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An overview of systemic lupus erythematosus

Systemic lupus erythematosus is a multisystem disease with manifestations ranging from trivial to life threatening. It is a chronic condition and affected patients require careful follow up.

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Systemic lupus erythematosus (SLE) is an autoimmune disorder that may affect any organ system. It is characterised by the presence of a wide range of autoantibodies, particularly those directed against nuclear antigens. Most individuals who are affected are women during their reproductive years; however, SLE also occurs in men, as well as women in other age groups. The most common manifestations of SLE are skin rash and arthralgias; the most serious include renal, central nervous system and thromboembolic disease.

This article provides a brief overview of the pathogenesis, clinical manifestations, management and changing prognosis of SLE.

Epidemiology and pathogenesis

The prevalence of SLE in Caucasians is 50 per 100,000. The disease is more common (and severe) in Australian Aboriginals and in people of Asian, Polynesian and African-American descent. About 90% of patients are female and most present during their child-bearing years.

A number of factors have been implicated in the pathogenesis of SLE. It is currently thought that SLE has a multifactorial aetiology, involving genetic susceptibility, female sex hormones and environmental factors. Abnormalities in every key facet of the immune system have been implicated, and pathogenic autoantibodies are a hallmark of the disease. The leading current theory is that these autoantibodies may be a result of deficient removal of apoptotic debris in patients with SLE.

Genetic susceptibility to SLE is demonstrated by the high concordance between monozygotic twins with the disease (20 to 60%) in contrast to dizygotic twins (5 to 10%). SLE occurs in approximately 5% of first-degree relatives of patients with the disease. Furthermore, inherited complement deficiencies are strongly associated with SLE.

The finding that SLE is most common in

IN SUMMARY

- **The diagnosis of systemic lupus erythematosus (SLE) can be simple, but at times the disorder can masquerade as other conditions such as infection or malignancy.**
- **A positive antinuclear antibody (ANA) test is not diagnostic alone for SLE; it is one of the 11 criteria, four of which are required for a definite diagnosis.**
- **It is important that care is shared between GPs and appropriate specialists because SLE is uncommon and has a very variable clinical expression. Patient education and support are important in achieving the best long-term outcome.**
- **Management of SLE must be tailored to the individual patient, reserving immunosuppression for those with life-threatening organ involvement.**
- **As survival of patients with SLE has improved, managing the late manifestations of the disease such as premature cardiovascular disease and minimising the adverse effects of treatment has become a growing challenge.**

Table. ACR criteria for the classification of SLE*

The presence of four or more of the following criteria is necessary for the classification of SLE:

- malar rash
- discoid rash
- photosensitivity
- oral ulcers
- arthritis
- serositis: pleuritis or pericarditis documented by ECG or rub, or evidence of pericardial effusion
- renal disorder: proteinuria >0.5 g/day or >3+, or cellular casts
- neurological disorder: seizures or psychosis without other cause
- haematological disorder: haemolytic anaemia, leukopenia (<4000 cells/μL), lymphopenia (<1500 cells/μL) or thrombocytopenia (<100,000 cells/μL in the absence of offending drugs)
- immunological disorder: anti-dsDNA, anti-Sm and/or antiphospholipid antibodies
- antinuclear antibodies (ANAs): abnormal ANA titre by immunofluorescence or equivalent assay at any point in time in the absence of drugs known to induce ANAs

* Adapted from Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25: 1271-1277, updated by: Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997; 40: 1725.

ABBREVIATIONS: ACR = American College of Rheumatology; SLE = systemic lupus erythematosus.

women of a childbearing age has led to the investigation of hormonal factors in its aetiology. Oestrogens appear to play a complex role in the pathogenesis and expression of SLE. Attempts to target the role of oestrogens in SLE with hormonal therapies have been disappointing.

Evidence for environmental factors include the observations that infections may trigger a disease flare and that sun exposure worsens the skin manifestations and may also induce a systemic flare.

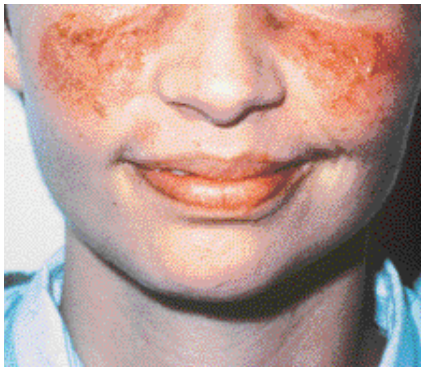


Figure 1. The typical malar rash of SLE.

