, grand mal seizures, and coma, and termed this a *dermatoneuro syndrome*. EEGs and CT

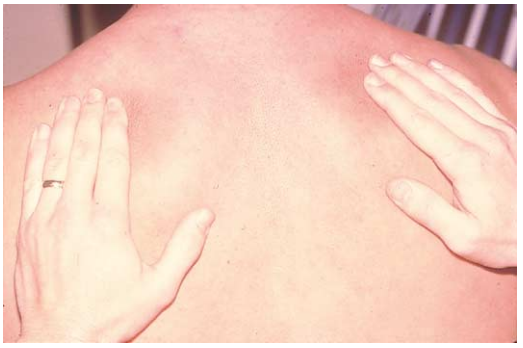

Fig. 1. Scleredema. Note lack of skin wrinkling with pressure.

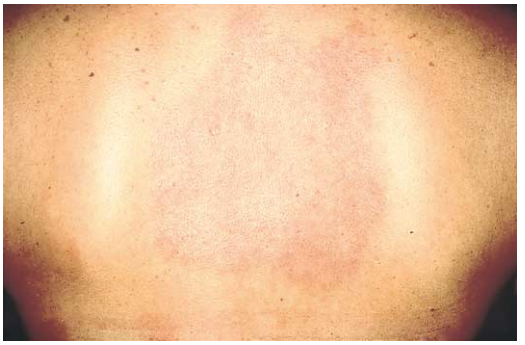

Fig. 3. Reticular erythematous mucinosis.

scanning at the time is without evidence of focal disease, although EEG changes, such as diffuse slowing, are seen if performed concurrent with seizure activity [26,30]. There has not been demonstrated mucin or immunoglobulin deposition in the brain, despite findings of focal demyelinization, gliosis, and cerebral edema, and increased protein in the cerebrospinal fluid [26,27,30].

Distinct pulmonary and coronary findings are difficult to establish, whereas gastrointestinal and renal findings are also nonspecific. Mucin deposition in Bowman's capsule, perivascular connective tissue, and renal papillae lead to a scleroderma-like renal disease [27]. An interesting recent report describes 15 renal dialysis patients who subsequently developed a scleromyxedema-like cutaneous disease. Their patients demonstrated dermal mucin deposition and fibroblast proliferation, but sometimes extending in deep samples through the fascia. Their patients' disease also lacked an associated paraproteinemia, was limited to the limbs and trunk, and none of them exhibited systemic manifestations of the disease [35]. The cause has yet to be elicited and should be considered as localized lichen myxedematosus associated with hemodialysis.

An increased frequency of cutaneous mucinoses in patients with HIV has also been noted, with a positive correlation to lichen myxedematosus but unknown correlation to the other mucinoses. The correlation may be limited to the local papular mucinosis form of the disease, and although cases have been reported with reticular erythematous mucinosis (REM) and scleredema, the association is likely coincidental [36,37].

Etiology

The etiology of scleromyxedema is obscure. Serum from patients with scleromyxedema has been shown to increase fibroblast proliferation in vitro [38] and the production of hyaluronic acid and prostaglandin E by fibroblasts [39]. Although most patients with scleromyxedema exhibit a paraproteinemia, purified immunoglobulin from patients' serum

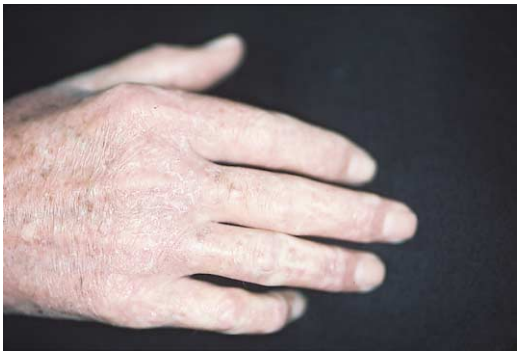

Fig. 2. Scleromyxedema.

Fig. 4. Generalized myxedema of hypothyroidism.

does not stimulate fibroblast proliferation, suggesting an unknown pathogenic circulating factor in the serum or an inherent fibroblast property [38]. There has been no correlation between the level of serum paraproteinemia or the amount of mucin deposition and the extent or progression of the clinical disease [26,30]. Little is known about the pathogenesis of scleromyxedema-associated central nervous system (CNS) disease. River et al [32] have suggested that increased cerebrospinal fluid paraprotein may lead to increased viscosity and sludging of the microcirculation in the CNS.

Histology

Histologically, the dermis is the site of primary involvement with extensive mucin deposition throughout the papillary dermis and around appendages [27,30]. The mucinous substance has been found to be composed predominantly of acid mucopolysaccharide [25,26,30]. Collagen production is increased, and collagen fibers are often displaced by the prominent mucin [25,26]. A key difference from scleredema is the marked proliferation of elongated and bipolar stellate fibroblasts [26,27, 30]. As in scleredema, the epidermis is spared, although it may be thinned over the thickened fibrotic dermis [27,30].

Treatment and prognosis

Numerous treatments have been tried for scleromyxedema: retinoids; dermabrasion; plasmapheresis and high-dose intravenous immunoglobulin; topical and intralesional hyaluronidase; corticotropin; topical, intralesional, and systemic corticosteroids; PUVA; grenz rays; electron-beam therapy; extracorporeal phototherapy; and topical dimethyl sulfoxide [27, 30]. Although a few of these have led to significant symptomatic improvement, none have demonstrated improved long-term results. Several chemotherapeutic agents have also been attempted, in hopes of interfering with plasma cell dyscrasia. Melphalan, granulocyte colony–stimulating factor, cyclosporine, 2-chlorodeoxyadenosine, and interferon-alfa have all been shown to lead to some improvement in limited case studies [26,27,30].

Scleromyxedema tends to lead a chronic course that is often recalcitrant to the variety of treatments currently available. The monoclonal gammopathy, however, does not correlate with the extent of the disease or its progression [26]. Potentially fatal complications can occur especially with neurologic involvement. Scleromyxedematous coma is perhaps the most devastating of these, with markedly increased morbidity and mortality [4,34].

REM

Clinical manifestations

Reticular erythematous mucinosis usually presents in early adulthood and is twice as common in women as in men, although there have been cases reported in as young as a prepubertal child [4,40]. Presentation is characterized by a macular and reticulated erythematous eruption on the central chest and upper back. An irregular but well-defined border is usually apparent caused by the frequent papular component at the periphery of the lesions. The papular lesions become confluent to plaques (Fig. 3). The extremities are spared, but lesions occasionally occur on the abdomen, face, and proximal upper extremities [41]. As with the scleredema and scleromyxedema, cutaneous lesions are usually asymptomatic, although sometimes pruritic [4,41]. Exposure to sunlight markedly increases the burning and itching in affected areas in most patients [4,41,42].

Differentiation from cutaneous lupus erythematosus (CLE) can be difficult. Clinical features shared by REM and CLE include female preponderance, photosensitivity, and response to antimalarials [4]. REM lacks antinuclear antibodies, periungal inflammation with dilated telangiectasias, and the histologic criteria of CLE. Although many patients with systemic lupus erythematosus (SLE) have later developed significant cutaneous mucinosis, there are no reports to date of patients with REM developing SLE [1].

Histology

As with the other diffuse cutaneous mucinoses, there are distinct histologic findings associated with REM. There is extensive perivascular and perifollicular mononuclear infiltrate, composed primarily of lymphocytes throughout the upper dermis [43]. Fibroblasts are normal in number and appearance, and collagen fibers appear similarly unchanged despite diffuse upper dermal edema and mucin deposition [4,43]. Mucin deposition is known to occur in systemic and cutaneous variants of CLE but the mucin deposition in CLE may extend into the subcutaneous tissue [4,44]. Other histologic findings consistent with variants of CLE, but not typically seen in REM, include epidermal atrophy, follicular hyperkeratosis, loss of the basal cell layer, and positive immunofluorescence of immunoglobulins at the dermal-epidermal junction

[1,44]. The infiltrate seen in CLE is also more mixed inflammatory as opposed to the predominantly lymphocytic infiltrate with REM [1,43,44].

Etiology

The etiology of REM remains elusive. Postulated etiologies of REM include (1) idiopathic photodermatosis, (2) viral infection, (3) disorder of mucin deposition, and (4) inherent immune disorder [45]. Attempts to induce lesions with visible light, ultraviolet A, and PUVA exposure have failed, although ultraviolet B, ultraviolet C, and solar-simulated radiation have occasionally triggered a delayed eruption on previously unaffected sites [4,42,46]. Viruslike tubular aggregates have been seen by electron microscopy in REM, SLE, and dermatomyositis; however, their significance is unknown and viral infection is considered unlikely to play a part in these disease processes [46,47].

Treatment and prognosis

Fortunately, treatment of REM is more successful than most of the other mucinoses. Despite lack of randomized controlled clinical trials, antimalarial drugs have been reported in numerous case series and individual cases to suppress photosensitivity and clinically improve the disease [4,41,43,46,48, 56]. Other therapies have been attempted without success when the disease fails to respond to antimalarials, including cyclosporine, antihistamines, and topical and systemic steroids [4,49].

Generalized myxedema of hypothyroidism

Clinical manifestations

Florid insufficient thyroid hormone leads to myxedema. Myxedema is associated with globally decreased metabolism from hypothyroidism with resultant tissue mucin deposition [50]. The skin in affected patients is usually cool and pale with a boggy nonpitting edema caused by mucin deposition. Myxedema is most evident in the face with characteristic thick lips, macroglossia, and most notably periorbital puffiness (Fig. 4). The extremities are also marked by acral swelling and keratoderma [4,51]. The duration of hypothyroidism before the onset of mucin deposition is not well described. By contrast, the skin of pretibial myxedema of hyperthyroidism is locally indurated with waxy nodules and plaques of varying color sometimes giving a peau d'orange appearance or resembling elephantiasis [4]. Pretibial myxedema, as implied, is usually localized to the anterior shins bilaterally, but is also occasionally seen in scar tissue, the upper legs, abdomen, and arms [4].

Associated anemia and vasoconstriction related to decreased metabolic rate and consequent hypothermia may enhance the pallor of the skin and give the appearance of livedo reticularis [51]. Carotenemia results from decreased hepatic conversion of beta carotene to vitamin A and also lower levels of low-density lipoprotein, the primary plasma carrier of carotene [50]. Occasional hypercholesterolemia and hypertriglyceridemia may result in other cutaneous findings, such as tuberous and eruptive xanthomas [4,50]. Additionally, patients in a hypothyroid state heal slowly and bruise easily because of increased capillary fragility and decreased levels of clotting factors [4,51].

Other dermatologic manifestations of hypothyroidism include slowed hair growth with diffuse hair loss of the scalp; eyebrows (madurosis); beard; and pubic region [4,52]. Hair is dry and brittle, with decreased luster, whereas the skin is xerotic and pruritic [4,51,52]. Nail growth is similarly slow, and nails become thin, brittle, and often striated with transverse grooves [4,8,51].

Systemic manifestations of hypothyroidism are vast and are not discussed here. It is important to note, however, that the mucin deposition that occurs in the skin also occurs in a number of other organs, such as the heart, bowel, and kidneys [51]. Numerous CNS manifestations can be seen in long-standing hypothyroidism. The most serious manifestation is myxedema coma. The development of myxedema coma is usually preceded by a physiologic stressor, such as an infection; cardiac event; or use of a drug that is poorly metabolized in hypothyroid patients (phenothiazine, phenobarbital, narcotics, and analgesics) [50,53]. Unlike scleromyxedematous coma, myxedema coma is not preceded by a viral-like prodrome. Patients may present with convulsions and other signs of severe hypothyroidism, such as effusions, ascites, bradyarrhythmias, and hypothermia [50].

Histology

Generalized myxedema is marked by acid mucopolysaccharide deposition in the skin and most other organs of the body [54]. Hyperkeratosis of the epidermis with plugging of hair follicles is seen, accompanied by prominent edema of the entire dermis, separating collagen bundles into fibers [4]. Mucin is found in most of the edematous spaces

and occasionally in the subcutis. It is important to note that there is not an associated proliferation of fibroblasts as occurs in scleromyxedema and pretibial myxedema of hyperthyroidism [4].

Etiology

Studies examining the skin ultrastructure have found quantitative and qualitative defects of dermal elastic fibers in patients with generalized myxedema of hypothyroidism [54]. The pathogenesis of decreased elastin and increased mucin deposition in generalized myxedema is not clear. It has been proposed that the abnormalities in elastin, mucin and collagen may represent the effects of decreased thyroid hormone on fibroblasts [54].

Treatment and prognosis

Therapy for hypothyroidism that returns the patient to the euthyroid state results in resolution of the generalized myxedema, and usually complete reversal of all associated signs and symptoms [4,53]. Levothyroxine is the most widely accepted and used therapy [53]. The treatment regimen depends on the severity of disease and the age of the patient being treated. Treatment should always be started at a low dosage and increased gradually to avoid complications, such as cardiac arrhythmias, angina, and myocardial infarction [53].

Although the prognosis for generalized myxedema of hypothyroidism is quite good, with complete resolution after several months of treatment in most cases, the myxedema recurs if treatment is discontinued. As mentioned previously, CNS manifestations are the most worrisome complications of long-standing myxedema. Peripheral neuropathies and paresthesias may become permanent with irreversible cognitive slowing and myxedema coma is associated with a 50% mortality [53,55]. Factors associated with a worse prognosis include body temperature less than or equal to 32.2°C, severe cachexia, prolonged hypotension or coma, greater age, cardiac complications, and high-dose thyroid hormone replacement [53,55].

Summary

The cutaneous mucinoses are a complex group of dermatologic diseases with local, follicular, or diffuse disease. The diffuse cutaneous mucinoses are remarkable not only for their dermal disease, but also for the numerous systemic manifestations. It is important that the clinical dermatologist be able accurately to diagnose and differentiate scleredema, scleromyxedema, REM, generalized myxedema of hypothyroidism, and pretibial myxedema of hyperthyroidism. Because of the variability of associated systemic manifestations, some with substantial morbidity and mortality, accurate diagnosis is vital for awareness and appropriate management.

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Cardiac disease and the skin

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Many cutaneous abnormalities are associated with cardiac disease. General signs found in cardiac patients include cyanosis, flushing, erythema, and digital clubbing. Multisystem disorders and inherited diseases are also associated with cutaneous and cardiac abnormalities.

General cutaneous signs of cardiac disease

Cyanosis

Cyanosis, the bluish discoloration of the skin and mucous membranes, results from an increased amount of reduced circulating hemoglobin. Cyanosis is apparent when the mean capillary concentration of reduced hemoglobin exceeds 5 gm/dL; it also results when nonfunctional hemoglobin, such as methemoglobinemia, is present in the blood. The lips, nail beds, ears, and malar prominences are recognized sites of cyanosis.

Cyanosis can be subdivided into central and peripheral types. Central cyanosis is the result of decreased arterial oxygen saturation and typically occurs in patients with congenital heart disease, impaired pulmonary function, and right-to-left shunting as well as during high altitude exposure. Circulating arterial blood is unsaturated or an abnormal hemoglobin derivative is present; therefore, both the mucous membranes and the skin are affected.

Peripheral cyanosis occurs in patients with normal arterial oxygen saturation, but with diminished blood flow and increased extraction of oxygen. It is seen with cold exposure, shock, congestive heart failure, and peripheral vascular disease. The mucous membranes of the oral cavity are often spared. Clinical differentiation between central and peripheral cyanosis can be difficult. Cardiogenic shock and pulmonary edema can result in a mixture of both types. The most common congenital cardiac lesion associated with cyanosis in adults is a combination of ventricular septal defect and obstruction of the pulmonary outflow tract (tetralogy of Fallot). Differential cyanosis involving the lower extremities, but sparing the upper extremities, occurs in patients with patent ductus arteriosus and pulmonary hypertension. Slight cyanosis of the lips and cheeks without clubbing of the fingers may suggest mitral stenosis [1].

Flushing

Flushing of the face, neck, and chest may occur from carcinoid tumors that have metastasized to the liver. Pheochromocytomas may cause periodic facial flushing associated with sweating and hypertension. Patients with severe mitral stenosis may have a malar flush with pinched and blue facies. Flushing seen with systemic mastocytosis is a result of histamine release from degranulated mast cells and is associated with hypertension. Generalized flushing may be seen in Sipple's syndrome (multiple endocrine neoplasias IIa), in which prostaglandin, serotonin, and catecholamine levels are increased. The term "Quincke pulsations" refers to flushing of the nailbeds that occurs when pressure is applied to the tip of the nail. Quincke pulsation is seen in aortic regurgitation and is synchronous with the heart rate [2].

Erythema

Dilated skin capillaries and/or an increased amount of saturated hemoglobin leads to redness of the skin. Massive capillary dilatation occurring with ery-

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throderma and exfoliative dermatitis may result in high-output cardiac failure. A "ruddy" complexion may be caused by polycythemia. Erythremia is a unique coloration caused by a combination of redness and cyanosis best demonstrated on the tongue, lips, nose, earlobes, conjunctiva, and fingertips. Erythema results when an increased amount of saturated hemoglobin produces the red coloration and an increased amount of desaturated hemoglobin produces cyanosis because of the body's inability to oxygenate the increased absolute amount of hemoglobin. The lack of nail clubbing may differentiate patients with polycythemia vera from those with cardiopulmonary disease who develop secondary polycythemia [3].

Clubbing

Clubbing is characterized by proliferation of the connective tissue between the nail matrix and the distal phalanx. The angle made by the proximal nail fold and the nail plate (Lovibond's angle) is greater than 180°. Cardiovascular causes of clubbing include cyanotic congenital heart disease, subacute bacterial endocarditis, congestive heart failure, and myxoid tumor.

Coronary artery disease (CAD)

In the United States, approximately 14 million adults have coronary artery disease. One third of the 1.5 million patients who develop myocardial infarctions each year will die [4]. Risk factors for CAD are cigarette smoking, hypertension, diabetes mellitus, hypercholesterolemia, and a family history of premature death caused by CAD.

Hyperlipoproteinemia/xanthomas

Hyperlipidemia is an important risk factor for the development of coronary artery disease (CAD). Xanthomas are localized infiltrates of lipids found in the dermis or tendons. Xanthomas are categorized by anatomical location and appearance. Early recognition of xanthomas by physicians may facilitate the diagnosis of CAD, diabetes, pancreatitis, and thyroid and renal disease.

Tendinous xanthomas arise in tendons, ligaments, and fascia. Their presence indicates a disturbance in cholesterol and lipoprotein metabolism. The Achilles tendon is a common and early site of involvement. Extensor tendons of the hands, knees, and elbows can also be involved.

Planar xanthomas are yellow macules and thin plaques occurring over the eyelids, neck, trunk, and axillae. Xanthelasma is a commonly recognized form that indicates hypercholesterolemia in adults younger than 40 years of age. Only 50% of patients with xanthelasma have hyperlipidemia. Xanthoma striatum palmari are flat, yellow-orange, linear lesions in the creases of the hand and are associated with elevation of cholesterol and triglycerides [5].

Tuberous xanthomas are yellow-red nodules on the elbows, knees, knuckles, buttocks, and palms. Tuberous xanthomas are associated with elevations of cholesterol and triglyceride and atherosclerotic vascular disease.

Eruptive xanthomas are 1- to 4-mm yellow papules with an erythematous halo around the base. They develop in crops over pressure points and extensor surfaces, and are most commonly seen when serum triglycerides exceed 2,000 mg/dL [6].

The relationship between hypertriglyceridemia and atherosclerosis is controversial. Data from the Prospective Cardiovascular Muenster (PROCAM) study revealed that CAD risk is high when triglycerides exceed 200 mg/dl and the high-density lipoprotein (HDL) cholesterol is low (<35 mg/dL). Patients with triglycerides >200 mg/dL had two times the rate of coronary events compared to patients with normal triglyceride levels [7]. The risk of coronary artery disease associated with hypertriglyceridemia may be a direct result of triglyceride-lipoprotein accumulation in atherosclerotic plaque formation. Alternatively, hypertriglyceridemia may be a marker for coronary artery disease and a feature of insulin-resistance syndrome [8].

Regression of xanthomas occurs with lipid-lowering therapy. The turnover rate of cholesterol in atherosclerotic coronary artery lesions was reported to be significantly slower compared to cutaneous xanthomas [9].

Earlobe crease

The association between the presence of an earlobe crease (ELC) and coronary artery disease remains controversial. Some studies indicate the significance of ELC as a marker for coronary artery disease [10,11] whereas others report that ELC is correlated only with advanced age rather than coronary artery disease [12,13]. It is not known if ELC is hereditary or acquired [14].

Peripheral vascular disease

In a series of 100 consecutive patients with CAD, 62% had peripheral vascular disease. The cutaneous signs of peripheral vascular disease include dry, shiny

extremities with diminished hair growth. Painful ulceration and atrophy of the skin and subcutaneous tissue will be seen [15].

Multisystem disease with cutaneous and cardiac signs

Systemic lupus erythematosus

Cutaneous findings observed with systemic lupus erythematosus (SLE) occur in 80% of patients during the course of their disease, and in 25% are the presenting sign [16]. Malar erythema, discoid lupus lesions, photosensitivity, and oral ulceration are 4 of the American Rheumatism Association's 11 criteria for the diagnosis of SLE. Nail changes observed include periungual telangiectasias, hyperkeratotic ragged cuticles, splinter hemorrhages, onycholysis, and red lunulae. Approximately 25% of patients have oral findings including ulcerations of the palate, buccal mucosa, and gingiva. Alopecia is common and can be diffuse or localized, with or without scarring.

Lupus hairs, short broken-off frontal hairs, occur in 30% of patients. Additional cutaneous findings include vasculitis, livedo reticularis, ulcerations, and pigmentary changes.

Cardiac disease contributes significantly to the morbidity and mortality of lupus patients. Pericarditis is present in 6% to 45% of patients and can be the initial manifestation of disease. An echocardiogram may identify pericardial effusion and tamponade. Pericardial lesions are present in 60% to 80% of autopsy cases.

Libman-Sachs "atypical verrucous endocarditis" is a characteristic cardiac lesion of SLE. Pea-size granular masses adhere to the underlying endocardium, most frequently affecting the mitral valve. Secondary bacterial endocarditis can develop on damaged heart valves and surgical valve replacement is the preferred treatment. Hypertension, valvular heart disease, acute myocarditis, conduction defects, coronary artery disease, and myocardial infarction have also been reported in SLE [17].

Scleroderma

Limited cutaneous scleroderma refers to symmetric skin thickening localized to the distal extremities and face. Patients may develop CREST syndrome of calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactylia, and telangiectasia. Sclerodactylia, calcinosis cutis, and trophic ulcers occur with disease progression. Limited cutaneous scleroderma has a more favorable prognosis unless pulmonary hypertension develops.

Diffuse cutaneous scleroderma is characterized by rapid development of symmetric skin fibrosis of the proximal and distal extremities, face, and trunk. Patients are at an increased risk to develop visceral disease early on. Pulmonary hypertension and cor pulmonale (right-sided heart failure) occur in 10% to 30% of patients and are associated with a poor prognosis. Early skin findings on the hands include erythema, edema, and Raynaud's phenomenon. Sclerosis giving a "bound-down appearance" occurs. Dilated nail fold capillary loops are present in 75% of systemic scleroderma patients. Diffuse chest involvement leads to cuirass-like restraint of respiratory movements [18]. Pigmentary changes, such as hyperpigmentation with bronzing or hypopigmentation with characteristic perifollicular pigment retention, occur [19].

Cardiac involvement includes arrhythmias, fibrinous pericarditis, pericardial effusions, angina, diastolic dysfunction, cardiomyopathy, and congestive heart failure. Focal myocardial lesions range from contraction band necrosis to fibrosis caused by vasospasm of the small coronary arteries. Fibrosis of the conduction system leads to arrhythmias and sudden death. Autopsy studies suggest there is a high prevalence of clinically unrecognized disease [20].

An abnormal exercise thallium scan indicates ischemia with decreased ejection fraction. Cardiovascular magnetic resonance with gadolinium contrast shows patchy fibrosis seen in scleroderma heart disease [21]. Gated myocardial spect scan may detect early diastolic dysfunction from patients with scleroderma [22].

Relapsing polychondritis

Relapsing polychondritis (RP) is a rare disease of unknown cause characterized by recurrent inflammation and destruction of cartilage. Autoantibodies to type II collagen have been found in two thirds of cases. Cutaneous findings include auricular chondritis with painful swelling of the pinna, but sparing the earlobes, saddle-nose deformity, chest wall deformity, vasculitis, and panniculitis. Cardiovascular involvement occurs in 24% to 52% of patients with RP and is the second leading cause of death [23].

Frequent cardiac examinations should be performed because of the relapsing nature of the disease. Severe aortic valve inflammation has been reported in asymptomatic patients [24]. Complete heart block related to fibrosis of the conduction system was reported in a patient who died within 3 months after

clinical diagnosis. Aortic aneurysms occur more often in the ascending aorta, but may be numerous in the abdominal aorta. Aortic disease may be clinically silent but result in fatal rupture. Careful cardiac examination and monitoring of aortic segments should occur at regular clinical visits [25].

Amyloidosis

Cardiac amyloidosis occurs in primary amyloidosis, myeloma-associated amyloidosis, and familial amyloidosis. Cardiac amyloidosis is usually of the primary or AL type. The amyloid fibril protein is derived from monoclonal immunoglobulin light chains. Congestive heart failure is present in ~25% of patients when the initial diagnosis is made. Electrocardiography shows either low voltage in the limb leads or anteroseptal infarction changes. Echocardiography is helpful for identifying and evaluating amyloid heart disease [26]. Arrhythmias, including atrial fibrillation, junctional tachycardia, premature ventricular complex, or heart block, are common features. Amyloidosis should be considered in a patient with refractory congestive heart failure and EKG findings consistent with low voltage or anteroseptal infarction.

Behcet's Disease (BD)

Behcet's Disease (BD) is characterized by recurrent oral and genital aphthous ulcers with uveitis. Other features include arthritis, cutaneous vasculitis, meningoencephalitis, and gastrointestinal ulcers. Painful oral ulcerations occur on the lips, tongue, buccal mucosa, gingiva, and pharynx. Lesions are 1 to 3 cm, sharply circumscribed with a yellow-fibrinous base, and heal without scarring. Genital aphthae occur on the vulva or scrotum. Genital lesions are clinically similar to oral aphthae, but may scar and occur less frequently [27]. Various cardiac abnormalities have been described, but are rare. Pericarditis, myocarditis, coronary artery aneurysm or occlusion, electrocardiographic disturbance, and aortic insufficiency have been reported in patients with Behcet's. Coronary artery aneurysm and thrombotic coronary occlusion have been associated with vasculitis [20].

Carcinoid syndrome

The classic triad of carcinoid syndrome includes cutaneous flushing, secretory diarrhea, and valvular heart disease. Telangiectasias, wheezing, and paroxysmal hypotension may also be present. Flushing is observed in 85% of patients. Flushing from bronchial tumors may last for days and be associated with excessive lacrimation, salivation, and facial edema. Serotonin is the most common secretory product of carcinoid tumors. Urinary 5-hydroxyindolaceticacid (5-HIAA), the biproduct of serotonin metabolism, is a reliable marker for tumor activity and response to therapy [28].

Carcinoid heart disease typically involves the tricuspid and pulmonary valves. Patients present with symptoms of right-sided heart failure, tricuspid insufficiency, and pulmonic stenosis. The essential lesion is referred to as a carcinoid plaque resulting from piling up of endothelium in areas subjected to the greatest concentrations of tumor products. Valvular lesions can result in severe valvular dysfunction leading to heart failure and death. Complete surgical resection is the only curative therapy [29]. Medically and surgically managed patients are treated preoperatively with octreotide. This somatostatin analog inhibits secretion by carcinoid cells. Octreotide relieves symptoms of diarrhea, flushing, and wheezing in 70% of patients but its benefit in preventing cardiac disease is unknown [30].

Degos' disease/malignant atrophic papulosis

Malignant atrophic papulosis is a rare, often fatal, disease that affects the gastrointestinal tract and other organs, including the heart. The skin lesions are papules with a porcelain white center, atrophy, and telangiectatic borders. These asymptomatic lesions are found on the trunk, extremities, and penis, sparing the face, palms, and soles.

Maud et al [31] reported a fatal case of malignant atrophic papulosis in a 22-year-old man who developed extensive thickening of the pleura and pericardium. This led to severe restrictive cardiopulmonary syndrome and death. The skin lesions were present 6 years before his death. Pleuritis and pericarditis are usually minor manifestations of this disease [32].

Hemochromatosis

Hemochromatosis is a common autosomal recessive disorder characterized by excess iron deposition in the liver and extrahepatic sites. Diabtes mellitus (bronze diabetes), hepatomegaly, cirrhosis, hypogonadism, arthropathy, and heart disease are present. The mutation Cys 282 Tyr within the HFE gene located on chromosome 6 may account for 70% to 100% of hereditary hemochromatosis cases. A less prevalent mutation is H63D [33].

Gray-to-bronze hyperpigmentation occurs on the face, extensor forearms, dorsal hands, and genitals. Koilonychia, pigmented mucous membranes, localized ichthyosis, and alopecia are additional cutaneous

findings. Cardiac involvement occurs in 15% of patients. Cardiomegaly, congestive heart failure, superventricular arrhythmia, and myocardial infarction can occur. Studies have recently shown a twofold increase in risk for the first acute myocardial infarction for carriers of the HFE Cys 282 Tyr mutation [34]. This mutation in the HFE gene is also associated with ischemic cardiomyopathy [35].

Kawasaki's disease

Kawasaki's disease, or mucocutaneous lymph node syndrome, is an acute febrile illness affecting children but rarely adults. Features include fever above 38.3°C for 5 days plus four of the five following criteria:

1. Edema, erythema, desquamation of the peripheral extremities.
2. Polymorphous exanthem.
3. Nonpurulent bilateral conjunctival injection.
4. Changes of the lips and oral cavity (strawberry tongue).
5. Acute nonpurulent cervical adenopathy.

The disease lasts 10 to 20 days and then subsides. Coronary arteritis leading to coronary aneurysm is characteristic and can be detected with echocardiography or coronary angiography. One to two percent of patients may die of myocardial infarction [17].

Infective endocarditis

The cutaneous stigmata of infective endocarditis aid in the diagnosis.

Petechiae, the most common cutaneous manifestation of endocarditis, are seen on the conjunctivae, palate, buccal mucosa, and upper extremities. Splinter hemorrhages, dark-red subungual linear streaks, frequently occur after nail trauma, but also occur in endocarditis.

