CHAPTER 80

# Clinical Features of Systemic Lupus Erythematosus

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**KEY POINTS**

- Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that is characterized by a relapsing-remitting course and a highly variable prognosis.
- SLE is characterized by the production of a broad array of autoantibodies. Anti-nuclear antibodies have the greatest sensitivity for the diagnosis, and anti–double-stranded DNA and anti-Smith antibodies have the greatest specificity.
- Women of childbearing age and African-American, Asian, and Hispanic populations have the highest incidence and prevalence of disease.
- Constitutional symptoms, rash, mucosal ulcers, inflammatory polyarthritis, photosensitivity, and serositis are the most common clinical features of the disease.
- Lupus nephritis is the most common of the potentially life-threatening manifestations.
- Atherosclerosis, a complication of long-standing SLE, requires aggressive risk factor modification.

Systemic lupus erythematosus (SLE) is the prototypic systemic autoimmune disease, characterized by diverse multisystem involvement and the production of an array of autoantibodies. Clinical features in individual patients can be quite variable and range from mild joint and skin involvement to severe, life-threatening internal organ disease. Criteria for the classification of SLE were initially developed by the American College of Rheumatology (ACR) in 1971, revised in 1982, and revised for a second time in 1997[1,2] (Table 80-1). A person must fulfill 4 of 11 criteria to be classified as SLE, all other reasonable diagnoses having been excluded. A patient does not have to manifest all 4 criteria simultaneously; the required 4 of 11 criteria can be fulfilled during a period of weeks or years. The ACR criteria were developed as a way to classify patients with SLE for the purpose of inclusion in clinical and epidemiologic studies. In clinical practice, these criteria are often cited to support a diagnosis of SLE. However, it should be emphasized that fulfillment of these classification criteria is not an absolute requirement for diagnosis. Rather, diagnosis typically rests on the judgment of an experienced clinician who recognizes a characteristic constellation of symptoms and signs in the setting of supportive serologic studies, after exclusion of alternative differential diagnostic possibilities. Despite widespread acceptance of the ACR criteria, several limitations affect their utility. The ACR criteria include only a subset of the various manifestations that might be present in an SLE patient. For example, despite the variety of neurologic syndromes that have been described in SLE, only seizures and psychosis are included in the ACR criteria. Proteinuria and urinary cellular casts are the only two renal criteria. Notably, a positive renal biopsy is not included in the criteria.

Against this background, the Systemic Lupus International Collaborating Clinics (SLICC) undertook an effort to revise the ACR criteria.[3] Through review of more than 700 SLE and control patient scenarios and validation in a separate sample, 17 elements were identified for inclusion into the revised criteria (11 clinical and 6 immunologic). A patient is classified with SLE if he or she (1) has biopsy-proven lupus nephritis with a positive anti-nuclear antibody (ANA) or anti–double-stranded (ds) DNA antibody or (2) fulfills four of the criteria, including at least one clinical criterion and one immunologic criterion. In contrast to the ACR criteria, the SLICC criteria would not allow a patient to be classified with SLE on the basis of clinical features alone. The revised criteria include more dermatologic and neurologic manifestations, as well as low complement levels and positive direct Coombs test in the absence of hemolytic anemia. Although the SLICC revision provides alternative criteria for use in research studies, it remains to be seen whether these criteria will ultimately replace the ACR criteria.

## EPIDEMIOLOGY

Prevalence and incidence rates of SLE vary widely in the literature. Reported prevalence frequencies range from 20 to 240 per 100,000 persons, and reported incidence rates range from 1 to 10 per 100,000 person-years.[4] This variation is partly the result of methodological differences between studies (e.g., different case definitions of SLE and methods of case ascertainment) and differing racial/ethnic compositions of the study populations. To determine more accurate and contemporary epidemiologic estimates for SLE in the United States, the Centers for Disease Control and Prevention (CDC) funded five large-scale, population-based lupus registries to conduct extensive lupus surveillance. The completed Georgia and Michigan lupus registries, composed primarily of Caucasian and African-American patients, reported incidence rates of 5.6 per 100,000 person-years and prevalences of 72.1 to 74.4 per 100,000 persons. African-American women had the highest rates. Peak disease incidence occurred during reproductive years; African-Americans had a lower mean age of onset compared with Caucasians.[5,6] Registries from California, New York, and the Indian Health Service are nearing completion and will

**TABLE 80-1** 1997 Update of the 1982 Revised American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus*

| Criterion | Definition |
|---|---|
| Malar rash | Fixed erythema, flat or raised, over the malar eminences, sparing the nasolabial folds |
| Discoid rash | Erythematous raised patches with adherent keratotic scale and follicular plugging; atrophic scarring may occur in older lesions |
| Photosensitivity | Skin rash as a result of unusual reaction to sunlight, determined by patient history or physician observation |
| Oral ulcers | Oral or nasopharyngeal ulceration, usually painless, observed by a physician |
| Arthritis | Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion |
| Serositis | Pleuritis-convincing history of pleuritic chest pain or rub heard by a physician or evidence of pleural effusions *or* pericarditis-documented by electrocardiogram or rub or evidence of pericardial effusion |
| Renal disorder | Persistent proteinuria >0.5 g/day, >3+ if quantification not performed *or*<br>cellular casts: may be red blood cell, hemoglobin, granular tubular, or mixed |
| Neurologic disorder | Seizures: in the absence of offending drugs or known metabolic derangements (e.g., uremia, acidosis, electrolyte imbalance) *or*<br>Psychosis: in the absence of offending drugs or known metabolic derangements (e.g., uremia, acidosis, electrolyte imbalance) |
| Hematologic disorder | Hemolytic anemia with reticulocytosis *or*<br>Leukopenia <4000/mm$^3$ *or*<br>Lymphopenia <1500/mm$^3$ *or*<br>Thrombocytopenia <100,000/mm$^3$ in the absence of offending drugs |
| Immunologic disorder | Anti-DNA: antibody to native DNA in abnormal titer *or*<br>anti-Smith: presence of antibody to Sm nuclear antigen *or*<br>Positive finding of anti-phospholipid antibodies based on (1) abnormal serum concentration of immunoglobulin (Ig)G or IgM anti-cardiolipin antibodies, (2) positive test result for lupus anticoagulant by using a standard method, or (3) false-positive serologic test for syphilis known to be positive for at least 6 mo and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test |
| Positive anti-nuclear antibody | An abnormal titer of anti-nuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndromes |

*The presence of four or more criteria is required for systemic lupus erythematosus classification. Exclude all other reasonable diagnoses.

provide robust incidence and prevalence estimates in the Asian, Hispanic, and Native-American populations. Previous studies suggest a higher prevalence of SLE in Asian and Hispanic populations.

Most patients with SLE are seen with their disease when they are between 15 and 64 years old.[7] Patients with pediatric-onset SLE (<16 years old) are more likely to be African-American than patients with later-onset SLE.[7] SLE tends to be more severe in men and in pediatric patients. Late-onset SLE (>50 years old) is characterized by a more insidious onset, with a higher occurrence of serositis and pulmonary involvement, and a lower incidence of malar rash, photosensitivity, alopecia, Raynaud's phenomenon, neuropsychiatric disease, and nephritis.[7]

## CLINICAL FEATURES

SLE has protean clinical manifestations that may differ dramatically from patient to patient. Just as the signs and symptoms of SLE vary widely among patients, so does the severity of disease. Some patients will have relatively mild disease that is no threat to a life-sustaining organ; other patients' disease will progress rapidly to life-threatening severity.

The great variability in the expression and severity of SLE constitutes a major challenge to accurate diagnosis. Although it is difficult to pinpoint their precise frequencies, it is clear that the most common presenting manifestations are constitutional symptoms (fever, fatigue, and/or weight loss), cutaneous manifestations (e.g., malar rash), and articular manifestations (arthritis and/or arthralgia). Each of these manifestations appears to be present in at least 50% of patients with lupus at the time of diagnosis. The other clinical features of SLE are much less likely to be presenting manifestations, although virtually any of them might be the first clue to the correct diagnosis. More commonly, these manifestations appear while the disease evolves. Taken together, various descriptive studies in the literature[1,8–12] support a cumulative frequency of symptoms and signs that is summarized in Table 80-2.

### Mucocutaneous Involvement

Mucocutaneous involvement is very common in SLE. Gilliam and colleagues have categorized cutaneous lupus erythematosus (LE) lesions as "lupus specific" or "lupus nonspecific" on the basis of the histopathologic finding of interface dermatitis[13,14] (Table 80-3). In a patient with lupus, the presence of lupus-specific lesions confirms the diagnosis of cutaneous LE; lupus nonspecific lesions can occur in diseases other than lupus. Lupus-specific lesions are further subdivided into acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE) lesions, on the basis of additional clinical and histopathologic information. Discoid lupus is the most common subtype of

**TABLE 80-2** Frequencies of Various Manifestations of Systemic Lupus Erythematosus*

| Manifestation | Frequency (%) |
|---|---|
| Constitutional symptoms (fatigue, fever, weight loss) | 90-95 |
| Mucocutaneous involvement (malar rash, alopecia, mucosal ulcers, discoid lesions, etc.) | 80-90 |
| Musculoskeletal involvement (arthritis/arthralgia, avascular necrosis, myositis, etc.) | 80-90 |
| Serositis (pleuritis, pericarditis, peritonitis) | 50-70 |
| Glomerulonephritis | 40-60 |
| Neuropsychiatric involvement (cognitive impairment, depression, psychosis, seizures, stroke, demyelinating syndromes, peripheral neuropathy, etc.) | 40-60 |
| Autoimmune cytopenia (anemia, thrombocytopenia) | 20-30 |

*Systemic lupus erythematosus is a heterogeneous disease that can affect virtually any organ system in variable ways.

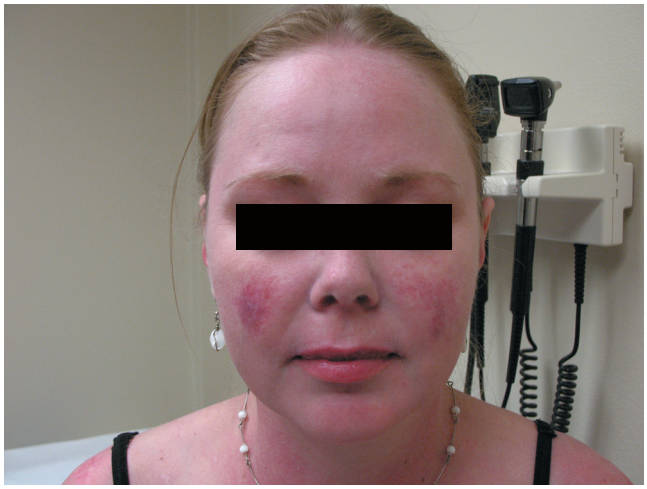

**Figure 80-1** Localized acute cutaneous lupus erythematosus (malar rash, butterfly rash). This lesion is characterized by macular or papular erythema in a malar distribution, sparing the nasolabial folds.

CCLE. SCLE and CCLE can occur as distinct isolated entities or as one of several manifestations of SLE. The risk of SLE varies with each cutaneous subset. One study of 161 patients with lupus-specific lesions showed that the classification criteria for SLE were present in 72% of patients with ACLE, 58% with SCLE, 28% with any form of discoid lupus, and 6% with localized discoid lupus confined to the head and neck. Many patients displayed more than one type of cutaneous lesion.[15]

### Acute Cutaneous Lupus Erythematosus

ACLE lesions can be localized or generalized. The hallmark feature of ACLE is localized to the malar region ("butterfly rash") and is characterized by confluent, macular, or papular erythema that last days to weeks, and appearing symmetrically on the cheeks and bridge of the nose. They do not appear on the nasolabial folds, which are sun-protected areas (Figure 80-1). Induration and scaling may occur.

**TABLE 80-3** Gilliam Classification of Skin Lesions Associated with Lupus

A. Lupus erythematosus (LE)-specific skin lesions
   1. Acute cutaneous LE (ACLE)
      Localized ACLE
      Generalized ACLE
   2. Subacute cutaneous LE (SCLE)
      Annular SCLE
      Papulosquamous SCLE
   3. Chronic cutaneous LE (CCLE)
      Classic discoid LE (DLE): (a) localized; (b) generalized
         Hypertrophic DLE/verrucous DLE
         Lupus panniculitis/profundus
         Mucosal DLE
         LE tumidus
         Chilblain LE
      Lichenoid DLE (DLE-lichen planus overlap)

B. LE-nonspecific skin lesions
   1. Cutaneous vascular disease
      Vasculitis
         Leukocytoclastic vasculitis
         Polyarteritis nodosa–like
         Vasculopathy
            Degos disease–like
            Atrophe blanche–like
            Periungal telangiectasia
            Livedo reticularis
            Thrombophlebitis
            Raynaud's phenomenon
            Erythromelalgia
   2. Nonscarring alopecia
      "Lupus hair"
      Telogen effluvium
      Alopecia areata
   3. Sclerodactyly
   4. Rheumatoid nodules
   5. Calcinosis cutis
   6. LE-nonspecific bullous lesions
   7. Urticaria
   8. Papulonodular mucinosis
   9. Cutis laxa/anetoderma
   10. Acanthosis nigricans (type B insulin resistance)
   11. Erythema multiforme (Rowell's syndrome)
   12. Leg ulcers
   13. Lichen planus

Erythema also commonly occurs on the forehead, eyelids, chin, and neck. The malar rash of SLE can be mimicked by a variety of other facial rashes, including acne, rosacea, seborrheic dermatitis, perioral dermatitis, atopic dermatitis, and erysipelas. If the diagnosis remains uncertain after an extensive clinical and serologic evaluation, biopsy of the rash can help to distinguish cutaneous lupus from other dermatologic conditions. It is important to remember that other forms of lupus-specific skin lesions, such as discoid lupus, can also occur in the malar distribution.

