SYSTEMIC LUPUS ERYTHEMATOSUS AND LUPUS-LIKE SYNDROMES

Elaine M Hay, Michael L Snaith

Classification criteria for systemic lupus erythematosus (revised 1982¹)

To be classified as having systemic lupus erythematosus, patients must have at least four of the following criteria in the course of their disease:

- Malar rash
- Photosensitivity
- Arthritis
- Renal disorder
- Haematological disorder
- Presence of anti-nuclear antibodies
- Discoid rash
- Oral ulcers
- Serositis
- Neurological disorder
- Immunological disorder

Systemic lupus erythematosus is one of a family of interrelated and overlapping autoimmune rheumatic disorders that includes rheumatoid arthritis, scleroderma, polymyositis, dermatomyositis, and Sjögren's syndrome. The disease can present as a wide variety of clinical features, reflecting the many organ systems that can be affected. This clinical diversity is matched serologically by a wide spectrum of autoantibodies, which tend to cluster in relation to the clinical pattern.

Systemic lupus erythematosus is rare: a general practice with 10 000 registered patients is unlikely to have more than three or four patients with the disease at any one time. It is nine times more common in women than in men, and nine times more common in Afro-Caribbeans and Asians than in white patients. Thus, general practitioners' experience will vary greatly according the ethnic mix of their registered population.

Clinical presentation

Consider systemic lupus erythematosus in a young woman presenting with "seronegative rheumatoid arthritis"

Jaccoud-type arthropathy; non-erosive deformity of fingers owing to tendons being affected.

Because lupus is so uncommon, one difficulty is considering the possibility in the first place, particularly if the presentation is atypical or the patient is elderly or male. Differentiating lupus from similar disorders can be difficult, particularly early in the course of the disease, because many of the clinical features are common non-specific complaints. Although classification criteria for lupus are widely accepted, they are more appropriate for classifying patients in clinical trials or epidemiological studies than for making a diagnosis in individual patients. Lupus should be considered when characteristic clinical features—most commonly arthralgia, mucocutaneous manifestations, and fatigue—occur in combination or evolve over time.

Arthralgia

Generalised arthralgia, with pronounced morning stiffness but little to find on examination, is characteristic, and pain may be considerable. Although symptoms may mimic early rheumatoid arthritis, joint swelling (synovitis) is much less noticeable. About 20% of patients will develop deformity (Jaccoud-type arthropathy) of the hands owing to tendons being affected. This is reversible in its early stages, but it can become permanent and joint instability may require surgery.

Classic malar "butterfly" rash of systemic lupus erythematosus after exposure to sunlight (reproduced with patient's permission).

Parvovirus "slapped cheek" rash.

Mucocutaneous manifestations

A wide variety of manifestations is possible. The classic malar "butterfly" rash is the textbook presentation; it usually presents abruptly after exposure to sunlight and lasts for several days or weeks. However, most facial rashes presenting in primary care are not caused by lupus. More common causes include acne rosacea and the parvovirus "slapped cheek" rash.

Factors that increase probability of associated connective tissue disease in patients with Raynaud's phenomenon

- Onset of condition in childhood or old age
- Asymmetrical manifestation of symptoms
- Severe disease threatening viability of peripheries
- Associated with other symptoms such as arthralgia, fatigue, rash, etc
- Associated with abnormal results of blood tests (such as raised erythrocyte sedimentation rate, anaemia, presence of antinuclear antibodies)

Radiograph showing changes of restrictive lung disease in patient with lupus—"shrinking lung" appearance and linear shadows. Pulmonary function tests may eventually stabilise, but pulmonary hypertension occasionally develops.

Rapid hair loss can be a useful marker of active disease and can lead to alopecia. The hair will, however, regrow when the disease remits unless the scalp is scarred. Ulceration of the mouth or, less commonly, the nose or vagina may or may not be painful, but it is also usually self limiting. Raynaud's phenomenon occurs in about half of patients at presentation, but it is less common and usually milder than with scleroderma or related syndromes. Conversely, most patients who present to their general practitioner with Raynaud's syndrome will not have systemic lupus erythematosus. If they are positive for antinuclear antibodies they are likely to eventually develop a connective disease.

Fatigue

Severe fatigue in conjunction with some of the above symptoms may reflect a flare up of the disease. Chronic fatigue, however, is almost invariable in established systemic lupus erythematosus and may reflect underlying depression or cardiovascular deconditioning.

Major organ disease

Patients greatly fear developing diseases of major organs such as the kidneys or central nervous system. Reassuringly, these do not occur in most patients, and when they do they are usually a relatively early feature. Nevertheless, they are potentially life threatening and are associated with a poorer prognosis overall.

