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Systemic lupus erythematosus

When to consider and management options

Background

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease that sometimes poses a diagnostic challenge, owing to the wide variety of clinical and immunological presentations. There can be a significant delay between onset of symptoms and the diagnosis of SLE. Appreciation of its typical presentations and diagnostic process can help general practitioners decide on the timing of specialist referral.

Objective

This article describes clinical and immunological manifestations that are required in the diagnosis of SLE, and provides an overview of management options.

Discussion

Some of the more common clinical and immunological manifestations of SLE are discussed and case studies to highlight the importance of accurate diagnosis are presented. Control of disease activity is crucial in alleviating symptoms, prevention of damage accrual and early mortality.

Keywords

lupus erythematosus, systemic; lupus erythematosus, discoid

CPD

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by multi-system manifestations. It is regarded as the prototypal connective tissue disease,[1] where the key pathogenesis relates to a dysfunctional immune system that results in over-production of various autoantibodies. Most of its pathology is mediated by either direct or indirect effects of these autoantibodies, as well as other components of the innate and adaptive immune systems.

The prevalence of SLE can vary greatly depending on race, disease definition and method of validation, but is generally accepted as a rare disease, affecting less than 0.1% of the population.[2–4] In Australia, SLE is more common and more severe in Indigenous Australians and descendants from South-East Asia.[5,6] It is nine times more common in females.[7] Generally speaking, SLE has a relapsing and remitting nature where patients experience episodes of symptom exacerbation interspersed with periods of relatively low disease activity.

Clinical presentation and diagnosis

While the clinical presentation of SLE can be quite diverse because the disease can affect virtually any organ system, patients typically present with symptoms relating to joint, skin or mucosal inflammation, or with a varying degree of haematological abnormality or constitutional features.[8] In some cases, patients may present with more serious and potentially life-threatening renal, neurological or cardiopulmonary complications.[9] Since the disease most commonly affects women of childbearing age, it is a diagnosis that should be considered when such a patient presents with symptoms relating to multiple systems.

Most SLE manifestations are the result of chronic inflammatory response at the affected end organ, which can be demonstrated using laboratory, imaging or histological measures. However, the lack of a gold standard test to confirm diagnosis often results in delays or misdiagnosis.

The Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) group has recently proposed a revised classification criteria,[10] which hopes to replace the 1997 American College of Rheumatology criteria,[11] to improve on the sensitivity and specificity (*Table 1*). These criteria are useful and give consistency in the

Table 1. SLICC classification criteria for systemic lupus erythematosus[10]

Clinical criteria	Immunologic criteria
Acute cutaneous lupus or subacute cutaneous lupus	ANA
Chronic cutaneous lupus	Anti-dsDNA
Oral ulcers or nasal ulcers	Anti-Sm
Non-scarring alopecia	Low complement
Synovitis involving two or more joints	Direct Coombs' test
Serositis	Antiphospholipid antibodies
Renal	
Neurologic	
Haemolytic anaemia	
Leukopenia (<4 000/mm^3) or lymphopenia (1 000/mm^3)	
Thrombocytopenia (<100 000/mm^3)	
Diagnosis of definitive SLE requires four or more criteria, with at least one clinical and one laboratory, with the exception of biopsy-proven LN (which requires fewer criteria). Criteria are cumulative and need not be present concurrently.	

classification of the disease, mainly for the purpose of research and surveillance. For clinicians, these criteria also serve as a good guide and reminder of the spectrum of disease, but, in clinical practice, many patients can present in a more forme fruste or atypical state.

Common clinical manifestations

Constitutional

Constitutional manifestations such as malaise, fatigue, fever and weight loss affect most patients at some time during their disease. They are, however, non-specific, and other non-SLE or non-rheumatological conditions (eg. infection and malignancy) can present the same way. Fibromyalgia is commonly observed in patients with SLE, but is considered a non-inflammatory complication of the disease. More sinister constitutional symptoms such as fever and weight loss warrant investigation before being attributed to lupus.

Musculoskeletal

Up to 95% of patients with SLE have intermittent arthritis.[12] The most common presentation is a symmetrical polyarthritis, affecting hands, wrists and knees. The degree of swelling is less prominent than seen in rheumatoid arthritis. Tenosynovitis is a relatively common musculoskeletal manifestation.[13] Joint deformities are uncommon, as are erosive changes on X-rays.[14] Myalgia is also a common manifestation, even though true myositis is relatively rare.

Cutaneous manifestations

The spectrum of cutaneous manifestations of lupus erythematosus (LE) is broad, but the most classical forms associated with systemic LE are the acute malar and chronic discoid lupus erythematosus (DLE) rash. Both can be quite photosensitive in nature.[15,16]

Acute malar rash is a slightly raised erythematous rash of the face, particularly cheeks and nose, with nasolabial sparing, known as the 'butterfly' rash. A worsening of the rash usually accompanies a flare of systemic disease. Sometimes a more generalised form over the body is present.

