GPs have key role in shared care of patients with SLE

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FIGURE 1
Malar rash in a patient with lupus. Around 60% of cases have cutaneous involvement

What are the clinical features of SLE?

SLE (SYSTEMIC LUPUS ERYTHEMATOSUS) IS A COMPLEX, HETEROGENEOUS AUTOIMMUNE DISEASE involving inflammatory processes in multiple organ systems. Classically, patients have an exacerbating and remitting course with increased morbidity and higher mortality compared with the general population.

Twenty to thirty years ago, the mortality rate was as high as 50% at five years. However, survival rates have improved considerably as a result of earlier recognition, introduction of corticosteroids and immunosuppressive therapy and the availability of effective treatment for co-morbid conditions. The current 20-year survival rate is 80%.[1,2]

GPs play a key role in early referral to specialist centres and subsequent shared care pathways for the management of these patients.

SLE mainly affects adults and is common in women between the ages of 20 and 40 years, with a female to male ratio of 9:1. First onset of SLE before puberty is uncommon, with paediatric lupus accounting for 8-15% of all cases.[3] Patients who are diagnosed postmenopause (late onset lupus) tend to have a milder form of the disease with an insidious onset, lower degree of disease activity, less multi-organ involvement but a significant risk of complications including accelerated atherosclerosis and premature death.

The prevalence in the UK is 28 per 100,000 suggesting that approximately 1 person in 3,500 will have lupus, but this is subject to ethnic variation.[4,5] The disease is most common in people of Caribbean or Asian descent. »



FIGURE 2
The hand on the right demonstrates the characteristic bluish discoloration of Raynaud's phenomenon in a patient with lupus, particularly in the distal part of the middle and index fingers, compared with the normal hand on the left



FIGURE 3
Alopecia and lupus rash on the forehead of a patient with SLE

The pathogenesis of SLE is multifactorial and encompasses multiple immunological, vascular and inflammatory processes,[6] which are triggered by a combination of environment (sunlight), genetics, infection and hormonal milieu. The hallmark of the disease is the formation of autoantibodies resulting in immune complex formation and complement activation.

CLINICAL FEATURES

Diagnosing SLE can be challenging because of the myriad of clinical features and substantial variability between patients.

GPs will commonly encounter constitutional symptoms, as well as skin and musculoskeletal manifestations, as these are the most common features. Non-specific symptoms such as overwhelming fatigue despite a good night's sleep, fever, weight loss and lymphadenopathy may be present. In such cases it is important to exclude infection, lymphoma, and solid organ tumours.

Major organ involvement may also occur (see table 1, p21) and includes renal, neuropsychiatric, cardiopulmonary, gastrointestinal, haematological and ocular features.

Skin

Cutaneous involvement is present in about 60% of cases[7,8,9] and typically manifests as a malar or butterfly rash that is often sun-induced. This is a macular or papular rash on the face that may spread to become a confluent symmetrical erythema over the bridge of the nose and malar bones, sparing the nasolabial folds (see figure 1, p19).

Active systemic disease is also associated with a generalised lupus rash, which can occur anywhere, and this may or may not be photosensitive. It can range from a maculopapular rash to annular, violaceous or urticarial lesions that are sometimes pruritic.

Discoid lupus is a cutaneous form of lupus characterised by a hyperkeratotic lesion with central atrophy, scarring and hypopigmentation.

Disfigurement caused by scarring, particularly on exposed areas such as the face, can pose cosmetic and psychological problems for patients.

Raynaud's phenomenon may also occur in SLE (see figure 2, left)

Joints

Joint involvement is inflammatory in nature with arthralgia, arthritis and/or tendinitis and occurs in about 90% of patients with SLE.[1] The knees, wrists and hands are the most frequent areas involved. Characteristically, it is symmetrical, episodic and accompanied by early morning stiffness. Joint damage is uncommon, non-erosive and associated with reducible deformities resulting from ligamentous and capsule laxity. This pattern is referred to as Jaccoud's syndrome. Early in the disease it can mimic changes in rheumatoid arthritis.

