Manifestations of Systemic Lupus Erythematosus

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ABSTRACT
Systemic lupus erythematosus (SLE) is a chronic, multifaceted autoimmune inflammatory disease that can affect any part of the body. SLE is a disease of unknown aetiology with a variety of presenting features and manifestations. Interest in the disease has been stimulated in recent years, and improved methods of diagnosis have resulted in a significant increase in the number of cases recognized. It is apparent that it can no longer be regarded as a rare disease. The majority of the pathology in SLE is related to deposits of immune complexes in various organs, which triggers complement and other mediators of inflammation. Symptoms vary from person to person, and may come and go, depend on what part of the body is affected, can be mild, moderate, or severe. Diagnosis can be difficult because lupus mimics many other diseases; it requires clinical and serologic criteria.

Keywords: systemic lupus erythematosus, clinical manifestations, laboratory abnormalities

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-systemic lupus erythematosus (SLE) is a disease that can affect persons of all ages and ethnic groups and both sexes, but more than 90% of new patients presenting with SLE are women in the childbearing years. SLE is a disease that affects multiple systems (1). SLE symptoms vary widely. Fatigue in SLE is probably multifactorial and has been related to not only disease activity or complications such as anemia or hypothyroidism (2). SLE is an autoimmune disorder characterized by multisystem microvascular inflammation with the generation of numerous autoantibodies, particularly antinuclear antibodies (ANA). The disorder was recognized as early as the Middle Ages, with the 12th century physician Rogerius being the first to apply the term lupus to the classic malar rash, and in
1872, Moric Kaposi first recognized the systemic nature of the disease (3). SLE affects the immune system, thus reducing the body’s ability to prevent and fight infection. In addition, many of the drugs used to treat SLE also suppress the function of the immune system, thereby further depressing the ability to fight infection. SLE affects the immune system, thus reducing the body’s ability to prevent and fight infection. In addition, many of the drugs used to treat SLE also suppress the function of the immune system, thereby further depressing the ability to fight infection. The most common infections involve the respiratory tract, urinary tract, and skin and do not require hospitalization if they are treated promptly. Other opportunistic infections, particularly Salmonella, herpes zoster, and Candida infections, are more common in patients with SLE because of altered immune status. The patient with lupus often has special nutritional needs related to medical conditions that may arise during the course of the disease. These conditions include steroid-induced osteoporosis or diabetes, cardiovascular disease, and kidney disease. Complications of lupus can be serious, even life-threatening (4,5).

Constitutional manifestations

The patients with SLE may present with various systemic manifestations. The general symptoms include: fever, malaise, arthralgias, myalgias, headache, and loss of appetite and weight. Nonspecific fatigue, fever, arthralgia, and weight changes are the most common symptoms in new cases or recurrent active SLE flares. Fatigue, the most common constitutional symptom associated with SLE, can be due to active SLE, medications, lifestyle habits, or concomitant fibromyalgia or affective disorders. Fatigue due to active SLE generally occurs in concert with other clinical and laboratory markers. Fever, another common yet nonspecific symptom of SLE, may also result from many causes, the most common of which include active SLE, infection, and drug fever. Careful history taking may help to differentiate these. Weight loss may occur in patients with active SLE. Weight gain may also be due to corticosteroid treatment or active disease such as nephrotic syndrome anasarca (6). These symptoms can mimic other autoimmune diseases, infectious diseases, endocrine abnormalities, chronic fatigue, and fibromyalgia (7).