DLE are characterised by slightly raised, scaly lesions that have a potential to scar. They can be found commonly on the scalp and face, and less commonly over the limbs and trunk. Only 5% of people with DLE have SLE, but conversely among individuals with SLE, 20% will have DLE.[17]

Subacute cutaneous lupus erythematosus is another lupus-specific rash. It is a common skin manifestation in drug-induced lupus. The rash is extremely photosensitive. The two main variants look as their names suggest: papulosquamous looks psoriasiform, and annular polycyclic gives a characteristic ring pattern.

Other cutaneous manifestations such as alopecia, oral ulcers, Raynaud's phenomenon, urticaria, lichen planus, vasculitis or nail fold infarcts are LE non-specific, but they often present at times when patients experience increased lupus disease activity.

Renal manifestations

Lupus nephritis (LN) is one of the more serious manifestations, and contributes significantly to mortality. It occurs in 30–50% of SLE patients during their disease course.[18,19] It is important to recognise that LN can be relatively 'silent', and symptoms are often driven by other organ involvement or non-specific constitutional symptoms. Renal involvement can be missed if urinalysis is not performed. Definitive diagnosis and information on prognosis can be obtained by renal biopsy, but presence of glomerular haematuria, proteinuria or casts, are the key features of LN.

Haematologic manifestations

The most frequent haematological manifestation of SLE is anaemia.[20] This is usually due to chronic inflammation, but sometimes an autoimmune haemolytic anaemia can be demonstrated. Leukopenia, such as lymphopenia or less commonly neutropenia, is also well recognised, but it rarely predisposes to infections. Thrombocytopenia may also be a recurring feature.

Serosal manifestations

Pleural and pericardial inflammation can occur during active SLE.[21] They can present as pleuritic chest pain, when associated with pleurisy or pericarditis. Less commonly, the presence of pleural or pericardial effusion may present with pleuritic chest pain with or without exertional dyspnoea. This symptom adds robustness to the criteria for identifying SLE. Other cardiopulmonary manifestations such

as interstitial lung disease, pulmonary hypertension or Libman–Sacks endocarditis are less common complications of the disease.

Common immunological manifestations

Antinuclear antibodies

The antinuclear antibodies (ANA) test is the serological hallmark of SLE. Up to 98% of patients with SLE will have a positive ANA,[22] making it highly sensitive and useful as a screening test. A negative ANA makes SLE very unlikely and other diagnoses should be sought to explain symptoms.

Both titre and pattern are relevant. A titre of 320 or greater is considered clinically significant.[23] Low-titre ANA can be found in an otherwise healthy population (*Table 2*).[24] The most common patterns observed in SLE are homogenous and speckled pattern while other patterns may be associated with other connective tissue disease. While the titre of ANA can fluctuate over time, it is not useful to repeat ANA testing unless there is still a question regarding the diagnosis. The finding of a positive ANA must be taken into context of the clinical manifestations. A positive ANA in the absence of the clinical features associated with connective tissue disease may be irrelevant. The test has generally poor specificity, and many autoimmune or non-autoimmune conditions can also be associated with a positive ANA (*Table 2*).

Other autoantibodies

Antibodies to double-stranded DNA (dsDNA) are specific for SLE. In some patients, an increase in anti-dsDNA titre may signify onset of disease flare.[25] Other autoantibodies, available on the extractable nuclear antigen-testing panel, can also be associated with SLE or other connective tissue diseases. Antibodies to Sm (anti-Smith), for example, are highly specific autoantibodies in SLE.

While antiphospholipid antibodies are not specific for SLE, they are part of the immunological abnormalities that can be associated with pregnancy morbidities and thrombotic complications. Testing should include anticardiolipin antibodies, lupus anticoagulant and anti-β2 glycoprotein 1.

Complements

Tissue deposition of immune complexes can fix complement in the classical pathway, and therefore results in a reduction of serum complement levels. C3 and C4 can be measured readily, and are now part of the SLICC classification criteria for SLE.[10] Complement levels are also used to gauge disease activity.[26]

Management

Systemic lupus erythematosus is a chronic inflammatory condition driven by a dysfunctional immune system. Sometimes patients are able to report known triggers, such as ultraviolet or hormonal exposure. Avoidance of these triggers would be sensible in preventing flares.

The overall aim of therapy is to control disease activity. Mild activity can be managed with non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose steroids, but more severe manifestations require prompt treatment with moderate-to-high doses of steroids to minimise organ damage. Steroid-sparing immunosuppressive medications should be considered early to prevent steroid-related morbidities.