The generalized form of ACLE refers to widespread macular or maculopapular erythema occurring in a photosensitive distribution on any area of the body. The palmar surfaces, dorsa of the hands, and extensor surfaces of the fingers are commonly involved. In contrast to Gottron's

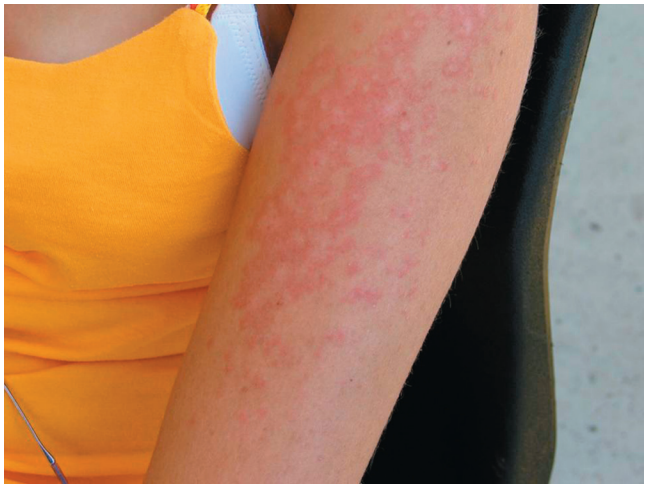

**Figure 80-2** Subacute cutaneous lupus (papulosquamous variant). Lesions typically appear on the back, neck, shoulders, and extensor surfaces of the arms, and usually spare the central area of the face. Lesions heal without scarring.

papules of dermatomyositis, the erythema of ACLE spares the metacarpophalangeal joints, and typically is located between the interphalangeal joints. In severe forms of ACLE, a widespread bullous eruption similar to toxic epidermal necrolysis (TEN) can occur. ACLE lesions heal without scarring, although temporary postinflammatory hyperpigmentation may be observed.

### Subacute Cutaneous Lupus Erythematosus

Subacute cutaneous lupus erythematosus (SCLE) is characterized by the presence of nonscarring, photosensitive lesions that can take one of two distinct forms: (1) papulosquamous lesions that resemble psoriasis, or (2) annular-polycyclic lesions with peripheral scale and central clearing (Figure 80-2). These two forms can occur concurrently in the same patient. SCLE has a predilection for the back, neck, shoulders, and extensor surfaces of the arms and usually spares the central face. The lesions typically last for weeks to months and heal without scarring. Rarely, a severe TEN-like eruption can evolve from SCLE lesions after sun exposure.[16] SCLE, particularly the annular subtype, is strongly associated with the presence of anti-SS-A/Ro antibody.[17] Several drugs are known to induce SCLE: angiotensin-converting enzyme inhibitors, terbinafine, hydrochlorothiazide, and calcium channel blockers are common culprits. Finally, SCLE has been implicated as a paraneoplastic syndrome.[18]

### Chronic Cutaneous Lupus Erythematosus

CCLE refers to a variety of subtypes of photosensitive lesions that can lead to skin atrophy and scar and that may persist for several months or years. Discoid lupus (DLE) is the most common subtype of CCLE. DLE is subdivided into localized discoid lupus (limited to head and neck) and generalized discoid (occurring above and below the neck) (Figures 80-3 and 80-4). The term "discoid" refers to the sharply demarcated disk-shaped appearance of the lesions, which are raised, erythematosus plaques with adherent

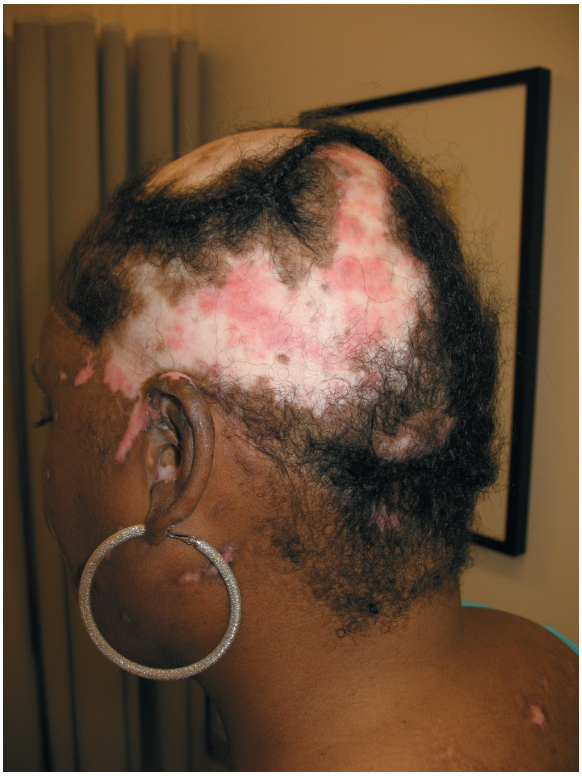

**Figure 80-3** Discoid lupus erythematosus on the face and scalp. Discoid lesions are a form of chronic cutaneous lupus and are commonly found on the scalp, face, and external ears. If untreated, these lesions can lead to permanent alopecia and disfigurement.

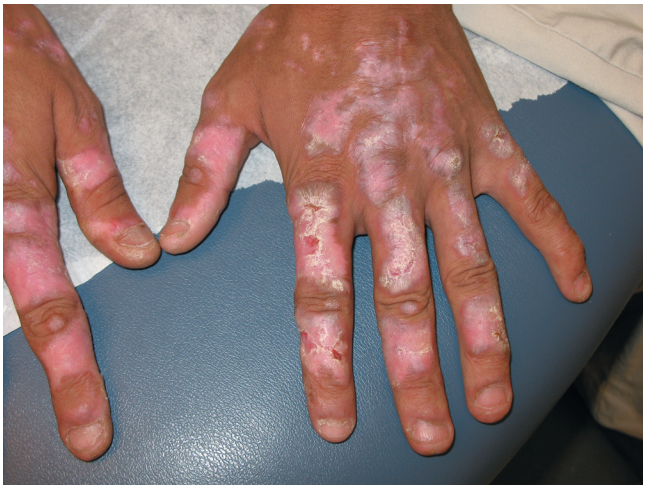

**Figure 80-4** Discoid lupus erythematosus on the dorsa of the hands. The lesions spare the proximal interphalangeal joints, a characteristic feature of lupus-specific rashes.

scales that commonly occur on the patient's scalp, face, and neck. The cheeks, nose, ears, and upper lip are classic locations for lesions. Typically, a raised, erythematous border denotes the actively expanding component. Follicular plugging is a characteristic finding. Left untreated, DLE can result in permanent alopecia and disfigurement. Squamous cell carcinoma has been described as a sequela of long-standing DLE; thus active surveillance of known lesions and

evaluation of changing lesions are critical.[19] Other subtypes of DLE include mucosal DLE (described in a subsequent section) and hypertrophic LE. Hypertrophic LE consists of chronic, indurated lesions that are covered by hyperkeratotic, multilayered scales. These lesions can be a source of diagnostic confusion because they may visually and histologically resemble squamous cell carcinoma.[20]

Other forms of CCLE include lupus panniculitis/profundus, chilblain lupus, and lupus tumidus. Lupus panniculitis is a lobular panniculitis that has a predilection for the scalp, face, arms, buttocks, and thighs. The lesions can result in depressed, sunken areas. When a cutaneous discoid lesion overlies the panniculitis, the entity is referred to as *lupus profundus*.[21] Biopsy is often necessary to secure the diagnosis because reports have described cases of T cell lymphoma that mimic panniculitis. However, biopsy should be performed carefully because the lesions have a tendency to break down. Lupus panniculitis is one of the few panniculitides that can occur above the waist. Lupus panniculitis is associated with a low risk of concomitant SLE. Chilblain lupus manifests as tender, erythematous, or violaceous papules or plaques occurring on acral areas, especially the fingers, toes, heels, nose, and ears. The lesions are brought on by cold, damp air. Chilblains lupus is more likely than idiopathic chilblains to be present even in warm weather.

Lupus tumidus lesions are characterized by edematous, erythematous plaques with a smooth surface. These lesions are highly photosensitive and have a predilection for the zygomatic region of the face. The epidermis is not involved; thus there is a lack of overlying scale or follicular plugging.

### Other Systemic Lupus Erythematosus Skin Lesions

Lupus-nonspecific skin lesions such as cutaneous leukocytoclastic vasculitis, bullous lesions, periungual erythema, and livedo reticularis can develop in patients with SLE. Cutaneous leukocytoclastic vasculitis most commonly presents as palpable purpura on the lower extremities. Bullous lupus erythematosus is a rare cutaneous manifestation characterized by subepidermal vesiculobullous skin changes, manifested by a nonscarring bullous eruption[22] (Figure 80-5). SLE may be associated with other bullous disorders such as bullous pemphigoid and dermatitis herpetiformis. The physical examination finding of periungal erythema represents dilation of the capillaries at the base of the nail. The physician can visualize these capillaries at the patient's bedside with a dermatoscope or ophthalmoscope. Other disorders associated with periungual erythema include scleroderma and mixed connective tissue disease (MCTD). Unlike scleroderma and MCTD, SLE is not associated with capillary dropout. Livedo reticularis is characterized by an erythematous to violaceous reticular or netlike pattern of the skin. It is highly associated with anti-phospholipid antibody syndrome.

### Photosensitivity

Photosensitivity occurs frequently in SLE. In one study, photo provocation testing caused an abnormal skin reaction to ultraviolet A, ultraviolet B, or visible light in more than 90% of patients with lupus.[23] Most abnormal skin reactions occurred 1 to 2 weeks after exposure to light, and persisted for weeks to months. Photosensitive patients may report worsening of their systemic disease symptoms, such as fatigue and joint pain, following sun exposure. During evaluation of a photosensitive patient, polymorphous light eruption (PMLE) and phototoxic medications are important diagnostic considerations.[24] Accurate differentiation between PMLE and lupus is essential because PMLE is treated by ultraviolet radiation phototherapy, but this treatment makes lupus worse. PMLE can occur concomitantly in patients with known SLE.

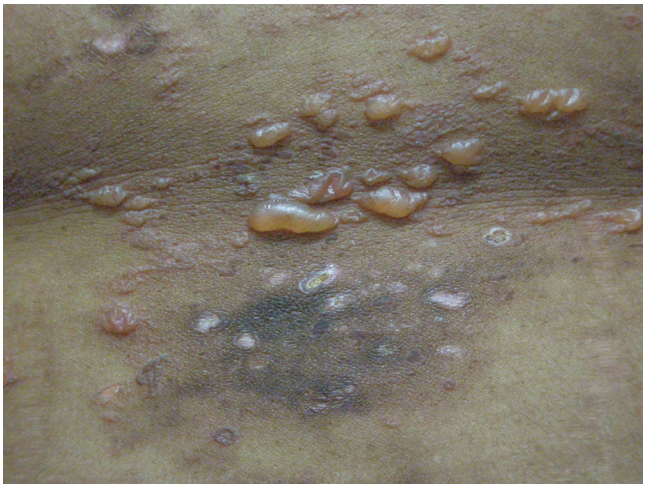

**Figure 80-5** Bullous lupus erythematosus. These lesions are a rare manifestation of lupus and are characterized by nonscarring bullous lesions.

### Alopecia

Scarring alopecia is a common complication of discoid lupus. Scalp discoid lesions most frequently develop on the vertex and parietal areas.[25] Nonscarring alopecia in patients with SLE can take several forms. "Lupus hair" is characterized by short, irregularly sized hair at the frontal hairline and is associated with active systemic disease.[26] Telogen effluvium manifests as diffuse hair thinning. Last, the incidence of alopecia areata (discrete areas of hair loss) is believed to be increased in cases of SLE.[27]

### Mucosal Ulcers

Nasal or oral lesions that represent the mucosal counterparts of cutaneous lupus commonly develop in patients with SLE.[28] Acute oral lupus lesions present as red macules, palatal erythema or petechiae, erosions, or ulcerations. These lesions are usually painless. Subacute oral lesions are rare, and are characterized by well-demarcated, round, red patches. Oral discoid lesions present as painful, well-demarcated, round, red lesions with white radiating hyperkeratotic striae. The buccal mucosa is the most commonly involved site. When the lesions evolve, they may take on a honeycomb appearance. Oral discoid lupus frequently involves the patient's lip and spreads from the vermilion border to the skin of the lip. Mucosal discoid lesions can

also occur on the conjunctiva and genital areas. In general, lupus oral ulcers have a gradual onset and can occur anywhere on the oral mucosa, with the most common locations the hard palate, buccal mucosa, and vermilion border.[29] These lesions are most commonly unilateral or asymmetric. The relationship between the presence of oral lesions and systemic disease activity remains unclear. Note that oral candidiasis and oral lichen planus can take on a similar appearance to SLE oral ulcers. The histopathology and immunopathology of mucosal lesions are similar to the alterations seen in the skin. Vasculitis is absent.

### Dermatopathology and Immunopathology

A skin biopsy is useful in the diagnosis of cutaneous lupus in the setting of an atypical clinical presentation. Immunofluorescence should always be performed, along with conventional histology. "Lupus-specific" skin lesions are characterized by an interface dermatitis consisting of a mononuclear cell infiltrate at the dermal-epidermal junction. Other pathologic findings present in lupus skin lesions include basal layer vasculopathic degeneration of keratinocytes, perivascular and periadnexal inflammation, follicular plugging, mucin deposition, and hyperkeratosis. These findings occur to different degrees in various lupus-specific skin lesions; discoid lesions show the most profound changes.[30] In contrast, early ACLE lesions may have minimal histopathologic findings and only a sparse lymphocytic infiltrate.

