Clinical review

Systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a multisystem autoimmune connective tissue disorder with various clinical presentations. It is prevalent among young women with a peak age of onset between the late teens and early 40s and a female to male ratio of 9:1. It is more common in certain ethnic groups, such as people with African or Asian ancestry. One study estimated the prevalence of lupus as 27.7/100 000 and as high as 206/100 000 in Afro-Caribbean women.[1] SLE is a chronic illness that may be life threatening when major organs are affected but more commonly results in chronic debilitating ill health. No single cause for SLE has been identified, though factors such as sunlight and drugs may precipitate the condition, and there is a complex genetic basis. Autoantibodies may be present for many years before the clinical onset of the disease, and there may be increasing numbers of antibodies just before symptoms develop, pointing to a multifactorial pathogenesis.[2]

Summary points

- Clinical presentations of systemic lupus erythematosus (SLE) range from chronic debilitating disease to life threatening organ dysfunction
- Early diagnosis is central to improving prognosis
- The antiphospholipid (Hughes) syndrome is commonly associated with SLE and can lead to recurrent thromboses and loss of pregnancy
- Malarial drugs, low dose corticosteroids, and immunosuppressive drugs are effective treatments, and newer agents such as mycophenolate mofetil and biological agents are promising
- Exogenous oestrogens may have a lower risk of lupus flares than previously thought but are still associated with a risk of thrombosis
- Accelerated atherosclerosis remains a considerable challenge

Sources and selection criteria

I used PubMed to identify references, supplemented by review articles and lectures from the American College of Rheumatology annual conference in 2005. Search terms included systemic lupus erythematosus, antiphospholipid syndrome, lupus nephritis, central nervous system disease in lupus, and fatigue. Articles were selected according to their impact on clinical practice. It is not possible to give a comprehensive guide to the management of all the possible complications of lupus so I have focused on areas where there is a consensus on management or where there have been major new developments.

Clinical presentation

The widely recognised presentation of a young woman with inflammatory arthritis and a butterfly facial rash is uncommon. Non-specific symptoms of fatigue, malaise, oral ulcers, arthralgia, photosensitive skin rashes, lymphadenopathy, pleuritic chest pains, headache, paraesthesiae, symptoms of dry eyes and mouth, Raynaud's phenomenon, and mild hair loss are more likely presentations. It is not surprising therefore that there is often considerable delay before the diagnosis is considered in patients with low grade disease. Patients may present acutely with major organ dysfunction that can affect virtually any organ, and diagnosis hinges on careful and thorough clinical evaluation and recognition of multisystem involvement. Renal involvement (lupus nephritis) presents insidiously, and if it is not detected early, the risk of progression to renal impairment is high.

The key to early diagnosis is clinical evaluation, which should include a complete systems review and examination and investigations guided by the extent of organ involvement. In primary care, a diagnosis of lupus or a related disorder is often apparent after clinical assessment, urinalysis for blood and protein, and basic investigations such as full blood count (often showing anaemia or cytopenia), renal and liver function, and acute phase reactants: a high erythrocyte sedimentation rate (ESR) with a normal C reactive protein (CRP) concentration are characteristic. A search for autoantibodies to nuclear antigens (antinuclear and antiDNA antibodies) and rheumatoid factor are the usual starting points while considering referral to specialist care. Antiphospholipid antibodies (anticardiolipin antibodies and the lupus anticoagulant) should be considered in women

Further references (w1-w13) are on bmj.com.

with previous morbidity in pregnancy or thrombotic events. In secondary care, more extensive testing is usually considered including detailed assessment of organ dysfunction and further autoantibody testing including complement levels and antibodies to the extractable nuclear antigens (ENA) such as Ro (SS-A), La (SS-B), ribonucleoprotein (RNP), and Sm.

It is difficult to predict which patients will progress to severe multisystem disease with a poor outcome. In general morbidity and mortality is higher in patients with extensive multisystem disease and multiple autoantibodies. Prognosis ultimately depends on the amount of damage (permanent scars or irreversible organ dysfunction) accrued over the course of the disease. Treatment therefore aims to eliminate inflammation and thrombosis, minimising damage. Accelerated atherosclerosis is now recognised as a major contributor to premature death through myocardial infarction and cerebrovascular disease.