Hydroxychloroquine is an effective treatment in SLE, especially for arthritis and rash. Furthermore, it has a protective effect in reducing damage accrual in the long term, and confers a survival benefit in SLE patients. Hydroxychloroquine is well tolerated and, when dosed appropriately, ocular toxicity is very rare.[27]

A range of immunosuppressive medications has been used as a steroid-sparing agent in SLE, such as cyclophosphamide and mycophenolate for lupus nephritis, although azathioprine and methotrexate are used commonly. Belimumab, which is a human monoclonal antibody that inhibits the activation of B-cells by interfering with a protein necessary for B-cell activity, has recently been approved by the Australian Therapeutic Goods Administration for treatment of moderately severe SLE.[28] This therapy is currently not easily accessed, as it has not been listed on the Pharmaceutical Benefits Scheme.

Other general measures that should be considered in SLE patients include cardiovascular risk reduction and optimisation of

Table 2. Conditions other than SLE associated with positive ANA[23,24]

Systemic autoimmune diseases	Organ-specific autoimmune diseases	Non-autoimmune associations
Scleroderma	Autoimmune hepatitis	Viral infections (Infectious mononucleosis, parvovirus, hepatitis C, HIV)
Sjögren's syndrome	Primary biliary cirrhosis	Bacterial infections (infective endocarditis, TB)
Polymyositis or dermatomyositis	Grave's disease	Parasitic infections
Rheumatoid arthritis	Hashimoto's thyroiditis	Malignancy
Mixed connective tissue disease	Idiopathic pulmonary fibrosis	Normal population 1:40 (25–30%) 1:80 (10–15%) 1:160 (5%)

bone protection. Patients with SLE are at significantly increased risk of premature atherosclerosis,[29] so smoking cessation and control of hypertension, dyslipidemia, obesity and hyperglycaemia are strongly recommended. Strategies to prevent osteoporosis should be considered in most patients because many are likely to require long-term glucocorticoid therapies.

Specialist referral to a rheumatologist is important to establish the diagnosis, to gauge disease activity and severity, and to guide disease management. However the role of the general practitioner (GP) is also imperative for the optimal management of this chronic disease. By better understanding the disease process and management, GPs can help patients comprehend the complexity of disease pathogenesis and priorities in treatment. GPs, working with the treating specialist, play a key part in the monitoring and management of the disease and associated co-morbidities. Furthermore, they are also well placed to offer patients ongoing support and counselling, especially for those who may find coping with a chronic disease difficult.

The case studies (see below) demonstrate the range and breadth of diagnostic challenges that can occur due to SLE.

Case study 1

A medical student, aged 24 years, presented with a 3-month history of fatigue and arthralgia. She has occasional mouth ulcers and alopecia. She has a photosensitive rash on her face. Investigation results:

- ANA 640 homogenous, positive anti-Ro, ESR 30, lymphopenia, low C3
- Normal urinary sediment and negative for protein.

She was diagnosed with SLE, and treated with NSAIDs as required and hydroxychloroquine.

Case study 2

A 35-year-old mother of two, presented with 6-month history of fatigue, lethargy and arthralgia. She has had intermittent episodes of chest pain with one presentation to emergency department without a specific cause found. She has now noticed increased swelling in her legs with puffy eyes. Investigation results:

- Urinary protein to creatinine ratio 0.38 (normal 0.02), MSU showed glomerular red cells, ESR 40, albumin 32
- ANA 1280 homogenous, positive anti-dsDNA and anti-Sm, low C3 and C4.

She was diagnosed with SLE, with renal biopsy showing Class IV lupus nephritis. She was treated with pulsed steroids and commenced on mycophenolate.

Case study 3

A sales executive, aged 48 years, presented with a prolonged episode of chest pain and was found to have acute coronary syndrome when she presented to emergency department. She was a non-smoker and had no relevant family history. Her background history included two episodes of pericarditis in her twenties, intermittent arthralgia and occasionally a low platelet count was noted. She also had two previous miscarriages. Investigation results:

- ANA 320 homogenous, positive anti-dsDNA, ESR 25, low neutrophil and platelet counts, low C3/4, normal urine sediment and no proteinuria
- Coronary angiogram found an irregular LAD with greater than 70% stenosis in the mid portion which was treated with thrombolysis, and a stent was inserted.

She was diagnosed with SLE, but current presentation was probably not due to active disease. She was started on hydroxychloroquine. In the next few months, she had an exacerbation of joint pain and was found to have synovitis at her wrists. Methotrexate was added to control her symptoms.

Conclusion

SLE is a multi-system autoimmune disease that is characterised by mostly chronic inflammatory effects on a variety of organs. Diagnosis of SLE can be challenging, but is based on demonstration of a number of clinical manifestations as well as immunological abnormalities. Referral to a rheumatologist is strongly recommended to assist with the diagnosis and make treatment recommendations. Management of SLE depends on the level of disease activity and can include general measures, NSAIDs and steroids. Immunosuppression is often required and specific targeted therapy is on the horizon.

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