Systemic Lupus Erythematosus for General Practitioners: A Literature Review

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داء الذئب الحصامي مرض جهازي مجهول السبب أو الأسباب . يمكن للمرض أن يأخذ شكلا حادا أو مزمنا . ويتظاهر سريريا بطيف واسع من الأشكال في كل عضو حيث تحدث الأضداد تلفا مناعيا في الأنسجة .

وفي هذه المراجعة للكتابات الطبية عن الموضوع نستعرض بالمناقشة المظاهر السريرية والنسيجية مع الاضطرابات المخبرية . ونلخص وسائل التشخيص والمعالجة والإنذار .

Systemic lupus erythematosus (SLE) is a multisystem disease of unknown etiology or etiologies.

The disease may be acute or chronic. A wide clinicopathological spectrum is expressed in each organ involved which is induced through multiple antibodies that result in immunologically mediated tissue injury.

In this literature review, the clinical and pathological features as well as laboratory abnormalities, measures for diagnosis, outlines of management, and prognosis are discussed.

Key Words: *Systemic lupus erythematosus.*

CLINICAL FEATURES

Systemic lupus erythematosus (SLE) is a multi-systemic disease. The clinical findings depend on the severity and extent of the disease. Most patients initially present with fatigue and fever; the latter may be of low grade or show periods of spiking. Weight loss may also occur.

MUCOCUTANEOUS CHANGES

In 85% of patients with SLE the skin, hair, or mucous membranes are involved. The skin lesions can be either acute, subacute, or chronic. The acute lesions are usually in the form of a butterfly rash which is the classic manifestation of lupus erythematosus. The lesion manifests by erythema and edema occupies mainly the malar skin, and characteristically tends to spare the nasolabial folds. The onset of these lesions is usually sudden and may last for hours, days, or weeks. Other skin lesions which may simulate this type of skin lesion are drug-induced photosensitive eruption, dermatomyositis, seborrheic dermatitis, or acne rosacea. Photosensitivity occurs in around 40% of patients with SLE and usually occupies exposed areas. Urticaria lesions, which may persist for a long time, may also occur. Vasculitic lesions may also exist in the form of palpable purpura, nail fold infarcts, digital ulcerations, Livedo reticularis, and erythema multiforme-like lesions.

Livedo reticularis is frequently correlated with the presence of anticardiolipin antibodies[1]. The presence of these antibodies also correlate with central nervous system disease, spontaneous abortions and thrombotic episodes[2]. Bullous lesions also occur rarely. The mucosal

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involvement usually seen are ulcers which may occur in the oral cavity, perianal area, conjunctiva and genitalia; but the most affected areas are the mouth and lips[3]. Sjorgens syndrome may complicate lupus in varying degrees.

SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS

Although these lesions may simulate discoid lupus erythematosus, they do not develop scarring and atrophy. Lesions appear as plaques with scales; a condition which can easily be mistaken for psoriasis or lichen planus. They may also occur in annular forms. These two lesions may exist simultaneously. The areas covered by these lesions are mainly the exterior aspects of the upper extremities, the V areas of the upper anterior chest and the upper back, the neck, and the face. This confirms the photosensitive nature of the lesions. Most of these patients show symptoms or other signs indicative of a systemic disease and demonstrate circulating antibodies directed against the Ro (SS-A) antigen4 .

Neonatal lupus erythematosus is a rare syndrome characterized by either cutaneos abnormalities similar to subacute cutaneous lupus erythematosus and/or cardiac abnormalities[5]. The skin lesions are usually photosensitive and tend to disappear spontaneously. The cardiac abnormalities are permanent and characterized mainly by conductive defects often in the form of complete congenital heart block. Mothers of these babies either have symptoms and signs of connective tissue disease or are completely asymptomatic and develop connective tissue disease later. They also have circulating anti-Ro antibodies. These antibodies are thought to be the cause of the skin and cardiac lesions in these neonates.

In patients with a second component of complement deficieny, subcutaneous lupus erythematosus may develop as well.