Management of SLE

Most stable patients can be managed jointly between primary and secondary care. Primary care can contribute to monitoring patients with regular urinalysis, measurement of blood pressure, and renal, lipid, and glucose profiles, especially in patients on corticosteroids. Blood monitoring of immunosuppressive agents can also be undertaken jointly with shared care protocols. Early identification of disease flares is important, and secondary care facilities should be rapidly accessible for these patients.

Fatigue

Fatigue is a common and debilitating symptom that has proved difficult to evaluate and treat. The pathogenesis of lupus fatigue is complex, and it impacts severely on the quality of life. Factors determining fatigue include depression, pain, poor sleep quality, poor physical fitness, perceived lack of social support, and disease activity.[w1] Fatigue can be severe even when lupus is in remission. Identification of contributory factors such as anaemia and hypothyroidism are worthwhile as is treatment for depression, a common occurrence in any chronic illness. Two clinical trials of supervised exercise programmes showed benefit in terms of aerobic capacity, quality of life, and depression, and one study showed improvements in fatigue without causing disease flares, though the beneficial effects disappeared when the exercise programmes stopped.[w2 3] Anecdotal evidence suggests that treatment with antimalarial drugs may also be useful, though this is controversial and there are no trials to support this.

Arthralgia and skin rashes

Patients with isolated cutaneous lupus, including discoid lupus, are unlikely to progress to systemic disease and often respond to topical therapies. Weak topical steroid preparations in combination with hydroxychloroquine are often useful. More recently, topical preparations of tacrolimus and pimecrolimus have shown benefit in small open case series.[w3 w4]

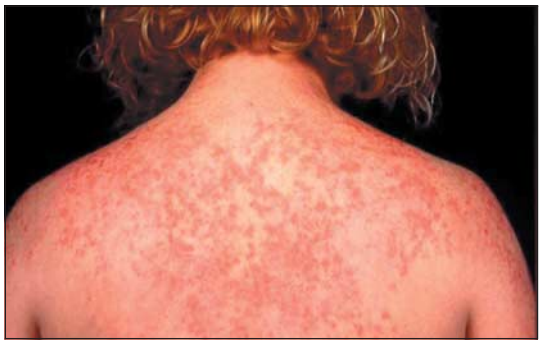

Fig 1 33 year old woman with anti-Ro (SS-A) antibodies and subacute cutaneous lupus responding to combination therapy with mepacrine and methotrexate

Though non-steroidal anti-inflammatory agents (NSAIDs) are widely prescribed for lupus patients with arthralgia, simple analgesics should be used. In particular the COX 2 selective agents are contraindicated because of the potential cardiovascular risks, and even conventional NSAIDs are not without gastrointestinal, renal, and cardiovascular risks.

Hydroxychloroquine remains the mainstay for patients with mild SLE, especially for those with arthralgia, skin rashes, alopecia, and oral or genital ulceration (fig 1). It should be considered in all patients as it is well tolerated and is disease modifying as well as having other useful properties including a weak antithrombotic action.[w5 w6] Other beneficial effects on serum lipids and blood glucose profiles and a lower risk of cataracts make it especially useful in patients who also need long term corticosteroids. Mepacrine is another safe antimalarial widely used in mild lupus, often in small doses and in combination with hydroxychloroquine when the latter has failed to produce a response on its own. Ocular toxicity is rare and, providing there is no major renal impairment and vision is checked annually, long term antimalarial therapy is relatively safe. No blood monitoring is needed, but patients should be warned about the risk of skin rashes, which may occur in 5-10% of patients and resolve on withdrawal.

