SYSTEMIC LUPUS ERYTHEMATOSUS

The connective tissue diseases or collagen diseases are a group of multisystem disorders with pathological changes in the connective tissue as well as in blood vessels. Specific manifestations distinguish the various connective tissue diseases from each other, but these diseases have overlapping features, that particularly in the early stages can make it difficult to differentiate between them. It included systemic lupus erythemaomatosis, systemic sclerosis, inflammatory myositis and Sjögren syndrome.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic Lupus Erythematosus (SLE) is an inflammatory multisystem disease with a variable course and prognosis. Clinical features include constitutional symptoms, as well as the effects of inflammatory changes that may occur in almost any organ system of the body. The most commonly involved systems are the skin and mucus membranes, joints, kidney, central nervous system and the lungs. Involvement of vital organs can have serious consequences. Involvement of one organ system e.g. the skin, joints or kidney, may dominate the clinical picture, but mild disease is often present in any other organs. Thus the diagnosis of SLE requires a high degree of suspicion.

EPIDEMIOLOGY

SLE occurs in all races worldwide. It is more common in black women of North America, oriental populations and the coloured population of South Africa. It is rare amongst black Africans. It is 12 times more common amongst women and then during their fertile years. Family and twins studies indicate genetics to be important in the etiology of SLE.
CLINICAL FEATURES

THE 1982 REVISED ACR CLASSIFICATION CRITERIA (SLE)
(4 or more required)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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<tr>
<td>1. Malar rash</td>
<td>Fixed erythema, flat or raised, over the malar eminences, sparing the nasolabial folds</td>
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<td>2. Discoid rash</td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging. Atrophic scarring may occur in older lesions</td>
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<td>3. Photosensitivity</td>
<td>Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation</td>
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<td>4. Oral ulcers</td>
<td>Oral or nasopharyngeal ulceration, usually painless, observed by a physician</td>
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<td>5. Arthritis</td>
<td>Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion</td>
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<td>6. Serositis</td>
<td>a) Pleuritis – convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion: or&lt;br&gt;b) pericarditis – documented by ECG or rub or evidence of pericardial effusion</td>
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<td>7. Renal disorder</td>
<td>a) Persistent proteinuria greater than 0.5g per day or greater than 3+ if quantitation is not performed&lt;br&gt;b) Cellular casts – may be red cell, haemoglobin, granular, tubular, or mixed</td>
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<td>8. Neurologic disorder</td>
<td>a) Seizures – in the absence of offending drugs or known metabolic derangement: e.g. uraemia, ketoacidosis, or electrolyte imbalance: or&lt;br&gt;b) Psychosis – in the absence of offending drugs or known metabolic derangement: e.g. uraemia, ketoacidosis, or electrolyte imbalance</td>
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<td>9. Hematologic disorder</td>
<td>a) Hemolytic anemia with reticulocytosis: or&lt;br&gt;b) Leukopenia – less than 4000/mm³ on more than two occasions: or&lt;br&gt;c) Lymphopenia – less than 1500/mm³ on more than two occasions: or&lt;br&gt;d) thrombocytopenia – less than 100,000/mm³ in the absence of offending drugs.</td>
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<td>10. Immunologic disorder</td>
<td>a) Positive LE cell preparation: or&lt;br&gt;b) anti-DNA: antibody to native DNA in abnormal titer: or&lt;br&gt;c) anti-Sm: presence of antibody to Sm nuclear antigen: or&lt;br&gt;d) false positive serologic test for syphilis, known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent Treponemal antibody test.</td>
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<td>11. Antinuclear antibody</td>
<td>An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time in the absence of drug</td>
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Constitutional complaints

Malaise, fatigue (often severe) and weight loss may be the presenting features or occur at any time in the course of the disease.

Dermatological involvement

Skin Manifestations

- The skin manifestations may be non-specific, but other lesions have a specific lupus histology.

Non-specific skin lesions include dilated capillaries at the nail base, bullous lesions, angioneurotic oedema, and buccal and nasal ulceration. Vasculitis in the form of splinter haemorrhages, larger vessel damage and gangrene affecting the fingers and toes is common.

Less common features of lupus are diffuse hyperpigmentation and lupus panniculitis. This is inflammation in fat tissue, that takes the form of a relapsing, nodular, non-suppurative lesion in subcutaneous fat tissue.

- Specific skin lesions of lupus.

1. The malar rash

The most characteristic lesion of lupus is the malar or butterfly rash of the face. It occurs in one-third of patients with SLE. This is a erythaematous elevated rash over the cheeks, roughly in the shape of a butterfly. It may be pruritic or painful and is often precipitated by sunlight. It may last for days or months. Large amounts of immune complexes are deposited at the epidermal-dermal junction and can be seen histologically with specific staining methods.
A similar lesion may occur in all sun exposed areas. The mechanism for this photosensitivity is thought to be certain light waves frequencies that damage DNA and lymphocytes in SLE patients. The damaged material then acts as an autoantigen.

2. Subacute Cutaneous Lupus Erythematosus.

These lesions are non-scarring (as opposed to the chronic lesions) and tend to come and go. They are very variable from erythematous papules or plaques with a slight scale forming round or annular lesions.