Immunofluorescence demonstrates granular deposition of immunoglobulin and complement components along the dermal-epidermal junction. Immunoglobulin (Ig)G and IgM are the most common immunoglobulin subtypes deposited. Various complement components, including C3, C1q, and the membrane attack complex, have also been identified. Direct immunofluorescence (DIF) of nonlesional, sun-exposed skin is referred to as the "lupus band test." Although a positive lupus band test is often seen in patients with SLE, this may also be seen in patients with other rheumatic diseases, as well as in healthy people. In one study, 20% of healthy young adults had a positive DIF in sun-exposed skin.[31] It is important to note that serologic testing with ANA, anti-dsDNA, and anti-Smith (anti-Sm) has largely supplanted use of the lupus band test in confirming the diagnosis of SLE. DIF of nonlesional, sun-protected skin is believed to be more specific for SLE.

## Musculoskeletal Involvement

### Arthritis

Arthritis and arthralgias are very common manifestations of SLE, present in as many as 90% of patients at some point during the course of their disease.[32] Severity of involvement can range from mild joint pain to deforming arthritis. Although any joint can be involved, lupus arthritis is characterized by a symmetric, inflammatory arthritis that predominantly affects the knees, wrists, and small joints of the hands.[33] Synovial effusions are typically small and not as inflammatory as those present in rheumatoid arthritis (RA). Hand deformities can occur as a result of ligamental and/or joint capsule laxity and joint subluxation. This manifestation is referred to as *Jaccoud's-like arthropathy* because it resembles the arthropathy that develops in patients with rheumatic fever (Figure 80-6). These deformities are typically reducible, although sometimes they can become fixed and are associated with disability. Jaccoud's-like arthropathy sometimes occurs in the foot, also.[34]

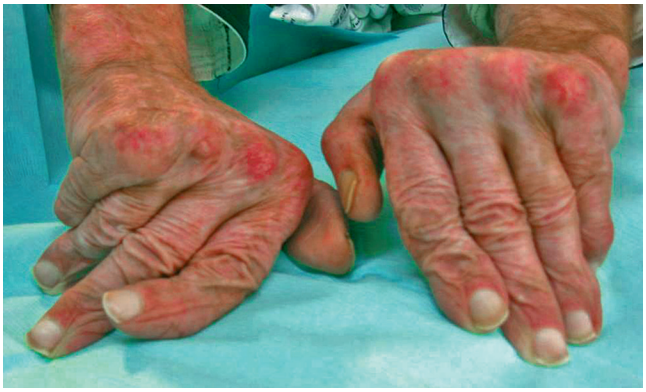

**Figure 80-6** Jaccoud's-like arthropathy. These hand deformities resemble those that develop in patients with a history of rheumatic fever and are caused by ligamentous and/or joint capsule laxity. Deformities in the hands, such as ulnar drift at the metacarpophalangeal joints, swan neck and boutonnière deformities, and hyperextension at the interphalangeal joint of the thumb, closely resemble the deformities seen in rheumatoid arthritis. The absence of erosions on radiographs and their reducibility distinguish this condition from the deforming arthritis of rheumatoid arthritis. *(Courtesy Dr. D. Vassilopoulos.)*

Although lupus arthritis is not classically associated with erosions on plain radiography, erosive disease has been described in a small subset of patients.[35] In addition, MRI studies have shown occasional erosions in some patients with lupus arthritis.[36] A subset of patients with SLE who also meet classification criteria for RA have historically been referred to as "rhupus." One study demonstrated the presence of marginal joint erosions on plain radiography in 60% of such patients [37] Erosive arthritis is commonly a feature of MCTD. Some studies have demonstrated an association between lupus erosive arthritis and the presence of anti-citrullinated protein antibodies (ACPA).[35] In addition to arthritis, tendinitis or tenosynovitis is frequently observed in patients with SLE.[38] Tendon rupture is a very uncommon occurrence.

Synovial biopsies from patients with lupus arthritis have shown a variety of abnormalities, including deposition of fibrin-like material, focal or diffuse synovial lining cell proliferation, vascular congestion, perivascular mononuclear cell infiltration, vasculitis, and obliteration of vessel lumina.[39] Radiographic studies of patients with SLE have revealed changes such as cystic bone lesions, periarticular soft tissue swelling, demineralization, acral sclerosis, joint subluxations, and erosions.[40,41]

### Avascular Necrosis

Avascular necrosis (AVN), also referred to as *aseptic necrosis* and *ischemic necrosis*, is a painful and disabling condition that occurs in some patients with SLE.[42] AVN is the end result of interruption of the blood supply to bone, leading to reactive hyperemia of adjacent bone,

demineralization, and then collapse. The most commonly affected sites include the femoral heads, tibial plateaus, and femoral condyles, but smaller joints can be involved as well. AVN is often bilateral, and joint effusions may occur. AVN of the femoral head should be suspected in a patient with SLE who has groin pain that is worsened with weight bearing and movement of the hip. The pain may radiate down the side of the thigh, and a limp might be evident. Although both plain radiographs and MRI can be helpful in the diagnosis of AVN, MRI is the more sensitive test. One prospective MRI study of 45 patients with SLE on glucocorticoid therapy demonstrated that silent osteonecrosis of the femoral head developed in 34% of patients.[43] However, MRI studies may be too sensitive an indicator, in that some lupus patients with suggestive MRI findings never progress to clinical symptoms of AVN. Therefore MRI findings should always be interpreted in the context of the clinical setting. The use of high doses of glucocorticoids is a well-known risk factor for AVN, but AVN has also been described in patients with SLE who have never used glucocorticoids. An MRI study of 72 newly diagnosed patients with SLE demonstrated that AVN typically developed within the first 3 months of initiation of high-dose glucocorticoids.[44] Epidemiologic studies have shown that high disease activity, as measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and the use of cytotoxic medications are also associated with AVN.[45,46]

### Myositis

Although myalgias occur commonly in SLE, true myositis is relatively rare. One study of patients with SLE at the National Institutes of Health (NIH) found a prevalence of myositis of 8%.[47] In most of those patients, myositis was one of the presenting features of SLE. Myositis usually involves the proximal upper and lower extremities. Histologic findings in SLE myositis are often less pronounced than those observed in polymyositis.

A biopsy study of 55 unselected patients with SLE demonstrated that several pathologic changes, including type II fiber atrophy, lymphocytic vasculitis, and myositis, were increased in patients with SLE compared with control patients.[48]

It is important to distinguish myositis secondary to SLE from drug-induced myopathies caused by glucocorticoids, antimalarial agents, colchicine, or statins because the treatment is very different. Muscle enzymes such as creatine phosphokinase (CPK) and aldolase are typically normal in patients with both glucocorticoid- and hydroxychloroquine-induced myopathy. Biopsy specimens usually reveal characteristic findings, including vacuolar changes in hydroxychloroquine myopathy and type II fiber atrophy in glucocorticoid myopathy in the absence of inflammation. Colchicine can result in a myopathy or neuromyopathy with elevation of serum CPK levels. Muscle histology reveals a vacuolar myopathy. Finally, it is important to think broadly about other potential causes of myopathy and myositis in patients with SLE, including thyroid disease, electrolyte abnormalities, and infectious myositis. One must also consider the possibility of MCTD because myositis can be a prominent feature of that disorder.

## Renal Involvement

### General Considerations

Renal involvement is common in SLE and is a significant cause of morbidity and mortality.[49,50] It is estimated that as many as 90% of patients with SLE will have pathologic evidence of renal involvement on biopsy, but clinically significant nephritis will develop in only 50%. The clinical presentation of lupus nephritis is highly variable, ranging from asymptomatic hematuria and/or proteinuria, to frank nephrotic syndrome, to rapidly progressive glomerulonephritis with loss of renal function. Lupus nephritis typically develops within the first 36 months of the disease, although there are exceptions. Thus periodic screening for the presence of nephritis is a critical component of the ongoing evaluation and management of patients with SLE. Routine screening procedures include inquiry about new-onset polyuria, nocturia, or foamy urine, and examination of the patient for the presence of hypertension or lower extremity edema. It is important to screen at regular intervals for the presence of proteinuria and/or hematuria and a change in serum creatinine. In patients with active SLE, screening at 3-month intervals is prudent.

### Types of Renal Involvement in Systemic Lupus Erythematosus

Several forms of renal involvement have been described in SLE, including immune complex–mediated glomerulonephritis (the most common form), tubulointerstitial disease, and vascular disease. Glomerulonephritis is characterized by immune complex deposition and inflammatory cell infiltration into the glomerulus. The pattern of glomerular injury is primarily related to the site of immune complex deposition. Tubulointerstitial and vascular disease can occur with or without immune complex–mediated glomerulonephritis. Tubulointerstitial disease has been observed in as many as 66% of SLE renal biopsy specimens[51] and is characterized by inflammatory cell infiltrates, tubular damage, and interstitial fibrosis. The presence of tubulointerstitial disease is a strong predictor of poor long-term renal outcome.[52]

Renal vascular lesions in SLE include "lupus vasculopathy," thrombotic microangiopathy (TMA), vasculitis, and nonspecific vascular sclerosis.[53,54] Lupus vasculopathy is defined as the presence of immunoglobulin and complement-containing thrombi within the glomerular capillary or arteriolar lumina. Inflammatory changes to the vascular wall are absent. TMA is characterized by the presence of fibrin thrombi within the glomerular capillary or arteriolar lumina and may be associated with the presence of antiphospholipid antibodies. The finding of TMA should prompt consideration of anti-phospholipid antibody syndrome nephropathy (APSN). The frequency of TMA was 24% in a study of 148 patients with biopsy-proven lupus nephritis.[55] The majority of patients with documented TMA were thought to have renal-limited TMA in that there was no identifiable alternative disease process to explain the TMA, such as thrombotic thrombocytopenic purpura hemolytic uremic syndrome (TTP-HUS), malignant hypertension, or the presence of anti-phospholipid antibodies. The patients with concomitant biopsy-proven lupus nephritis and TMA

had higher levels of proteinuria, higher serum creatinine concentrations, and a worse renal prognosis. Although exceedingly rare, true vasculitis characterized by leukocyte infiltration and fibrinoid necrosis of arterial walls can occur. Nonspecific sclerotic vascular lesions characterized by fibrous intimal thickening are commonly observed. The presence of such vascular lesions is associated with decreased renal survival.[56] In one study of 341 patients with lupus nephritis, renal vascular lesions were identified in 82% of patients. Vascular immune deposits were the most common lesion observed (74% of patients).[57] In addition to the lupus-related renal lesions described previously, unrelated renal abnormalities may develop in patients with SLE. Such pathologic lesions include focal segmental glomerulosclerosis (FSGS), hypertensive nephrosclerosis, diabetic nephropathy, and thin basement membrane disease.[58] In an SLE patient in whom renal disease is suspected, renal biopsy is critical in distinguishing between these potential causes and in guiding appropriate management decisions.

## Laboratory Evaluation

### Urinalysis

A urinalysis with microscopy is essential in the screening and monitoring of lupus nephritis.[59] Hematuria, pyuria, dysmorphic red blood cells, red blood cell casts, and white blood cell casts may all be present. Red blood cell casts are very specific, but not sensitive, for the diagnosis of glomerulonephritis. Early morning urine specimens, which tend to be concentrated and acidic, are ideal for the detection of red blood cell casts. White blood cells, red blood cells, and white blood cell casts may indicate the presence of tubulointerstitial involvement. Hematuria in the absence of proteinuria might be to the result of urolithiasis, menstrual contamination, or bladder pathology, particularly transitional cell carcinoma in a patient with previous cyclophosphamide exposure.

Accurate measurement of proteinuria is critical because proteinuria is a very sensitive indicator of glomerular damage. In addition, studies of chronic kidney disease have shown that the magnitude of proteinuria is a strong predictor of glomerular filtration rate decline.[60] Normal daily protein excretion is less than 150 mg. Although the gold-standard tool is an accurately collected 24-hour urine protein, this test can be cumbersome for patients and is prone to errors in undercollection and overcollection. Thus many clinicians are currently using the random spot urine protein-to-creatinine ratio for convenience. Use of the spot ratio is controversial because data suggest that the spot ratio often is not representative of the findings in a timed collection, especially in the range of 0.5 to 3.0 (the range of most lupus nephritis flares).[61] However, a spot ratio can be a helpful screening test for the presence of proteinuria, and is useful in differentiating nephrotic from non-nephrotic range proteinuria.[62] A urine dipstick should not be used for the quantification of proteinuria because it reflects protein concentrations and varies depending on the volume of the sample. Many experts currently recommend calculation of the protein: creatinine ratio from a 12- or 24-hour urine collection as the gold standard of proteinuria assessment.[63]

### Measurement of Renal Function

Although easy to measure, serum creatinine is a fairly insensitive indicator of early decline in glomerular filtration rate (GFR). Creatinine is freely filtered across the glomerulus and is also secreted by the proximal tubule. While GFR falls, the rise in serum creatinine is counteracted by increased tubular creatinine secretion. In addition, hemodynamic changes, such as those caused by treatment with angiotensin-converting enzyme inhibitors or nonsteroidal anti-inflammatory drugs, are a common cause of changes in serum creatinine levels in the absence of progression of underlying renal disease. However, trending serum creatinine during a period of time is a reasonable method by which to follow a patient's renal function. Many clinicians prefer to utilize equations that estimate GFR, such as the Modification of Diet in Renal Disease (MDRD) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study equations. The CKD-EPI equation is more accurate than the MDRD equation in patients with higher GFRs. Whichever method is chosen, the detection of changes in renal function during a period of time is more important than the absolute level when following lupus nephritis patients in clinical practice.

