Systemic lupus erythematosus

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Systemic lupus erythematosus (SLE or lupus) is a chronic inflammatory autoimmune disease of unknown aetiology that is subject to periods of exacerbation and remission. Treatments aimed at controlling disease activity remain primarily by immunosuppression, the prescribing of which is dependent on the development of any multisystem complications. With the establishment of dedicated lupus clinics using a multidisciplinary team approach, prognosis is better and treatment options continue to improve.

Systemic lupus erythematosus (SLE or lupus) is a chronic inflammatory autoimmune disease of unknown aetiology that commonly affects women of childbearing age. Similar to many other rheumatological diseases, it has a variable course and outcome and is subject to periods of exacerbation and remission. Frequently affecting the musculoskeletal system and skin, lupus can also cause inflammatory changes in the kidneys, lungs, heart and central nervous system. Owing to the diversity of potential systemic involvement, patients can present with a variety of different symptoms and are often referred to a host of different specialists, which can influence not only their acceptance of the disease, but also its management and the treatment options (Isenberg and Horsfall, 1998). Lethargy and fatigue are described as the most disabling of lupus symptoms.

Classification

The disease is classified as follows:
- Systemic lupus erythematosus (SLE), a diffuse multisystem disease affecting the skin and internal organs;
- Discoid lupus erythematosus (DLE), primarily affecting the skin;
- Drug-associated lupus-like syndromes related to drugs such as hydralazine, procainamide, phenytoin, minocycline and, more recently, celecoxib and to some anti-TNF drugs. Resolution of symptoms occurs after withdrawal of the drug in most cases;
- Antiphospholipid (Hughes’) syndrome, a form of lupus that manifests itself with a history of venous and arterial thrombosis and miscarriage.

Prognosis

Although mortality studies have shown considerable improvement in the past 20 years, lupus is still described as a disease of significant mortality. Complications such as renal disease, hypertension and neuropsychiatric involvement significantly worsen prognosis.

In those patients who also have antiphospholipid syndrome, mortality rates can increase, with significant morbidity arising from persistent disease activity (Drenkard et al, 1994). The most common causes of death include infections, atherosclerotic disease or organ failure resulting from active lupus (Trager and Ward, 2001), with malignancy suggested in a recent UK study (Moss et al, 2002). Lupus nephritis, responsible for up to 22 per cent of patients progressing to end-stage renal disease, requires dialysis or transplantation (Fraenkel et al, 2002).

Epidemiology

Reported as the most common connective tissue disease, lupus is 10 to 20 times more common in women than in men and is most likely to develop between the ages of 15 and 40 (Hakim and Cluney, 2002). Prevalence in the UK varies from 12.5 to 26 cases per 100,000 persons.

Causes of lupus

Although the cause of lupus is unknown, a number of different factors occurring at the same time are thought to be responsible. Stimuli include hormonal changes, environmental triggers such as ultraviolet light or exposure to certain drugs. There is also a genetic predisposition to developing lupus.

The immune response in lupus

The normal response of the immune system is to challenge and defend when the body is subject to attack from foreign substances (antigens) such as bacteria, viruses, fungi and parasites. Two broad categories can be described in the body’s immune response: first, cell-mediated immunity and, second, humoral immunity. Cell-mediated immunity destroys and contains harmful or foreign cells by activating T-lymphocytes. These cells are able to recognise ‘self’ and ‘non-self’, and will not react against ‘self’ cells. Humoral immunity relates directly to antibody and complement formation. Antibodies produced by B-lymphocytes recognise extracellular antigens, and are deposited throughout the body via the circulatory system. When an antigen is encountered, the cell-mediated response will release T-lymphocytes that can be either memory, killer, suppressor or helper T-cells. Working in conjunction with the T-cells, the humoral response will release B-cells as plasma cells or memory B-cells, which then secrete antibodies in order to destroy the antigen.

Cytokines that are produced by T-helper cells enhance the B-cells’ antibody response, increasing the antibody production. Cytotoxic T-cells respond when directly attacked, and then transform the B-cells into antibody-producing plasma cells. These B-cells manufacture the
specific antibody, which binds to the antigen and triggers the complement system (Douglas, 1998).

