SYSTEMIC LUPUS ERYTHEMATOSUS: PATHOGENESIS, CLINICAL MANIFESTATIONS AND DIAGNOSIS

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder with a broad spectrum of clinical presentations (1). There is a peak age of onset among young women between the late teens and early 40's and a female to male ratio of 9:1. Ethnic groups such as those with African or Asian ancestry are more at risk of developing the disorder and it may be more severe compared to Caucasian patients. 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.

This module will describe in detail the epidemiology, pathogenesis, clinical features and diagnosis of SLE.

Learning Outcomes:

At the end of this module participants should be able to:

1. Outline the epidemiology of SLE
2. Describe, explain and critically evaluate the evidence for the pathogenesis of SLE in terms of genetics and environmental and hormonal factors.
3. Describe the clinical manifestations of SLE in the musculoskeletal, dermatological, renal, respiratory, cardiovascular, central nervous, gastrointestinal and haematological systems.
4. Describe and evaluate the evidence for the existence of patterns of SLE expression in specific subsets of patients depending on age, gender, ethnicity and social class.
5. Classify and assess patients according to their severity of systems and use appropriate diagnostic criteria to influence both the morbidity and mortality of patients with SLE.

EPIDEMIOLOGY

There are many epidemiological studies on SLE from around the world and there is extensive data from the European Union (EU) and the United States of America (USA) (2-14).

Incidence

The incidence of SLE in the general population varies according to the characteristics of the population studied, i.e. age, gender, race, ethnic/national origin or period of time studied, but also depending on changes in classification criteria. In the EU, the annual incidence ranges between 3.3 cases per 100,000 persons per year in Iceland (7) and 4.8 cases per 100,000 persons per year in Sweden (5) (Table 1). In the USA, the annual incidence of SLE ranges from 1.8 to 7.6 cases per 100,000 persons per year (Table 2). The incidence of SLE may be increasing - for example the incidence of SLE in Rochester, Minnesota increased by a factor of 2.5 from the years 1950-1954 (4) to the years 1975-1979 (10).

Table 1: Incidence of SLE in several studies in Europe.

Location	Date	Incidence*
Sweden (5)	1982	4.8
Nottingham(6)	1989	3.7
Iceland (7)	1990	3.3
Birmingham (9)	1991	3.8

* Incidence rates per 100,000 persons per year; including males and females.

Table 2: Incidence of SLE in several studies in the USA.

Location	Date	Incidence*
San Francisco (2)	1973	7.6
Baltimore (3)	1977	4.6
Rochester (4)	1979	2.2
Rochester (10)	1992	5.8

* Incidence rates per 100.000 persons per year; including males and females.

Prevalence

Several prevalence studies in the general population also show marked variation. This variability may result from methodological differences in case ascertainment and socio-economic factors. However, true geographic differences cannot be excluded and may result from differences in genetic or environmental factors.

In 1982, Hochberg et al. (12) in England and Wales reported a prevalence of 12.5 cases per 100,000 women of all ages, and was higher at 17.7 in women of 15 to 64 years of age. More recent studies by Hopkinson et al. (6) indicate a prevalence of 25 cases per 100,000 persons in Nottingham and those of Johnson et al. (9) a prevalence of 28 cases per 100,000 persons. The highest prevalence in Europe has been described in Sweden with 39 cases per 100,000 persons (Table 3). The overall prevalence in the USA ranges between 14.6 and 50 cases per 100,000 persons (including white and black people) (Table 4).

Table 3: Prevalence of SLE in several studies in Europe.

Location	Date	Prevalence*
Finland (11)	1978	28.0
England-Wales (12)	1982	12.5**
Sweden (5)	1982	39.0
England (Leicester) (8)	1989	26.1
Iceland (7)	1990	36.0
England (Nottingham) (6)	1990	24.6
England (Birmingham) (9)	1991	27.7
Ireland (14)	1993	25.4

* Prevalence rates per 100.000 persons; both sexes combined.

** Females only.

Table 4: Prevalence of SLE in several studies in the USA.

Location	Date	Prevalence*
San Francisco (2)	1973	50.8
Rochester (3)	1980	40.0
Hawaii (13)	1989	41.8

* Prevalence rates per 100.000 persons; including males and females.

PATHOGENESIS

The pathogenesis of lupus remains unclear although the concept of apoptosis goes some way to explaining how the immune system may recognise predominantly intracellular antigens. Autoantigens are released by necrotic as well as apoptotic cells. Defects in the clearance of apoptotic cells have been described in SLE which may lead to aberrant uptake by macrophages which then present the previously intracellular antigens to T and B cells thus driving the autoimmune process (15). Recent work has expanded these concepts and dissected out possible defects in clearance of apoptotic bodies including complement deficiencies, defects in macrophage handling and presentation of these antigens to the immune system.

The most striking recent studies have demonstrated the development of autoantibodies years before the onset of clinical features of SLE and the antiphospholipid syndrome (APS) (16,17). These investigators utilised the United States Department of Defence serum repository containing some 30 million samples from service personnel taken at regular intervals. They identified 130 individuals with SLE and showed that autoantibodies to DNA developed in 72 patients on average 2.7 years prior to diagnosis and up to 9.3 years earlier. They also described the prevalence of other autoantibodies such as anti-nuclear, anti-Ro, anti-La, anti-Sm, anti-RNP (16) and anti-phospholipid antibodies (aPL)(17) prior to the development of clinical SLE. Antinuclear antibodies occurred earlier than anti-DNA antibodies and a significant number of these patients had a rise in the anti-DNA titres just prior to diagnosis. Interestingly, anti-Sm and anti-RNP antibodies appeared shortly before diagnosis suggesting a crescendo of autoimmunity resulting in clinical illness. This data also suggests that autoantibodies alone do not necessarily result in clinical disease and that other factors possibly genetic and environmental may be important. It may be possible in the future to predict the onset of clinical features of lupus by clinical assessment and monitoring the development of various lupus autoantibodies.

The potential pathogenicity of anti-DNA antibodies remains controversial. Several animal models and experiments suggest that these auto-antibodies are capable of producing renal lesions in severe combined immunodeficiency (SCID) mice. However, the evidence is less convincing in humans. This is especially true with the insights gained from therapy with B cell depleting agents such as rituximab where there is often a rapid clinical response with only moderate reductions in anti-DNA antibody levels (18).

Cytokine patterns may also be important in the pathogenesis of lupus. Recent studies have highlighted the over-expression of the type I interferon pathway in patients – the so-called 'interferon signature'. A large study has shown an association of a common interferon regulatory factor 5 (IRF5) haplotype driving elevated expression of multiple unique isoforms of IRF5 as an important genetic risk factor for SLE (19).

Abnormal signal transduction may also be important in the pathogenesis of SLE. For example decreased expression of TCR zeta chain, PKC theta, decreased PKC dependent protein phosphorylation, impaired translocation of NF-kB p65 and decreased production of IL-2 as well as functional variants in the signal transducer and activator of transcription 4 (*STAT4)* genes have all been described in T cells from SLE patients (19, 20).

Genetics

Genetic susceptibility to lupus is inherited as a complex trait and studies have suggested that several genes may be important. In particular an interval on the long arm of chromosome 1, 1q23–24, is linked with SLE in multiple populations. Clinically it is widely accepted that active SLE is characterised by elevated erythrocyte sedimentation rates but normal C-reactive protein (CRP) levels. Both CRP and complement as well as serum amyloid P protein are important in clearing apoptotic cell debris and the genes for CRP have been mapped to chromosome 1, 1q23–24, the so-called pentraxin locus. Russell and colleagues examined the inheritance of polymorphisms at the pentraxin locus in a family-based association study of SLE and found strong linkage disequilibrium within each of the *CRP* and serum amyloid P genes (21). They demonstrated that an allele of *CRP* 4 was associated with SLE. Furthermore there were two haplotypes that were significantly associated with reduced basal CRP expression: *CRP* 2 and *CRP* 4 and an allele of *CRP* 4 was associated with ANA production. Thus the authors proposed a genetic explanation of the link between low CRP levels, antinuclear autoantibody production and the contribution of these to the development of human SLE.

Another large study of individuals and multi-case families with SLE suggested that a single nucleotide polymorphism (SNP) within the programmed cell death 1 gene (PDCD1) is associated with the development of lupus in both European and Mexican populations. The authors showed that the associated allele of this SNP alters a binding site for a transcription factor located in an intronic enhancer, suggesting a mechanism through which it can contribute to the development of SLE (22).

Environmental factors

Sunlight is the most obvious environmental factor that may exacerbate SLE. Other factors have been considered and crystalline silica was the focus of studies from the south eastern United States where occupational exposure was hypothesised as a risk for developing lupus. A case control study found that more patients (19%) than controls (8%) had a history of medium- or high-level silica exposure from farming or trades suggesting that this may be associated with the development of SLE in a proportion of individuals though occupational exposure may be often difficult to quantify accurately (23). A further study found associations with self-reported occupational exposure to mercury, mixing pesticides for agricultural work and among dental workers although the actual numbers exposed was relatively small. Unlike scleroderma though there was no association with solvent use (24).