Immune abnormalities play an important role in the pathogenesis of SLE; however, it is not clear which are of primary importance and which are secondary phenomena. Defects in complement pathways, T-cells, B-cells and cytokine production are thought to contribute to the production of pathogenic autoantibodies. These autoantibodies are directed towards nuclear antigens that are displayed on the cell surface during apoptosis, and thus failure of apoptosis may lead to increased autoantibody production. The most important of these are the antinuclear antibodies (ANAs) that contribute to tissue and cell injury.

Clinical features

The clinical features of SLE vary from mild involvement of a single system (typically skin rash or arthralgias) to fulminant multisystem disease. SLE has been referred to as 'the great mimic' and is frequently diagnosed only after other conditions (e.g. infection or malignancy) have been excluded.

The American College of Rheumatology criteria for the classification of SLE are listed in the Table. The presence of four out of 11 criteria in a patient gives a 95% sensitivity and 97% specificity for the diagnosis of SLE.

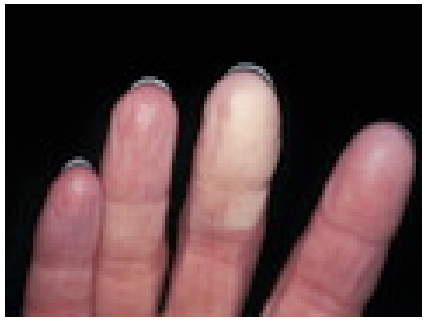


PHOTO COURTESY OF PROFESSOR STEVEN KOSSARD, SYDNEY

Figure 2. Raynaud's phenomenon occurs often in patients with SLE and may predate other features of the disease by many years.

General

Active SLE commonly leads to fevers, weight loss and fatigue. Fever secondary to active SLE must be differentiated from fever due to infection. This may be difficult as infection can also trigger a disease flare.

Dramatic weight loss can occur with severe, active SLE. Milder weight loss may be due to loss of appetite, medication side effects, depression or gastrointestinal involvement.

Fatigue is very common, but should only be attributed to SLE if other signs of active disease are present. The causes of fatigue are often multifactorial, and may be similar to those occurring in patients without SLE. Examples include depression, anaemia, stress and sleep disorders. Unfortunately, fatigue can prove very difficult to treat.

Dermatological

Most patients with SLE will have skin lesions at some time. The typical erythematous butterfly rash across the nose and cheeks occurs in about 50% of patients (Figure 1). Other manifestations include patchy temporary hair loss and diffuse maculopapular rashes. Sun exposure exacerbates the skin lesions in about 30% of patients with the condition.

Raynaud's phenomenon is common in patients with SLE and may predate other features of the disease by many years (Figure 2). Discoid lesions occur in 15% of patients and may lead to scarring. These

lesions are circular with a red rim and a scaly centre. SLE develops in 5% of patients presenting with discoid skin lupus (Figure 3).

Musculoskeletal

Arthralgia is one of the most common clinical features of SLE, occurring in about 90% of patients at some stage. Arthralgia may present as a migratory pattern affecting small and large joints. Alternatively, it may present in a similar fashion to early rheumatoid arthritis with symmetrical involvement of the proximal interphalangeal and metacarpophalangeal joints (Figure 4). Unlike rheumatoid arthritis, there is typically little swelling around the joints. Moreover, joint deformity and radiological erosions are uncommon.

A small number of patients with SLE have a deforming arthritis (Jaccoud's arthropathy). Occasionally, avascular necrosis may develop (e.g. at the hip, shoulder or knee). Although this feared complication is related to the dose and duration of corticosteroid therapy, it can also occur in patients with SLE independently of corticosteroid use.

Renal

Renal disease has previously been the largest contributor to mortality in patients with SLE. Most patients with SLE will have evidence of immune abnormalities on renal biopsy but only 30% develop clinical renal disease. This usually presents with proteinuria and can progress to the nephrotic syndrome.

Other presentations of renal disease include hypertension and microscopic haematuria. There are several types of renal histological lesions, and these are very important in guiding prognosis and therapy. Renal biopsy is essential in all patients with SLE and suspected renal involvement.