Musculoskeletal manifestations

Involvement of the musculoskeletal system is extremely common in patients with SLE (8). Patients most often seek medical attention for joint pain, with small joints of the hand and wrist usually affected, although any joint is at risk. Joint pain is one of the most common reasons for the initial clinical presentation in patients with SLE (9,10). Arthralgia, arthritis, osteonecrosis (avascular necrosis of bone), and myopathy are the principal manifestations. Arthritis and arthralgias have been noted in up to 95 percent of patients with SLE (11). These symptoms may be mistaken for another type of inflammatory arthritis and can precede the diagnosis of SLE by months or years. Arthralgia, myalgia, and frank arthritis may involve the small joints of the hands, wrists, and knees. In contrast to rheumatoid arthritis, SLE arthritis or arthralgia may be asymmetrical, with pain that is disproportionate to swelling (12,13). The arthritis and arthralgias of SLE tend to be migratory, morning stiffness is usually measured in minutes. The arthritis of SLE is generally considered to be nondeforming. The presence of anti-citrulline containing peptide (anti-CCP) antibodies was found in 8 percent of patients with SLE (14,15). Osteoporosis, often due to glucocorticoid therapy may increase the risk of fractures. Some SLE patients have myositis that can be proved by biopsy (16,17).

Dermatological manifestations

Lupus was first described as a dermato logic condition. Cutaneous manifestations of SLE comprise four diagnostic criteria and multiple other clues to a potential diagnosis of lupus (1). The first is malar rash, which is characterized by an erythematous rash over the cheeks and nasal bridge. It lasts from days to weeks and is occasionally painful or pruritic. The second feature is photosensitivity, which may be elicited from patients who are asked if they have any unusual rash or symptom exacerbation after sun exposure. The third feature may be discoid rash. Discoid lesions often also develop in sun-exposed areas but are plaque like in character, with follicular plugging and scarring. They may be part of systemic lupus or may represent discoid lupus without organ involvement, which is a separate diagnostic entity. Alopecia is the fourth and often less-specific cutaneous feature of SLE. It often affects the
temporal regions or creates a patch like pattern of hair loss. Other cutaneous manifestations related to but not specific to SLE include Raynaud phenomenon, livedo reticularis, panniculitis (lupus profundus), bullous lesions, vasculitic purpura, telangiectasias, and urticaria (2). Diagnosis of lupus panniculitis was considered on clinical and histopathological grounds. Between 70 and 80% of patients develop skin lesions during the course of disease. Approximately 20% of them have skin lesions as an initial presentation. The pathognomonic lupus or butterfly rash across the nose occurs in only 30% of patients with SLE. The acute lupus rash may be present elsewhere. Discoid or disc-shaped skin lesions, pathognomonic for discoid lupus, can manifest also in SLE. Photosensitivity rash can appear even after mild sun exposure (3). Livedo reticularis, a reddish purple rash, is usually present in patients with severe vasculitis or in individuals with elevated APL. Alopecia with patchy or diffuse loss of hair with scalp scarring is another skin manifestation. Raynaud’s phenomenon can cause bluish discoloration of digits and blanching of the skin (18).

Renal manifestations

Although almost in all cases deposits of immunoglobulin are found in the glomeruli, only one half has clinical nephritis (2). Urine analysis of asymptomatic patients often shows hematuria and proteinuria. Renal failure and sepsis are two main causes of death in patients with SLE. The kidney is the most commonly involved visceral organ in SLE. Although only approximately 50% of patients with SLE develop clinically evident renal disease, biopsy studies demonstrate some degree of renal involvement in almost all patients. Glomerular disease usually develops within the first few years of SLE onset and is usually asymptomatic. Acute or chronic renal failure may cause symptoms related to uremia and fluid overload. Acute nephritic disease may manifest as hypertension and hematuria. Nephrotic syndrome may cause edema, weight gain, or hyperlipidemia (3). Lupus nephritis is a common and potentially devastating manifestation of SLE. In general, lupus nephritis occurs in more than half of SLE patients. Lupus nephritis is primarily caused by the deposition of immune complexes. The classification of lupus nephritis is based on renal biopsy. If possible, a biopsy should be obtained in any patient in whom renal involvement is suspected. Renal biopsy need not be done routinely in patients with normal creatinine values and normal urine analysis (6).