In autoimmune diseases such as lupus, antibodies are produced against the body’s own tissues and are termed autoantibodies. Antibodies to DNA (deoxyribonucleic acid) are found in high levels in the serum of patients with lupus, and can be subsequently deposited in the tissues, particularly in the kidneys, lungs, heart and brain. Immunoglobulins, more specifically the IgG antibody, prompt a non-specific defence mechanism known as the complement system, which is designed to become active when there has been bacterial invasion. This complement system becomes overactive in lupus and is often measured in times of flare.

Autoantibodies that can be measured in the blood include elevations of anti-nuclear antibody (ANA) (these can appear homogenous or as a speckled pattern), alongside antibodies found against other components of the nucleus, such as extractable nuclear antigen (ENA). Anti-Sm antibodies are highly specific for lupus, and other autoantibodies, for example, anti-Ro, anti-La, anti-RNP, and anti-P, identify particular patterns of disease. Autoantibody measurement is an invaluable aid to a diagnosis of lupus.

Pregnancy and lupus

All women with lupus need to be closely monitored during pregnancy, especially those who carry antiphospholipid antibodies, and those who are lupus anticoagulant positive and have a history of previous foetal loss. These women often require treatment with low-dose aspirin throughout their pregnancy and may be given subcutaneous heparin both during pregnancy, to prevent miscarriage, and postnatally.

The foetal death rate is as high as 45 per cent when lupus develops during a pregnancy, with serious maternal complications if lupus nephritis develops. Those women carrying the anti-Ro and/or La autoantibodies are at more risk of their infant developing complications after birth such as neonatal heart block and lupus skin rash. Low-dose prednisolone may be required if the disease flares either during birth (less common) or after it (more common). Women with lupus requiring contraception or hormone replacement therapy should be given progesterone-only preparations so as to prevent a hormone-induced lupus flare (Jarek, 1997).

Lupus and the skin

Patients with lupus classically present at some stage of their disease with a rash. A photosensitive malar or butterfly rash indicates systemic disease. The rash extends from the cheeks and over the bridge of the nose, sparing the nasolabial folds. It is usually erythematous but it can be macular with raised papules and/or plaques, with lesions healing without a scar. Acute photo-sensitive rashes can occur elsewhere and typically heal without scarring.

Subacute lupus is frequently associated with antibodies to anti-Ro/SS-A and these rashes are seen as or serpiginous (polycyclic) or with some central areas of scaling (psoriasiform). Areas of depigmentation can result, especially in dark skins.

Discoïd lupus begins as erythematous papules or plaques that develop into a larger discoïd (coin-shaped) chronic lesion with a central area of epithelial thinning, leading to atrophy with follicular plugging, and resulting in depressed central scarring, depigmentation and

### TABLE 1. DRUG TREATMENTS AND POTENTIAL SIDE-EFFECTS FOR PATIENTS WITH LUPUS

| Non-steroidal anti-inflammatory drugs (NSAIDs) | For symptomatic relief of joint and muscle pain. Side-effects include gastro-intestinal bleeding, which has been reduced by the introduction of the newer Cox-2 inhibitors. |
| Low-dose aspirin (75–150mg) used in the treatment of recurrent thromboses and anti-phospholipid syndrome. Given daily for anti-coagulation purposes. |
| Effective drugs for the treatment of skin and joint symptoms, also beneficial in treating lethargy. Hydroxychloroquine is commonly prescribed, with mepacrine. Side-effects of hydroxychloroquine are few, but can include gastro-intestinal disturbance. Rash and visual acuity need to be checked yearly. Mepacrine can cause a yellowish skin discolouration. |
| Corticosteroids | Prednisolone can be used as an oral daily dose or as an intravenous bolus (methylprednisolone). It has substantial anti-inflammatory effects and is able to suppress disease activity. Dosage is dependent on the severity of the disease. Following response, the aim of treatment is always to maintain steroids at the lowest possible dose in order to avoid steroid-induced complications such as diabetes, osteoporosis and hypertension. |
| Immunosuppressants | Used primarily in systemic lupus. The most commonly used drugs for lupus include azathioprine, methotrexate and, in systemic complications of lupus, cyclophosphamide. Monthly blood testing is essential to detect bone marrow suppression or liver abnormalities. Cyclophosphamide is less toxic when given intravenously and is particularly effective in the treatment of lupus nephritis. Counselling of patients before the start of therapy with cyclophosphamide is essential owing to known side-effects: reduction in fertility, haemorrhagic cystitis, or even potential bladder cancer. |

Drug treatment is always balanced with the management of disease activity, particularly in multiple organ involvement.