Haematological

The most common haematological abnormalities in patients with SLE are:

- anaemia – usually due to the anaemia of chronic disease but may also be secondary to haemolysis (Coombs' test positive)
- thrombocytopenia – mild thrombocytopenia is common and may be the only presenting feature in some patients
- lymphopenia – usually mild and rarely leads to infectious complications.

The antiphospholipid antibody syndrome is characterised by recurrent miscarriage and venous and/or arterial thrombosis in the presence of antiphospholipid antibodies. Antiphospholipid antibodies are detected by the finding of lupus anticoagulant (or lupus inhibitor), anticardiolipin antibodies, a false-positive biological test for syphilis or a positive test for β_2 glycoprotein antibody. These antibodies are found in 30 to 40% of patients with SLE, but not all of these patients will have recurrent thrombosis. They can also occur in individuals without SLE. Antiphospholipid antibodies may be drug-induced, follow infection (e.g. hepatitis C, HIV or *Mycoplasma* infection) or occur spontaneously. The risk of recurrence of thrombosis in patients with the syndrome is very high and long-term anticoagulation is required.

There are a number of clinical scenarios in which the optimal management of patients with antiphospholipid antibody syndrome remains controversial. One scenario includes the use of prophylaxis treatment (e.g. with low-dose aspirin) in patients with the syndrome and no history of thrombosis or pregnancy loss. The optimal target international normalised ratio (INR) is also controversial in patients with the syndrome and thrombosis (we currently aim for a standard target INR of 2 to 3).

Pulmonary

Pleurisy and pleural effusions occur in about 60% of patients with SLE at some stage. Lupus pneumonitis is an uncommon condition, presenting with fever, cough and shortness of breath, and may be difficult to differentiate from infection. It requires treatment with corticosteroids to reduce inflammation and prevent pulmonary fibrosis.

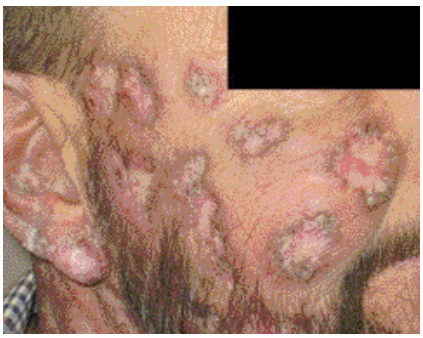


Figure 3. Discoid lesions occur in about 15% of patients with SLE and can lead to scarring.

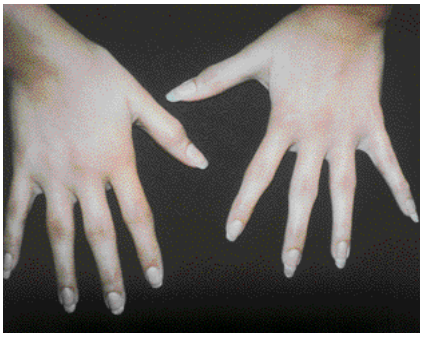
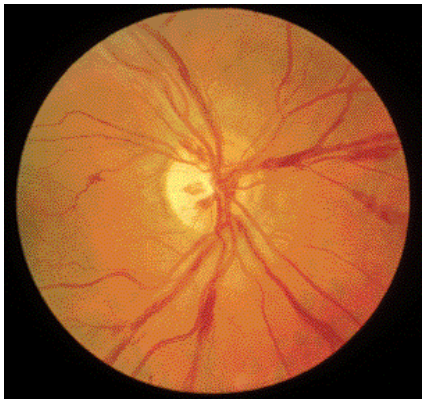


Figure 4. Symmetrical arthritis of the small joints of the hands. Deformity and erosions are very uncommon.

Cardiac

Pericarditis is common in SLE, but it is unusual for it to cause tamponade or restriction. Myocarditis and sterile endocarditis (Libman-Sacks) do not commonly occur.

Recently, it has become apparent that patients with SLE have an excess cardiovascular mortality. This is partly due to inflammation itself as well as to abnormal lipid profiles (often secondary to long-term prednisone use) and possibly the antiphospholipid antibody syndrome or other lupus-related factors. Other traditional cardiac risk factors are



PHOTOLIBRARY

Figure 5. Retinal vasculitis is a rare but serious complication of SLE.

important in patients with SLE, including hypertension, smoking and obesity.