Lupus nephritis

The most dramatic advances in treatment have been for patients with lupus nephritis—a powerful predictor of prognosis. The established and widely used regimen of long term high dose monthly or quarterly intravenous "pulse" cyclophosphamide pioneered by the National Institutes of Health (NIH) has been challenged on several fronts. Recent studies have shown that short courses of low dose pulse cyclophosphamide followed by azathioprine achieve similar results to the NIH regimen with less toxicity.[4] Mycophenolate mofetil, widely used in organ transplantation, is also showing tremendous potential in randomised controlled trials as both induction and maintenance therapy for severe proliferative lupus nephritis and may eventually supersede the use of cyclophosphamide for most patients.[5 6]

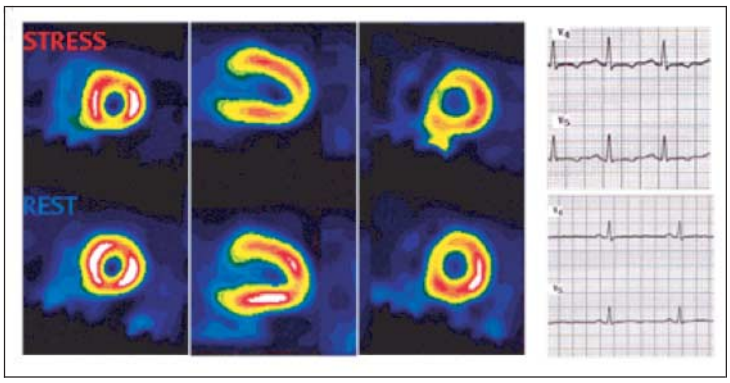

Fig 2 Woman aged 43 years with a 20 year history of SLE, lupus nephritis, and antiphospholipid syndrome presenting with angina. Nuclear medicine Myoview scan shows reversible ischaemia with S-T changes on stress. Coronary angiography confirmed diffuse coronary artery disease

Central nervous system disease

Central nervous system (CNS) disease in lupus remains a challenge in terms of pathogenesis, assessment, and treatment, and it may be better to consider CNS disease in terms of separate syndromes. Indeed the American College of Rheumatology classification criteria for CNS lupus has changed considerably from just seizures and psychosis to 19 different syndromes.[w7] There is now a clear distinction between CNS manifestations due to lupus and those due to the antiphospholipid (Hughes) syndrome (APS). Neuropsychiatric manifestations attributable to antiphospholipid syndrome include strokes, seizures, movement disorders, transverse myelopathy, demyelination syndromes, transient ischaemic attacks, cognitive dysfunction, visual loss, and headaches including migraine.[7] The differential diagnosis between multiple sclerosis and demyelination associated with APS may be difficult on imaging grounds,[w8] though electroencephalography may indicate cerebrovascular insufficiency in antiphospholipid syndrome.[8] Seizures are an important feature—in lupus patients these are more likely to be associated with antiphospholipid syndrome than with cerebral vasculitis, which is extremely rare in practice.[9]

The treatment of CNS lupus varies according to the particular clinical syndrome—for example, organic brain syndromes and psychosis are managed by multidisciplinary teams with corticosteroids, immunosuppression, and antipsychotic medication. There is no consensus on the ideal immunosuppressive agent (there are no clinical trials), though intravenous cyclophosphamide, methotrexate, and azathioprine may be considered. Predominantly thrombotic manifestations such as strokes, transient ischaemic attacks, seizures, and cognitive dysfunction associated with antiphospholipid antibodies may need anticoagulation.

Antiphospholipid (Hughes) syndrome

Though initially described in the context of SLE, it is clear that antiphospholipid syndrome is a syndrome in its own right that may complicate various autoimmune disorders. The hallmarks of arterial and venous thromboses and recurrent morbidity in pregnancy, often with livedo reticularis and thrombocytopenia, have stood the test of time.[10] Many clinical features arise from thrombosis in any organ system. Catastrophic antiphospholipid syndrome, characterised by severe widespread thrombosis, occurs in about 1% of patients with antiphospholipid syndrome and remains a serious complication with a poor prognosis. Treatment includes plasma exchange, corticosteroids, and intravenous immunoglobulin but immunosuppression, especially with cyclophosphamide, increases mortality.[11]

Pulmonary hypertension is a rare complication of lupus and may also be associated with antiphospholipid antibodies.[w9] Advances have been made in identifying patients with pulmonary hypertension associated with autoimmune rheumatic diseases. Treatment with agents such as sildenafil and bosentan, as well as the more established epoprostenol (prostacyclin) analogues, is promising.