CHRONIC CUTANEOUS LUPUS ERYTHEMATOSUS

Chronic cutaneous lupus erythematosus is usually revealed as a discoid skin lesion. These discoid lesions develop in up to 25% of patients with SLE[6] but may occur without association with either serologic or clinical features of SLE. Discoid lesions may antedate or occur concurrently with or after the development of SLE. Typically, lesions start as one or more papules, usually on the butterfly area of the face, scalp, ears, or forehead. Rarely, they may occur on the trunk and extremities. With the progression of the lesions, papules and plaques appear with bright erythema, edema, and ultimately show the typical central atrophy and depression. As the plaque continues to enlarge, it retains its active edematous edge and erythematosus appearance and the center continues to fade and atrophy .

MUSCULOSKELETAL MANIFESTATIONS

Most common manifestations are arthralgia or mild arthritis with morning stiffness which may occur in up to 95% of patients[7]. Most commonly affected joints are proximal inter-phalangeal joints (PIPs) in 82% of patients; followed by knees, wrists, and metacorpophalangeal joints (MCPs) elbows, and ankles. Analysis of synovial fluid is clear or slightly cloudy and with normal viscosity, and usually non-inflammatory. Arthritis may antedate the diagnosis of SLE by months or years and sometimes may be misdiagnosed as rheumatoid arthritis. The arthritis in SLE is usually non-deforming and symmetrical but sometimes in long standing disease, especially if it involves PIPs and MCPs joints, may lead to deformities which mimic those of rheumatoid arthritis. These deformities are characteristically reducible. Tenosynovitis was also observed in up to 13% of SLE patients[8]. Radiological examination of the joints revealed normal joint spaces with no erosions. Septic arthritis is rather uncommon, however, secondary infections do exist, especially with salmonella, brucella, gonococci, meningococci, and other organisms. To guard against these secondary infections it is

recommended that joint aspirations and synovial fluid cultures be performed especially if effusions develop acutely and occur in a mono-articular pattern. Idiopathic osteonecrosis of bone is a relatively common problem, with incidence varing from 5% to 10%[9]. Use of corticosteroids could play a part in inducing this problem. The most affected sites (which can be bilateral) are femoral heads. Bone scan, computerized tomography (CT) and magnetic resonance imaging (MRI) are useful in picking up early osteonecrosis[10]. Five to ten percent of patients with SLE have inflammatory myopathy, but only half of these patients show clinical evidence of myopathy[11]. Medications such as steroids and hydroxychloroquine may contribute to its pathogenesis.

CARDIAC MANIFESTATIONS

Pericarditis is the most common cardiac manifestation and occurs in up to 30% of patients[12] who usually present with substernal or pericordial pain, which is aggravated by breathing, coughing and swallowing, and relieved by bending forward. However, it may be asymptomatic. Friction rub may be present. Cardiac tamponade and constrictive pericarditis are rarely seen[13,14].

Myocarditis rarely occurs and should be suggested in patients with tachycardia out of proportion to body temperature, unexplained cardiomegaly, and/or heart failure, ventricular dysrhythmia or conduction defects .

Valvular Disease: Nonbacterial verrucous vegetations initially described by Libman and Sacks are still demonstrated at autopsy in 15% to 60% of patients with SLE[15].

Coronary Artery Diseases: Recently, acute myocardial infarction in lupus patients has been seen more often. This is most probably due to atherosclerosis[15]. Hypercholesterolemia and hypertension were found to be significant risk factors. On the other hand, coronary atherosclerosis is much rarer[16]. The lupus anticoagulant and antiphospholipid antibodies may be associated in the pathogenesis of this problem[17], and these antibodies should be carefully sought since their presence may influence the management of the patients by using antiplatelets and/or anticoagulants prophylactically.

Raynaud's Phenomenon: Occurs in approximately 17% to 30% of patients[18]. It may involve fingers, ears, nose, and tongue. May occassionaly lead to gangrene.