Janeway lesions, hemorrhagic infarcted macules and papules on the palms and soles, more commonly occur in acute endocarditis.

Clubbing of the fingers occurs after prolonged, untreated subacute bacterial endocarditis. Gangrene of the extremities results from secondary embolization.

Inherited diseases

Marfan's syndrome (MS)

Marfan's syndrome is an autosomal dominant disorder of connective tissue with abnormalities of the musculoskeletal, cardiovascular, and ocular system. Severe MS is characterized by (1) long, thin extremities associated with other skeletal changes, (2) dislocation of the lens, and (3) aortic aneurysms that originate at the base of the aorta.

Marfan's syndrome is caused by a mutation in the fibrillin gene (FBN1), a major component of extracellular microfibrils [36]. Fibrillin is abundant in the ascending aorta, suspensory ligament of the lens, periosteum, and skin. The incidence of MS is 1 in 10,000 in most racial and ethnic groups. Approximately 25% of patients do not have an affected parent and may represent a mutation.

Patients tend to be thin with scant subcutaneous fat; adults may develop centrifugal obesity. Cutaneous manifestations include striae distensae present on the pectoral, deltoid, buttock, and thigh areas. Inguinal and incisional hernias are common. Elastosis perforans serpiginosa occurs in Marfan's variant.

Mitral valve prolapse occurs early in life and, in 25% of patients, progresses to mitral regurgitation. Weakness of the aortic media leads to aortic dilatation and diffuse aneurysm. The ascending aorta is the most severely affected region because it is exposed to more pulsatile fatigue. Aortic dissection, aortic rupture, and cardiac failure from mitral or aortic valve regurgitation are the predominant causes of death in more than 90% of patients. Echocardiography monitors aortic root involvement and valvular heart disease in Marfan's patients [37]. Aortic distensibility measured by MRI may be an index of early aortic involvement before dilatation occurs [38].

Ehlers-Danlos syndrome (EDS)

Ehlers-Danlos Syndrome is a heterogeneous group of inherited disorders of connective tissue. EDS is characterized by hyperelastic skin and hypermobile joints. There are currently nine numeric types of EDS with inheritance patterns including autosomal dominant, autosomal recessive, and X linked. Type I patients have ''cigarette paper'' scars. Type IV patients have extensive scars and hyperpigmentation over bony prominences; the skin is thin and subcutaneous vessels are visible. In type VIII, the skin is more fragile than hyperextensible, heals with pigmented scars, and bruises easily. Molluscum psuedotumors are fleshy nodules seen in the ulnar forearms and shins of patients with EDS.

Cardiac abnormalities may lack a consistent pattern in patients with EDS. An earlier study of 19 patients found mitral valve prolapse in 78% of patients with types I and III. Other reported cardiac abnormalities included aortic root enlargement and congenital heart

defects including bicuspid aortic valves, atrial septal defects, and ventricular septal defects [39].

Dolan et al [40] did not find an increased prevalence of cardiac abnormalities in 33 patients with EDS (30 type I, II, or III and 3 type IV). In this series, mitral valve prolapse was found in 6% of EDS patients and in 7% of age-matched controls. None of the type IV EDS patients had any echocardiographic abnormalities. EDS may be relatively more benign from a cardiac point of view than previously thought.

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum (PXE) is an inheritable systemic connective tissue disorder affecting the elastic tissue in the body. PXE is inherited through both autosomal dominant (10%) and recessive (90%) disorders. The gene responsible has been mapped to chromosome 16. Pathogenic mutations in MRP6, a member of the ABC transporter gene family, have been identified in eight kindreds with PXE [41]. The cutaneous findings are yellow papules that coalesce into plaques on any elastic redundant skin. Lesions are found on the neck, axillae, popliteal, and antecubital fossa. Angioid streaks result from pathologic fractures in Bruch's membrane.

Patients develop angina, congestive heart failure, and mitral valve prolapse. Sudden death was reported in a 26-year-old female; autopsy revealed stenotic epicardial coronary arteries with degenerated elastic fibers [42].

Mitral valve prolapse (MVP) has been identified by echocardiography in 71% of patients with PXE. In PXE, MVP may be a direct expression of damage to the valve cusp by the disease itself, or the prolapse is secondary to other cardiovascular defects causing valve dysfunction [43]. Frequent cardiovascular findings are coronary artery disease, peripheral vascular disease, hypertension, calcifications of peripheral arteries, cardiomyopathy, mitral stenosis, and mitral valve prolapse.

Fabry's disease

Fabry's disease is an X-linked inborn error of glycosphingolipid metabolism caused by a deficiency of α-galactosidase A. Patients develop progressive accumulation of globotriaosylceramide and related glycosphingolipids in vascular endothelial lysosomes of the kidney, heart, skin, and brain.

Angiokeratoma corporis diffusum is the classic cutaneous finding of Fabry's disease. Lesions begin as clusters of red to blue-black nonblanchable papules located in the bathing trunk distribution. Other clinical features include painful neuropathy, renal failure, stroke, and myocardial infarction.

Cardiac disease seen with Fabry's disease includes angina, myocardial infiltration, myocardial infarction, mitral value prolapse, congestive heart failure, and hypertension [44]. Mitral valve prolapse has been documented in affected males and heterozygote females [45]. Treatment of Fabry's disease with recombinant α-galactosidase A replacement therapy cleared mitral vascular endothelial deposits of globotriaosylceramide from the kidneys, heart, and skin, reversing the pathogenesis [46].

Noonan's syndrome (NS)

Noonan's syndrome (NS) is an autosomal dominant disease with variable phenotypic expression that affects 1:1000 to 1:2500 live births. The clinical features include hypertelorism, epicanthal folds, depressed nasal root, low-set ears, a low posterior hairline, webbed neck, and short stature. Ninety percent of patients have pectus excavatum or pectus carinatum. Approximately 50% of patients have congenital cardiac abnormalities. Pulmonary valve stenosis, hypertrophic cardiomyopathy, septal defects, and patent ductus arteriosus are features. Twenty-five percent to forty percent of patients have cutaneous findings that include lymphedema, dystrophic nails, keloid formation, and keratosis pilaris atrophicans [47]. Controversy exists over the distinction of Noonan's syndrome and cardio-facio-cutaneous syndrome (CFC). Some authors suggest that they are different phenotypes of the same condition. Patients with CFC have polyhydramnios during pregnancy, gastrointestinal dysfunction with failure to thrive, and significant global developmental delay with mental retardation and hydrocephalus. Cardiac findings in severe CFC include pulmonic stenosis, patent ductus arteriosus, atrial and ventricular septal defects, and left ventricular hypertrophy [48].

Werner syndrome (WS)

Werner syndrome (WS) is an autosomal recessive disorder characterized by (1) growth arrest at puberty, (2) cataracts before age of 40, (3) premature balding and graying, (4) atrophic skin and leg ulcers, and (5) premature atherosclerosis and midlife death. Additional disorders seen with Werner syndrome include type II diabetes, osteoarthritis, osteoporosis, and hypogonadism.

Positional cloning studies have identified WRN as the gene responsible for WS [15]. WRN functions as an exonuclease, helicase, and RNA polymerase.

Studies have identified specific polymorphism within WRN that may modulate the risk of atherosclerosis. WRN may be associated with other age-related disorders [49].

Leopard syndrome (LS)

Leopard syndrome is an autosomal dominant disorder with the acronym referring to the following: L, multiple lentigines; E, EKG changes; O, ocular hypertelorism; A, abnormalities of the genitalia; R, gross retardation; and D, deafness. Lentigines are multiple and frequently present at birth, but may increase during puberty. Lentigines may be generalized but spare the lips and oral mucosa. The characteristic facial appearance is a triangular-shaped face with frontal bossing, hypertelorism, and low-set ears. Genital hypoplasia with hypospadias and cryptorchidism occurs. Female patients have ovarian hyperplasia or absent ovaries.

EKG changes show access deviation, first-degree AV block, bundle branch block, and complete heart block. Associated anatomical abnormalities include ventricular hypertrophy, hypertrophic cardiomyopathy, and subaortic stenosis.

Carney complex/myxoma

Carney complex is a rare autosomal dominant multisystem disorder characterized by multiple nail plasias and lentigines. The genetic defect has been localized to chromosome 2 (2p16). Clinical manifestations include lentigines and blue nevi of the skin and mucosa, cutaneous and cardiac myxomas, testicular tumors, adrenal tumors, and pituitary adenomas. These cases have been referred to by the acronyms LAMB (lentigines, atrial myxoma, mucocutaneous myxoma, and blue nevi) or NAME (nevi, atrial myxoma, myxoid neurofibroma, and ephelides) [50].

Seventy-five percent of cardiac myxomas develop in the left atria. Embolization occurs in 30% to 40% of patients with myxomas. Constitutional symptoms of fatigue, fever, erythematous rash, arthralgias, weight loss, anemia, and infections may occur. Echocardiography, CT, and MRI aid in identification of cardiac myxomas [51].

Naxos disease

Naxos disease is an autosomal recessive disorder studied in patients from the Greek islands of Naxos and Milos. The hallmarks include arrhythymogenic right ventricular cardiomyopathy (ARVC) associated with palmoplantar keratoderma and wooly hair. ARVC is a heart muscle disorder with fibro-fatty replacement of right ventricular myocytes and localized left ventricular fibrosis. Clinical cardiac features beginning in adolescents are life-threatening ventricular arrhythmias, heart failure, and sudden death. Wooly hair is present at birth and palmoplantar keratoderma develops in infancy. A mutation in the gene encoding plakoglobin (chromosome 17q 21) has been identified from patients with Naxos disease. Plakoglobin is vital component of the desmosomes and adherens junctions [52].

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Cutaneous nephrology

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Normal renal function is integral to many of the body's metabolic and biochemical processes. Conditions either directly or indirectly causing renal impairment can be expected to have possible systemic complications. Careful examination of the skin may allow the physician to appreciate cutaneous manifestations in patients with known renal disease. Conversely, and perhaps more importantly, thorough inspection of the integument may reveal markers for occult renal disease.

Many hereditary syndromes display multisystem impairment based on a single genetic defect. For example, the deficiency of α-galactosidase A in Fabry's disease causes an accumulation of glycosphingolipids in smooth muscle and endothelial cells throughout the body. Similarly, acquired diseases targeting the common structures of various organs, such as blood vessels, display multisystem effects.

This article discusses hereditary and acquired disorders displaying both cutaneous and renal manifestations. Additional topics include the expected dermatologic findings among patients with chronic renal failure, the cutaneous changes that occur in patients on dialysis, and cutaneous manifestations observed in the patient with a renal transplantation. Finally, the cutaneous manifestations of renal malignancy are detailed.

Inherited conditions with cutaneous and renal manifestations

Neurofibromatosis (von Recklinghausen's disease) is an autosomal dominant disorder; perhaps 50% of cases represent new mutations. Multiple subtypes of the disorder have been described. Neurofibromatosis type I (OMIM: *162200) accounts for most cases. The classic cutaneous features of the disorder include multiple café-au-lait spots; neurofibromas; and axillary freckling (Crowe's sign). Lisch nodules (pigmented iris hamartomas) are another classic finding. Less commonly reported are involuted neurofibromas described as blue-red maculae and pseudoatrophic maculae. Nonessential hypertension occurs frequently as a complication of neurofibromatosis, most commonly secondary to renal artery stenosis. Pheochromocytomas are less commonly responsible for hypertension in this setting [1,2].

Segmental (type V) neurofibromatosis is a rarer disorder. Classic cutaneous findings are present but limited to one, or occasionally several, dermatomes. This condition has been associated with renal agenesis [3].

Tuberous sclerosis (Bourneville's disease, OMIM: 191100) is a neurocutaneous disorder defined by the triad of seizures, mental retardation, and a variety of unique skin findings. It is inherited in an autosomal dominant pattern with variable penetrance; a small majority of cases are new mutations. The first recognizable cutaneous lesions are congenital hypopigmented maculae. These so-called *ash leaf maculae* vary in size and are present on the trunk and limbs of most of those with tuberous sclerosis. Angiofibromas (adenoma sebaceum) are also found in most cases. They are 0.5- to 4-mm smooth, dome-shaped, red-pink papules usually located on the face, especially the malar area. Shagreen patches (collagenomas) are less common. Periungual fibromas (Koenen's tumors) and pitting of tooth enamel are also well-documented findings. Renal lesions may be present in as many as half the patients with tuberous sclerosis. The most commonly reported tumors are epithelial cysts (which may be multiple); angiomyolipomas;

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and malignant tumors. Angiomyolipomas are benign tumors composed of fat, smooth muscle, and vessels. They cause chronic renal failure in approximately 1% of those with tuberous sclerosis [4,5]. Malignant renal tumors can develop at a much younger age in this setting versus sporadic renal carcinoma and has been reported in children [6].

Fabry's disease (OMIM: *301500) is inherited in an x-linked recessive fashion. Deficiency of α-galactosidase A (ceramide trihexosidase) causes intracellular accumulation of glycosphingolipid throughout the body. Hemizygous males are most commonly diagnosed in childhood or early adolescence. Carrier females are usually asymptomatic but atypical hemizygotes with limited disease are rarely detected. Cutaneous findings of Fabry's disease include hypohidrosis and multiple telangiectasias. These vascular lesions usually appear before puberty between the umbilicus and the knees. These nonblanchable punctate dark red maculae and papules number in the hundreds to thousands and are collectively known as *angiokeratoma corporis diffuscum*. Smaller purple maculae may also be seen on the lips. Corneal opacities are frequently observed. Hypertension and renal failure are late complications of Fabry's disease. Early renal failure has been reported but more commonly proteinuria or lipiduria develop in childhood, progressing to uremia over several years, usually in the fourth or fifth decade [7]. Preliminary trials using recombinant human α-galactosidase A replacement enzyme therapy continue and seem very promising [8,9].

Pseudoxanthoma elasticum (OMIM: 264800, 177850, 264810, 177860) is a disease with multiple patterns of inheritance. Elastic tissue proliferation, calcification, and fragmentation lead to characteristic cutaneous ocular and cardiovascular findings. Soft, yellow papules coalescing to form thickened ''cobblestone'' or ''chicken skin'' plaques in flexural areas are commonly seen. Renal artery involvement may lead to hypertension. Localized periumbilical pseudoxanthoma elasticum with perforation may be precipitated by chronic renal failure and may represent a limited form of hereditary pseudoxanthoma elasticum [10].

The nail-patella syndrome (also termed *osteo-onychodysplasia* or *Fong's syndrome*) (OMIM: 161200) is a rare autosomal-dominant disease. Findings include dysplastic nails and hypoplastic or absent patellae and frequent radial head dislocations. Skeletal anomalies of the elbow, knee, and iliac crests are common. Glaucoma and renal disease are additional features. More than 90% of patients with the nail-patella syndrome exhibit cutaneous findings. Hypoplasia of the nails may be present but triangular lunulae are more characteristic. Fingernails are more frequently involved than toenails. Renal impairment occurs in 30% to 50% of patients. Proteinuria is the earliest and most common concern. Progression to renal failure occurs in a minority of patients. Appropriate, periodic monitoring of renal function is recommended [11]. Angiotensin converting enzyme–inhibitors have been used to treat renal involvement [12].

Birt-Hogg-Dubé syndrome (OMIM: *135150) is an autosomal-dominant disorder defined by the triad of fibrofolliculomas, trichodiscomas, and acrochordons occurring in the hundreds. Typically, these small, skin-colored papules develop in multiples over the face, neck, and superior trunk beginning in early adulthood. The condition has been reported in association with colonic polyps and renal carcinoma. Recently, possible association with various familial renal neoplasms has been reported and appropriate radiographic screening in this population advocated [13].

Partial lipodystrophy (OMIM: 151660) presents as a gradual, insidious loss of subcutaneous fat from the face and upper body. It is a rare disease with various forms of hereditary reported. Associated complement abnormalities and the presence of IgG, C3 nephritic factor are helpful diagnostically. More than 90% of those afflicted develop mesangiocapillary glomerulonephritis. As many as one half of these progress to chronic renal failure. An increased risk of developing autoimmune diseases is also reported [14].

Acquired systemic disorders with cutaneous and renal manifestations

Lupus erythematosus (LE) is an autoimmune collagen-vascular disorder affecting the skin or other organ systems. Those with chronic cutaneous LE or subacute cutaneous LE are at low risk for renal disease and when present it is usually mild. Signs of nephropathy (proteinuria and hematuria) among patients carrying these diagnoses, however, may indicate an elevated risk of developing systemic LE (SLE) [15]. Among patients with chronic cutaneous LE, hypocomplementemia may be a marker for silent nephritis [16]. Periodic urinalysis of those with primarily cutaneous forms of LE is prudent.

Cutaneous findings, such as a malar (or butterfly) rash, photosensitivity, and cutaneous vasculitis, are common among patients with SLE. Using sensitive diagnostic techniques, renal involvement can be detected in most of those with SLE. Renal biopsy has revealed focal proliferative, diffuse proliferative,

or membranous glomerulonephritis in approximately three fourths of SLE patients [17]. Early aggressive, multidisciplinary intervention is indicated for managing SLE. Even with such a coordinated effort, renal failure indicates a poor prognosis for those with SLE.

The antiphospholipid antibody syndrome may present with cutaneous findings, such as livedo reticularis or Raynaud's phenomena. This hypercoagulability disorder may manifest itself in the kidney by thrombotic microangiopathy or large-vessel thrombosis. Although the incidence of renal disease in patients with antiphospholipid antibodies remains unclear, their presence may have a significant negative impact on the course of those with end-stage renal disease (ESRD). Antiphospholipid antibodies may be seen without associated illness in a small percentage of the population; spontaneously in the primary antiphospholipid syndrome; or in association with infection (such as HIV or hepatitis C) or autoimmune disorders, especially SLE [55].

Systemic sclerosis is a multisystemic connective tissue disease of unknown etiology. In established disease, cutaneous findings include indurated, hidebound skin with a shiny appearance. The face may have a taut, pinched look. Telangiectasias may be prominent on the face, lips, and fingertips. Hyperpigmentation of long-effected areas is common as is calcinosis cutis. Precipitous renal deterioration has been described but is fortunately rare. When severe skin and kidney involvement do occur, typically it is within the first few years after diagnosis. Frequent monitoring and early intervention when indicated are advised. Scleroderma renal crisis has been rare since the introduction of angiotensin converting enzyme–inhibitors for the treatment of this disease [18,19].

The cholesterol embolization syndrome is an acute, multisystem disorder seen primarily among patients with atherosclerotic vascular disease. It is increasingly diagnosed as a cause of acute renal insufficiency. Livedo reticularis may be seen in up to one half of patients with cholesterol embolization syndrome (Fig. 1). Ischemic changes of the digits may also be seen. Deep skin biopsy may be helpful in differentiating this condition from other forms of systemic vasculitis [20].

Hyperoxaluria may develop either primarily or secondarily. Primary oxalosis is a group of rare disorders, autosomal recessively inherited, with at least three distinct forms identified. Overproduction of oxalate with deposition in the kidney may progress to ESRD. Secondary hyperoxaluria may develop in chronic renal failure regardless of cause. Cutaneous manifestations of hyperoxaluria include livedo reticularis and necrotizing livedo reticularis resulting from intravascular occlusion of arterioles [21,22].

Henoch-Schönlein purpura is a systemic small-vessel vasculitis of unknown etiology. It classically presents in children or young adults with early distal lower extremity macular purpura progressing to palpable plaques, which may ulcerate. Arthralgias, abdominal pain, and renal impairment are variably present. The incidence of nephritis is estimated to be between approximately 25% and 50%. The appearance of truncal purpura may be a predicative factor of renal involvement. A minority of patients experience serious sequelae including chronic glomerulonephritis. Cutaneous biopsy revealing IgA deposition in vessel walls is helpful diagnostically [23,24].

Polyarteritis nodosa is an acute multisystem disorder causing necrotizing vasculitis of small- and medium-sized muscular arteries. Narrowing of affected vessels and microaneurysm formation result in tissue infarction, hemorrhage, and ultimately organ dysfunction. Approximately one third of patients with polyarteritis nodosa have cutaneous findings that include crops of tender, red, 0.5- to 1-cm subcutaneous nodules coursing over arteries. These nodular lesions are most common on the distal lower extremities. Livedo reticularis, superficial ulcerations, and cutaneous necrosis especially of digits may also be seen. Renal involvement occurs in most of those with systemic polyarteritis nodosa. Renal insufficiency is associated with poor prognosis. Early diagnosis and aggressive therapy are essential to obtain remission. The combined use of corticosteroids and cytotoxic agents (such as pulse methylprednisolone and cyclophosphamide) has been recently advocated [25–27].

Wegener's granulomatosis is also a necrotizing vasculitis affecting multiple organ systems. Approximately one half of those with Wegener's granulomatosis display skin findings. Mucocutaneous nasal granulomas may be seen early. Purpuric plaques and nodules of the lower and sometimes upper extremities may be seen. Less common cutaneous findings include livedo reticularis and Raynaud's phenomena. Renal involvement in Wegener's granulomatosis may be occult or symptomatic with edema and hypertension. Precipitous renal failure may occur but is not common. Again, early recognition and aggressive therapy are required if a poor outcome is to be avoided [25,27].

Cryoglobulinemia results from the presence of circulating immunoglobulins with the ability to reversibly precipitate in the cold. Originally reported in multiple myeloma and macroglobulinemia, they have subsequently been found in connective tissue diseases, chronic infections, acute and chronic glo-

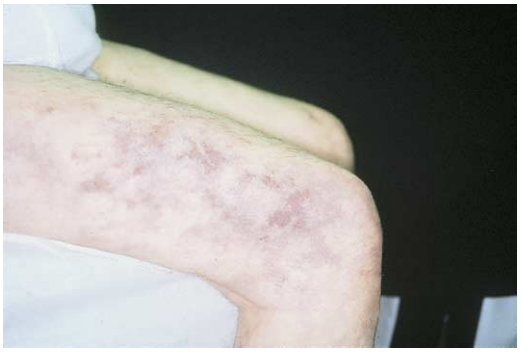

Fig. 1. Livedo reticularis secondary of cholesterol emboli.

merulonephritis, renal transplantation, and other varied conditions. A classification system based on the population of immunoglobulins found within an individual has been established [28].

Most patients with cryoglobulinemia presents with arthralgia, fatigue, and purpura. Purpura may be macular or palpable; may be associated with hemorrhage, crusts, or ulceration; and tends to be more acral in location. Other cutaneous presentations include Raynaud's phenomena and cold-induced urticaria. Glomerulonephritis occurs in approximately 50% of patients and may rapidly progress to acute renal failure or slowly to chronic disease. Treatment should be focused on any underlying primary disease when identified. Supportive therapy may include avoidance of lower temperatures and nonsteroidal anti-inflammatory agents. More severe disease has been treated with corticosteroids, immunosuppressive agents, plasmapheresis, and interferon-alpha [28].

Amyloidosis also occurs because of the deposition of aberrant proteins throughout various organ systems. Primary (idiopathic) and secondary forms of the disorder exist. In systemic amyloidosis, the most common skin findings are periorbital purpura (Fig. 2) and so-called *pinch purpura* of the limbs. Other findings include small waxy, translucent papules tending to coalesce most commonly about the eyes, nose, and mouth. When renal disease occurs, proteinuria with progression to renal failure is common [29].

Gout, sarcoidosis, and diabetes mellitus are also systemic diseases with well-documented effects on both the integument and the kidney. Nephrolithiasis is a common manifestation of gout. Nephrocalcinosis and granulomatous interstitial nephritis are reported causes of renal failure in sarcoidosis [30,31]. Diabetes may have profound effects on renal function. A review of the myriad cutaneous manifestations of these diseases is beyond the scope of this article.

Cutaneous findings related to ESRD

End-stage renal disease is the unfortunate common end point of many processes. Regardless of cause, a reproducible spectrum of progressive skin changes may be observed. Chronic renal failure contributes to anemia with resulting universal pallor of the skin. The deposition of carotinoids and urochromes leads to a yellow shading of the integument. A photodistributed hyperpigmentation may occur secondary to increased levels of β–melanocyte-stimulating hormone [32,33]. Platelet dysfunction may lead to widespread ecchymoses. Xerosis and decreased skin turgor are common, possibly a consequence of chronic dehydration. Decreased sebum production may contribute to generalized ichthyosis. Pruritus is a frequent symptom and often leads to excoriation, which may be the most impressive finding on examination. Findings of more advanced disease include uremic frost, a rare event, and, among patients with secondary hyperparathyroidism, cutaneous or vascular calcification. Nail changes may occur in 30% to 50% of patients. Half-and-half (Lindsay's) nails have an opaque, white, proximal half with a normal to red-brown distal half (Fig. 3) [33,34].

Cutaneous findings in dialysis patients

Maintenance hemodialysis and peritoneal dialysis are lifesaving procedures. Dialysis does not, however, eliminate many of the cutaneous signs and symptoms of ESRD. Additionally, a minority of dialysis patients develop further skin conditions, such as perforating disorders and bullous disorders.

Pruritus afflicts between 60% and 90% of dialysis patients and in some cases is constant [34–36]. Hypotheses abound but the exact cause of pruritus

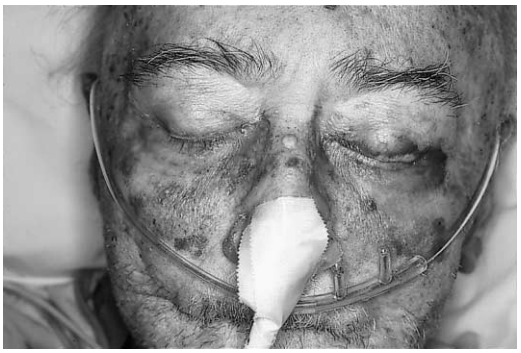

Fig. 2. Primary systemic amyloidosis in a patient with multiple myeloma.

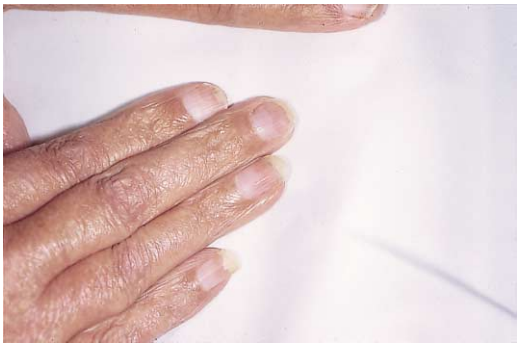

Fig. 3. Half-and-half nails in a patient with renal insufficiency.

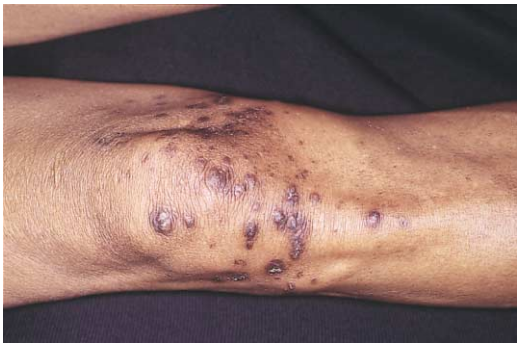

Fig. 5. Kyrle's disease in a patient with renal failure on hemodialysis.

in this setting remains undetermined. The temporal relationship between dialysis and pruritus is varied. Treatment with emollients with or without topical steroids is usually less than satisfactory. Although treatment with antihistamines is usually disappointing, administration of erythropoietin has been reported effective and may work by reducing plasma histamine concentrations [37]. Many patients experience relief from ultraviolet B (but not ultraviolet A) exposure. Other therapies including parathyroidectomy have met with varied success [34,36].

As in untreated ESRD, ecchymoses and purpura are common and can be extensive. Again, platelet dysfunction is involved; the necessary use of anticoagulants in this population compounds the problem.

The development of blistering disorders among patients on hemodialysis is well documented. Crops of delicate 0.25- to 1-cm vesicles occur most commonly on the extensor forearms and dorsal hands (Fig. 4). Other photoexposed areas may become involved. Milia, atrophic scarring, and hyperpigmentation may develop. Investigation proves most of these eruptions to be porphyria cutanea tarda or pseudoporphyria. In porphyria cutanea tarda, porphyrin levels are elevated. Among coexistent infections and processes, hepatitis C is becoming more frequently recognized. Various environmental agents have also been reported to contribute to porphyria cutanea tarda in this population. Porphyrin levels remain normal in pseudoporphyria. When a cause can be found, medications are usually to blame. Avoidance of sunlight and the elimination of other identifiable triggers are essential for treating both conditions. The sequential use of erythropoietin to boost the hemoglobin followed by phlebotomy to reduce iron stores has been advocated for the treatment of porphyria cutanea tarda associated with ESRD [38].

The acquired perforating dermatosis seen in ESRD and dialysis patients is thought to be unique from the other primary perforating disorders (Kyrle's disease, elastosis perforans, serpiginosa, reactive perforating collagenosis, and perforating folliculitis). The unifying feature of these disorders is the transepidermal elimination of altered dermal substances.

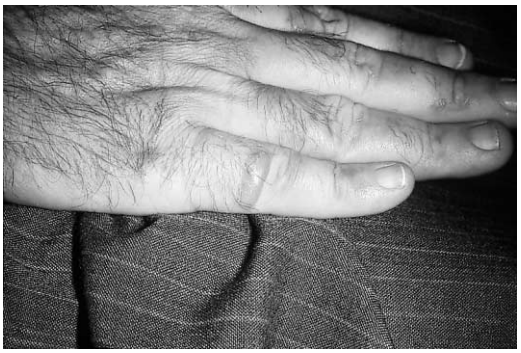

Fig. 4. Bullous dermatosis of renal failure. Note the tense blister on the lateral fifth finger.

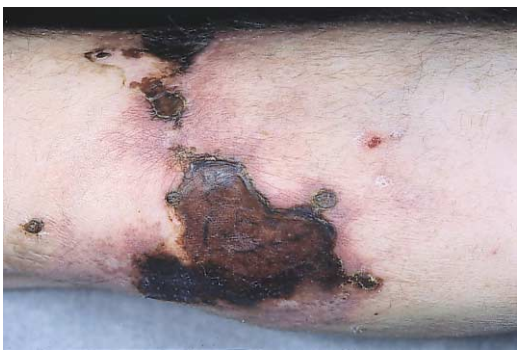

Fig. 6. Reticulated, necrotic lesions on the thigh of this patient with renal failure secondary to amyloidosis.

