INTRODUCTION

The term “connective tissue disease” (CTD) may be taken to refer to any disease that targets the connective tissues of the body. Diseases in which inflammation or weakness of collagen tends to occur may also be referred to as collagen diseases. Some of these conditions may result from genetic abnormalities leading to inborn errors and are congenital in presentation. These conditions are discussed elsewhere, especially in Chapter 6. Many CTDs are characterized by inflammation in tissues as a result of autoimmunity. The related term “collagen vascular disease” refers to disorders that are typically associated with collagen and blood vessel abnormalities and that are usually autoimmune in nature. There may or may not be associated vacuities. CTDs can have genetic associations, and can also be caused by environmental factors, but are often idiopathic. The autoimmune CTDs may also be referred to as disorders that are typically associated with collagen and blood vessel abnormalities and that are usually autoimmune in nature. There may or may not be associated vacuities. CTDs can have genetic associations, and can also be caused by environmental factors, but are often idiopathic. The autoimmune CTDs may also be referred to as systemic autoimmune diseases, which again may have both genetic and environmental causes. Genetic factors may create a predisposition toward developing these autoimmune diseases. They are characterized as a group by overactivity of the immune system, resulting in the production of autoantibodies. Immune complexes may be formed and contribute to pathogenesis. Cell-mediated immunity also plays a role. Diagnosis of most of these disorders is usually a clinico-pathologic exercise, including extensive laboratory testing; histopathology alone is seldom, if ever, the “gold standard” for diagnosis.

LUPUS ERYTHEMATOSUS

Lupus erythematosus (LE) is a multifaceted autoimmune disease that affects multiple organ systems. Its clinical manifestations range from limited cutaneous involvement to fatal systemic illness. Cutaneous forms of LE occur two to three times more commonly than systemic lupus, and they, therefore, represent an important subcategory of the disease. As the underlying mechanism and pathogenesis of cutaneous lupus is similar, the various different forms will be discussed under one umbrella term of cutaneous LE. Similarly, as the therapy for cutaneous lupus, in all its forms, has extensive overlap, it will also be discussed together. Cutaneous disease is the presenting symptom in 23% to 28% of cases of systemic lupus, while 72% to 82% of systemic lupus patients manifest at least one cutaneous symptom through the course of their illness (1).

Clinical Overview

A combination of clinical and laboratory data was used to devise the Criteria for the Classification of Systemic Lupus Erythematosus set forth by the American Rheumatism Association (ARA) in 1972. Since then, there have been modifications of laboratory criteria to reflect the changes in diagnostic technology (2,3). A position paper on the revision of the 1982 criteria for systemic lupus erythematosus (SLE) recommends skin biopsy, but not of alopecia or oral lesions, and comprehensive antibody studies, including SSA and SSB (Ro and La) in the workup of LE (1).

The initial ARA criteria were developed primarily for the distinction of patients with SLE from those with other autoimmune diseases. These criteria are still widely used to diagnose patients with LE. The classification is based on 11 criteria, which are not meant to be either restrictive or exclusive to the diagnosis of SLE:

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers, usually painless
5. Arthritis, not erosive, involving two or more peripheral joints, with tenderness, swelling, or effusion
6. Serositis (pleurisy or pericarditis)
7. Renal disorder (persistent proteinuria exceeding 0.5 g/day or cellular casts)
8. Neurologic disorders (seizures or psychosis)
9. Hematologic disorders (hemolytic anemia, leukopenia of less than 4,000/mm³, lymphopenia of less than 1,500/mm³, or thrombocytopenia of less than 100,000/mm³)
10. Immunologic disorder (positive LE cell preparation, anti-DNA in abnormal titer, antibody to Sm nuclear antigen, or false-positive serologic test for syphilis)
11. Antinuclear antibody

The diagnosis of SLE is applied if 4 or more of the 11 criteria are present serially or simultaneously.
A diagnosis of SLE may also be rendered in a patient who has at least three of the following four symptoms: (a) a cutaneous eruption consistent with LE, (b) renal involvement, (c) serositis, or (d) joint involvement (4). Although there is no single serologic gold standard test to detect SLE, the diagnosis does require serologic abnormality.

Even though the prognosis of SLE has been improved by early diagnosis and new treatments, the mortality rate of the disease is between 15% and 25% (4). Death usually results from infection or severe nephritis (5). A recent meta-analysis of lupus patients showed that patients with SLE are at increased risk of lymphomas, specifically non-Hodgkin lymphoma, independent of the risk associated with chronic immunosuppressive therapy (6).

Cutaneous changes of LE may be subdivided according to the morphology of the clinical lesion and/or its duration (acute, subacute, or chronic). Differentiation between LE subtypes is based on the constellation of clinical, histologic, and immunofluorescence findings (7). Histologic findings alone may not be sufficient to classify correctly the subtype of the eruption (8). Not every case of LE can be assigned with certainty to a category because intermediate forms and transitions from one type to another occur. Clinically distinct subtypes are addressed below.

**Chronic Cutaneous Lupus Erythematosus:**

**Discoid Lupus Erythematosus, Verrucous Lupus Erythematosus, Tumid Lupus Erythematosus, Lupus Erythematosus Panniculitis/Profundus**

**Discoid Lupus Erythematosus**

**Clinical Summary.** Characteristically, lesions of discoid lupus erythematosus (DLE) consist of well-demarcated, erythematous, slightly infiltrated, “discoid” plaques that have prominent adherent thick scale and follicular plugging. Early and active lesions are erythematous, corresponding with cutaneous inflammation (Fig. 10-1A). Old lesions often appear atrophic and have hypo- or hyperpigmentation and may have scarring. Occasionally, lesions may show verrucous epidermal hyperplasia, especially at their periphery (9). Uncommonly, malignant neoplasms have been reported in lesions of DLE, including basal cell carcinoma, squamous cell carcinoma, and atypical fibroxanthoma (10).

In many instances, the discoid cutaneous lesions are limited to the face, where the malar areas and the nose are predominantly affected. In addition, the scalp, ears, oral mucosa, and vermilion border of the lips may be involved. In patients with discoid lupus limited to the head and neck, conversion to SLE is rare (5% to 10%) (11).

In patients with disseminated DLE, discoid lesions are seen on the upper trunk and upper limbs, usually, but not always, in association with lesions on the head (12). SLE may eventually develop in up to 20% of these patients (13). Although discoid cutaneous lesions are typical of patients with chronic cutaneous LE, they are also seen in 14% of the patients with SLE (14).

**Histopathology.** In most instances of discoid lesions, a diagnosis of LE is possible on the basis of a combination of histologic findings (Fig. 10-1B–E). Changes may be apparent at all levels of the skin, but all need not be present in every case. The findings are summarized as follows:

1. **Stratum corneum:** hyperkeratosis with follicular plugging
2. **Epithelium:** thinning and flattening of the stratum malpighii, hydropic degeneration of basal cells, dyskeratosis, and squamatization of basilar keratinocytes
3. **Basement membrane:** thickening and tortuosity, correlating with deposition of immune reactants (Fig. 10-2)
4. **Stroma:** a predominantly lymphoplasmacytic infiltrate arranged along the dermal-epidermal junction, around hair follicles and eccrine glands, and in an interstitial pattern; interstitial mucin deposition; edema, vasodilation, slight extravasation of erythrocytes
5. **Subcutaneous:** possible slight extension of the inflammatory infiltrate

The stratum corneum is usually hyperkeratotic. Parakeratosis is not conspicuous, and it may be absent. Keratotic plugs are found mainly in dilated follicular openings (Fig. 10-1B, C), but they may occur in the openings of eccrine ducts as well. Follicular channels in the dermis may contain concentric layers of keratin instead of hairs.

The epidermal changes vary with the clinical character of the lesions; there may be thinning and flattening of the stratum malpighii. A clinically verrucous lesion shows a hyperplastic epidermis with hyperkeratotic scale that simulates a hypertrophic actinic keratosis or even a superficially invasive squamous cell carcinoma (Fig. 10-3A, B) (15).

The most significant histologic change in LE is hydroptic degeneration of the basal layer, also referred to as liquefactive or vacuolar degeneration. This change is characterized by vacuolar spaces beneath and between basal keratinocytes (Fig. 10-1C). In its absence, a histologic diagnosis of LE should be made with caution and only when other histologic findings greatly favor such a diagnosis. In addition to liquefactive degeneration, basal keratinocytes may show individual cell necrosis (apoptosis) and acquire elongated contours similar to their superficial counterparts rather than retain their normal columnar appearance (squamatization). Frequently, the undulating rete ridge pattern is lost and is replaced by a linear array of squamati zed keratinocytes (Fig. 10-1C) (8).

The basement membrane, normally delicate and inconspicuous, appears thickened and tortuous in longstanding lesions (Fig. 10-1E). This change becomes more apparent with periodic acid–Schiff (PAS) stains, and may be found along the follicular-dermal junctions as well. These findings correlate with locations of immune reactant deposits found on direct immunofluorescence testing of affected skin (Fig. 10-2). By contrast, in areas of pronounced hydropic degeneration of the basal cells,
Discoid lupus erythematosus. A: An adult with discoid plaques of lupus erythematosus on the upper back. Areas of erythema show stromal inflammation, and paler zones demonstrate scarring. B: The epidermis has lost its rete ridge pattern and shows follicular plugging. There is a brisk mononuclear inflammatory infiltrate near the dermal–epidermal junction and around appendages. The faint bluish background is mucin among collagen bundles. C: Focal subepidermal vacuolization and lymphoplasmacytic infiltrates approximating squamatized basilar keratinocytes. Thickening of the basement membrane is noticeable around follicular ostia. D: Lymphoplasmacytic infiltrates surround eccrine coils in the deep dermis. Interstitial mucin deposits are present in the adjacent stroma. E: Combination Alcian blue–periodic acid–Schiff stain demonstrating a thickened and tortuous basement membrane zone and abundant interstitial mucin deposits among collagen bundles.

The inflammatory infiltrate in the dermis is usually lymphocytic admixed with plasma cells (Fig. 10-1C, D).

The PAS-positive subepidermal basement zone may be fragmented and even absent (16). Capillary walls may also show thickening, homogenization, and an increase in the intensity of the PAS reaction.

Its distribution is a clue to the diagnosis of LE. In active lesions, the infiltrate can be found approximating the dermal–epidermal junction associated with hydropic degeneration. In hair-bearing areas, the infiltrate is located around folliculosebaceous units and eccrine glands (Fig. 10-1C). Frequently, hydropic changes in
The dermis may show edema, ectatic vessels, and foci of hemorrhage. In dark-skinned persons, melanophages are commonly seen. Increased amounts of ground substance (hyaluronic acid) are common in the middle and lower dermis and are best demonstrated with colloidal iron or Alcian blue stains (Fig. 10-1E) (17). Fibrinoid deposits in the dermis are encountered only rarely in discoid lesions.

Colloid bodies, referred to in lichen planus as Civatte bodies, are apoptotic keratinocytes that present as round-to-ovoid, homogeneous, eosinophilic structures. They may be seen in lesions of DLE and also in other inflammatory processes where there is damage to basilar keratinocytes (poikiloderma, lichen planus, fixed drug eruption, and lichenoid keratoses). They measure approximately 10 μm in diameter and are present in the lower epidermis or in the papillary dermis. When located in the dermis, colloid bodies are PAS positive and diastase resistant and, on direct immunofluorescence staining, are often found to contain immunoglobulins (Igs) (IgG, IgM, IgA), complement, and fibrin. This staining does not represent an immunologic phenomenon but is the result of passive adsorption.

Pathogenesis. Refer to the end of discussion of SLE.

Differential Diagnosis. The epidermal changes seen in DLE must be differentiated from lichen planus since both diseases may show hydropic degeneration of the basal cell layer. In lichen planus, there is wedge-shaped hypergranulosis and triangular elongation of rete ridges described as “saw-toothing,” which are not observed in DLE; in DLE, the rete ridge pattern frequently appears flat. In addition, lichen planus shows a superficial infiltrate (not superficial
and deep) and lacks plasma cells and stromal mucin. (For a discussion of the overlap of lichen planus with lupus erythematosus, see Chapter 7.)

Patchy dermal lymphocytic infiltrates may be seen in five disorders that begin with the letter L (called the five Ls). They are LE, lymphocytic lymphoma, lymphotoma cutis, polymorphous light eruption of the plaque type, and lymphocytic infiltration of the skin of Jessner. Some may also add lues (syphilis) and Lyme disease.