Neuropsychiatric manifestations

Neuropsychiatric manifestations of lupus are reported in 25 to 75% of patients and can involve all parts of the nervous system (1). One study showed that the incidence of elevated APL antibodies in patients with neurological symptoms is approximately two times higher than in those without neurological symptoms. Moreover, APL antibodies antedated neurological symptoms in 81% of patients (2). SLE may be generalized or partial and may precipitate status epilepticus. Aseptic menigitis, myelopathy, optic neuropathy, or other demyelinating disorders may also require urgent evaluation. Transverse myelitis with spastic paraparesis is a rare but serious complication of SLE (3). The CNS Lupus nomenclature has been revised to catalog many manifestations. Cognitive disorders may be variably apparent in patients with SLE (19,20). Formal neuropsychiatric testing reveals deficits in 21-67% of patients with SLE. Whether this represents true encephalopathy, neurological damage, medication effects, depression, or some other process is unclear (21-23). Stroke and transient ischemic attack (TIA) may be related to antiphospholipid antibody syndrome or vasculitis. Migraine headaches may also be linked to antiphospholipid syndrome, although this is less clear (24). Headache and mood disorders may be the most commonly reported neurologic manifestation of SLE, but cause and effect may be difficult to distinguish. Neuropathies can be peripheral, autonomic, or cranial. Transverse myelitis is coincident with a lupus flare and is a rheumatologic emergency (25-27).

Pulmonary manifestations

Pulmonary manifestations of SLE may manifest acutely or indolently, representing many complications (1). Serositis can affect both the cardiac and pulmonary systems, and cardiac and pulmonary serositis often coexist. Pleurisy with pleuritic chest pain with or without pleural effusions is the most common feature of acute pulmonary involvement in SLE. Shortness of breath or dyspnea may be due to many causes. Serositis due to pericardial or pulmonary effu-
sions, pulmonary embolism, lupus pneumonitis, chronic lupus interstitial lung disease, complement-mediated pulmonary leukoaggregation, or infection may be related to lupus disease (2). Pulmonary vascular involvement in SLE is also observed. This includes diffuse alveolar hemorrhage, thromboembolic disease, and pulmonary hypertension. Pulmonary hypertension without underlying parenchymal lung disease rarely occurs with symptomatic dyspnea or right-sided heart failure (3). Most seriously, hemoptysis may herald diffuse alveolar hemorrhage, a rare, acute, life-threatening pulmonary complication of SLE. Thromboembolic disease associated with antiphospholipid antibodies can lead to acute pulmonary embolism with acute pulmonary hypertension (4).

**Gastrointestinal manifestations**

Ulceration in the mouth is a common feature of SLE. Oral ulceration is actually one of the eleven criteria used by the American College of Rheumatology to classify SLE. Gastrointestinal symptoms secondary to primary SLE and adverse effects of medication are common among persons with SLE (1,2). Abdominal pain in SLE is significant because it may be related to active lupus, including peritonitis, pancreatitis, mesenteric vasculitis, and bowel infarction. Nausea and dyspepsia are common symptoms in patients with active SLE and are sometimes difficult to correlate with objective evidence of gastrointestinal involvement. Jaundice due to autoimmune hepatitis may also occur. Gastrointestinal symptoms are common in patients with SLE and can be due to primary gastrointestinal disorders, complications of therapy or SLE itself (3). Abnormalities of liver function, however, are not included in the diagnostic criteria of SLE, and the liver is generally not regarded as a major target organ for damage in patients with SLE. Hepatitis from lupus (lupus hepatitis), although uncommon, manifests as a mild elevation in liver enzymes (aspartate transaminase [AST], alanine transaminase [ALT], lactate dehydrogenase [LDH], alkaline phosphatase), usually in a setting of active lupus. Lupoid hepatitis is a separate entity, where the liver is the main organ of involvement. Serologic differentiation may be possible at times and in general involves the presence of anti-ribosomal P and dsDNA autoantibodies in lupus hepatitis versus anti-smooth muscle and auto-liver-kidney-mitochondrial (LKM) antibodies in lupoid hepatitis (28,29).