Mucosal ulceration

Mucosal ulceration is another common feature, occurring in up to half of all patients with SLE. Typically, the ulcers are superficial and painless and mainly found on the hard palate, buccal cavity and vermiform border, but may occur in the nose.[3] Lupus-induced mucosal ulceration may need to be distinguished from that caused by drugs such as methotrexate which can also cause oral mucositis as well as ulceration.

Alopecia

Patients may develop diffuse alopecia when the disease is active but this is usually reversible. Hair regrowth normally occurs once disease control is achieved. Patchy alopecia (see figure 3, above) may lead to scarring, particularly if it is associated with discoid rash and this can be permanent and very distressing for patients.

Table 1

1997 Update of the 1982 American College of Rheumatology (ACR) classification criteria for SLE and other clinical features

System	Feature	Definition	Other features
Cutaneous	1 Malar rash	Fixed erythema, flat or raised, over the malar eminences, sparing the nasolabial folds	Alopecia, Raynaud's phenomenon, general rash, subacute cutaneous LE, urticaria, bullous lesions, vasculitis, panniculitis
	2 Discoid rash	Erythematosus 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, from patient history or observed by a physician	
	4 Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician	
Musculoskeletal	5 Nonerosive arthritis	Involving 2 or more peripheral joints, characterised by tenderness, swelling or effusion	Arthralgia, myalgia, myositis, tendinitis, ligamentous laxity, osteonecrosis
Cardiopulmonary	6 Pleuritis or pericarditis	Pleuritis - convincing history of pleuritic pain or rub heard by a physician or evidence of a pleural effusion **or** Pericarditis - documented by ECG or rub or evidence of pericardial effusion	Pleural effusions, myocarditis, pneumonitis, Libman-Sacks endocarditis, interstitial fibrosis, pulmonary hypertension, shrinking-lung syndrome, dyspnoea
7 Renal		Persistent proteinuria >0.5g/day or >3+ if quantification not performed **or** Cellular casts – may be red cell, haemoglobin, granular, tubular or mixed	Nephrotic syndrome, renal insufficiency, renal vein thrombosis, hypertension
8 Neurological		Seizures – in the absence of offending drugs or known metabolic derangement, e.g. uraemia, ketoacidosis, electrolyte imbalance **or** Psychosis - in the absence of offending drugs or known metabolic derangement, e.g. uraemia, ketoacidosis, electrolyte imbalance	Organic brain syndrome, cranial neuropathies, peripheral neuropathies, cerebellar signs, stroke, transverse myelopathy
Laboratory	9 Haematological disorder	Haemolytic anaemia with reticulocytosis **or** Leucopaenia >4,000/mm^3 on ≥ 2 occasions **or** Lymphopaenia < 1,500/mm^3 on ≥ 2 occasions **or** Thrombocytopaenia <100,000/mm^3 in the absence of offending drugs	Anaemia of chronic disease, autoimmune haemolytic anaemia, lupus anticoagulant, thrombosis, splenomegaly, lymphadenopathy
	10 Immunological disorder	Anti-DNA: antibody to native DNA in abnormal titre **or** Anti-Sm: presence of antibody to Sm nuclear antigen **or** Positive finding of antiphospholipid antibodies (lupus anticoagulant or anticardiolipin antibodies)	Hypocomplementaemia, Anti-Ro, Anti-La Anti-RNP
	11 Positive ANA	Abnormal titre of antinuclear antibody at any point in the absence of drug	
Constitutional		-	Fever, malaise, anorexia, weight loss, lymphadenopathy
Gastrointestinal		-	Pancreatitis, hepatitis, peritonitis, ascites, vasculitis, ischaemia, subacute bowel obstruction

Adapted from *Systemic Lupus Erythematosus: A Companion to Rheumatology*[3]

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Cardiorespiratory symptoms

Cardiorespiratory symptoms are common. Patients may present with chest pain on inspiration caused by lupus-induced pleurisy or pericarditis, which may be associated with effusions. This needs to be distinguished from pleurisy secondary to infection and pulmonary embolus, both of which can occur in lupus patients. Chest pain on exertion may occur because of premature or accelerated coronary artery disease. Breathlessness on exertion may be caused by ischaemic heart disease or less commonly acute pneumonitis, chronic lung fibrosis or pulmonary hypertension.