### Renal Biopsy

When a patient with SLE has clinical or laboratory features that suggest the presence of nephritis, a renal biopsy should be performed to confirm the diagnosis, evaluate the degree of disease activity, and determine an appropriate course of treatment. The importance of renal biopsy was emphasized in the ACR's guidance document for the case identification, treatment, and monitoring of lupus nephritis.[64] According to this document, biopsy is highly recommended for patients who meet any of the following criteria: (1) increasing serum creatinine without compelling alternative causes, (2) confirmed proteinuria of greater than or equal to 1 g/24 hours, (3) proteinuria greater than 0.5 g/24 hours plus hematuria, or (4) proteinuria greater than 0.5 g/24 hours plus cellular casts. Proteinuria can be measured by a 24-hour collection or spot protein to creatinine ratio.

Before renal biopsy, ultrasonography is recommended to assess kidney size and structure and to rule out renal vein thrombosis. Kidney size of less than 75% of normal is a relative contraindication to biopsy.[65] SLE glomerulonephritis is classified by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) into six categories on the basis of light microscopic, immunofluorescent, and electron micrographic findings[66] (Table 80-4 and Figure 80-7).

An individual biopsy might exhibit just one of the ISN/RPS pathologic classes or a combination of classes. Class I is characterized by normal-appearing glomeruli on light microscopy and mesangial immune deposits on immunofluorescence. Class II is characterized by mesangial proliferation on light microscopy and mesangial deposits on immunofluorescence. Class III and IV lupus nephritis lesions are highly inflammatory and are characterized by immune complex deposition in the subendothelial space. They have traditionally been described as "proliferative" because of the presence of proliferating endocapillary cells within the glomeruli. They are believed to be inter-related lesions that

**TABLE 80-4** International Society of Nephrology/Renal Pathology Society Classification of Lupus Nephritis

| WHO Type | |
|---|---|
| Class I | **Minimal Mesangial Lupus Nephritis**<br>Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence |
| Class II | **Mesangial Proliferative Nephritis**<br>Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits<br>Few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy |
| Class III | **Focal Lupus Nephritis**<br>Active or inactive focal, segmental, or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations |
| Class IV | **Diffuse Lupus Nephritis**<br>Active or inactive diffuse, segmental, or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is subdivided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits, but with little or no glomerular proliferation |
| Class V | **Membranous Lupus Nephritis**<br>Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations<br>Class V nephritis may occur in combination with class III or class IV, in which case both are diagnosed<br>Class V nephritis may show advanced sclerotic lesions |
| Class VI | **Advanced Sclerotic Lupus Nephritis**<br>≥90% of glomeruli globally sclerosed without residual activity |

WHO, World Health Organization.

Modified from Weening JJ, et al: The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 15:241, 2004.

differ in the distribution of endocapillary immune complex deposition. Class III denotes that less than 50% of glomeruli are involved, and class IV denotes that 50% or more of glomeruli are involved. Class IV lesions are subcategorized according to whether most glomeruli show focal (<50% of the glomerular tuft) or global (≥50% of the glomerular tuft) involvement. These lesions are further described as active (A), chronic (C), or a mixture of the two (A/C). Both active and chronic lesions are taken into consideration when determining whether the designation of class III or class IV is most appropriate. Thick subendothelial immune deposits form classic "wire loop" lesions. Sometimes, wire loop lesions are present in the absence of cellular proliferation. Class V lupus nephritis is characterized by immune complex deposition in the subepithelial space, resulting in widespread thickened capillary loops. These findings are similar to those observed in idiopathic membranous nephritis. However, the presence of concomitant mesangial deposits, C1q deposition on immunofluorescence, or tubuloreticular inclusion bodies would favor the diagnosis of lupus. This lesion is commonly manifested clinically as nephrotic range proteinuria. Class V nephritis may occur in a pure histopathologic form or in combination with features of class III or class IV nephritis. Class VI nephritis is defined by the presence of more than 90% globally sclerotic glomeruli. In addition to the type of glomerular pathology, the ISN/RPS classification system dictates that tubulointerstitial disease and/or vascular disease should be noted on the diagnostic line. However, it is important to note that the class of lupus nephritis is based entirely on the glomerular pathology.

Immunofluorescence studies are an important supplement to the findings on light microscopy. Immunofluorescence reveals the type and pattern of immune complex deposition. Lupus nephritis is characterized by a granular pattern of immunofluorescence along the glomerular basement membrane, mesangium, and/or tubular basement membranes. The characteristic findings of lupus nephritis are sometimes referred to as the "full-house" pattern, because IgG, IgM, IgA, C3, and C1q are all found in the deposits. Electron microscopy is useful in more precisely localizing the sites of immune complex deposition. The finding of tubuloreticular inclusion bodies within endothelial cells is strongly suggestive of the diagnosis of lupus nephritis. However, because tubuloreticular inclusion bodies are associated with increased levels of interferon (IFN)-α, chronic viral infections such as hepatitis B/C and HIV must be ruled out.

Renal biopsy is especially important because urinary parameters such as hematuria and the degree of proteinuria imperfectly predict the underlying renal pathology.[67,68] For example, hematuria might be absent in patients with severe class IV nephritis, and proteinuria can be modest in patients with class V nephritis. A repeat renal biopsy may be indicated in certain clinical settings (e.g., if a patient is not responding appropriately to therapy, if a patient unexpectedly worsens after having achieved a good response to therapy, or to determine whether residual proteinuria after a course of treatment is the result of ongoing active lupus nephritis vs. glomerulosclerosis). Repeat renal biopsy can be useful in detecting class transformation that occurs in 15% to 50% of lupus nephritis patients during the course of their disease. Class transformation can occur spontaneously or as a result of treatment.

## Outcome

Each ISN/RPS histopathologic class portends a distinct renal prognosis. Patients with class I and class II nephritis have an excellent renal prognosis and do not require any specific therapy. In contrast, the long-term renal prognosis of class III or class IV nephritis is poor in the absence of immunosuppressive therapy. Although the long-term renal prognosis of class V nephritis is more favorable than that of class III or class IV nephritis, class V patients are more likely to suffer from morbid complications of the nephrotic syndrome, including cardiovascular disease, thromboembolic disease, and hyperlipidemia. Several epidemiologic studies

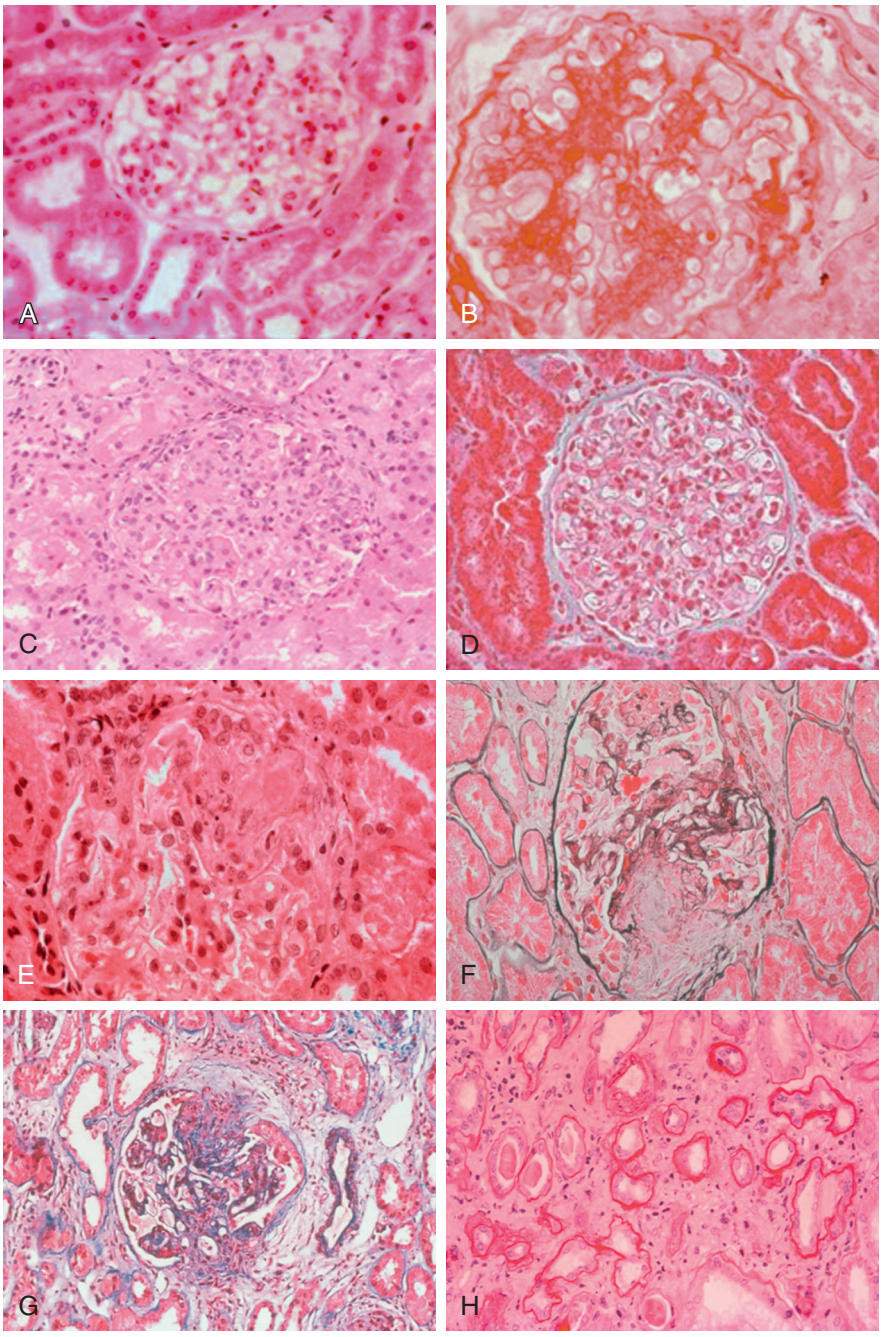


**Figure 80-7** **A** through **D**, World Health Organization types of lupus. (See Table 80-4 for a detailed description of histologic findings.) **A**, Normal glomerulus (type I). **B**, Mesangial proliferative (type II). **C**, Proliferative nephritis. Dramatic increase in mesangial and endocapillary cellularity produces a lobular appearance of the glomerular tufts and compromises the patency of most capillary loops. When less than 50% of glomeruli are involved, nephritis is denoted as focal (type III). When more than 50% of glomeruli are involved, nephritis is denoted as diffuse (type IV). **D**, Membranous nephropathy (type V). In membranous lupus nephropathy, the capillary walls of the glomerular tuft are prominent and widely patent, resembling "stiff" structures with decreased compliance. **E** through **H**, High-risk histologic features suggesting severe nephritis. **E**, Fibrinoid necrosis with karyorrhexis in a patient with focal proliferative glomerulonephritis. **F** and **G**, Cellular crescents with layers of proliferative endothelial cells and monocytes lining Bowman's capsule along with a predominantly mononuclear interstitial infiltrate. **H**, Severe interstitial fibrosis and tubular atrophy. Note the thickening of the tubular basement membranes and tubular epithelial degeneration with separation of residual tubules caused by deposition of collagenous connective tissue among tubules.

have defined demographic, clinical, and histopathologic factors associated with renal outcome in patients with lupus nephritis. Studies have shown that African-Americans and Hispanics/Latinos generally experience a worse renal prognosis than white and Chinese populations. The reasons for this disparity most likely involve a combination of genetic and socioeconomic factors.

## Pleuropulmonary Involvement

Pleuropulmonary manifestations of SLE are diverse and can involve any aspect of the lung (Table 80-5).

### Pleuritis

Pleuritis will develop in as many as 50% of patients with SLE. Clinically apparent pleural effusions are typically small, bilateral, and exudative.[69] Pleuritis is commonly manifested by pleuritic chest pain, but pleural effusions may be asymptomatic and detected on routine chest radiography performed for another purpose. Massive pleural effusions requiring pleurocentesis and/or pleurodesis are uncommon but have been reported.[70] The presence of pleuritis usually corresponds to active SLE in other organ systems.[71] Thoracoscopic evaluation has demonstrated nodules on the visceral pleura with immunoglobulin deposits detected on immunofluorescence. The differential diagnosis of pleural effusions in a patient with SLE includes infection, malignancy, and heart failure. In addition, pleural effusions are a common feature of drug-induced lupus. In the absence of infection, high levels of serum C-reactive protein (CRP) have been found to correlate well with the presence of pleuritis and other forms of serositis in SLE.[71,72]

**TABLE 80-5** Pleuropulmonary Manifestations of Systemic Lupus Erythematosus

| Manifestation | Key Features |
|---|---|
| Pleuritis | May occur with or without effusion<br>May correlate with elevated serum C-reactive protein |
| Pleural effusion | May be asymptomatic<br>Usually small, bilateral, exudative<br>Common feature of drug-induced lupus<br>Must exclude infection, malignancy, heart failure |
| Acute pneumonitis | Severe respiratory illness with fever, cough, pulmonary infiltrates, hypoxemia<br>Pleural effusion may be present<br>High mortality rate<br>Bronchoscopy with bronchoalveolar lavage might be necessary to exclude infection |
| Chronic interstitial lung disease | May develop after acute pneumonitis or in a more insidious fashion<br>Presents as dyspnea on exertion, pleuritic chest pain, nonproductive cough<br>High-resolution computed tomography is more sensitive than chest radiograph in detecting disease<br>Must exclude infection, pulmonary edema, malignancy |
| Diffuse alveolar hemorrhage | Presents as dyspnea and cough, alveolar infiltrates, fall in blood hemoglobin level<br>Hemoptysis may not be present<br>Diffusion capacity of carbon monoxide typically increased<br>Bronchoscopy with bronchoalveolar lavage confirms the diagnosis and excludes infection<br>High mortality rate |
| Pulmonary arterial hypertension | Presents as dyspnea on exertion, fatigue, chest pain, nonproductive cough<br>Diagnosis should be confirmed with right heart catheterization<br>Exclude secondary causes of pulmonary hypertension, including thromboembolic disease |
| Shrinking lung syndrome | Dyspnea, low lung volumes, elevation of hemidiaphragms in the absence of lung parenchymal involvement |