Unique clinical and epidemiologic features allow for differentiating these disorders [34,39,40]. Acquired perforating dermatosis may affect as many as 10% of those on chronic hemodialysis. It is more common among blacks and those with ESRD secondary to diabetes. Its clinical presentation is variable, although pruritus is invariably present. Hyperpigmented keratotic papules and nodules most commonly occur on the trunk and proximal extremities (Fig. 5). Central keratinous plugs may be seen as unexcoriated lesions. Treatment is often unsatisfactory. Topical and intralesional steroids have been used. Topical and oral retinoids may be used with variable success. Ultraviolet B may help to control underlying pruritus [34].

Metastatic calcifications may occur in dialysis patients as a result of perturbed calcium or phosphate metabolism. As calcium salts precipitate in the skin and its supporting tissues, benign nodular calcification (calcinosis cutis) or calciphylaxis may be seen clinically. In the former, firm plaques and nodules are seen most commonly about the joints and fingertips. Occasionally a chalky discharge may be elicited from such lesions. Thought sometimes painful, the process is not life threatening. The condition may clear with correction of calcium and phosphate levels; surgical resection may be used for more stubborn cases.

Calciphylaxis is a critical condition with a high rate of associated mortality. It is a more generalized process with painful purpuric plaques seen symmetrically, often with associated necrosis. A reticulated pattern is often seen. The abdomen, buttocks, and thighs are frequently affected (Fig. 6). Medical management to normalize calcium and phosphorus levels and limited debridement of necrotic areas is sometimes helpful. Parathyroidectomy is not recommended unless severe hyperparathyroidism exists [41–43].

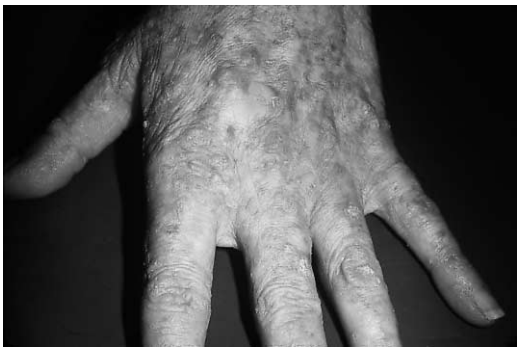

Fig. 7. Multiple viral warts on the dorsal hands of this renal allograft recipient on long-term immunosuppressive therapy. This patient also developed multiple squamous cell carcinomas.

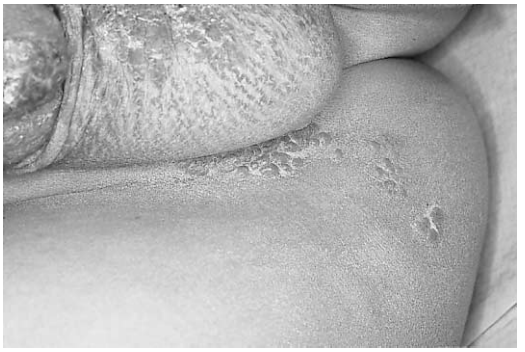

Fig. 8. Herpes simplex in a renal allograft recipient.

Recently, a possible association between Grover's disease, a usually transient, pruritic eruption of truncal keratotic papules, and chronic renal failure and/or hemodialysis has been posited [44].

Cutaneous findings in renal transplant patients

The now almost mundane practice of renal transplantation has created a large population of patients fortunate to have escaped the rigors of dialysis. Unlike dialysis, transplantation does improve or eliminate many of the skin findings of ESRD. Transplantation may, however, lead to its own spectrum of skin problems.

The necessity for chronic immunosuppression creates an opportunity for infectious agents. An increased prevalence of cutaneous viral, bacterial, and fungal infections is well documented (Figs. 7–9) but a complete discussion of this issue is beyond the scope of this article. Compromised immunosurveillance leads to an increased number of cutaneous neo-

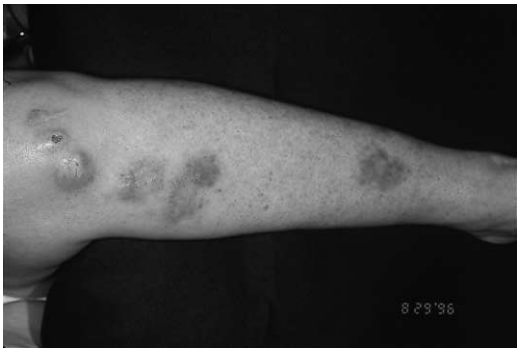

Fig. 9. Multiple dermal nodules in this renal allograft recipient are caused by infection with *Mycobacterium chelonea.*

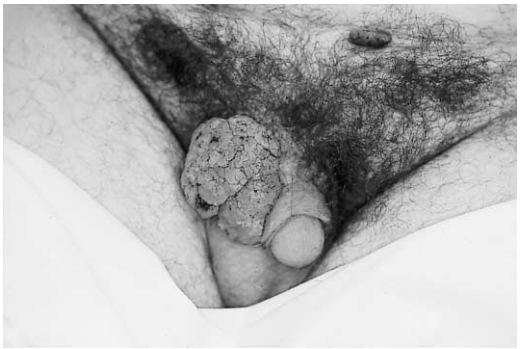

Fig. 10. Verrucous carcinoma in this renal allograft recipient.

plasms. Warts and actinic keratoses are more common and if untreated may progress to invasive squamous cell carcinoma (Fig. 10) [45]. Cutaneous and vermilion squamous cell carcinoma, malignant melanoma, and Kaposi's sarcoma are more common among renal transplant patients than the general population [46]. Malignant fibrous histiocytomas and atypical fibroxanthomas also may occur at a higher incidence [47]. Ramsay et al [48] have delineated risk factors associated with nonmelanoma skin cancer in this population. Once identified, such patients should be examined frequently and suspicious lesions treated aggressively. The importance of ultraviolet protection must be stressed to the patient. Topical and oral retinoid therapy also may be appropriate in some cases.

Cutaneous manifestations of renal malignancy

Certain cutaneous findings may alert one to the possibility of occult renal malignancy. The sign of Leser-Trélat is a rather nonspecific syndrome consisting of an acute increase in the size or number of seborrheic keratoses with or without associated pruritus. It has been reported in conjunction with various benign conditions and occult malignancies including renal cell carcinoma [49]. A hereditary syndrome featuring multiple cutaneous leiomyomas and an increased incidence of renal cell carcinoma has been described [56]. Cutaneous metastatic renal carcinoma is a rare event. Asymptomatic pink to violaceous nodules between 0.5 and 2.90 cm are most frequently found on the head, neck, or trunk. Larger, exophytic tumors in excess of 5 cm have been reported [50]. Subungual metastatic renal cell carcinoma has also been reported with variable clinical presentation [51]. Congenital malignant rhabdoid tumor is a rare entity, which may present as a cutaneous nodule to the neck or back [52].

Miscellaneous

Cutaneous nephrocolonic fistulization is a rare event, which presents as a painful, discharging opening usually of one flank. It represents a direct communication between the kidney and the skin. It has been reported as a complication of renal calculi and genitourinary tuberculosis [53,54].

Summary

There are numerous cutaneous findings that may be related to coexistent renal disease. An astute clinician may use careful skin examination to make early diagnosis of renal conditions in some cases, and institute appropriate therapy as soon as indicated.

Acknowledgment

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DERMATOLOGIC CLINICS

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Paraneoplastic dermatoses

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Throughout history, physicians have had the ability to diagnose some systemic illnesses based on a skin abnormality. From anecdotal associations to statistically significant relationships, skin findings can be valuable in signaling a disease before other manifestations occur. Many of these relationships are controversial, especially when a common skin finding, such as a seborrheic keratosis, occurs in a patient with cancer. In 1976, Helen Ollendorff Curth set criteria that should be met before a skin disease can be called a paraneoplastic dermatosis: (1) both conditions start at approximately the same time; (2) both conditions follow a parallel course; (3) in syndromes, neither the onset nor the course of either condition is dependent on the other; (4) a specific tumor occurs with a specific skin manifestation; (5) the dermatosis is not common in the general population; and (6) a high percentage of association between the two conditions is noted. Currently, only the first two of these criteria should be met to declare a skin disease a paraneoplastic dermatosis [1].

This article lists only classic paraneoplastic dermatoses. The complete pathophysiology of the skin disease in relation to the tumor cannot always be explained. These dermatoses can occur before or after the diagnosis of internal malignancy and in some cases can herald recurrence of a malignancy.

Necrolytic migratory erythema

Necrolytic migratory erythema (NME) is the skin manifestation of the glucagonoma syndrome, which is typically caused by glucagon secretion from a carcinoma of the alpha islet cells of the pancreas. The syndrome can include NME, glucose intolerance, weight loss, anemia, hair and nail changes, hypoaminoaciduria, psychiatric disturbances, and thromboembolic disease [2].

Necrolytic migratory erythema was first described in 1942 by Becker [3]. Patients develop erythematous maculae and papules, often annular or arciform, on the central face, lower abdomen, perineum, groin, buttocks, and thighs. These scaling maculae and papules progress to erosions secondary to epidermal necrosis. The skin disease has a waxing and waning course that does not seem to follow the course of the glucagonoma. NME can be an early or late manifestation of glucagonoma syndrome, but it is typically a late sequelae [2].

The exact pathophysiology of NME is not known, but is probably related to catabolism from increased levels of glucagon [4]. Although NME is related in clinical and histologic appearance to acrodermatitis enteropathica, zinc levels are inconsistent [4]. Deficiencies in chemotaxis, however, have been reported in mononuclear and polymorphonuclear cell populations, which could be related to zinc uptake [68].

Histologically, NME shows subcorneal and epidermal clefts, keratinocytes with pyknotic nuclei, confluent parakeratosis, and a characteristic absence of acantholysis. Immunofluorescence is negative.

Necrolytic migratory erythema often goes undiagnosed for long periods of time. When suspected, the clinician should be aggressive. Seventy-five percent of glucagonomas are metastatic at the time of diagnosis [5]. Work-up should include serum glucagon levels, CT scan, celiac angiography, or endoscopic ultrasonography. Although the gold standard for treatment of glucagonoma is surgery, a few medical treatments for this syndrome are available. Somatostatin

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seems to work well in some cases, secondary to its ability to decrease glucagon secretion [4]. Intravenous amino acids have been reported as successful in other cases [2]. Other older treatments include iodoquinol, hydrocortisone, dacarbazine, a high-protein diet, and chemotherapy.

Cushing's syndrome

Cushing's syndrome is a condition of ectopic production of adrenocorticotrophic hormone. It is similar to Cushing's disease, which is a result of a pituitary tumor. They are both a condition of glucocorticoid excess and symptoms can be indistinguishable [6]. Neoplastic processes that cause Cushing's syndrome include oat cell lung cancer, carcinoma of the thymus, pancreatic carcinoma, pheochromocytoma, medullary thyroid carcinoma, and cancers of the male and female reproductive organs [6–8].

Noncutaneous findings include hypertension, weight loss, muscle wasting, hypokalemia, and hyperglycemia [8]. Possible cutaneous findings are hyperpigmentation, edema, facial plethora, truncal obesity, soft tissue fullness in the supraclavicular and cervical areas, acne vulgaris, striae, atrophic skin, telangiectasia, and ecchymoses [8–10].

Cushing's syndrome can usually be diagnosed clinically, but laboratory values, such as a low serum potassium, elevated urine cortisol levels, and a corticotropin level not suppressible with the administration of dexamethasone, are also highly suggestive of this condition [6]. The development of Cushing's syndrome is a poor prognostic indicator for the neoplastic process because it is a late manifestation of neoplastic disease.

Carcinoid syndrome

Carcinoid tumors were named in the early 1900s because they seemed "similar to carcinoma" [11]. Although carcinoid tumors typically have a good prognosis compared with other types of cancer, the carcinoid syndrome can be an ominous set of signs and symptoms. Carcinoid tumors are comprised of amine precursor and decarboxylation cells. Eighty-five percent of carcinoid tumors develop in the gastrointestinal tract, but they can also develop in other sites, such as the lung, ovary, thymus, kidney, and prostate [11]. Usually, the carcinoid syndrome presents only after metastases have occurred [11]. Primary carcinoid tumors are multiple in 15% to 20% of cases [12].

Patients can present with diarrhea, flushing or cyanosis, asthma, edema, hypoalbuminemia, and right-sided heart failure [11]. Less common findings are telangiectasia or pellagra-like skin findings [12]. A few cases of scleroderma-like skin have been reported in carcinoid syndrome [13]. The substances responsible for carcinoid syndrome have been identified but the exact pathogenesis has yet to be explained. Serotonin, kallikrein (bradykinin), substance P, neuropeptide K, prostaglandins E and F, and neurokinin A have all been found to be elevated in cases of carcinoid syndrome.

Patients with this syndrome can usually be diagnosed clinically, but definitive diagnosis can be made by finding elevated 5-hydroxyindoleacetic acid in the urine [12]. Treatment of carcinoid tumors is surgical removal [11]. Other medical treatments are somatostatin, methysergide, cyproheptadine, ketanserin, beta blockers, phenothiazine derivatives, histamine-receptor antagonists, and kallikrein inhibitors [11]. In advanced cases, chemotherapy for the carcinoid tumor is employed.

Sign of Leser-Trélat

The sign of Leser-Trélat was first reported in 1890, and was actually first reported as an increase in the number of cherry angiomas in patients with cancer [14]. Through the years, this sign has evolved to refer to an increase in number or size of seborrheic keratoses in patients with internal malignancy. Although the sign is controversial and the seborrheic keratoses themselves require no treatment, the sign is widely accepted as a warning to physicians that a thorough internal malignancy work-up is in order.

The sign of Leser-Trélat is most often found in patients with adenocarcinoma of the stomach or colon [14], but has also been reported numerous times in patients with hematopoietic, breast, lung, ovarian, and uterine malignancies [15,16]. Treatment of the malignancy results in involution of seborrheic keratoses approximately half of the time [17].

The sign can appear as early as 5 months before the diagnosis of the malignancy or as late as 9.8 months after the diagnosis [15]. Associated pruritus is reported in many patients, and most often the seborrheic keratoses erupt on the trunk [14].

Many theories have been set forth for the pathogenesis of eruptive seborrheic keratoses in the setting of an internal malignancy. Elevated levels of growth factors, disrupted epidermal cell turnover regulation, and impeded host defense have been suggested as causes of this condition [16]. The arguments against

the existence of the sign of Leser-Trélat have been that seborrheic keratoses are common findings in the general population, and that patients with cancer are more likely to find these keratoses because of their heightened concern for abnormalities of any organ [18].

Acanthosis nigricans

Acanthosis nigricans is characterized by velvety hyperpigmentation and papillomatosis of the skinfolds. The neck, axillae, antecubital, and popliteal fossae are affected most commonly. Benign acanthosis nigricans is associated with insulin-resistant disorders including diabetes mellitus, obesity, and polycystic ovary syndrome. Malignant acanthosis nigricans is most strongly associated with intra-abdominal adenocarcinoma, with gastric carcinoma detected in 45% of cases [19]. Paraneoplastic acanthosis nigricans has also been reported in association with carcinoma of the lung, liver, uterus, breast, and ovary and with lymphoma and mycosis fungoides [19].

Malignant acanthosis nigricans develops more abruptly and progresses more rapidly and diffusely than its benign counterpart. Mucosal surfaces may exhibit a papillomatous appearance and the palms may show tylosis or a rugose hyperkeratosis referred to as *tripe palms*. Alopecia and pruritus have also been reported in malignancy-induced acanthosis nigricans. Eruptive seborrheic keratoses (sign of Leser-Trélat) and florid cutaneous papillomatosis may occur simultaneously [19,20,69].

Acanthosis nigricans may present before, after, or concurrent with the diagnosis of malignancy. In one review, 69% of cases of malignant acanthosis nigricans presented before the diagnosis of malignancy [19].

Acanthosis nigricans may improve with treatment of the underlying cancer. This supports the hypothesis that a tumor product acts as a growth factor, stimulating keratinocytes to proliferate. Transforming growth factor-α is one potential agent.

Tripe palms

Tripe palms are hyperkeratotic with exaggeration of the normal dermatoglyphics. This gives the palms a rugose, velvety appearance resembling tripe, the gut lining of bovine species. Tripe palms are associated with malignancy in over 90% of cases [19,20]. Acanthosis nigricans may coexist with tripe palms. In patients with both acanthosis nigricans and tripe palms, gastric carcinoma is the most common underlying malignancy. Lung cancer is the most frequently associated neoplasm in those without accompanying acanthosis nigricans [21,22]. Like acanthosis nigricans, tripe palms may present before the diagnosis of malignancy and should prompt a comprehensive search for cancer [22,23].

Hypertrichosis lanuginosa acquisita

One of the most ominous paraneoplastic conditions is hypertrichosis lanuginosa acquisita. This is the sudden appearance of downy, soft, nonpigmented hair on the body. It was first reported in 1865 in a patient with breast cancer [24]. The most common associated malignancy is that of the lung, followed by colorectal carcinoma [24]. Other reported associated malignancies are bladder, ovarian, uterine, and pancreatic [25]. Hair growth typically occurs on the face, but can also occur on the trunk, limbs, and ears [26]. Palms, soles, and genital areas are usually spared. Histology of the hair follicle shows hypertrophy [27].

Hypertrichosis can be caused by thyrotoxicosis; local trauma; corticosteroids; porphyria; or drugs, such as penicillamine, phenytoin, and spironolactone [26,28]. When these potential causes have been eliminated, a work-up for malignancy must be performed. Numerous studies have been done to find a consistent hormonal abnormality, but this search has been fruitless [24]. Hypertrichosis lanuginosa acquisita can be found in association with other signs and symptoms, including glossitis, glossodynia, diarrhea, adenopathy, and acanthosis nigricans [26]. In some cases, the hypertrichosis resolves with treatment of the tumor [27].

Acquired ichthyosis

Acquired ichthyosis resembles autosomal dominant ichthyosis vulgaris both clinically and histopathologically. Like ichthyosis vulgaris, acquired ichthyosis most commonly involves the skin on the extensor surfaces of the extremities with relative sparing of the flexural skinfolds, palms, and soles. The involved skin exhibits rhomboidal scales with free, slightly elevated margins. Histologically, acquired ichthyosis shows hyperkeratosis with a decreased or absent granular layer similar to inherited forms of ichthyosis vulgaris.

Many systemic diseases and medications have been implicated in the development of acquired ichthyosis, including AIDS, sarcoidosis, leprosy, and malignancy. Lymphoreticular malignancies, particularly Hodgkin's lymphoma, are the most common

cancers associated with the onset of ichthyosis [29]. Patients with new-onset ichthyosis in association with cancers of the breast, lung, and cervix have also been reported [29]. Acquired ichthyosis tends to develop after the diagnosis of malignancy has been made and its course may parallel that of the underlying neoplasm [29,30].

The pathogenesis of acquired ichthyosis is unknown. Cooper et al [31] demonstrated normal epidermal lipid synthesis in patients with lymphoma and acquired ichthyosis. This contrasts to ichthyosis vulgaris where epidermal lipid synthesis is increased. Dermal lipid synthesis was decreased in all patients with Hodgkin's lymphoma irrespective of clinical skin involvement [29].

The treatment of choice for acquired paraneoplastic ichthyosis is targeted at the underlying malignancy. The course of the ichthyosis frequently parallels the course of the inducing neoplasm [29,30]. Skin-directed therapies include topical lubricating agents and keratolytics [29]. Even with appropriate topical care, it is unlikely that the process will regress without successful treatment of the underlying cancer.

Bazex's syndrome

Bazex's syndrome is characterized by papulosquamous plaques on the acral surfaces of the ears, nose, hands, and feet. These lesions are often symmetric and exhibit a violaceous erythema. Bullous lesions and hyperpigmentation have also been reported. The fingernails are involved in more than 75% of cases reported [19]. Nail changes include longitudinal and horizontal ridging, thickening, subungual debris, and discoloration.

Nearly all patients with Bazex's syndrome are males and most have a coexistent squamous cell carcinoma of the upper aerodigestive tract. Ninety-three percent (105 of 113) of patients in one review were male and 48% (54 of 113) had a squamous cell carcinoma of the oropharynx or larynx [32]. Squamous cell carcinoma originating from the lung, esophagus, thymus, vulva or an unknown primary accounted for an additional 39 cases [32].

The skin manifestations of Bazex's syndrome most often precede the diagnosis of malignancy but they may appear simultaneously or appear after the detection of a neoplasm [32]. In one review, cutaneous changes preceded the diagnosis of malignancy by an average of 11 months in over 60% of patients with Bazex's syndrome [19].

The treatment of choice for Bazex's syndrome is effective eradication of the underlying tumor. In most reported cases, the dermatosis improves with cancer treatment or worsens as the underlying malignancy progresses [32,33]. Nail dystrophy may persist after effective cancer therapy and resolution of other cutaneous changes [32,33].

The cause of Bazex's syndrome is unknown. Antigen cross-reactivity between tumor and skin has been postulated as has the presence of a tumor-derived keratinocyte growth factor [33]. Patients exhibiting clinical findings consistent with Bazex's syndrome should undergo extensive cancer screening.

Erythema gyratum repens

Another classic paraneoplastic dermatosis is erythema gyratum repens. This cutaneous disease presents as rapidly migrating concentric rings of erythema with trailing scale on the trunk and proximal extremities [34,35]. It is often intensely pruritic and when the underlying tumor is treated, the pruritus improves [36]. Lung cancer is the most common associated malignancy, but many others have been reported, including tumors of the breast, cervix, stomach, pharynx, anus, bladder, and bowel [35]. Eighty percent of the time the skin disorder precedes diagnosis of the tumor [37]. Males are affected twice as commonly as females [35]. Histology shows hyperkeratosis, parakeratosis, acanthosis, and hydropic degeneration with pigment incontinence.

Paraneoplastic pemphigus

Paraneoplastic pemphigus (PNP) was first described in 1990 and is now recognized as a distinct autoimmune blistering disorder associated with both benign and malignant lymphoproliferative processes. Clinically, it is characterized by blistering and erosions of the oropharynx and of the cutaneous surfaces of the trunk and extremities. Lichenoid skin changes are frequently observed. The palms and soles may be involved and an inflammatory paronychia is present in some patients. Intractable stomatitis is the most constant feature. The stomatitis is frequently the first sign of disease and is the least likely to respond to treatment [38].

Biopsy of lesional skin in a patient with PNP shows epidermal suprabasilar acantholysis, vacuolar degeneration of the basal layer with keratinocyte necrosis, and inflammation. Inflammation is a distinguishing characteristic not typically seen in other types of pemphigus and may relate to a presumptive antitumor immune response hypothesized in PNP

[38]. Direct immunofluorescence of perilesional skin exhibits epidermal, intracellular IgG and complement and linear staining at the dermal-epidermal junction. Indirect immunofluorescence reveals antibodies directed against the epidermal cell surface and the basement membrane zone. Characteristically, serum of patients with PNP also reacts with transitional epithelium as opposed to other forms of pemphigus. These antibodies are most commonly targeted against desmosomal plakins, including periplakin and envoplakin. Desmoplakins, desmoglein 1, desmoglein 3, plectin, and BPAG1 are also targets in some individuals [37–39]. The antigens targeted in PNP are present in transitional epithelium and respiratory epithelium and stratified squamous epithelium [38].

Most cases of paraneoplastic pemphigus occur in patients with known lymphoproliferative malignancies. Two thirds of patients with paraneoplastic pemphigus have a known malignancy at the time of presentation [38]. Non-Hodgkin's lymphoma and chronic lymphocytic leukemia are present in 42% and 29% of cases, respectively [38]. Castleman's disease and thymoma are also frequently associated with paraneoplastic pemphigus [38]. It is imperative to screen for occult malignancy in those patients presenting with paraneoplastic pemphigus. A complete blood cell count, chemistry profile, serum protein electrophoresis, and a CT scan of the chest, abdomen, and pelvis are recommended in addition to physical examination of the liver, spleen, and lymph nodes [38].

The pathogenesis of this autoimmune phenomenon is speculative. Hypotheses include tumor production of epidermal moieties that stimulate an antitumor immune response that cross-reacts with the skin. Enhanced cytokine production and activity stimulated by the underlying lymphoproliferative diseases has also been implicated in the development of autoimmunity [38].

The treatment of PNP depends on the inducing disease. PNP associated with benign processes generally responds well to treatment of the underlying disease and surgical resection of these tumors is indicated when possible. Effective treatment of malignancy is not always associated with improvement in the skin changes of PNP. In particular, stomatitis may persist despite cancer ablation. Prednisone and cyclosporine in combination with mycophenolate mofetil have shown some benefit in patients with otherwise intractable disease [38,40]. Other immunosuppressive agents, including azathioprine and cyclophosphamide, have shown limited utility [38].

Paraneoplastic pemphigus is associated with a high mortality rate. Death can occur secondary to sepsis, bleeding, multiorgan failure, and respiratory failure. Associated autoimmune cytopenias and direct involvement of the respiratory epithelium by paraneoplastic pemphigus antibodies may play a role in these events [38].

Dermatomyositis

Classic findings of cutaneous dermatomyositis include a heliotrope rash of the periorbital skin and Gottron's papules. The heliotrope rash is a violaceous erythema of the periorbital skin. Gottron's papules are flat-topped erythematous papules and plaques over the extensor surfaces of the joints, which may exhibit scale and telangiectasia. Other cutaneous manifestations of dermatomyositis include poikiloderma, periungual telangiectasia, and scalp pruritus and erythema. Muscle involvement manifests as proximal muscle weakness with frequent elevations in creatine kinase levels and aldolase.

Dermatomyositis may be idiopathic or paraneoplastic. It is estimated that 25% of patients with dermatomyositis have had or will develop a malignancy [19]. The malignancy may be present before the diagnosis of dermatomyositis or may occur simultaneously or after identification of dermatomyositis [19,41]. In one study, 7 of 23 patients (30%) developed dermatomyositis subsequent to a diagnosis of internal malignancy. In three of these seven patients, the development of dermatomyositis prompted a malignancy screening that detected recurrent neoplasia. Nine of the 23 patients (39%) were diagnosed with malignancy at the time of presentation with dermatomyositis. In the remaining seven patients (30%) malignancy was detected after the diagnosis of dermatomyositis was confirmed but remote from the original cancer screening [42–45,67]. In another study of 34 patients with malignancy and dermatomyositis, 85% of patients were diagnosed with malignancy before or within 1 year of the diagnosis of malignancy [19].

The most common malignancies associated with dermatomyositis include genital neoplasms in women and respiratory tract neoplasms in men [42]. Sigurgeirsson et al [43] reported a 17-fold increase risk for the development of ovarian cancer in women with dermatomyositis. Eighteen (30%) of 61 cancers in this study originated in the breast or ovary. Seventeen (28%) of 61 cancers originated in the respiratory tract. In another study, cancers of the breast, uterus, or ovary accounted for 17 of 34 dermatomyositis-associated malignancies and those of the lung, pharynx, or larynx accounted for an additional 8 cases [44].

Paraneoplastic dermatomyositis may be suspected in a patient with poorly controlled dermatomyositis or with a flare of previously well-controlled disease [42]. Other factors that may be predictive for a paraneoplastic etiology include older age and male gender [45]. The presence of interstitial lung disease, cardiac or esophageal complications, and calcinosis have been reported to be indicators of benign idiopathic dermatomyositis [41,45].

Patients with dermatomyositis warrant a comprehensive, age-appropriate cancer screening. This screening should be repeated in any patient with a flare of disease, in those patients whose dermatomyositis is difficult to treat, or on a yearly basis [41].

Sweet's syndrome

Sweet's syndrome was first reported in 1964 by Sweet [46]. He reported eight women with combinations of fever, neutrophilic leukocytosis, raised painful plaques, and a neutrophilic infiltrate in the dermis. Since then, an association has been found with Sweet's syndrome and cancer. Most notably, there is an association with acute myelogenous leukemia [66]. Solid tumors have also been reported with Sweet's syndrome, most commonly genitourinary tumors [1].

Idiopathic Sweet's syndrome typically clears with oral steroids, has a female predilection, and can follow an upper respiratory infection. Malignancy-associated Sweet's syndrome has no gender predilection, is not preceded by upper respiratory infection, and commonly has laboratory abnormalities of erythrocytes and platelets [47,48]. Neutrophilia is less common in malignancy-associated Sweet's syndrome than in the idiopathic variety [48]. If the diagnosis of Sweet's syndrome is made, a complete blood count should be checked. If this is normal, no further workup is necessary [1]. Treatments for Sweet's syndrome include oral steroids, colchicine, potassium iodide, indomethacin, clofazamine, and dapsone [47,48]. Often, in acute myelogenous leukemia–associated disease, a relapse of Sweet's syndrome signals a relapse of the leukemia [48]. Extracutaneous manifestations can occur in Sweet's syndrome including renal, ocular, musculoskeletal, and pulmonary findings [47].

Multicentric reticulohistiocytosis

Multicentric reticulohistiocytosis (MRH) is a disease with cutaneous and rheumatologic manifestations. Cutaneous disease presents with violaceous papules and nodules on the hands, knees, shoulders, wrists, hips, elbows, ankles, feet, and spine [49]. Arthritis mutilans occurs in approximately 50% of patients, and the classic "opera glass hand" is a result of shortening and tapering of digits [49,50]. Twenty-eight percent of patients with MRH develop a malignancy of some kind, but no predominant type of cancer has been found [49]. Some associated cancers are pancreatic adenocarcinoma, squamous cell cancer of the lung, and metastatic melanoma [51].

One third of patients with MRH have constitutional symptoms, such as weight loss, weakness, and fever [50]. The disease seems to be a result of the destructive effects of proteinases [50]. The pathology of MRH includes a multinucleate giant cell infiltrate with ground-glass, periodic acid–Schiff stain–positive cytoplasm in the upper dermis [51].

Numerous therapies have been attempted, but unfortunately none have proved to be effective. Treatments that have been reported include oral and intralesional steroids, nonsteroidal anti-inflammatory drugs, psoralen plus ultraviolet A, antimalarials, cyclophosphamide, chlorambucil, azathioprine, vincristine, methotrexate, and nitrogen mustard [50].

Cutaneous amyloidosis

Amyloidosis can occur in primary or secondary forms, and systemic and cutaneous forms. Primary systemic amyloidosis is often seen with multiple myeloma or other B-cell neoplasms [65]. Secondary systemic amyloidosis rarely involves the skin and in 75% of these cases a renal cell carcinoma is the primary tumor [52].