In the absence of significant subepidermal vacuolization, LE must be differentiated from the other six diseases:

- In lymphocytic lymphoma, atypical lymphocytes are present, are tightly packed, have an interstitial distribution (“Indian filing”), and do not surround pilosebaceous units as in LE.
- In lymphotoma cutis (see Chapter 31), the infiltrate usually is heavier than in LE, may have an interstitial component, shows no tendency to arrange itself around pilosebaceous structures, and often contains an admixture of larger, paler lymphocytes arranged in lymphoid follicles, mimicking germinal center formation.
- In the plaque type of polymorphous light eruption, there is often a prominent band of papillary dermal edema. The infiltrate is more intense in the superficial dermis than in deep dermis and is occasionally admixed with neutrophils. It does not have a folliculocentric arrangement and is not usually accompanied by stromal mucin deposition (see Chapter 12).
- In Jessner lymphocytic infiltration of the skin, the dermal infiltrate may be indistinguishable from that seen in early, nonscarring, or purely dermal lesions of LE; however, plasma cells and mucin are absent. The presence of increased numbers of B lymphocytes in the infiltrate may also help distinguish this from LE (see later text) (18).
- In lues, lichenoid lymphoplasmacytic infiltrates are not associated with mucin deposits. Confirmatory antitreponemal antibody immunohistochemical stains or silver stains, such as a Steiner stain, are positive in lues and negative in lupus.
- In Lyme disease, there are lymphoplasmacytic infiltrates around dermal vessels. Silver and immunohistochemical stains should reveal spirochetal organisms, although they are sparse and difficult to detect.

As will be discussed in later sections, particular forms of LE may be associated with certain drug exposures. 5-Fluorouracil (5-FU) and capecitabine (a pro-drug of 5-FU) have been associated with the induction of DLE-like lesions. Other reported causes of drug-induced discoid lupus include uracil-tegafur (UTF) and infliximab.

**Verrucous Lupus Erythematosus**

**Clinical Summary.** An exaggerated proliferative epithelial response may occur in approximately 2% of patients with chronic cutaneous LE. These are manifest as verrucous-appearing lesions (Fig. 10-3A). Clinically, two types of lesions have been reported in this subset of LE. Lesions may simulate hypertrophic lichen planus or keratoacanthomas. They occur on the face (nose, chin, and lips), arms, dorsal aspects of the hands, and occasionally the back. The presence of typical DLE lesions elsewhere is a helpful clue to the diagnosis.

**Histopathology.** Histologically, the epidermis is papillomatous and hyperplastic, and is surmounted by hyperkeratotic scale. Large numbers of dyskeratotic keratinocytes are seen in the lower portion of the epithelium, associated with a bandlike mononuclear infiltrate (Fig. 10-3B). Older lesions show a thickened basement membrane zone. A second pattern consists of a cup-shaped, keratin-filled crater surrounded by an acanthotic epidermis with elongated rete ridges and a sparse mononuclear infiltrate. These changes, in the presence of a deep dermal perivascular, periappendageal, and interstitial infiltrate and mucin deposition, suggest a diagnosis of verrucous LE. CD123, a marker for plasmacytoid dendritic cells, typically marks large numbers of mononuclear cells in LE. The marker has been reported to be of utility in distinguishing hypertrophic LE from squamous cell carcinomas (19).

**Pathogenesis.** Refer to the end of discussion of SLE.

**Differential Diagnosis.** Histologically, lesions may simulate hypertrophic lichen planus, keratoacanthomas, and squamous cell carcinomas. Careful examination of the basement membrane zone for thickening and tortuosity, and stromal mucin deposition helps distinguish these entities.

**Principles of Management.** Refer to the end of discussion of SLE.

**Tumid Lupus Erythematosus**

**Clinical Summary.** The dermal form of LE without epithelial changes is known as tumid LE or lupus erythematosus tumidus (LET). Clinically, affected patients display indurated urticarial papules, plaques, and nodules without erythema, atrophy, or ulceration (Fig. 10-4A).

**Histopathology.** Histologically, superficial and deep dermal perivascular, interstitial, and periappendageal lymphocytic infiltrates associated with stromal mucin deposits are observed (Fig. 10-4B, C) (20). Unlike discoid lupus, in which discoid lesions may coexist with SLE, the diagnosis of LET typically excludes the presence of SLE (21). Changes at the dermal–epidermal junction, such as liquefaction degeneration or basement membrane thickening are not seen.

**Pathogenesis.** Refer to the end of discussion of SLE.
Histopathology. Subcutaneous adipose tissue may be involved with or without inflammation in the dermis or dermal–epidermal junction. Salient histologic findings include a predominantly lobular panniculitis with lymphocytic infiltrates and plasma cells, occasionally forming germinal centers. Although typically described as a lobular panniculitis, septal involvement is reported in 82% of patients in one study (23). Vascular changes include endothelial prominence, thrombosis, calcification, or perivascular fibrosis (“onion-skin” appearance). Fat necrosis occurs with fibrin deposition and lymphocytic nuclear dust which eventuates into hyalinization of adipose lobules (Fig. 10-5A, B). Stromal mucin deposition is conspicuous in well-established lesions. The intensity of the infiltrates lessens over time as the hyalinization progresses.

Pathogenesis. Refer to the end of discussion of SLE.

Differential Diagnosis. Some observers believe that LE profundus may represent a subcuticular T-cell dyscrasia related to CTD, which has an indolent biological behavior (24). Other feel that lupus panniculitis may be...
differentiated from subcutaneous panniculitis-like T-cell lymphoma (SPTCL) by histologic features: the absence of other features of LE and the presence of a monoclonal, predominantly α/β CD8 cytotoxic phenotype in atypical lymphocytes favors SPTCL (23).

**Principles of Management.** Refer to the end of discussion of SLE.

**Subacute Cutaneous Lupus Erythematosus**

Clinical Summary. Subacute cutaneous lupus erythematosus (SCLE), described in 1979, represents about 9% of all cases of lupus erythematosus. It is characterized by extensive, erythematous, symmetric nonscarring and nonatrophic lesions that arise abruptly on the upper trunk, extensor surfaces of the arms, and dorsa of the hands and fingers. This eruption has two clinical variants: (a) papulosquamous lesions and (b) annular to polycyclic lesions (Fig. 10-6A). Frequently both types of lesions are seen. In some instances, vesicular and discoid lesions with scarring may coexist.

Patients with SCLE may have mild systemic involvement, particularly arthralgias. Approximately 50% fulfill at least four of the criteria for SLE. Conversely, 10% to 15% of SLE patients exhibit cutaneous lesions of SCLE (25). Severe SLE, with renal or cerebrovascular disease, develops in only 10% of SCLE cases (26,27). Serologic studies show 70% of affected patients to have the anti-Ro (SSA)
antibody. Patients with SCLE often bear the HLA-DR2 and HLA-DR3 phenotype. SCLE may occur asynchronously with other CTDs such as Sjögren syndrome and morphea.

Histopathology. See the histopathology section of neonatal LE and Fig. 10-6B.

Pathogenesis. Refer to the end of discussion of SLE.

Differential Diagnosis. Subacute LE is a commonly reported phenotype in drug-induced lupus erythematosus (DILE). About 25 to 30% of cases of SCLE may be attributable to medications, and numerous medications have been reported to cause DILE with a subacute morphology (28). Distinguishing a medication induced reaction can be difficult, though systemic symptoms are typically absent in DILE as opposed to SCLE. The most common medications implicated include hydrochlorothiazide, ACE inhibitors, Calcium channel blockers, tumor necrosis factor (TNF) inhibitors, terbinafine, and chemotherapeutic agents (29), though the list is long and ever-expanding (28).

Principles of Management. If the onset of the eruption coincides with the administration of a new medication, particularly one on the above list, discontinuation may permit resolution of the eruption. Notably, some patients may have “drug-unmasked” lupus rather than pure “drug-induced” lupus. If the eruption persists, sunscreens and therapeutic agents as discussed at the end of the section on systemic lupus are used.

Neonatal Lupus Erythematosus

Clinical Summary. Neonatal LE has clinical and histologic skin changes and serologic findings similar to those of SCLE. Children of mothers with active SLE or Sjögren syndrome may develop LE-like symptoms in the neonatal period. Anti-Ro/SSA is the predominant autoantibody and is found in approximately 95% of cases. This may result in a transient syndrome characterized by widespread erythematous desquamate polycyclic, annular, usually non-scarring lesions. Atrophy may be present in some cases. There is typically central facial involvement. Less common cutaneous manifestations include urticarial lesions (30). There is associated photosensitivity, transient thrombocytopenia, mild hemolytic anemia, leukopenia, and congenital heart block.

Histopathology of SCLE and Neonatal LE. Histologic changes differ in degree from those in the discoid lesions and are most intense at the dermal–epidermal interface (Fig 10-6B). They consist of the following:

1. Hydropic degeneration of the basal epithelial layer, sometimes severe enough to form clefs and subepidermal vesicles
2. Colloid bodies in the lower epidermis and papillary dermis (common)
3. Edema of the dermis, which is more pronounced than in discoid lesions
4. Focal extravasation of erythrocytes and dermal fibrinoid deposits (common)
5. Less prominent hyperkeratosis and inflammatory infiltrate than in discoid lesions (31)

Pathogenesis. Neonatal LE is related to passage of maternal IgG antinuclear antibodies (particularly anti-Ro/SSA, anti-La/SSB, or anti-U1RNP autoantibodies) through the placenta. These changes have their onset at birth to 2 months and usually resolve in the first 6 to 9 months of life with decreasing levels of maternal antibodies. Heart block occurs in approximately 50% of affected infants, usually without associated skin lesions, and may be fatal. Of interest, individuals affected with transient neonatal LE may develop SLE as young adults (20). Animal model studies suggest that reactivity to the p200 region of the Ro52 protein and antibodies targeting calcium channel blockers may have a role in cardiac involvement in affected children (32). Of interest, multigenerational genetic studies suggest that mothers of neonates with lupus accumulate genetic risk preferentially from neonatal lupus children’s grandparents (32).

Differential Diagnosis. The eruption in the clinical setting of a neonate born to a mother with LE and interface changes on biopsy is characteristic.

Principles of Management. Treatment includes management of the cutaneous eruption as well as cardiomyopathy. All children with suspected neonatal lupus require immediate evaluation of the cardiac conduction system. Parents of children with neonatal lupus should be evaluated, as this may be the presenting sign of previously subclinical disease. Fluorinated steroids, intravenous immunoglobulin, and hydroxychloroquine are used in the prevention and treatment of the disease.

Systemic Lupus Erythematosus

Clinical Summary. In SLE, the cutaneous manifestations usually appear less suddenly than in SCLE and are less pronounced, such that the signs and symptoms of systemic disease usually overshadow the often subtle form of skin involvement. Usually systemic manifestations, especially arthritis, precede the cutaneous lesions. Only 20% of SLE patients demonstrate prominent cutaneous features at the onset of their disease, but approximately 80% will exhibit cutaneous lesions in the course of their disease (33,34).

The cutaneous manifestations consist of malar erythema, photosensitivity, palmar erythema, periungual telangiectases, diffuse hair loss as a result of telogen effluvium, and urticarial vasculitis or bullous lesions. The erythematous lesions of SLE consist of erythematous, slightly edematous patches without scaling or atrophy. As a rule, the patches are ill-defined. The most common site of involvement is the malar region, but any area of the skin may be involved, particularly the palms and fingers. Occasionally, lesions show a petechial, vesicular, or ulcerative component. Senescent lesions may assume the appearance of poikiloderma atrophicans vasculare.
Well-defined “discoid” lesions with atrophic scarring, as seen typically in DLE, occur in about 15% of the patients with SLE. They may precede all other clinical manifestations of SLE. A relatively benign course characterizes SLE in most patients with preceding DLE (35); however, many patients usually have had persistent multiple abnormal laboratory findings from the beginning. This is in contrast to cases of simple DLE, in which most abnormal laboratory findings are transient.

Two variants of SLE—SLE with genetic deficiency of complement components and bullous SLE—bear mention. In the former, the onset of SLE occurs in early childhood and is transmitted in an autosomal recessive fashion and often affects several siblings (36). Deficiencies of C2 and C4 result in extensive lesions similar to DLE, with scaling, atrophy, and scarring associated with sensitivity to sunlight. There can be associated central nervous system involvement and glomerulonephritis, which may be fatal (37).

In bullous SLE, subepidermal blisters may arise in previously involved or uninvolved areas. They may form large hemorrhagic bullae or herpetiform vesicles, which arise suddenly, and are clinically similar to lesions of bullous pemphigoid or dermatitis herpetiformis.

Rowell syndrome is a distinct clinical presentation of lupus with erythema multiforme–like lesions. Patients have speckled antinuclear and anti-La antibodies and test positive for rheumatoid factor (38).

The coexistence of SLE and diffuse systemic sclerosis (scleroderma) or dermatomyositis has been repeatedly described. It is known as overlap syndrome and refers to the coexistence of two related but separate diseases. Similarly, there are reports of systemic lupus and coexistent eosinophilic fascitis (39,40). Such instances of overlap are in contrast to mixed connective tissue disease (MCTD), which is recognized as a separate disease entity.

Many drugs are associated with induction of LE, the majority of which induce predominantly systemic symptoms such as arthritis, serositis, lymphadenopathy, and fever. A few are associated with specific cutaneous manifestations. They are listed in Table 10-1, and are discussed further in the section on drug-induced lupus erythematosus in Chapter 11.