### REFERENCES


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Diagnosing lupus

Most patients will describe fatigue, malaise, rash, arthritis and weight loss. A diagnosis is made by making a systematic analysis of previous medical history, and undertaking a physical examination and serological investigations. Assessment of disease activity is crucial at all stages of managing lupus, but primarily at diagnosis in order to classify systemic involvement.

History from the patient will support initial information given by the referring physician, including any exposure to allergens, co-morbidities, social and family history and any previous exposure to drugs that may have triggered a lupus-like response. A full physical multisystem examination is performed. Investigations commonly requested include a full haematological screening and plasma viscosity, C-reactive protein, uric acid and electrolytes, liver function tests, calcium, phosphate, fasting glucose, lipids, thyroid-stimulating hormone, and complement levels. Full antibody screening is performed, including ANA immunofluorescence, DNA, crithidia, ss-DNA/antihistone (to eliminate drug-induced lupus), ENA (anti-Sm, anti-Ro, anti-La, and anti-RNP), antiphospholipid antibodies and lupus anticoagulant.

Other important assessments, both for diagnosis and ongoing management, include regular dipstick of urine for protein and blood, weight, body mass index and blood pressure measurement.

Managing and treating lupus

The aim of medical management is to control flares of the disease and reduce the risk of damage to internal organs, which often necessitates drug regimes that include immunosuppressants and steroids. Table 1 (p31) indicates the specific uses of these drugs.

The wider multidisciplinary team is vital in supporting medical management of lupus and in enabling patients to gain control over their disease. Newly diagnosed lupus patients should be offered nurse specialist, physiotherapist and occupational therapist consultations. Lupus nurse specialists are increasing in the UK, with most major centres offering this service to patients. These posts are often supported by funds raised by the self-help group Lupus UK, which also provides a patient helpline and excellent written information about all aspects of living with lupus (www.lupusuk.com).

Advice regarding sun protection to prevent photosensitive flare is vital, as up to 50 per cent of patients exhibit these symptoms (Gladman and Urowitz, 1995).

Managing a lupus flare

General symptoms such as increased lethargy/fatigue, increased arthralgias, exacerbation of rash, recurrent crops of non-healing atrophic ulcers and alopecia will indicate a flare. Serological investigations will often reveal changes in inflammatory marker. Other indications include a reduced platelet and white cell count (often seen as leucopenia and lymphopenia), a drop in complement levels (C3 and C4) and high levels of anti-DNA antibodies. Signs of possible systemic involvement include:

- Peripheral oedema and proteinuria (renal);
- Breathlessness and chest pain (pulmonary and cardiac);
- Headaches, mood changes, seizures (cerebral);
- Breathlessness, fatigue, bleeding and bruising with anaemia (haematological).

Immediate management of a lupus flare depends on the clinical findings, which may include increased doses of immunosuppressants or prescribing other immunosuppressants. Oral prednisolone is usually given to control the immediate symptoms. Active ongoing lupus can be life-threatening and serious systemic involvement needs to be treated as soon as possible.

Patient support

The value of meeting others with lupus cannot be underestimated as lupus, although more common than multiple sclerosis, remains a relatively unknown disease by the general population. Patients with lupus may not have the opportunity to meet others unless they attend a dedicated lupus clinic or are members of Lupus UK. Serious systemic complications are always the biggest fear for patients with lupus, which is an area that is addressed in detail during the consultation with the nurse specialist.

Future developments

Lupus research is on-going, and although no cure is yet available, treatments are effective if the disease is caught early. Newer immunosuppressant drug therapies include mycophenolate mofetil (MMF), a drug ‘borrowed’ from organ transplantation that has been proven to be effective in patients with cyclophosphamide-resistant lupus nephritis. Leflunomide has previously been effective in treating rheumatoid arthritis and is being evaluated in lupus. Tacrolimus has improved skin disease in patients with lupus who are resistant to cyclophosphamide or to cyclosporin.

Other novel therapies currently under trial include co-stimulatory molecule blockers, monoclonal antibodies and anti-cytokine therapies (Gescuk and Davis, 2002).

Conclusion

Lupus is a complex disease to diagnose, treat and manage. Patients are encouraged to take control of their lupus, managing it through support mechanisms such as Lupus UK.

It is important that patients are referred early for diagnosis and that they are also referred to members of the wider health professional team. Self-management and patient empowerment enable patients to make informed choices about their life. Meeting others with lupus allows them to share their experiences.