Cutaneous amyloidosis has further subdivisions. The primary, macular, and lichenoid types originate from keratinocytes and are sometimes seen with thyroid cancer or multiple endocrine neoplasia. Nodular cutaneous amyloidosis is made up of light chain material from immunoglobulins and can be seen with plasmacytoma. Secondary cutaneous amyloidosis occurs with benign and malignant epidermal tumors, such as intradermal nevi and ulcerated basal cell carcinomas [65]. When amyloid occurs in the skin, it typically presents as smooth, waxy, nonpruritic papules and plaques, particularly on the face. The eyelids can have these papules or classically show "pinch purpura" after Valsalva's maneuver, vomiting, or proctoscopy. Other cutaneous findings include alopecia, nail dystrophy, pigmentary changes, and bullous lesions [6]. The actual amyloid material on biopsy can be stained purple with crystal violet and shows apple-green birefringence with Congo red and

thioflavine-T [6]. In 40% to 50% of cases, amyloid can be detected in clinically uninvolved skin [52].

Laboratory abnormalities can include elevated liver function tests, anemia, thrombocytosis, elevated serum creatinine, and hypercalcemia, especially with myeloma [52]. If amyloidosis is suspected, a serum and urine immunoelectrophoresis is in order [6].

Erythroderma

Erythroderma is an exfoliative dermatitis with a dramatic clinical presentation characterized by widespread erythema and scaling of the skin. It may begin as scattered erythematous, pruritic patches that become more generalized with time. The palms and soles are usually spared [53,54]. Patients may exhibit alopecia and nail dystrophy. Lymphadenopathy is present in many patients with erythroderma and lymph node biopsies of enlarged nodes most commonly exhibit dermatopathic lympadenopathy [54–57]. Hepatosplenomegaly may also be detected. Pruritus may be severe and paroxysmal [54,56,57]. Patients may also complain of headaches, malaise, photosensitivity, and a chilly sensation [54,56,57]. Hypothermia or hyperthermia may develop with serious cardiovascular consequences [54]. The most common cause of death in two large series was pneumonia [54,55].

Erythroderma has many potential causes including pre-existing dermatoses, drug reactions, and malignancy. Lymphomas and leukemias are the most common cancers associated with erythroderma, accounting for 4% to 17% of cases in several series [54,55,57]. Erythroderma associated with cancers of the liver, lung, thyroid, and prostate have also been reported [54]. In one study, an underlying cause for erythroderma was not discovered in 47% of patients [55].

There are no reliable clinical differentiating markers helpful in determining the cause of erythroderma [54,55,57]. History may be helpful in establishing a medication as the inducing agent or revealing the presence of a prior skin disease. Skin biopsy may be helpful in those patients with mycosis fungoides but frequently multiple biopsies over months or years are required to make the diagnosis. Histopathologic evaluation is of limited use in the search for an underlying cause of erythroderma outside of the realm of lymphoma [55].

In paraneoplastic erythroderma, skin changes most commonly present before the diagnosis of malignancy is made. In one series, 20 of 24 patients with erythroderma and mycosis fungoides, Hodgkin's lymphoma, or other lymphomas or leukemias exhibited skin changes up to 25 years before the diagnosis of malignancy [54]. Screening for occult malignancy in those patients with persistent erythroderma without a known cause is warranted and should be repeated at regular intervals.

Treatment of the underlying malignancy is imperative once the diagnosis has been made. Skin-directed therapy with lukewarm soaks, topical emollients, and topical steroids is also indicated. Antihistamines may alleviate pruritus. Patients with mycosis fungoides may be treated with topical nitrogen mustard; retinoids; phototherapy, including photophoresis; and total-body electron beam radiation. Systemic chemotherapy is also used in some patients. Fluid and electrolyte balance should be monitored and patients should be observed for the development of cutaneous, pulmonary, or systemic infection.

The course of erythroderma depends largely on its cause, paralleling the course of malignancy in those patients with cancer-associated exfoliative dermatitis [53]. The pathogenesis of erythroderma is unknown, although numerous cytokines and adhesion molecules have been implicated in the development of this increased epidermal turnover and exfoliation [53].

Coagulopathy

One half of patients with malignancy have laboratory evidence of disordered hemostasis and approximately 5% of cancer patients manifest thromboembolic disease [58]. Hypercoagulability may be secondary to tumor production of tissue factor, a procoagulant, or to tumor enhancement of platelet aggregation and release of plasminogen activator [58]. This hypercoagulable state may lead to disseminated intravascular coagulation with resultant thrombosis or bleeding caused by consumptive coagulopathy. Cutaneous signs of hypercoagulability include Raynaud's phenomenon; acral ischemia and gangrene; superficial venous occlusion (Trousseau's syndrome and Mondor's disease); and purpura. Mucinous adenocarcinomas, myeloproliferative cancers, and metastatic cancers are the malignancies most commonly associated with the development of thrombosis [59,60]. Malignant melanoma has also been associated with the development of disseminated intravascular coagulation [60]. Treatment of the malignancy may adversely impact the already abnormal hemostasis [60]. Long-term improvement can be expected, however, only if the underlying malignancy is effectively treated.

Cryoglobulinemia

Cryoglobulinemia is characterized by a cold-induced precipitation of immunoglobulin or cryoglobulin in blood vessels of the skin and internal organs. Type I cryoglobulinemia describes a solitary monoclonal cryoglobulin and is frequently associated with multiple myeloma, Waldenström's macroglobulinemia, and other B-cell malignancies. Type II and type III cryoglobulinemias are mixed cryoglobulins. Type II cryoglobulinemia consists of two immunoglobulins forming immune complexes. The cryoglobulin in type II disease is monoclonal and again associated with B-cell malignancies. Type II cryoglobulinemia may also be associated with connective tissue diseases and hepatitis C. Type III cryoglobulinemia encompasses an immune complex process in which the participating immunoglobulins are polyclonal. Type III cryoglobulinemia is associated with collagen vascular disease, hepatitis B, and hepatitis C.

The clinical presentation of cryoglobulinemia is dominated by signs of vascular occlusion. Purpura is the most consistent cutaneous finding. Raynaud's phenomenon, livedo reticularis, ischemia, and gangrene of the extremities may be present. Patients may or may not give a history of cold intolerance. The kidneys, liver, nervous system, and musculoskeletal system may also be affected [61].

The diagnosis of cryoglobulinemia can be confirmed by the isolation of a cryoprecipitate in the patient's serum and by skin biopsy. Biopsy of the skin reveals eosinophilic and homogenous intravascular material. Inflammation is absent in type I cryoglobulinemia. Types II and III cryoglobulinemia are characterized by leukocytoclastic vasculitis. The treatment of cryoglobulinemia induced by malignancy is aimed at the underlying neoplasm.

Clubbing

Clubbing is a symmetric soft tissue hypertrophy of the digits that can be congenital or acquired [1]. Neoplasia, especially bronchogenic carcinoma and mesothelioma, is a common cause of acquired digital clubbing [49]. The neoplastic variety is a result of a change in oxygenation in the digits. One simple test for clubbing involves the ratio of the thickness of the finger at the base of the nail to the thickness at the distal interphalangeal joint. If the ratio is larger than 1.00, it is diagnostic of clubbing [62]. Other traditional signs for clubbing include Curth's sign, which is a loss of the normal 180-degree angle between the middle and terminal phalanges at the interphalangeal joint, and Lovibond's sign, which means the angle between the curved nail plate and the proximal nail fold is more than 180 degrees [1]. Clubbing is typically painless, but 10% to 20% of patients with clubbing advance to hypertrophic osteoarthropathy, which is the painful involvement of bones and joints [62]. Histologically, there is subungual edema, increased connective tissue, and an accompanying lymphocytic infiltrate [6]. The curvature of the nail is caused more by subungual edema than by increased connective tissue [62].

Cronkhite-Canada syndrome

Cronkhite-Canada syndrome was first reported in 1955 in reference to two patients who had gastrointestinal dysfunction, pigmentary abnormalities, alopecia, and atrophy of the fingernails and toenails [63]. The nails typically shed, and the pigmentation changes are lentigo-like maculae that occur because of an increase in melanin within the basal layer [64].

This is a rare, noninherited disorder that shows a male predilection. Patients often have associated symptoms like diarrhea, weight loss, and neurologic symptoms. Colon carcinomas are present in approximately 14% of these patients [6].

Summary

Skin manifestations of systemic disease and malignancy are protean. The recognition of a potentially paraneoplastic dermatosis as such must prompt an investigation for occult malignancy. Lack of familiarity with cutaneous clues of internal malignancy may delay diagnosis and treatment of cancer. It is important to consider a paraneoplastic process in the differential diagnosis of a number of eruptive and treatment-resistant dermatoses. These dermatoses may be the first sign of an occult neoplasm. Their recognition may assist in cancer detection and the swift induction of appropriate therapy.

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DERMATOLOGIC CLINICS

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Cutaneous manifestations of gastrointestinal diseases

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There are a myriad of dermatologic disorders associated with gastrointestinal (GI) diseases. This article covers the common dermatologic conditions that may be associated with underlying GI diseases and several uncommon conditions that the dermatologist should recognize as being associated with GI disorders. Table 1 presents an outline of the diseases that are covered.

Inflammatory bowel diseases

Inflammatory disorders of the bowel discussed here include ulcerative colitis (UC), Crohn's disease, and bowel bypass syndrome. Both UC and Crohn's disease (the traditional inflammatory bowel diseases [IBD]) can present with abdominal pain, GI bleeding, or diarrhea. Bowel bypass syndrome consists of a bacterial overgrowth in the blind loop associated with a dermatosis-arthritis syndrome.

Crohn's disease and UC

Crohn's disease is usually subdivided on the basis of involvement of the GI tract (GIT) with regional ileitis-enteritis involving the small bowel, granulomatous colitis involving the colon, and ileocolitis involving both the small and large intestines. The entire mucosal wall is affected in Crohn's disease. Associated extraintestinal findings include arthritis or arthralgias in 10% to 23%; conjunctivitis, uveitis, and episcleritis in 1% to 13%; and many skin findings. Nonspecific skin findings, such as fistulas and fissures, are found commonly in Crohn's disease. Painless anal fissures occur in 50% to 60% of patients. Crohn's disease may have oral findings of cobblestoning, ulcerations, and nodules. Metastatic Crohn's lesions showing sarcoidal-type granulomatous histology can be seen in the skin or mucosa and correlates to disease activity (Fig. 1). Erythema nodosum, pyoderma gangrenosum (PG), pustular reactions including pustular vasculitis, and aphthous stomatitis are associated with both Crohn's and UC and are discussed separately.

In UC, the mucosa and submucosa of the colon are affected. Uncommonly, arthritis or arthralgias are seen in UC. Occasionally, a toxic arthritis with swelling and pain of the large joints is seen. Pustular reactions can be seen and include PG, pustular vasculitis, pustular reactions, and pyoderma vegetans of the Hallopeau type. Fistulas and fissures may be seen but are more common in Crohn's disease. Oral lichen planus (LP) may be seen in UC. Thrombophlebitis develops in up to 10% of UC patients.

PG

Brunsting et al [1] in 1930 described a small cohort of patients who developed characteristic extensive necrotic ulcerations with well-defined undermined borders and that healed with scarring. Four of these patients had underlying UC. Although UC is the most common disease associated with PG in adults, a number of other diseases have been associated with

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Table 1
Cutaneous manifestations of common gastrointestinal disorders

Gastrointestinal disorders	Cutaneous disorders
Inflammatory bowel disease	
Ulcerative colitis	Neutrophilic tissue reactions
Crohns' disease	Pyoderma gangrenosum
Bowel-bypass syndrome	Sweet's syndrome
	Pustular vasculitis or reactions
	Erythema nodosum
	Aphthous stomatitis
Nutritional and metabolic disorders	
Malabsorption	Acrodermatitis enteropathica
Gluten-sensitive enteropathy	Dermatogenic enteropathy
Alcoholic liver disease	Pancreatic panniculitis
	Porphyria cutanea tarda
	Dermatitis herpetiformis
Infections	
Hepatitis B and C	Porphyria cutanea tarda
	Erosive or oral lichen planus
Helicobacter pylori	Sweet's syndrome
Malignancies	
Specific cutaneous signs of gastrointestinal malignancy	
Glucagonoma	Necrolytic migratory erythema
Carcinoid	Flushing
Upper respiratory carcinoma	Bazex's syndrome
Esophageal carcinoma	Palmar-plantar hyperkeratosis
	Koilyonychia
	Glossitis
Nonspecific cutaneous signs of gastrointestinal malignancy	Acanthosis nigricans
	Erythema nodosum
	Metastatic skin lesions
	Sister Mary Joseph's nodules
	Hypertrichosis lanugosa
Gastrointestinal polyposis syndromes and cancer	Gardner's syndrome
	Cronkhite-Canada syndrome
	Peutz-Jeghers syndrome
	Cowden disease
	Muir-Torre syndrome
Gastrointestinal hemorrhage	
Vascular disorders	Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)
	Kaposi's sarcoma
	Necrotizing angiitis
	Pseudoxanthoma elasticum
	Ehlers-Danlos syndrome
	Degos' disease
	Henoch-Schönlein purpura

underlying conditions (Table 2). PG occurs in 0.5% to 20% of patients with Crohn's disease.

Pyoderma gangrenosum is an uncommon ulcerative disorder of uncertain etiology. Several hypotheses have been proposed, including a role for impaired cellular immunity and abnormal neutrophil function [2,3]. The clinical presentation may vary but classically begins as a papulopustule that becomes necrotic and expands easily with minimal trauma. Pathergy is invariably present. The clinical presenta-

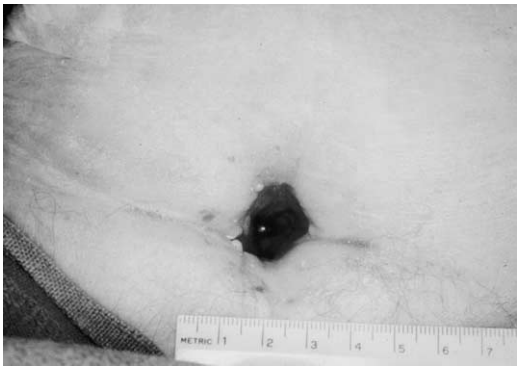

Fig. 1. Metastatic Crohn's disease

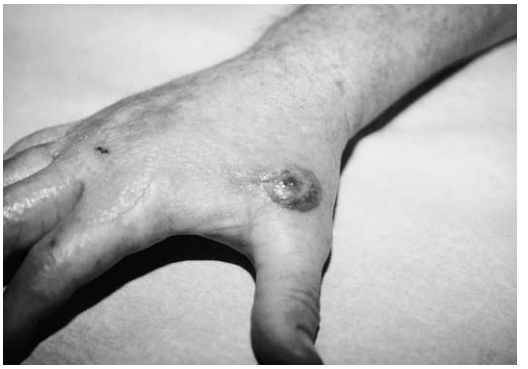

Fig. 2. Ulcerative pyoderma gangrenosum occurring in a patient with ulcerative colitis.

tion is subdivided into four types: (1) ulcerative, (2) pustular, (3) bullous, and (4) vegetative [4]. Classic ulcerative PG presents with a painful necrotic ulcer with undermined border (Fig. 2). This type typically is an enlarging necrotic ulcer with a violaceous undermined border. Although it has the appearance of an infectious ulcer, ulcerative PG typically is sterile. Patients with ulcerative PG often have underlying systemic disease, in particular arthritis and IBD. Pustular PG begins as painful sterile pustules but does not seem to progress to ulceration (Fig. 3). The pustular eruption may persist for months. Pustular PG has been reported in IBD, polycythemia rubra vera, and hepatobiliary cirrhosis [4]. This variant has also been referred to as *vesiculopustular eruption*, *pustular eruption of UC*, *pustular vasculitis*, or *pustular PG*. Since its first description in patients with leukemia, bullous PG has also been reported in IBD, myelofibrosis, and in otherwise healthy individuals [5]. In bullous PG, lesions present first as tense bullae, then painful erosions that rapidly become necrotic ulcers (Fig. 4). Vegetative PG begins as a superficial ulcer without undermined borders and slowly develops into a vegetative or exophytic lesion (Fig. 5). The eruption typically is localized and occurs commonly on the trunk. This variant often occurs in apparently healthy individuals.

Histologic findings may vary somewhat with the age of the lesion and the clinical subtype of PG. Early lesions of ulcerative PG demonstrate mild to moderate perivascular lymphocytic infiltrate and endothelial swelling, and a dense neutrophilic infiltrate in the dermis. Neutrophils may even invade the epidermis. There is neither true vasculitis nor any evidence of circulating immune complexes in lesional skin [6]. Vegetative PG and late stages of PG are characterized by granulomatous infiltrates of histiocytes, neutrophils, and giant cells. The bullous variant shows

Table 2
Diseases associated with pyoderma gangrenosum and Sweet's syndrome

Pyoderma gangrenosum	Sweet's syndrome
Ulcerative colitis	Ulcerative colitis
Crohns' disease	Crohns' disease
Diverticulitis	Diverticulitis
	Helicobacter pylori infection
	Yersinia enterolitica
Rheumatoid arthritis	Rheumatoid arthritis
Behçet's disease	Behçet's disease
Systemic lupus erythematosus	
Lymphoma or leukemia	Lymphoma or leukemia
Myeloproliferative disorders	Myeloproliferative disorders
Carcinoma of breast, lung, colon, and prostate	Carcinoma of breast, lung, colon, and prostate
AIDS	AIDS
	Autoimmune disorders
	Pregnancy

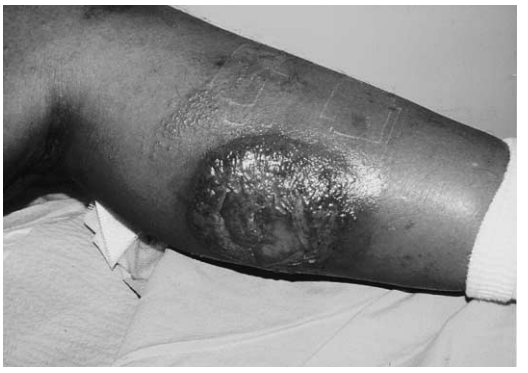

Fig. 3. Pustular pyoderma gangrenosum in a 16-year-old with ulcerative colitis.

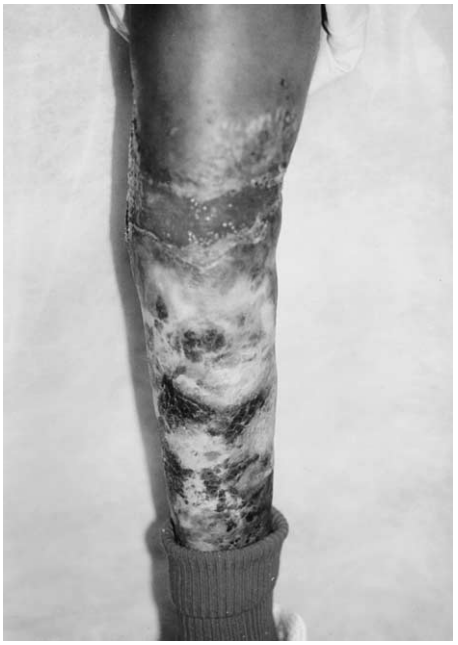

Fig. 4. Extensive scarring caused by erosive pyoderma gangrenosum in a patient with ulcerative colitis.

neutrophil-rich infiltrates and multilocular intraepidermal bullae [3].

Management of PG

Evaluation of a patient with PG is given in Table 3. Once the diagnosis of PG is made, evaluation and treatment of the underlying associated disease are imperative for management of skin involvement. Local wound care is important with careful attention given to minimizing trauma or manipulation of the ulcer. Debridement should be avoided or kept at a minimum. Local intralesional corticosteroid injections

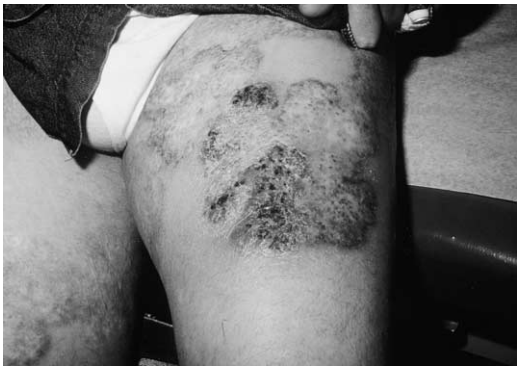

Fig. 5. Vegetative pyoderma gangrenosum.

Table 3
Evaluation of patient with Pyoderma gangrenosum

Complete history, including emphasis on drug intake, GI symptoms, constitutional symptoms
Physical examination, including gynecologic examination in women and prostate examination in men
Laboratory evaluation:
Hematologic
Complete blood count with differential
Estimated sedimentation rate
Peripheral smear
Chemistries
Renal, liver, and bone evaluation
Serum electrophoresis, if indicated
Hormone
TSH and thyroxine
Autoimmune
ANA/ profile; antiphospholipid antibody
RF
Antineutrophilic antibody (p-ANCA; c-ANCA)
Cryoglobulins
Skin
Biopsy
Wound cultures
Chest radiograph if indicated
Gastrointestinal evaluation if suggestive

Abbreviations: ANA, antinuclear bodies; ANCA, antineutrophilic cytoplasmic antibody; RF, rheumatoid factors; TSH, thyroid-stimulating hormone.

may be performed as monotherapy or in conjunction with systemic therapy. Systemic corticosteroids remain the mainstay of therapy with high doses often being necessary (1 to 2 mg/kg/d). Steroid-sparing agents, such as mycophenolate mofetil, azathioprine, cyclosporine, and methotrexate, have been reported to be of benefit [3,4]. In cases of PG associated with UC or Crohn's disease, sulfasalazine and dapsone have been shown to be quite effective for both GI disease and PG. Recent reports of topical tacrolimus ointment have shown promise in local treatment of the ulcer [7].

Sweet's syndrome

Sweet's Syndrome (SS) was first described in eight women as a distinct acute febrile syndrome associated with a neutrophilic dermatosis [8]. The clinical features include (1) fever; (2) peripheral neutrophilic leukocytosis; (3) painful erythematous juicy plaques and nodules on the extremities, head, and neck; and (4) a dense neutrophilic infiltrate within the dermis. These lesions can remain for weeks to months without intervening therapy. Since the initial description, SS

has been associated with many diseases (see Table 2). The most common clinical settings in which SS occurs are (1) classic SS, (2) paraneoplastic or malignancy-associated SS, and (3) drug-induced SS. The disease is more common in women, except for the malignancy-related form where the incidence is about equal in both sexes. Classic SS is usually associated with infection of the upper respiratory tract or GI tract 1 to 3 weeks before the skin manifestations. Recently, SS was reported in association with *Helicobacter pylori* infection [9]. Classic SS is often associated with IBD. Malignancy-associated SS occurs in 20% of SS patients, with lymphoproliferative disorders being most commonly noted. Solid tumors of the GI tract, genitourinary tract, and breasts have been reported in 15% of patient [7]. In drug-induced SS, the medications most frequently incriminated include granulocyte colony-stimulating factor, minocycline, trimethoprim-sulfamethoxazole, all-*trans* retinoic acid, and oral contraceptive pills [10].

Clinically in all forms, abrupt onset of fever and painful erythematous plaques and nodules follows a prodrome of low-grade fever or pharyngitis 1 to 3 weeks before onset. The skin lesions have pronounced edema, making the lesions appear vesicular (Fig. 6). The lesions coalesce into large irregularly shaped plaques. The eruption tends to occur on the head and neck and upper extremity area. The episodes can be recurrent in up to 50% and are associated with arthralgia, myalgia, headache, and generalized malaise and lasts for variable periods of time if untreated. The lesions heal without scarring. Oral lesions are uncommon in classic SS but are more prone to occur in malignancy-associated SS. Pathergy may be present. Extracutaneous involvement in SS includes GI tract, bone, central nervous system, liver, kidney, eyes, and lungs. [10,11]

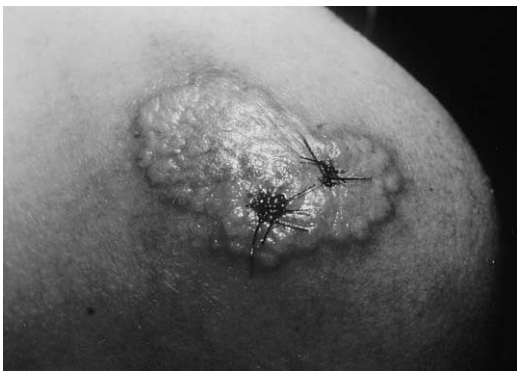

Fig. 6. Erythematous plaque of Sweet's syndrome.

Histologic evaluation of the plaques demonstrates a dense neutrophilic infiltrate in the superficial dermis and edema of the papillary dermis. Leukocytoclasia and karyorrhexis (fragmented neutrophil nuclei) are common findings but no true leukocytoclastic vasculitis is present. Direct immunofluorescence is negative.

When first described by Sweet, there were no associated systemic manifestations. Despite this, Sweet hypothesized that the dermatosis was reactive in nature. The clinical pattern and histology suggest that SS is a hypersensitivity reaction to a bacterial, viral, or even tumor antigen. The pathogenesis, however, remains unclear. Several theories have been proposed, including circulating autoantibodies, immune complexes, and cytokines. Recently, Going [13] and others have demonstrated excessive production of interleukin-1 and other proinflammatory cytokines and have proposed a central role for these cytokines in the pathogenesis of SS [12].

The rapid resolution of skin lesions with systemic corticosteroids supports the reactive nature of this entity. Steroid-sparing agents, such as sulfones, colchicine, and supersaturated potassium iodide, have been used successfully in SS [10].

Bowel-associated dermatosis arthritis syndrome

Bowel bypass syndrome was initially described following bypass surgery for morbid obesity. The condition may begin as soon as several days postsurgery and typically consists of an influenza-like prodrome of fever, chills, and malaise. This is followed by the appearance of small, indurated, painful papules and sterile pustules localized to the upper trunk and upper extremities, commonly in the deltoid area. There is a concomitant nonerosive arthritis and polyarthraligia of the fingers, hands, and wrists. The condition lasts about 2 weeks but has been reported to recur. Subsequent to its initial description, bowel bypass syndrome has been reported in patients with UC and Crohn's disease [14,15].

Histologically, there is a mononuclear perivascular infiltrate, with edema and sometimes neutrophils extending into the epidermis, forming the clinical pustule. There is no true leukocytoclastic vasculitis.

This disorder now is more correctly termed *bowel-associated dermatosis-arthritis syndrome* [15]. The pathogenesis is thought to involve circulating immune complexes, which are deposited into skin and joints. Ely [16] proposed that bacterial peptidoglycans resulting from overgrowth of GI bacteria in the postsurgical blind loop are involved in the formation of immune complexes, in turn activating complement

followed by subsequent deposition into the appropriate site. Immune complex and complement deposition have been reported in the skin but this is not a consistent feature [15,17].

Therapy includes tetracycline, dapsone, prednisone, sulfapyridine, and surgical re-establishment of the bypass segment.

Pustular reactions

Pyoderma gangrenosum, SS, and bowel-associated dermatosis-arthritis syndrome have similar histologic features and as such may represent a spectrum of pustular reactions and vasculitides seen in IBD. In addition to these, pustular reactions have been commonly reported in IBD.

Pustular vasculitis refers to an entity consisting of pustules on a purpuric base, with histologic features of SS or leukocytoclastic vasculitis. It is associated with serum sickness-like manifestations, such as fever, arthralgias, myalgia, and arthritis. Pustular vasculitis has been reported with bowel bypass surgery, UC, Behçet's disease, rheumatoid arthritis, and chronic bacteremia [3]. The pathogenesis of this entity seems to involve immune complex deposition. Treatment includes corticosteroids, colchicine, thalidomide, and dapsone [18].

Nutritional and metabolic disorders

Cutaneous eruptions associated with malabsorption

Many skin findings can be seen in association with malabsorption, some of which are the result of it, some in association with it, some caused by the disease process itself, and some because of a genetic susceptibility to the different diseases. Table 4 lists some of the skin findings seen in patients with malabsorption. Malabsorption can result in loss of many vitamins and essential elements that can result in eczematous eruptions, alterations in nail and hair, and changes in skin texture. There are several cutaneous eruptions specifically associated with malabsorption.

Table 4
Skin findings associated with malabsorption

Nonspecific	Specific
Acquired ichthyosis	Essential fatty acid deficiency
Hair and nail changes	Zinc deficiency
Hyperpigmentation	Acrodermatitis enteropathica
Altered skin texture	Vitamin B deficiency
Eczematous eruptions	Dermatogenic enteropathy
	Dermatitis herpetiformis

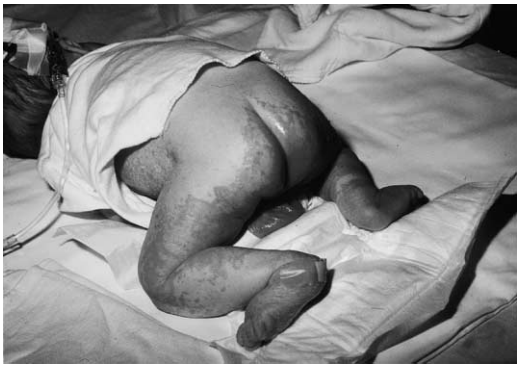

Fig. 7. Acrodermatitis enteropathica–like eruption in an infant with cystic fibrosis.

Acrodermatis enteropathica

Decreases in serum zinc levels secondary to malabsorption result in characteristic cutaneous abnormalities, which include acral dermatitis, alopecia, an eczematous dermatitis, and diarrhea. There is an inherited autosomal recessive disease, acrodermatitis enteropathica, which also results in the same characteristic skin eruption and is caused by a defect in zinc absorption [19]. Patients with acrodermatitis enteropathica develop a periorificial and perianal eczematous erythematous eruption shortly after birth or after weaning off breast milk (Fig. 7). The defect is caused by an inability to absorb zinc from the diet. This distinct cutaneous eruption should be considered when evaluating infants with failure to thrive and diarrhea because infants with cystic fibrosis and other malabsorption syndromes may present with acrodermatitis enteropathica skin findings.

There have been reports of malabsorption occurring in patients with exfoliative dermatitis. Dermatogenic enteropathy, as it is referred, consists of steatorrhea, in proportion to the extent of dermatitis. The steatorrhea reverses with successful treatment of the dermatitis [20]. The mechanism of this entity is unknown.