3. Chronic Discoid Lupus.

The chronic cutaneous lesions or discoid lesions of lupus may occur as the sole manifestation of the disease or as part or a systemic involvement. These lesions begin as erythematous plaques with scales. They may become thickened and develop a depigmented centre. Follicular plugging occurs with scarring. They occur on any sun exposed area and when wide spread they usually indicate other organ involvement. It is commonly found on the scalp with hair loss and areas of alopecia. Alopecia is a common feature of lupus.

The skin lesions of lupus:

Non-specific
Specific
- Butterfly rash
- Subacute, non-scarring
- Chronic discoid

Musculoskeletal involvement

Arthralgia occurs in 90% of patients, is polyarticular and often symmetrical. The pain may be continual, episodic or flitting in nature. Early-morning stiffness is common. Often few objective signs of arthritis can be found despite the patient complaining of a lot of joint pain. Severe arthritis with joint deformity occurs in 10% of cases.
Characteristically the arthritis of SLE is non-erosive, with no bone destruction as opposed to rheumatoid arthritis. The pathology is a perivascular infiltration of the joint capsule and tendons, resulting in laxity of these ligaments and joint subluxations and deformities. Only mild synovitis occurs, unlike the highly proliferative synovitis of rheumatoid arthritis. The finger deformities look identical to those of rheumatoid arthritis, but without the erosions or bone destruction of rheumatoid arthritis.

N.B. Both SLE and rheumatoid arthritis can cause severe finger deformities, but characteristically on X-ray there are no erosions in the SLE cases.

Synovitis of tendon sheaths is common and frequently results in tendon rupture. Patella or Achilles tendons ruptures are well described.

Other musculoskeletal features include:

- Subcutaneous nodules in 1-5% of patients. They are indistinguishable from those found in rheumatoid arthritis.
- Calcinosis which is also seen in systemic sclerosis.
- Chondritis.
- Avascular necrosis usually of the shoulder, hip or knee. This is a serious complication occurring in 5 to 10% of SLE patients, and is often, but not always associated with corticosteroid therapy

Myalgia occur in up to 60% of SLE cases, although a true myositis is rare.

**Pulmonary disease**

Pleuritic pain or pleuritis occurs in 40-60% of patients, while pleural effusions can be found in 20-30%. They are usually of small volume. Lung function tests and X-rays of the chest are often worse than the patient seems clinically. Lung fibrosis as well as interstitial pneumonitis can be expected in 15% of cases and pulmonary hypertension can on rare occasions be found. This is very serious. An acute pneumonitis mimicking bacterial infection with fever, cough and at times haemoptysis can occasionally be encountered.
Lung complications of SLE
- Pleuritic pain/pleuritis 40-60%
- Pleural effusions 20—30%
- Lung fibrosis 15%
- Pulmonary hypertension – rare.
- Acute pneumonitis

Renal involvement

Renal disease is very common and the most common cause of death in SLE patients. The urine of all SLE patients must be tested at each visit for proteinuria. The presence of proteinuria of more than 0.5g per 24 hours, or the presence of casts, are regarded as evidence of kidney involvement in an SLE patient. The World Health Organization (WHO) has subdivided renal lupus into four major categories according to biopsy-derived information. There is a difference of opinion as to precisely when renal biopsy should be undertaken in lupus patients, but this is mainly of specialist concern. Any SLE patient with proteinuria must be evaluated by a physician experienced in renal SLE.

N.B. Test the urine of all SLE patients at each visit for proteinuria.

Nervous system involvement

Manifestations of lupus affecting the nervous system can be subdivided into central or cerebral effects, peripheral lesions, and psychological aspects.

♦ Central cerebral involvement

Up to 40% of SLE patients suffer from headaches or migraine. Grand mal seizures occur in 5 % of cases, and hemiplegia may be due to primary neurological disease or secondary to hypertension, or associated with antiphospholipid antibodies. A variety of organic brain syndromes with poor memory and intellectual deficit are all well recognized and difficult management problems.
Movement disorders (chorea or ballismus) occur in a small group of patients. This is often linked to the presence of antiphospholipid antibodies.

♦ Peripheral neuropathy

Ten % of patients develop a peripheral sensory neuropathy in the course of their disease. Occasionally cranial nerve involvement is encountered, usually with severe active systemic disease, presenting with visual defects, tinnitus, vertigo, nystagmus, ptosis or facial palsies.

♦ Psychological aspects

Up to 70% of SLE patients suffer a variety of psychiatric abnormalities, including depression and anxiety. Whether these are the result of non-specific psychological stresses associated with a debilitating chronic disease or specifically caused by the disease itself is unknown.

Emotional lability, personality change, impairment of judgement, and difficulty in performing simple tests of cognitive function such as recall of serial numbers, all indicate organic involvement. The major psychoses, notably paranoia, schizophrenia, and hypomania, are well documented to occur with SLE.

Serositis

Serositis is common in SLE presenting as pleurisy, pericarditis or peritonitis.

Cardiac Involvement
Pericardial disease, usually in the form of a pericardial rub, is the most common, but most of the patients have little or no clinical symptoms. Large pericardial effusions are rare.