Epstein Barr virus (EBV) has also been identified as a possible factor in the development of lupus. EBV may reside in and interact with B cells. Gross et al (25) found a high frequency of EBV infected B cells in lupus patients compared to controls and these infected cells are predominantly memory B cells. There was no relationship with immunosuppressive therapy and furthermore patients with active lupus flares had more infected cells than patients with quiescent disease. Although other studies have suggested a causative role for EBV in SLE, these authors are more cautious and despite their findings of increased frequencies of infected cells, increased viral loads, and viral gene expression, they have not interpreted this as directly implicating EBV in the development of SLE and argue that it is also possible that the immune dysregulation of SLE may result in aberrant EBV expression. In contrast, studies in a mouse model found that direct introduction of the whole EBV nuclear antigen 1 protein can elicit IgG antibodies to Sm and to double-stranded DNA (dsDNA) thus supporting a putative role for EBV in the development of lupus. The paradox remains that although 90% of the adult population are infected by EBV, the prevalence of SLE remains low emphasising the multi-factorial nature of the pathogenesis of SLE.

Hormonal factors

SLE is a disease of women of child-bearing age and there have been many anecdotal reports of exogenous oestrogens exacerbating lupus or increasing the risk of developing this disorder. Oral contraceptive use in the Nurses Health Study was associated with a slightly increased risk of developing SLE with a relative risk versus never users of 1.9 (26). Hormone replacement therapy (HRT) has been associated with an increased risk of developing SLE though another study failed to show any increased risk. Several small studies have suggested that HRT is unlikely to increase the risk of flares in SLE though these studies in general have been small retrospective case series. The definitive prospective study is the SELENA trial which randomised women with SLE to receive HRT or placebo (27). Although there was no increase in major flares in the HRT group, there were significantly more mild to moderate flares in the HRT group compared to the placebo group. A number of women, including one in the placebo group, developed thrombotic events. Recent data has swung against the long term use of HRT although there may still be a role for using it for limited periods in women with SLE who are aPL negative who have severe menopausal symptoms. This study will inform patients and clinicians of the potential risks and confirms the view that HRT is contraindicated with women with aPL.

The use of the combined oestrogen containing oral contraceptive pill has been discouraged in lupus patients following anecdotal reports of serious disease flares. Two randomised controlled trials investigated the oral contraceptive pill in women with lupus. Petri et al randomised 183 women with inactive or stable low grade lupus activity to receive either a combined low dose oestrogen containing oral contraceptive pill or a placebo for one year (28). All participants practised other effective birth-control methods.

There were no differences in the rates of severe or mild to moderate disease flares in either treatment group and the authors suggest that this type of contraception may be considered in women with lupus who need effective birth control especially when receiving cytotoxics, for amelioration of menstrual disease flares and protection against steroid related bone loss.

Furthermore, Sánchez-Guererro et al. (29) randomised 162 women with SLE to combined oral contraceptive pills, progestin only pills or a copper intra-uterine device. At the end of one year there were no differences in disease activity scores or flare rates. This study included asymptomatic aPL positive patients and 4 patients (2 in each of the hormone groups) suffered venous thrombotic events. There was a higher infection rate in those women assigned to the intra-uterine device.

Taken together these studies provide some reassurance for lupus patients with mild stable disease who are aPL negative who wish to consider the use of the oral contraceptive pill. Both studies however highlight the thrombotic risk inherent in lupus patients, even if aPL are absent.

CLINICAL MANIFESTATIONS

Musculoskeletal involvement

Joints

Arthralgia occurs in about 90% of all patients with SLE. Characteristically, it is polyarticular, symmetrical, episodic and flitting in nature. The patients' symptoms often exceed the objective clinical findings and usually there is no clinically overt arthritis. Synovial effusions are uncommon and of small volume when they do occur. However, approximately 10% of SLE patients do have a deforming Jaccoud's arthritis. In contrast to patients with rheumatoid arthritis, the deformities are not usually associated with synovial hypertrophy or bony erosions. In fact, tenosynovitis is more common than erosive synovitis and is the cause of the "swan-neck" deformities and ulnar deviation seen in the Jaccoud's arthritis of lupus. Examination of the synovial fluid usually reveals a white cell count of less than 3000/mm^3, predominantly mononuclear cells. The fluid is often positive for rheumatoid factor and anti-nuclear antibody. Approximately, 1-2% of SLE patients also meet the American College of Rheumatology (ACR) criteria for definite or classical rheumatoid arthritis and have an erosive arthropathy .

Muscles

Clinically obvious muscle involvement has been reported in 30-50% of SLE patients. However, myalgia, muscle weakness and tenderness, may be due to a variety of other complications. Thus both corticosteroid and rarely chloroquine therapy may cause a myopathy. In addition, myalgia may be induced by an adjacent arthralgia, although only 5% of lupus patients have met the ACR criteria for both SLE and polymyositis.

Dermatological involvement

Cutaneous lesions may occur in up to 85% of SLE patients. The butterfly rash is erythematous, often blotchy, and found mainly over the malar bones and across the bridge of the nose (Fig. 1). Although it is the best known skin lesion, it is merely one of numerous ways in which lupus manifests cutaneously. Lesions such as maculopapular and discoid lesions, splinter haemorrhages, dilated capillaries at the nail base, bullous lesions, angioneurotic oedema, *livedo reticularis* (Fig. 2) and buccal, genital and nasal ulceration have also been described. Vasculitic skin lesions are usually found at the nailfolds and finger tips (Fig 3) or on the extensor surface of the forearm. When they occur around the malleoli, they may lead to tender, deep, leg ulcers which can take months to heal.

Many SLE rashes are exacerbated by ultraviolet light and indeed generalized lupus flares may follow exposure to direct sunlight with inadequate protection (Fig 4). A particularly photosensitive rash is subacute cutaneous lupus erythematosus (SCLE) which is often associated with anti-Ro antibodies (Fig. 5). Babies born to mothers with anti-Ro and/or anti-La antibodies are at risk of neonatal lupus syndrome (Fig 6).

The deposition of immunoglobulins at the dermal-epidermal junction in skin biopsies from patients with lupus was first reported over 40 years ago. These immunoglobulins are usually of the IgG or IgM isotype. Approximately, 90% of biopsies from lupus skin lesions have such immunoglobulin deposits which usually appear as a band along the dermal-epidermal junction, giving rise to the name the "lupus band test". In patients with SLE, deposition of immunoglobulin and complement may be found in clinically normal skin and is thus a useful adjunct to diagnosis since no such deposition is found in patients with discoid lupus or control subjects.