Dermatitis herpetiformis

Dermatitis herpetiformis is a chronic pruritic subepidermal blistering disease that is associated with mucosal changes in the small bowel indistinguishable from celiac sprue or gluten-sensitive enteropathy

[21]. Although most patients have no intestinal symptoms, 20% to 70% may demonstrate asymptomatic steatorrhea. Clinically, intensely pruritic subepidermal bullae and vesicles develop over the head and neck area and the extensor surfaces of the elbows and knees. Dermatitis herpetiformis usually begins in adulthood but childhood dermatitis herpetiformis has been reported. There is an increased risk for development of intestinal lymphoma in patients with long-standing dermatitis herpetiformis. Histologically, there is a subepidermal bulla with collections of neutrophils in the dermal papillae. Direct immunofluorescence demonstrates granular deposits of IgA in the dermal papillae. The pathogenesis of dermatitis herpetiformis is thought to involve these deposits of IgA with subsequent activation of complement [21]. One hypothesis is that IgA is directed against gluten protein or other antigens, which originate in the GI tract [21]. These immunoreactants are either deposited in the skin or cross-react with skin components, resulting in subepidermal blisters. Factors other than IgA seem to be involved in blister formation. There is no evidence for a role of circulating immune complexes in the pathogenesis of dermatitis herpetiformis.

Miscellaneous cutaneous diseases associated with GI diseases

LP

Lichen planus has been associated with several GI disorders. These include hepatitis B and C, IBD, and primary biliary cirrhosis. Erosive or oral LP seems to be associated most frequently with hepatitis C infection. Skin lesions are very pruritic, flat-topped, polygonal violaceous papules or plaques. The eruption is bilateral and symmetric and involves the wrists and flexor surfaces. There may be lacy white streaking or Wickham's striae on the buccal mucosa. Erosive LP presents as painful erythematous erosions on mucosal surfaces. In addition to erosive LP, there are several clinical patterns seen including follicular, vesicular, annular, hypertrophic, and atrophic LP.

Histologic findings are quite distinctive and include hypergranulosis, necrotic keratinocytes, colloid bodies, and an interface dermatitis of the basement membrane. A band-like infiltrate of lymphocytes is seen in the papillary dermis.

Although LP is a distinct dermatologic disorder, it may also be viewed as a reaction pattern to systemic disease, infection, or a response to an exogenous agent. As such, evaluation for systemic causes is warranted once the diagnosis of LP is made. Although the pathogenesis of LP is unknown, recent data suggest that LP is immunologically mediated [22]. In early lesions, CD4+ helper T cells and Langerhans' cells predominate, suggesting that the pathogenesis somehow involves antigen presentation. Older lesions have a preponderance of CD8+ suppressor cells. These cytotoxic T cells and their cytokines are responsible for the histologic finding of liquefaction degeneration at the dermal-epidermal junction.

Porphyria cutanea tarda

Porphyria cutanea tarda is a photoexacerbated subepidermal blistering disorder seen commonly in patients with liver disease. Porphyria cutanea tarda has been associated with alcoholic liver disease, hepatitis B and C, and hepatic tumors.

In general, the porphyrias are a group of photosensitive blistering disorders resulting from elevated levels of porphyrin intermediates in the heme pathway. Porphyrias result from inherited or acquired enzymatic abnormalities within heme synthesis pathway. Elevated levels of circulating uroporphyrias react with ultraviolet radiation to generated reactive free radical derivatives that induce blister formation in the papillary dermis.

Pancreatic panniculitis

Pancreatic panniculitis occurs predominately in alcoholics but has been reported in patients with pancreatic cancer. It presents as erythematous painful plaques and nodules on the extremities or trunk [23]. In addition to the skin lesions, arthritis, polyserositis, and pancreatitis may be present. This type of lobular panniculitis has characteristic histologic features of basophilic degeneration of lipocytes, leading to the formation of ghost cells, calcification, and saponification of the dermal collagen and necrosis.

Acute pancreatitis may also be associated with periumbilical ecchymosis (Turner's sign) or ecchymosis of the flank (Cullen's sign). This is caused by extravasation of hemorrhagic peritoneal fluid into the skin.

Cutaneous syndromes and the GI tract

There are a number of genodermatoses and cutaneous diseases associated with GI disorders. Table 5 lists some of the more common skin diseases and genodermatoses associated with GI malignancy and their systemic associations.

Table 5
Cutaneous syndromes associated with gastrointestinal diseases and malignancy

Syndrome	Inheritance	Cutaneous findings	Internal associations
With increased risk of malignancy	DEFECT		
Gardner's syndrome (familial polyposis syndrome)	AD Chromosome 5	Osteoma, desmoid tumors epidermoid cysts, dental anomalies	Intestinal polyposis, colon cancer, thyroid cancers, retinal abnormalities
Cronkhite-Canada syndrome	Acquired	Alopecia, nail dystrophy; macular hyperpigmentation	GI polyps, colon carcinoma, diarrhea, abdominal pain
Cowden's disease (multiple hamartoma syndrome)	AD Mutation PTEN Gene/chromosome 10	Hamartomas of mucous membranes, facial tricholemmonas, papillomas Palmar-plantar keratoses, scrotal tongue	Hamartomas and malignancy of colon, breast, thyroid, renal, and bladder; colonic polyps
Muir-Torre syndrome	AD Mutation in MSH2 gene on chromosome 2	Sebaceous gland tumors, BCC with sebaceous differentiation, keratoacantoma, epidermoid cysts	Nonpolyposis colon cancer, laryngeal cancer, duodenal and endometrial cancer
Peutz-Jeghers syndrome	AD	Periorificial and mucosal lentigines, pigmented maculae hands and feet	Hamartomatous polyps throughout GI tract, increased incidence of malignancy throughout GI tract, ovarian tumors, pancreatic carcinoma, gallbladder cancer, GI bleeding, pancreatic carcinoma
Howell-Evans' syndrome		Palmar-plantar hyperkeratosis	Esophageal carcinoma
Bazex's Syndrome	Acquired	Acrodermatitis, nail dystrophy	Esophageal, laryngeal, tongue carcinoma
MEN type I (Wermer's syndrome)	AD Mutation in MEN I gene on chromosome 11	Multiple facial angiofibromas, collagenomas, lipomas, confetti-like hypopigmented macules	Pituitary, parathyroid, pancreatic endocrine abnormalities, peptic ulcer disease, Zollinger-Ellison syndrome, gastronoma, insulinoma, carcinoid
MEN IIA (Sipple's syndrome)	AD Mutation in *RET* gene on chromosome 10	Amyloidosis	Medullary thyroid carcinoma, pheochromocytoma, hyperparathyroidism, Zollinger-Ellison syndrome, Cushing's syndrome, malignant melanoma, pituitary adenoma,
MEN IIB	AD Mutation in *RET* gene on chromosome 10	Multiple mucosal neuromas, marfinoid body habitus, nasal neuromas	Hirschprung's disease, cervical medulloblasoma increased risk of malignancy Medullary carcinoma of thyroid, pheochromocytoma, muscle weakness and atrophy, ganglioneuromas of GI tract, colonic diverticula, thickened corneal nerves, diarrhea

Abbreviations: AD, autosomal dominant; BCC, basal cell carcinoma; GI, gastrointestinal; MEN, multiple endocrine neoplasia; MSH, ; PTEN, .

Enodermatoses with malignant potential

Gardner's syndrome

Gardner's syndrome, or familial adenomatous polyposis, is an autosomal dominant inherited disorder with a high degree of penetrance [24]. It is thought to be caused by a gene defect on chromosome 5. The incidence is about 1:3000 to 1:6000. It is important to recognize this syndrome early in life because there is almost a 100% chance of colonic carcinoma in these patients before the age of 40. There are a number of cutaneous findings that should alert the physician to this diagnosis. These include multiple epidermoid cysts, desmoid tumors, osteomas, dental abnormalities, and ocular pigmented lesions (Fig. 8). The epidermoid cysts differ from common cysts in that they are multiple, develop in childhood, and cluster on the head and neck. Desmoid tumors, which are uncommon in the general population, occur in 10% of these patients [24]. The pigmented lesions in the fundus may be congenital and occur in 90% of patients. Other neoplasms may be seen and include duodenal carcinoma, endocrine tumors, thyroid carcinoma, and hepatoblastoma.

Cronkhite-Canada syndrome

Cronkhite-Canada syndrome is a rare acquired disorder presenting in adulthood with diffuse alopecia, macular hyperpigmentation, onychodystrophy, and GI polyposis [25,26]. The cutaneous symptoms often precede the systemic symptoms. Alopecia occurs in all hair bearing areas and is rapidly progressive. The nail dystrophy is generalized and may show onycholysis, onychoschizia, and onychomadesis. The macular hyperpigmentation is lentiginous and diffuse but excludes the mucosa. Laboratory findings usually reflect the degree of diarrhea and protein-losing enteropathy and include hypokalemia, hypocalcemia, and hypoalbuminemia. Anemia may be secondary to chronic GI bleeding from polyps. The polyps are regarded as hamartomatous but as many as 15% of patients develop carcinoma of the stomach, colon, and rectum [24]. Although the pathogenesis in unknown, several hypotheses have been proposed and include nutritional deficiency, enzyme deficiency, altered mucosal vasculature or altered mucosal secretions, infections, and altered immunity. Although many of the cutaneous manifestations can be explained as a consequence of the diarrhea and protein-losing enteropathy, their appearance before the GI symptoms suggests mechanisms other than simple loss.

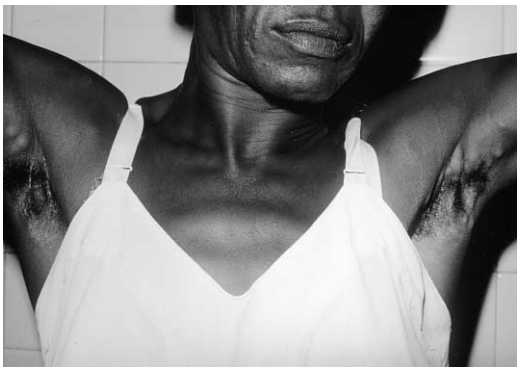

Fig. 8. Multiple epidermoid cysts in axillae of patient with Gardner's syndrome.

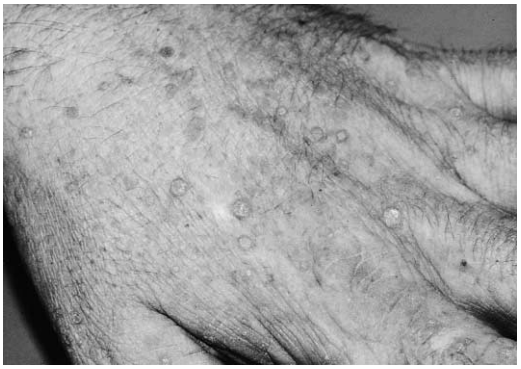

Fig. 9. Acral keratoses in a patient with Cowden's disease.

Cowden disease

Cowden disease, or multiple hamartoma syndrome, is an autosomal dominant disorder of the skin, mucosa, and multiple organs. Recent molecular genetic studies suggest that there is a defect in the gene coding for a tumor suppressor gene on chromosome 10, designated PTEN/ MMAC1 [27]. Distinctive skin findings include multiple facial trichilemmomas and warty acral keratoses (Fig. 9). The mucosal papules often give a cobblestone appearance to the oral cavity and are considered pathognomonic for the syndrome. Other skin findings include lipomas, hemangiomas, scrotal tongue, and neuromas [28]. Approximately one third of patients with Cowden disease have hamartomatous polyps of the GI tract with little potential for malignant conversion. Commonly, bleeding and anemia may be seen. Patients with Cowden disease do have an increased risk of malignancy of breast and thyroid and as such require careful screen-

ing and follow-up. Criteria for diagnosis include family history and the presence of one of the characteristic facial tumors or family history and keratoses of palms and soles and acral areas or the presence of facial trichilemmomas and oral mucosal papillomas or fibroma [29].

Muir-Torre syndrome

In Muir-Torre syndrome, multiple sebaceous tumors with or without keratoacanthomas are seen in combination with low-grade visceral malignancies [24,30]. Most of the malignancies have their origin in the GI tract, usually the colon, and these often arise from adenomatous polyps. Other malignancies reported include non-Hodgkin's lymphoma, and tumors of the larynx, duodenum, stomach, kidney, ovary, and uterus [30]. Sebaceous neoplasms include adenomas, hyperplasia, epithelioma, and carcinoma. As expected, most of these neoplasms are found in the head and neck area. Because sebaceous adenomas are uncommon in general, some authors suggest that the diagnosis of a solitary sebaceous adenoma (especially of the eyelid) warrants further evaluation for internal malignancies.

Multiple endocrine neoplasia syndromes

The multiple endocrine neoplasia (MEN) syndromes are an uncommon group of proliferative disorders that affect endocrine glands. Several of these syndromes also involve the GI tract. The major syndromes include three genetically distinct disorders: (1) MEN I (Wermer's syndrome); (2) MEN IIA (Sipple's syndrome); and (3) MEN IIB (previously referred to as MEN III) [31]. Genetic studies have recently suggested that germline mutations in the *ret* proto-oncogene found on chromosome 10 are involved in malignant transformation in MEN IIA and B [27,31]. The defect in MEN I has been linked to chromosome 11 [27,31].

The MEN I was first described by Erdheim but Wermer [32] subsequently suggested a genetic basis for the disease. In addition to endocrine hyperplasia and neoplasia, many patients have evidence of gastrin-producing tumors of the duodenum (Zollinger-Ellison syndrome); carcinoid tumors of the GIT; and carcinoid of the lung. Skin findings in MEN I include multiple facial angiofibromas, collagenomas, lipomas, hypopigmented maculae, and gingival papules.

The MEN IIA consists of medullary carcinoma of the thyroid and pheochromocytoma. It is inherited in an autosomal dominant fashion, with the genetic defect involving the *ret* proto-oncogene. Hirschsprung's disease or aganglionic megacolon has been associated with MEN IIA and demonstrates the same genetic defect in the *ret* proto-oncogene found on chromosome 10. A variant of MEN IIA demonstrates hereditary cutaneous amyloidosis [31].

The MEN IIB demonstrates more cutaneous manifestations than MEN IIA. The main features of this syndrome include multiple mucosal neuromas, medullary carcinoma of the thyroid, pheochromocytomas, GI ganglioneuromatosis, and ocular neuromas [31]. Other clinical manifestations include a marfinoid habitus, skeletal abnormalities, and joint laxity. The putative defect in MEN IIB maps to chromosome 10 and seems to involve the *ret* proto-oncogene.

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome consists of GI polyposis and cutaneous pigmented maculae on the mucosal areas and skin [29]. It is uncommon, with the incidence estimated to be 1 in 29,000 live births. The polyps are most frequently found in the jejunum and ileum but can occur anywhere in the GI tract. Commonly, GI symptoms of bleeding or obstruction are presenting features. Initially, these polyps were viewed as hamartomatous but recent data suggest there is significant increase in the incidence of malignancy of the GI tract, breast, ovary, and testes [29]. The tan-brown pigmented maculae resemble lentigines, appear in early childhood, and cluster on mucosal surfaces but can be also found on soles, palms, and fingers.

Howell-Evans' syndrome

In 1958, Howell-Evans et al [33] reported two kindred with diffuse hyperkeratosis of palms and soles (tylosis) and esophageal carcinoma. In this syndrome, patients develop palmar-plantar hyperkeratosis in adulthood and develop esophageal carcinoma before the age of 65. There may be an associated oral leukoplakia. The association of tylosis and esophageal carcinoma has been reported in other families and seems to be inherited in an autosomal dominant fashion [34]. Adult onset of tylosis or hyperkeratosis palmaris et plantaris has been reported with other malignancies, including colon and lung, but differs from benign tylosis, which has its onset early in life.

Plummer-Vinson syndrome

Plummer-Vinson syndrome is a rare syndrome consisting of palmar-plantar hyperkeratosis and post-

cricoid web [29]. In this syndrome, patients have postcricoid web, koilonychia or spoon nails, angular stomatitis, and painful glossitis. These cutaneous changes may be secondary to long-standing iron deficiency anemia. Esophageal carcinoma occurs in about 15% of patients.

Bazex's syndrome

Acrokeratosis paraneoplastica, or Bazex's syndrome, is an acquired symmetric erythematous psoriasiform dermatosis affecting the hands, feet, ears, and nose [29]. Nail anomalies and dystrophy are common and often are very severe. Bazex's syndrome is usually associated with carcinoma of the larynx, esophagus, and tongue. The cutaneous manifestations may occur years before the malignancy is detected.

Carcinoid syndrome

Carcinoid syndrome represents a constellation of findings secondary to a tumor of amine precursor uptake and decarboxylation cells (APUDoma) of the intestinal or respiratory tract. Symptoms include flushing, diarrhea, wheezing, and abdominal pain, with or without weight loss. Most tumors are found in the GI tract but symptoms develop when the liver is involved. The flushing is episodic at first and consists of a range of skin colors. With time, persistent erythema and poikiloderma may develop. Glossitis and photoaccentuated pellagra-like eruption may be seen. These are thought to be caused by a shift toward increased serotonin production by the tumor, resulting in niacin deficiency [28]. Elevated levels of 5-hydroxyindoleacetic acid are found in the urine of affected patients.

Glucagonoma

Necrolytic migratory erythema is an uncommon cutaneous eruption most often seen in patients with glucagonoma, a tumor of the pancreatic islet cells, but has been reported with other malignancies [29]. This characteristic eruption consists of recurrent episodes of painful erythema, followed by blisters or erosions and desquamation. The perineum, abdomen, perioral, and flexural areas are most often affected. Angular cheilitis and painful glossitis also occur. Pathogenesis may be related to metabolic derangements of amino acid toward excess glucagonoma production [35,36].

Cutaneous syndromes associated with hemorrhage

There are a number of dermatoses associated with GI hemorrhage as a prominent feature. Some of the more common ones are listed in Table 6. Vascular

Table 6
Cutaneous syndromes associated with gastrointestinal hemorrhage

Syndrome	Inheritance	Cutaneous findings	Internal associations
Hereditary hemorrhagic telangiectasia	AD	Telangiectasia of skin, oral mucosa	GI hemorrhage, epistaxis, arterial aneurysms; AV malformations in liver, lung, eye
Blue rubber bleb news syndrome	AD	Compressible SQ hemangiomas	GI vascular malformations, GI hemorrhage
Kaposi's sarcoma		Violaceous papules, nodules	GI lesions, hemorrhage
Necrotizing angiitis		Palpable purpura	GI bleeding, perforation, ischemia
Henoch-Schöenlein purpura		Palpable purpura	Abdominal cramping and pain, hematuria, glomerulonephritis
Degos' disease		atrophic Erythematous papules	Vasculitis of GIT, infarction, bleeding, CNS infarcts
Ehlers-Danlos syndrome type IV	AD, AR	Easy bruising, thin translucent skin	Arterial rupture, GI hemorrhage, uterine rupture
Pseudoxanthoma elasticum	AD, AR	Waxy yellow papules, flexural areas, elastosis perforans serpiginosa	GI hemorrhage, Angioid streaks in eyes, coronary hear disease, vascular calcification

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; AV, arteriovenous; CNS, central nervous system; GI, gastrointestinal; GIT, gastrointestinal tract; SQ, subcutaneous.

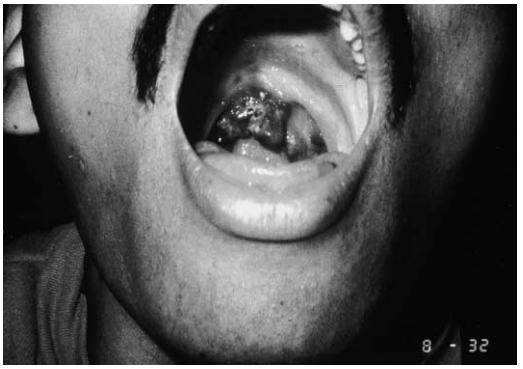

Fig. 10. Oral lesions of Kaposi's sarcoma in a patient with AIDS.

anomalies, connective tissue disorders, vasculitis, and malignancies can have GI bleeding. It is important to recognize those patients at risk for hemorrhage before problems arise.

Hereditary hemorrhagic telangiectasia

Hereditary hemorrhagic telangiectasia, or Osler-Weber-Rendu disease, is an autosomal dominant inherited disorder with characteristic small telangiectasia primarily on mucosal surfaces [37]. Telangiectasia are also found on the nose, hands, feet, and chest. The skin findings appear in adolescence or early adulthood. Arteriovenous malformations and aneurysms may develop throughout the GI tract and result in recurrent painless bleeding. GI bleeding usually occurs in the fourth or fifth decade and tends to be chronic. Epistaxis is the presenting sign in over 80% of patients and may present in adolescence. Other organs, such as the liver, lung, and eye, may have vascular malformations.

Kaposi's sarcoma

Kaposi's sarcoma is a vascular neoplasm associated with HIV infection (epidemic) and in elderly men of Mediterranean ancestry. The epidemic variant is often multifocal and occurs in the skin, the mucosa, and the GI tract. GI involvement is seen in 50% to 80% of patients with skin involvement and virtually 100% of patients with oral lesions (Fig. 10). GI bleeding may be significant. The typical lesion is an irregularly shaped violaceous papule, plaque, or tumor. Recently, herpes virus type 8 has been implicated in the pathogenesis of Kaposi's sarcoma [38].

Necrotizing angiitis

Necrotizing angiitis from a number of causes can involve the GI tract, resulting in bleeding, diarrhea, cramps, or obstruction. The ultimate damage depends on the size of the affected vessels. The classic vasculitic process that involves the skin and GIT is Henoch-Schönlein purpura. Henoch-Schönlein purpura is the triad of leukocytoclastic vasculitis of the skin, abdominal pain or cramping, and microscopic hematuria [39]. The disease typically presents in childhood or adolescence but can be seen in all ages. The disease is commonly preceded by an upper respiratory tract infection. It usually lasts about 4 weeks. Leukocytoclastic vasculitis, which is a vasculitis of the capillaries, presents as palpable purpura and recurs in crops and is accompanied by fever and malaise. Direct immunofluorescence of the skin reveals deposits of IgA at the dermoepidermal junction. These IgA deposits are almost pathognomonic for Henoch-Schönlein purpura. In addition to skin deposits, IgA deposits can be found in the kidneys of affected individuals and are thought to contribute to the renal disease seen. The pathogenesis is unclear but most likely involves these IgA deposits.

Degos' disease

Malignant atrophic papulosis of Degos' is a rare disorder manifesting as thrombotic papules in the skin, GI tract, and central nervous system. The very distinctive skin lesions, atrophic porcelain white papules with a rim of erythema, may precede the GI symptoms by months to years (Fig. 11). Histologic examination of a papule reveals epidermal atrophy overlying a wedge-shaped area of dermal necrosis,

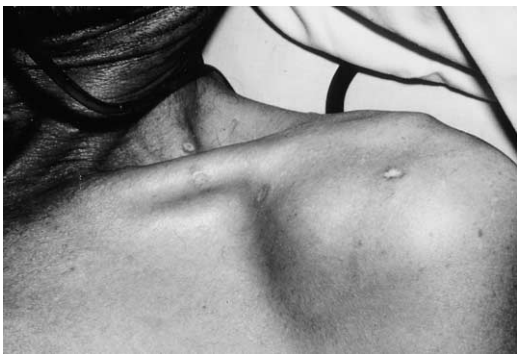

Fig. 11. Atrophic porcelain white papules in a patient with Degos' disease.

mucinous degeneration, and thrombotic vasculitis. It was thought that Degos' disease was uniformly fatal until several years ago when nonfatal familial cases and HIV-associated cases were reported [40,41]. Bleeding may occur as a result of thrombotic vasculitis within GI tract.

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum is a genetically inherited disorder of elastic tissue, with an incidence of 0.6 per 100,000 people [42]. It is characterized by abnormal calcification and progressive degeneration of elastic tissue in multiple organs, including the skin, GI tract, the eyes, and the cardiovascular system. The vascular calcification and altered elastin within the GI tract result in hemorrhage early in life, more commonly from the upper GI tract. Skin manifestations are quite distinctive. Small waxy yellow papules typically appear in the skin in early adolescence, giving the appearance of "plucked chicken skin." The lesions have a predilection for flexural areas and the neck and axillae but over time can occur in a generalized distribution. With time, the skin becomes lax and hangs in folds and clinically resembles cutis laxa. Elastosis perforans serpiginosa, one of the perforating collagenoses, may be associated with pseudoxanthoma elasticum.

Angioid streaks, which occur in Bruch's membrance, are seen in the eyes of most patients, as are retinal hemorrhage and detachment. Angioid streaks are associated with pseudoxanthoma elasticum 85% of the time but may be seen in other diseases, such as Paget's disease of bone, lead poisoning, idiopathic thrombocytopenia, and sickle cell disease [42]. Vascular alterations result in peripheral vascular disease, cerebral accidents, premature myocardial infarction, and hypertension subsequent to renal artery involvement.

Pseudoxanthoma elasticum is divided into four subtypes: types I dominant and recessive and types II dominant and recessive. The classic form, type I recessive, has the highest incidence of GI involvement, whereas types II dominant and recessive have minimal or no visceral involvement [37]. Genetic consultation and counseling are important in determining prognosis and potential complications later in life. Although the pathogenesis is not fully understood, there seems to be progressive calcification of elastin fibers with subsequent fragmentation and clumping, abnormal deposition of proteoglycans in the skin and urine of patients, and abnormal elastin degradation [43].

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome (EDS) is an inherited disorder of collagen metabolism, with joint laxity and hyperextensibility, skin hyperextensibility, and skin fragility as common features [37]. Although there are currently 10 distinct subtypes, only type IV EDS is associated with GI findings. EDS type IV may be inherited in an autosomal dominant or recessive pattern. Point mutations, deletions, and splicing defects have been reported but the biochemical defect resulting in abnormal type III collagen is not known. Several studies have suggested that mutations in type III procollagen gene (COL3A1) result in the type IV EDS phenotype [44].

Skin and joint hyperextensibility and abnormal scar formation are not common features of type IV EDS. Type IV EDS is characterized by thin translucent skin, easy bruisibility and ecchymoses, and GI bleeding secondary to rupture of arterial blood vessels or aneurysms. The vascular fragility is manifest at an early age and bleeding can be severe and life threatening. The most common sites of rupture are the large vessels of the abdomen, descending aorta, renal and splenic arteries, and uterine rupture in the postpartum period.

Summary

Prompt recognition of cutaneous diseases or manifestations associated with the gastrointestinal tract may be lifesaving at times, and may lead to early preventive intervention to decrease risk of malignancy.

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DERMATOLOGIC CLINICS

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Neurocutaneous disorders

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"Neurocutaneous disorders" is a catch-all phrase that includes all disorders involving both the nervous systems and the skin. These may range from disorders in which cutaneous findings are essential to diagnosis, to those with less significant involvement of the skin. In light of the variety of disorders that involve the skin and the nervous system, this article will review a few of the more essential diagnoses and those with recent advancements in diagnosis and management. Many of these diseases are single-gene disorders for which the genes have been discovered during the past few years. This article is divided into sections that highlight disorders transmitted by different inheritance patterns.

Autosomal dominant

Neurofibromatosis

Neurofibromatosis (NF) is one of the most common neurocutaneous conditions and consists of eight distinct forms of neurofibromatosis. The first two types are the most common and are autosomal dominant disorders with somewhat overlapping features: neurofibromatosis type 1, also referred to as von Recklinghausen's disease, and the less common NF type 2.

Neurofibromatosis type 1 (NF-1)

NF-1 is one of the most common autosomal dominant disorders in humans, with an occurrence of $\sim$1 in 3000 persons. NF-1 accounts for 96% to 97% of all cases of NF and results from defects in the NF-1 gene on chromosome 17 [1].

Etiology and pathogenesis

The large gene for NF-1 is located on the long arm of chromosome 17 at 17 ql 1.2 and spans at least 300 kbp of DNA [2]. Neurofibromin, the protein encoded by this gene, has several likely functions. This protein is essential for negative regulation of the *ras* proto-oncogene in the cell [3,4]; therefore, it serves as a tumor suppressor.

Although NF-1 is inherited as an autosomal dominant disorder, 30% to 50% of cases are thought to result from spontaneous new mutations, most of which are paternal in origin [5]. Somatic mosaicism for NF-1 has recently been identified [1]. Some of the mosaic patients express disease in limited areas of the skin, a variant referred to as segmental NF [6].

Clinical features and presentation

In 1987, a panel convened at the National Institutes of Health and presented a consensus statement enumerating the clinical diagnostic criteria for NF-1 and NF-2 [7]. For NF-1, the diagnostic criteria are met if two or more of the following features listed are present: (1) six or more café au lait (CAL) macules greater than 5 mm in prepubertal patients and greater than 15 mm in postpubertal patients; (2) two or more neurofibromas of any type, or one plexiform neurofibroma; (3) axillary or inguinal freckling; (4) optic nerve glioma; (5) two or more Lisch nodules (iris harmatomas); (6) a distinctive osseus lesion such as sphenoid wing dysplasia or cortical thinning of long bones, with or without pseudoarthrosis; and (7)

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a first-degree relative with NF-1 based on the preceding criteria.

The cardinal dermatologic features of NF-1 are CAL spots, neurofibromas (Fig. 1), axillary and inguinal freckling, and pigmented iris harmatomas. CAL macules typically appear either at birth or during the first few years of an affected person's life. When CAL macules overlay the spine, this suggests the possibility of a plexiform neuroma and the potential of spinal dysraphism.

In patients with NF-1, the most common benign tumor is a neurofibroma, which may be either circumscribed (cutaneous or subcutaneous) or noncircumscribed (plexiform). For women, neurofibromas occur in almost 90% in the periareolar location; thus, breast examination is one of the best ways to detect subtle disease in an adult woman. Plexiform neurofibromas (Fig. 2) can wrap in and around vital structures and cause pronounced disfigurement, including compromised hearing. These are specific for NF-1 [8]. Surgical treatment is the primary treatment option.