Neurological

Difficulties with defining CNS disease in patients with SLE have made its true prevalence hard to estimate. There are now 19 clinical syndromes recognised by the American College of Rheumatology as being true SLE-related neuropsychiatric disease. These may be classified as central or peripheral. Examples of neurological abnormalities include seizures, stroke, peripheral neuropathy and cranial nerve lesions. Psychiatric manifestations range from mild depression to severe psychosis.

The main principles of treatment are firstly to exclude other treatable conditions (e.g. infection), secondly to treat active SLE, particularly if other evidence of disease activity is present, and thirdly to manage the neurological abnormality as would be done in the absence of SLE (e.g. treat epilepsy with antiepileptic drugs).

Gastrointestinal

Gastrointestinal problems often manifest as troublesome but not life-threatening symptoms. Diarrhoea, vague abdominal discomfort and nausea are common in patients with SLE. Rarely, SLE leads to peritonitis and bowel perforation from vasculitis of the intestine. Mild hepatitis and abnormal liver function tests are a common finding, and pancreatitis may occasionally occur.

Ocular

Secondary Sjogren's syndrome is common in patients with SLE. Optic neuritis and conjunctivitis may occur. A rare but serious ocular complication of SLE is retinal vasculitis (Figure 5), which may lead to rapid blindness and must be treated early with immunosuppression.

Problems during pregnancy

Patients with SLE are at risk of complications during pregnancy for both the mother and the child. Pre-pregnancy counselling should be considered, and it is crucial that patients with SLE are seen by an obstetrician with experience in managing high-risk pregnancies.

There are conflicting reports concerning the effect of pregnancy on patients with SLE. It was previously thought that as many as 30 to 50% of women have a flare in their disease during pregnancy, and that this may occur in any trimester. More recent case control studies have not found an increase in disease activity during pregnancy, possibly due to more aggressive treatment and careful monitoring during pregnancy.

The major predictors of a disease flare during pregnancy are activity of disease immediately before the pregnancy and the presence of renal disease. Pre-eclampsia occurs more commonly in women with SLE than in those without, and it can be difficult to differentiate from SLE-related nephritis.

Another issue for patients with SLE and the antiphospholipid antibody syndrome is recurrent fetal loss. Management of this condition requires close monitoring and treatment with heparin (or low molecular weight heparin) with or without aspirin.

Other potential problems for the fetus include preterm delivery and neonatal lupus. The latter occurs due to the passive transfer of maternal autoantibodies across the placenta. The most important of these are anti-SSA (anti-Ro) and anti-SSB (anti-La) antibodies, which are responsible for congenital heart block.

The use of medication during pregnancy (and breastfeeding) remains a controversial issue in women with SLE. Prednisone only crosses the placenta in small amounts and is considered relatively safe for the fetus. However, it may contribute to maternal weight gain, fluid retention, hypertension and gestational diabetes. The role of hydroxychloroquine remains controversial. Recently, there have been studies demonstrating its safety the mother and fetus, and evidence has shown that its withdrawal may lead to SLE flares during pregnancy. For this reason, it is now often continued during pregnancy. However, it remains a category D medication and, in today's climate of practising medicine, it is wise to ask the patient to give written informed consent before prescribing this medication during pregnancy.

Laboratory findings

There are numerous autoantibodies that may be demonstrated in the serum of patients with SLE. ANAs, which are detectable in almost all patients with SLE, may be present for many years prior to the onset of SLE symptoms. These antibodies can also be found in a small percentage of the normal population, particularly in low titre (1:40 or 1:80). Higher titres are more likely to be clinically significant. They occur commonly in patients who have other autoimmune diseases and infections. The presence of these antibodies should not be interpreted as being diagnostic in their own right. A repeatedly negative ANA test means that SLE is very unlikely.

Other useful antibodies include anti-dsDNA and anti-Sm antibodies. Although they are only present in about 60% and 20% of patients with SLE, respectively, they are highly specific for the disease. The anti-dsDNA antibody titre can be useful in monitoring disease activity.

Other common laboratory findings in patients with SLE include increased levels of polyclonal immunoglobulins and low complement levels (C3 and C4) in active disease.