Figure 1 - Malar rash

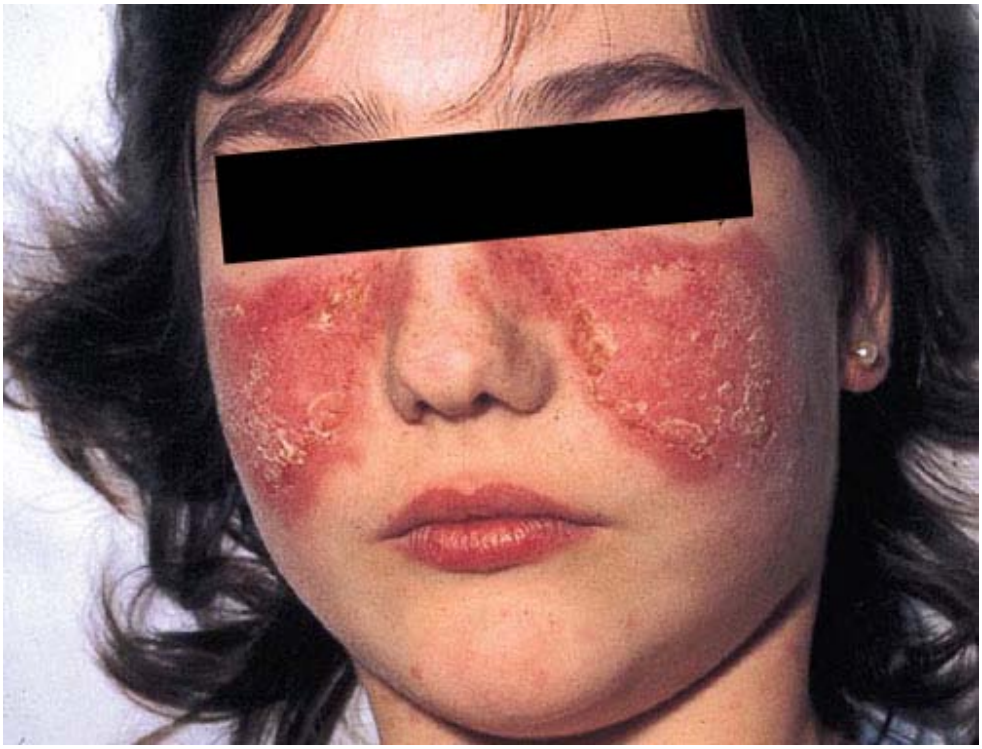


Figure 2 - Livedo reticularis

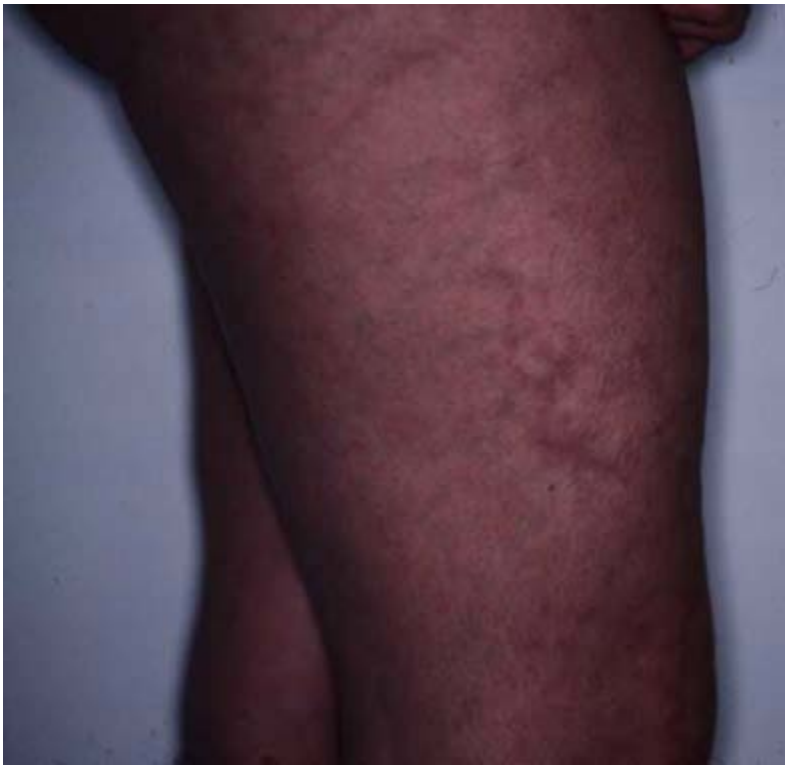


Figure 3 – Periungual erythema and nailfold vasculitis

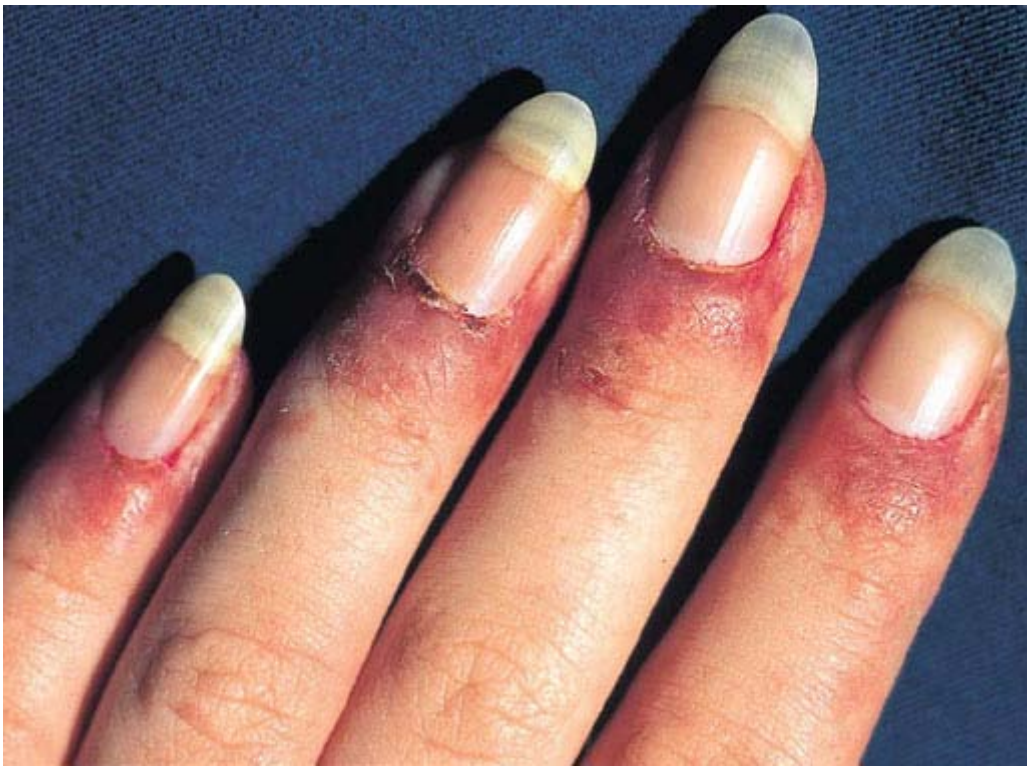


Figure 4 - Acute diffuse cutaneous lupus

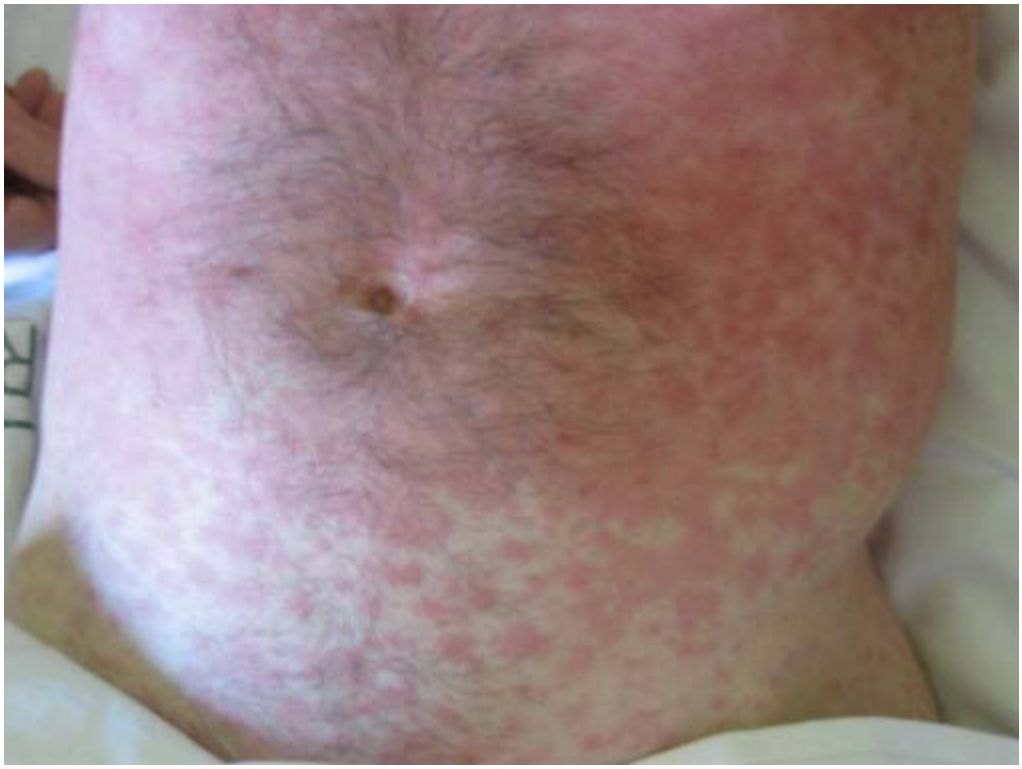


Figure 5 - Subacute cutaneous lupus erythematosus

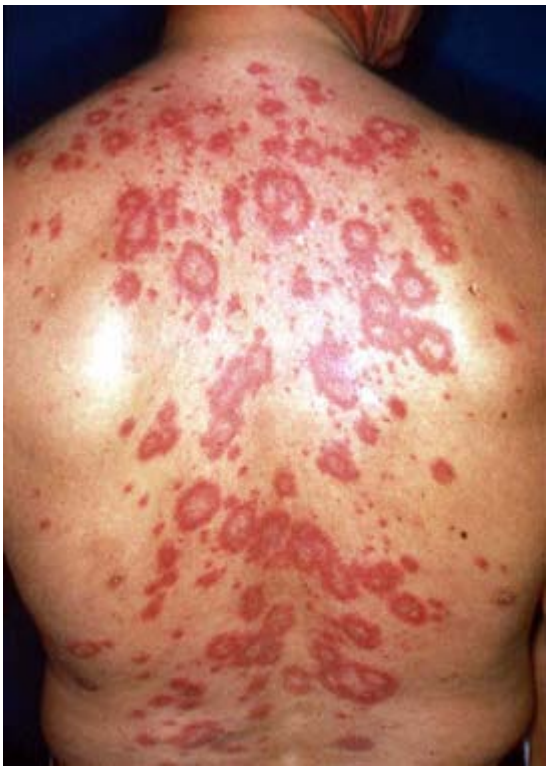
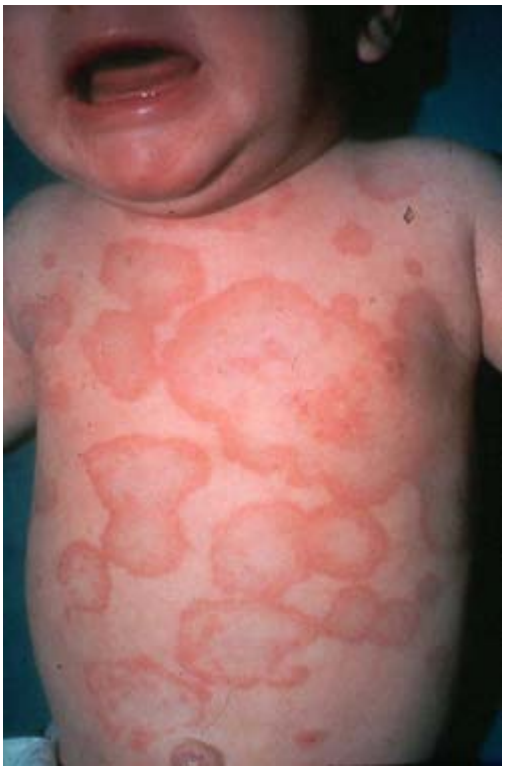