Renal disease occurs in 20-50% of all patients at some time during their disease, but end stage renal failure is rare (<5%). The start of disease may be insidious, and patients should therefore have regular dipstick testing of their urine for protein to facilitate early and aggressive treatment.

"*Cerebral lupus*" is probably overdiagnosed. For example, anxiety and depression are common but are usually caused by psychological stresses associated with a painful, unpredictable, chronic illness rather than reflecting cerebral lupus. Management should focus on personal social problems such as isolation or marital stress. Headaches have a wide variety of possible causes. "Tension headache" can be difficult to distinguish from "lupus headache"—both may be unremitting and unresponsive to simple analgesics. The latter is extremely uncommon, however, and is usually associated with other features of active disease. Migraine is more common in patients with lupus than in the general population, particularly in patients with antiphospholipid antibodies.

Cardiopulmonary disease—Pleurisy and pericarditis may be presenting features, and pleuritic pain may mimic that of infection or embolism. Although lung disease is uncommon, it is difficult to treat.

Investigations

The erythrocyte sedimentation rate should not be relied on to dictate treatment decisions

If the test for antinuclear antibodies is negative, systemic lupus erythematosus is extremely unlikely

Blood tests are useful for confirming the diagnosis of systemic lupus erythematosus and for differentiating between various subsets of the disease but are less useful for monitoring disease activity. The most useful screening tests are a complete blood count, erythrocyte sedimentation rate, and testing for antinuclear antibody.

There is often a normochromic normocytic anaemia when the disease is active. Leucopenia or lymphocytopenia is common and is useful for differentiating between systemic lupus erythematosus and rheumatoid arthritis. Thrombocytopenia is an uncommon but well recognised complication of lupus. Measuring C reactive protein can be a useful test for distinguishing between a lupus flare and infection: it usually remains normal in a flare, unless accompanied by serositis or synovitis, but is elevated in infection. The erythrocyte sedimentation rate will be elevated in both and occasionally remains considerably elevated when the disease seems to be clinically quiescent.

Kidney biopsy in systemic lupus erythematosus

- May not be crucial for diagnosis of lupus glomerulonephritis if confirmatory features are present—known active systemic lupus erythematosus, urinary sediment with protein, casts, haematuria, and negative urine cultures
- Important as a guide to management when there is doubt as to the reversibility of renal damage

More than 95% of patients with systemic lupus erythematosus have antinuclear antibodies. However, such antibodies may be found in other autoimmune disorders and (in low concentration) in chronic infection and elderly people. Fewer than half of patients with lupus have antibodies to double stranded DNA at presentation: thus it is not a good screening test. However, rising titres of these antibodies, particularly if accompanied by falling concentrations of C3 and C4, may herald the start of renal disease. C3 and C4 are insensitive diagnostically. Antibodies to soluble cellular antigens (such as La, Ro, U1 RNP, and Jo-1) can be useful for distinguishing between lupus subsets.^{2,3} Antiphospholipid antibodies (such as anticardiolipin antibodies or lupus anticoagulant) identify a subset of patients at particular risk of thromboembolic complications or fetal loss.

Management

Patient support groups

- Support groups for patients with lupus can be most helpful for providing reassurance and reducing a patient's sense of isolation
- Further details can be obtained from:
Lupus UK
51 North Street, Romford, Essex RM1 1BA
Telephone (01708) 731251

The clinical diversity of systemic lupus erythematosus makes it one of the most difficult autoimmune rheumatic disorders to manage. General practitioners play a vital role in supporting patients with lupus and coordinating treatment, which can easily become fragmented among various hospital specialists. Close liaison between specialists and general practitioners is crucial for optimal patient care

Treatments for systemic lupus erythematosus

Non-steroidal anti-inflammatory drugs
For symptomatic relief

Antimalarial drugs (chloroquine, hydroxychloroquine)
For rashes, arthritis, and malaise

Corticosteroids
For severe flare
For maintenance treatment (in low doses)

Immunosuppressive drugs (azathioprine, methotrexate, cyclophosphamide, etc)
For severe flare (in conjunction with corticosteroids)

Additional treatments
For hypertension
For infection
For cerebral lupus (such as anticonvulsants)
For thrombosis
For haematological disorders (such as splenectomy)

Firstly, patients need explanation and reassurance, as the liability to episodic flare engenders insecurity and apprehension. It should be emphasised that serious complications are rare and that most patients have a normal life expectancy.

Preventing lupus flares

Patients should avoid exposure to sunlight (including sunbeds), which, as well as precipitating acute or subacute skin lesions, may also cause a generalised lupus flare. Sunscreens with a high protection factor (factor 15 or higher) effective against ultraviolet A and B should be applied liberally, and long sleeved clothes and sunhats should be worn in sunny weather. Topical corticosteroid preparations are sometimes helpful for chronic skin lesions but should be used sparingly to avoid thinning of the skin.