### Lupus Pneumonitis

Acute lupus pneumonitis is a rare manifestation of SLE that presents as a severe, acute respiratory illness with fever, cough, pulmonary infiltrates, and hypoxemia. Chest radiography usually reveals bilateral, lower lobe, acinar infiltrates that often occur in conjunction with a pleural effusion. Histopathologic findings are nonspecific and include diffuse alveolar damage, inflammatory cell infiltrates, hyaline membranes, and alveolar hemorrhage.[73] Immunofluorescence studies have demonstrated granular deposits of IgG and C3 within the alveolar septa.[74] Because clinical and pathologic features of acute lupus pneumonitis are nonspecific, careful evaluation is critical to exclude other potential pulmonary processes such as infection. If routine blood and sputum cultures are nondiagnostic, bronchoscopy with bronchoalveolar lavage can be useful in detecting pulmonary pathogens. A "tree and bud" pattern on high-resolution CT (HRCT) may suggest the presence of an atypical pneumonia. Acute lupus pneumonitis is associated with significant morbidity and mortality. One series of 12 patients reported a mortality rate of 50%, with deaths from respiratory failure, opportunistic infection, and thromboembolic events. Three of the surviving patients progressed to chronic interstitial pneumonitis.[75]

### Chronic Interstitial Lung Disease

Chronic interstitial lung disease is a rare manifestation of SLE. It occurs more commonly in other connective tissue diseases such as systemic sclerosis, RA, and polymyositis/dermatomyositis. Interstitial lung disease in the setting of SLE can develop after one or more episodes of acute pneumonitis but can also occur in an insidious fashion.[75] Symptoms are similar to those seen in patients with idiopathic interstitial lung disease and include dyspnea on exertion, pleuritic chest pain, and chronic, nonproductive cough. The diagnosis of interstitial lung disease is often made on the basis of clinical-radiologic findings; lung biopsy is not routinely performed. Chest radiography results might be normal early in the disease but can show reticular opacities. Pulmonary function studies show a restrictive pattern with reduction in total lung capacity and reduction in the diffusion capacity of carbon monoxide (DLCO). HRCT is more sensitive than chest radiography in detecting

interstitial lung disease and in distinguishing reversible lesions (ground-glass opacities) from irreversible fibrotic lesions. Nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP) are the most common patterns detected on histopathology and HRCT. Before making the diagnosis of interstitial lung disease, it is important to exclude infection, pulmonary edema, and malignancy.

### Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH) is a life-threatening manifestation of SLE that occurs in less than 2% of patients. It is characterized by acute or subacute onset of dyspnea and cough in the setting of new alveolar infiltrates on chest radiography and a fall in blood hemoglobin level. Similar to other causes of DAH, hemoptysis is not universally present. Although most patients are too ill to undergo formal pulmonary function tests, the DLCO is typically increased in the setting of DAH because of the presence of extravascular hemoglobin within the alveoli. Bronchoscopy with bronchoalveolar lavage (BAL) is important in ruling out infection and confirming the diagnosis. Characteristic findings include visualization of blood in the airways and serosanguineous BAL fluid that does not clear with continued lavage. Hemosiderin-laden macrophages may be present in the BAL fluid. Various histopathologic patterns have been described in lupus DAH, including bland pulmonary hemorrhage, capillaritis, diffuse alveolar damage, and vasculitis of small arterioles and small muscular pulmonary arteries. DAH usually occurs in the setting of serologically and clinically active SLE, and lupus nephritis is the most common concurrent SLE manifestation. However, DAH occasionally may be the initial manifestation of SLE. Mechanical ventilation is often required,[76] and infectious complications are common. Despite aggressive therapy, the mortality rate from DAH continues to be 50%.

### Pulmonary Hypertension

Pulmonary hypertension (PH) is a rare, devastating complication of SLE that is defined as a mean pulmonary artery pressure greater than 25 mm Hg at rest on right heart catheterization. PH can be secondary to a variety of disorders, such as pulmonary disease, leading to hypoxemia, chronic thromboembolic disease, pulmonary veno-occlusive disease, or left-sided heart disease. Pulmonary arterial hypertension (PAH) is a subtype of PH that is defined by a normal pulmonary capillary wedge pressure and elevated pulmonary capillary resistance on right heart catheterization. Symptoms of PH include dyspnea on exertion, fatigue, chest pain, and nonproductive cough. Physical examination findings may include a pronounced second pulmonary heart sound, a left parasternal lift, and signs of a volume-overloaded state. Chest radiography and HRCT are important in excluding lupus pneumonitis. Chest radiography may show cardiomegaly and a prominent pulmonary artery segment. The electrocardiogram often shows right axis deviation. Pulmonary function studies demonstrate a reduction in DLCO. Although transthoracic Doppler echocardiography is an adequate screening test for PH, the diagnosis should be confirmed by catheterization of the right side of the heart. Similar to interstitial lung disease, PAH more commonly occurs in association with scleroderma and MCTD.

In a patient with SLE who has been diagnosed with PH, an evaluation must be performed for secondary causes. Ventilation and perfusion (V/Q) lung scan and/or helical CT are useful in excluding chronic thromboembolic disease. Echocardiography can rule out left heart failure and intracardiac shunting. A sleep study can be useful in ruling out obstructive sleep apnea. An evaluation for interstitial lung disease is necessary. Some studies suggest that PAH occurs more commonly in patients with Raynaud's phenomenon. Autopsy findings suggest that the pathogenesis of PAH in the setting of SLE is likely to be multifactorial, including both primary vascular and inflammatory/immune-mediated mechanisms. Macrophages and lymphocytes are present within the vascular plexiform lesions. In addition, IgG and complement are deposited within the pulmonary artery walls.

### Other

Shrinking lung syndrome occurs in a small subset of patients with SLE and should be considered when evaluating a patient with SLE who has unexplained dyspnea and pleuritic chest pain.[77,78] The syndrome is characterized by decreased lung volumes in the setting of normal lung parenchyma. The cause of the disorder remains controversial. Diaphragmatic myopathy, abnormal chest wall expansion, phrenic neuropathy, and pleural inflammation/fibrosis have been reported as possible factors. The prognosis of this syndrome seems to be good, and progressive respiratory failure is uncommon.

Although symptomatic bronchiolar disease is uncommon in SLE, abnormalities in pulmonary function studies have been reported in as many as two-thirds of patients with SLE.[79] One study of nonsmoking patients with SLE found that 24% of patients had pulmonary function studies consistent with small airway disease. Rare case reports of bronchiolitis obliterans organizing pneumonia (BOOP) in the setting of SLE have been described.[80]

Last, a syndrome known as "acute reversible hypoxemia" has been observed in patients with active SLE. This syndrome is characterized by hypoxemia and an abnormal alveolar-arterial $pO_2$ gradient in the absence of parenchymal lung disease. Pulmonary vascular endothelial cell injury and leukoagglutination secondary to complement activation is thought to be one potential mechanism

## Cardiovascular Involvement

Cardiovascular disease is a frequent complication of SLE and may involve the pericardium, myocardium, valves, and coronary arteries.

### Pericarditis

Pericarditis, with or without an effusion, is the most common cardiac manifestation of SLE, occurring in more than 50% of patients with SLE at some point during the course of their disease.[81] Pericardial effusions are usually small and asymptomatic and typically are detected on echocardiography performed for another indication. Consistent with this

observation, necropsy studies have shown that histopathologic evidence of pericarditis is much more common than clinically symptomatic disease during life.[82] Symptomatic pericarditis classically presents as sharp, precordial chest pain that is improved when the patient is in the upright position. A pericardial rub and tachycardia may be detected on cardiac auscultation. The electrocardiogram demonstrates diffuse ST segment elevation. Similar to pleuritis, pericarditis usually occurs in the setting of active SLE in other organ systems. Although rare, SLE pericarditis complicated by large effusions and tamponade physiology has been reported. Purulent effusions necessitating pericardiocentesis have also been described, but rarely. The differential diagnosis of precordial chest pain in a patient with SLE includes costochondritis, gastroesophageal reflux disease, pulmonary embolism, myocardial ischemia, pleuritis, pneumonitis, and pulmonary hypertension.

### Myocarditis

Myocarditis, an uncommon manifestation of SLE, should be suspected in a patient presenting with various combinations of the following clinical features: unexplained heart failure or cardiomegaly, unexplained tachycardia, and unexplained electrocardiographic abnormalities. Echocardiography can confirm the presence of systolic or diastolic dysfunction and/or global hypokinesis. If myocarditis is suspected, an endomyocardial biopsy may be helpful in confirming the diagnosis and excluding other causes of cardiomyopathy such as hydroxychloroquine toxicity. The distinguishing pathologic finding of hydroxychloroquine toxicity is myocyte vacuolization in the absence of active myocarditis. Histopathologic findings of SLE myocarditis include perivascular and interstitial mononuclear cell infiltration and sometimes fibrosis and scar.

### Valvular Abnormalities

Several valvular abnormalities have been described in patients with SLE, including Libman-Sacks endocarditis (also known as "atypical verrucous endocarditis"), valvular thickening, valvular regurgitation, and valvular stenosis. One transesophageal echocardiographic (TEE) study demonstrated a prevalence of valvular abnormalities of 61% in patients with SLE compared with 9% of controls, with vegetations present in 43% of patients with SLE compared with none of the controls.[83] Valvular thickening with a predilection for the mitral and aortic valves was the most common abnormality, occurring in 50% of patients with SLE. Valvular regurgitation and stenosis were detected in 25% and 4% of patients, respectively.[83] In this study, the presence and progression of valvular disease were not associated with SLE disease activity or treatment. During a follow-up period of as long as 5 years, some valvular abnormalities resolved and some new lesions occurred. The combined incidence of stroke, peripheral embolism, congestive heart failure, infective endocarditis, need for valve replacement, and death was 22% among patients with valvular disease compared with 15% in patients without valvular disease.[83]

Libman-Sacks endocarditis has been recognized in multiple pathologic studies as a characteristic valvular abnormality in SLE. Libman-Sacks verrucae typically appear as pea-sized, flat or raised, granular lesions that occur most commonly on the ventricular aspects of the mitral valve posterior leaflet.[84] The verrucae often extend onto the adjacent left ventricular mural endocardium and may lead to adherence of the leaflet and chordae tendineae to the ventricular mural endocardium, resulting in valvular regurgitation. All four valves may be involved, but recent studies suggest a predominance of left-sided lesions. The lesions are frequently clinically silent because they are typically found on the undersurface of valve leaflets, surrounded by fibrous tissue. Histologically, two types of verrucae have been described: (1) active lesions consisting of fibrin clumps with infiltrating lymphocytes and plasma cells, and (2) healed lesions consisting of dense vascularized fibrous tissue with or without calcification. Combinations of active and healed lesions also occur. Verrucae typically do not contain polymorphonuclear cells; thus the presence of such cells should prompt consideration of infectious endocarditis. Immunopathologic studies have demonstrated immunoglobulin and complement deposition in a granular pattern at the base of the valve, along the valve leaflet, and within the verruca itself. Cardiac murmurs are frequently heard in patients with SLE. They may simply result from high-flow states such as fever and anemia, or they may reflect cardiac pathology such as mitral valve prolapse or infective endocarditis. When a new murmur is evaluated, a transthoracic echocardiogram (TTE) is an appropriate first test. However, TEE should be used in the event of a nondiagnostic TTE or in a patient with suspected thromboembolic events. TEE has been shown to be superior to TTE for detection of Libman-Sacks endocarditis.[85] Although thromboembolic events are believed to be rare complications of Libman-Sacks endocarditis, one study showed that valvular heart disease detected on TTE was associated with the presence of cerebral infarcts on MRI.[86] Systematic reviews have suggested that the presence of valvular abnormalities in SLE are associated with anti-phospholipid antibody[87,88]. One study of 1656 patients with SLE determined that the odds of valvular heart disease in patients with SLE with anti-phospholipid antibodies was three times higher than in SLE patients without anti-phospholipid antibodies. The risk for valvular heart disease was greatest for patients with lupus anticoagulant or IgG anticardiolipin antibodies.[88]

### Coronary Artery Disease

Both intramural and extramural coronary artery disease is increased in patients with SLE. Necropsy studies have demonstrated fibrous intimal proliferation of small intramural coronary arteries and obstruction of these arteries with hyaline material.[89] These lesions are similar to those observed in pathologic studies of renal and central nervous system tissue in patients with SLE. The large epicardial coronary arteries may be obstructed because of arterial emboli, in situ thrombosis, vasculitis, or atherosclerotic disease. True coronary artery vasculitis is exceedingly rare. In contrast, atherosclerotic disease is a well-recognized complication of long-standing SLE.[90] Autopsy studies have demonstrated atherosclerosis in 25% to 40% of patients with SLE. One epidemiologic study demonstrated that young women with SLE have a 50-fold higher risk of myocardial infarction compared with age-matched controls.[91] A

multicenter inception cohort determined that male sex and older age at SLE diagnosis were significantly associated with the presence of atherosclerotic disease.[92] Although patients with SLE are more likely to have classic atherosclerotic risk factors such as hypertension and exposure to glucocorticoids, these risk factors alone do not fully account for the increased risk of atherosclerosis seen in patients with SLE.[93] Although the precise mechanisms of accelerated atherosclerosis in SLE are not completely understood, it is likely that an interplay between traditional cardiovascular risk factors and autoimmune related factors is important. One example of a nontraditional, autoimmune-related factor is pro-inflammatory high-density lipoprotein (piHDL) cholesterol. In the setting of inflammation, HDL can become pro-inflammatory rather than anti-inflammatory. One study demonstrated a piHDL prevalence of 45% in women with SLE compared with 20% of female patients with RA and 4% of control women.[94] In another study, piHDL was positively associated with measures of subclinical atherosclerosis.[95]A recent prospective study of 210 women with SLE was undertaken to try to develop a risk score that could be utilized to predict the presence and progression of carotid plaque.[96] As a result, the Predictors of Risk for Elevated Flares, Damage Progression, and Increased Cardiovascular Disease in Patients with SLE (PREDICTS) panel was developed. This panel comprises four novel biomarkers (piHDL function, leptin levels, soluble TNF-like weak inducer of apoptosis [TWEAK levels], homocysteine levels), and two traditional cardiovascular risk factors (age ≥48 years, history of diabetes). A high score that used the PREDICTS panel was associated with a 28-fold increased odds of baseline carotid plaque and plaque progression in women with SLE. It remains to be determined how risk profiles such as this can be utilized in clinical practice to aid in selection of preventative treatments for patients with SLE at high risk for atherosclerosis.