Primary antiphospholipid syndrome rarely progresses to SLE. Antiphospholipid syndrome in patients who already have SLE, however, considerably increases the risk of damage and death.[12] The spectrum of clinical features of antiphospholipid syndrome continues to broaden with descriptions of renal artery stenosis,[13] metatarsal fractures,[14] avascular necrosis,[w10] and abnormalities of vascular function.[15] One of the features distinguishing Hughes syndrome from other coagulopathies is the tendency to develop heart valve disease, sometimes progressing rapidly to replacement.

Treatment remains controversial in terms of the level of anticoagulation required to prevent recurrent thromboses. Clinical trials suggest that for most patients with recurrent venous thrombotic events a target international normalised ratio (INR) of 2.0-3.0 provides reasonable protection against further thrombosis with a low risk of bleeding.[16 17] Patients at high risk of recurrent arterial thrombosis may continue to need higher target ratios of 3.0-4.5. Precise control is critical in this prothrombotic condition, and we encourage self testing in our unit, which has improved outcome.[18]

Cardiovascular risk

Women with SLE are at a considerably increased risk of premature atherosclerosis (fig 2). This seems to be independent of traditional cardiovascular risk factors, and lupus itself may contribute to the development of atherosclerosis. Inflammatory disease activity over long periods of time probably results in endothelial and vascular damage leading to atherosclerosis. Intensive management of disease activity with aggressive reduction of risk factors will be critical to improving outcome—an approach that is similar to management in diabetes. The role of corticosteroids remains unclear. Corticosteroids, especially in high doses, produce glucose intolerance, hypertension, central obesity, and dyslipidaemia. Low dose corticosteroids and other drugs such as antimalarials and immunosuppressive agents, however, may actually reduce the risk of atherosclerosis by minimising vascular damage.[19-21]

Tips for general practitioners

- Consider lupus when symptoms arise in several systems, especially in patients with African or Asian ancestry. An increased erythrocyte sedimentation rate with a normal C reactive protein concentration is characteristic of lupus in the absence of infection. Testing for antinuclear antibodies and rheumatoid factor is useful. Consider early referral to a specialist
- Antiphospholipid syndrome should be considered in patients with unexplained thrombotic events or losses of pregnancy, or both. Screening includes anticardiolipin antibodies and the lupus anticoagulant
- Urinalysis and evaluation of renal function and blood pressure may detect early renal disease, which is treatable
- Accelerated atherosclerosis is prevalent in autoimmune rheumatic diseases—intensive modification of risk factors and control of inflammatory disease are essential

Pregnancy, contraceptive pills, and hormone replacement therapy

SLE particularly affects young women, and pregnancy is associated with higher risks of complications. In general, providing that lupus is in remission at conception, the outcomes are good but may still be poorer than in otherwise healthy women.

Morbidity in pregnancy is common, especially if women have antiphospholipid antibodies. Complications include recurrent early loss of pregnancy, fetal death, pre-eclampsia, intrauterine growth restriction, and preterm delivery; and women are at increased risk of maternal thrombosis especially in the puerperium.

Risks of pregnancy increase markedly in the presence of lupus nephritis, hypertension, and active disease, especially at the time of conception, and pregnancy is contraindicated until remission can be achieved. Though pulmonary hypertension in lupus is uncommon, in pregnancy it confers a high risk of maternal death. All women with lupus should receive careful counselling before planning a pregnancy, both in terms of control of the disease and medications potentially toxic to the fetus.[w11] Specialist multidisciplinary units may increase the chances of successful outcomes.

Further information for patients

St Thomas Lupus Trust (www.lupus.org.uk)—St Thomas' Lupus Trust, Louise Coote Lupus Unit, Gassiot House, St Thomas' Hospital, London SE1 7EH (tel: 020 7188 3562)

Hughes Syndrome Foundation (www.hughes-syndrome.org)—The Hughes Syndrome Foundation, Louise Coote Lupus Unit, Gassiot House, St Thomas' Hospital, London SE1 7EH (tel: 020 7188 8217)

Lupus UK (www.lupusuk.com)—LUPUS UK, St James House, Eastern Road, Romford, Essex RM1 3NH (tel: 01708 731251)

Arthritis Research Campaign (www.arc.org.uk)—Arthritis Research Campaign, Copeman House, St Mary's Court, St Mary's Gate, Chesterfield, Derbyshire S41 7TD (tel: 0870 850 5000 or 01246 558033)

The role of exogenous hormones such as the contraceptive pill and hormone replacement therapy (HRT) in exacerbating or precipitating lupus has been controversial. Oestrogens might increase the risk of a disease flare in women with lupus. Two randomised controlled studies, however, recently suggested that use of the contraceptive pill does not significantly increase the risk of disease activity or disease flares over one year.[22 23] A further randomised placebo controlled study of HRT showed significantly more mild to moderate flares (but no increase in major flares) in the HRT group compared with the placebo group.[24] All these studies emphasise the risk of thrombosis associated with lupus, especially in the presence of antiphospholipid antibodies.