PULMONARY MANIFESTATIONS

Pleuritis with or without effusion is the most common pulmonary problem encountered ; it occurs in around 45% to 56% of patients[19]. It may occur in association with the presence of pericarditis. The effusion is usually bilateral and scanty, but can be massive. The analysis of the pleural fluid reveals an exudate with less than 10,000 mononuclear cells, glucose level is normal, and fluid pH is usually higher than 7.35. Lactic acid dehydrogenase levels are lower than 500 ul.

Although pulmonary infections occur more frequently in lupus patients, problems such as acute lupus pneumonitis are sometimes seen[20]. Patients present with severe dyspnea of recent onset as well as tachypnea, fever, and hypoxia. Clinical examination reveals bilateral basal crackles. Radiological examination of the chest reveals alveolar infiltrates mainly seen at lung bases. Pulmonary hemorrhage sometimes occurs. Diffuse pulmonary fibrosis may occur (chronic lupus pneumonitis)[21].

Pulmonary hypertension is now a well-known complication of SLE. It mimics idiopathic pulmonary hypertension. Raynaud's phenomenon is noticed to occur in more than 75% of patients in association with pulmonary hypertension. The prognosis is usually poor.

Pulmonary embolism may occur and is usually associated with the presence of lupus anticoagulant and antiphospholipid antibodies[22].

GASTROINTESTINAL MANIFESTATIONS

Abdominal pain is the most common manifestation encountered. Nausea and diarrhea do occur as well. The abdominal pain correlates with the activity of the disease and its etiology is obscure. However, mesenteric artery narrowing or occlusion may be a cause. The latter may also predispose to mucosal ulcerations and perforations[23]. Pancreatitis[24] and hepatomegaly (30%)[25] are also encountered. Occasionally jaundice and chronic active hepatitis may occur[24]. Slight to moderate splenomegaly is present in 20% of patients and more common in children[25]. Peritonitis and subacute spontaneous bacterial peritonitis may occur. Lymphadenopathy occurs in approximately 50% of patients .

NEUROPSYCHIATRIC MANIFESTATIONS

The clinical features of neuropsychiatric lupus are shown in Table I. A number of pathogenic mechanisms have been suggested to explain these neuropsychiatric manifestations. Among these is immunocomplex vasculitis which gives rise to infarction and hemorrhage. Another mechanism is the contribution of antineuronal antibodies which are directed against neuronal cell membrane[26]. Antibodies to ribosomal-protein antigens occur in approximately 12% to 25% of SLE patients and is found in most patients with lupus psychosis[27].

Table 1

Most Frequent Neurologic Manifestations of SLE*

Seizures
Organic mental syndromes
Cranial nerve disorders
Hemiparesis and paresis
Peripheral neuropathy
Intracerebral hemorrhage
Status epilepticus
Tremor or chorea

* Ann Park and Naomi F. Rothfield. Systemic lupus eythematosus. In: Warren A. Katz: Diagnosis and Management of Rheumatic Diseases. 2nd ed, Philadelphia, J. B. Lipincott Company, 1988;456.

Thrombosis was also suggested as another mechanism of producing neuropsychiatric symptoms, and anticardiolipin antibody association has been described[28]. Serum antibodies to DNA and serum complements are not strongly associated with active neuropsychiatric lupus .

Cerebrospinal fluid (CSF) examination may reveal elevation of cell count and/or protein. A low CSF glucose should point towards infection. Antinuclear antibodies and immune complexes may be detected[29]. Complement component levels are also very low. Electroencephalography (EEG) shows wide nonspecific abnormalities. CT and MRI are also helpful in demonstrating structural abnormalities, e.g., hemorrhages, ventricular dilatation, large infarcts, and parenchymal damage. In a few patients Angiography may help in distinguishing between embolic disease, vasculopathy, and/or atherosclerosis .

COAGULATION ABNORMALITIES

Clinical thrombosis has been observed in about 10% to 15% of patients with SLE[30]. This is usually associated with antiphospholipid antibodies. Large arterial vessel involvement which may result in gangrene of digits or part of a limb is very infrequent.