Table 10-1

<table>
<thead>
<tr>
<th>Drugs Related to Induction of Lupus Erythematosus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics</td>
</tr>
<tr>
<td>Procainamide</td>
</tr>
<tr>
<td>Quinidine</td>
</tr>
<tr>
<td>Tocainide</td>
</tr>
<tr>
<td>Antihypertensive</td>
</tr>
<tr>
<td>Hydralazine</td>
</tr>
<tr>
<td>Methyldopa</td>
</tr>
<tr>
<td>β-Blockers</td>
</tr>
<tr>
<td>Hydrochlorothiazide*</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors Clonidine</td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
<tr>
<td>Isoniazid</td>
</tr>
<tr>
<td>Minocycline</td>
</tr>
<tr>
<td>Penicillin</td>
</tr>
<tr>
<td>Streptomycin</td>
</tr>
<tr>
<td>Tetracycline</td>
</tr>
<tr>
<td>Griseofulvin</td>
</tr>
<tr>
<td>Terbinafine</td>
</tr>
<tr>
<td>Ciprofloxin</td>
</tr>
<tr>
<td>Rilampicin</td>
</tr>
<tr>
<td>Antithyroid</td>
</tr>
<tr>
<td>Propylthiouracil</td>
</tr>
<tr>
<td>Methimazole</td>
</tr>
<tr>
<td>Thiamazole</td>
</tr>
<tr>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Ethosuxamide</td>
</tr>
<tr>
<td>Phenytoin*</td>
</tr>
<tr>
<td>Valproate</td>
</tr>
<tr>
<td>Anticholesterol</td>
</tr>
<tr>
<td>Statins</td>
</tr>
<tr>
<td>Gemfibrozil</td>
</tr>
<tr>
<td>Biological agents</td>
</tr>
<tr>
<td>Interleukin 2</td>
</tr>
<tr>
<td>Etanercept</td>
</tr>
<tr>
<td>Infliximab†</td>
</tr>
<tr>
<td>Interferon α</td>
</tr>
<tr>
<td>Efalizumab*</td>
</tr>
<tr>
<td>Hormones</td>
</tr>
<tr>
<td>Estrogen</td>
</tr>
<tr>
<td>Leflunomide*</td>
</tr>
<tr>
<td>Sulfasalazine</td>
</tr>
<tr>
<td>Penicillamine</td>
</tr>
<tr>
<td>Fluorouracil agents*</td>
</tr>
<tr>
<td>Gold salts</td>
</tr>
<tr>
<td>Sertraline†</td>
</tr>
<tr>
<td>Ticlopidine*</td>
</tr>
<tr>
<td>Bupropion*</td>
</tr>
<tr>
<td>Lansoprazole*</td>
</tr>
<tr>
<td>Reserpine</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Hydroxyurea</td>
</tr>
<tr>
<td>Clozapine</td>
</tr>
<tr>
<td>Zafirlukast</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

*Associated with subacute cutaneous lupus–like syndrome.
†Associated with chronic cutaneous lupus–like syndrome.
Histopathology. Early lesions of SLE of the erythematous, edematous type may show only mild, nonspecific changes. In well-developed lesions, the histologic changes correspond to those described for SCLE (Fig. 10-6B): Hydropic degeneration of the basal cell layer occurs in association with edema of the upper dermis and extravasation of erythrocytes. Fibrin deposits in the connective tissue of the skin are often seen in erythematous lesions. They appear as granular, strongly eosinophilic, PAS-positive, diastase-resistant deposits between collagen bundles, in the walls of dermal vessels, in the papillary dermis, or beneath the epidermis in the basement membrane zone. Fibrinoid deposits are not specific for LE. They are seen in association with vascular injury, particularly in leukocytoclastic vasculitis.

Subcutaneous fat is often involved in SLE. Changes similar to those in lupus profundus may be seen but are usually milder: There may be focal mucin deposition associated with a predominantly lymphocytic infiltrate. Adipocytes may be separated by edema and fibrinoid deposits. These histologic changes in subcutaneous fat produce no clinically apparent lesions.

 Occasionally, palpable purpuric lesions in SLE patients show a leukocytoclastic vasculitis histologically indistinguishable from leukocytoclastic vasculitis of other causes. There is endothelial cell swelling, a neutrophilic inflammatory infiltrate, nuclear dust, perivenular fibrin deposition, and stromal hemorrhage. Urticaria-like lesions may occur and show either a leukocytoclastic vasculitis or a perivascular mononuclear infiltrate not diagnostic of LE (41). In addition, white atrophic lesions may occur in SLE that both clinically and histologically resemble those of malignant atrophic papulosis of Degos (42).

Bullous SLE shows two histologic inflammatory patterns: one neutrophilic and one mononuclear. The neutrophilic type simulates dermatitis herpetiformis or linear IgA disease with the formation of papillary microabscesses (Fig. 10-7A, B) (43). Nuclear dust is seen in the papillary microabscesses and in the upper dermis around and within the walls of blood vessels. Direct immunoelectron studies have localized immunoreactant deposits to beneath the lamina densa; and consist of IgG with or without IgM, and often IgA in a linear or granular pattern. Some patients may also have circulating anti–basement zone antibodies and antibodies directed against type VII collagen. The latter antibodies are similar but not identical to those in epidermolysis bullosa acquisita (44).

The subepidermal blister associated with a mononuclear inflammatory infiltrate arises in longstanding lesions of cutaneous LE (Fig. 10-8A, B). It likely corresponds to an altered dermal–epidermal interface resulting from inflammation and immune complex deposition. This type of change is a part of the spectrum of LE rather than a distinct entity.

Systemic Lesions. Much of the tissue damage in SLE results from deposition of antibody–antigen complexes in affected organ systems.

A detailed presentation of the arthritic, serosal and cardiac manifestations and classifications of glomerulonephritides is beyond the scope of this section but can be found in the review by Dooley et al. (45).

Antiphospholipid syndrome occurs in patients with SLE and other autoimmune diseases who develop immunoglobulins that can prolong phospholipid-dependent coagulation tests. These immunoglobulins occur in association with SLE and other autoimmune diseases but are found unassociated with them as well. One of these, lupus anticoagulant, occurs in about 10% of SLE patients.

**Figure 10-7** Bullous lupus erythematous, neutrophilic. 
A: There are broad-based subepidermal blisters associated with marked papillary dermal edema and large numbers of neutrophils. Neutrophils are also present around vessels and among collagen bundles throughout the dermis. Faint interstitial mucin deposits and nuclear dust are present. B: The papillary dermal abscesses simulate findings of dermatitis herpetiformis. The dermal changes as noted in A, however, would not be seen in dermatitis herpetiformis.
Affected patients are at greater risk for thromboembolic disease, including deep venous thrombosis, pulmonary emboli, and other large-vessel thrombosis. Other findings include recurrent fetal wastage, renal vascular thrombosis, thrombosis of dermal vessels (Fig. 10-9A, B), and thrombocytopenia. Anticardiolipin antibody, a second type of antiphospholipid antibody, occurs five times more often than lupus anticoagulant antibody. It is associated with recurrent arterial and venous thrombosis, valvular abnormalities, cerebrovascular thromboses, and essential hypertension (Sneddon syndrome) (46). Other cutaneous findings include livedo reticularis, necrotizing purpura, disseminated intravascular coagulation, and stasis ulcers of the ankles (47).

Pathogenesis. The etiology of LE is considered to be multifactorial (Table 10-2). Studies have demonstrated numerous defects in the innate and adaptive immune system resulting in a widespread loss of self-tolerance. These abnormalities include but are not limited to abnormal responses to ultraviolet radiation, abnormal antigen-presenting-cell function, plasmacytoid dendritic cell function, numerous HLA associations, polymorphisms in TNF-α promoters, abnormal keratinocyte apoptosis, and polymorphisms in the genes coding for interleukin 1 (IL-1) receptor antagonist and IL-10 promoter sequence (48). Aberrant stimulation of intracellular Toll-like receptors (TLRs), specifically TLR7 and TLR9, by endogenous antigens may play a crucial role in the autoimmune

**Figure 10-8** Bullous lupus erythematosus, mononuclear. A: A broad subepidermal cleft is present beneath an epidermis that has lost its rete ridge pattern and is surmounted by hyperkeratotic scale. The stroma contains perivascular and periappendageal inflammatory infiltrates. B: Adjacent to the zone of dermal–epidermal separation is a thickened eosinophilic basement membrane zone. Melanophages are scattered in the superficial dermis.

**Figure 10-9** Lupus anticoagulant syndrome. A: A superficial dermal vessel is surrounded by lymphocytes. B: High magnification of pale eosinophilic intravascular thrombus.
Other markers that have been examined include antinucleosome antibodies, which may be more prevalent in SLE patients and may develop earlier than anti-dsDNA antibodies. This assay, however, is not widely available and has not been rigorously evaluated (51). At a titer of 1:20, about 20% of patients with DLE, most patients with systemic scleroderma, and as many as 5% of normal persons may have a positive reaction. The presence of anti-Sm is indicative of associated lupus nephritis. Anti-nRNP antibodies are of diagnostic significance only at high titers where they indicate MCTD. ANA-negative sera should be examined for the presence of anti-Ro/SSA and La/SSB antibodies, characteristic of subacute and neonatal LE and SLE with genetic deficiency of complement components.

Direct immunofluorescence studies detect immunoreactant deposits in affected tissues, particularly the skin and kidneys. A skin biopsy (3- to 4-mm punch) is submitted

### Table 10-2

<table>
<thead>
<tr>
<th>Genetic</th>
<th>Environmental precipitants</th>
<th>Hormonal influences</th>
<th>Autoimmunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-DR2</td>
<td>Drugs</td>
<td>Predisposition of women in childbearing years</td>
<td>Every aspect of immune system affected:</td>
</tr>
<tr>
<td>HLA-DR3</td>
<td>Ultraviolet light</td>
<td></td>
<td>B cells</td>
</tr>
<tr>
<td>HLA-B8</td>
<td>Possibly diet</td>
<td></td>
<td>Abnormal B-lymphocyte maturation and activation</td>
</tr>
<tr>
<td>HLA-DR3</td>
<td></td>
<td></td>
<td>Hypergammaglobulinemia</td>
</tr>
<tr>
<td>HLA-DQ23</td>
<td></td>
<td></td>
<td>Decreased peripheral T lymphocytes</td>
</tr>
<tr>
<td>HLA-DRw52</td>
<td></td>
<td></td>
<td>T-cell hyperactivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increased percentage of CD29⁺ (memory helper) T cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Preferential loss of CD4, CD45R⁺ (suppressor inducer) cells in active LE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Defective T-suppressor function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CD123⁺ plasmacytoid dendritic cells</td>
</tr>
<tr>
<td></td>
<td>Environmental precipitants</td>
<td></td>
<td>Normal number of NK cells but decreased NK-cell activity (deficient in active cytotoxicity)</td>
</tr>
<tr>
<td></td>
<td>Hormonal influences</td>
<td></td>
<td>Lymphocytotoxic antibodies in sera of 80% of SLE patients</td>
</tr>
<tr>
<td></td>
<td>Autoimmunity</td>
<td></td>
<td>Nuclear membrane targets</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chromatin targets</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ribonucleoprotein targets</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abnormal stimulation of TLR7 and TLR9 by endogenous antigens</td>
</tr>
</tbody>
</table>

feedback loop between T cells and B cells (49). The common final pathway involves the production of autoantibodies that mediate tissue damage (50).

The initial screening test for antinuclear antibodies (ANAs) is indirect immunofluorescence, which provides limited but clinically useful information. Many other assays are available for more specific characterization of ANAs and include immunodiffusion, enzyme-linked immunosorbent assays, immunoprecipitation, and immunoblots. Indirect immunofluorescence detects nuclear, homogeneous, rim, speckled, and nucleolar patterns. The fluorescence ANA test can be regarded as a specific marker for SLE in a rim pattern with a titer of 1:160 or higher and is indicative of the presence of anti–native or double-stranded (ds) DNA antibodies. Although anti-dsDNA has generally been regarded as the most specific marker of SLE, the lack of sensitivity makes a negative test unhelpful.
in saline-impregnated gauze or phosphate-buffered saline, snap frozen, sectioned, and incubated with fluorescein-conjugated antisera to IgA, IgM, IgG, and the third component of complement (C3). In a positive test, there is continuous granular deposition of usually two or more immunoreactants in a band along the dermal–epidermal junction (Fig. 10-2). Variables that affect test results are the site of the biopsy (sun exposed vs. sun protected), duration of the lesion (acute, subacute, chronic), and preceding therapy. The frequency and implications of positive results in DLE and SLE are summarized in Table 10-3 (52–54).

