INVITED ARTICLE

SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Systemic lupus erythematosus (SLE) is a syndrome commonly affecting young women. The clinical manifestations are extremely varied and any major organ of the body may be involved. Misdiagnosis is not uncommon in early SLE where symptoms and signs may be few. Auto-antibodies to DNA, RNA and other cell nucleus antigens are frequently present. Circulating immune complexes may deposit in major organs, causing inflammation and tissue damage by a number of mechanisms. The lupus disease is marked by exacerbations and remissions. Management is dependent on accurate assessment of clinical activity and severity. Patient education and co-operation in management affect outcome of the disease. With good management, the ten year survival may exceed 90%.

Keywords: Systemic lupus erythematosus, initial manifestations, serology, management, prognosis.

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INTRODUCTION

Systemic lupus erythematosus is a syndrome with marked diversity in clinical pattems, pathophysiology and prognosis. The etiological and inciting factors remain unidentified. The clinical heterogeneity and immunologic derangements reflect a great degree of host variability to different etiologic stimuli. Studies on the immunopathogenesis of human lupus have been helped by the availability of excellent animal models of mice (New Zealand black and F1 hybrids) which develop the disease spontaneously. The NZ mice mirrors humans in sex and immunologic characteristics, thus allowing the elucidation of many mechanisms involved in the disease as well as different approaches to treatment.

PREVALENCE

SLE is not a rare illness. The current higher frequency reflects a greater awareness of the disease, longer survival and perhaps, a higher incidence of the disease.

The prevalence has been estimated from approximately 1 in 250 women in Jamaica[1] to 1 in 4312 in New Zealand[2]. In Hawaii[3], the age-adjusted prevalence rates per 100,000 persons at risk were Caucasian 5.8, enthic Chinese 24.1, ethnic Filipino 19.9, mixed Hawaiian 20.4 and ethnic Japanese 18.2.

CLINICAL MANIFESTATIONS

The initial manifestations of 183 Chinese patients[4] are summarised in Table I. Major clinical manifestations were skin and mucous membrane (52%), fever and malaise (48%), arthralgias/arthritis (44%) and swelling of face/legs (36%). Lupus nephritis (on clinical criteria) was present in 74% of patients. Neuropsychiatric manifestations although rare at initial diagnosis were observed in 30% of patients at follow-up. The CNS complications of lupus are the least understood and most subject to analysis.

DIAGNOSIS

The diagnosis of SLE is made largely on on clinical grounds with the support of certain laboratory tests. The 1982 revised criteria for SLE has eleven criteria[5] (Table II). The presence of four or more of these criteria either simultaneously or serially in a given patient is said to be diagnostic of SLE. These

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Table I - Initial Manifestations of SLE in 183 Chinese patients

Manifestations	%
Skin and mucous membrane	52
Fever, malaise	48
Arthritis or arthralgia	44
Swelling of face/leg	36
Lymphadenopathy	8
Gastro-intestinal	7
Respiratory	7
Thrombocytopenic purpura	4
Neuropsychiatric	4
Haemolytic anaemia	3
Cardiovascular	3

Table II - 1982 revised Criteria of the American Rheumatism Association for the classification of SLE

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Serositis
   a) pleuritis and
   b) pericarditis
7. Renal disorder
   a) proteinuria 0.5 gm/24 hr or 3+, persistently or
   b) cellular disorder
8. Neurological disorder
   a) seizures or
   b) psychosis (having excluded other causes, eg drugs)
9. Haemotologic disorder
   a) haemolytic anaemia or
   b) leucopenia or 4.0 x 10^9/l on two or more occasions
   c) lymphopenia or 1.5 x 10^9/l on two or more occasions
   d) thrombocytopenia 100 x 10^9/l
10. Immunologic disorders
    a) positive LE cell or
    b) raised anti-native DNA antibody binding or
    c) anti-Sm antibody or
    d) false positive serologic test for syphilis, present for at least six months
11. Anti-nuclear antibody in raised titre

criteria include the presence of malar rash, discoid lesions, photosensitivity, oral ulcers, non-erosive arthritis, serositis (pleuritis, pericarditis), renal involvement, seizures or psychosis, haematologic abnormalities (haemolytic anaemia, leukopenia, lymphopenia, or thrombocytopenia), immunologic abnormalities (positive LE cells, anti-DNA antibody, anti-Sm antibody, or a false positive serologic test for syphilis) and a positive anti-nuclear antibody (ANA). These criteria are 96% sensitive and 96% specific. It should be noted that these criteria are not always met simultaneously and that SLE often presents initially with an isolated clinical finding or findings followed months or even years later by additional manifestations that permit the diagnosis to be firmly established. It is not uncommon for SLE to be initially misdiagnosed as rheumatoid arthritis, idiopathic thrombocytopenic purpura, or fever of unknown origin. Repeated evaluations over time are crucial to proper diagnosis in these cases.

SEROLOGY

SLE is manifested by a polyclonal autoantibody response. In this disease antibodies to native DNA, histones, Sm, nuclear RNP, SS-A (anti-Ro) and SS-B (anti-La) are all present[6]. Most patients with SLE have three or more antibodies in the serum.

