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Systemic lupus erythematosus

An improving prognosis

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Patients with systemic lupus erythematosus (SLE) now have an 85 to 90% 10-year survival rate. However, the challenge remains to ensure that young women with SLE, the group mainly affected by the disease, survive with low morbidity beyond this time.

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Australian Rheumatology Association

Systemic lupus erythematosus (SLE) is a complex multisystem autoimmune inflammatory disorder of unknown aetiology. Its immunopathogenesis is characterised by B cell dysfunction, autoantibody production and immune complex deposition in affected organs. It is considered the prototypical connective tissue disorder. Although it can be fatal, overall the prognosis has improved dramatically over the past few decades.

This article reviews the diagnosis and management of SLE, including the new anti-B cell biological therapies.

EPIDEMIOLOGY

SLE is a rare disease, affecting approximately 0.1% of the Australian population. Peak onset of disease occurs between the ages of 15 and 50 years and it is much more common in women. The disease is found more often worldwide in certain ethnic groups, including African Americans, Hispanic Americans and Polynesians.[1] In Australia, SLE has been found to be more prevalent in people of Asian descent and in Indigenous peoples, who also have more severe disease with a higher incidence of renal disease and damage accrual.[2]

CLINICAL FEATURES AND DIAGNOSIS

The diagnosis of SLE has been considered difficult because of the disorder's wide-ranging effects on different systems and variable pattern of disease (chronic and indolent or a relapsing/remitting pattern). The range of clinical features is summarised in Figure 1.

The most common clinical manifestations include fatigue, systemic symptoms such as fever and malaise, and skin and joint involvement. The less frequent but more serious manifestations include renal, pulmonary, cardiac and central nervous system disease.

Haematological involvement may manifest as cytopenias or lymphadenopathy.

Diagnosis relies on the presence of some of these typical clinical features and supportive serology. A positive antinuclear antibody (ANA) test at a titre of more than 1:160 is almost mandatory for the diagnosis to be made. Often a number of extractable nuclear antibodies (eNAs) will be positive, including those to the Smith antigen (anti-Smith antibody; anti-Sm), which is specific for SLE, and ribosome P (anti-RNP antibody), which is associated with certain manifestations of SLE such as neuropsychiatric involvement. Although these autoantibodies are associated with SLE, they do not necessarily imply more severe disease or a worse prognosis. Other supportive serological findings include decreased C3 and C4 complement levels and elevated antibodies to double-stranded DNA (anti-dsDNA). The presence of these findings often correlates with active disease, particularly renal lupus (lupus nephritis). The diagnostic work-up should include renal function tests and a urinalysis for proteinuria and renal casts, which can detect early renal disease.

Classification criteria such as those developed by the American College of Rheumatology (ACR) provide a guide to diagnosis but are not always definitive when applied to individual cases.[3] The ACR criteria are outlined in Box 1, and application of these criteria is outlined in the two case studies in Box 2.