Cautious sampling and interpretation of findings are necessary to avoid false-positive and false-negative results. The presence of only one type of immunoreactant, particularly in an intermittent distribution, may be seen in chronically sun-exposed skin or with underlying disorders such as rosacea. False-negative results are often found in acute or subacute lesions and treated lesions. Optimally, an established lesion, present for 3 months or longer, that has not been treated is submitted for study (55).

Differential Diagnosis. Lichenoid eruptions, including lichenoid eruptions related to medications, dermatomyositis and overlap syndromes may show similar histologic features. Correlation with clinical presentation and serologic studies is necessary.

Principles of Management. The treatment modalities for LE cover a wide range of immunosuppressant topical and systemic agents. Typically, the extent of disease dictates the course of therapy. All patients benefit from sun protection with broad spectrum UV blocking chemical and physical agents. Limited cutaneous disease of discoid lupus can be treated with topical mid to high potency steroids. This is often insufficient, however, and systemic therapy with hydroxychloroquine or other antimalarials is necessary; some feel administration of hydroxychloroquine may decrease progression to overt SLE. Patients who fail to respond or with extensive, disfiguring, or symptomatic disease may require more aggressive therapy. These may include methotrexate, thalidomide, prednisone, azathioprine, or mycophenolate mofetil. Of particular importance in discoid lupus is meticulous sun avoidance, which is responsible for many flares in the disease. Subacute cutaneous lupus is similarly treated, though in this instance the strong association with medication-induced disease warrants a thorough review of the patients’ medication list to identify potential triggers. Lupus profundus, due to the subcuticular location of the disease process is not amenable to topical steroids, and patients typically are treated with antimalarials. Systemic lupus is typically treated with systemic immunosuppressants including prednisone, cyclophosphamide, mycophenolate mofetil, methotrexate, and azathioprine. Case reports and small studies have examined the efficacy of thalidomide, high-dose intravenous immunoglobulins, and rituximab or TNF inhibitors, with varying response rates (56). Bullous lupus is often particularly responsive to dapsone and other anti-neutrophilic agents.

### Jessner Lymphocytic Infiltration of the Skin

#### Clinical Summary

Jessner lymphocytic infiltration of the skin, first described in 1953 (57), is not a well-understood entity. It is characterized by asymptomatic papules or well-demarcated, slightly infiltrated red plaques, which may develop central clearing. In contrast to lesions of chronic LE, the surface shows no follicular plugging or atrophy. Lesions arise most often on the face but may also involve the neck and upper trunk (58). Although this disorder has been reported to occur in childhood (59), affected patients are usually middle-aged men and women. Some authors consider this entity to exist on the spectrum of LE and some consider it to be identical to tumid lupus (60,61).

Variable numbers of lesions persist for several months or several years. They may disappear without sequela or recur at previously involved sites. The eruption may be precipitated or aggravated by sunlight.

#### Histopathology

The epidermis may be normal or slightly flattened. In the dermis, there are dense perivascular and interstitial infiltrates composed of small, mature lymphocytes admixed with occasional histiocytes and plasma cells (Fig. 10-10A, B). The infiltrate may extend around follicular structures and into subcutaneous adipose tissue.

<table>
<thead>
<tr>
<th>Site</th>
<th>Involved</th>
<th>Uninvolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun exposed (e.g., dorsal forearm)</td>
<td>Positive in &gt;90% of untreated lesions</td>
<td>Almost always negative for inactive LE</td>
</tr>
<tr>
<td>Sun exposed (e.g., volar forearm)</td>
<td>Positive in &gt;80% of untreated SLE</td>
<td>With active LE: positive in &gt;91%</td>
</tr>
<tr>
<td>Non–sun exposed (e.g., buttock)</td>
<td>Positive result may indicate renal involvement</td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 10-3**

**Direct Immunofluorescence in Lupus Erythematosus**

<table>
<thead>
<tr>
<th>Site</th>
<th>Discoid LE</th>
<th>Systemic LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun exposed (e.g., dorsal forearm)</td>
<td>Positive in &gt;90% of untreated lesions</td>
<td>Positive in 80%–90% of untreated lesions</td>
</tr>
<tr>
<td>Sun exposed (e.g., volar forearm)</td>
<td>Almost always negative</td>
<td>Positive in &gt;80% of untreated SLE</td>
</tr>
<tr>
<td>Non–sun exposed (e.g., buttock)</td>
<td>Negative</td>
<td>With active LE: positive in &gt;91%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With inactive SLE: positive in 33%</td>
</tr>
</tbody>
</table>

---

**Connective Tissue Diseases**
Pathogenesis. Opinion varies as to whether Jessner lymphocytic infiltrate of the skin is a distinct entity. The following four views have been expressed: (a) clinical, histologic, and immunohistochemical findings warrant its distinction as a separate entity (62); (b) although some cases represent a distinct entity, others are LE; (c) all cases are LE; or (d) it represents an abortive or initial phase of either LE, plaque type of polymorphous light eruption, lymphocytoma cutis, or lymphocytic lymphoma. In support of the notion that Jessner lymphocytic infiltrate is a form of LE, studies of CD123, a plasmacytoid dendritic cell marker, known to have an effector role in lupus, have shown similar patterns of staining in the inflammatory cells (60). Isolated reports of Jessner lymphocytic infiltrate have been reported in association with angiotensin-converting enzyme inhibitor, enalapril, and a synthetic polypeptide, glatiramer acetate, used to treat multiple sclerosis (63,64). Isolated familial cases have also been reported (65).

Immunohistochemical studies indicate that the predominant cells of lymphocytic infiltrate of the skin are mature T lymphocytes. Phenotyping studies show predominantly CD4+ T helper cells (66). Other studies have suggested a CD8+ cytotoxic phenotype (65). Rearrangement of the T-cell receptor gene has not been detected in the limited number of cases studied. The relative paucity of B lymphocytes may assist in separation of this entity from lymphocytoma cutis, which usually displays larger B-cell components, with or without associated germinal center formation. Lymphoma cutis may be distinguished with cell-marker analysis, which will show a high proportion of B lymphocytes with a less mature phenotype than expected in skin, or cells with aberrant expression of surface antigens.

Differential Diagnosis. The histologic differential diagnosis of lymphocytic infiltration of the skin includes the other six of the seven Ls: LE, polymorphous light eruption, lymphocytoma cutis, lues, Lyme disease, and lymphoma. Jessner lymphocytic infiltrate is limited to sun-exposed skin and lacks the hyperkeratosis, atrophy, interface changes, mucin, and direct immunofluorescence findings noted in lupus. Therefore, lupus should be excluded with serologic and direct immunofluorescence studies. Serologic studies and the clinical distribution of lesions allow separation of lues and Lyme disease from Jessner lymphocytic infiltrates. Approximately 10% of cases of lupus lack interface alterations and that show negative direct immunofluorescence studies. These cases may initially be placed into the holding category of “lymphocytic infiltrates of the skin.” Polymorphous light eruptions usually show prominent papillary dermal edema; however, plaque-type polymorphous light eruption may histologically overlap with lymphocytic infiltration of the skin. Clinical features may sometimes separate these two entities.

A poorly understood entity histologically similar to Jessner lymphocytic infiltrate is palpable migratory arcosiform erythema. This entity differs clinically in that it is slightly pruritic and tends to involve the trunk and
proximal extremities. It waxes and wanes over days to weeks rather than months. Differences in histology have been reported but have not been validated by multiple studies (67).

**Principles of Management.** Mid-potency topical steroids are typically utilized for symptomatic management. Sun avoidance is encouraged. In recalcitrant cases, antimalarial drugs and/or corticosteroids are useful in controlling this disorder. Other therapies have included methotrexate, gold, thalidomide, and photodynamic therapy.

**MIXED CONNECTIVE TISSUE DISEASE**

**Clinical Summary.** Overlapping findings of SLE, scleroderma (systemic sclerosis), and polymyositis associated with the presence of high titers of anti-U1 ribonucleoprotein (RNP) antibodies have been recognized since 1972 as MCTD (68). The first clue to the diagnosis is usually a positive, high-titer speckled ANA. The clinical presentation includes, but is not limited to, edema of the hands, acrosclerosis, Raynaud phenomenon, synovitis of one or more joints, and myositis that is documented with biopsy or serum elevations of muscle enzymes. Esophageal hypomotility and pulmonary disease may be seen as well. The diagnosis of MCTD may not be made at the outset because symptoms may present in an asynchronous fashion. Cutaneous LE lesions are found in approximately half of the patients. They cover the entire spectrum of cutaneous LE. Most commonly there are diffuse, nonscarring, poorly demarcated subacute lesions, but some patients show malar eruptions as seen in SLE or persistent scarring lesions of DLE.

Patients with high-titer anti-U1 RNP antibodies have a low prevalence of renal disease and life-threatening neurologic complications. Although the prognosis of MCTD is comparable to that of SLE, death may occur from progressive pulmonary hypertension and cardiac complications (69).

**Histopathology.** If cutaneous lesions of LE are present, the histologic findings correspond to the type of lesion described in the section on DLE and SLE. MCTD, in contrast with most cases of SLE, has no antibodies to DNA. The absence of such antibodies accounts for the rarity of renal disease.

Indirect immunofluorescence studies show the presence of very high titers of serum antibodies directed against extractable ribonucleasesensitive antigens known as small nuclear ribonucleoproteins (snRNPs). They characterize MCTD but are not specific for it, and produce a fine speckled ANA pattern at high dilutions. This speckled pattern corresponds to the widespread distribution of snRNPs in the nucleus at sites of active gene transcription, where messenger RNA is being processed.

Direct immunofluorescence staining of normal skin shows deposition of IgG in a speckled pattern in epidermal nuclei. Although this finding is typical of MCTD, it is found occasionally also in patients with SLE and other CTDs (70). In addition, patients with MCTD may show a subepidermal lupus band in normal skin. Such a band has been observed in normal sun-exposed skin in about 20% of the cases.

**Pathogenesis.** The pathogenesis of MCTD is not fully understood, but shows some similarities to LE. Like LE, MCTD is a manifestation of autoimmunity and loss of self-tolerance, driven by aberrations in both innate and adaptive arms of the immune system. Triggering of this process, similar to LE, occurs through interactions of the innate immune system, through TLR with apoptotic cells that have undergone antigen structural modification.

**Differential Diagnosis.** The differential diagnosis includes many stand-alone diseases that make up the constellation of MCTD. These include polymyositis, SLE, and systemic sclerosis. Although there are distinct serologic patterns that distinguish SLE from MCTD, the underlying immunologic aberration is believed to be similar.

**Principles of Management.** Similar to other CTDs, the extent of disease dictates the treatment course, and sun protection is essential. For mild disease with arthritic symptoms and cutaneous lesions, nonsteroidal anti-inflammatory agents and topical steroids may be all that is required. Hydroxychloroquine may be used as an adjuvant. For more aggressive disease, systemic steroids and alternate immunosuppressive agents may be required. Pulmonary involvement, in the form of pulmonary hypertension is treated with phosphodiesterase inhibitors and the endothelin receptor antagonist ambrisentan and the synthetic prostaglandin epoprostenol. Phosphodiesterase inhibitors and calcium channel blockers may be used for treatment of Raynaud phenomenon. Intravenous immunoglobulin has been used in recalcitrant cases with success (71).

**DERMATOMYOSITIS**

**Clinical Summary.** Dermatomyositis manifests as an inflammatory myopathy with characteristic cutaneous findings. In the absence of cutaneous findings, the diagnosis of polymyositis is applied. Cutaneous findings alone, without muscular involvement, have been termed **amyopathic dermatomyositis** or **dermatomyositis sine myositis** (72).

Both dermatomyositis and polymyositis are uncommon diseases that have a similar incidence. Both have two peaks of occurrence: one in childhood and one between the ages of 45 and 65 years (73). The cutaneous eruption and inflammatory myositis may occur asynchronously. Their appearance may be separated by months to years.

The four systemic and single cutaneous diagnostic criteria for dermatomyositis are symmetric proximal muscle
weakness, elevated muscle enzymes, an abnormal electromyogram in the absence of neuropathy, consistent muscle biopsy changes, and cutaneous findings (73). Involvement of the skeletal muscles causes progressive weakness, pain, and eventual muscle atrophy. The proximal muscles of the extremities and the anterior neck muscles are among the first to be involved. Involvement of the pharynx may result in dysphagia and aspiration. Involvement of the diaphragm and the intercostal muscles may lead to respiratory failure. Arthritis and arthralgias occur in up to 25% of cases. Interstitial lung disease is becoming increasingly recognized as a frequent occurrence in patients with dermatomyositis (74). Less common systemic manifestations include dysphagia, dysphonia, and cardiac conduction abnormalities, which portend a worse prognosis. Both traditional dermatomyositis and amyopathic dermatomyositis are strongly associated with internal malignancies, as discussed below.