Screening for anti-nuclear antibodies (ANA), or anti-nuclear factor (ANF) is an important step in the diagnosis of SLE. Using Hep2 cell lines as substrate, a positive ANA test can be obtained in about 98% of patients. The common pattern of staining is the peripheral pattern which correlates with antibodies to dsDNA. Other patterns include speckled, homogenous and nucleolar. The antigenic determinants giving rise to speckled pattern staining include Sm, nRNP, SS-B and Scl 70. The commonest pattern in 150 patients in Singapore was speckled pattern[7]. Anti-dsDNA antibodies rarely occur in other autoimmune conditions apart from SLE. Depending on the assay method and activity of the disease, they are detectable in 50-75% of patients. Measurement of anti-DNA antibodies level is an imprecise predictor of clinical activity. Patients may have elevated levels of anti-DNA antibodies without any clinical signs of disease. Increased anti-DNA antibodies bear no correlation with any particular manifestation of lupus except nephritis.

Anti-SS-A (Ro) often accompanied by anti-SS-B (La) is found in SLE with a prevalence ranging between 20 and 30%[8]. These antibodies are found in up to 70% of patients with primary Sjogren's syndrome and in the sicca complex associated with SLE . A high prevalence (63%) of anti-SS-A (Ro)[9] was observed in our local lupus population. The anti-SS-A (Ro) is associated with a number of clinical phenomena such as the ANA-negative subset of SLE patients and those with a characteristic non-scarring dermatitis called subacute lupus erythematosus (SCLE).

Antiphospholipid antibodies occur in approximately 21-65%[10] of lupus patients. The lupus anticoagulant is an antibody (usually IgG or IgM or both) which blocks the activation of the prothrombin-activated complex that comprises Factor Xa, V calcium and phospholipid. A clear correlation between the presence of lupus anticoagulant and elevated levels of anti-cardiolipin antibodies have been observed and known to be associated with an increased frequency of thromboembolic phenomena, thrombocytopenia and recurrent fetal loss. The mechanisms underlying these observations remain unclear[11].

MANAGEMENT AND TREATMENT

SLE is a complex, chronic disease which is characterised by relapses and remissions. There are no homogenous groups of patients and no fixed treatment protocols. In the management of patients, assessment of overall clinical activity and severity is required. Specific organ damage such as the kidneys and brain calls for more aggressive therapy. Non-life-threatening manifestations such as alopecia, arthralgias and skin rashes require less toxic therapeutic interventions.

Patients education is an extremely important but neglected aspect of management. Lupus patients have to learn to cope with a disease which is life-long and potentially disabling. Lupus support groups exist to help sufferers re-adjust their lives. Advice on follow-up, sun-exposure, pregnancy and potential causes of disease exacerbations is given initially at diagnosis and reinforced during clinic visits.

PHARMACOLOGICAL APPROACH

There are four main groups of drugs in the treatment of SLE: non-steroidal anti-inflammatory drugs (NSAID), anti-malarials, corticosteroids and cytotoxic drugs.

The patient with mildly active lupus consisting of arthralgias and skin rashes can be managed with combinations of NSAID and/or anti-malarials. Hydroxychloroquine (Plaquenil) 200-400 mg/day is the anti-malarial drug of choice. Initial and six-monthly ophthalmological examinations are recommended although retinal toxicity is rare.

Corticosteroids are the drugs of choice when there is evidence of lupus affecting the lungs, hearts, kidneys, brain or gut. Systemic steroids in the range of 1 mg/kg of prednisolone per day is required in the acutely-ill patient with fever, vasculitic rash or pleuritis. Large bolus doses of corticosteroids infused intravenously (1 gm methylprednisolone succinate on three successive days) have used for both life-threatening and moderately active lupus. The main interest regarding pulse therapy has centred on lupus nephritis. Rapid improvement in renal function has been observed. In an uncontrolled study, pulse methylprednisolone was given to 27 patients with lupus nephritis and 12 with non-renal manifestations of lupus. Seventeen (63%) of the renal lupus patients and 7 (58.3%) of the non-renal lupus patients showed clinical response[12]. A double-blinded controlled study by Edwards[13] showed no significant difference between the pulse and non-pulsed group in 21 patients. Acute complications of pulse methylprednisolone include anaphylaxis, seizures, cardiac arrhythmias and sudden death.

The use of immunosuppressives in lupus patients has yielded variable results. Azathioprine can be used as an adjunct to corticosteroid therapy in lupus nephritis. Cyclophosphamide has been the most extensively studied of all the alkylating agents in lupus. The drug can be given as an intermittent bolus of intravenous cyclophosphamide at doses of 0.5 - 0.75 gm/metre squared body surface area either monthly or every 3 months and as combination oral therapy with low dose corticosteroid. A recent NIH study suggests that intravenous cyclophosphamide is effective in preventing end-stage renal failure[14].