Both axially and inguinal freckling constitute another major diagnostic criterion. Freckling often develops during puberty and sprays of freckles sometimes overlay plexiform neurofibromas. Optic nerve glioma is estimated to occur in 15% of patients with NF-1 [1]. Although these tumors usually develop by the time the patient is 10 years old, symptoms of proptosis, decreased visual acuity, or precocious puberty (caused by pituitary compression) may not occur until years later. Treatment of optic nerve gliomas is often surgical and results in loss of vision; chemotherapeutic management is being investigated [9]. Lisch nodules are iris harmatomas. Early development of Lisch nodules will be detectable with careful examination under a slit lamp by the age of 6 years [10]. Distinctive osseus lesions of NF-1 include sphenoid wing dysplasia, which often results

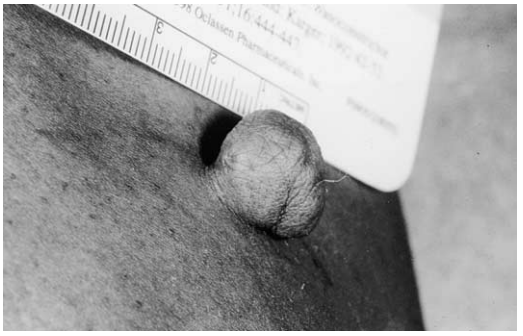

Fig. 1. Neurofibroma.

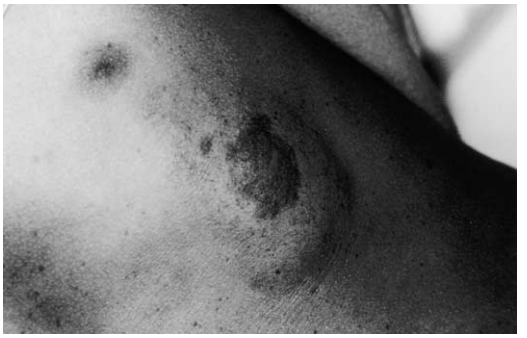

Fig. 2. Plexiform neurofibroma of the chest.

in pulsating exophthalmos or pseudoarthrosis of the tibia or fibula. This can predipose individuals to pathologic fractures and false joint formation. Only one long bone per patient is usually affected, and males are more commonly affected than females [10].

In addition to the diagnostic criteria described above, NF-1 can be compounded by a broad spectrum of complications, such as stenosis of the renal arteries, aqueduct stenosis, optic glioma, and learning disabilities; overt mental retardation is uncommon [11].

NF-1 is an extremely variable disorder. Clinical presentation ranges from benign, predominant cutaneous expression to severe disfigurement and life-threatening complications. The disorder is variable both between families and within families. Since additional features develop as a patient ages, careful clinical follow-up is imperative [12].

Malignant risk

Patients with NF-1 have an estimated 3% to 15% lifetime risk of malignant disease. The two most common types of malignant tumors are neurofibrosarcoma and optic nerve gliomas [13]. Neurofibrosarcoma consists of cells histologically similar to Schwann and perineural cells. An estimated 50% of patients with neurofibrosarcoma have NF-1. Other malignancies associated with NF-1 include malignant myeloid disorders, carcinoid, rhabdomyosarcoma, osteosarcoma, Wilm's tumor, ganglioneurofibroma, and medulloblastoma [10]. Patients with NF-1 who also present with juvenile xanthogranulomas have been recently shown to have a greater statisitical risk of developing chronic myelogenous leukemias [14].

Screening and management

Diagnosis should be confirmed on the basis of outlined requirements, and should also include slit lamp examinations of all first-degree relatives of an index case, as well as a complete review of the condition, its inheritance pattern, and natural history [15].

Annual physical and ophthalmologic examinations during school years as well as audiology, speech, and language examinations before elementary school are recommended. Blood pressure should be checked once or twice a year. Growth abnormalities, scoliosis, and rapid enlargement or pain associated with neurofibromas should be monitored closely [1]. Treatment of NF-1 is primarily symptomatic; cure is not yet possible. Multicenter trials of medications to limit growth of optic nerve gliomas and plexiform neurofibromas have been initiated [1].

Neurofibromatosis type 2 (NF-2)

NF-2, also known as central neurofibromatosis, accounts for about 3% of cases of NF and results from defects in the NF-2 gene on chromosome 27. Much less common than NF-1, the incidence of NF-2 is estimated at 1 in 50,000 [16]. Some evidence suggests that there are two subtypes of NF-2, a milder Gardner variant, and a more severe Whishart type [17]. In this review, the two variants will be discussed as one entity.

Etiology and pathogenesis

The gene for NF-2 is located on chromosome 22 at 22ql1 [1]. In patients with NF-2, loss of heterozygosity for this region of chromosome 22 has been demonstrated in acoustic neuromas, neurofibromas, and meningiomas [18]. As discussed under the pathogenesis of NF-1, the protein encoded by the NF-2 gene may also act as a tumor suppressor.

Clinical features and presentation

The diagnostic criteria for NF-2 are either (1) bilateral eighth nerve masses confirmed by CT or MRI or (2) a first-degree relative with NF-2 and either a unilateral eighth nerve mass or two of the following: neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacity [7]. Skin manifestations in NF-2 are less prominent than in NF-1. CAL tend to be fewer in number and show less distinct hyperpigmentation. Intertriginous freckling is not present. Neurofibromas, especially the plexiform variant, are the least common cutaneous finding in NF-2 [19].

One characteristic skin finding includes cutaneous and subcutaneous schwannomas, the most common of the various tumors seen in NF-2. Schwannomas typically present as superficial, discrete, slightly raised papules in which the surface is rough, often pigmented, and covered by excess hair [16].

Although formerly referred to as acoustic neuromas, eighth nerve tumors are actually vestibular schwannomas. In a study of 93 patients with unilateral vestibular schwannomas [20], none met the diagnostic criteria for NF-1, but 5 had clinical findings of NF-2. Of patients with NF-2, 85% are estimated to have development of posterior subcapsular cataracts [21,22].

Screening and management

Molecular testing of all persons at risk of an inherited gene mutation for NF-2 from a parent has been recommended [23]. If test results are positive, baseline neurologic, audiologic, and radiographic (MRI) evaluations of the head and entire spine should be performed. If no tumors are detected, these evaluations are recommended every 3 years. For patients known to have NF-2, annual or biannual neurologic, audiologic, and radiographic evaluations are recommended when these patients are between 15 and 45 years of age [12].

Mutation analysis is available for NF-1 by using protein truncation assays, and for NF-2 by using single-stranded conformation polymorphism and direct DNA sequencing [23]. With current techniques, $\sim$70% of mutation in the NF-1 gene and 60% of mutations in known familial cases of NF-2 can be detected [24].

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is the second most common neurocutaneous disorder. The transmission is autosomal dominant; however, $\sim$65% to 85% of cases arise from spontaneous mutations [25]. The incidence of TSC is estimated between 1:6,000 and 1: 10,000 individuals [26], and there is no predilection for gender or race [27]. In 1908, Vogt [27] described the classic triad of adenoma sebaccum, seizures, and mental retardation, but less than a third of patients display all of these features.

Etiology and pathogenesis

Tuberous sclerosis is a disorder of cellular differentiation and proliferation [28]. Two TSC genes have been identified; one is on chromosome 9q34 (TSCl) and the other is on chromosome 16pl3 (TSC2) [29,30]. The TSC2 gene on chromosome 16 is adjacent to the gene for adult polycystic kidney disease [29]. Linkage analysis has shown that half of tuberous sclerosis families have inherited the TSC 1 gene, while the other half have inherited the TSC2 gene. Jones and colleagues [31] found TSC 1 mutations to be less common among sporadic cases, and mental retardation to be significantly less frequent in these carriers. Harmatomatous lesions of TSC are thought

to occur as a consequence of inactivation of a tumor suppressor gene [32,33].

Clinical features and presentation

Cutaneous findings include hypomelanotic macules, facial angiofibromata, ungual fibromas (Fig. 3), and the shagreen patch. Hypomelanotic macules are seen in at least 90% of affected patients, but these lesions are not specific for tuberous sclerosis because one or two often occur in the general population [34]. These lesions are not considered major features unless they are numerous [35]. The earliest detectible abnormalities in TS are hypopigmented macules and rhabdomyomas, both of which are often present at birth. Facial angiofibromata are found in 75% of all patients with tuberous sclerosis. Ungual fibromas are fleshy lesions that occur beneath the nails. They occur in only 25% of affected persons, arise in early adulthood, and are fairly specific for tuberous sclerosis [27]. A shagreen patch is a cluster of connective tissue hamartoma that appears as an irregularly shaped plaque with a green to red hue, and is commonly found on the patient's back or flank.

Central nervous system lesions of tuberous sclerosis include cortical hamartomas (tubers), focal cortical dysplasia, subependymal nodule, subependymal giant cell astrocytoma, and retinal phakoma (astrocytomas); spinal cord involvement is rare [34, 36,37].

Although traditionally recognized as a neurologic and dermatologic disorder, renal lesions are significant in tuberous sclerosis [38]. Renal involvement exists in up to 80% of patients and may lead to significant morbidity and mortality. One study cited renal disease as the leading cause of death in adults with tuberous sclerosis [39]. Angiomyolipomas are by far the most frequent renal lesion, and the risk of hemorrhagic complications appears to be related to the size of the lesion [40]. Other organ system involvement includes cardiac, ophthalmologic, and pulmonary.

Fig. 3. Periungual fibroma of tuberous sclerosis.

Screening and management

Prenatal diagnosis is difficult because genetic transmission can be from one of two chromosomes and the majority of cases are actually new mutations. Family members should undergo a physical examination with Wood's lamp to accentuate ash-leaf spots and dilated funduscopy to delineate retinal phakomas [41]. For inherited cases, genetic counseling of parents is important because $\sim$50% of offspring will be afflicted.

Basal cell nevus syndrome (Gorlin syndrome)

The basal cell nevus syndrome is a rare autosomal dominant condition that consists of developmental anomalies and susceptibility to cancer, especially basal cell carcinoma (BCC). While the first cases were described in 1894, the genetic basis of this disorder has been elucidated only recently [42].

Etiology and pathogenesis

The basal cell nevus syndrome (BCNS) is caused by mutations in the PTCH gene that resides on chromosome 9q [43]. All families in which BCNS has been reported have a causative gene that links to this site. The PTCH protein is involved in the hedgehog-signaling pathway; activation of this pathway causes increased expression of several genes.

Clinical features and diagnosis

The three abnormalities traditionally considered to be most characteristic of the syndrome are basal cell carcinomas, pits of the palms and soles (Fig. 4), and cysts of the jaw [44]. While the pathogenesis of BCC in this syndrome is similar to sporadic cases of BCC, what distinguishes these lesions is the large number starting at an early age, predominantly between puberty and 35 years of age [45]. Nevoid basal cell carcinomas most commonly arise on the face, neck, and upper trunk, but may occur anywhere. In a few instances, death has resulted from invasion of the brain, lung, or peritoneum; there are only rare cases of metastasis reported [46,47].

Palmar or, less commonly, plantar pits, are small defects in the stratum corneum that occur in 65% of patients with basal cell nevus syndrome. These 1- to 2-mm asymmetric lesions rarely occur on the sides or dorsa of the fingers or toes and appear to be age related because they are rarely seen in children [44].

Fig. 4. Palmar pits of basal cell nevus syndrome.

Cases of basal cell carcinoma arising from the base of palmar or plantar pits has been reported [48].

Jaw cysts, also called odontogenic keratocysts, occur in more than 80% of patients and are often the first detectable abnormality of the basal cell nevus syndrome. In spite of widespread extension throughout the jaws, cysts are usually asymptomatic and are often detected radiographically during routine dental check-ups [44].

Skeletal abnormalities frequently include a large head circumference with frontal and biparietal bossing, low occiput, and increased interorbital distance [49]. Calcification of the falx cerebri is seen in at least 85% of adult patients [44], and abnormalities of the rib, spine, and phalanges are present in 33% to 50% of patients [50].

In addition to skin tumors, a proclivity to other types of neoplasia exists. Patients with the basal cell nevus syndrome are more likely to have medulloblastoma, meningioma, ovarian fibroma, ovarian fibrosarcoma, fibrosarcoma of the jaws, cardiac fibroma, fetal rhadomyoma, and lymphatic cysts of the mesentery [44].

Screening and management

Diagnosis is made only when multiple typical defects are present on examination of the patient. The types and severity of abnormalities may vary significantly, even among a family known to have members with BCNS [44]. The first finding that a dermatologist will encounter are numerous BCCs arising at an early age. The patient should then be questioned regarding other family members who have findings consistent with BCNS. It is important to realize, however, that 25% to 30% of cases are caused by spontaneous mutations and, therefore, there are no affected family members [43]. Radiologic evaluation for jaw cysts, calcification of the falx, and associated skeletal abnormalities should be conducted [50].

Cryotherapy is the treatment of choice because it is the best tolerated and leaves minimal scarring. Different types of surgery, including Moh's technique [51], electrodessication and curettage [52], topical 5-fluorouracil [53], and oral retinoids [54] have all been used successfully.

Epidermal nevus syndrome

Epidermal nevus syndrome (ENS) is a rare condition that refers to the association of epidermal nevi with abnormalities in other organ systems, including the nervous, skeletal, cardiovascular, and urogenital systems [55]. Although most cases occur sporadically, autosomal dominant transmission has also been reported [56,57]. Both sexes are affected equally, and the age of diagnosis ranges from birth to 40 years. More recently, Happle [58] has defined some subvariants of ENS, including the Schimmelpenning syndrome.

Etiology and pathogenesis

Epidermal nevi arise from the pluripotential germinative cells in the basal layer of the embryonic epidermis. These basal layer cells give rise to keratinocytes and to skin appendages. While nevi have been classified according to their predominant cell component, different areas of the same lesion may show different components, and predominant tissue may vary as the lesion develops [55].

Clinical features and diagnosis

Epidermal nevi are the cornerstone cutaneous finding that should prompt the clinician to search for abnormalities in other organ systems and, when both are present, diagnose ENS. While the head and neck area are the most common sites of occurrence, epidermal nevi may involve any part of the body, with many different patterns of distribution (Fig. 5). In more than 80% of patients, the onset of epidermal nevi is in the first year of life. Various cutaneous associations of epidermal nevi have been described [55]. Vascular nevi, hypopigmentation, CAL, multiple acquired nevocellular nevi, small congenital nevocellular nevi, and dermatomegaly have all been described [57].

Abnormalities of the nervous, skeletal, cardiac, and renal systems are the most commonly associated with ENS [57]. Until Rogers [55], there was no study of a large number of unselected patients with epidermal nevi to determine the frequency of other organ system abnormalities. Out of 119 patients

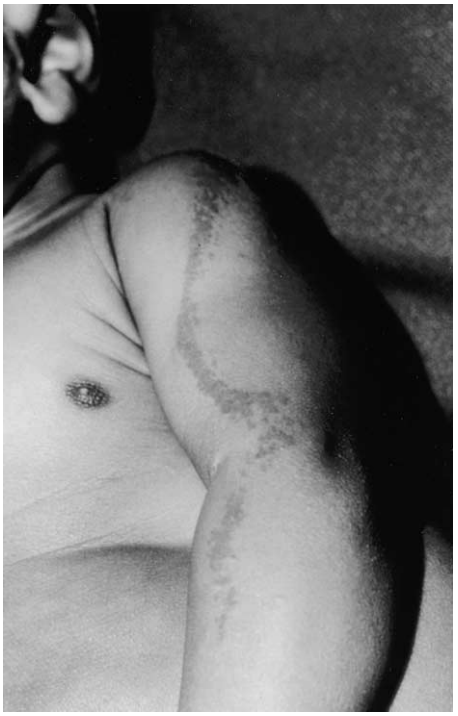

Fig. 5. Epidermal nevus of upper extremity.

with epidermal nevi, 33% were noted to have one or more abnormalities in other organ systems, 16% were noted to have two or more abnormalities, and 5% were noted to have five or more abnormalities. Skeletal abnormalities, including various bone deformities, bone cysts, atrophies, and hypertrophies have been reported in 15% to 70% of persons with epidermal nevus syndrome [59,60]. Neurologic abnormalities, including ocular defects, mental retardation, and seizures are seen in $\sim$15% of patients [57,60]. Mental retardation and seizures may be associated with cerebrovascular malformations, cortical atrophy, hydrocephalus, and intracranial calcifications.

Epidermal nevi in patients with this syndrome may undergo malignant transformation in much the same way as isolated epidermal nevi; however, this is generally limited to the nevus sebaceus of Jadassohn and its associated systematized nevus syndrome [57,61]. Visceral malignancies associated with the epidermal nevus syndrome include Wilm's tumor [57]; nephroblastoma [62]; adenocarcinoma of the salivary gland [63], esophagus, and stomach [56]; breast cancer [56]; astrocytoma [64]; and mandibular ameloblastoma [64,65].

Screening and management

Any patient with epidermal nevi, especially those with extensive or numerous lesions, should be investigated for associated systemic manifestations of ENS. A careful family history should also be obtained to check for autosomal dominant cases; genetic counseling may then be useful. Epidermal nevi with an epidermolytic hyperkeratosis pattern can be associated with gonadal mosaicism and, consequently, transmission of the genes responsible for epidermolytic hyperkeratosis (ie, keratins 1 and 10) to offspring [66].

Autosomal recessive

Xeroderma pigmentosum

Xeroderma pigmentosum (XP) is an autosomal recessive disease characterized by sun sensitivity, photophobia, early onset of freckling, and subsequent photodamage and neoplastic changes on sun-exposed surfaces. Its frequency in the population is estimated to be $\sim$1:1,000,000 in the United States. Neurologic abnormalities are seen in up to 30% of XP patients [67,68]. These neurologic abnormalities may be mild, such as hyporeflexia, or severe, such as mental retardation, sensorineural deafness, spasticity, or ataxia.

Etiology and pathogenesis

XP is a disorder in which there are inherited defects in the excision repair of thymine dimers in DNA damaged by ultraviolet radiation [69]. XP has been divided into seven different complementation groups that have different DNA-repair defects. It has been suggested that XP neurological disease is caused by the patients' DNA-repair defect [70]. It is hypothesized that there is a lethal accumulation of unrepaired neuronal DNA damaged not by UV radiation, which cannot reach the nervous system, but by intraneuronal metabolites and/or physicochemical events.

Clinical features and presentation

In patients with XP and neurological involvement, there may be somatic abnormalities present at birth or no manifestations of the disease. The earliest manifestation of XP occurs at 1 to 2 years of age and is commonly an acute sun sensitivity reaction [68]. This is seen as prolonged erythema, edema, and blistering after sun exposure. Freckling occurs during early childhood followed by cutaneous telangiectasias, atrophy, or actinic keratoses [67]. Later in childhood, neoplasms may occur. Basal cell carcinomas are the most commonly reported skin cancer, followed by squamous cell carcinomas and then melanoma.

Ocular abnormalities in XP are manifest on the tissues exposed to ultraviolet radiation, namely the lids, conjunctiva, and cornea. Neoplasms of the eye occur most frequently at the limbus, followed by the cornea and conjunctiva. The most frequently reported histologic type reported was squamous cell carcinoma, followed by epithelioma/basal cell carcinoma, and then ocular melanoma. In patients with ocular neoplasms, half of ocular neoplasms occurred by age 11.

Neurologic abnormalities may develop in infancy or may be delayed until the second decade [67]. The most common neurologic abnormality is low intelligence, which is seen in 80% of patients with neurologic involvement. Abnormal motor activity, consisting primarily of spasticity and ataxia, is seen in 30% of patients. Somatic abnormalities are confined almost exclusively to patients who had XP with neurological deficits. A slow rate of growth was noted in 23% of patients. Secondary sexual development is delayed in 12% of patients. Internal neoplasms may also be increased in XP patients. The most common cause of death of patients with XP is cancer, followed by infection. The survival probability of XP patients with neurologic abnormalities is not significantly different from that of the patients with XP without neurologic abnormalities [68].

Screening and management

Treatment is based on early diagnosis of skin neoplasms and protection of the skin from ultraviolet radiation. Patients and their families need to be educated to recognize suspicious-looking lesions and to perform regular self-examinations. Large areas of involvement have been treated with dermatome shaving or dermabrasion [71]. Oral isotretinoin has been shown to prevent skin cancers in xeroderma pigmentosum, but because of its toxicity, it should only be used in patients with multiple skin cancers [72]. This disorder is the first in which cutaneous gene therapies have successfully delivered the targeted gene product via a cutaneous delivery system. Recent studies have proven the efficacy of the bacterial DNA repair enzyme T4 endonuclease V, delivered topically, in lowering the rate of development of actinic keratoses and basal cell carcinomas [73]. Prenatal diagnosis of XP is possible by measuring UV-induced unscheduled DNA synthesis in cultured amniotic fluid cells or by DNA diagnosis of trophoblast cells [74].

Ataxia-telangiectasia

Ataxia-telangiectasia (AT) is an autosomal recessive, multisystem disease characterized by progressive cerebellar ataxia, oculocutaneous telangiectasias, x-ray hypersensitivity, predisposition to lymphoid malignancies, and profound dysfunction of both humoral and cell-mediated immune systems. Estimates of its incidence range from 1:40,000 [75] to 1:300,000 [76], with $\sim$1% of the Caucasian population in the United States being heterozygous carriers of the AT gene.

Etiology and pathogenesis

Exposure of normal mammalian cells to ionizing radiation results in a delay of progression from G1 to S phase and G2 to mitosis, as well as inhibition of DNA synthesis [77]. Cultured AT cells have abnormal radioresistant DNA synthesis and fail to activate the G1/S or G2/M checkpoints in response to ionizing radiation [78]. AT cells also show chromosomal instability and hypersensitivity to DNA-damaging agents such as radiographs and radiomimetic agents such as bleomycin [79]. The gene mutated in AT (ATM) has been isolated, spans 184 kb of genomic DNA, and has 66 exons on chromosome 11q23.1 [80]. The protein product of ATM is a constitutively expressed 350-kd nuclear phosphoprotein [81].

Clinical features and presentation

Ataxia telangiectasia typically presents between 12 and 18 months of age, when a child is beginning to walk. The child may have difficulty with control of body posture and body movement. They may start to walk later than usual and may fall to one side, or exhibit swaying movements while walking or standing. The ataxia worsens with progressive hypotonia, decreased deep tendon reflexes, and intention tremor. The diagnosis of ataxia telangiectasia is typically made at 7 years of age [82]. By 8 to 10 years of age, the child is usually confined to a wheelchair. Dysarthric speech, drooling, choreoathetosis, and myoclonic jerks become prominent. Muscle atrophy develops, particularly involving muscles of the extremities [82,83]. Mental function is normal early on but may decline slightly in later years.

Ocular telangiectasias appear between the ages of 3 and 5 years old and remain unchanged throughout life. They are the most prominent in the canthal regions and do not extend beyond the limbic regions. Most patients develop vertical and horizontal saccadic apraxia, gaze nystagmus, or strabismus [83]. Visual acuity is unaffected and funduscopic examination is normal.

Subsequent to the ocular telangiectasias, cutaneous telangiectasias may develop on the malar prominences, ears, eyelids, anterior chest, popliteal and antecubital fossae, and the dorsa of the hands and

feet. Cutaneous telangiectasias usually appear before 10 years of age.

Patients with AT have abnormalities of both humoral and cellular immune systems. Serum IgA and IgE are deficient or absent [84]. Subtypes of IgG are reduced and low molecular weight IgM has also been observed [84–86]. Circulating anti-IgA antibodies are common [87]. The thymus is absent or hypoplastic, and the spleen may be reduced in size [83].

Patients with AT are predisposed to malignancy, and some develop multiple neoplasms. The cancers are most frequently neoplasms of the lymphoid system [76]. The risk for lymphoma is 250-fold and 750-fold greater for Caucasian and African-American patients with AT, respectively, compared with the normal population [88].

Defective endocrine function is also often present. Secondary sexual characteristics are poorly developed. Breast development in female patients is minimal and genitalia are prepubertal in both sexes. Patients may have ovarian agenesis or testicular hypoplasia. Growth is typically retarded [82].

Heterozygotes for the AT gene are at a higher risk for neoplasia, especially female breast cancer. Radiography exposure in heterozygous women may predispose them to the development of breast cancer. Some studies estimate that ataxia-telangiectasia heterozygotes account for 5% of all deaths caused by neoplasms before the age of 45 [89].

Screening and management

Treatment for AT is supportive, and includes physical and occupational therapy to prevent contractures in patients with neurologic dysfunction, antibiotics for infection, and chest physiotherapy for pulmonary bronchiectasis. All available data supports the use of all standard chemotherapeutic agents when treating cancers in AT patients, with the exception of bleomycin and radiation therapy. These agents may lead to extensive tissue necrosis [79].

Prenatal diagnosis has been achieved by measurement of amniotic α-fetoprotein levels, by increased spontaneous breakage of chromosomes of fetal amniocytes, and by the presence of a clastogenic factor in the amniotic fluid [90].

X-linked dominant

Incontinentia pigmenti

Incontinentia pigmenti (IP) is a rare X-linked dominant disorder that affects the skin, teeth, eyes, central nervous system, and skeletal system [91]. As an X-linked trait, it is usually lethal to males, hence the preponderance of females with this condition. In fact, females represent about 98% of babies born with IP [92]. IP is a multisystem disorder with prominent features of mosaicism or cutaneous patterns that connote an individual comprised of two or more different cell lines [92]. Researchers have recently described the genetic etiology of incontinentia pigmenti [93].

Etiology and pathogenesis

The X-linked dominant and male-lethal disorder incontinentia pigementi (IP) is caused by mutations in a gene called NEMO [93]. The NEMO gene codes for the protein NF-kappa B essential modulator. This gene is involved in various pathways including inflammation and apoptosis. The primary defect in IP is the failure of cells to resist apoptosis, which results in early cell death [92].

Cytogenetic studies of sporadic cases of IP exhibit an X/autosomal translocation involving a breakpoint at Xpl1, which suggests a gene locus on Xpl1. Linkage analysis of familial IP, however, has identified a second locus in the Xq28 region [94].

Clinical features and diagnosis

Incontinentia pigmenti (IP) is characterized by skin lesions that are arranged in a linear pattern [95] and evolve through four classic stages that may occur concurrently or nonsequentially [91]. Linear inflammatory vesicles or bullae appear at birth or during the first 2 months of life and may last from weeks to months (Fig. 6) [91]. Lesions are filled with eosinophils, and the inflammatory response is thought to represent a selection against the functionally defective cell clone [96]. The second stage consists of linear, hyperkeratotic warty or verrucous plaques that replace the inflammatory lesions [91]. These lesions usually spontaneously disappear within

Fig. 6. Linear blisters of incontinentia pigmenti.

several months, but may last until 1 year of age [97]. As the warty lesions resolve, the child is left with persistent pigmentation. The pigmentation may persist for many years, slowly fading until it is barely perceptible by the second or third decade of life [98,99]. The presence of hypopigmented or depigmented linear macules on the lower extremities and trunk, is the final phase that appears during adulthood [91].

Common systemic manifestations include dental anomalies, ophthalmic anomalies, and central nervous system findings. Dental anomalies affect both primary and secondary dentition and include hypodontia (small teeth), partial anodontia (lack of teeth), delayed eruption of teeth, impacted dentition, and malformed crowns (conical teeth) [91]. Ophthalmic abnormalities include strabismus, cataracts, coloboma, optic atrophy, anophthalmia, microphthalmia, and retinal vasculopathy [100]. Central nervous system findings include seizures, mental retardation, ataxia, spastic abnormalities, microcephaly, cerebral atrophy, hypoplasia of the corpus callosum, periventricular white matter damage, ischemic strokes, hydrocephalus, and cerebral edema [101,102]. Malignancies such as kidney tumors, leukemias, retinoblastoma, and paratesticular rhabdomyosarcoma have been reported in children with IP [103].

Screening and management

IP follows an X-linked dominant pattern of inheritance; therefore, a careful family history in a suspect patient is crucial for confirmation of the diagnosis and future genetic counseling. Since the Xq28 region has been identified as the locus in familial cases, the development of gene testing may soon become available [94]. With the exception of hyperplastic retinopathy, there are no treatable features of IP [92].

Menkes disease

Menkes disease (MD), also known Menkes' kinky hair syndrome, is an X-linked recessive disorder of copper metabolism that is characterized by progressive neurological degeneration, abnormalities of the skin and hair, and death in childhood. The estimated incidence of MD ranges from 1:100,000 to 1:250,000 live births [104,105].

Etiology and pathogenesis

The defective gene in MD (ATP7A or MNK) has been localized to chromosome Xp13.3 by linkage analysis [106] and encodes a copper-transporting ATPase [107]. MNK belongs to a large family of cation-transporting P-type ATPases [107].

Loss of MNK function in MD results in failure of copper transfer across the gastrointestinal tract, blood-brain barrier, and placenta [108]. There is a retention of copper in the duodenum, kidney, spleen, pancreas, skeletal muscle, and placenta [109].

Clinical features and presentation

MD most often occurs in male infants who usually appear normal at birth [108]. Affected infants typically present at 2 to 3 months of age with the loss of previously attained developmental milestones, seizures, hypotonia, and failure to thrive [108]. Scalp hair and eyebrows are short, sparse, and twisted, giving the characteristic kinky appearance. Hair is least abundant in the parietal and occipital regions [110]. The hair is hypopigmented and may be gray or white in color.

Patients have a jowly facial appearance, with eyelid ptosis and loose, stretchy skin, especially at the nape of the neck and on the trunk [108]. Osseous deformities such as pectus excavatum are common, as well as wormian bones of the skull, metaphyseal spurs on long bones, and flaring of the ribs. Most patients with MD die by the age of 3 years because of infection or neurological disease [111].

Screening and management

Copper-histidine therapy normalizes serum copper, ceruloplasmin, dopamine, and norepinephrine levels after 3 months of treatment [112]. Early treatment is associated with improved neurological functioning, including decreased seizures. In a minority of patients, however, connective tissue disorders persist [112]. Lysyl oxidase may not incorporate copper-histidine well enough. Prenatal diagnosis of MD is possible for known or suspected female carriers by testing cultured chorionic villus cells for elevated copper content and abnormal egress of radiolabeled copper [113].

Sporadic

Poems syndrome

POEMS syndrome is an uncommon multisystem disorder characterized by polyneuropathy, organomegaly (hepatomegaly, splenomegaly, or lymphadenopathy), endocrinopathy, monoclonal gammopathy, and skin changes [114]. The syndrome usually presents in the fifth or sixth decade of life and is more common in men (2.5:1) Mean survival after diagnosis is 8 years [115].

Etiology and pathogenesis

The etiology and pathogenesis of POEMS syndrome is unknown, but it is thought that increased activity of proinflammatory cytokines [116] and overproduction of vascular endothelial growth factor may contribute [117]. It has recently been shown that patients with POEMS syndrome have elevated serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1 (IL-1) [116].