The possibility of coronary artery disease must be considered in any SLE patient who is seen with chest pain and/or shortness of breath, and one should have a low threshold for a functional evaluation with a cardiac stress test. Cardiac catheterization might also be necessary for diagnosis and therapeutic intervention. It is important to evaluate these patients for the presence of anti-phospholipid antibodies because coronary artery thrombosis may be a manifestation of the anti-phospholipid antibody syndrome. Evaluation for and treatment of modifiable risk factors such as obesity, smoking, hypertension, and hyperlipidemia are important in mitigating the development and progression of atherosclerotic disease.

## Neuropsychiatric Involvement

### General Considerations

Neuropsychiatric lupus (NPSLE) consists of a broad range of neurologic and psychiatric manifestations that can involve any aspect of the central or peripheral nervous system. With the intention of improving the terminology and classification of NPSLE, an ACR subcommittee categorized NPSLE into 19 distinct syndromes encompassing the central and peripheral nervous systems (CNS and PNS)[97] (Table 80-6). The extent of this classification system underscores the complexity of NPSLE. CNS disorders range from diffuse processes such as acute confusional state, headache, psychosis, and mood disorders, to more focal processes such as seizures, myelopathy, and chorea. It is notable that the ACR classification system has removed the cryptic term "lupus cerebritis" from the vernacular. Although the ACR case definitions are very helpful in providing a framework in which to study NPSLE, accurate attribution of neuropsychiatric manifestations remains challenging. It is often difficult to distinguish whether neuropsychiatric symptoms are to the result of active SLE or other factors such as infection, metabolic abnormalities, severe hypertension, adverse effects of medications, or independent neurologic or psychiatric problems. No laboratory or imaging study is sufficiently sensitive or specific to confirm the diagnosis of neuropsychiatric SLE. Instead, the diagnosis is made on a case-by-case basis and is based on a thorough clinical evaluation that is corroborated by findings (or lack thereof) on brain imaging, serologic testing, lumbar puncture, and neuropsychiatric assessment. Correct attribution to SLE or to alternative causes is essential in ensuring that appropriate treatment is administered.

**TABLE 80-6** American College of Rheumatology Classification of Neuropsychiatric Syndromes in Systemic Lupus Erythematosus

| Central Nervous System | Peripheral Nervous System |
|---|---|
| Aseptic meningitis | Guillain-Barré syndrome |
| Cerebrovascular disease | Autonomic disorder |
| Demyelinating syndrome | Mononeuropathy, single/multiplex |
| Headache | Myasthenia gravis |
| Movement disorder | Cranial neuropathy |
| Myelopathy | Plexopathy |
| Seizure | Polyneuropathy |
| Acute confusional state | |
| Anxiety disorder | |
| Cognitive dysfunction | |
| Mood disorder | |
| Psychosis | |

See reference 97.

### Pathogenesis

Multiple pathogenic mechanisms are undoubtedly involved in the various NPSLE syndromes, but in most cases, the precise pathogenesis is unknown. In addition, mechanisms are likely to vary depending upon whether the manifestation involves the CNS or the PNS. The underlying mechanisms of CNS manifestations can be grouped into two broad categories: primary injury to the vasculature and primary injury to the brain parenchyma. A combination of the two categories can also occur. Vascular injury can take several forms, including (1) damage to both large and small vessels via thromboembolic events, often as a consequence of anti-phospholipid antibodies; (2) a bland vasculopathy of small vessels characterized by vascular hyalinization,

perivascular inflammation, and endothelial proliferation; and (3) atherosclerotic lesions. In contrast, true vasculitis of cerebral blood vessels with an inflammatory infiltrate within the vessel walls is exceedingly rare. Primary injury to brain parenchyma can occur through the action of autoantibodies, cytokines, chemokines, and infiltrating cells, often in the setting of a breached blood-brain barrier. Several autoantibody subtypes are believed to play a role in some CNS manifestations of SLE. In addition to their well-established role in thrombotic events, leading to cerebral ischemia, anti-phospholipid antibodies might bind directly to neuronal cells, leading to neuronal cell damage. Anti-phospholipid antibodies have been associated with diffuse cognitive impairment, even in the absence of an ischemic event. Antiribosomal P antibodies have been associated with the CNS manifestations of psychosis, depression, and mood disorders in some studies. Although antiribosomal P antibodies are detected in only approximately 14% of patients with SLE, the specificity of these antibodies for SLE is thought to be greater than 90%.[98] Finally, a subset of anti-DNA antibodies that cross-reacts with the *N*-methyl-D-aspartate receptor (NMDAR) might be involved in cognitive dysfunction in SLE. Binding of these antibodies to neuronal cells leads to apoptotic, non-inflammatory cell death. Histopathologic studies on post-mortem human brain tissue have demonstrated multiple CNS abnormalities, including large and small multifocal infarctions, hemorrhage, bland small vessel vasculopathy, cortical atrophy, brain edema, and demyelination.

### Approach to Diagnosis

The diagnostic evaluation of a patient with potential NPSLE is tailored to the presenting neuropsychiatric manifestation. Depending on the manifestation, consultation with a neurologist and/or a psychiatrist is advised. The most important first step is exclusion of an alternative explanation for the neuropsychiatric symptoms/signs. Lumbar puncture with cerebrospinal fluid (CSF) examination is useful for exclusion of an infectious origin. Mild lymphocytic pleocytosis and elevated CSF protein are sometimes observed in CNS lupus but are not uniformly present. CSF findings are not sensitive or specific enough to confirm a diagnosis of neuropsychiatric SLE. It is important to recognize that infection is a common cause of CNS symptoms in patients with SLE who are hospitalized with altered mental status,[99] and must be rigorously ruled out. Progressive multifocal leukoencephalopathy (PML) is a rare infection that also merits consideration in a patient with SLE who is seen with symptoms of CNS dysfunction. PML occurs more frequently in patients with SLE than in patients with other rheumatic diseases, even in the absence of significant immunosuppressive therapy.[100,101] Thus, in an SLE patient with unexplained new neurologic symptoms, polymerase chain reaction (PCR) of the CSF for the presence of JC virus should be performed. In situations in which PCR is negative, a brain biopsy might be needed to confirm the diagnosis. Electromyography and nerve conduction studies are important in the setting of suspected peripheral neuropathy. Electroencephalogram (EEG) is necessary in the evaluation of seizure. Neuropsychological testing may be helpful in the setting of suspected cognitive dysfunction.

MRI is the preferred imaging modality in patients with suspected NPSLE. The most commonly noted abnormalities are small, hyperintense, T2-weighted, focal white matter lesions located in the periventricular and subcortical white matter of the frontoparietal regions of the brain. However, these findings are nonspecific and can be observed in other disease processes such as atherosclerotic vascular disease and multiple sclerosis. Other common MRI findings include cortical atrophy, ventricular dilation, cerebral edema, diffuse white matter abnormalities, gray matter abnormalities, infarction, leukoencephalopathy, and hemorrhage.[102] MRI is especially useful in detecting the presence of infarcts, hemorrhage, and myelopathy, and sometimes can help to exclude infectious conditions such as brain abscess.[102] MRI is most likely to show abnormalities in the setting of focal neurologic deficits, seizures, chronic cognitive dysfunction, and anti-phospholipid antibody–mediated disease and is less likely to show abnormalities in the setting of headache, acute confusional state, and psychiatric syndromes. A study of 74 patients with new-onset neuropsychiatric lupus found normal MRI results in 42% of patients.[103] Given the wide variety of potential MRI findings, it is critical that MRI findings (or lack thereof) are interpreted in the context of the individual patient case.

Estimates of the prevalence of NPSLE have varied widely in the literature, largely depending on the extent to which headache and/or mild cognitive abnormalities have been included in the analysis. However, the preponderance of these studies suggests that CNS manifestations predominate versus PNS manifestations. Several of the more common syndromes and associated differential diagnoses are described in the following paragraphs.

### Selected Neuropsychiatric Lupus Syndromes

Headaches are reported in more than 50% of patients with SLE, but attribution of the headache to SLE is extremely difficult. Both migrainous and tension-type headaches have been described. One meta-analysis[104] determined that the prevalence of primary headache syndromes was not different between SLE and control patients, and that headache was not related to SLE disease activity. The evaluation of headache in an SLE patient should be similar to that in a non-SLE patient and should be directed by the presence or absence of worrisome features such as fever, meningismus, altered mental status, and focal neurologic signs.

Cognitive dysfunction, manifested primarily by deficits in thinking, memory, and concentration, is increasingly recognized in patients with SLE. Some have estimated a prevalence of as much as 80%, although serious cognitive impairment is much less common. Some studies suggest that cognitive dysfunction may be associated with the presence of anti-phospholipid antibodies, but a causal relationship has not been definitively established. Documentation of the presence and extent of cognitive dysfunction via neuropsychiatric testing can be useful in establishing a baseline in a particular patient that can be followed during a period of time, particularly when a therapeutic intervention is under consideration.

Psychiatric disorders such as psychosis, depression, and anxiety can occur in SLE, and consultation with a psychiatrist is highly recommended in the evaluation of patients

with these symptoms. A patient with SLE who is seen with psychosis represents a distinct diagnostic and therapeutic challenge. The differential diagnosis includes CNS infection, primary schizophrenia, systemic metabolic abnormalities, and psychosis occurring as a side effect of glucocorticoid therapy or illicit drugs. Steroid-induced psychosis is dose dependent and typically occurs within the first 2 weeks of treatment initiation.

Although rare, demyelinating syndromes such as optic neuritis and myelitis can occur as part of the spectrum of NPSLE. Optic neuritis is characterized by pain with eye movement, central visual field loss, and a waxing and waning course.[105] Optic neuritis should be differentiated from ischemic optic neuropathy, which typically presents with acute, painless loss of vision and lack of significant improvement in vision with time.[106] Myelitis is characterized by the onset of bilateral lower extremity paresthesia, numbness, and weakness that can rapidly progress to involve the upper limbs and the muscles of respiration. A sensory level is usually noted, and autonomic involvement of the bowel and bladder is common. Bandlike pain or discomfort around the abdomen is a characteristic symptom. It is important to differentiate myelitis from other causes of myelopathy, including infection, structural spinal cord abnormalities, and vascular insult to the spinal cord. Spinal cord MRI is the critical first test. CSF examination is important to rule out infection.

The combination of optic neuritis and myelitis presents a special clinical challenge because this combination of features can occur in the setting of SLE, multiple sclerosis (MS), or neuromyelitis optica (NMO).[107] Complicating matters, the clinical presentation of anti-phospholipid antibody syndrome can mimic demyelinating disease. A thorough clinical history, MRI, CSF analysis, and serologic testing are helpful in distinguishing these entities. NPSLE and MS can have identical white matter lesions on brain MRI. Spinal cord lesions may differ in that MS spinal cord lesions usually span an area measuring less than two spinal segments, but SLE lesions are often longitudinally extensive with involvement of more than three spinal cord segments. Although oligoclonal bands may be present in the CSF of both SLE and MS patients, the absence of oligoclonal bands and the presence of a pleocytosis significantly lessen the likelihood of MS. Although a positive ANA has been described in as many as 27% of patients with MS,[108] more specific subserologies such as anti-dsDNA and anti-Sm favor the diagnosis of SLE. NMO is an autoimmune disease of the CNS characterized by episodes of optic neuritis, myelitis, or both. In the majority of patients, NMO is a relapsing disease that occurs unpredictably.[109] The diagnosis of NMO includes the presence of optic neuritis and myelitis in conjunction with two of the following three supportive criteria: presence of the NMO IgG antibody (antibody to aquaporin 4), absence of brain lesions diagnostic of MS, and longitudinally extensive myelitis on MRI.[109] Patients with the NMO antibody with some features of the disease who do not fulfill all of these diagnostic criteria are sometimes described as having "NMO spectrum disorder." The NMO antibody is present in as many as 80% of patients with NMO and has a specificity of greater than 90% for the diagnosis of NMO. SLE and NMO may occur concurrently in a given patient.

Patients with SLE are at increased risk of stroke; ischemic stroke is more common than intracerebral hemorrhage.[110] Studies have demonstrated an association between the presence of anti-phospholipid antibodies (aPL) and/or valvular heart disease and the risk of stroke.[81] Brain MRI is a critical test in the diagnosis of ischemic or hemorrhagic stroke, and magnetic resonance angiography (MRA) can detect vessel aneurysms. Echocardiography, carotid ultrasound, and electrocardiography are important diagnostic tests in the setting of suspected thromboembolic cerebrovascular disease.