Two distinctive cutaneous lesions are found in dermatomyositis. One is violaceous, slightly edematous peri-orbital patches involving the eyelids, known as the heliotrope rash. The other is discrete red-purple papules over the knuckles, knees, and elbows, known as Gottron papules. These may evolve into atrophic plaques with pigmentary alterations and telangiectasia and are then known as Gottron sign. Patients also frequently display a diffuse, purple-tinted violaceous erythema over their scalp, face, V-neck of the chest, upper back, deltoids (“shawl sign”), or lateral hips (“holster sign”).

Other cutaneous findings include periungual telangiectasia, hypertrophy of cuticular tissues associated with splinter hemorrhages, photosensitivity, and poikiloderma. Often, lesions resembling the erythematous–edematous lesions seen in SCLE or SLE may be found. Subcutaneous and periarticular calcification may occur, particularly in children. Calcinosis is usually seen in the proximal muscles of the shoulders and pelvic girdle. Childhood onset may also be associated with lipodystrophy and insulin resistance (75). Uncommon cutaneous findings include gingival telangiectasia, angiokeratomas, panniculitis, flagellate erythema, scleromyxedematous lesions, and pityriasis rubra pilaris–like lesions (76–79).

Retrospective analyses indicate an increased risk of development of neoplasms during the first, and to a lesser degree, in the second year after a diagnosis of dermatomyositis is rendered (80). Incidences range from 6% to 50% in various reports, likely due to the asynchronous development of malignancy in relation to the dermatomyositis. Some series fail to show a significant difference between affected patients and the control population. If malignancy arises with dermatomyositis, it usually occurs in adults. Various tumors have been reported. Cancers of the lung, ovary, and lymphatic and hematopoietic systems are most frequently reported (81). Larger population-based studies have suggested an incidence of carcinoma at between 20% and 25% (82). The association with ovarian malignancy may be particularly strong and should not be overlooked, as screening for ovarian neoplasms is not often included in standard age-appropriate malignancy screening. Other tumors reported include lung, prostatic, pancreatic, and gastrointestinal carcinomas. In younger males, testicular carcinoma is more prevalent. In Asians, there is an increased association with nasopharyngeal carcinoma (83).

**Histopathology.** Dermatomyositis may show only nonspecific inflammation, but frequently the histologic changes are indistinguishable from those seen in SLE. There is epidermal atrophy, basement membrane degeneration, vacuolar alteration of basilar keratinocytes, a sparse lymphocytic inflammatory infiltrate around blood vessels, and interstitial mucin deposition (Fig. 10-11A, B) (84). With severe inflammatory changes, there may be an associated subepidermal fibrin deposition. Although immune complexes are not detected at the dermal–epidermal junction as in LE, it should be remembered that up to 50% of subacute cutaneous lupus biopsies can also have a negative direct immunofluorescence.

**Figure 10-11 Dermatomyositis.** A: An atrophic epidermis shows marked vacuolar alteration of basilar keratinocytes associated with a sparse lymphocytic inflammatory infiltrate around superficial dermal vessels. B: Marked vacuolar alteration of basilar keratinocytes associated with sparse lymphocytic infiltrates and papillary dermal melanophages.
Old cutaneous lesions with the clinical appearance of poikiloderma atrophicans vasculare usually show a band-like infiltrate under an atrophic epidermis with hydropic degeneration of the basal cell layer (see also the section on poikiloderma atrophicans vasculare). Gottron papules overlying the knuckles also show vacuolization of the basal cell layer with acanthosis rather than epidermal atrophy (85). Subcutaneous tissue may show focal areas of panniculitis associated with degeneration of adipocytes in early lesions. Extensive areas of calcification may be present in the subcutis at a later stage (see calcinosis cutis, Chapter 17).

Magnetic resonance imaging permits noninvasive assessment of muscle inflammation and may serve as a guide in locating a site for muscle biopsy. Tender proximal muscles of an extremity yield more useful information than atrophic, weak muscles, which show end-stage changes. Three types of changes may be observed in active disease: (a) interstitial inflammatory infiltrates composed of lymphocytes and macrophages, (b) segmental muscle fiber necrosis (loss of skeletal muscle transverse striation, hyalinization of the sarcoplasm, fragmentation and/or phagocytosis of degenerated muscle fragments), or (c) vasculopathy (86). The latter entity may be seen in the childhood form and shows immune complex deposition in vessel walls (87). Old lesions usually show a rather nonspecific picture of atrophy of the muscle fibers and diffuse interstitial fibrosis with relatively little inflammation.

**Systemic Lesions.** Changes in organs other than the skin and the striated muscles occur only rarely in dermatomyositis, in contrast to SLE and systemic scleroderma. The myocardium may show changes identical to those in the skeletal muscle but less severe. Ulcerative lesions in the gastrointestinal tract, caused by vascular occlusions, have also been described (88).

**Pathogenesis.** As with LE, the pathogenesis of the disease is uncertain. Associated antibodies include PM1, Jo1 (may correlate with pulmonary fibrosis), Ku (associated with sclerodermatomyositis), and Mi2. Recently reported markers include autoantibodies to 155kd, and 5e antigens, and have been reported to be associated with amyopathic dermatomyositis (89). Recent studies have suggested that titers of anti-CADM140/MDA5 autoantibodies may predict outcomes in patients with dermatomyositis and interstitial lung disease (90).

The landscape of antibody-specific associations is rapidly changing and readers are encouraged to consult the primary literature. A single case of a cutaneous eruption mimicking dermatomyositis after treatment with imatinib mesylate has been reported (91). Medications, including hydroxyurea, quinidine, nonsteroidal anti-inflammatory agents, d-penicillamine, isoniazid, TNF-α inhibitors, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, have been reported to induce or exacerbate dermatomyositis.

**Differential Diagnosis.** Differentiation of the cutaneous lesions of dermatomyositis from those of SCLE or SLE may be impossible on a histologic basis. One study indicates possible differences in lymphocyte populations present in skin biopsies. CD4/CXCR-3+ lymphocytes predominate, as compared with lupus, where CD8 and CD20 lymphocytes predominate (92). It may also be impossible to distinguish between dermatomyositis and lupus on clinical grounds in cases in which muscular weakness is mild or absent, as may be seen in the early stage of dermatomyositis. The most important laboratory test in such cases is the lupus band test, which is always negative in lesions of dermatomyositis (93), whereas in lesions of LE it is positive in 90% of the cases. Other tests that are usually negative in dermatomyositis and often positive in LE include urinalysis and renal function tests, as well as tests for ANA, anti–native DNA antibodies, and antibodies to ribonucleoprotein. Rarely, patients with dermatomyositis demonstrate a positive Ro antibody titer. Patients with active myositis show an elevation of serum creatine kinase and aldolase.

**Principles of Management.** On the whole, the prognosis of dermatomyositis is favorable, especially when treatment with corticosteroids is used. Sun protection is essential. Other therapeutic agents include methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, intravenous immunoglobulins and cyclosporine. The mortality has been reported to be approximately 14% in some series, with metastatic malignancy a frequent cause of death (94). Different manifestations of dermatomyositis may require different treatments, and it is essential to evaluate patients thoroughly for internal disease and direct treatment accordingly.

**POIKILODERMA ATROPHICANS VASCULARE**

**Clinical Summary.** Clinically, the term poikiloderma atrophicans vasculare is applied to lesions that, in the early stage, show erythema with slight, superficial scaling, a mottled pigmentation, and telangiectases. In the late stage, the skin appears atrophic and the erythema is less pronounced than in the early stage, but the mottled pigmentation and the telangiectases are more pronounced. The clinical picture then resembles that of chronic radiation dermatitis. Poikiloderma atrophicans vasculare may be seen in three different settings: (a) in association with genodermatoses, (b) as an early stage of mycosis fungoides, and (c) in association with dermatomyositis and, less commonly, LE.

**Histopathology.** In early-stage poikiloderma atrophicans vasculare, there is moderate thinning of the stratum malpighii, effacement of the rete ridges, and hydropic degeneration of the basal cells. In the upper dermis there is a
Poikiloderma-like lesions as features of early mycosis fungoides may be seen in one of two clinical forms: either as the large plaque type of parapsoriasis en plaques, also known as poikilodermatous parapsoriasis (see Chapter 7), or as parapsoriasis variegata, which, shows papules arranged in a netlike pattern (see Chapter 7). Although these two types of parapsoriasis represent an early stage of mycosis fungoides, not all cases progress clinically into fully developed mycosis fungoides (97). Cases in which no progression toward mycosis fungoides is observed have been described also as idiopathic poikiloderma atrophicans vasculare (98).

The third group of diseases in which poikiloderma atrophicans vasculare occurs is dermatomyositis and SLE. Dermatomyositis is much more commonly seen as the primary disease than LE, and the association with dermatomyositis often is referred to as poikilodermatomyositis. In contrast to mycosis fungoides, in which poikilodermatous lesions are seen in the early stage, the lesions found in dermatomyositis and SLE generally represent a late stage.

**Differential Diagnosis.** As discussed above, changes of poikiloderma atrophicans vasculare may be seen in genodermatoses, parapsoriasis, early stages of cutaneous T-cell lymphoma, in association with dermatomyositis and, less commonly, LE.

**Principles of Management.** Underlying cause and disease extent determines therapy. With predominantly cutaneous disease, sun avoidance, topical steroids, and disease-modifying agents such as methotrexate, mycophenolate mofetil, or antimalarials are commonly employed. For significant muscle involvement, systemic steroids are the
treatment of choice. Other agents used to treat myositis include intravenous immunoglobulin or biologics, including rituximab and TNF antagonists.

**SYSTEMIC AND LOCALIZED SCLEROSIS (SCLERODERMA/MORPHEA)**

**Clinical Summary.** Scleroderma (from the Greek skleros, hard, and derma, skin) is the principle clinical finding in a group of disorders characterized by thickening and fibrosis of the skin. This group of disorders is divided into the systemic form (systemic sclerosis, emphasizing coexistent visceral involvement), and the localized forms (linear including en coup de sabre, and localized/generalized morphea). As there is significant histologic overlap between systemic sclerosis (scleroderma) and morphea (localized scleroderma), they will be discussed together in this section. They are somewhat analogous to the purely cutaneous form of LE (DLE) and the cutaneous plus visceral involvement in SLE. Localized and systemic scleroderma may coexist. In such instances, the manifestations of morphea/localized scleroderma arise first and are extensive, whereas those of systemic scleroderma are mild and nonprogressive (99). Rarely, the manifestations of systemic scleroderma precede those of morphea (100).

Variants of morphea include circumscribed morphea, linear morphea (includes coup de sabre), pansclerotic morphea, atrophoderma of Pasini and Pierini, and eosinophilic fasciitis of Shulman. The latter disease differs sufficiently from morphea, and will be discussed separately.

**Morphealocalized Scleroderma**

**Clinical Summary.** In morphea, or localized scleroderma, the lesions usually are limited to the skin and to the subcutaneous tissue beneath the cutaneous lesions. Occasionally the underlying muscles and rarely the underlying bones are also affected.

Morphea may be clinically divided according to morphology and number, or extent, of lesions. Variable classifications exist. According to morphology, lesions have been described as guttate, plaque, linear, segmental, and subcutaneous, and generalized. More recently, lesions have been categorized as circumscribed, generalized, linear, mixed, and pansclerotic. Eosinophilic fasciitis, even though it is the fascial component of subcutaneous morphea, is discussed separately because of its different clinical and histologic appearance.

Guttate, or drop-like, lesions typically occur in association with lesions of the plaque type. Guttate lesions are small and superficial; they resemble the lesions of lichen sclerosus et atrophicus but do not show hyperkeratosis or follicular plugging. Lesions of the plaque type, the most common manifestation of morphea, are round or oval but through coalescence may assume an irregular configuration. They are indurated, have a smooth surface, and are ivory colored. As long as they are enlarging, they may show a violaceous border, the so-called lilac ring. Both types of lesions may be seen in circumscribed and generalized morphea (101).

Lesions of the linear type occur predominantly on the extremities and on the anterior scalp. When one or several extremities are involved, there is often, in addition to induration of the skin, marked atrophy of the subcutaneous fat and of the muscles, resulting in contractures of muscles and tendons and ankyloses of joints. In children it may result in impaired growth of the affected limb (102). On the anterior portion of the scalp and on the forehead, linear morphea often has the configuration of the stroke of a saber (coup de sabre).

Segmental morphea occurs on one side of the face, resulting in hemiatrophy. Occasionally, morphea en coup de sabre and facial hemiatrophy occur together (103). This manifestation of morphea typically occurs in children and can be associated with neurologic deficits (104). Due to a high incidence of overlap between the two conditions and the similar histopathology, some authors feel that they represent slightly different manifestations of the same process. Retrospective studies have estimated the coincidence of the conditions at between 36% and 42% (103,106).

In subcutaneous morphea (morphea profunda), the involved skin feels thickened and bound to the underlying fascia and muscle. The involved plaques are ill defined, and the skin of these plaques is smooth and shiny. Occasionally, the lesions may become bullous (107).