Oral contraceptive pills containing low doses of oestrogen are probably safe with mild lupus but should be used with caution by patients with severe lupus since they can theoretically cause a flare. They are contraindicated in patients with migraine, hypertension, a history of thrombosis, or high titres of anticardiolipin antibodies. Progestogen-only oral contraceptives are safe. Intrauterine devices should be avoided if possible because of an increased risk of infection. The evidence for use of hormone replacement therapy is not yet clear enough to be able to give general advice: probably the best policy is cautious introduction of low dose oestrogen when the disease is quiescent with closer than usual monitoring.

Differentiating between a lupus flare and infection can be difficult. Infection is an important cause of mortality in patients with systemic lupus erythematosus, particularly in those taking corticosteroids or immunosuppressive drugs. Furthermore, intercurrent infection can precipitate a lupus flare. Hence it is important to maintain a high index of suspicion and regard any flu-like or feverish episode lasting more than a day or two as infection unless proved otherwise. Sulphonamides should usually be avoided because they may cause rash or sudden profound neutropenia.

Symptomatic and supportive treatment

Most common symptoms of systemic lupus erythematosus can be safely treated symptomatically. Arthralgia, headaches, and non-specific chest pains may be helped by non-steroidal anti-inflammatory drugs or simple analgesics. Blood pressure should be checked regularly and hypertension treated intensively, particularly if there is renal disease.

Corticosteroid treatment for a severe lupus flare

Continuous oral treatment

Starting dose of prednisolone is usually 0.75-1 mg/kg
Treatment continued at same dose for 4-10 weeks depending on clinical response
Careful reduction can then be attempted

Intravenous pulses

Methylprednisolone 0.5-1.5 g repeated 1-3 times
Suppresses symptoms and may modify outcome, but avascular necrosis remains a risk

Intramuscular or oral minipulses

Such as 100-125 mg prednisolone acetate intramuscularly
Safer and cheaper than and probably as effective as other methods for symptomatic relief

Disease modifying drugs

Corticosteroids have transformed the outlook for patients with lupus but at a considerable price: much of the increased mortality late in the course of the disease (due to infection, cardiovascular disease, or fracture complications) may be attributable to these drugs. Once an acute episode is under control the dose of corticosteroid should be slowly reduced; complete withdrawal is optimal, but many patients are best managed with a small maintenance dose of perhaps 5 mg or less a day. The dose of prednisolone should not be increased for non-specific constitutional symptoms in the absence of corroborative physical signs or abnormal laboratory results, even though this may make the patient feel better. Few lupus complications require immediate corticosteroid treatment—it is often best to wait and see for a day or two to avoid frequent increases in dose for non-specific symptoms. Arthralgia in systemic lupus erythematosus responds poorly to low dose prednisolone and usually does not warrant a high dose.

Antimalarial drugs—Chloroquine phosphate (250 mg daily or alternate days) or hydroxychloroquine (200-400 mg daily) is the mainstay of treatment for skin or joint disorders. At these doses ocular complications are extremely rare, but it is prudent to use the lowest effective dose. Rheumatologists and ophthalmologists continue to disagree about the need for routine screening. Hydroxychloroquine is safer, though more expensive, than chloroquine. The total dose of chloroquine should not exceed 300 g, but it is not clear whether there should be such a limit for hydroxychloroquine.

Immunosuppressive drugs—Azathioprine, methotrexate, and cyclophosphamide are generally reserved for life threatening diseases of major organs such as the kidneys. They should be instituted and monitored at specialist centres, with appropriate counselling given about the short and long term side effects. Cyclophosphamide, whether continuous oral, pulse, or intravenous, is of proved benefit in treating renal lupus but is often associated with side effects that can be severe (such as infertility, premature menopause, or bladder cancer). Gamete storage should be offered before start of treatment when possible. Mesna should be used to reduce the risk of bladder toxicity with intravenous treatment, but oral mesna is not feasible for patients receiving continuous oral treatment. All these immunosuppressive drugs have the potential to suppress bone marrow activity, and frequent checks of complete blood count and differential white cell count are mandatory.

Outcome with systemic lupus erythematosus

Early studies reported that fewer than half of patients survived five years after diagnosis, but this figure has steadily improved. Recent studies report five year survival rates of 86-88% and 10 year survival rates of 76-87%. Patients who are non-white, male, or at the extremes of the age range fare worst. Most patients with lupus die from causes unrelated to the disease, but deaths (such as those due to infection or ischaemic heart disease) are increasingly related to treatment. Renal replacement therapy ensures that death from renal failure is uncommon.

Pregnancy with systemic lupus erythematosus

There is no evidence for reduced fertility in patients with systemic lupus erythematosus, and pregnancy presents little hazard for the mother if the lupus is mild or stable. Pre-existing renal disease may, however, worsen during pregnancy, and complications such as hypertension may be more difficult to control. Pre-eclamptic toxæmia may be difficult to distinguish from renal flare.