Renal complications

Lupus glomerulonephritis is one of the most important systemic complications, occurring in about 30% of patients with SLE in the UK.[10] Other manifestations of renal involvement include microvascular thrombosis presenting with a slow increase in proteinuria, haematuria, worsening renal function, and uncontrolled hypertension, or rarely vasculitis.

Careful screening tests for renal disease need to be undertaken as it is asymptomatic. Urinalysis, looking for haematuria and proteinuria, is the most important and effective method to detect and monitor lupus nephritis. However, it is essential to exclude other conditions that can present with these features such as infection, menstrual blood loss and renal stones.

It is important for patients with confirmed proteinuria and/or haematuria to be referred promptly to hospital for further assessment. This will involve quantifying protein loss by measurement of 24-hour urine protein excretion, urine protein:creatinine ratio or albumin:creatinine ratio on spot urine samples. Renal function should be assessed by serum creatinine and estimated GFR.

Beware of new onset or worsening hypertension as this correlates strongly with proliferative nephritis and seek expert advice if this happens.

Renal disease in lupus is classified using the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis, which is based on biopsy findings as was its predecessor the WHO classification.[11] This has important prognostic implications and is used to guide therapeutic decisions, see table 2, right.[12]

Neuropsychiatric manifestations

Neuropsychiatric manifestations of lupus are well recognised but uncommon and include:

- epileptic seizures
- psychosis
- aseptic meningitis
- stroke
- transverse myelitis

Stroke may be caused by premature atherosclerosis, thrombosis, emboli and occasionally vasculitis.

Other symptoms

Ophthalmic manifestations are uncommon but potentially serious and need prompt specialist assessment.[13] Gastrointestinal manifestations are also possible but these are uncommon and rarely recognised (see table 1, p21).

Table 2

International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of Lupus Nephritis[11]

Clinical classification	Histological classification
Class I	Minimal mesangial proliferative LN
Class II	Mesangial proliferative LN
Class III and subclasses	Focal LN
Class IV and subclasses	Diffuse LN
Class V	Membranous LN
Class VI	Advanced sclerosis LN

Box 1

Drug-induced lupus

Certain drugs can provoke an autoimmune reaction with the formation of autoantibodies (ANA, anti-histone antibodies) and a clinical syndrome mimicking SLE. Severe nephritis and CNS involvement are rare. In the majority of cases, withdrawing the offending medication results in the disappearance of autoantibodies and resolution of clinical features.
The most common culprits include: minocycline; phenytoin; procainamide; hydralazine; quinidine; methyldopa; isoniazid; and chlorpromazine.

Box 2

Pregnancy and SLE

Women with SLE should be referred for pre-pregnancy counselling. As most women who develop SLE are of childbearing age, pregnancy and the issues surrounding it are of major importance. Lupus itself does not reduce fertility however factors such as high disease activity, hypertension, lupus nephritis, anti-phospholipid antibodies and immunosuppressive therapy may alter the outcome of pregnancy.

Pregnancy can effect lupus by increasing disease activity several fold[25,26] especially if there is active disease at the time of conception. It is vital that stable disease is achieved for at least six months before pregnancy to reduce the risk of flares during, and in, the postpartum period. Other risks for increased activity are cessation of corticosteroids and hydroxychloroquine.

The presence of Ro and La antibodies is associated with around a 1% risk of congenital heart block and 10% risk of neonatal lupus rash. Anti-cardiolipin antibodies and lupus anticoagulant antibodies are associated with significant increase in pregnancy loss, intrauterine growth restriction and preterm birth.

Drugs that are safe to use in pregnancy include: prednisolone; azathioprine; hydroxychloroquine; heparin; and low-dose aspirin. At present evidence suggests that MMF, leflunomide, cyclosphosphamide and methotrexate must be avoided and should be stopped at least three months before a planned pregnancy. Warfarin should be changed to heparin and aspirin during pregnancy.

Anorexia and abdominal pain with guarding because of serositis are the most common manifestations.