Clinical features and presentation

Cutaneous findings are present in virtually all patients. The most common skin finding is hyperpigmentation, which occurs in more than 90% of patients [117]. The distribution is generally diffuse, although there may be localization to the extensor surfaces of the extremities, back, neck, or axillae [118,119]. Hypertrichosis is also common, particularly on the extensor surfaces, malar areas, and forehead [118,119]. Leukonychia, clubbing of the fingers, and hyperhidrosis have been described frequently [120]. Cutaneous angiomas are common and may resemble renal glomeruli on histologic examination. Peripheral polyneuropathy is the most frequent presenting sign of POEMS syndrome [121]. The neuropathy is distal and bilateral, with a progressive proximal spread.

Hepatomegaly is common in POEMS, but liver function tests are usually normal [122]. There are also reports of idiopathic cirrhosis [123] or regenerative nodular hyperplasia [122]. Lymph node biopsy shows findings consistent with Castleman's disease. Splenomegaly, when present, is often caused by splenic localization of Castelman's disease [120]. This latter variant has been shown to be associated with HHV-8 infection [124].

A variety of endocrinopathies are associated with POEMS syndrome, including diabetes mellitus or glucose intolerance [121], hypogonadism with impotence, gynecomastia, or secondary amenorrhea, and hypothyroidism [118,125]. In men, serum testosterone is usually low, and impotence is the most common endocrinological complaint [125].

The plasma cell dyscrasia of POEMS syndrome is characterized by a monoclonal component. The monoclonal component is almost always IgA or IgG [126]. Painless sclerotic bone lesions are present in most patients and may represent a variant of osteosclerotic myeloma [115]. POEMS syndrome is progressive. Late involvement of the respiratory musculature leads to bronchopneumonia, the most common cause of death from POEMS syndrome [127].

Screening and management

Patients with solitary plasma cell tumors have responded well to radiotherapy [120] or surgical ablation [123]. High-dose corticosteroids have been used with some success, but relapses are common. Systemic chemotherapy has also been tried, often in combination with high-dose corticosteroids [121]. Neurotoxic chemotherapy agents such as vincristine should be avoided in POEMS syndrome patients [128]. All-trans-retinoic acid has recently been used in combination with radiotherapy to treat POEMS syndrome and has resulted in lowered levels of proinflammatory cytokines along with a platelet count and gammopathy that paralleled the levels of the cytokines [129].

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DERMATOLOGIC CLINICS

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Current therapy

Laser hair removal

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Long-term hair removal requires that a laser or light source damage one or more growth centers of hair. To do so, an appropriate target or chromophore must be identified. The major hair growth center has always been thought to be the hair matrix. As has now been described, however, new hairs may evolve from the dermal papilla, follicular matrix, or the bulge. Although the pluripotential growth sites of the arrector pili–associated bulge are only 1 to 1.5 mm below the skin surface, the other growth sites are often as deep as 3 to 7 mm in the skin. Because of the skin depth of these sites, significant energies must be applied for effective hair removal. Not only must each follicle be damaged, however, but the surrounding tissue, especially the epidermis, must be protected from damage. By doing so, adverse sequelae, such as scarring and permanent pigmentary changes, may be lessened. Melanin, the only endogenous chromophore in the hair follicle of pigmented hair, can be targeted effectively by lasers and light sources throughout the visible light spectrum. The longer melanin-absorbing wavelengths, seen with current lasers and light sources, are preferred because of their reduced scattering in the dermis and consequent greater depth of penetration.

The pluripotential cells of the bulge, dermal papilla, and hair matrix must be treated in the anagen cycle for effective hair removal. If the damage is not permanent during this cycle, follicles move into the telogen stage as they fall out. All of the follicles may become synchronized after the first laser treatment. The hair follicles then return to the anagen phase during the natural hair cycle. This cycle varies depending on the anatomic location. It is shortest on the face and longer on the body, varying between several weeks to several months.

Selective photothermolysis describes the use of selected wavelengths to destroy particular targets in the skin. In tandem with the principle of selective photothermolysis is the concept of thermal relaxation time [1,2]. Thermal relaxation time is used to describe the limitation of thermal damage when a desired target absorbs a particular wavelength in an amount of time that is equal or less than that target's thermal relaxation time. With the right combination of wavelength, energy, and pulse duration, it is possible to target the hair follicle precisely without causing injury to the surrounding structures. One way to achieve greater injury to the hair follicle is by increasing the pulse duration of the laser exposure. The thermal relaxation time for hair follicles that are 200 to 300 μm in diameter is approximately 40 to 100 millisecond. If pulse duration were the only factor, then the ideal laser pulse duration should lie between the thermal relaxation time for epidermis, which is approximately 3 to 10 millisecond, and the thermal relaxation time for hair follicles. There are other factors, however, to consider. If a laser or light source delivers its energy through a large beam, an increase in skin penetration occurs. Greater depth of penetration provides a greater chance of reaching hair growth centers.

In human skin, about 15% to 20% of incident light at 700 nm penetrates to a depth of 3 mm. By using a large spot size, scattering of light in the dermis is lessened, leading to greater depth of penetration. In addition, whenever a melanin-absorbing laser or light source is used for hair removal, competing epidermal melanin must be protected from damage. This is usually accomplished by cooling the skin surface. Currently popular cooling techniques include contact and cryogen cooling. Cold gel cooling, used exten-

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sively in the past, does not seem to be as consistent in its cooling ability.

Laser and light sources currently cleared by the Food and Drug Administration

Historically, there have been three somewhat different methods of using the concept of selective photothermolysis for the removal of hair. In the first two, either a laser or nonlaser light is used selectively to target hair follicles. Here, the light is absorbed by a normal component of the follicular apparatus, melanin. In the third, now rarely used technique an exogenous chromophore applied to the hair was used to absorb laser energy. The currently used wavelengths for laser or light source hair removal are as follows:

Ruby 694
Alexandrite 755
Diode 810
QS Nd:YAG 1064
Millisecond Nd:YAG 1064
Flashlamp 590-1100

Normal-mode ruby laser

Normal-mode millisecond ruby lasers produce 694-nm red light. This 694-nm laser light is well absorbed by melanin-containing hair. In the first published study evaluating the use of a ruby laser on human hair, Grossman et al [3] used a 270-microsecond pulsed ruby laser. The laser contained a contact cooling device that was designed to maximize delivery of light to the deeper portions of the hair follicle while minimizing epidermal damage. This contact device contained a sapphire lens that was cooled to 4°C. The laser energy was delivered through a 6-mm spot size.

In the study, 13 human volunteers (12 men and 1 woman) were treated. All had Fitzpatrick skin phenotypes I to III; all had brown or black hair. Treated areas were from the back or thigh. Both shaved and epilated sites were treated. The treated sites were evaluated using fluences of 30, 40, and 60 J/cm^2. Hair counts were determined 1, 3, and 6 months after laser treatment. Hair regrowth was defined as the percentage of terminal hairs present after treatment as compared with the number before treatment. Immediately after treatment, all sites became erythematous and edematous. There was rare purpura, epidermal whitening, or epidermal ablation. In evaluating the 1-, 3-, and 6-month results, the authors noted a statistically significant growth delay at 1 and 3 months for all used fluences. At 6 months there was significantly less hair only at the 60 J/cm^2 shaved sites. Hyperpigmentation, present in three subjects, had cleared by the 6-month follow-up visit. Two subjects had transient hypopigmentation; no scarring was noted. The authors found that the presence of a hair shaft was not absolutely necessary for temporary hair removal. This effect resulted from the ample melanin contained in both the follicular epithelium and papilla. At 6 months, however, there was significant hair loss only at shaven sites treated with the highest fluences. This suggests that the presence of a hair shaft actually enhances selective photothermolysis. Of the 13 subjects in the aforementioned study, 7 were followed up to 2 years after laser exposure. At 1 year and 2 years after laser treatment, four of the seven still had obvious hair loss confined to the laser-treated sites and three had complete or nearly complete hair regrowth. In all seven participants, there was no significant change in terminal hair counts 6 months, 1 year, and 2 years after laser exposure. The fact that hair counts were unchanged 6 months after laser treatment suggests that 6-month follow-up may be sufficient to determine final results of laser hair removal.

This study further evaluated what seemed to be two distinct laser hair removal responses: temporary growth delay and permanent hair loss. Temporary growth delay seems to be caused by laser damage induction of the telogen phase. Permanent hair loss seems to be associated with miniaturization of hair follicles.

Anderson et al [4] in a 10-site multicenter study evaluated hair removal efficacy in 183 patients (30 men and 153 women) treated up to six treatments during the course of 1 year. All body sites were represented, and skin types I to V were included. The laser was a 694-nm, 3-millisecond ruby laser. Subjects were treated with the highest fluence tolerated, with a range of 10 to 60 J/cm^2. All were evaluated at baseline and 6 months after the final treatment. Re-treatments were undertaken at 6- to 12-week intervals depending on degree of hair regrowth. Of the 183 initially treated subjects, 80% were treated with a 7-mm spot size with fluences between 20 and 60 J/cm^2. Twenty percent were treated with a 10-mm spot size with fluences between 10 and 24 J/cm^2. The mean average number of treatments was 4.5. Nineteen percent of the treated subjects had 100% hair loss in the treatment area, regardless of the number of treatments, body sites, skin type, or hair color. Only 2% had less than 25% hair loss or total regrowth. The mean treatment fluence for subjects with 100% hair loss at the 6-month

follow-up was 32 J/cm^2 (range, 20 to 40 J/cm^2). After a single treatment, 67% of subjects showed greater than 50% hair loss in the treated area. After multiple treatments, the percentage of subjects with greater than 50% hair loss increased to 90%. Most subjects had greater than 75% hair loss at 6 months following the final treatment. After a single treatment, most subjects showed either no change in color or texture of hairs. By the final 6-month follow-up visit, however, more than 90% of subjects showed finer hair and greater than 80% had lighter hair. The greatest response was noted in the axilla and bikini region, whereas the thighs and upper lip showed the poorest response. No scarring or textural changes were noted, although 6% of treated individuals were reported to have hyperpigmentation at 6 months. The incidence of hypopigmentation was 3%. Histologic evaluation showed miniaturization of treated hair follicles.

Although the ruby laser was the first universally accepted successful laser hair removal system (Figs. 1 and 2), it is no longer the most widely used. Some of the ruby lasers were very slow in their delivery of laser pulses making the system somewhat impractical for the treatment of large anatomic areas. Ruby lasers tend to produce greater quantities of heat than most other hair removal lasers. Other systems, described later, although not necessarily more effective, have become more popular than ruby lasers.

Normal-mode alexdrite laser

Finkel et al [5] were among the first group to evaluate the efficacy of the 755-nm alexandrite laser in removing unwanted hair. They treated 126 patients (10 men and 116 women) with a 2-millisecond alexandrite laser. Among the 116 female patients, 77 had facial hair, 15 had bikini and leg hair, 4 had axillae hair, 10 had areolar hair, and 10 had abdominal hair. The 10 male patients had backs or chests treated. The study was undertaken over a 15-month period.

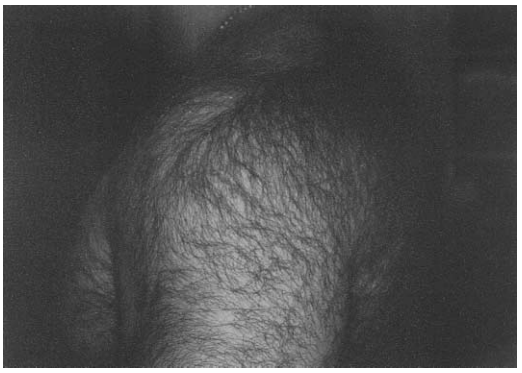

Fig. 1. Unwanted hair before treatment with a 694-nm millisecond ruby laser.

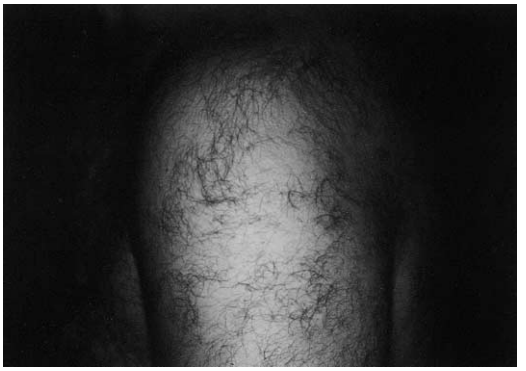

Fig. 2. Four months after one treatment with a ruby laser. Some hair loss noted. More sessions are required.

All subjects were treated with a 2-millisecond alexandrite laser at 20 to 40 J/cm^2 (average of 25 J/cm^2). Cooling of the epidermis was accomplished with a then popular cooling gel. The total number of treatments varied between three and five sessions. Treatment intervals varied between 1 and 2.5 months. The authors noted light erythema in 10% of treated patients. The erythema lasted up to several days. Superficial burns and blistering were noted in 6% of patients. Healing occurred within 10 days. Transient hypopigmentation was noted in 6% of individuals. Hypopigmentation lasted up to 3 months. The average hair loss after treatment was 45%. The numbers did vary, however, in different anatomic areas. As expected, there was progressive improvement with each laser hair removal session. The average amount of hair present 3 months after the final treatment was markedly less than that seen after the first session. Eighty-eight percent hair loss was reported by the end of the study. The results varied from 95% of hairs removed from the sideburns; 90% of hairs removed from the upper lip, bikini, legs, axillae, and periareolar breast area; 85% of hairs removed from the chin and male backs and chest areas; and 75% of hairs removed from the abdomen. The authors found that treatment with this particular 2-millisecond alexandrite laser was extremely fast because of the five pulse per second repetition rate.

Narukar et al [6] evaluated both a 20-millisecond and 5-millisecond pulse duration alexandrite laser in skin phenotypes IV to V. All individuals were treated with less than 20 J/cm^2. In this study, better results were obtained with the 20-millisecond pulse duration. Longer pulse duration laser hair removal

systems may be more beneficial in individuals with darker complexions.

These findings must be contrasted with the observations of Nanni and Alster [7]. They also evaluated the hair removal efficacy of one laser treatment session using different alexandrite laser pulse durations. In their study, they examined the hair removal clinical efficacy and side effect profile of a 5-, 10-, or 20-millisecond duration pulsed alexandrite laser.

Thirty-six subjects (9 men and 27 women; age range 18 to 68 years; average 31 years) were evaluated. Only terminal hairs were treated. Hair was treated from the upper lip, back, or lower extremities. Subjects had Fitzpatrick skin phototypes I to V. Fluences of 15 to 20 J/cm^2 (average of 18 J/cm^2) were delivered. Comparisons were made between the 5-, 10-, and 20-millisecond pulse durations. An immediate erythematous skin response was an observed end point in the laser-irradiated sites. All laser-treated areas displayed a significant delay in hair regrowth compared with a control area at 1 week and 1 and 3 months. No significant differences were seen in hair regrowth rates between the use of 5-, 10-, and 20-millisecond pulse durations. An average of 66% hair reduction was recorded at the 1-month follow-up, 27% average hair reduction was observed at the 3-month follow-up, and only a 4% hair decrease remained at the 6-month follow-up visit. The authors noted that after the one treatment used in this study, there was on average no significant reduction in hair growth by the 6-month follow-up. Complications were limited to immediate posttreatment erythema in 97% of treated sites; minimal intraoperative treatment pain in 85%; transient hyperpigmentation in 3%; and mild blistering in less than 1% (one case) of treated subjects. Of note, although hyperpigmentation was observed at all pulse durations in certain individuals, it was generally of less severity and resolved more rapidly in the 20-millisecond pulse duration treated areas. These findings were consistent with those seen by Narkuar et al [6]. Average duration of hyperpigmentation was 6 weeks.

The authors noted that, in contrast to the findings of Narkuar et al [6], all pulse durations resulted in equivalent hair removal. What was not determined in this study was whether a slightly shorter pulse duration might be more effective in thinner hair, whereas a correspondingly longer pulse duration might more be more effective in thicker, larger hairs.

It should be noted that higher fluences (up to 40 J/cm^2) are often necessary when the ruby laser is used to achieve long-term hair reduction. Because the alexandrite laser penetrates deeper into the dermis when compared with the ruby laser, such high fluences may not be required. Nevertheless, the fluences used in this study were conservative and may have led to a reduced rate of efficacy. Higher fluences may be required to maximize potential efficacy.

The authors compared the effect of pulse duration and multiple treatments on alexandrite laser hair removal efficacy [8]. Fourteen subjects (3 men and 11 women) between the ages of 19 and 51 were studied. Treatment sites included the chin, neck, back, bikini, and lower leg; Fitzpatrick skin phenotypes were I to III. All subjects had black or brown terminal hairs.

An alexandrite laser with a pulse duration of 2 millisecond, energy fluence of 25 J/cm^2, 7-mm spot size was compared with an alexandrite laser with a pulse duration of 10 millisecond, energy fluence of 25 J/cm^2, and a 7-mm spot size. Consecutive treatment and evaluations occurred at 2- to 3-month intervals for a total of three treatment visits. Posttreatment complications, such as erythema, pigmentary changes, and scars, were evaluated. Two-millisecond and 10-millisecond laser treatment results were compared, side by side, for a given anatomic site. Manual terminal hair counts were performed at baseline and compared with similar evaluations at 6 months following the final treatment. The average percentage of hair reduction was 33.1% for the 2-millisecond pulse duration and 33.9% for the 10-millisecond pulse duration alexandrite laser. There was a slightly greater, albeit statistically insignificant, loss of thicker hairs (such as those seen on the back of men) with the 10-millisecond alexandrite laser. The most common posttreatment complication was perifollicular erythema. This developed immediately after treatment and resolved within 24 to 48 hours. No cutaneous pigmentary changes or scarring was noted 6 months after the final treatment.

This study was unique, in that it was the first to compare two different pulse durations after multiple treatments. It should be noted that that the results showed a greater degree of improvement than that seen in the studies by Nanni and Alster [7]. This is probably caused by the greater number of treatments received by the author's patients. Currently, a 3-millisecond alexandrite laser with up to an 18-mm spot size and cryogen cooling of the skin is one of the most popular laser hair removal systems (Figs. 3 and 4).

Diode laser

An 810-nm diode laser is also one of the more popular available hair removal systems. Dierickx et al [9] evaluated the effectiveness and safety of a pulsed

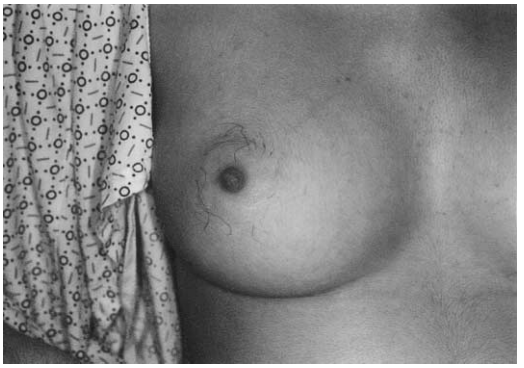

Fig. 3. Unwanted hair before treatment with a 755-nm millisecond alexandrite laser.

diode laser in the permanent reduction of unwanted hair. Ninety-five subjects were evaluated. Most had Fitzpatrick II to III skin phenotypes (ranging from II to VI) and dark hair. Subjects were treated and examined at baseline, 1, 3, 6, 9, and 12 months after treatment. The objective of the study was not only to investigate effectiveness and safety of a pulsed diode laser in the permanent reduction of pigmented hair, but also to study the fluence-response relationship. The authors also evaluated one versus two treatments. The 810-nm diode laser delivered pulse durations from 5 to 20 millisecond and fluences from 15 to 40 J/cm^2. Laser energy was delivered over a 9×9 mm area. The handpiece contained an actively cooled convex sapphire lens that, when pressed against the subject's skin slightly before and during each laser pulse, provides thermal protection for the epidermis.

Treatment results demonstrated two different effects on hair growth: hair growth delay and permanent hair reduction. A measurable growth delay was seen in all patients (100%) at all fluence-pulse width configurations tested; this growth delay was sustained for 1 to 3 months.

Clinically obvious long-term hair reduction usually required greater than or equal to 30 J/cm^2. After two treatments at 40 J/cm^2 with a 20-millisecond pulse duration, the average permanent hair reduction at the end of the study was 46%. Two treatments significantly increased hair reduction as compared with one treatment, with an apparently additive effect. At a fluence of 40 J/cm^2, the initial treatment removed approximately 30% of terminal hairs, and the second treatment given 1 month later removed an additional 25%.

Of note, hair regrowth stabilized at 6 months at all fluences; there was no further hair regrowth between 6, 9, and 12 months in this study. This stabilizing of hair regrowth or hair count is consistent with the clinically accepted growth cycle of many hair follicles. This has also been observed with other wavelength laser systems

In addition to statistically significant hair reduction, treatment with the laser also showed reduction in hair diameter and reduction in color of regrowing hairs. Regrowing mean hair diameter decreased by 19.9%.The hairs remaining after treatment were lighter and thinner.

The typical expected posttreatment response of perifollicular erythema and edema was noted. Approximately 20% of patients exhibited pigment changes, which resolved in 1 to 3 months. Most pigment changes were transient, but with darker skin types and higher fluences, some persistent pigment changes were noted. This laser continues to be a very popular hair removal system (Figs. 5 and 6).

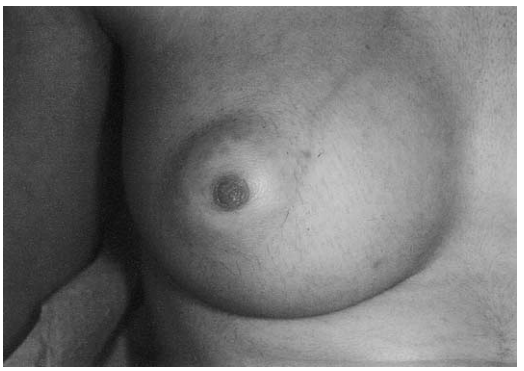

Fig. 4. Six months after four treatments with an alexandrite laser.

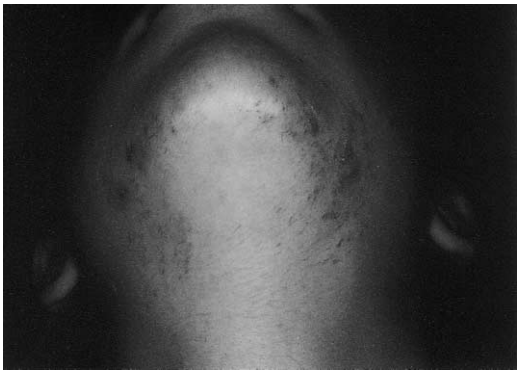

Fig. 5. Unwanted hair before treatment with an 810-nm millisecond diode laser.

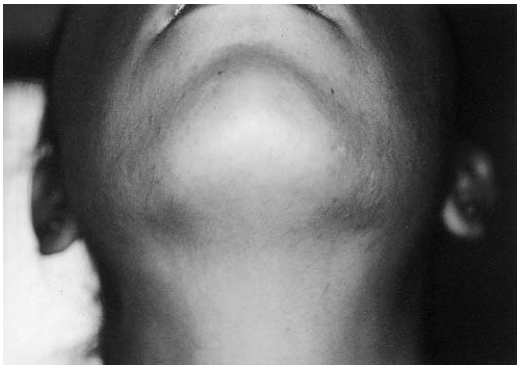

Fig. 6. Six months after four treatments with a diode laser.

Intense pulsed nonlaser light source

Gold et al [10] published the first significant series of patients treated with a nonlaser, broad-spectrum, multiwavelength light source used for hair removal. They evaluated hair removal efficacy in 31 subjects. Patients ranged in age from 14 to 74 years. Although a variety of anatomic sites were treated, the most common areas were the neck (27%); lip (22%); and chin (19%). Delivered fluences ranged between 34 and 55 J/cm^2. Energy was delivered in sequences of between two and five pulses, each pulse varying between 1.5 and 3.5 millisecond in length. Interpulse delay time varied between 20 and 50 millisecond. Seventy percent of subjects showed greater than 75% clearance.

The authors only followed patients for 12 weeks. There could be no claim of long-term hair removal. In addition, patients were treated only one time. This has been seen in subsequent studies. It is expected that the results improve after multiple treatments. Of note, the authors did not delineate which Fitzpatrick skin phenotypes were treated. It might be expected that the complication rate rises if darker skin types are treated.

This nonlaser hair removal device, although clearly effective, has dropped in popularity because of its longer learning curve than is seen with many other effective hair removal lasers.

Nd:YAG laser

One of the very first studied hair removal lasers was a short-pulsed nanosecond Q-switched Nd:YAG laser. The effect of this laser, it was at one time thought, could be potentiated with an exogenous laser-absorbing chromophore (carbon). The study was an initial pilot evaluation, using this technique, in 60 subjects of varying skin types and hair colors [11]. Most treated sites were on the face. A proprietary suspension of 10 μm carbon particles was applied to the skin and irradiated with 2 to 4 J/cm^2 of Q-switched Nd:YAG laser light (1064 nm, 10 Hz, 10 ns pulse duration, 7 mm spot size). Up to a 70% reduction in hair growth and a reduction of hair coarseness and hair lightening was noted 3 months after laser treatment. Local anesthesia was generally not necessary. No scarring or pigmentary changes were reported.

Unfortunately, a subsequent study of 12 patients determined that one treatment had no long-term benefit [7]. This study compared wax epilation and carbon suspension Q-switched Nd:YAG (2.6 J/cm2, 7 mm spot size) laser irradiation with and without prior waxing. At 3 months follow-up there was 70% to 86% hair regrowth at all sites except for the wax epilation alone, which had 100% regrowth. By 6 months there was 100% regrowth in all sites (33). Switched Nd:YAG laser hair removal treatments at the current time seem to be only of historic interest. It seems that the very short nanosecond pulses delivered from such systems simply do not create enough thermal damage to promote long-term hair removal.

The author recently studied a millisecond Nd:YAG laser on 15 healthy, adult volunteers, ranging in age from 28 to 69 years of age, with a total of 29 treated areas. All subjects had Fitzpatrick I to III skin phenotypes with brown or black hair [12].

Treatment, through a contact cooling device, was then undertaken using a millisecond 1064-nm Nd:YAG laser. Laser energy was delivered through a 2-mm diameter spot size, 30-millisecond pulse duration and fluence of 125 to 130 J/cm^2 for facial hair and 150 J/cm^2 for nonfacial hair. Hair reduction varied between 50% and 60% at 90 days. The perceived

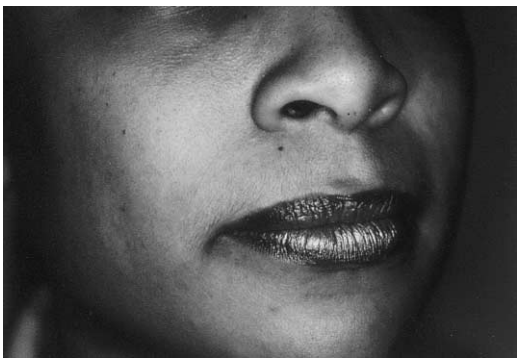

Fig. 7. Three months after two treatments with an Nd:YAG laser. Note Fitzpatrick V individual without pigmentary changes.

reduction of facial hair was greater than that of non-facial hair. No complications or adverse effects were reported at any of the follow-up examinations.

In a somewhat similar study, a millisecond Nd:YAG laser was evaluated using 15- to 30-millisecond pulse durations and fluences of 50 to 60 J/cm^2 (S. Kilmer, personal communication, 2000). Twenty-five subjects with 100 treatment sites were evaluated. Skin phenotypes I to V were evaluated; anatomic sites included the face, arms, legs, axilla, bikini, and back. Response was assessed 3 months after a single treatment. The median hair count reduction 3 months after a single treatment was 32% for treatment parameters of 60 J/cm^2 and 30 millisecond and 24% for the treatment parameters of 50 J/cm^2 and 15 millisecond. The epidermal response 1 day following treatment included erythema, edema, and infrequent blistering. At the 3-month follow-up visit, minimal hyperpigmentation was noted in only 5 of 100 treated sites. No hypopigmentation was noted.

Because such cooled millisecond systems are less well absorbed by epidermal melanin than all of the previously described systems, the Nd:YAG lasers have now become very popular for the treatment of ethnic or tanned skin (Fig. 7).

Summary

Laser hair removal created controversy when it was first described over 5 years ago. It has now become an accepted modality for long-term hair reduction. It rivals electrolysis in the successful treatment of small hair-bearing areas. It surpasses any modality in the treatment of larger hair-bearing anatomic areas.

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DERMATOLOGIC CLINICS

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Current therapy

The current status of curettage and electrodesiccation

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Curettage and electrodesiccation (CE) is a technique widely used in the destruction of benign and selected malignant cutaneous neoplasms. CE is mainly used by dermatologists and family practice physicians, whereas plastic surgeons and other surgeons excise most benign and malignant lesions. The use of CE for the treatment of skin cancer has been widely extolled and also fervently criticized. Some practitioners treat most nonmelanoma skin cancers (NMSC) with CE, and others have called for abandoning the technique in the treatment of such lesions. A thorough review of the literature reveals that CE has both virtues and flaws. In taking a rational approach to the treatment of benign and malignant cutaneous lesions it is essential to learn the basis for CE, the likely cure rates for given lesions, the proper technique, and the expected level of cosmesis. As the surgical treatment of skin cancer has become firmly entrenched in the field of dermatology it is valuable to examine this technique in depth and to come to some thoughtful conclusions about its use for patients with skin cancer and assorted benign skin lesions. Last year a remarkably complete and exhaustive favorable review of curettage, electrosurgery, and skin cancer was published by Sheridan and Dawber [1]. This article is a must read for anyone performing curettage; however, I am writing with a slightly different perspective, that of a dermatologic surgeon. Although I believe that CE has value and I use this technique frequently, I disagree with some of the truisms expressed in the literature about CE and attempts to define carefully what I believe are the strengths and limitations of this technique.

History of CE and reported cure rates

Historically, most benign and malignant skin lesions were excised. High cure rates have been reported throughout the dermatology and surgery literatures for excision of NMSC with standard permanent section margins. In the largest series reported for standard excision, Lauritzen et al [2] reported a 96.6% 10-year cure rate for the standard excision of basal cell carcinoma (BCC), although the verification of patient follow-up in this series is not clear.

The origin of electrodesiccation of skin lesions dates back to 1911 when Clark [3] noted superficial tissue drying or desiccation when he applied a high voltage, low current to the skin through a monoterminal electrode. Clark [3] reported the treatment of a variety of skin lesions including some BCC with electrodesiccation alone. Most lesions were clinically cured over a 1-to 2-year follow-up, and he reported one recurrence. The technique of electrodesiccation became available to the office practitioner through the development of instrumentation, such as the original Hyfrecator units produced by the Birtcher Corporation. The literature surrounding the original implementation of curettage is actually quite sparse.