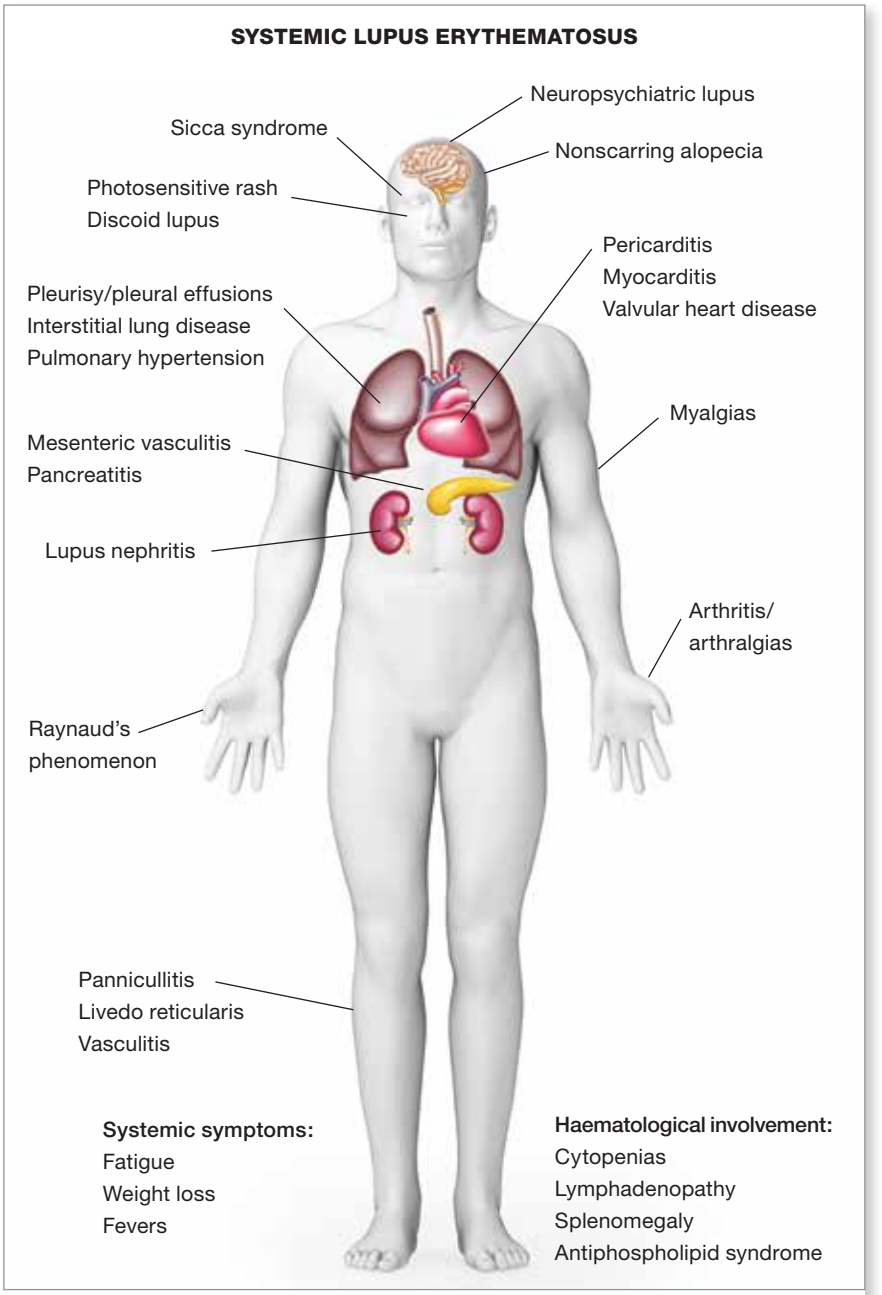

Figure 1. The spectrum of clinical manifestations of SLE.

FIGURE 1 OUTLINE © SHUTTERSTOCK/SEBASTIAN KAULITZKI

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid antibodies are found in up to 30% of patients with SLE and a percentage of these will develop the autoimmune thrombophilia syndrome known as antiphospholipid syndrome (APLS). Patients with SLE and APLS have a poorer prognosis.

The diagnosis of APLS requires the occurrence of a clinical event and the presence of one or more antiphospholipid antibodies, detected on two occasions at least 12 weeks apart. Clinical events may be either arterial or venous thromboembolism or pregnancy morbidity such as recurrent miscarriages, pre-eclampsia, eclampsia or placental insufficiency. The antiphospholipid antibodies are anticardiolipin, anti-B2-glycoprotein 1 and the lupus anticoagulant. The lupus anticoagulant carries the highest risk of a clotting event.

Treatment of APLS includes prophylactic therapy (e.g. with low-dose aspirin) and anticoagulation (with warfarin or low molecular weight heparin injections, depending on the clinical context). The latter may be lifelong in some patients.[4] Women with APLS who wish to conceive may require treatment during conception, pregnancy and postpartum with a combination of aspirin and

1. 1997 ACR CRITERIA FOR THE CLASSIFICATION OF SLE*

The presence of four or more of the following criteria indicates a likely diagnosis of SLE.