DIAGNOSIS

The diagnosis of SLE is traditionally based on a combination of clinical features and laboratory findings. Classification criteria have been established by the American College of Rheumatology (ACR),[14] see table 1, p 21). These stipulate that a minimum of four out of a possible 11 ACR criteria should be present in order for a patient to be classified as having SLE for the purposes of clinical trials and other studies.

Some patients may never achieve four criteria or may fall within the spectrum of overlap syndromes or mixed connective tissue disease. In such cases, patients with three ACR classification criteria, of which at least one must be clinical and one must be serological (an autoantibody), may be diagnosed by an expert (rheumatologist or nephrologist) as having lupus if other diagnoses are excluded and they have relevant features. These include biopsy-proven glomerulonephritis or other clinical manifestations that are not in the ACR criteria but suggestive of lupus, for example alopecia, skin vasculitis, Raynaud's phenomenon (see figure 2, p 20) and lung fibrosis.

Investigations

Any patient with suspected clinical features of lupus should be investigated for the presence of autoantibodies including anti-nuclear antibody (ANA), anti-double stranded DNA (ds-DNA) or antibodies to extractable nuclear antigens (ENA), as well as low complement (C3 and C4) levels. Early clues often come from abnormal haematological indices (low haemoglobin because of haemolysis, low platelet count, low white cell count most often lymphopaenia) and raised ESR without raised CRP. Inflammatory markers showing raised ESR and normal CRP levels are characteristic of SLE and related conditions such as primary Sjögren's syndrome.

Drug-induced lupus

It is important to establish what medications the patient is taking to rule out drug-induced lupus (see box 1, opposite).

Newer agents, such as anti-TNFα drugs, have been associated with a lupus-like illness.

MANAGEMENT

Treatment is varied and dependent on the clinical manifestations. It is best planned by an appropriate specialist depending on disease severity and organ involvement. GPs should refer patients initially to a rheumatologist and, if available to them, one with a specialist interest in SLE, who can oversee/co-ordinate the overall care of the patient. However, other specialist care may be enlisted, for example a nephrologist in the case of diagnosing and managing lupus nephritis. Other system-specific disease may also require relevant specialist input. Treatment will often include the use of corticosteroids, by various routes, at different points in disease management.

In addition, some experts advocate the use of hydroxychloroquine, an antimalarial, as a principal drug in all SLE patients. It is beneficial in the management of mucocutaneous, musculoskeletal, serosal and constitutional symptoms. Recently, it has been shown in several studies to have cardioprotective and survival enhancing properties, by reducing total cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides (TG).[15,16,17] Patients require annual visual acuity monitoring because of the risk of hydroxychloroquine-related maculopathy but this is rare if the dose does not exceed 6.5mg/kg/day.[18]

Other agents used in addition to reduce the risk of cardiovascular disease in these patients include aspirin, anti-hypertensive agents especially ACE inhibitors, and cholesterol-lowering drugs. Patients should also be given advice on lifestyle to influence modifiable risk factors such as smoking, obesity and exercise.

As UV light is a major factor known to initiate or exacerbate cutaneous disease, patients must be fully informed about the importance of sun avoidance and/or protection with clothing and high factor sunscreen, usually SPF 25 and above. Local treatment is with topical or intralesional steroids, but long-term use must be avoided. In severe and/or refractory cases, systemic steroids are used. Topical tacrolimus, a calcineurin inhibitor, may also be used as adjunctive therapy.[19]

Joint symptoms can be managed with analgesics and NSAIDs. The latter need to be used with caution to avoid worsening the disease-associated risk of premature atherosclerosis. Control of active disease may require immunosuppressive treatment with corticosteroids, methotrexate, azathioprine or ciclosporin. These disease modifying anti-rheumatic drugs (DMARDS) need to be regularly monitored. Only hydroxychloroquine, corticosteroids and azathioprine are licensed for use in lupus.