Generalized morphea comprises very extensive cases showing a combination of several types described above. It is seen mainly in children, in whom it has been described as disabling pansclerotic morphea, but may also occur in adults. Rarely, bullous lesions are seen in patients with generalized morphea (108).

There are several reported cases of morphea that involve the superficial reticular dermis (superficial morphea) as contrasted with its usual involvement of the deep reticular dermis (109). The clinical impact of the depth of involvement is unclear. The coexistence of lesions of morphea and lichen sclerosus et atrophicus is worthy of note.

**Histopathology.** The different types of morphea/localized scleroderma cannot be differentiated histologically. Rather, they differ in regard to severity and depth of involvement of the skin. Therefore, it is of great importance that the biopsy specimen includes adequate subcutaneous tissue because most of the diagnostic alterations are seen in the lower dermis and in the subcutis.

Early inflammatory, intermediate, and late sclerotic stages exist. In the early inflammatory stage, found particularly at the violaceous border of enlarging lesions, the reticular dermis shows interstitial lymphoplasmacytic infiltrates with or without eosinophils among slightly thickened collagen bundles (Fig. 10-13A). As lesions become
established, the inflammatory infiltrates surround eccrine coils and are associated with hypocellular collagen bundles and reduced numbers of surrounding adipocytes (Fig. 10-13B). A much more pronounced inflammatory infiltrate than that seen in the dermis often involves the subcutaneous fat and extends upward toward the eccrine glands. Trabeculae subdividing the subcutaneous fat are thickened because of the presence of an inflammatory infiltrate and deposition of new collagen. Large areas of subcutaneous fat are replaced by newly formed collagen, which is composed of fine, wavy fibers rather than bundles and stains only faintly with hematoxylin–eosin (110). Vascular changes in the early inflammatory stage generally are mild both in the dermis and in the subcutaneous tissue. They may consist of endothelial swelling and edema of the walls of the vessels (111).

In the late sclerotic stage, as seen in the center of old lesions, the inflammatory infiltrate has disappeared almost completely, except in some areas of the subcutis. The epidermis is normal. The collagen bundles in the reticular dermis often appear thickened, closely packed, and hypocellular. They stain more deeply eosinophilic than in normal skin (Fig. 10-13C, D). In the papillary dermis, where the collagen normally consists of loosely arranged fibers, the collagen may appear homogeneous.

Eccrine glands appear markedly atrophic, have few or no adipocytes surrounding them, and appear surrounded by newly formed collagen (Fig. 10-13B). Instead of lying near the dermal–subcutaneous junction as in normal skin, eccrine glands appear higher in the dermis as a result of the replacement of most of the subcutaneous fat by newly formed collagen. This collagen consists of thick, pale, sclerotic, homogeneous, or hyalinized bundles with only few fibroblasts (hypocellular). Few blood vessels are seen within the sclerotic collagen; they often have a fibrotic wall and a narrowed lumen. Elastic stains show thick elastic fibers arranged parallel to hypocellular collagen strands and parallel to the epidermal surface (Fig. 10-13E) (112).

The fascia and striated muscles underlying lesions of morphea may be affected in the linear, segmental, subcutaneous, and generalized types. The fascia shows fibrosis and sclerosis similar to that seen in subcutaneous tissue. The muscle fibers appear vacuolated and separated from one another by edema and focal collections of inflammatory cells (113).

---

**Figure 10-13** Morphea. A: The early inflammatory phase of morphea, where there is an interstitial lymphoplasmacytic infiltrate distributed among deep dermal collagen bundles. Collagen bundles are minimally swollen. B: Over time, collagen bundles become thickened, hypocellular, and swollen. Lymphoplasmacytic inflammatory infiltrates separate such collagen strands, surround eccrine coils in the deep dermis, and are associated with loss of adipocytes around eccrine apparatus. C: An established lesion of morphea: a “square” appearance in a punch biopsy. Note that appendages such as pilar apparatus are absent. Inflammation is sparse and localized at the dermal–subcutaneous interface. D: The trabeculae subdividing the subcutaneous fat are thickened and there is a patchy lymphoplasmacytic infiltrate. Pale, thickened collagen bundles appear arranged parallel to each other. E: Elastic stains demonstrate thick, coarse elastic fibers separated by collagen. They have a somewhat parallel array.
Bullae, seen only on rare occasions in generalized and in subcutaneous morphea, arise subepidermally, probably as a result of lymphatic obstruction, causing subepidermal edema.

**Differential Diagnosis.** Contrasting features of morphea and lichen sclerosus et atrophicus are summarized in Table 10-4. They include relatively little epidermal change in morphea, as compared with thinning of the rete ridges, follicular plugging, and interface alterations of lichen sclerosus (LS). The reticular dermal changes of fibrosis and inflammation in morphea contrast with the edema and loss of elastic tissue in LS. Histologic differentiation of the late stage of morphea from lichen sclerosus et atrophicus may cause difficulties, particularly in view of the fact that the two conditions may coexist.

**Pathogenesis.** There are conflicting data regarding *Borrelia burgdorferi* infection in cases of morphea. Studies indicating that such a relationship exists are primarily
from Europe (114). Studies in North America and some from Europe have resulted in negative findings (115).

Differential Diagnosis and Principles of Management. There is significant overlap between morphea and systemic scleroderma in pathogenesis, differential diagnosis, and principles of management. Please refer to the end of the section of systemic scleroderma.

Systemic Scleroderma

Clinical Summary. In systemic scleroderma, in addition to involvement of the skin and the subcutaneous tissue, visceral lesions are present, leading to death in some patients. The indurated lesions of the skin are not sharply demarcated or "circumscribed," as in morphea, although a few well-demarcated morphea-like patches may occasionally be seen.

Cutaneous involvement usually starts peripherally on the face and hands, gradually extending to the forearms. Facial changes include a masklike, expressionless face, inability to wrinkle the forehead, a beaklike nose, and tightening of the skin around the mouth associated with radial folds. The hands show nonpitting edema involving the dorsa of the fingers, hands, and forearms; this may be one of the first signs of the systemic inflammation of this disease, and physicians should be alert to this possibility. Gradually the fingers become tapered, the skin becomes hard, and flexion contractures form. These changes are referred to as acrosclerosis and are associated with Raynaud phenomenon, which may precede other manifestations by months or even years. Microscopic examination of the nail fold capillary beds shows tortuosity and redundancy of capillary loops with dilation of the arterioles and venules. Such abnormalities may occasionally be seen in patients with localized scleroderma and herald coexisting or evolving systemic sclerosis (116).

Systemic sclerosis with limited scleroderma, known as CREST syndrome, is associated with Raynaud phenomenon in virtually all affected patients. This variant of acrosclerosis, which frequently but not invariably has a favorable prognosis, consists of several or all of the following manifestations: Calcinosis cutis, Raynaud phenomenon, involvement of the Esophagus with dysphagia, Sclerodactyly, and Telangiectases. Death from visceral lesions is infrequent in the CREST syndrome (117).

In about 5% of the cases, the cutaneous lesions first appear on the trunk as so-called diffuse systemic scleroderma, often sparing the peripheral portions of the extremities. Raynaud phenomenon is absent in such patients. There are, however, transitional forms starting out as acrosclerosis with Raynaud phenomenon but then extending to the proximal portions of the arms and to the trunk. In both forms of systemic scleroderma, the skin in the involved areas is diffusely indurated and, as a result of diffuse fibrosis of the subcutaneous fat, becomes firmly bound to the underlying structures. The skeletal musculature is affected, resulting in weakness and atrophy. Contractures of the muscles and tendons and ankyloses of the joints may develop.

Occasional manifestations pertaining to the skin include diffuse hyperpigmentation, which is seen mainly in diffuse systemic scleroderma. Macular telangiectases on the face and hands, calcinosis cutis located on the extremities, and ulcerations, especially on the tips of the fingers and over the knuckles, occur predominantly in acrosclerosis. In addition, vascular ulcers on the lower extremities resembling those seen in atrophie blanche may occur in patients with acrosclerosis.

Histopathology. The histologic appearance of the skin lesions in systemic scleroderma is similar to that of morphea, so that histologic differentiation of the two types is not possible. One small study stated that the two conditions may be differentiated based upon the pattern of the inflammatory infiltrate and presence or absence of papillary dermal involvement (118). In early lesions of systemic scleroderma the inflammatory reaction is less pronounced than in morphea, so that only a mild inflammatory infiltrate is present around the dermal vessels, around the eccrine coils, and in the subcutaneous tissue. The vascular changes in early lesions are slight, as in morphea (119). By contrast, in the late stage, systemic scleroderma shows more

<table>
<thead>
<tr>
<th>Table 10-4</th>
<th>Contrasting Features of Morphea and Lichen Sclerosus et Atrophicus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermis</td>
<td>Relatively normal</td>
</tr>
<tr>
<td>Dermal-epidermal junction</td>
<td>No hydric degeneration</td>
</tr>
<tr>
<td>Dermis</td>
<td>Appears homogenized</td>
</tr>
<tr>
<td>Subcutis</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Lichen Sclerosus et Atrophicus</td>
<td>Thinning of rete</td>
</tr>
<tr>
<td></td>
<td>Follicular plugging</td>
</tr>
<tr>
<td></td>
<td>Hydropic degeneration of basilar cells</td>
</tr>
<tr>
<td></td>
<td>Often subepidermal bullae</td>
</tr>
<tr>
<td></td>
<td>Marked edema</td>
</tr>
<tr>
<td></td>
<td>Elastic fibers absent</td>
</tr>
<tr>
<td></td>
<td>No inflammation or fibrosis</td>
</tr>
</tbody>
</table>

| Lever's Histopathology of the Skin | From European studies have resulted in negative findings (115). |
pronounced vascular changes than morphea, particularly in the subcutis. These changes consist of a paucity of blood vessels, thickening and hyalinization of their walls, and narrowing of the lumen. Even in the late stage of systemic scleroderma, the epidermis appears normal, only occasionally showing disappearance of the rete ridges. Aggregates of calcium may also be seen in the late stage within areas of sclerotic, homogeneous collagen of the subcutaneous tissue (see also calcinosis cutis, Chapter 17).

**Systemic Lesions.** Internal organs are often affected in scleroderma, but their involvement varies greatly in extent and degree. Involvement does not necessarily imply functional compromise, and in many affected patients systemic scleroderma ultimately comes to a standstill. The clinical symptoms produced by reduced pliability, vascular compromise, and subsequent loss of function can be found in the gastrointestinal tract, lungs, heart, and kidneys, as well as the skin. In the gastrointestinal tract, submucosal fibrosis and replacement of the muscularis by fibrosis with intimal thickening of blood vessels give rise to difficulties in swallowing, regurgitation, and malabsorption and eventually ileus. In the lungs, interstitial fibrosis, degeneration of alveolar spaces, and intimal thickening of arteries result in dyspnea and cor pulmonale. Cases of pulmonary carcinoma (predominantly bronchioloalveolar) have been observed and are associated with the presence of pulmonary fibrosis (120). The most serious consequences arise in the kidneys. Adventitial fibrosis may affect interlobar, arcuate, and interlobular arteries, and mucoid degeneration affects arcuate and interlobular arteries. Uremia occurs more frequently than rapidly evolving renal failure and hypertension. The latter entity, termed scleroderma renal crisis, is associated with “onion-skin” hyperplasia of arterial walls and may be fatal (121).

**Pathogenesis.** The pathogenesis of systemic scleroderma/morphea, as with LE, is uncertain and may be multifactorial.

The triad of vascular compromise, collagen matrix aberrations, and presence of serologic autoimmune mediators contributes in variable degrees to symptoms and clinical findings in scleroderma and morphea (Table 10-5). Although a relationship to retroviral disease has been suggested, it is speculative and may reflect molecular mimicry of viral antigens (122). Genetic markers of scleroderma have been studied with DNA microarrays and indicate differential expression of genes in endothelial cells, B lymphocytes, and fibroblasts between scleroderma and normal biopsies (123).

**Microvascular Changes.** Involved vessels are primarily precapillary arterioles. Changes in the microvasculature have been noted in clinically normal skin. Perivascular edema and functional changes in endothelial cells can be detected early (124). Precapillary arterioles then show endothelial proliferation and mononuclear inflammatory infiltrates, followed by intimal proliferation and luminal narrowing (125). Corresponding electron microscopic findings include vacuolization and destruction of endothelial cells, reduplication of the basement membrane, enlargement of the rough endoplasmic reticulum in pericytes and fibroblasts, and perivascular fibrosis. There are some data to suggest that hyperplasia of the pericytic cells at the peripheral superficial aspect of the advancing border of the sclerosis may play an role in the fibrosing process through synthesis of collagenous matrix material and recruitment of fibroblasts through release of cytokines (126). Although widespread arteriolitis may be present in early stages, only rarely does it progress to a necrotizing arteriolitis and eventuate in periarteritis nodosa (127).