Figure 6 - Neonatal lupus



Lupus nephritis

More than 70% of patients with SLE have renal involvement at some stage of their disease. The World Health Organisation (WHO) classification for lupus nephritis has been updated to allow more accurate descriptions of renal histopathology specimens by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) (30) (Fig. 7 - 9) (Table 5). These descriptions allow better communication between pathologists translating static images from histology slides into meaningful descriptions of the huge variety of biopsy appearances for clinicians. Of the different pathological classes, diffuse proliferative glomerulonephritis (Class IV) has the worst prognosis, resulting in 11-48% of patients with end stage renal disease at 5 years.

Figure 7 - Kidney Biopsy: Class III (Focal Proliferative) Lupus Nephropathy

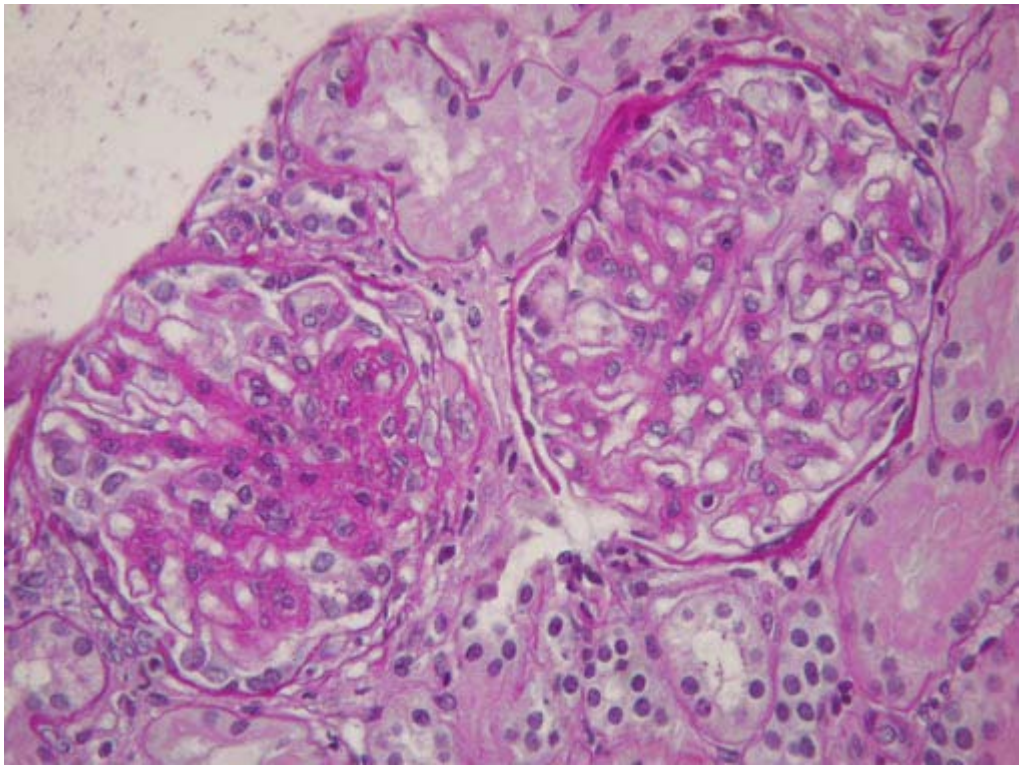


Figure 8 - Kidney Biopsy: Class IV (Diffuse Proliferative) Lupus Nephropathy

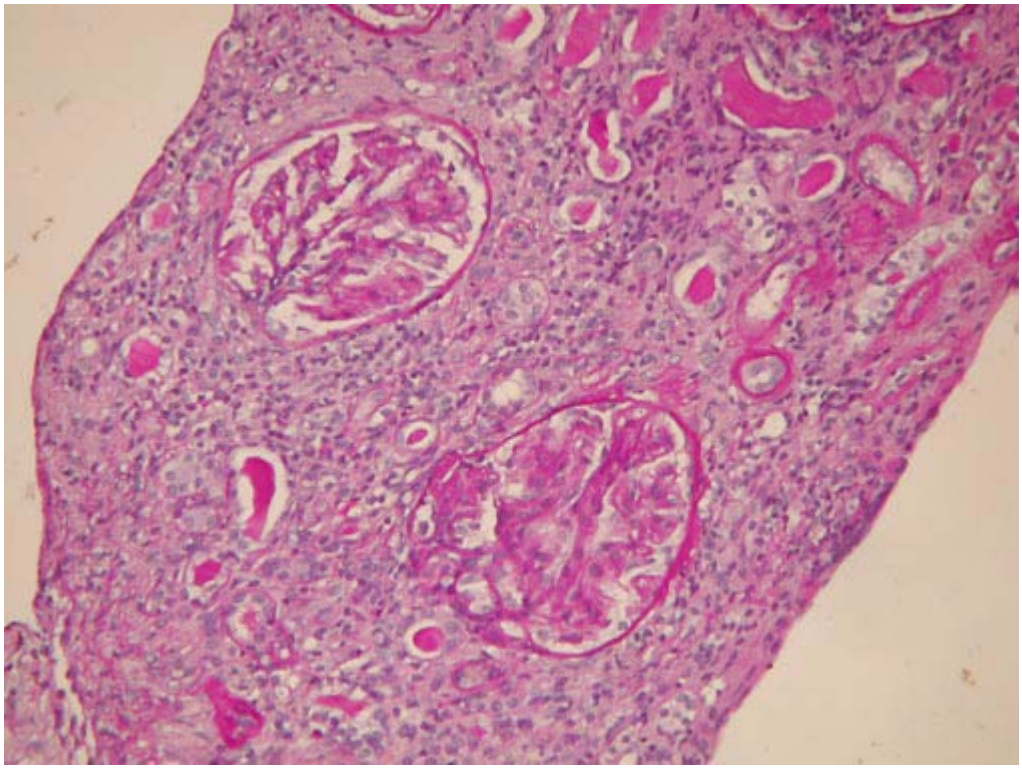


Figure 9 - Kidney Biopsy: Class V (Membranous) Lupus Nephropathy

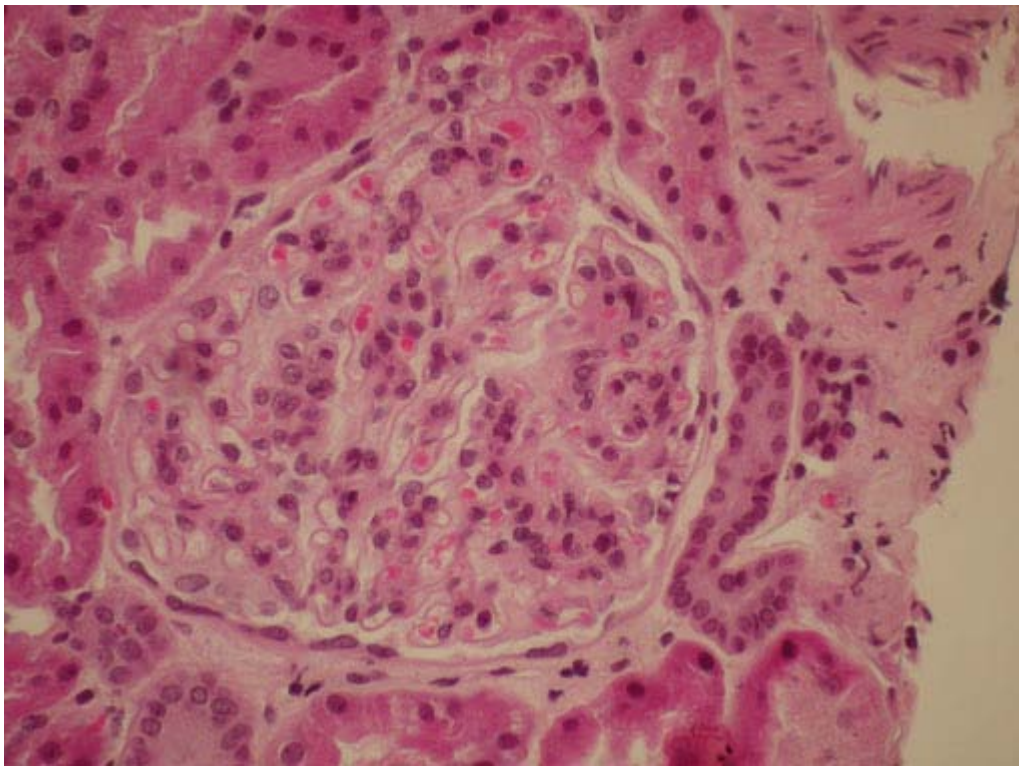


Table 5: International Society of Nephrology/Renal Pathology Society 2003 classification of lupus nephritis