**Cardiac manifestations**

Autoimmune vascular injury in SLE may predispose to atherosclerotic plaque. An increased incidence of risk factors for atherosclerosis has been noted. Heart failure or chest pain must be carefully examined in patients with SLE. Pericarditis that manifests as chest pain is the most common cardiac manifestation of SLE, manifesting as positional chest pain that is often relieved when the patient leans forward. Myocarditis may occur in SLE with heart failure symptomatology. Coronary vasculitis manifesting as angina or infarction is rarely reported. Libman-Sacks endocarditis is noninfectious but may manifest as symptoms similar to those of infectious endocarditis. More commonly, accelerated ischemic CAD is associated with SLE and may present indolently as atypical angina equivalents. While its cardiac manifestations have been adequately studied, there is paucity of information on its vascular manifestations (5).

**Vascular manifestations**

There is paucity of information on its vascular manifestations. With increasing longevity of lupus patients, peripheral vascular disease has become an important cause of morbidity. Raynaud’s phenomenon occurs in one third of patients at the onset of SLE. Patients with SLE rarely develop ischemic digits or digital ulcers. Raynaud’s phenomenon can affect the fingers, toes, ears, nose, and even the tongue. Livedo reticularis also is commonly seen in SLE and is due to spasm of the ascending arterioles. Patients with SLE can also develop inflammatory vascular disease in the form of vasculitis. Vasculitis in SLE is due to a complex interplay between immune cells, endothelial cells, deposition of autoantibodies, and immune complexes. There have also been reports of SLE and Takayasu’s arteritis (4).

**Ocular manifestations**

Ocular manifestations of lupus are a reflection of systemic disease. The presence of ocular manifestations should alert the clinician to the likely presence of disease activity elsewhere. The most common ocular manifestation of SLE
is keratoconjunctivitis sicca (KCS), occurring in approximately of 25% of patients. Conjunctivitis, interstitial keratitis, episcleritis, and diffuse or nodular scleritis are less common. The severity of episcleritis and scleritis may closely mirror the activity of systemic disease. Necrotizing scleritis is rare in patients with SLE. Retinal involvement in SLE is the second most common ocular manifestation after KCS. The classic finding in lupus retinopathy is the cotton-wool spot, which has been correlated with avascular zones on fluorescein angiography. The histopathological findings include infiltration of vessel walls with fibrillar material causing vascular constrictions and widespread hyaline thrombus formation. Typically, the vessel walls are free of inflammatory cells. Therefore, it is not considered as a true vasculitis. Immunofluorescence staining reveals deposition of IgG with C1q and C3. It was shown that 88% of patients with lupus retinopathy have active systemic disease and a significantly decreased survival rate. Therefore, close monitoring and aggressive treatment of these patients is critical. Uveitis, though rare, may occur also in the absence of retinal involvement. Choroidopathy is much less common in SLE than is retinopathy. Transudation of fluid through Bruch’s membrane may result in multifocal retinal pigment epithelium (RPE) and serous retinal detachments. Although more extensive pathological findings are seen in the choroid as compared to retina, they appear to be subclinical. The neuroophthalmological manifestations of SLE are associated with damage to the optic nerve and brain, most likely as a result of the ischemic process. However, a clinical picture similar to optic neuritis is reported as well. Therefore, all patients with ocular lupus should be carefully evaluated for systemic involvement to detect potentially treatable and preventable complications of the disease (30,31).