A role for adhesion molecules in the evolution of lesions of scleroderma has been suggested: they are believed to bind mononuclear cells to endothelial cells and facilitate diapedesis of inflammatory cells into the connective tissue. Interactions with connective tissue components may lead to the release of cytokines and growth factors, narrowing the blood vessels, and resulting in hypoperfusion of the affected organs.
resulting in upregulation of matrix production by fibroblasts and changes in fibroblast phenotype, eventuating in fibrosis (128).

Collagen Matrix Aberrations. Analysis of collagen in affected skin has shown excess production of connective tissue components normally present in the dermis, including types I, III, V, VI, and VII collagen, fibronectin, and proteoglycans (129,130). Other studies suggest that fibroblasts in localized and systemic scleroderma express markers of smooth muscle differentiation (myofibroblasts), which may account for their different biological behavior (131). Some observers have found loss of CD34+ dendritic cells in affected areas, a finding of uncertain significance (132).

Serologic/Immunologic Markers. Most patients with systemic sclerosis (>90%) and approximately 50% of those with localized scleroderma (morphea) have a positive ANA. The pattern may be homogeneous, speckled, or nucleolar. When using the human laryngeal carcinoma cell line HEp-2, more than 90% of patients with morphea or acrosclerosis have a detectable anticientromere antibody. In patients with systemic sclerosis, this antibody is not usually detected. Instead, 20% to 40% of them have antibodies to Scl-70. This antigen has been identified as DNA topoisomerase I, an intracellular enzyme involved in the uncoiling of DNA before it is transcribed. Antibodies to this enzyme hinder its function. The presence of antibodies to Scl-70 correlates with systemic sclerosis, whereas the presence of anticientromere antibodies correlates with morphea or CREST and suggests a more favorable prognosis (133). Antischistone antibodies have been shown to be positive in cases of morphea, particularly in generalized morphea and linear scleroderma. Although not particularly sensitive, anti-single-stranded DNA is considered very specific for linear scleroderma (134).

In some cases of systemic scleroderma, epidermal nucleolar IgG deposition is seen even in clinically normal skin as a result of high serum concentrations of antibody to nucleolar antigen (135). Although subepidermal and vascular deposits are regularly absent in the skin in scleroderma, kidney biopsies in patients with renal involvement show diffuse vascular deposits of immunoglobulins, predominantly IgM, or of complement in the intima of the interlobular and arcuate arteries, which by light microscopy often exhibit fibromucinous alterations (136).

Differential Diagnosis. Sclerodermoid changes in the skin may be seen unassociated with scleroderma or morphea in numerous other settings. These include in association with genetic, metabolic, neurologic, and immunologic disorders, with occupational or chemical exposures, in association with malignancy, or as sequelae of infection (72). Genetic disorders that may show sclerodermatosus cutaneous changes include phenylketonuria, progeria, Rothmund–Thomson syndrome, and Werner syndrome. Individuals at risk of occupational scleroderma include jackhammer and chain saw operators and those exposed to polyvinyl chloride, silica, and epoxy resins. Patients with metabolic disorders such as porphyria cutanea tarda, primary systemic amyloidosis, Hashimoto disease, carcinoid syndrome, and childhood diabetes mellitus may show similar cutaneous changes. Chronic graft-versus-host disease frequently shows scleroderma-like changes, and scattered reports in the literature indicate such changes may arise subsequent to silicone and paraffin injections in cosmetic procedures (137). Chemical agents have been known to induce thickening and hardening of the skin. Specific compounds include polyvinyl chloride, bleomycin, pentazocine, L-5 hydroxytryptophan and carbidopa (138), Spanish rapeseed oil (139), and L-tryptophan (eosinophilia-myalgia syndrome) (140).

Chemotherapy associated sclerodermoid changes in the skin have been reported with bicalutamid, taxane, mitomycin C, paclitaxel, and carboplatin. Of note, sclerodermoid changes may arise in association with plasma cell dyscrasias. Although there are increased numbers of IgG4 plasma cells in immunoglobulin G4-related disease that affects visceral organs with lymphoplasmacytic infiltrates and fibrosis, IgG4 plasma cells are not seen in greater numbers in scleroderma (141,142).

Principles of Management. Similar to limited LE, the clinical extent and severity of disease is the determining factor in treatment. In cases of limited cutaneous morphea, topical high potency steroids, or alternately, intranasal steroids may be used. For more extensive lesions, phototherapy, including UVB1, PUVA, and narrow band UVB may be utilized with varying levels of success. Adjunct agents include antimalarials such as hydroxychloroquine. More aggressive immunosuppressive regimens are utilized in rapidly evolving cutaneous disease and include a combination of corticosteroid and methotrexate, with thalidomide and TNF inhibitors potentially having a role. In those with progressive systemic sclerosis, aggressive immunosuppressive therapy is commonly used and includes combinations of methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, and intravenous immunoglobulin. Studies examining anti-TNF agents, including infliximab and etanercept, have shown variable improvement (143). In cases where morphea or scleroderma compromise joint mobility with contractures, physical therapy and/or surgical intervention are used. Physical therapy should be initiated early as a preventive measure when joints are involved.

ATROPHODERMA OF PASINI AND PIERINI

Clinical Summary. In atrophoderma of Pasini and Pierini there are areas on the trunk, particularly the back, in which the skin appears slightly depressed and has a slate-gray
color but shows no other surface changes. The lesions are asymptomatic, bilateral, symmetric, and sharply and irregularly demarcated, measuring from 1 to 10 cm in diameter. In old lesions, the center of the depressed area may feel slightly indurated.

Histopathology. The histologic changes in early lesions usually are slight and nonspecific, consisting of some thickening of the collagen bundles and a mild, scattered, chronic inflammatory infiltrate (144). Older lesions show no inflammatory infiltrate, but in the deeper layers of the dermis they may show collagen bundles that not only are thickened, but also appear tightly packed. In addition, indurated areas may show homogeneous, hyalinized collagen bundles. Because the collagen bundles in the skin of the back normally are rather thick, it may be difficult to determine whether the collagen shows any changes. It is therefore desirable to take a biopsy specimen not only from the lesion, but also from normal skin, either from an area nearby or from the opposite side with subcutaneous fat for comparison.

Pathogenesis. Some authors believe that atrophoderma of Pasini and Pierini is a disease entity sui generis, as suggested by the original describers. This is supported by the fact that in atrophoderma, the atrophy comes first and the sclerosis possibly appears later; whereas in morphea, the sclerosis comes first and the atrophy appears later (145).

Differential Diagnosis. Most observers view the clinical presentation of atrophoderma to be distinct from that of morphea: Atrophoderma has an earlier onset (second to third decade) and protracted course of 10 to 20 years, and lesions lack a violaceous ring, which characteristically surrounds lesions of morphea. Microscopic findings show similarities to morphea, suggesting that atrophoderma of Pasini and Pierini may be a distinct, abortive variant of morphea (146). To support this view there exist instances of coexistent morphea and atrophoderma, as well as reports of transformation of lesions of morphea into atrophoderma. A relationship of this disorder to B. burgdorferi infection has been reported but needs more studies to be confirmed (147).

Principles of Management. There presently are no randomized placebo-controlled studies showing efficacy of any one agent. Variable success has been reported using topical steroids, penicillin, tetracycline, and antimalarials. In instances where serologic studies are positive for B. burgdorferi, treatment with oral doxycycline for several weeks led to clinical improvement (148).

EOSINOPHILIC FASCIITIS (SHULMAN SYNDROME)

Clinical Summary. First described in 1974 (149), eosinophilic fasciitis is a scleroderma-like disorder characterized by inflammation and thickening of the deep fascia. It has a rapid onset associated with pain, swelling, and progressive induration of the skin leading to exaggerated deep grooving of the skin around superficial veins. This disorder is often accompanied by a peripheral eosinophilia, hypergammaglobulinemia, and elevated erythrocyte sedimentation rate and has been associated with aplastic anemia. Other rare associations include polycythemia rubra vera, cutaneous T-cell lymphoma, borreliosis, and autoimmune thyroid disease (150). Simvastatin and phenytoin have been reported to cause eosinophilic fasciitis (151). Eosinophilic fasciitis may have its onset with unusual physical exertion. It has been reported in association with t-tryptophan ingestion (152). The latter association is known as eosinophilia–myalgia syndrome, which is clinically and histologically similar to eosinophilic fasciitis.

Eosinophilic fasciitis often involves one or more extremities. The induration may cause a decreased range of motion and, in severe cases, even joint contractures (153,154). In only a few cases are there lesions on the trunk, and the face is almost invariably spared. In nearly all reported cases, Raynaud phenomenon and visceral lesions of scleroderma have been absent. Only very few instances of incontestable eosinophilic fasciitis have shown evidence of Raynaud phenomenon (155) or mild pulmonary fibrosis (156). The disorder has a varied course: Some patients improve spontaneously, others improve with corticosteroids, and still others may have relapses and remissions.

Histopathology. A deep wedge biopsy to skeletal muscle including fascia is essential to making the diagnosis of eosinophilic fasciitis. The fascia is markedly thickened, appears homogeneous, and is permeated by a mononuclear inflammatory infiltrate (Fig. 10-14A–C). The infiltrate in the fascia may contain an admixture of eosinophils (157). The underlying skeletal muscle in some cases shows myofiber degeneration, severe inflammation with a component of eosinophils, and focal scarring; in other cases, however, it is not involved.

In most cases, the adipose tissue shows no significant changes, except that the fibrous septa separating deeply-located fat lobules are thicker, paler staining, and more homogeneous and hyalinized than normal dermal connective tissue. In other cases, however, the collagen in the lower reticular dermis appears pale and homogeneous, and the entire subcutaneous fat is replaced by horizontally oriented, thick, homogeneous collagen containing only few fibroblasts and merging with the fascia (158).

Pathogenesis. Although it was initially thought that eosinophilic fasciitis was a new syndrome, it soon became apparent that the disorder represents a variant of morphea. Eosinophilic fasciitis may share features with generalized morphea, including inflammation and fibrosis of the fascia, peripheral eosinophilia, and hypergammaglobulinemia (159). ANAs are present in a significant number of cases (160). The term morphea profunda, analogous to LE profundus, has been applied to this disorder (161).
Nevertheless, because of its acute onset in most cases, its usual limitation to the structures underlying the skin, and its tendency to resolve, eosinophilic fasciitis deserves recognition as a distinct variant of morphea (162).

**Differential Diagnosis.** The differential diagnosis includes other sclerosing disorders, such as eosinophilia–myalgia syndrome (EMS) after L-tryptophane ingestion, hypereosinophilic syndromes, systemic sclerosis, Churg–Strauss syndrome, and/or peripheral T-cell lymphomas with cutaneous involvement (154).

**Principles of Management.** The first-line therapy for eosinophilic fasciitis is systemic corticosteroids. Remission of symptoms can be achieved in 3 to 6 months. Numerous alternative therapies have been examined in steroid refractory cases; however, none have shown reliable and durable responses.

Figure 10-14  Eosinophilic fasciitis.  
A: A deep biopsy including fascia. The subcutaneous septum and the fascia appear thickened and contain an inflammatory infiltrate.  
B: A widened fascia contains an interstitial inflammatory infiltrate that extends to involve adjacent adipose lobules.  
C: Among fibrotic bands of collagen is an infiltrate composed of lymphocytes, plasma cells, and occasional eosinophils.
NEPHROGENIC SYSTEMIC FIBROSIS

Clinical Summary. Nephrogenic systemic fibrosis, previously referred to as nephrogenic fibrosing dermopathy, is a systemic disorder characterized by symmetric thickening of the skin of the trunk and extremities. It was first recognized in a group of renal transplant patients in 1997 (163). The nomenclature changed when respiratory symptoms and related cardiac changes were recognized. All patients have some degree of renal impairment (164). Initially dialysis was suspected as a predisposing factor; however, up to 10% of patients had never received dialysis (165). There are equal sex and age distributions, and children have been affected. The cause is believed to be exposure to low stability gadolinium-based contrast agents in association with impaired renal function. Genetic predisposition may be a factor as well (166,167).

Clinically, nephrogenic systemic fibrosis presents as limited or widespread areas of symmetric thickening and hardening of the skin that may resemble scleroderma. The borders of involved areas may be sharply demarcated, serpentine, or ameboid. The skin becomes smooth and shiny or may acquire a peau d’orange appearance. Involvement over joints may lead to contractures. Although typically asymptomatic, patients may complain of muscular weakness, pruritus, and pain (165,167–169). In contrast to scleromyxedema, the face is typically spared. Pulmonary involvement may give rise to respiratory symptoms. Muscle weakness occurs with involvement of skeletal muscles and fascia. Patients with muscle weakness may have sensory motor polyneuropathy by electromyography and nerve conduction studies. Although cardiac fibrosis has been reported, impaired cardiac function has not been documented (169–172).