Class I
Minimal mesangial lupus nephritis
Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II
Mesangial proliferative lupus nephritis
Purely mesangial hyper-cellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits
May be a few isolated sub-epithelial or sub-endothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III
Focal lupus nephritis[a]
Active or inactive focal, segmental or global endo- or extra-capillary glomerulonephritis involving <50% of all glomeruli, typically with focal sub-endothelial immune deposits, with or without mesangial alterations
Class III (A)
Active lesions: focal proliferative lupus nephritis
Class III (A/C)
Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)
Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV
Diffuse lupus nephritis[b]
Active or inactive diffuse, segmental or global endo- or extra-capillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse sub-endothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental(IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class IV-S (A)
Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)
Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)
Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)
Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)
Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V
Membranous lupus nephritis
Global or segmental sub-epithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed
Class V lupus nephritis show advanced sclerosis
Class VI
Advanced sclerosis lupus nephritis
≥90% of glomeruli globally sclerosed without residual activity

[a] Indicate the proportion of glomeruli with active and with sclerotic lesions.
[b] Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents.
Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.

Lungs

The immunosuppressive therapy required by many SLE patients predisposes them to concurrent infection. The lungs are a frequent target for this "secondary" infection and bacteria (including tubercule bacilli), viruses and fungi may all cause pneumonia in lupus patients.

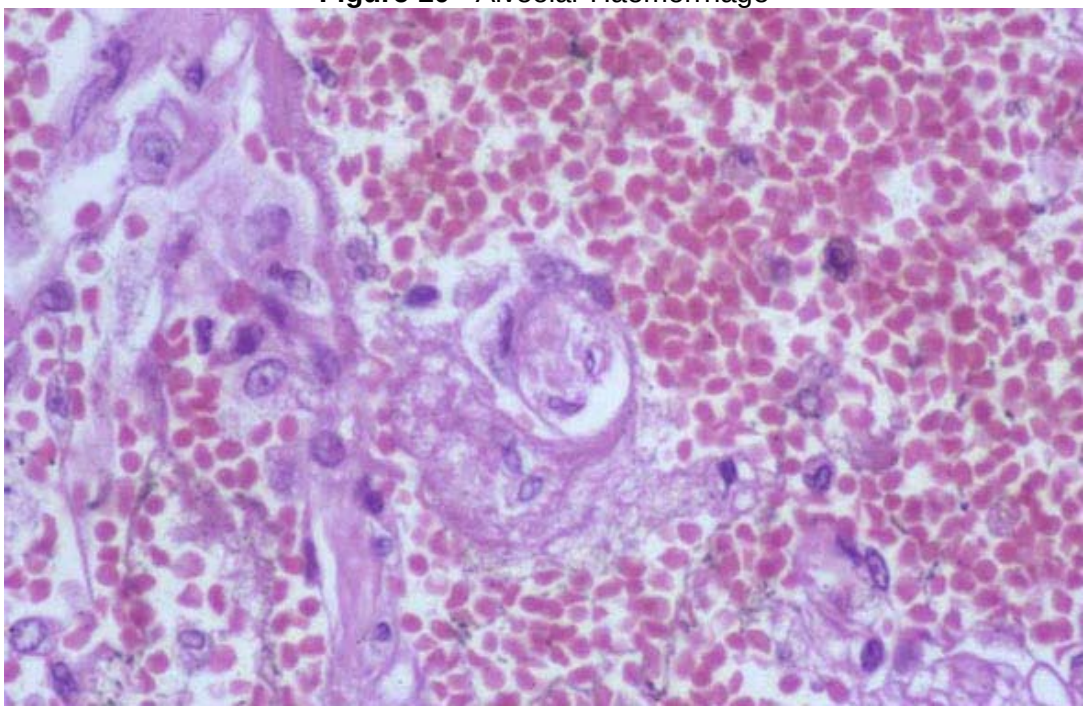
Parenchymal alterations, attributable to SLE itself, have been described in 18% of patients. These patients had interstitial fibrosis, pulmonary vasculitis and interstitial pneumonitis. However, many non-specific pulmonary lesions previously attributed to SLE, such as alveolar haemorrhage (Fig. 9), alveolar wall necrosis, oedema and hyaline membranes, are probably secondary to factors such as intercurrent infection, congestive heart failure, renal failure and oxygen toxicity.

In the relatively few cases studied, immune complex deposition has been closely correlated with histological evidence of inflammatory lesions in the pleural (and pericardial) membrane.

Abnormal pulmonary function tests, notably diminished total lung capacity and flow rates, in clinically mild patients with dyspnoea, poor diaphragmatic movement, basal crepitations and occasionally cyanosis and clubbing, are found in up to 50% of SLE patients. A similar proportion of SLE patients may have an acute lupus pneumonitis with a mononuclear cell infiltrate detectable in the alveolar septae. These patients frequently complain of dyspnoea, pleuritic chest pain and coughs. Haemoptysis is less common and true pulmonary haemorrhage from necrotizing alveolar capillaritis is rare.

Pleural effusions may be found in about half of these patients (and in other SLE patients especially during generalized disease flares). The effusions are normally small to moderate in size and are usually exudates (i.e. protein content >3 g/100 ml). They are rarely haemorrhagic and usually have a glucose concentration double that found in rheumatoid effusions (normally, 20 mg/100 ml or less).

Figure 10 - Alveolar Haemorrhage



Heart

Pericardium

Abnormalities of the electrocardiogram, notably of the T wave, are the most frequent manifestation. A pericardial rub may be more common than a significant pericardial effusion. Histological abnormalities vary from occasional foci of fibrinoid degeneration and inflammatory cell infiltrates to far more extensive lesions. Adhesive chronic pericarditis and very large effusions causing tamponade are very rare.

Myocardium

Whilst true myocardial involvement is less frequent than pericardial disease, prolongation of the PR interval (approximately 10%), fibrinoid degeneration, myocardial infarction and coronary stenosis due to arteritis are occasionally seen. New imaging techniques such as cardiac MRI suggest that myocardial involvement may be more common than previously thought.

There is increasing evidence that premature accelerated atherosclerosis considerably increases the risk of cardiovascular events in patients with SLE and this is described in a separate module of this course.

Valves

Systolic murmurs are frequently heard in around 30% of SLE patients. However, they probably reflect the hyperdynamic circulation consequent upon the anaemia often found in these individuals. In contrast, diastolic murmurs are uncommon.

Libman-Sacks endocarditis has long been described as a feature of SLE. Although found in up to 50% of autopsied cases, it rarely causes clinically significant lesions. Histologically, the lesions are small (1-4 mm) vegetations (verrucae) comprising proliferating and degenerating valve tissue with fibrin and platelet thrombi. They are most frequently found adjacent to the edges of the mitral and tricuspid valves. aPL may contribute to the development of Libman-Sacks endocarditis and studies suggest that there is a selective deposition of aPL and complement within the walls of the small junctional vessels in the active portions of the verrucous endocardial lesions.

Central nervous system lupus

The ACR classification criteria for central nervous system (CNS) lupus has changed considerably from seizures and psychosis. The ACR nomenclature now includes 19 different syndromes that are classifiable (31) (Table 6). An emerging concept is the distinction between CNS manifestations due to lupus and those due to the APS. A wide variety of neuropsychiatric manifestations attributable to APS have been described including strokes, seizures, movement disorders, transverse myelopathy, demyelination syndromes, transient ischaemic attacks, cognitive dysfunction, visual loss and headaches including migraine.

Table 6: Neuropsychiatric syndromes observed in SLE.

Central nervous system:
Aseptic meningitis
Cerebrovascular disease
Demyelinating syndrome
Headache (including migraine and benign intracranial hypertension)
Movement disorder (chorea)
Myelopathy
Seizure disorders
Acute confusional state
Anxiety disorder
Cognitive dysfunction
Mood disorder
Psychosis
Peripheral nervous system:
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)
Autonomic disorder
Mononeuropathy, single/multiplex
Myasthenia gravis
Neuropathy, cranial
Plexopathy
Polyneuropathy

Gastrointestinal problems

A wide variety of non-specific gastrointestinal clinical features has been described amongst SLE patients. Abdominal pain (especially common in children) occurs in about 20% of cases. Its precise cause is rarely determined though ileal and colonic perforations and regional enteritis have been described. Pathologically, necrotizing vasculitis is usually found when perforation occurs. Ascites, dysphagia and pancreatitis are occasionally seen. Hepatomegaly and/or liver function test abnormalities may be found in up to 30% of patients. However, the laboratory abnormalities may be related to SLE therapy.