Severe organ disease is managed initially with pulsed intravenous corticosteroids and cyclophosphamide therapy and once remission is achieved, patients are put on maintenance therapy usually with azathioprine. Mycophenolate mofetil (MMF) is increasingly being used for inducing and maintaining remission but is not yet licensed for lupus. Newer biological drug therapies, such as rituximab, a monoclonal anti-CD20 chimeric antibody that targets and depletes B cells but not plasma cells, are being investigated for use in lupus. Further guidance may be sought by consulting the EULAR recommendations on the management of SLE.[9]

As most women who develop SLE are of childbearing age, pregnancy and the issues surrounding it are of major importance (see box 2, opposite).

Monitoring

Monitoring disease activity, response to therapy and accumulation of long-term damage can be performed using validated objective scoring systems. Common methods include the BILAG (British Isles Lupus Assessment Group) Index and SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) for measuring disease activity and SLICC/ACR (Systemic Lupus International Collaborating Clinics) damage index for recording multi-organ damage.[20,21]

PROGNOSIS

SLE has a bimodal pattern of mortality, demonstrating an early peak, less than five years from diagnosis and a later peak, more than five years after diagnosis, increasingly due to cardiovascular complications.[2] Early death in lupus is usually due to active disease, lupus nephritis and/or sepsis. As longevity of patients with »

key points

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The prevalence of systemic lupus erythematosus (SLE) is 28 per 100,000 suggesting that approximately 1 person in 3,500 will have lupus, but this is subject to ethnic variation. The disease is most common in people of Caribbean or Asian descent. SLE mainly affects adults and is common in women between the ages of 20 and 40 years, with a female to male ratio of 9:1.

The pathogenesis of SLE is multifactorial and encompasses multiple immunological, vascular and inflammatory processes, which are triggered by a combination of environment (sunlight), genetics, infection and hormonal milieu.

Diagnosing SLE can be challenging because of the myriad of clinical features and substantial variability between patients. Cutaneous involvement is present in about 60% of cases and typically manifests as a malar or butterfly rash. Joint involvement is inflammatory in nature with arthralgia, arthritis and/or tendinitis and occurs in about 90% of patients with SLE. Mucosal ulceration is another common feature, occurring in up to half of all patients with SLE. Patients may develop diffuse alopecia when the disease is active but this is usually reversible. Cardiorespiratory symptoms are common with chest pain on inspiration due to lupus-induced pleurisy or pericarditis, which may be associated with effusions.

Lupus glomerulonephritis is one of the most important systemic complications, occurring in about 30% of patients with SLE in the UK. Careful screening tests for renal disease need to be undertaken as it is asymptomatic. Neuropsychiatric manifestations of lupus are well recognised but uncommon and include epileptic seizures, psychosis, aseptic meningitis, stroke and transverse myelitis.

The diagnosis of SLE is traditionally based on a combination of clinical features and laboratory findings and any patient with suspected clinical features of lupus should be investigated for the presence of autoantibodies.

Treatment often includes corticosteroids, by various routes, at different points in disease management. In addition, some experts advocate the use of hydroxychloroquine, an antimalarial, as a principal drug in all SLE patients. It is beneficial in the management of mucocutaneous, musculoskeletal, serosal and constitutional symptoms. Patients must be fully informed about the importance of sun avoidance and/or protection with clothing and high factor sunscreen. In severe and/or refractory cases, systemic steroids are used.

As longevity of patients with lupus increases they are at risk of increasing co-morbidities, either due to the disease and/or its treatment. These include premature atherosclerosis, hypertension, dyslipidaemias, diabetes, osteoporosis, avascular necrosis, infection and malignancies.

lupus increases they are at risk of increasing co-morbidities, either due to the disease and/or its treatment. These include:

- premature atherosclerosis
- hypertension
- dyslipidaemias
- diabetes
- osteoporosis
- avascular necrosis
- infection
- malignancies (especially non-Hodgkin's lymphoma and lung cancer in smokers)

Lupus patients develop cardiovascular disease earlier than the general population and overall women have a 5-6 fold increased risk of myocardial infarction, stroke and congestive heart failure.[22,23,24]

GPs can assist specialists in addressing risk factors, as well as the prompt evaluation and management of these co-morbidities.

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Useful information

Lupus UK
www.lupusuk.org.uk

European League Against Rheumatism (EULAR)
www.eular.org

Arthritis Research Campaign UK
www.arc.org.uk

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