There is an increased rate of fetal loss, particularly during the second trimester, in patients with high titres of antiphospholipid antibodies. Pregnancies in such women should be monitored carefully in specialist units. Overall, there is no increased risk of fetal abnormalities, but drug treatment during pregnancy may pose problems. Antimetabolites are contraindicated because of teratogenesis, but low dose prednisolone, chloroquine, and azathioprine are probably safe.

Magnetic resonance image showing avascular necrosis of hips. Avascular necrosis may affect any joint, and treatment with high dose corticosteroid is a particular risk factor.

Severe lupus glomerulonephritis: appearance confirms end stage renal failure with glomerular loss. Continued treatment with immunosuppressive drugs and high dose corticosteroids is unlikely to achieve any improvement in function and would probably result only in further toxicity. (With less histological change, further immunosuppression might be justified to delay need for dialysis).

Lupus-like syndromes

Livedo reticularis in patient with antiphospholipid syndrome.

Drugs implicated in causing lupus-like syndromes

Common

- Hydralazine
- Procainamide
- Anticonvulsants (phenytoin, hydantoin, primidone)
- Isoniazid

Rare

- Chlorpromazine
- Penicillamine
- Practolol
- Antithyroid drugs (propylthiouracil, methylthiouracil)
- Methyl dopa

Clinical features of overlap syndromes

- Raynaud's phenomenon
- "Sausage" digits
- Periungual vascular distortion
- Hyperglobulinaemia and presence of antibodies to several soluble nuclear and cytoplasmic antigens
- Relative lack of cerebrosis, antibodies to DNA, and immune complex glomerulonephritis
- Eventual outcome of cardiopulmonary disease

Sausage fingers of patient with mixed connective tissue disease.

Antiphospholipid syndrome

This may occur in patients with coexisting systemic lupus erythematosus or occur alone (primary antiphospholipid syndrome). It is characterised by thrombosis, livedo reticularis, and sometimes thrombocytopenia together with the lupus anticoagulant or antiphospholipid antibodies.

Subacute cutaneous lupus erythematosus

Intense photosensitivity and antibodies to La and Ro are the essential features of this relatively rare syndrome.

Discoid lupus erythematosus

In this condition lesions are obviously discoid, systemic features are rare and mild, and autoantibodies are low in titre.

Incipient lupus

Some patients do not progress to very active disease, and their condition is characterised by mild arthralgia, rashes, or serositis with weak positivity for antinuclear antibodies.

Neonatal lupus syndrome

A small proportion of babies born to mothers with systemic lupus erythematosus (which is often mild and may even have been unrecognised) develop the neonatal lupus syndrome. This syndrome appears to be restricted to babies whose mothers have antibodies to Ro (SS-A) or La (SS-B) antigens. A self limiting skin rash, which may be severe, is the most common presentation. Rarely, babies may have permanent heart block secondary to a conduction defect, which may require treatment with a cardiac pacemaker.

Drug induced lupus

Lupus-like syndromes may occasionally be induced by some drugs. They mostly consist of arthralgia with positivity for antinuclear antibodies, and renal disease is rare. Antibodies to DNA are rare, but antihistone antibodies are characteristic. The syndrome usually resolves when the offending drug is withdrawn, but antinuclear antibodies persist for months after.

Overlap syndromes

It has been suggested that the only true lupus syndrome consists of nephritis, photosensitivity, serositis, and antibodies to DNA. While this might be too purist a view, it is often difficult to categorise patients; criteria such as those for systemic lupus erythematosus¹ or those suggested for mixed connective tissue disease⁴ do not cover all situations. Convention, however, prefers some form of categorisation, and the syndromes usually termed overlap (though some prefer the term undifferentiated connective tissue disease) tend to have certain characteristic features. Patients also prefer their doctor to be able attach a label to their condition that is acceptable to others and carries some certainty with regard to prognosis and management.

Prognosis is on a case by case basis, depending on the rate of progression and severity and nature of involvement of organ systems. Management is similar in principle to that for systemic lupus erythematosus: the pattern of involvement dictating the treatment. It is clear that mixed connective tissue disease, for example, is not a robust syndrome; clinical expression tends to focus on a scleroderma-like, rheumatoid-like, or myositis-like syndrome, often with cardiopulmonary features dictating the outcome.

Elaine M Hay is senior lecturer in community rheumatology at the Staffordshire Rheumatology Centre, Stoke on Trent, and Michael L Snaith is senior lecturer in rheumatology at the Institute for Bone and Joint Medicine, University of Sheffield Medical School.

The ABC of Rheumatology is edited by Michael L Snaith.

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