Haematological abnormalities

Red blood cells

A normochromic, normocytic anaemia is frequently found in SLE patients, with concomitant low levels of both the serum iron and iron binding capacity. This abnormality appears to be related, as in other diseases, to chronic inflammation and shunting of elemental iron from erythroblasts to macrophages.

Iron-deficiency anaemia may be induced by non-steroidal anti-inflammatory drugs, which can cause gastrointestinal haemorrhage. Excessive blood loss from menorrhagia, sometimes related to severe thrombocytopenia, may have the same effect.

Haemolytic anaemia as detected by the Coombs' test is another rare feature of SLE. Autoimmune thrombocytopenia occasionally manifests simultaneously with haemolytic anaemia: this condition is known as Evan's syndrome.

Platelets

Two forms of thrombocytopenia (platelet count < 100 x 10^9/l) are found in SLE. Firstly, it may be encountered in a chronic form, generally associated with mild disease. Secondly, it may occur in an acute form, similar to idiopathic autoimmune thrombocytopenic purpura. This latter association is with disease carrying a greater morbidity and mortality.

Platelet destruction appears to be mediated by anti-platelet antibodies and aPL are also associated with thrombocytopenia as well as with thrombosis.

White blood cells

Persistent leucopenia (< 4.0 x 10^9/l) is one of the ACR criteria for the classification of SLE. It probably results from a combination of destruction of white cells by autoantibodies, decreased marrow production, increased or marginal splenic pooling, and complement activation. It should also be noted that the immunosuppressive drugs used in the treatment of SLE may cause a marked leucopenia.

Serological abnormalities

The serum from SLE patients may bind to an extensive array of molecules including nucleic acids (antinuclear antibodies) and phospholipid binding proteins (lupus anticoagulant, anticardiolipin antibodies, β2 glycoprotein 1 antibodies). Antibodies may also be detected against diverse cells including leukocytes, erythrocytes, platelets and neurones. In addition to these autoantibodies, numerous other abnormalities are evident, including the LE cell phenomenon, hypocomplementaemia, elevated levels of acute phase proteins, gamma globulins and circulating immune complexes.

Non-specific features

Fever, lymphadenopathy, hair loss and Raynaud's phenomenon are all commonly found in SLE patients. Fever in lupus patients may be striking and often requires extensive investigation to exclude concurrent infection, although a normal CRP in this context usually suggests a low likelihood of sepsis.

Lymphadenopathy may also be dramatic in SLE, to such an extent that lymph node biopsy may have to be performed to exclude malignancy. Some patients seem more prone to this feature than others and in this group the degree of lymphadenopathy may reflect general disease activity. Splenomegaly occurs in about 10% of patients.

PATTERNS OF DISEASE EXPRESSION IN SPECIFIC SUBSETS

An important question is whether the age at onset of the disease, the gender, or the autoantibody pattern, can modify the disease expression and define specific SLE subsets. The "Euro-Lupus" studies have provided major insights into these areas of inquiry. This cohort is composed of 1,000 patients with SLE that have been followed prospectively since 1991. These patients have been gathered by a European consortium - the "Euro-Lupus Project Group" - that includes more than 40 investigators from seven European countries who have substantial experience in the management of SLE patients. This consortium was originated as part of the network promoted by the "European Working Party on SLE". The general characteristics of this cohort at the beginning of the study were published in 1993 (Tables 7 and 8) (32).

Table 7: Clinical manifestations in a series of 1,000 European SLE patients.

SLE manifestation	Prevalence (%)
Arthritis	84
Malar rash	58
Fever	52
Photosensitivity	45
Nephropathy	39
Serositis	36
Raynaud's phenomenon	34
Neurologic involvement	27
Oral ulcers	24
Thrombocytopenia	22
Sicca syndrome	16
Livedo reticularis	14
Thrombosis	14
Lymphadenopathy	12
Discoid lesions	10
Myositis	9
Haemolytic anemia	8
Lung involvement	7
Subacute cutaneous lesions	6
Chorea	2

Table 8: Prevalence of serological features in a series of 1,000 SLE patients.

Serological features	Prevalence (%)
Antinuclear antibodies	96
Anti-DNA antibodies	78
Anti-Ro (SSA) antibodies	25
Anti-LA (SSB) antibodies	19
Anti-RNP antibodies	13
Anti -Sm antibodies	10
Rheumatoid factor	18
IgG Anticardiolipin antibodies	24
IgM Anticardiolipin antibodies	13
Lupus anticoagulant	15

Effects of age

Age-specific incidence rates have been estimated in several studies and peak incidence rates have been described in the 15 to 44 (32), 20 to 39 (8), 25 to 44 (4), 35 to 54 (3) and 50 to 59 (12) year age period. Age-specific incidence rates in males are difficult to interpret because of the small numbers of cases but SLE can appear in older males. Thus, peak rates occurred in the 50 to 59- year age group (12) and in those aged 65 and older (32).

SLE can appear at all ages. However, in most patients, the symptoms of SLE appear between 15-40 years, with a mean between 29-32 years (32). Conversely, SLE can appear before 15 years of age in 8-15% of the patients and in a similar percentage in older age groups (above 55 years-old) (32). In recent studies (3,7), the mean age of appearance of symptoms has increased from 41 to 47 years.

Several studies have suggested that age at symptom onset can modify the clinical and immunological characteristics of SLE. In the "Euro-Lupus" cohort (32), 76 out of the 1,000 patients with SLE (8%) developed the disease before the age of 14. Female/male ratio (7:1) was lower than the general SLE population (10:1). In addition, the clinical and immunological patterns of SLE in childhood onset patients differs slightly from the disease in other SLE patients. Childhood onset patients are more likely to have severe organ involvement, especially nephropathy, at presentation. Other major manifestations, such as neurologic involvement, thrombocytopenia and hemolytic anemia, were also common initial features in the childhood onset group. However, during the disease evolution, the pattern was quite similar in childhood onset and adult patients. Interestingly, the initial diagnosis in the childhood onset group was delayed, presumably because doctors are reluctant to diagnose SLE in childhood patients and because typical signs and symptoms are less common. This is reflected in a mean five year delay in establishing the diagnosis of SLE in the childhood onset group.

On the other hand, although SLE has traditionally been considered a disease of young women, several reports have described SLE in older populations. In the "Euro-Lupus" cohort (32), 90 patients (9%) developed the disease after the age of 50. Although some authors have found no differences in the female/male ratio related with aging, the observations of this cohort suggest that female predominance is not so pronounced in the older onset group (5:1). The clinical expression of SLE in older patients differs in several aspects from the disease in young adults. The most common manifestations in the older-onset patients are themselves interesting, and the clinical picture best resembles patients with drug-induced SLE, primary Sjögren's syndrome, or polymyalgia rheumatica. Thus, in the "Euro-Lupus" cohort, typical SLE manifestations, such as malar rash, photosensitivity, arthritis or nephropathy, were less common than in the younger patients. In contrast, sicca syndrome was common.

Although the explanation for this apparent age-related variability in the expression of the disease is still unclear, demographic factors and differences in genetic predisposition or responsiveness of an aging immune system may be implicated. It has been speculated that older and younger patients may have different genetic determinants of disease and respond to different triggering mechanisms. Alternatively, the less florid expression of SLE both clinically and immunologically in older patients may reflect senescence of the immune system.

Effects of gender

Clinical studies have consistently demonstrated a female predominance. Thus, in the largest American series of 1,103 patients (33), 88% were females and in the largest European series (32) with 1,000 patients, 91% were females. In general, this percentage ranges between 78 and 96% in the majority of studies, with a female/male ratio of approximately 10:1. This excess of females is especially noteworthy in the 15 to 64 year age group, where ratios of age and sex specific incidence rates show a six to tenfold female excess. No such excess was noted in the 14 and younger and in the 65 and older age groups. These age-related differences in the female/male ratios may well be related to hormonal changes.

In the "Euro-Lupus Cohort" (32), 92 out of the 1,000 (9%) patients with SLE were men. Overall experience with male SLE patients is not extensive and the precise frequency of clinical and serological features differs from study to study. The clinical expression and immunological features of SLE in men and women both at disease onset and during the follow-up period noted several interesting clinical differences. Firstly, a higher prevalence of serositis was found in the male patients at presentation. In contrast, arthritis tended to occur less commonly in these patients, although the difference was not statistically significant. This atypical presentation is relevant because it can lead to a delay in diagnosis. Secondly, during disease evolution, a lower prevalence of arthritis was found in the males. The prevalence of nephropathy, neurological involvement, thrombocytopenia, vasculitis and serositis was similar in both groups. In addition, no significant immunological differences were found between men and women

Effects of ethnic and social factors

The incidence and prevalence of SLE has consistently been found to be higher in patients with African ancestry. For example, a study in Birmingham, England, found a higher age-adjusted incidence and prevalence in Afro-Caribbeans than in whites (9). Incidence rates (age-adjusted) were 25.8 and 4.3 per 100,000 persons per year in Afro-Caribbeans and whites, respectively, and prevalence rates were 112 and 21 per 100,000 persons. In this study, the age distribution of incident cases differed significantly, with a younger median age in Afro-Caribbean females of 34.5 years, compared with 41 years in white females. There was also an excess prevalence of SLE among Asians from the Indian sub-continent compared with whites. In Birmingham (9), the age-adjusted incidence and prevalence rates of SLE in Asians were 20.7 and 46.7 per 100,000 persons compared with 4.3 and 20.7 per 100,000 persons in whites, respectively.