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Nonerosive arthritis
- Pleuritis or pericarditis
- Renal disorder – persistent proteinuria >0.5 g per day or >3+, or cellular casts
- Neurological disorder – seizures or psychosis without other cause
- Haematological disorder – haemolytic anaemia (with reticulocytosis), leukopenia(<4000/μL on two or more occasions), lymphopenia (<1500/μL on two or more occasions) or thrombocytopenia (<100,000/μL in the absence of offending drugs)
- Immunological disorder – anti-dsDNA, anti-Sm or positive finding of antiphospholipid antibodies on an abnormal serum level of IgG or IgM anticardiolipin antibodies, or a positive test result for lupus anticoagulant using a standard method, or a false-positive test result for at least six months confirmed by *Treponema pallidum* immobilisation or fluorescent treponemal antibody absorption test
- Positive antinuclear antibody

* Adapted from: Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997; 40: 1725.

2. DIAGNOSING SLE

Case study 1

A 24-year-old woman presents with a recent onset of polyarthralgia. There is little to find objectively on examination. Laboratory investigation reveals antinuclear antibody (ANA) of 1:40 and anti-dsDNA is negative. Does she have lupus?

Answer. There are insufficient criteria to make a diagnosis of lupus. The ANA of 1:40 is not a significant titre. However, things may evolve in time and she should be followed.

Case study 2

An 18-year-old girl of Chinese ethnicity reports hair thinning, migratory polyarthralgia and a photosensitive erythematous skin rash. Urinalysis shows 3+ proteinuria. Blood tests show ANA 1:2560 with anti-dsDNA antibodies elevated. Does she have lupus?

Answer. This patient clearly meets criteria for the diagnosis of SLE and potentially has renal involvement. Early rheumatology review is very important.

unfractionated heparin to minimise the risk of pregnancy-associated morbidity.[5]

TREATMENT

Treatment of SLE includes therapy with disease-modifying antirheumatic drugs (DMARDs) to control the disease and reduce the frequency of flares (through immunomodulation/immunosuppression) and also management of complications of the disease and its therapy. General aspects of management to consider include photoprotection, contraception in all women, vaccinations, smoking cessation and general lifestyle advice. Practical treatment tips for patients with SLE are listed in Box 3.

General management

Photoprotection minimises the development of photosensitive rashes and the likelihood of systemic disease flares involving internal organs. Exposure of the skin to sunlight should be avoided if possible, unless a high grade (UV 30+) sunscreen is applied.

Contraception should be considered in all women with SLE because of the risk of fetal and maternal adverse outcomes in unplanned pregnancies, particularly in the setting of active disease. High-dose oestrogen contraception should be avoided due to a possible risk of exacerbating disease and the increased risk of thrombosis, particularly in women with APLS.[6] Low-dose oestrogen or progesterone only contraceptives are suitable alternatives.

As patients with SLE may be immunosuppressed because of the disease (through immune-mediated cytopenias) or its treatment, regular vaccinations, including yearly influenza vaccination, should be maintained. Live vaccines should be avoided if the patient is immunosuppressed.

Smoking cessation should be encouraged as smoking increases not only the incidence but also the severity of SLE.[7]

General lifestyle advice including healthy diet and exercise is also important to reduce long-term cardiovascular risk and promote wellbeing.

Conventional DMARD therapy

With regard to disease-modifying treatment, the antimalarial agents and in particular hydroxychloroquine are being increasingly used for the long-term treatment of SLE. Some clinicians advocate that all patients with SLE should be treated with hydroxychloroquine. This drug is effective in the treatment of the most common symptoms of the disease, namely cutaneous and joint manifestations. It also reduces the risk of more significant complications of the disease such as renal lupus, and improves patient survival.[8] Hydroxychloroquine, despite its category D rating, is often used in pregnancy as a safer alternative to other disease-modifying agents. There are now several clinical trials demonstrating the safety of hydroxychloroquine use in pregnant patients with SLE. The benefits in controlling the disease often outweigh any potential risks. Hydroxychloroquine is generally well tolerated but carries a very rare but important risk of ocular toxicity with long-term cumulative use; regular eye checks are mandated.