A potential mimic of CNS lupus is posterior reversible encephalopathy syndrome (PRES). This syndrome was first described in a case series of 15 patients in 1996.[111] Two of the original 15 patients were known to have SLE. PRES is a clinical-radiologic syndrome characterized by headache, decreased consciousness, visual changes, and seizures in the context of posterior cerebral white matter edema. It has been associated with a variety of conditions, including hypertension, eclampsia, renal disease, immunosuppressive therapies, post–solid organ transplantation, and autoimmune disease. When PRES occurs in the setting of active SLE, it is unclear whether PRES is a manifestation of CNS lupus, or whether it is a complication of a concomitant condition such as immunosuppressive therapy, renal disease, or hypertension.

SLE is also associated with peripheral neuropathy. One large study of more than 2000 patients with SLE demonstrated a 6% prevalence of peripheral neuropathy, with 67% of the neuropathies attributable to SLE.[112] The most common type of neuropathy was a sensory or sensorimotor axonal polyneuropathy. Of the patients, 17% had biopsy-proven small-fiber neuropathy. This is an increasingly recognized subtype of peripheral neuropathy that is not included in the 1999 ACR case definitions for NPSLE. Small-fiber neuropathies affect unmyelinated C fibers, with symptoms of burning pain and paresthesias. Nerve conduction studies are normal. The diagnosis is confirmed by a skin biopsy that demonstrates decreased intraepidermal nerve fiber density. A devastating, large-fiber vasculitic neuropathy leading to mononeuritis multiplex can also develop in patients with SLE. Autonomic neuropathies, cranial neuropathies, inflammatory demyelinating polyneuropathies, and abnormalities of the neuromuscular junction resembling myasthenia gravis have also been described. When encountering a SLE patient with peripheral neuropathy, it is essential for the physician to consider and rule out non-SLE etiologies such as infections (e.g., HIV, syphilis, Lyme disease, leprosy), malignancy, endocrine disorders (e.g., diabetes mellitus, hypothyroidism), toxins (e.g., alcohol, heavy metals), vitamin deficiency (e.g., vitamins $B_{12}$, $B_6$), and drugs (e.g., hydroxychloroquine, colchicine, vitamin $B_6$ excess).

## Gastrointestinal Involvement

SLE can involve any part of the gastrointestinal system. Dysphagia is noted in as many as 13% of patients, and manometric studies have detected abnormalities of esophageal motility.[113] Decreased peristalsis is most commonly observed in the upper one-third of the esophagus. In contrast to scleroderma, involvement of the lower esophageal

sphincter is rare in SLE.[114] A variety of potential pathogenic mechanisms have been described, including muscle atrophy, inflammation of esophageal muscle, and ischemic or vasculitic damage to the Auerbach plexus.

Abdominal pain, sometimes accompanied by nausea and vomiting, has been reported in as many as 40% of patients with SLE and can be to the result of SLE-related causes, medication side effects, and non–SLE-related causes such as infection.[115] When evaluating an SLE patient with abdominal pain, it is critical for the physician to rule out non-SLE conditions. It is important to note that when patients are treated with glucocorticoids and/or other immunosuppressives, clinical signs of an acute condition in the abdomen, such as rebound tenderness, can be masked. Thus delay in diagnosis is common. SLE-related causes of abdominal pain may include peritonitis, pancreatitis, mesenteric vasculitis, and intestinal pseudo-obstruction. Although autopsy studies have revealed evidence of peritoneal inflammation in as many as 72% of patients with SLE,[115] the presence of ascites is rare. If a patient with SLE is seen with abdominal pain and ascites, paracentesis is warranted to rule out infection. Peritonitis can also occur in the setting of mesenteric ischemia, bowel infarction, and pancreatitis. Thus abdominal imaging is an important part of the initial evaluation.

Pancreatitis caused by SLE is uncommon and usually is associated with active SLE in other organs. When considering the possible diagnosis of pancreatitis, it is important to note that elevated serum amylase may be misleading—it has been observed in patients with SLE in the absence of pancreatitis.[116] Although glucocorticoids and azathioprine have been associated with the development of pancreatitis in nonpatients with SLE, these medications do not seem to play a major role in the development of pancreatitis in patients with SLE.[117] It is important to rule out non-SLE causes of pancreatitis, such as biliary disease, alcohol consumption, and hypertriglyceridemia.

Mesenteric vasculitis is a very rare manifestation of SLE. Patients with this condition can be seen with a range of symptoms, from cramping, bloating, and anorexia, to an acute condition in the abdomen with diarrhea and gastrointestinal hemorrhage. Accurate diagnosis and prompt treatment are essential to prevent the potential catastrophic complications of necrotic bowel, perforation, and sepsis. Abdominal radiography may show distention of bowel loops, thickening and thumbprinting of the bowel wall, and/or free air in the abdomen. Ultrasonography may be useful in demonstrating bowel wall edema and thickening. Abdominal CT is thought to be the most useful imaging modality for the early diagnosis of mesenteric ischemia and can demonstrate prominence of mesenteric vessels with a palisade pattern supplying dilated bowel loops, ascites, and bowel wall thickening with a double-halo sign.[118] Gastroscopy and colonoscopy can sometimes reveal findings of ischemia and ulceration. Because lupus mesenteric vasculitis typically involves the small vessels (arterioles and venules) of the bowel submucosa, mesenteric angiography is usually nondiagnostic. However, angiography can be helpful in ruling out larger vessel causes of mesenteric ischemia, such as polyarteritis nodosa, atherosclerotic disease, or thrombosis resulting from anti-phospholipid antibody disease.

Liver test abnormalities have been described in as many as 60% of patients with SLE at some point during the course of their illness, but clinically significant liver disease is rarely a direct manifestation of SLE.[119] For this reason, the presence of liver disease should prompt a search for non-SLE causes, including medications such as nonsteroidal anti-inflammatory drugs, methotrexate, and azathioprine. Abnormal liver enzymes may be caused by hepatic steatosis as a result of obesity, concomitant diabetes mellitus, or treatment with corticosteroids. Infections such as viral hepatitis, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) must also be excluded. Once medications and infections have been ruled out as possible culprits, persistent liver test abnormalities should prompt an investigation with an abdominal ultrasound and possibly a liver biopsy. Lupus hepatitis is believed to be a distinct entity from autoimmune hepatitis.[120] Lupus hepatitis is typically characterized by the presence of lobular inflammation with a paucity of lymphoid infiltrates. These findings contrast with those of autoimmune hepatitis, in which periportal (interface) inflammation and dense lymphoid infiltrates predominate. Although ANA is frequently seen in both disorders, anti–smooth muscle and anti-LKM antibodies are more frequently noted in autoimmune hepatitis than in lupus hepatitis. Rarely, nodular regenerative hyperplasia complicates SLE. This disorder causes diffuse nodularity of the liver with little fibrosis and can result in portal hypertension. Nodular regenerative hyperplasia is also associated with the presence of anti-phospholipid antibodies in some patients.[121] Vascular disorders of the liver such as Budd-Chiari syndrome, hepatic veno-occlusive disease, and hepatic infarction have been described, especially in the setting of anti-phospholipid antibodies.

Other rare gastrointestinal manifestations of SLE include intestinal pseudo-obstruction and protein-losing enteropathy. Intestinal pseudo-obstruction is characterized by decreased intestinal motility caused by dysfunction of the visceral smooth muscle or enteric nervous system.[122] The small bowel is more frequently involved than the large bowel. Presenting symptoms include abdominal pain, nausea, vomiting, and abdominal distention. Patients with protein-losing enteropathy experience abdominal pain, profound pitting edema, and diarrhea in the context of hypoalbuminemia. Other causes of hypoalbuminemia, such as nephrotic syndrome from renal disease, must be excluded.

## Occular Involvement

SLE can affect the eye in a variety of ways. The most common ocular manifestation is keratoconjunctivitis sicca (KCS), which can occur in the presence or absence of secondary Sjögren's syndrome.[123] Retinal abnormalities can be detected on ophthalmoscopic examination as retinal hemorrhages, vasculitic-appearing lesions, cotton wool spots, and hard exudates. SLE retinopathy is believed to be an immune complex–mediated vasculopathy and/or the result of microthrombotic events. The presence of retinal abnormalities has been shown to correlate with lupus nephritis, CNS lupus, and the presence of anti-phospholipid antibodies.[124] Episcleritis and scleritis can occur in SLE. Uveitis is extremely rare. Discoid lupus can involve the lower eyelid and conjunctiva. Glucocorticoids and antimalarial agents, two medications commonly used for the treatment of SLE, can affect the eye. Posterior subcapsular cataracts, elevated

intraocular pressure, and central serous maculopathy are well-described complications of glucocorticoid therapy, and maculopathy is a rare but serious complication of the use of hydroxychloroquine and chloroquine. The risk of retinal toxicity is low if the daily dose of chloroquine is kept below 3 mg/kg of ideal body weight and the daily dose of hydroxychloroquine is kept at or below 6.5 mg/kg of ideal body weight.

## Hematologic Involvement

Hematologic involvement is common in SLE; all three blood cell lines can be affected. When evaluating a patient with the hematologic abnormalities as described later, it is always necessary to consider the potential of myelosuppression from medications such as methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide. In addition, glucocorticoids are a common cause of lymphopenia and leukocytosis secondary to neutrophilia.

### Anemia

Anemia of chronic disease (ACD) is the most common anemia in SLE. It is a normochromic, normocytic anemia characterized by the presence of low serum iron, low transferrin, and normal to increased serum ferritin. ACD can coexist with anemias resulting from other processes. Autoimmune hemolytic anemia (AIHA) should be suspected in the setting of the following laboratory abnormalities: increased serum unconjugated bilirubin, increased lactate dehydrogenase (LDH), increased reticulocyte count, and reduced serum haptoglobin. The direct Coombs test is typically positive and usually is mediated by warm-reacting IgG anti-erythrocyte antibodies. The peripheral blood smear demonstrates spherocytosis. Some reports have suggested an association between AIHA and the presence of anticardiolipin antibodies.[125,126] A positive direct Coombs test can occur without hemolysis. AIHA may be the presenting manifestation of SLE, or it may predate full-blown SLE by many years.

Microangiopathic hemolytic anemia (MAHA), characterized by the presence of schistocytes on peripheral blood smear, should prompt consideration of thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP-HUS). TTP is a syndrome consisting of MAHA, thrombocytopenia, fever, neurologic symptoms, and renal involvement, and may be associated with SLE. Because MAHA, thrombocytopenia, neurologic symptoms, and renal involvement can also occur in catastrophic anti-phospholipid antibody syndrome (CAPS), anti-phospholipid antibodies should always be measured as part of the evaluation. Blood loss, renal insufficiency, pure red cell aplasia, and medication-induced myelotoxicity are additional potential causes of anemia in patients with SLE.

### Leukopenia

Leukopenia occurs in approximately 50% of patients with SLE and can occur secondary to lymphopenia and/or neutropenia. One study of 158 newly diagnosed, clinically active patients with SLE demonstrated that 75% of patients had lymphocyte counts lower than 1500 cells/μL, and that lymphopenia eventually developed in 93% of patients.[127] The presence of lymphocytoxic antibodies in some patients with SLE correlates with lymphopenia and with disease exacerbation.[128] Lymphopenia may be a side effect of treatment with glucocorticoids or other immunosuppressive agents. Neutropenia resulting from SLE can result from immune-mediated destruction or marrow suppression.

### Thrombocytopenia

Mild thrombocytopenia is noted in as many as 50% of patients with SLE, but severe thrombocytopenia can also occur. Thrombocytopenia can be the result of immune-mediated platelet destruction similar to immune thrombocytopenic purpura (ITP). The platelet IIb/IIIa antigen is the primary target. Thrombocytopenia can also be caused by a consumptive process such as TTP or splenomegaly. Antithrombopoietin antibodies have been found in the sera of some patients with SLE and have been correlated with lower platelet counts.[129] Chronic, low-level thrombocytopenia is a characteristic feature of the anti-phospholipid antibody syndrome. Similar to AIHA, isolated ITP may predate the development of complete SLE by several years.[130]

## Lymphadenopathy and Splenomegaly

Lymphadenopathy commonly occurs in association with active SLE and is characterized by the presence of enlarged, soft, nontender lymph nodes. Lymphadenopathy can be focal or generalized; the cervical, axillary, and inguinal regions are typically involved. Lymph node histopathology demonstrates reactive hyperplasia and varying degrees of coagulative necrosis. The presence of hematoxylin bodies is specific for SLE. Histologic features of Castleman's disease have been reported.[131] The differential diagnosis of lymphadenopathy in a patient with SLE includes infection and/or a lymphoproliferative process; lymph node biopsy is sometimes required for diagnosis. Splenomegaly can be observed in patients with SLE and may be associated with hepatomegaly. Histopathologic studies demonstrate periarterial fibrosis (onion-skin lesions). Splenic atrophy and functional asplenism have also been reported.[132]

# DIAGNOSIS

Establishing the diagnosis of SLE can be challenging because of its heterogeneous disease manifestations and waxing and waning clinical course. No clinical manifestation or laboratory test can serve as a definitive diagnostic test. Instead, SLE is diagnosed on the basis of a constellation of characteristic symptoms, signs, and laboratory findings in the appropriate clinical context. Although the ACR classification criteria (see Table 80-1) cannot always be relied upon for diagnostic purposes in individual patients, they serve as useful reminders of the wide variety of clinical features that can be seen in SLE.