Histopathology. Histologic findings of nephrogenic systemic fibrosis may be subtle and require incisional biopsies to include fascia (Fig. 10-15A–C). Sections show spindled fibroblasts that extend into subcutaneous septa and subjacent fascia (Fig 10-15B). Collagen bundles are thickened. Cytoplasmic processes of fibrocytes surround collagen bundles. Such areas may demonstrate factor XIIIa–positive stellate fibroblastic cells and CD68-positive multinucleated giant cells (Fig. 10-15C–E).

Immunohistochemical stains show fibrocyte reactivity with CD34 in a membranous pattern and procollagen I in a cytoplasmic pattern (165,166). Such cells may represent a class of circulating fibrocytes that home to areas of cutaneous injury and play a crucial role in wound healing. One study showed the presence of myofibroblastic cells in early lesions of nephrogenic systemic fibrosis (173).

Pathogenesis. In vitro and in vivo studies have been undertaken to explain the etiopathogenesis of nephrogenic systemic fibrosis. It appears that low-stability gadolinium–chelate complexes, which were used in contrast imaging instead of iodinated compounds, dissociated and released gadolinium ions. As a result, cytokines are released by the free or complexed gadolinium, in turn stimulating peripheral blood monocytes. Stimulated monocytes stimulate fibroblasts, resulting in fibrosis of the skin. Detection and quantification of gadolinium in skin biopsies with synchrotron x-ray fluorescence spectroscopy supports the theory that tissue deposits of gadolinium are associated with the development of tissue fibrosis (174,175). As awareness of this disorder has increased and alternate gadolinium compounds have been administered under strict guidelines, the incidence of nephrogenic systemic fibrosis is declining (176).

Differential Diagnosis. The differential diagnosis includes other fibrosing and sclerodermoid cutaneous disorders. These include scleromyxedema, eosinophilic fasciitis, sclerodermoid graft-versus-host disease, sclerodermoid porphyria cutanea tarda, morphea, and lipodermatosclerosis. Most of these entities can be excluded based on the history and laboratory studies.

Principles of Management. Due to the elucidation of the cause of the disease and its rarity, there are numerous case studies of treatments but no controlled trials. The primary treatment at this point is prevention, through careful avoidance of gadolinium in patients with renal failure, and adequate IV hydration in cases where its use cannot be avoided. Treatments in the literature have included extracorporeal photopheresis, imatinib mesylate, UVA1, systemic steroids, plasmapheresis, cyclophosphamide, and topical steroids. Renal transplantation may result in marked improvements in appropriate patients.

LICHEN SCLEROSUS ET ATROPHICUS

Clinical Summary. LS encompasses the disorders known as lichen sclerosus et atrophicus, balanitis xerotica obliterans (LS of the male glans and prepuce), and kraurosis vulvae (LS of the female labia majora, labia minora, perineum, and perianal region) (177). LS is an inflammatory disorder of unknown etiology that affects patients 6 months of age to late adulthood. In both male and female patients genital involvement is the most frequent, and often the only, site of involvement. Extragenital lesions may occur with or without coexisting genital lesions.

Lesions of LS are characterized by white polygonal papules that coalesce to form plaques. Comedo-like plugs on the surface of the plaque correspond to dilated appendageal ostia. The plugs may disappear as the lesion ages, leaving a smooth, porcelain-white plaque. Solitary or generalized lesions may become bullous and hemorrhagic.

In male patients, involvement of the glans and prepuce often results in phimosis. Although the literature is dominated by reports of LS in incompletely or uncircumcised men (178), occurrences in circumcised men are reported as well (179). Neoplasms have been infrequently
documented in association with LS; however, a cause-and-effect relationship has not been established.

In female patients, contiguous involvement of the labial, perineal, and anal areas has been described clinically as “figure 8” or “keyhole” lesions (180). Many cases of childhood LS in girls resolve by menarche (181). If lesions persist, atrophy of the labia and narrowing of the vaginal orifice may ensue. In contrast to lichen sclerosus et atrophicus of the skin, which rarely itches, there is often severe pruritus in the vulvar region.

The premalignant potential in LS has been debated extensively and remains ill defined. The most recent large population-based study detected a small increased risk of squamous cell carcinoma in patients with LS. Because

**Figure 10-15 Nephrogenic systemic fibrosis.** A: An incisional specimen that shows deep dermal thickening and septal widening. B: Subcutaneous septae are widened by many spindle-shaped fibroblasts. C: High magnification of spindle-shaped fibrocytes, some of which are multinucleated in a thickened subcutaneous septum. Note little residual normal collagen. D: A different example of nephrogenic systemic fibrosis in which fibrocytes are distributed diffusely throughout the dermis. E: High magnification shows multinucleated fibroblastic cells. Note the difference between the spindle-shaped fibrocytes (lower half) and normal collagen bundles (upper half).
neoplasms have arisen in areas adjacent to lesions of LS, long-term follow-up of patients with lichen sclerosus et atrophicus is recommended.

Of interest, lesions of LS may koebnerize (be provoked by trauma) as well as coexist with morphea (182, 183). In extensive cases of morphea, lichen sclerosis et atrophicus may become superimposed. It is then best recognized by finding pale superficial dermal collagen, as compared with hypocellular compacted deep dermal collagen, and the presence of follicular plugging. Cases of both extragenital and genital LS have also been reported in the setting of graft-versus-host disease (184).

Histopathology. The salient histologic findings in cutaneous lesions of lichen sclerosus et atrophicus are (a) hyperkeratosis with follicular plugging, (b) atrophy of the stratum malpighii with hydropic degeneration of basal cells, (c) pronounced edema and homogenization of the collagen in the upper dermis, and (d) an inflammatory infiltrate in the mid-dermis.

The hyperkeratosis is so marked that the horny layer is often thicker than the atrophic stratum malpighii, which may be reduced to a few layers of flattened cells (Fig. 10-16A, B). The cells of the basal layer show hydropic degeneration. The rete ridges often are completely absent, although they may persist in a few areas and show irregular downward proliferation. In such proliferations, hydropic degeneration of the basal cells usually is pronounced.

Keratotic plugging of appendageal ostia is often associated with atrophy and disappearance of appendageal structures. Keratotic plugging is not apparent in mucosal lesions. In the latter areas, particularly the vulva, squamous hyperplasia adjacent to the atrophic epidermis can be found in about one third of patients with LS. There may be varying degrees of “dysplasia” consisting of disorderly arrangement of the cells and enlarged, hyperchromatic nuclei.

Beneath the epidermis is a broad zone of pronounced lymphedema (Fig. 10-16A, B). Within this zone, the collagenous fibers are swollen and homogeneous and contain only a few nuclei. They stain poorly with eosin and other connective tissue stains. The blood and lymph vessels are dilated, and there may be areas of hemorrhage. Elastic fibers are sparse and, in old lesions, are absent within the area of lymphedema (185). In areas of severe lymphedema, clinically visible bullae may form; they are found in subepidermal locations (186). Shrinkage within the area of lymphedema may occur during the process of dehydration of the specimen, resulting in the formation of pseudobullae, which often are located intradermally.

Except in lesions of long duration, an inflammatory infiltrate is present in the dermis. The earlier the lesion, the more superficial is the location of the infiltrate. In very early lesions and at the periphery of somewhat older lesions, the infiltrate may be found in the uppermost dermis, in direct apposition to the basal layer. Soon, however, a narrow zone of edema and homogenization of the collagen displaces the inflammatory infiltrate further down, so that, in well-developed lesions, the infiltrate is found in the mid-dermis. The infiltrate can be patchy, but it is often band-like and composed of lymphoid cells admixed with plasma cells and histiocytes. In old lesions in which the infiltrate is slight or absent, the collagen bundles in the midportion and lower dermis may appear swollen, homogeneous, and eosinophilic, thus appearing sclerotic (hence lichen sclerosus). Cases of overlap of morphea and LS may be seen and demonstrate the histologic changes of both disorders in their respective locations of the dermis (Fig. 10-17A–C).

Figure 10-16 Lichen sclerosus. A: Lichen sclerosus showing a subepidermal zone of pallor. A “trilayered” or “striped” appearance: compact hyperorthokeratotic scale and atrophic epidermis (dark pink/red), a pale dermis (white), and subjacent, variably dense interstitial lymphocytic inflammatory infiltrate (blue) delineating the depth of this process. B: An established lesion, showing a thick hyperkeratotic scale, an atrophic epidermis, and pale superficial dermal stroma with rare lymphocytes and plasma cells. A cleft-like space separates an atrophic epidermis from a pale dermis.
Pathogenesis. Studies suggest an increased rate of matrix turnover or a dysregulated remodeling response. Studies examining the components of the dermal matrix have demonstrated increases in the matrix proteins tenascin and fibrinogen, which serve as scaffold proteins on which new collagen is deposited. Similar increases in tenascin and fibrinogen have been demonstrated in scleroderma and morphea, suggesting that this is may be a nonspecific change (187).

Investigations into the presence of papilloma virus in vulvar and penile LS have shown no relationship between the two. One study showed 26.5% of cases of vulvar LS to contain Epstein-Barr virus with polymerase chain reaction. A causal relationship has not been established (188,189).

In the epidermis, intercellular edema separates epidermal cells that show degenerative changes. There is nearly a complete absence of melanosomes within the

Figure 10-17 Lichen sclerosus overlap with morphea. A: Low-power overview of a lesion showing morphea in the deep dermis and lichen sclerosus in the superficial dermis. B: The superficial dermis shows pallor associated with loss of the overlying epidermal rete ridge pattern and hyperkeratosis. C: The deep dermis shows compacted, hypocellular collagen bundles, and loss of appendageal structures.
keratinocytes. Immunoperoxidase and Fontana-Masson stains of melanocytes have shown there is both a loss of melanocytes and decreased transfer of melanosomes to keratinocytes (190). In contrast with morpha, where the basement membrane zone is continuous, in LS numerous invaginations and holes have been noted at the level of the lamina lucida and lamina densa (190,191).

**Differential Diagnosis.** Very early lesions may resemble lichen planus because of the apposition of the inflammatory infiltrate to the basal layer. However, the basal cells are not replaced by flattened squamous cells as in lichen planus but appear hydropic, and a subepidermal zone of edema usually has already begun to form in some areas in lichen sclerosus et atrophicus.

Old lesions of lichen sclerosus et atrophicus may resemble morpha, with thickening and eosinophilia of the collagen bundles in the midportion and lower dermis and only a slight inflammatory infiltrate. Nevertheless, the epidermis in morpha, although it may be thin, shows neither hydropic degeneration of the basal cells nor follicular plugging, and the upper dermis in morpha has intact elastic fibers and shows no edema. In lesions in which lichen sclerosus et atrophicus develops either secondarily to morpha or simultaneously with it, there are, in addition to the epidermal and subepidermal changes of lichen sclerosus et atrophicus, changes indicative of morpha in the lower dermis and in the subcutaneous fat. A definite diagnosis of both lichen sclerosus et atrophicus and morpha in the same lesion can be made only if the newly formed collagen extends into the subcutaneous fat and consists of faintly staining, homogeneous collagen (192).

**Principles of Management.** Topical corticosteroids are the mainstay of therapy in LS. Use of high potency topical steroids for long periods of time is the primary treatment. Calcineurin inhibitors tacrolimus and plicrolimus have been used in steroid resistant disease or as steroid sparing agents. Calcineurin inhibitors should be used with caution, however, because of concerns regarding malignant potential with the use of these agents and the potential of development of squamous cell carcinoma in lesions of LS (193).

**FIBROBLASTIC RHEUMATISM**

**Clinical Summary.** This rare condition is characterized by a combination of progressive inflammatory arthritis and fibrotic nodules typically involving the skin of the hands. It may occur in children as well as adults. Patients typically present with the sudden onset of polyarthritis and develop a progressive inflammatory polyarthritis, with cutaneous nodules typically in the form of periungual papules that may mimic multicentric reticulohistiocytosis. Patches or plaques of erythema, sclerodactyly, and Raynaud phenomenon may be associated findings.

**Histopathology.** The skin nodules are characterized by mononuclear cell infiltrates, fibroblastic proliferation with myofibroblastic differentiation (194,195), dermal fibrosis with thickened collagen fibers, and decreased or absent elastic fibers.

**Pathogenesis.** The pathogenesis of fibroblastic rheumatism is unknown. There are no significant laboratory findings.

**Differential Diagnosis.** The differential diagnosis includes rheumatoid nodules and rheumatoid arthritis, which show different histologic and serologic findings.

**Principles of Management.** This condition is variably but often inexorably progressive, but it may be responsive to immunosuppressive therapy, especially in its early stages (196). Corticosteroids and methotrexate are the mainstays of therapy. Earlier therapeutic intervention correlates with a better response.

**REFERENCES**


96. ConneCTive Tissue Diseases 10

361


111. O’Leary PA, Montgomery H, Ragsdale WE. Dermatohistopathology of various types of scleroderma [review]. Arch Dermatol 1957;75:78.