Novel treatments

There have been major advances in the treatment of SLE, especially with biological agents. Rituximab is a chimeric human-murine monoclonal antibody directed against CD-20 on B cells and their precursors but not against plasma cells. Rituximab is widely used in the management of lymphoma and is relatively safe and well tolerated. Several open studies have shown dramatic and long lasting remissions after only two to four infusions in patients who were previously unresponsive to conventional and even novel immunosuppressive agents such as mycophenolate mofetil.[25 w12] The optimum combination of rituximab with methylprednisolone and cyclophosphamide remains unclear.

Intravenous immunoglobulins are increasingly being used in the treatment of resistant lupus, though there have been no large randomised trials. They also have a role in patients who have concomitant infection and active lupus, in whom immunosuppression is risky, and have been used in the treatment of many clinical manifestations in SLE.[w13]

Clinical trials are currently assessing the potential of various peptides and biological agents such as abatacept (CTLA4 Ig) and epratuzmab in lupus. To date no medications of any class have ever been officially licensed for use in lupus, and these trials offer hope that several agents may be registered specifically for lupus patients.

Conclusion

Lupus was once considered a rare disease with a universally fatal outcome. The past 20 years have shown that this disorder is common and treatable. Most patients now have almost normal life spans. Delay in diagnosis, especially in patients with low grade disease, remains a problem, but the future is promising in terms of potential new treatments. The remaining challenges include improving the quality of life for patients by minimising use of corticosteroids, reducing infections and fatigue, and minimising cardiovascular risks that still claim considerable loss of life.

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Ethical approval: Not required.

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A memorable patient

Heartbroken, not heartsink

From the start our relationship was an uneasy one. As a young GP, I struggled to cope with this prickly, querulous woman who treated me with an air of irritated disapproval and deep dissatisfaction. Nothing pleased her, and whatever I did was wrong. Despite my best efforts, little changed as time passed, and the sight of her name on my appointment list became a heartsink moment. However, we battled on together—I wary and cautious, she imperious and demanding, both equally unsatisfied.

It was perhaps 10 years later that my partners and I were trying to improve the quality of the data we held on longstanding patients by asking them to complete a questionnaire. At our next consultation, my heartsink patient handed me the practice questionnaire, duly completed. In the family history section she had written in some detail of how her brother had been killed in the second world war.

It was my habit to run briefly through the questionnaire with any patient who brought one in. Seeing what she had written, I said cautiously, "Tell me about him."

After a moment of hesitation, she talked without pause for several minutes. She told me of their childhood together and their growing up; of outings, holidays, and escapades; of this adored older brother who always looked out for her and with whom she felt safe and secure. I'm not sure I had ever seen her smile before, but she was smiling now as, lost in time, she recalled those years. She finished by saying she felt her life too had ended on the day her brother died.

From that day our relationship steadily improved. Consultations were never easy, but my new understanding of her helped me cope. I felt she had shared something very precious with me. Perhaps she felt she had allowed someone to get a little closer to her. As the years passed, she often mentioned her beloved brother, recalling an incident or an amusing moment, always smiling as she did so. I smiled too, for I no longer saw her as a heartsink patient but as a sad, angry lady whose terrible loss had shaped her adult life.

Our final consultation before my retirement was typically testing; she was not going to let me off lightly even at this stage. Then came the moment to say farewell. We had known each other for more than 30 years.

"I shall miss our chats," she said, not mentioning her brother.

"I shall miss them too," I said, understanding.

We both smiled, but this time we each had a tear in the eye.

Ruth Booker *retired general practitioner, Twickenham (rgarrod@aol.com)*

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