RENAL MANIFESTATIONS

Renal pathology in SLE occurs in around 50% of patients and has a wide spectrum of clinical pictures and courses, and usually affects glomeruli, but tubules and vessels may also be affected. A summary of the clinical features and course of lupus nephritis are shown on Table 2. It provides a universal classification of lupus nephritis to help in assessment, treatment, and study of these patients. The most widely used scheme for the classification of lupus nephritis is the one described by a committee sponsored by the World Health Organization[31] (Table 3).

Urinalysis should be done to look for hematuria (with dysmorphic erythrocytes). hyaline, granular, leukocytes, and/or erythrocyte

Table 2:

Lupus Nephritis: Summary of Clinical Features and Course*

	Focal Proliferative	Diffuse Proliferative (DPLN)	Membranous (MLN)	Mesangial (MesLN)
Onset	During 1st year SLE in about half..	During 1st year SLE in the majority.	During 1st year SLE in half..	Perhaps characteristic of all SLE from onset..
Clinical Manifestations	Proteinuria in all, hematuria often. Nephrotic syndrome rare. Occasional mild renal insufficiency. Hypertension absent.	Proteinuria and hematuria in all. Nephrotic syndrome at onset in over half, eventually in almost all. Renal insufficiency at onset in most: occasionally severe. Hypertension not common.	Proteinuria in all at onset with rare exceptions. Nephrotic syndrome at onset in half, eventually in four fifths. Microscopic hematuria in half. Occasional hypertension and minimal renal insufficiency at onset.	No clinical features of renal disease in some; minimal proteinuria and/or hematuria in others. Occasional mild renal insufficiency. Hypertension absent.
Transition	Transitions to DPLN or MLN may occur.	Transition to MesLN (with some glomerular sclerosis) or MLN may occur in or association with remission.	Rare transition to DPLN	Development of nephrotic syndrome with transition to DPLN or MLN may occur.
Progression	Renal insufficiency does not develop.	Progression to death within 2 years in half of the unremitted. Death due to uremia or of active SLE, often with infection. No progressive renal insufficiency during remission.	Slowly progressive renal insufficiency during persistent nephrotic syndrome.	No progression unless transition occurs; subsequent course then determined by the form of lupus nephritis that develops.
Mortality	5-year mortality < 10%.	5-year mortality < 25%.	5-year mortality < 25%.	Ig and C in mesangium
Pathology	Focal mild proliferative; Ig G and C3 In mesangium.	Cell proliferation; crescents. Lumpy bumpy Ig and C along GBM (subendothelial)	Thick GBM. Granular Ig and C on GBM (epithelial side)	

GBM: Glomerular basement membrane.

*Peter H. Schur. Clinical features of SLE. In: Kelly WN Harris ED, Ruddy S, and Sledge CB (eds). Textbook pf Rheumatology. 4th ed, Philadelphia, WB Saunders Company, 1993; 1027.

Table 3

World Health Organization Classification of Lupus Glomerulonephritis*

1. Normal glomeruli
2. Pure mesangial nephritis
3. Focal segmental glomerulonephritis
4. Diffuse proliferative glomerulonephritis
5. Membranous glomerulonephritis
6. Advanced sclerosis glomerulonephritis

* Baldwin DS, Gluck MC, Lowerstein J, et al. Lupus Nephritis: Clinical course as related to morphologic forms and their transitions. Am J Med 1977;62:12-30

casts. Urine sediment is of crucial importance in initial assessment and monitoring of renal disease activity. A 24-hour excretion of protein, endogenous creatinine clearance, or radioisotope clearance techniques are also helpful. The value of the renal biopsy is controversial[32], but nevertheless renal biopsy can provide evidence for estimating prognosis and the rationale for adopting certain types of medications .