SLE is more common in women with African ancestry but is thought to be uncommon in West Africa suggesting that environmental factors, possibly infections, may contribute to the development of lupus in women whose ancestors migrated from West Africa. However, when this was examined in women who had recently migrated from West Africa, the prevalence of lupus was similar to that in Afro-Caribbean women but much lower in European women (34). This data suggests that SLE is not uncommon in West Africa and that there is a genetic basis for the higher risk of lupus in these women.

Effects of familial or hereditary factors

There is a genetic basis for lupus highlighted by the significant concordance rates in identical twin studies and increased risk of having affected siblings/parents. However, the frequency of SLE in relatives is relatively low and ranges between 3 and 18% and there are no major differences in the clinical expression of the disease between patients with an affected relative (familial SLE) and patients with sporadic SLE (35).

Effects of the autoantibody pattern

SLE with high titer anti-dsDNA antibodies

High titers of anti-dsDNA are associated with disease activity in SLE. In the "Euro-Lupus" cohort (32), anti-dsDNA antibodies were associated with a higher prevalence of nephropathy, hemolytic anemia and fever. In contrast, patients with high titer anti-dsDNA antibodies have a lower prevalence of thrombosis and sicca syndrome.

SLE with anti-ENA antibodies

Anti-Ro (SSA) antibodies, often accompanied by anti-La (SSB), are found in 20 and 30% of SLE patients. The former have been found to be associated with a higher prevalence of subacute cutaneous lesions and sicca syndrome, but with a lower prevalence of thrombocytopenia. Anti-La (SSB) may be associated with malar rash, subacute cutaneous lesions, photosensitivity, arthritis, serositis, and thrombosis. The prevalence of anti-U1-snRNP was 13%.

Patients with these antibodies had a higher incidence of Raynaud's phenomenon, myositis and lymphadenopathy. Anti-Sm antibodies occurred in 10% of patients and was more prevalent in those with oral ulcers and myositis, but less in those with sicca syndrome (32).

SLE with rheumatoid factor

The presence of rheumatoid factor has been found in 18% of the patients. Interestingly, these patients have a higher prevalence of sicca syndrome, but a lower prevalence of nephropathy (32).

SLE with aPL

aPL are strongly associated with thrombosis, spontaneous fetal losses and thrombocytopenia. In the "Euro-Lupus" cohort, IgM anticardiolipin antibodies were also associated with haemolytic anaemia and although this has rarely been reported it has been suggested that aPL may react with the cell wall of either erythrocytes or platelets, causing their destruction either by complement or by receptor mediated entrapment by the reticulo-endothelial system.

CLINICAL DIAGNOSIS, CLASSIFICATION CRITERIA AND ASSESSMENT OF DISEASE ACTIVITY AND DAMAGE

The clinical diagnosis of SLE hinges on careful and very thorough assessment of the presenting clinical features, examination of all the organ systems and selected investigations. Symptoms often occur intermittently and cumulatively over many months and years. Oral ulcers, arthralgia, hair fall, Raynaud's phenomenon, photosensitive rashes, pleuritic chest pains, headaches, fatigue, fevers and lymphadenopathy are just a few of the many non-specific presenting features of this disease. Clinical examination of all organ systems including routine urinalysis and blood pressure measurement is mandatory. Simple investigations may yield useful information. For example, a grossly elevated erythrocyte sedimentation rate (ESR) with a normal C-reactive protein (CRP) is a strong pointer to lupus and related connective tissue diseases. Blood count abnormalities such as anaemia, neutropenia, lymphopenia and thrombocytopenia are also common. Serologically, anti-nuclear antibodies are highly sensitive but not specific and anti-dsDNA antibodies are specific but not sensitive and it is important to recognise that a negative result for anti-dsDNA antibodies does not exclude a diagnosis of lupus.

There are no diagnostic criteria for lupus and the ACR classification criteria (1) are often misused in this context and can result in missed diagnosis/under-treatment. For example a patient may present with arthritis, Raynaud's phenomenon, malaise, fevers, lymphadenopathy, oral ulcers and a positive ANA. This patient clearly may have SLE but does not fulfil the 4 criteria needed for classification by the ACR criteria but investigation and treatment should not be delayed until these criteria are fulfilled. The ACR criteria were specifically designed to be highly specific for research studies to enable consistency between studies and have been updated to include antiphospholipid antibodies in the criteria (Table 9).

The objective assessment of lupus has depended on a number of disease activity scoring systems which usually give a single numeric value.

The British Isles Lupus Assessment Group (BILAG) is emerging as a useful tool in clinical trials as it describes disease activity based on the physician's intention to treat and also gives a clear picture of affected organs and systems. It has recently undergone revision and is being validated (36). Other disease activity scoring systems have also been updated including the SLEDAI 2K and an adjusted mean SLEDAI-AMS that describes disease activity over time.

Table 9: The 1997 modified classification criteria for SLE

Classification criteria	
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcer	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Non-erosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling or effusion
Serositis	Pleuritis: Convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion
a) Pleuritis	
b) Pericarditis	Pericarditis: documented by ECG or rub or evidence of pericardial effusion
Renal disorder	Proteinuria: greater than 0.5 grams per day or greater than +++ if quantification not performed
a) Persistent proteinuria	
b) Cellular casts	Casts: may be red cell, haemoglobin, granular, tubular or mixed
Neurologic disorder	See ACR definitions of 19 separate syndromes (Ref 91)
Hematologic disorder	
a) Hemolytic anemia	With reticulocytosis
b) Leukopenia	Less than 4000/mm^3 total on 2 or more occasions
c) Lymphopenia	Less than 1500/mm^3 total on 2 or more occasions
d) Thrombocytopenia	Less than 100,000/mm^3 in the absence of offending drugs
Immunologic disorder	
a) Anti-DNA	Antibody to native DNA in abnormal titre
b) Anti-Sm	Presence of antibody to Sm nuclear antigen
c) Positive finding of antiphospholipid antibodies	1. Abnormal serum level of IgG or IgM anticardiolipin antibodies 2. A positive test result for lupus anticoagulant using a standard method 3. A false positive serologic test for syphilis, known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponema antibody absorption test
Antinuclear antibody	Abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time, and in the absence of drugs known to be associated with 'drug induced lupus' syndrome

This classification is based on 11 criteria. For the purposes of identifying patients in clinical studies, a person must have SLE if any four or more of the 11 criteria are present, serially or simultaneously, during any interval of observation (Refs 91,131).

Damage describes irreversible events resulting from lupus disease activity and its treatment. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index is validated and widely used to describe damage (37). The link between damage and an increased risk of morbidity and mortality is now clear. Clearly therefore it behoves clinicians to try, as far as possible, to achieve disease remission although studies highlight the inadequacies of current therapies in achieving this aim and prolonged disease remission is quite a rare achievement.

Another important outcome measure is the risk of cancer associated with lupus. This has been a controversial area but a recent very large study of 9,547 patients from 23 centres confirmed an increased risk of lymphoma, especially non-Hodgkin's lymphoma, among patients with SLE (38). An update of this study did not show a strong association between treatment with immunosuppressive agents and overall risk of cancer although older studies have documented the well known risk of bladder cancer with long term cyclophosphamide use (39).

Table 10: Clinical manifestations related to SLE in the "Euro-Lupus Cohort" during the 10-year prospective study (1990-2000).

SLE manifestations	**1990-2000**	**1990-1995**	**1995-2000**	
	(n=1,000)	**(n=1,000)**	**(n=840)***	**p****
	No. (%)	**No. (%)**	**No. (%)**	
Malar rash	311 (31.1)	264 (26.4)	144 (17.1)	<0.001
Discoid lesions	78 (7.8)	54 (5.4)	50 (5.9)	
Subacute cutaneous lesions	67 (6.7)	46 (4.6)	21 (2.5)	0.023
Photosensitivity	229 (22.9)	187 (18.7)	112 (13.3)	0.002
Oral ulcers	125 (12.5)	89 (8.9)	61 (7.3)	
Arthritis	481 (48.1)	413 (41.3)	240 (28.6)	<0.001
Serositis	160 (16)	129 (12.9)	52 (6.2)	<0.001
Nephropathy	279 (27.9)	222 (22.2)	57 (6.8)	<0.001
Neurologic involvement	194 (19.4)	136 (13.6)	97 (11.5)	
Thrombocytopenia	134 (13.4)	95 (9.5)	76 (9.0)	
Hemolytic anemia	48 (4.8)	33 (3.3)	24 (2.9)	
Fever	166 (16.6)	139 (13.9)	62 (7.4)	<0.001
Raynaud's phenomenon	163 (16.3)	132 (13.2)	74 (8.9)	0.003
Livedo reticularis	70 (7.0)	55 (5.5)	30 (3.6)	
Thrombosis	92 (9.2)	72 (7.2)	41 (4.9)	0.049
Myositis	43 (4.3)	40 (4)	11 (1.3)	<0.001

*Number of patients that continued in the study in 1995.
**All p values are a comparison between the frequencies in the 1990-1995 and in the 1995-2000 periods.