Plasmapheresis is reserved for patients resistant to conventional drug therapy. The benefits derived from plasmapheresis have been attributed to the removal of circulating immune complexes that are inadequately cleared by the reticuloendothelial system and reduction of the concentration of antibodies and inflammatory mediators. The greatest experience with plasmapheresis is in lupus nephritis. Plasmapheresis has to be synchronised with immunosuppression to achieve better results. The application of plasmapheresis is limited by cost, availability and the problem of vascular access.

TOTAL LYMPHOID IRRADATION (TLI)

TLI has profound immunosuppressive effects on both cellular and humoral immunity. It reduces levels of anti-nuclear antibodies and anti-DNA antibodies[15]. The major improvement in severe lupus nephritis appear to be associated with a reduction in proteinuria and an increase in serum albumin.

PROGNOSIS

There is a striking improvement of survival in SLE. In the early 1940s, the mortality was approximately 95% within the first 18 months of the onset of disease. Now five year survival rates of 98% have been reported by Grigor et al[16]. Earlier diagnosis, increased recognition of mild disease and a more conservative use of corticosteroids have contributed to improved survival statistics. Certain organ system involvement, particularly renal and CNS disease clearly affect prognosis. Rubin et al[17] described a bimodal pattern of mortality. Early deaths are usually caused by active lupus and/or intercurrent infection, while death later in life is related to atherosclerotic cardiovascular disease. The morbidity and mortality of lupus are also influenced by the socio-economic status, literacy rate and pattern of usage of health facilities of a lupus population[18].

CONCLUSION

SLE may appear in any number of organ systems. It is a great masquerader of other diseases. It is not unusual for the patient to present initially to the psychiatrist, haematologist or a dermatologist. A high index of suspicion is required and long term follow-up may reveal the disease. Once diagnosed, assessment of disease severity and progress of the disease will influence treatment. Therapy is based on the strategy of generalised suppression of the immune system. Survival statistics of lupus have improved considerably. Delineation of the nature of the primary immunological lesion in SLE will undoubtedly affect new modalities of therapy and further enhance survival curves.

REFERENCES

1. Hughes GRV. Connective Tissue Diseases (2nd edition). Blackwell Scientific Publications. Oxford 1979
2. Meddings J, Grennan DM. The prevalence of systemic lupus erythematosus (SLE) in Dunedin. NZ Med J 1980; 91:205-6
3. Serdula MK, Rhoads GG. Frequency of systemic lupus erythematosus in different ethnic groups in Hawaii. Arthritis Rheum 1979; 22:328-33
4. Feng PH, Boey ML. Systemic lupus erythematosus in Chinese: The Singapore experience. Rheumatol Int 1982; 2:151-4
5. Tan EM, Cohen AS, Fries JF et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1983; 25:1271-7.
6. Tan EM. Antibodies to nuclear antigens (ANA): Their immunobiology and medicine. Adv Immunol 1982; 33:167-240
7. Fong KY, Boey ML, Howe HS, Feng PH. Antinuclear antibodies in systemic lupus erythematosus Med J Malaysia 1989; 44:151-5
8. Clark G, Reichlin MM, Tomasi TB. Characterisation of a soluble cytoplasmic antigen reactive with sera from patients with systemic lupus erythematosus. J Immunol 1969; 102:117-22
9. Boey ML, Peebles CL, Tsay G, Feng PH, Tan EM. Clinical and autoantibody correlations in Orientals with systemic lupus erythematosus. Ann Rheum Dis 1988; 47:918-23
10. Petri M, Rheinschmidt MM, Whiting-O'Keefe Q et al. The frequency of lupus anticoagulant in systemic lupus erythematosus. Ann Intern Med 1987; 106:524-31
11. Boey ML, Colaco CB, Gharavi AE, Elkon KB, Loizou S, Hughes GRV. Thrombosis in systemic lupus erythematosus: Striking association with the presence of circulating anticoagulant. Br Med J 1983; 287:1025-6
12. Howe HS, Boey ML, Feng PH. Methylprednisolone in Systemic lupus erythematosus. Singapore Med J 1990; 31:18-21
13. Edwards JCW, Snaith ML, Isenberg DA. A double blind controlled trial of methylprednisolone infusions in systemic lupus erythematosus using individualised outcome assessment. Ann Rheum Dis 1987;46: 773-6
14. Austin HA, Klippel JH, Balow JE et al. Therapy of lupus nephritis: Controlled trial of prednisolone and cytotoxic drugs. N Engl J Med 1986;316: 614-9
15. Strober S, Farinas MC, Field EH et al. Treatment of lupus nephritis with total lymphoid irradiation: Observations during a 12 to 79 month follow-up. Arthritis Rheum 1988;31:850-8
16. Grigor R, Edmons J, Lewoknia R, Bresnihan B, Hughes GRV. Systemic lupus erythematosus. A prospective analysis. Ann Rheum Dis 1978;37: 121-8
17. Rubin LA, Urowitz DD, Gladman DD. Mortality in systemic lupus erythematosus: the bimodal pattern revisited. Quart J Med 1985; 55: 87-98
18. Ginzler EM, Diamond HS, Weiner M et al. A multicenter study of outcome in systemic lupus erythematosus. Arthritis Rheum 1982;25: 601-11