Levels of serum complements (CH50, C3, and C4 components) have been found to correlate with the degree of activity of glomerular disease on renal biopsy[33]. Consequently, a fall in the levels of serum complements could be a predictor of an imminent flare of lupus nephritis. Assaying of anti-dsDNA antibodies, circulating immune complexes, immunoglobulin levels, cryglobulins, C-reactive protein, and erythrocyte sedimentation rate could be of some value in monitoring these patients.

MENSTRUAL ABNORMALITIES AND PREGNANCY

Menorrhagia does occur sometimes and it may be due to thrombocytopenia or the presence of an inhibitor of one of the clotting factors. During the initial six months of treatment, menses usually cease, but as the patient improves and the steroid dose is reduced, the menstrual periods return .

Untreated patients may have a high incidence of stillbirths and spontaneous abortions. Well controlled patients on low dose steroids usually have successful pregnancies[34]. Slight flare-up of the disease may occur in the immediate prepartum and postpartum periods[34], but most patients recover after around two weeks with the increase of steroid dose. Congenital abnormalities were noticed in children, especially congenital heart block which is associated mainly with patients who have a high level of anti Ro, but this is not always the case .

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Revised criteria for classification of SLE published in 1982 may help in diagnosis (Table 4) , although they were developed for the classification of groups of patients. In clinical practice, every patient must be considered independently as signs and symptoms may develop over time.

SLE must be differentiated from other disorders which may have similar features with the disease. These disorders are rheumatoid arthritis, rheumatic fever, idiopathic thrombocytopenic purpura, subacute bacterial endocarditis, gonococcal or meningococcal septicemia with arthritis and skin lesions, other infections, drug reactions (serum sickness), lymphoma, leukemia and sarcoidosis .

LABORATORY FINDINGS

Anemia, which may occur in up to 50% of patients[35], may reflect a broad spectrum of etiologies, e.g., inflammation, renal insufficiency, blood loss, dietary insufficiency, medications, hemolysis, or a combination of these factors. Leukopenia, lymphopenia, and thrombocytopenia may occur.

The erythrocyte sedimentation rate is not a good guide to the disease activity as it tends to remain high in some patients, even without disease activity. C-reactive protein is often low, but it may rise in the presence of infection[36].

Table 4

1982 Revised Criteria for Classification of SLE*

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds.
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging, atrophic scarring may occur in older lesions.
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician.
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion.
6. Serositis	a. Pleuritis - convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion OR
	b. Pericarditis - documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a. Persistent proteinuria greater than 0.5 g/day or greater than 3+ if quantitation not performed OR
	b. Cellular casts - may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	a. Seizures - in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance OR
	b. Psychosis - in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	a. Hemolytic anemia - with reticulocytosis OR
	b. Leukopenia - less than 4000/mm total on 2 or more occasions OR
	c. Lymphopenia - less than 1500/mm on 2 or more occasions OR
	d. Thrombocytopenia - less than 100,000/mm in the absence of offending drugs
10. Immunologic disorder	a. Positive LE cell preparation OR
	b. Anti-DNA antibody native to DNA in abnormal titer OR
	c. Anti-Sm - presence of antibody in Sm nuclear antigen OR
	d. False-Positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test.
11. Antinuclear antibody	An abnormal titer of antinuclear 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 syndrome.

*Tan Em, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271.

Table 5:

Guidelines for Management of SLE*

Symptoms	Therapy	Exceptions
Asymptomatic	Monitor lab tests and urinalysis	Patient with previously aggressive disease, a rising FARR and falling serum complement levels. Rx corticosteroids. Patient with previous fetal losses, positive LAC (lupus anticoagulant) or anticardiolipin antibody who is now pregnant: Rx corticosteroids (dosages tailored to suppress autoantibody production) and low-dose aspirin (to be discontinued 10 days prepartum). Postpartum patient who has previously flared postpartum: Rx short-term coriosteroids over 4 to 6 weeks.
Mild Disease Joint Pain	Analgesics, aspirin. or nonsteroidal drugs (NSAAIDs) cautiously.	
Any combination of joint pain, malaise, fatigue, mild skin rash, mucosal ulceration, or alopecia with normal complement and no antibody levels,	NSAIDs or aspirin and antimalarial therapy and low dose-corticosteroids (<20 mg per day) if no response in 2 months or side-effects from NSAIDs or aspirin Sunscreen and avoidance of sun exposure for those with skin disease. Monitor lab tests and urinalysis monthly.	Patient with previously aggressive disease whose disease is difficult to control: Rx corticosteroids>20 mg per day. Patient pregnant: Rx corticosteroids >20 mg per day. Patient pregnant: would not initiate antimalarial therapy in a patient already pregnant. Previous ocular toxicity for antimalarials: Rx corticosteroids alone.
Moderate disease Fever, mild weight loss, extensive skin rash, mucosal ulceration +/ - anti-DNA, C3.	Corticosteroids 40 mg to 60 mg and antimalarial drugs.	Same as the last two items above.
Severe Disease Major organ involvement, active renal sediment, proteinuria, pleurisy, pericarditis, abdominal pain. Peripheral neurological involvement. Serum complement, anti-DNA antibodies, anemia, thrombocytopenia, leukopenia.	Corticosteroids or >60 mg prednisone per day.	
Very severe disease Diffuse proliferative nephritis, active pulmonary hemorrhage, CNS disease. Laboratory parameters as above.	High-dose corticosteroid therapy, IV boluses of methylprednisolone, IV bolus of cyclophosphamide, (??) Plasmapheresis (especially for pulmonary hemorrhage).	

* Ann Parke and Naomi F. Rothield. Systemic lupus erythematosus. In: Warren A. Katz: Diagnosis and Management of Rheumatic Diseases. 2nd ed, Philadelphia, J.B. Lippincott Company, 1988;462.

Antinuclear antibodies appear in almost all patients with SLE. Those antibodies may be seen in other conditions, e.g., old age, certain medications, subacute bacterial endocarditis, rheumatoid arthritis, and other connective tissue diseases, chronic active hepatitis and primary biliary cirrhosis.

Antibodies reacting with double-stranded DNA (dsDNA) are almost unique to patients with SLE and this test demonstrates one of the most specific tests in rheumatology.

Other antinuclear and anticytoplasmic antibodies (e.g. Ro [SSA], La [SSB], Sm, RNP Jo-1) are diagnostically valuable in SLE and other connective tissue diseases.

False-positive STS may also be seen in 5% to 10% of SLE patients. These are associated with lupus anticoagulant and are usually manifested as prolongation of partial thromboplastin time (PTT). Both these tests measure antiphospholipid antibodies such as anticardiolipin antibodies.

Circulating immunocomplexes may be detected and serum complements tend to be depressed in active systemic disease or nephritis.

MANAGEMENT

The method of approach to the management of SLE is determined primarily by the clinical presentation (Table 5).

Other general measures which are of help in the management of patients with SLE are the avoidance of sun and use of sunscreens during exposure. Rest periods are important at the time of flare-up. If a patient is in remission, normal daily activity and work can be resumed. Physiotherapy treatment may also be helpful in strengthening the muscles. Pregnancy should be avoided when there is a major disease activity and when patients are under immunosuppressive therapies. Oral contraceptives may occasionally lead to a flare-up of the disease. It is important to be aware of the fact that patients with SLE are prone to infections and should be assessed carefully for this complication. Hospitalization is necessary during periods of exacerbation, especially in patients with central nervous system, renal, hemolytic, and cardiopulmonary problems.

PROGNOSIS OF SLE

Survival of SLE patients has shown steady improvement in the last few decades[19]. Five-year survival rate in patients receiving steroid treatment may reach 94%[37]. The improvement in the survival rate could be explained by early diagnosis, a better use of immunological and serological studies, judicial use of steroids, immunosuppressants and antibiotics, an increase of patients' awareness of the disease, or amelioration of the natural history of the disease itself.

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