**Obstetric manifestations**

Pregnancy outcome appears to be worse in SLE patients. SLE causes an increased rate of fetal death in utero. Pregnant women with SLE are at higher risk of spontaneous abortions, stillbirths or fetal retardation. In patients with APL, the risk of recurrent miscarriages is increased. Researchers have now identified two closely related lupus autoantibodies, anticardiolipin antibody and lupus anticoagulant, that are associated with risk of miscarriage. One-third to one-half of women with lupus have these autoantibodies, which can be detected by blood tests. Pregnancy should be timed when disease is in remission (3). About 3% of babies born to mothers with SLE will have neonatal lupus, caused by maternal antibodies crossing the placenta, and may be another consequence of SLE during pregnancy (4).

**Endocrine manifestations**

Thyroid dysfunction is more frequent in SLE patients than the general population and may have a genetic basis, 3-24 % of patients with lupus also have autoimmune thyroid disease. Controversy whether SLE is an independent risk factor for thyroid disease or whether young to middle aged women who are most at risk for SLE are also at risk for autoimmune thyroid disease (32). Moreover, SLE patients with antithyroid peroxidase (anti TPO) antibodies were more likely to have thyroid dysfunction than the control group, 14% of patients with SLE have anti-TPO and anti-thyroglobulin (anti-Tg) and 68 % of patients with SLE and thyroid disease vs. 5-6 % in general population (33,34). Type 1 and Type 2 diabetes mellitus can be seen but is not common in patients with lupus (35). Fracture rates are higher in lupus than expected (5 x higher than the general population) (14). Vitamin D deficiency is common in SLE partly due to avoidance of sun exposure. Prolonged glucocorticoid use can suppress pituitary function, it is important to always taper steroids over time (36).

**Hematologic manifestations**

Patients with SLE have a complex array of abnormalities involving their immune system. A history of multiple cytopenias such as leukopenia, lymphopenia, anemia, or thrombocytopenia may suggest SLE, among other etiologies. Leukopenia and, more specifically, lymphopenia are common in SLE, this and hypocomplementemia may predispose persons with SLE to frequent infections. Anemia is occasionally overlooked in young menstruating women. Hemolytic anemia may occur. Thrombocytopenia may be mild or part of a thrombotic thrombocytopenic purpura (TTP)-like syndrome or antiphospholipid antibody syndrome (APS). ESR is elevated frequently during active disease. Can be seen significantly elevated levels
of total cholesterol and triglycerides in patients with lupus compared to controls. C-reactive protein levels are not necessarily elevated. History of recurrent early miscarriages or a single late pregnancy loss may be clues to lupus or isolated APS. A family history of autoimmune disease should also raise further suspicion of SLE. Plasma homocysteine levels appear to be another risk factor for stroke in SLE. Autoantibodies in SLE are directed against a wide variety of self antigens. Autoantibodies directed against nuclear self antigens are the most characteristic of SLE. Commonly found target nuclear antigens in SLE include native DNA, de-natured DNA, histone, Smith, U1-RNP, SSA, SSB, and ribosomal. Although patients with SLE almost uniformly present with a positive ANA test, other conditions exhibit positive ANA as well. Therefore, it can be helpful, in diagnosing SLE, to look for these more-specific autoantibodies to help in establishing the diagnosis. It is also worth while to check for antiphospholipid (APL) antibodies because SLE and APL commonly coexist and are often found together in patients with prior thrombotic events or frequent miscarriages (4,9,10,14,33,34).

CONCLUSIONS

Systemic lupus erythematosus is a chronic autoimmune connective tissue disorder, with a heterogeneous presentation. Systemic lupus erythematosus is an immune-mediated systemic disease associated with diverse abnormalities of the skin, kidney, and haematological and musculoskeletal systems. The general symptoms are not specific. Common manifestations may include arthralgias and arthritis, malar and other skin rashes, pleuritis or pericarditis, renal or CNS involvement, and hematologic cytopenias. SLE is protean in its manifestations and follows a relapsing and remitting course. Disease severity is wide ranging, SLE can present major challenges because of accrued organ damage, coagulation defects. SLE is characterized by an autoantibody response to nuclear and cytoplasmic antigens. It is potentially fatal depending on organ involvement.

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