Use of the dermal curette was reported in 1870 by Piffard [4]. Several years later Wigglesworth [5] reported the use of the dermal curette in the treatment of a variety of skin lesions including psoriasis and syphilitic condylomata. In 1902, Fox [6] introduced the Fox model curette, which has remained the most popular type of curette to this day. As

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dermatology evolved in the 1950s and 1960s an increasing number of epithelial tumors were primarily treated by CE or by curettage alone. At this time many dermatologists received little training in surgery, and most large lesions were handled either through excision by general surgeons or plastic surgeons or by radiation therapy. As dermatologists explored avenues for office-based treatment of cutaneous tumors the technique of CE was embraced as an efficient method for the removal of benign lesions and NMSC.

In the 1960s and early 1970s a number of large series reported cure rates for the treatment of NMSC by CE. In 1960, Knox et al [7] reported a cure rate of 96% to 98% for 765 BCC and squamous cell carcinoma (SCC) treated by CE, and in 1966 he reported a cure rate of 98% to 99% for CE in 1493 tumors [8]. In the 1960s and 1970s numerous other authors reported large series with cure rates ranging from 88% to 100% for CE of NMSC [9–15]. These studies have been rightly criticized for selection bias and a lack of long-term follow-up, yet they have formed the basis for CE as a treatment regimen. In addition, several authors published large series regarding cure rates for curettage alone. In the early to mid-1970s Reymann [16–18] reported cure rates of 92% to 98% in the three separate publications of separate series for the treatment of BCC by curettage alone. Using similar technique, McDaniel [19,20] reported two series with cure rates of 92% to 93%. Notably, in a subsequent study with longer follow-up, Reymann [21] reported cure rates of 87% to 90% for the same study groups. The latter article sheds light on what many in the surgical community have long believed, which is that, given adequate follow-up, the recurrence rate following removal of NMSC is substantially higher than that routinely reported with a 2- to 5-year series.

Types of curettes

Although there are many types of curettes, most clinicians use a combination of standard round and oval head Fox curettes with or without delicate angle oval Cannon curettes. The standard Fox round head curette has a rectangular handle with a tapered cylindrical extension to the head, which is round with a thicker dull side and a thin sharp side. The Fox oval curette has the same handle, but the head is oval with its longest axis along the length of the curette. The Cannon angled oval curette has a more delicate (thinner) handle and the head is tilted at a slight angle to facilitate curettage. Curettes are labeled by size from 0 to 8 based on the approximate diameter of the longest axis in millimeters. There are some specialty sizes and the size of a ''given size'' curette may vary from vendor to vendor and should be checked.

Technique

Benign lesions

Curettage and electrodesiccation or curettage alone is a superior technique for the treatment of a variety of benign skin lesions for which the seborrheic keratosis is a prototype. The lesion to be removed must have a point at which it can be detached from an underlying firm dermis. Many seborrheic keratosis may be treated with cryotherapy; however, larger lesions are readily treated by CE, which avoids the necrosis caused by cryotherapy and allows healing to commence at once. For CE the site is prepared with alcohol or other suitable preparation and anesthetized with 1% lidocaine with epinephrine. All alcohol is allowed to dry completely to prevent possible ignition. The lesion is then removed by smooth strokes of the curette with the head of the curette held at an acute angle to the skin. Typically, seborrheic keratoses are gritty and peel off of the underlying dermis easily, particularly on the trunk and extremities. The author generally starts the curettage with a larger curette and finishes the depth and edges with a smaller instrument for finer control. On the forehead the underlying dermis may be very sebaceous and more care must be taken to determine the appropriate depth of curettage. Often following such a superficial removal there is minimal bleeding, and electrodesiccation may be unnecessary. The lesion has been fully removed when a flat off-white dermis with regularly spaced hair follicles, pinpoint bleeding, and no intervening epidermal tissue, is seen. Healing of such procedures is very fast, often within 10 days, and produces minimal scarring. There is no need for limitation of activity.

NMSC

The premise of CE is that using a curette the clinician can distinguish precisely between disease (tumor) and a normal dermis. Most nodular and superficial BCC and some SCC have a less cohesive texture than normal epidermis and dermis and are delineated from healthy tissue by curettage. Sturm and Leider [22] note that ''solid cutaneous malignancies are felt to the hand that wields the curet as soft,

yielding and easily dislodged whereas healthy fibrous tissue is hard, unyielding and almost impossible to dislodge except by cutting, which the curet does not really do.'' On the other hand, all who have performed CE know well that many superficial SCCs are firm and keratotic and, although likely removable by curettage, have the tendency to be removed as chunks that tear away from the underlying dermis and peripheral epidermal tissues. Most authors who are proponents of CE recommend vigorous and precise curettage before electrodesiccation. Most commonly a large or medium curet is used to remove the bulk of the tumor, and small residual foci are removed with a smaller curet.

Two techniques may be used at curettage and have been reviewed in a detailed fashion [23]. In the pen technique (Fig. 1) the curet is held like a pencil in the dominant hand and the lesion is stabilized with the nondominant hand. Most clinicians use this technique. In the potato peeler technique, which has been touted for larger tumors, the curet is held in the distal interdigital joint of the index, middle finger, ring finger, and pinky. Using the thumb to brace against the tissue the lesion is then peeled from the dermis. It is essential that the area to be treated is braced firmly to provide a taught surface for the curet. Curettage is performed vigorously until all tumor is removed by tactile feel and until a firm dermis with pinpoint bleeding is observed. A great deal has been written about the feel of curettage, its relative underappreciation, and even its superiority to surgical margins. In their thorough review of CE last year, Sheridan and Dawber [1] stated that ''this feel is both undeniably and readily learnt.'' On the other hand, Salasche [24] has definitively demonstrated that even in highly experienced hands tumor is left behind by curettage in 12% to 30% of facial BCC. The author believes that the ''feel'' is far more reliable on the trunk and proximal extremities where the dermis is thick and taut, and it has been clearly demonstrated that the recurrence rate for NMSC following CE is much lower at these locations. In the author's estimation his ''feel'' is at its weakest on the eyelid, medial cheek, and eyelid, which float during the curettage procedure, and on the nose where follicular BCC is beyond the feel of the curet.

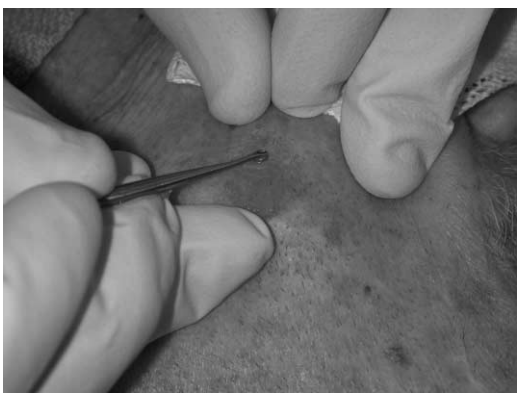

Fig. 1. Pen curettage and electrodesiccation technique for removal of squamous cell carcinoma in situ on the cheek.

Some authors believe that electrodesiccation and subsequent curettage of the char affects a higher cure rate [1], but the data to support this assertion are weak. Likewise, it is not clear that performing three cycles of CE is statistically more effective than one thorough curettage. It is clear that those who have reported the highest cure rates always destroy a substantial peripheral margin around their initial curettage. This is accomplished most readily by electrodesiccation and then curettage of a rim of 2 to as much as 8 mm of tissue around the initial defect [7,13]. Several authors note that any undermined epidermis at the periphery of the curettage site should be trimmed away with scissors [25].

Cure rates

It is hard to reconcile the highly disparate cure rates reported by various authors for CE of NMSC lesions. As noted previously, all of the large series from the 1960s and 1970s report cure rates for CE well over 90%. These articles paint a glowing testimonial of the technique, extolling high cure rates, superior cosmesis, and, in some cases, superiority over other long-tested methods of tumor extirpation. Reading these articles and taking the reported cure rates at face value one would be inclined to treat almost all NMSC with CE. Most of these series, however, suffer from selection bias and severely inadequate follow-up. In 1971, Crissey [26] noted that ''The evaluation of these and other published statistics on cure rates is a frustrating experience. The reports themselves leave much to be desired in matters of clarity, and those who have been on the firing line will know that the selection of cases for the different methods is subject to so many variables, gross and subtle, that severe biases creep into the data of the most conscientious and skilled observers.'' In analyzing the 13 prior available studies for CE Crissey [26] compiled a cumulative 92.6% cure rate. He added that certain lesions responded poorly to CE. Specifically, he noted that CE was usually unsuitable for large cutaneous carcinomas, lesions of the nose

greater than 1 cm, lesions of the margin of the eyelid and the vermilion border of the lip, lesions involving cartilage, and sclerosing epitheliomas. It was really not until the late 1970s that a series with proper statistical analysis and adequate follow-up was published for cure rates following CE. In 1977, Kopf et al [27] published an exhaustive review of data compiled at New York University. Depending on the setting, private office versus academic setting, New York University physicians compiled cure rates for CE of BCC ranging from 81.8% to 94.2%. The cure rate for CE of recurrent lesions in this study was 66%. An improved cure rate for resident performed procedures was noted following greater supervision by attending physicians later in the study period. In a multivariate analysis of the same data for patients followed for 5 years the recurrence rate for CE for 758 BCC treated between 1955 and 1969 was 26%, as opposed to a 9.6% recurrence rate for 659 BCC treated by surgical excision or radiation [28]. Commenting on these data, Salasche [29] noted that guidelines for defining the role of CE were confusing and that ''foremost in this regard is the almost wishful expectation of a 95% 5-year cure rate following C&D.'' In 1991, Silverman et al [30] reported a detailed review of cure rates following CE at the New York University Skin and Cancer Unit from 1955 to 1982 with emphasis on data from 1973 to 1982. Multivariate analysis identified low-, intermediate-, and high-risk sites for recurrence following CE of primary BCC. The neck, trunk, and extremities were considered low-risk sites with a 5-year recurrence rate of 8.6%. The scalp, forehead, and temples were of intermediate risk with a 12.9% recurrence rate. High-risk sites, such as the nose, eyelids, chin, jaw, and ear, had a recurrence rate of 17.5%. The authors noted that to achieve a 95% cure rate for CE at middle-risk sites, lesions should measure less than 1 cm in diameter, and that in high-risk areas a 95% cure rate for CE may be achieved by selecting lesions less than 6 mm in diameter. Although others have continued to report much higher cure rates [25], most in the dermatologic surgery community feel that the New York University data reflect the reality of CE in daily practice quite accurately and that their high-, intermediate-, and low-risk stratification is valuable in planning appropriate care for a given tumor.

CE followed by excision: effectiveness in eradicating tumor at given sites

Any oncologic surgeon stresses that complete tumor extirpation is essential to affect cure. Historically, the gold standard for removal of a tumor has been, and remains, complete excision with reliable negative margins. In the favorable curettage literature the feel of a negative margin has been stressed as equal to surgical margin control, and some strong proponents of CE have gone so far as to suggest that ''conventional surgical excision (is) a crude method of extirpating cutaneous malignancies,'' and that ''simple curettage has a certain surety'' [22].

To test such statements it is useful to examine the available data regarding complete excision and meticulous histology following curative CE for BCC. Several excellent studies have been performed to assess the presence of residual tumor following seemingly definitive curettage or CE. In 1983, Salasche [24] performed CE (three cycles) on selected BCC and subsequently excised the defect with a 1-mm margin. This tissue was then analyzed for the persistence of tumor nests using Mohs' surgery. Residual BCC was identified in 12% of extranasal lesions and in 30% of nasal and paranasal lesions. Shortly thereafter, Edens et al [31] published a similar study in which tumor persisted in 37% to 45% of cases following CE of either one or three cycles, respectively. Suhge d'Aubermont and Bennett [32] reiterated these findings with a similar study that demonstrated persistent tumor in 46.6% of BCC on the head treated by CE, but in only 8.3% of truncal lesions treated by CE.

Numerous authors have acknowledged the persistence of tumor following CE but point to a higher clinical cure rate than that which might be expected when tumor is left behind. A mantra long referred to by those who write about CE is that because of healing and scar formation, somehow in the maturation process of the scar, residual BCC is destroyed and this leads to an augmented cure rate. Two studies have definitively demonstrated that over a 1- to 3-month period persistent BCC is in fact not eradicated but remains present at the site of CE [33,34]. Even in the face of what should be considered relatively overwhelming evidence to the contrary some prominent dermatologists continue to suggest that tumor may somehow magically disappear when still present in scar tissue following a destructive procedure. In reconciling tumor persistence with clinical cure rates it has always been the author's impression that many individuals are simply living with residual tumor. Incidentally, such tumor may be very difficult to detect clinically, particularly when it is at the base of a curettage scar. This hypothesis seems to the author to be much more tenable than the disappearing basal cell hypothesis. It is the author's suspicion that many

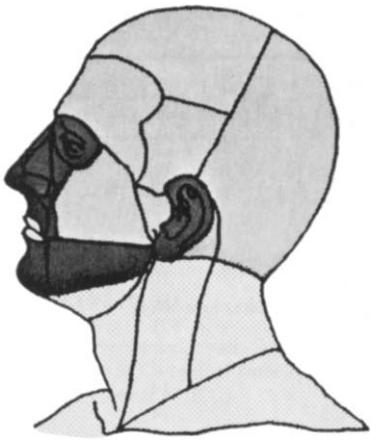

Fig. 2. High-risk anatomic sites are represented by the darkest areas, the middle-risk sites by the intermediate areas, and the low-risk sites by the lightest areas. Included in the low-risk sites are the trunk and extremities.

individuals die with undetected or undiagnosed persistent BCC.

Recurrence

As a Mohs' surgeon the author is well acquainted with the recurrent NMSC. Part of what interested the author in first studying the issue of CE for NMSC when he was a dermatologic surgery fellow was his impression that almost all primary NMSC that subsequently recurred had originally been treated by CE. In the last 6 years of operating as a dermatologic surgeon the author has removed hundreds of recurrent lesions of NMSC. Of these tumors, less than one dozen were originally treated either by excision or Mohs' surgery. Despite frequent recurrences and despite literature evidence to the contrary, many dermatologists in areas the author has practiced persist in quoting a cure rate of 95% across the board for CE for facial BCC. There is also a tendency of some physician authors to minimize the implications of recurrent NMSC. For example, in their 1972 paper Whelan and Deckers [13] noted that ''when there is a recurrence after electrocoagulation, it occurs on the surface of the scar, is quickly detected, and may be expeditiously recoagulated.'' This may be true in some cases for small superficial NMSC on the trunk and extremities, and the author has certainly retreated small superficial truncal recurrences with CE. It is the author's experience, however, that recurrence on the head and neck is frequently either infiltrative at a peripheral margin or occurs at the deep margin, is often overlooked as scarring for years, and can have devastating consequences. The author agrees with Spencer et al [33] who recognized that ''a relatively benign primary BCC can become an aggressive, invasive, destructive recurrence that is much more difficult to treat.'' In addition, recurrence is often multifocal, necessitating removal of the entire prior treated site to achieve an adequate cure rate (Figs. 2 and 3) [30,35]. Even most physicians who recognize CE as a valuable primary treatment modality for NMSC recognize the ineffectiveness of CE for the treatment of recurrent lesions [1]. The author thinks that the practicing dermatologist should choose a procedure that offers a high cure rate, particularly when the implication of recurrence is significant.

Histologic subtypes

It is widely agreed that infiltrative (morpheaform and micronodular) BCCs are not readily treated by

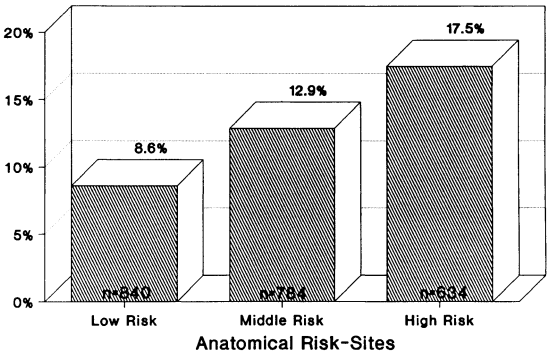

Fig. 3. Five-year recurrence rates by anatomic risk sites for BCCs treated from 1995 to 1982 ($P < .001$). N refers to the number of BCCs.

CE and are best treated by excisional means [1]. Many physicians obtain biopsies of lesions and treat them subsequently by various methods depending on the histologic subtype of tumor identified by the biopsy specimen. Other physicians obtain biopsy and destroy multiple lesions and then re-treat by excisional means any tumors that are found to be infiltrative on histology. The problem with these treatment models lies in the fact that the histopathology of NMSC is heterogeneous in a given lesion. Jones et al [36] reported that 40% of BCC are composed of more than one histologic subtype and that 13% of tumors classified on biopsy as nodular BCC in fact have a component of infiltrative BCC. Even given the limitations that are imposed by a partial biopsy, however, it is clearly reasonable to base treatment decisions at least in part on histologic subtype. For example, although a reading of nodular BCC does not guarantee that a lesion is amenable to curettage at an appropriate location, a reading of infiltrative BCC discourages this form of treatment.

Cosmesis

In 1963, Sweet [11] wrote that the cosmetic results from curettage and electrodesiccation were ''. . . so astoundingly good that I think they would justify this form of treatment even if the recurrence rate were far higher.'' Numerous other authors who have promoted the technique of CE or curettage alone have extolled the cosmetic virtues of curettage over surgical excision. With regard to curettage alone Reymann [17] noted that ''it must be emphasized that after treatment solely with curettage, the cicatrices are much more satisfactory than those resulting from any other type of therapy.'' In contrast, Eptstein [37] noted in 1977 that ''surgical excision produces cosmetic results clearly superior to CE'' and that ''the dermatology profession should stop trying to justify the second-rate cosmetic results obtainable by CE and abandon the technique in treating BCC.'' To date there have been no blinded studies of the cosmetic outcome of CE versus excision.

Fig. 4. Recurrent basal cell carcinoma following curettage and electrodesiccation at high-risk site. (*From* Silverman MK, Kopf AW, Grin CM, et al. Recurrence rates of treated basal cell carcinomas. Part 2: Curettage-electrodesiccation. J Dermatol Surg Oncol 1991;17:720–6; with permission.)

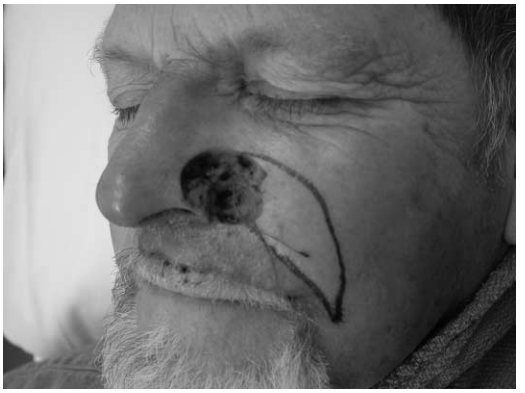

Fig. 5. Extensive defect following Mohs' surgery. (*From* Silverman MK, Kopf AW, Grin CM, et al. Recurrence rates of treated basal cell carcinomas. Part 2: Curettage-electrodesiccation. J Dermatol Surg Oncol 1991;17:720–6; with permission.)

Clearly, the cosmetic result following both CE and excision is site dependent. On the trunk and extremities CE often leads to a flat, white macule or patch, but may lead to a raised or depressed oval scar, or occasionally a long-standing keloidal scar. Even if the eventual result is satisfactory, often CE sites remain pink and elevated for a period of months before improving (Figs. 4 and 5). Surgical excision at these sites frequently leads to a fine line but can produce either a spread scar or a keloidal scar. On the face CE may heal with a fine white patch or macule; however, despite many claims to the contrary, healed CE sites on the face are often depressed, sometimes markedly so, often retract free margins as they heal, and can produce a firm rope-like scar caused by wound contraction. It is important to note that a skillfully performed surgical excision on the face often leads to a scar that is almost imperceptible even on close inspection (Figs. 6–9), whereas CE can never do this. In general, it is the author's belief that excision or Mohs' surgery followed by proper

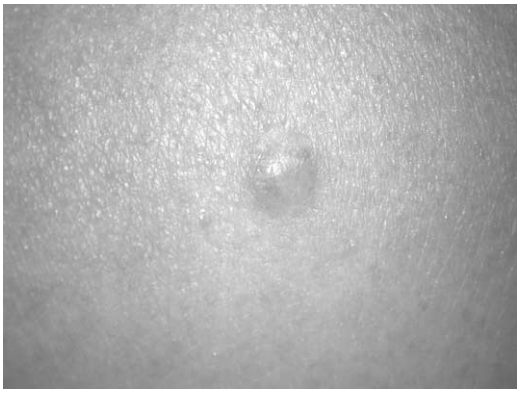

Fig. 6. Typical curettage site on the back at 2 months. Note pink color and elevation. Frequently the site is pruritic.

repair more often leads to an aesthetic scar than does CE.

CE, where, and why?

In choosing how to treat NMSC it is important to incorporate many factors in developing a formula for the most appropriate care. The author's practice has broken down the treatment of benign skin lesions and NMSC based on location and histologic subtype.

Benign lesions

The author routinely uses CE for the treatment of a wide variety of benign lesions ranging from pyogenic granulomata to seborrheic keratoses to verrucae. Many of these lesions are clearly more readily destroyed than excised. In particular, for seborrheic keratoses the technique is unparalleled. The advantage of CE over cryosurgery herein lies in the fact that healing begins immediately following CE. In addition, given that for benign lesions only a gentle curettage is needed the resultant scar is often nearly imperceptible. In addition, recurrence is basically a nonissue because the original lesion is benign.

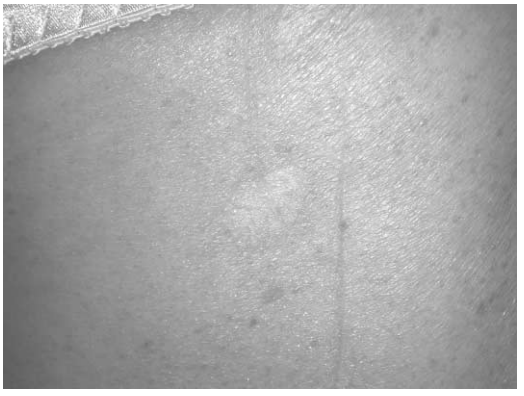

Fig. 7. Well-healed currettage site at 1 year. Note flat, white, soft, supple scar. This is an excellent result and in this case is likely superior to the result that would have been achieved surgically.

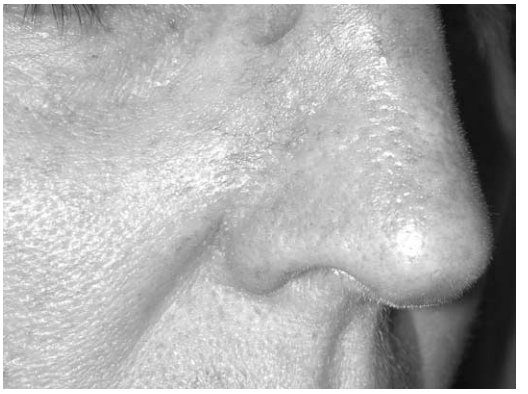

Fig. 8. One month following surgical excision and linear repair of 1.5 by 1.5 cm basal cell carcinoma in nasofacial sulcus. This cosmetic result could not be duplicated by curettage and electrodesiccation at this location. Also, cure rate would be much lower. Note small retained suture at junction of cheek and nose.

NMSC

A CE is an expedient and suitable form of treatment for selected NMSC and is widely used in

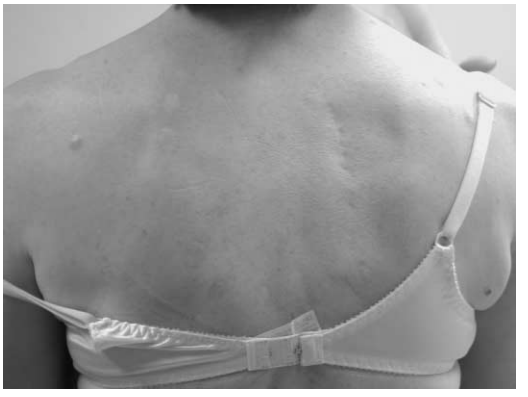

Fig. 9. Multiple curettage sites at various stages of healing. Note well-healed flat white scars, somewhat newer flat pink scars, and several fresh elevated pink scars (scapular regions). Also note long linear repair from much larger infiltration tumor.

the author's department within a set of defined guidelines. Except in the isolated case of the long-term patient with many skin cancers, lesions routinely undergo biopsy first and are treated on a subsequent visit. It is found that even to the relatively skilled eye some lesions that are believe to be nodular or superficial BCC or superficial SCC are histologically something else. Because CE can complicate further care by enlarging the primary lesion it is rational to postpone further care pending the biopsy result. All biopsies are shave biopsies to avoid disturbing the underlying dermis. Punch biopsies, which poke through to the subcutis and simulate deep tumor extension, make subsequent CE difficult. If a punch biopsy has been performed elsewhere the author routinely proceeds with surgical treatment. Based on histology the author only considers treating nodular or superficial BCC, hypertrophic actinic keratoses, in situ squamous carcinomas without extensive follicular involvement, and superficially invasive squamous carcinomas in select locations. On the face CE is generally reserved for invasive lesions that are under 1 cm in diameter, and rarely if ever is CE used to treat invasive NMSC of the nose, ear, lip, eyelid, or hair-bearing scalp. On the trunk and proximal extremities many NMSC are treated with CE. In general, these lesions are either superficial or nodular BCC or small minimally invasive SCC. Rarely is a lesion greater than 2 cm and in fact most lesions destroyed by CE are 1 cm or less. In these instances, particularly when a patient presents with 10 to 20 or even more small BCCs, it is believed that biopsy of each lesion with subsequent immediate destruction is likely reasonable. Such patients already require many visits, and in the interest of a reasonable degree of expediency the occasional biopsy that is returned as infiltrative BCC is accepted. It is the author's practice always to obtain biopsy by shave biopsy. Curettage specimens are inherently inferior, suffer from massive crush artifact, and should be avoided. Those who read their own slides can attest to the fact that only a high-quality biopsy specimen is acceptable.

In considering when to treat a given lesion by CE the author tries to make an assessment of lesion depth, the thickness of the dermis, and the lack or abundance of deeply seated hair follicles. Lesions that are relatively more broad and superficial and that are located in areas with thick dermis (particularly the trunk and extremities) are well suited to CE. In these locations superficial lesions tend to just wipe off of the thick underlying dermis and are also in general quite well defined on clinical examination. At such sites the procedure of CE is also much less invasive than a surgical excision, requires minimal wound care effort, and leads to a very high cure rate. On the other hand, even at these locations the author tends not to curet lesions that have any substantial depth. The reasons for this are several. First, a deep CE treatment site may take many weeks to heal and often leads to a substantial depression or paradoxically elevated firm scar. Second, the author's faculty is not convinced of their ability to determine the depth of a clinically deep lesion by use of the curet. Deep nodular lesions on the trunk and extremities are removed by excision. It has been widely stated that if, during curettage, the curet pokes through to fat the procedure should be abandoned in favor of excision. It is their contention that one should never start a curettage when there is any realistic chance of extension into the subcutis. It is not usually difficult to make this decision before tumor removal.

Before treating any invasive SCC by CE the author ensures that the lesion is well differentiated; only superficially invasive; and located in an area with a thick firm dermis, such as the back or proximal extremity. When treating SCC in situ, the author considers histologic evidence of deep follicular extension in the decision to use CE or excisional means. Not all in situ lesions are alike. Many in situ SCC on the trunk and extremities affect only the interfollicular epithelium and are readily destroyed by CE. On the other hand, SCC in situ on the distal nose may burrow far down hair follicles requiring Mohs' surgery or at least full-thickness excision to affect cure.

For facial lesions the decision to treat by CE must always be considered a judgment call. The author is the most surgically aggressive member of the faculty. He treats almost all invasive tumors on the face by excisional means. The author finds that excision takes scantly longer at these sites, produces a more aesthetic scar, provides an extremely high cure rate, a high degree of patient satisfaction, and requires minimal wound care. Many authors note that small lesions on the face are amenable to curettage. This clearly is true; however, precisely those lesions that are tiny and hence amenable to CE are also extremely easy to excise with minimal impact and a faster healing course because the small wound has been sutured. Nonetheless the author believes CE of selected lesions on the face can be extremely valuable. Very superficial BCC and in situ SCC without follicular involvement can simply be peeled from the underlying dermis and are readily cured. Because the depth of curettage in these cases is so minimal the procedure has an extremely low morbidity and is ideal. Some clinicians feel comfortable treating somewhat larger more invasive nodular NMSC by CE and the literature does support this as being within the

standard of care, so long as the procedure is done within appropriate guidelines as previously enumerated. As dermatologists become more facile and experienced with surgical excision, however, they find themselves using this technique more often than CE. Contrary to the criticisms of some physicians that this is for financial gain, surgical excision is clearly less productive financially than CE. Minute for minute and expense for expense nothing but cryosurgery generates more income than CE. Clearly, excision has a higher overall cost than CE and this must be factored into the decision about how to treat NMSC; however, the higher cure afforded by a well-planned surgical excision can cut back on the expenditures for future tumor recurrence.

It is important to consider when treating NMSC that the lesion is in fact cancerous. It is essential to offer patients a treatment option with the highest cure rate available by a reasonable means. When the author began practicing at his current location over 5 years ago the primary treatment method for most NMSCs was CE. The nearest dermatologic surgeons were well over an hour away and the plastic surgery department was overwhelmed with large serious cases. When he arrived he was greeted by literally hundreds of recurrent facial tumors, some of them quite devastating, almost all of which had been treated by CE. With the increased availability of excision and Mohs' surgery and with a true paradigm shift in the treatment of NMSC, there has been a dramatic reduction in the number of recurrences in the area and within the department. The author continues to use the time-honored technique of CE for selected tumors and affects a high cure rate in these cases. It is presumed that CE will remain a workhorse, where appropriate, for years to come. From the author's vantage point, however, the era of CE as the most used primary treatment for NMSC in dermatology has come and gone. As the dermatology profession continues to refine and improve on its surgical skills the treatment of NMSC will continue to evolve. It is important to continue to use older techniques where valuable; however, it is equally important to define and recognize the limitations of older therapies and move forward by incorporating new available treatment modalities.

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