MORBIDITY AND MORTALITY STUDIES

The natural history of SLE is characterized by episodes of relapses or flares, interchanging with remissions, and the outcome is highly variable ranging from permanent remission to death. However, both morbidity and mortality have improved over the years due to a number of reasons, including the more conservative use of corticosteroids and of modified immunosuppressive regimens. Additionally, there is much more information on factors such as organ involvement and accelerated atherosclerosis that may predict morbidity and mortality. The "Euro-Lupus Cohort" has been instrumental in clarifying some of these factors (40). (See also Atherosclerosis section in this module).

The frequencies of the main lupus manifestations during the initial 10 years of the prospective "Euro-Lupus Cohort" (Table 8) are slightly lower than those reported in several large series from America (41,42) and Asia (43) in the last decade (Table 11). In this European cohort, active nephropathy was diagnosed in 27.9 % of the patients (40), and ranges between 40.2% in an American series (41) and 74% in an Asian series (43). These lower frequencies of SLE clinical manifestations could be due to genetic or environmental differences between Europeans and Americans or Asians but could also reflect the effect of medical care during the study. Furthermore, there was a lower frequency of most SLE manifestations during the last 5 years of this prospective study (1995-2000) (40), compared with the cumulative clinical manifestations during the initial 5 years of the study (1990-1995). For instance, the frequency of active lupus nephropathy during the last 5 years was 6.8% compared to a cumulative prevalence of 22.2% during the initial 5 years of the study. These lower frequencies in the last 5 years probably reflect the effect of therapy and of medical care during the study, but may also reflect natural remissions which may occur with advancing age and the menopause.

Table 11: Comparison of the main clinical manifestations related to SLE in several large series reported during the last decade.

Authors	Petri et al. (40)	Wang et al. (41)	Alarcón et al. (39)	"Euro-Lupus Cohort"
No. of patients	574	539	555	1,000
Geographical area	America	Asia	America	Europe
Malar rash	331(57.7)	410 (76.1)	322 (58)	311 (31.1)
Discoid lesions	162 (28.2)	30 (5.6)	107 (19.3)	78 (7.8)
Photosensitivity	335 (58.4)	222 (41.2)	334 (60.2)	229 (22.9)
Oral ulcers	219 (38.2)	185 (34.3)	293 (52.8)	125 (12.5)
Arthritis	NR	272 (50.5)	489 (88.1)	481 (48.1)
Nephropathy	319 (55.6)	399 (74)	223 (40.2)	279 (27.9)
Neurologic involvement	NR	123 (22.8)	67 (12.1)	194 (19.4)
Thrombocytopenia	NR	161 (29.9)	NR	134 (13.4)
Haemolytic anaemia	NR	102 (18.9)	NR	48 (4.8)

NR: Not reported

Over the past 50 years, survival has improved dramatically in patients with SLE. Whereas earlier studies in the 50´s, reported a survival rate of less than 50% at 5 years, more recent studies show that over 93 % of patients with SLE survive for 5 years and 85 % survive for 10 years. In the "Euro-Lupus Cohort", 10 years from entry into the study survival was 92 % (40). These improved survival rates may be related to the advances in general medical therapies such as antihypertensive agents, antibiotics, availability of renal dialysis and transplantation and the wider availability of intensive therapy units. Improvements in the understanding of the pathogenesis of the disease, earlier diagnosis and inclusion of milder cases in recent studies are also relevant. In particular, advances in the careful use of cytotoxic drugs, immunosuppressive drugs and high-dose prednisolone. Furthermore, the slightly higher survival in this European cohort when compared with the American series may be also due to predominance of Caucasian patients in the present cohort (97.1%); it is known that race influences outcome in SLE and Blacks and Hispanic Americans of mestizo or native Indian origin have a poorer outcome.

The improved survival of patients with SLE has been associated with an alteration in the patterns of mortality. The "Euro-Lupus Cohort" showed a similar percentage of active SLE (26.5%), thromboses (26.5%) and infections (25%) as the main causes of death in the 10 year observational period. However, it is important to stress that when the causes of death during the initial 5 years were compared with those during the ensuing 5 years, active SLE and infections (28.9%, each) appeared to be the most common causes during the initial 5 years, while thromboses (26.1%) became the most common cause of death during the last 5 years (40) (Table 12).

Table 12: Causes of death in the "Euro-Lupus Cohort" during the 10-year prospective study (1990-2000).

Causes of death	**1990-2000**	**1990-1995**	**1995-2000**
	(total = 68)	**(total = 45)**	**(total = 23)**
	No. (%)	**No. (%)**	**No. (%)**
Active SLE	18 (26.5)	13 (28.9)	5 (21.7)
Multi-system	5 (7.4)	4 (8.9)	1 (4.3)
Renal	6 (8.8)	4 (8.9)	2 (8.7)
Cardio-pulmonary	3 (4.4)	3 (6.7)	0 (0)
Hematologic	1 (1.5)	1 (2.2)	0 (0)
Neurologic	3 (4.4)	1 (2.2)	2 (8.7)
Infections	17 (25)	13 (28.9)*	4 (17.4)***
Bacterial sepsis	15 (22.1)	11 (24.4)	4 (17.4)
Pulmonary	6 (8.8)	4 (8.9)	2 (8.7)
Abdominal	5 (7.4)	4 (8.9)	1 (4.3)
Urinary	4 (5.9)	3 (6.7)	1 (4.3)
Fungal	1 (1.5)	1 (2.2)	0
Viral	1 (1.5)	1 (2.2)	0
Thromboses	18 (26.5)	12 (26.7)	6 (26.1)
Cerebral	8 (11.8)	5 (11.1)	3 (13)
Pulmonary	4 (5.9)	3 (6.7)	1 (4.3)
Coronary	5 (7.4)	3 (6.7)	2 (8.7)
Other	1 (1.5)	1 (2.2)	0 (0)
Malignancies	4 (5.9)	3 (6.7)	1 (4.3)
Breast	1 (1.5)	1 (2.2)	0 (0)
Lung	2 (2.9)	1 (2.2)	0 (0)
Lymphoma	1 (1.5)	1 (2.2)	0 (0)
Gastric bleeding	2 (2.9)	2 (4.4)**	0 (0)
Obstetric	1 (1.5)	1 (2.2)	0 (0)
Suicide	1 (1.5)	1 (2.2)	0 (0)
Surgical	1 (1.5)	1 (2.2)	0 (0)
Accident	1 (1.5)	0 (0)	1 (4.3)
Unknown	14 (20.6)	7 (15.6)	7 (30.4)

*In 6 patients, the cause of death was attributed to infection plus other factors (active SLE in 5 and thrombosis in 1).

**In 2 patients, the cause of death was attributed to gastric bleeding plus other factors (active SLE in 1 and infection in 1).

*** In 1 patient, the cause of death was attributed to infections plus active SLE.

SUMMARY POINTS

- SLE is a multisystem autoimmune disorder with a broad spectrum of clinical presentations.
- There is a peak age of onset among women between the late teens and early 40's and a female to male ratio of 9:1.
- Ethnicity, age at onset, gender and clinical and immunological features at onset can all influence the prevalence and clinical disease evolution.
- The pathogenesis of SLE is complex and includes genetic, environmental, ethnic and immunological factors.
- The diagnosis of SLE depends on thorough clinical assessment and careful investigation. There are no diagnostic criteria.
- Criteria for classification of SLE as well as for describing central nervous system disorders and the pathologic description of lupus nephritis have been validated.
- Several systems have been validated for describing disease activity and the SLICC/ACR criteria are used to describe damage.
- The antiphospholipid syndrome may co-exist with SLE and contribute to morbidity and mortality. Classification criteria for APS have been updated.
- There have been significant improvements in long term survival but patients with SLE still have higher risks of premature mortality compared to the general population.
- Factors contributing to mortality include major organ involvement, especially nephropathy, thrombosis, accelerated atherosclerosis and an increased risk of cancer.

RECOMMENDED TEXTS

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2. Systemic lupus erythematosus. Ed Lahita RG 3rd Edition Academic Press 1999.

3. Hughes syndrome. Ed Khamashta MA. 2nd Edition Springer 2006.

SLE: Internet links

http://www.lupus.org The Lupus Foundation of America

http://www.lupusuk.com The official website of Lupus UK

http://www.mayoclinic.com/health/lupus/DS00115

http://www.lupus.org.uk St Thomas' Lupus Trust

http://www.lupusresearchinstitute.org

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