Other DMARDs used in the specialist

3. PRACTICAL TREATMENT TIPS FOR PATIENTS WITH SLE

- Avoid sun exposure unless using high-grade (UV 30+) sunscreen
- Consider contraception, particularly if SLE is active. Avoid high-dose oestrogen
- Have annual influenza vaccinations
- Avoid live vaccines
- Maintain healthy diet and exercise
- Address cardiovascular risk factors such as hypertension and hypercholesterolaemia
- Stop smoking
- If using the antimalarial drug hydroxychloroquine, which is effective in treating skin and joint SLE, regular eye checks are essential

treatment of SLE include azathioprine, cyclophosphamide, methotrexate and mycophenolate mofetil.

The management of lupus nephritis has changed in recent years with the finding that mycophenolate mofetil is an as effective and better-tolerated alternative to cyclophosphamide.[9] Mycophenolate is available on the PBS for this maintenance therapy (WHO Class III, IV and V lupus nephritis) and is being increasingly used as a first-line therapy for mild to moderately severe lupus nephritis, cyclophosphamide therapy being reserved for severe disease.

NSAIDS

NSAIDs are used to provide symptomatic relief for fever and malaise associated with SLE. However, they may cause elevated creatinine levels or liver function test results.

Systemic corticosteroids

Systemic corticosteroids are often needed in patients with SLE to control acute flares and are also used in the longer term at low doses to control disease. Where corticosteroids cannot be avoided, care should be taken to manage their side effects, in particular bone health.

Biological DMARDs: anti-B cell therapies

There have been great developments in the field of rheumatology in the use of biological agents for the treatment of rheumatic diseases (biological DMARDs). The development of the tumour necrosis factor (TNF) inhibitors in particular has revolutionised the treatment of rheumatoid arthritis and seronegative spondyloarthropathies. However, anti-TNF drugs are not effective in the treatment of SLE and overall the progress in this area has been disappointing.

Anti-B cell therapies for SLE are showing promise. Rituximab, an anti-CD20 monoclonal antibody) used for the treatment of other autoimmune conditions including vasculitis and rheumatoid arthritis, has been evaluated. Case series and a recent meta-analysis of studies suggest it may be effective for the treatment of renal and joint disease as well as cytopenias.[10,11] Unfortunately, larger controlled trials have not shown convincing results.[12]

Belimumab (a human B lymphocyte stimulator [BLys] neutralising antibody) is another anti-B cell agent that has shown modest efficacy in the treatment of lupus.[13] It is being increasingly used in the USA, where it is the first new drug in about 50 years for SLE to receive FDA approval. It is TGA approved for use in highly active SLE.

Rituximab and belimumab are only available in Australia through special access schemes and this limits their use. Based on currently published phase III clinical trials, the efficacy of these anti-B cell agents is modest. However, individual patients sometimes have an excellent response to these treatments.

There is ongoing research into other biological agents and there are likely to be new treatments available for SLE within the next 10 years.

PROGNOSIS

Although SLE can be a fatal disorder, overall the prognosis has improved dramatically over the past few decades. The 10-year survival rate is now 85 to 90%, compared with a figure of 50% for five-year survival 30 years ago.[14] As such, SLE should be regarded as a chronic living disorder rather than as an acute fatal disease. In that context, longer term quality of life and comorbidities become important issues. Management of the consequences of long-term immunosuppression, including infection, becomes crucial. Cancer risk is increased, including lymphoma, and patients should have age-appropriate screening as well as investigation of lymphadenopathy if it occurs.

The largest cause of mortality in the long term in SLE, however, is the development of premature cardiovascular disease, probably secondary to chronic inflammation.[15] Prevention of cardiovascular risk, therefore, is as important as management of the disease itself. Such prevention includes the use of low dose aspirin and statins, the maintaining of good blood pressure control and the cessation of smoking.

CONCLUSION

Once thought to be a rare and frequently fatal disease, the outlook for patients with SLE has changed. It should now be considered a chronic living disease with an 85 to 90% 10-year survival.

However, while congratulating ourselves on this positive change, we need to remind ourselves that this disorder predominately affects young women and that after ten years of living with SLE, they are still relatively young women. The challenge remains to ensure their survival with low morbidity into the second decade of the disease and beyond. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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