Myocarditis should be suspected in SLE patients with arrhythmias, conduction defects, cardiomegaly or unexplained tachycardia. Endocarditis in the form of nonbacterial vegetations (Libman Sacks nodules) vary from mild valvular thickening (common but with little or no functional problems) to large vegetations affecting the function of the valve. These are rare.

Coronary artery disease may be caused by coronary arteritis (rare) or generalised atherosclerosis that is common in late stage SLE.

**Liver Disease**

Serious liver disease is rare in SLE, although hepatomegaly is common. There is a strong correlation between active SLE, the use of non-steroidal antiinflammatory agents and raised liver enzymes. Should a young woman, with a polyarthritis of unknown cause, use a non-steroidal and her liver enzymes rise, SLE must be strongly suspected.

**Haematopoietic involvement**

A normochromic, normocytic anaemia, the ‘anaemia of chronic disease,' is present in up to 70% of patients with active disease.

Coomb’s positive haemolytic anaemia occurs in 10% of patients. Leucopenia and lymphopenia are the most frequent abnormalities of the white blood-cell count. In contrast, leucocytosis is rare in the absence of infection.

Thrombocytopenia (platelets less than 100 000/mm³) is common. This is rarely associated with bleeding episodes in lupus patients.
Other clinical manifestations of lupus

Raynaud’s phenomenon is found in 30% of patients. Cutaneous vasculitis, ulcers and gangrene of the fingers and toes are all well recognized in lupus patients. Vasculitis may manifest as necrotic ulcers, small cutaneous infarcts or leg ulcers around or just above the malleoli. Anorexia, nausea, vomiting, or diarrhoea will occur at some point during the course of the disease in over half of lupus patients, but frequently the cause will turn out to be iatrogenic. Abdominal pain is found in 10% patients the cause of which is usually mild, non-specific gastroenteritis. Very rarely a life-threatening mesenteric vasculitis can occur.

Pregnancy and lupus

Fertility is normal in the SLE patient and the majority of pregnancies do not adversely affect the mother. A flare up of the disease, especially renal involvement, may require the introduction of or increase in corticosteroids.

In contrast fetal outcome is much less certain. Spontaneous abortion and still birth occurs in 20% of pregnancies. There is a strong correlation between spontaneous abortion and the presence of antiphospholipid antibodies in the mother's serum. Lupus mothers who have anti-Ro or anti-La antibodies are prone to develop the neonatal lupus syndrome, with congenital conduction defects of the heart as well as skin rashes.

Lupus in males

SLE in males, especially Caucasian males, is uncommon, and does not differ from that seen in women.

Lupus in the elderly

Onset of SLE over the age of 60 years accounts for 10% of all SLE cases. The clinical onset of disease is more insidious, milder, and has a lower incidence of severe renal and neurological complications.
The antiphospholipid antibody syndrome and lupus

The clinical features associated with the antiphospholipid syndrome are venous and arterial thrombosis, thrombocytopenia, cerebral disease (including cerebrovascular accident, transient ischaemic attacks, chorea), recurrent fetal loss, and pulmonary hypertension. The syndrome may occur as a primary disease unassociated with any other disease, or as secondary disease. It is often associated with SLE, but also occurs in a variety of other diseases, including drug-induced lupus, rheumatoid arthritis, and acute infection.

Autoantibodies in systemic lupus erythematosus

The chapter on laboratory tests must now be consulted.

THE TREATMENT OF LUPUS

It is evident that the diverse effects of lupus require a variety of treatments. These will be divided into pharmacological and other approaches. However, it must be stressed that a number of general measures may be most useful, including those listed below.

1. Rest as appropriate
2. Avoidance of overexposure to heat and sunlight.
3. Attempting to adhere to a low fat diet and considering the addition of fish-oil derivatives.
4. Avoiding medium or high-oestrogen contraceptive pills. The use of progesterone only or the lowest possible oestrogen pill (or other methods of contraception) is advised.

Pharmacological

Lupus patients are treated with four main groups of drugs, often in combination. In general the patient with mildly active lupus can be managed with combinations of non-steroidal anti-inflammatory drugs and antimalarials. Corticosteroids in the main are required when non-steroidal anti-inflammatory drugs and antimalarials are
insufficient to relieve the symptoms. Corticosteroids are usually taken by mouth. Various controlled trials of immunosuppressive drugs in lupus have been reported. The group from the National Institutes of Health have argued strongly that intravenous boluses of cyclophosphamide, monthly in the first instance, subsequently every 3 months, are the treatment of choice in patients with severe renal involvement. The problems of side-effects have made others more wary about its routine use. Many European groups prefer to use steroids and maintenance doses of azathioprine.

**Diet therapy**

Supplementation of the diet by fish oils has been shown to be beneficial. In a double-blind cross over study in which all the lupus patients were put on to low-fat diets, those who were concurrently taking 10g of fish oil per day, were shown to have done significantly better over a 6–month period.

**Intravenous high-dose gammaglobulins**

A claim that this approach was of value in patients with severe renal lupus has not been substantiated.