The erythrocyte sedimentation rate may be elevated in patients with active disease due to multiple factors (e.g. anaemia and increased immunoglobulin levels). The C-reactive protein level, on the other hand, is frequently normal and not of great use in assessing disease activity. It is important in follow up to monitor the urine for protein and cells.

Management

GPs play an integral role in the management of patients with SLE. Early diagnosis and assessment of severity of the disease is crucial in its management. Care is likely to be needed for many years and requires close co-operation between specialists and GPs.

Patient education is an essential part of managing SLE. Life-threatening manifestations may be asymptomatic in their early stages (e.g. renal disease) and so education is needed to ensure patient follow up and adherence. The state and territory-based Lupus Associations for patients with SLE are valuable resources for education material, newsletters and counselling.

Treatment of SLE depends on the clinical manifestations. Some patients require only sun avoidance and careful follow up. Topical corticosteroids can be used sparingly for skin involvement. Other topical agents (e.g. tacrolimus, pimecrolimus) have shown promise in small case series and trials. However, their routine use is not recommended as their risk/benefit profile is not yet clear. NSAIDs are used for patients with mild arthralgias.

With increased recognition of the risk of cardiovascular disease in patients with SLE, it is important to treat risk factors such as hypertension, hypercholesterolaemia and smoking. Unlike in other high-risk groups (e.g. patients with diabetes), there is little direct evidence for specific target levels for cardiac risk factors in patients with SLE.

Various diets or dietary supplements are marketed as being beneficial in SLE. There is evidence that large quantities of omega-3 fish oil are almost as beneficial as NSAIDs in mild SLE.[1] These oils may also prevent more serious flares and be of benefit to cardiovascular health. There is no convincing evidence for other dietary therapies in SLE.

Hydroxychloroquine is helpful for patients with nonlife-threatening manifestations that do not respond to treatment with NSAIDs.[2] It is of use in managing skin lesions, arthritis and fatigue. Hydroxychloroquine may also help prevent more serious disease flares, improve lipid profiles, decrease the risk from anticardiolipin antibodies and improve survival in patients with SLE. It is usually very well tolerated, with rash, neuropathy and myopathy only occasionally developing. Retinopathy is a rare but serious complication of hydroxychloroquine use and should be monitored for with regular ophthalmological review and patient education.

Corticosteroids are the mainstay of treatment for severe or life-threatening disease in patients with SLE. They are often combined with immunosuppressive agents such as cyclophosphamide or azathioprine. As patients are often young and may require treatment for a long time, there is interest in minimising drug

toxicity. The desire to find less toxic treatment has driven the development of several new agents as well as changing the way established agents are used. For example, cyclophosphamide is now often administered as intermittent intravenous pulses rather than as continuous daily tablets, with less cumulative toxicity.

There are numerous trials in progress involving agents that target B-cells or T-cells. Some are novel agents whereas others are already established treatments for other diseases. For example, rituximab, which is used to treat lymphomas, is now being studied in SLE, with encouraging results in small case series. Mycophenolate mofetil, which is used in renal transplantation, is also proving to be successful in SLE nephritis as a less toxic alternative to cyclophosphamide.

Prognosis

Five- and ten-year survival in patients with SLE has improved in the last few decades. This is partly due to improved treatment and partly to increased recognition of milder disease. About 90% of patients with SLE will be alive at 10 years after diagnosis. There is a broad spectrum of severity of disease that can be partially predicted by the degree of organ involvement and the number of American College of Rheumatology criteria a patient fulfils.

Early deaths tend to relate to active disease, whereas late deaths tend to be due to side effects of treatment such as infection and premature cardiovascular disease. Many patients need little or no treatment and some experience a clinical and even serological 'remission' in which treatment can be stopped.

One of the major challenges in SLE is the management of potentially life-threatening problems that become more apparent in the second decade after diagnosis (e.g. premature vascular disease). This may be achieved by improved patient education, exercise, tighter control of serum lipid levels, aggressive management of hypertension and cessation of smoking.

Summary

Today, SLE only occasionally results in early deaths due to active inflammatory disease. It has become a chronic 'living disease'. However, before we become too complacent about our success in prolonging life to greater than a decade, it is salutary to remember that many of these patients are in their teens or twenties at the time of diagnosis. They are still in their twenties or thirties after a decade of illness. Challenges remain for the long haul – that is, survival to the second decade and beyond. We are only beginning to understand what these challenges are and how they can be best addressed. MT

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