## Serologic Tests

Serologic tests play an important role in the diagnosis of SLE. SLE is the prototypic systemic humoral autoimmune disease. As such, it is characterized by production of a

**TABLE 80-7** Autoantibodies and Clinical Significance in Systemic Lupus Erythematosus

| Autoantibody | Prevalence in SLE (%) | Clinical Associations |
|---|---|---|
| **Anti-nuclear Antibody** | | |
| Anti-dsDNA | 60 | 95% specificity for SLE; fluctuates with disease activity; associated with glomerulonephritis |
| Anti-Smith | 20-30 | 99% specificity for SLE; associated with anti-U1RNP antibodies |
| Anti-U1RNP | 30 | Antibody associated with mixed connective tissue disease and lower frequency of glomerulonephritis |
| Anti-Ro/SS-A | 30 | Associated with Sjögren's syndrome, photosensitivity, SCLE, neonatal lupus, congenital heart block |
| Anti-La/SS-B | 20 | Associated with Sjögren's syndrome, SCLE, neonatal lupus, congenital heart block, anti-Ro/SS-A |
| Anti-histone | 70 | Also associated with drug-induced lupus |
| Anti-phospholipid | 30 | Associated with arterial and venous thrombosis, pregnancy morbidity |

SCLE, Subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus.

wide variety of autoantibodies, which often provide important diagnostic information[133] (Table 80-7). Studies using antigen array technologies have demonstrated the presence of over 100 different autoantibodies in patients with SLE. The hallmark serologic feature is the presence of ANAs, as reflected by a positive ANA test. The gold standard method for detecting ANA is indirect immunofluorescence by using a human epithelial cell tumor line (HEp2 cell line). With this method, the ANA test is highly sensitive; it is positive in more than 95% of people with SLE. Because of a desire for automation and cost savings, some laboratories are utilizing the enzyme-linked immunosorbent assay (ELISA) or multiplex assays as the method of testing for ANA. However, the ELISA and multiplex methods are less accurate than the immunofluorescence method, resulting in a higher false-negative rate. Positive ANA tests also occur in many other autoimmune diseases, including RA, scleroderma, polymyositis, and autoimmune thyroiditis, among others. ANAs are also detectable in low titers (<1 : 80) in many people without autoimmune disease, especially in the elderly.[134] Therefore a positive test is not sufficient to establish the diagnosis of SLE. On the other hand, a negative test can be helpful in ruling out SLE. Although ANA$^-$ SLE has been reported, it is very rare with the immunofluorescence method of testing. In those rare instances, other tests (e.g., anti-Ro/SS-A) usually confirm the presence of lupus-associated autoantibodies.[135]

Once it has been established that ANAs are present, it is important to determine which particular nuclear antigens may be the target of the autoantibodies because some of these antigen-specific responses provide great diagnostic specificity. The most important of these tests is the test for anti-dsDNA antibodies. Anti-dsDNA antibodies are present in no more than 50% to 60% of patients with SLE, so their absence does not exclude the possibility of SLE. However, the presence of these antibodies is highly specific for SLE and therefore can be very helpful in establishing a definitive diagnosis. Similarly, antibodies to the Sm antigen have great specificity for SLE, but these antibodies are present in even fewer patients with SLE (~30%). The Sm antigen is a component of extractable nuclear antigens (ENAs), a term that refers to a heterogeneous mixture of non-DNA nuclear antigens that can be "extracted" from cells in the laboratory. These antigens are primarily ribonucleoproteins that can be divided into two major subsets based on their susceptibility to digestion by ribonuclease. The ribonuclease-sensitive antigens are designated RNP. Ribonuclease-resistant antigens are designated Sm (because these antibodies were first detected in a patient named Smith). Unlike anti-Sm, anti-RNP is not specific for SLE. However, high titers of anti-RNP antibodies can be helpful in supporting the diagnosis of MCTD.[136]

Numerous other autoantibodies can be found in patients with SLE. Antibodies to cytoplasmic antigens, such as Ro and La (SS-A and SS-B), can be found in some patients with SLE. Although these autoantibodies lack both sensitivity and specificity for SLE, they sometimes are associated with distinct clinical syndromes. The best example of such a relationship involves the presence of anti-Ro antibodies in more than 90% of cases of neonatal lupus.[137,138] Anti-Ro antibodies are also seen with increased frequency in patients with SCLE.[139] Other autoantibodies may be directed against cell surface molecules or against circulating proteins. For example, antibodies to blood components can be responsible for hemolytic anemia, neutropenia, or thrombocytopenia, and antibodies to phospholipids and phospholipid binding proteins can be detected in some patients with SLE with or without anti-phospholipid syndrome (see Chapter 82). It should be noted that rheumatoid factor (anti-IgG) can be found in 15% to 20% of people with SLE, whether or not joint disease is present.[140] ACPA can also be present.

Complement consumption arising from immune complex disease may lead to hypocomplementemia in patients with SLE.[141,142] Because hypocomplementemia is rare in other diseases, its presence in a patient with SLE can provide valuable supportive evidence for the diagnosis. Moreover, because hypocomplementemia most likely reflects complement activation by immune complexes, its presence is often a sign of active disease. However, hereditary complement deficiencies may be found in patients with SLE (C1q, C2, C4), so absence of a particular complement component does not always reflect consumption.[143–145] For this reason, it is often necessary to measure more than one complement component (e.g., C3 and C4) before concluding that hypocomplementemia is to the result of active disease.

The utility of serologic tests in assessing disease activity and predicting disease flares remains a topic of controversy. In the absence of a hereditary complement deficiency, hypocomplementemia is a reliable indicator that the disease is active, but normal complement levels do not rule out active

disease. Titers of anti-dsDNA antibodies correlate with disease activity in some patients, but not in others. One recent study attempted to resolve the long-standing debate about the prognostic value of changes in lupus serology.[146] In this study, patients with clinically quiescent lupus underwent monthly monitoring for levels of anti-dsDNA, C3a, C3, C4, and CH50 to identify patients with serologically active, clinically quiescent disease. These patients were then randomly assigned to treatment with corticosteroids or placebo to determine whether treatment of serologically active disease could prevent impending clinical flares. The results were equivocal. Some patients with serologically active disease flared, and some flares were apparently prevented. However, in most control subjects, serologic deterioration was not followed by a clinical flare, and most of the flares that occurred in the original patient population that had been monitored were not preceded by serologic deterioration. Thus there remains no substitute for knowledge of a particular patient's disease pattern or whether there is an association between clinical and serologic manifestations in that patient.

## DIFFERENTIAL DIAGNOSIS

Because of the involvement of multiple organ systems and the lack of specificity of symptoms and/or signs, many systemic diseases can mimic SLE. Thus, before a diagnosis of SLE is established, a comprehensive search for infectious, malignant, and other autoimmune diseases must be undertaken.

Several viral infections can produce symptoms and signs that are present in SLE. In addition, many viral illnesses are associated with the production of autoantibodies. A careful patient history with serologic testing for the potential pathogen should help to secure the correct diagnosis. Patients with classic parvovirus B19 are seen with fever, rash, symmetric inflammatory polyarthritis, and cytopenias. Furthermore, the presence of ANA, anti-dsDNA, and hypocomplementemia has been observed in a few cases. Cytomegalovirus and EBV can mimic SLE in that patients often are seen with fatigue, cytopenias, abdominal pain, and liver test abnormalities. Patients with acute HIV infection typically are seen with fever, diffuse lymphadenopathy, and oral ulcers. Inflammatory arthritis and positive autoantibodies can develop in patients with hepatitis B and C.

Malignancy, particularly non-Hodgkin's lymphoma, can manifest with constitutional symptoms, joint pain, cytopenias (including autoimmune hemolytic anemia), lymphadenopathy, rash, and a positive ANA. Physicians must be particularly alert to the possibility of malignancy in older patients seen with new lupus-like syndromes. It is important to ensure that patients undergo appropriate malignancy screening tests.

Other autoimmune diseases such as RA, dermatomyositis, and Still's disease often share similar clinical features with SLE. Differentiating between these disorders might be difficult in early phases of the disease. Patients with RA and SLE may develop a symmetric inflammatory arthritis with a predilection for the wrists and small joints of the hands. ANA and rheumatoid factor (RF) may be elevated in both disorders, although ACPA suggests RA, and anti-dsDNA or anti-Sm suggests SLE. The photosensitive, erythematous rashes of dermatomyositis and SLE can appear clinically and histopathologically identical. A careful patient history and supporting serologies will aid in making the correct diagnosis. Physicians must also consider MCTD when evaluating a patient for possible SLE. MCTD is a syndrome characterized by a high-titer anti-RNP antibody in conjunction with clinical features that are often present in SLE, scleroderma, and/or polymyositis. Patients frequently are seen with puffy, swollen hands and Raynaud's phenomenon. In contrast to SLE, an erosive arthritis that looks very similar to RA can develop in patients with MCTD.

Careful evaluation for drug-induced lupus should be undertaken in every new patient in whom the diagnosis of SLE is suspected. This is especially important in an older person who is seen with a lupus-like syndrome. Arthralgia, myalgia, fever, and serositis are common manifestations. A wide variety of drugs have been implicated in the development of drug-induced lupus; minocycline, procainamide, hydralazine, isoniazid, IFN-α, and TNF inhibitors are well-known culprits. Hydrochlorothiazide is associated with SCLE. All of these drugs may cause a positive ANA. Minocycline is occasionally associated with anti-dsDNA antibodies and perinuclear-staining anti-neutrophil cytoplasmic antibodies (P-ANCA), and TNF inhibitors can cause positive anti-dsDNA antibodies. Anti-histone antibodies are present in more than 95% of cases of drug-induced lupus, with the exception of those cases caused by minocycline. However, anti-histone antibodies cannot be used to confirm a diagnosis of drug-induced lupus because up to 80% of idiopathic patients with SLE will also produce anti-histone antibodies.

## NEONATAL LUPUS

Neonatal lupus is a passively acquired autoimmune disease of neonates that results from transplacental passage of maternal anti-SS-A and/or anti-SS-B antibodies.[132] It can occur in mothers with SLE, in those with Sjögren's syndrome, or in patients in whom an autoimmune disease has not been diagnosed. Neonatal lupus can involve multiple organ systems, including heart, skin, liver, and the hematologic system; the most severe complications are congenital complete heart block and cardiomyopathy.[147,148] The term *neonatal lupus* stems from early observations that the skin lesions in affected newborns were similar to the lesions of SCLE.

Congenital complete heart block is associated with a neonatal mortality rate as high as 20%, and most patients will eventually require a permanent pacemaker. This complication occurs in as many as 2% of babies born to mothers who are positive for anti-Ro/SS-A and/or anti-LA/SS-B antibodies. Thus maternal antibodies are essential but not sufficient to cause disease. Once a woman has given birth to a baby with complete heart block, the risk for recurrence in a subsequent pregnancy is approximately 17%. Once a woman has given birth to a baby with cutaneous features of neonatal lupus (without heart block), the risk for heart block in a subsequent pregnancy is 18%.[149] Evidence from in vitro studies suggests that during fetal development, fetal cardiocytes undergo apoptosis that results in expression of Ro/SS-A and La/SS-B on the cell surface. Binding of anti-Ro/SS-A and/or anti-La/SS-B to fetal cardiocytes leads

to inflammatory injury and subsequently to fibrosis of the atrioventricular (AV) node and surrounding tissue. The sinoatrial (SA) node may also be involved. Prospective studies have shown that the vulnerable period for the fetal heart is between 16 and 24 weeks of gestation. Thus it is recommended that mothers with anti-Ro/SS-A and/or anti-La/SS-B antibodies undergo monitoring with fetal echocardiography beginning at 16 weeks of gestation. The hope has been that detection of early stages of heart block (first-degree and second-degree block) might allow for treatment that would prevent progression to third-degree heart block. Currently, the treatment of choice is maternal administration of a fluorinated glucocorticoid such as dexamethasone. Fluorinated glucocorticoids are preferred because of their ability to cross the placenta and enter the fetal circulation. However, treatment of incomplete fetal heart block remains controversial because the benefits have not been clearly delineated, and glucocorticoids have been associated with several fetal side effects such as intrauterine growth retardation, oligohydramnios, and adrenal suppression. Complete heart block is irreversible even with treatment, and first- or second-degree heart block may or may not reverse with treatment. Complicating matters, complete heart block can occur in the absence of preceding first- or second-degree block. In addition to conduction blocks, structural cardiac abnormalities have been observed in the setting of neonatal lupus, including, but not limited to, patent ductus arteriosus, ventricular septal defect, atrial septal defect, and patent foramen ovale. Myocarditis and pericarditis have also been described.

Rash, a common manifestation of neonatal lupus, consists of erythematous, annular lesions that resemble the annular subtype of SCLE. The rash typically occurs on the scalp, face, trunk, and extremities with a predilection for the periorbital area; it often develops after exposure of the newborn to ultraviolet light. Lesions typically occur within the first 4 to 6 weeks of life but may be present at birth. The rash is self-limiting and does not necessitate treatment. Lesions tend to resolve by 6 months of age, at which time maternal anti-Ro/SS-A and/or anti-La/SS-B antibodies are no longer present in the baby's circulation. Lesions develop in approximately 25% of babies born to anti-SSA/SS-B positive mothers. Less common manifestations of neonatal lupus include hepatic, hematologic, and neurologic involvement.[150] Hepatic manifestations include asymptomatic elevation of liver function tests, hepatitis, hepatomegaly, cholestasis, and cirrhosis. Hematologic manifestations include thrombocytopenia, autoimmune hemolytic anemia, and leukopenia. Neurologic complications, including myelopathy, seizures, and aseptic meningitis, have been reported.


Full references for this chapter can be found on ExpertConsult.com.

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