Systemic Lupus Erythematosus in Singapore

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Abstract

The major initial clinical manifestations of systemic lupus erythematousus (SLE) were skin and mucous membrane involvement (52%), fever and malaise (48%), arthritis and arthralgias (44%). Lupus nephritis was diagnosed in 74% of patients and diffuse proliferative nephritis was the commonest histologic picture encountered. Except for a higherprevalence of anti-SS-A (Ro) (63%), other autoantibodies were within the normal range reportedfrom Western countries. There was no significant association between HLA-A, B or DR specificities in 51 Chinese patients, nor was there any differences seen in the polymorphism of tumour necrosis factor alpha gene (TNF-a).

Arthritis was less commonly seen in males with SLE. Prevalences of leukopenia and antibodies to anti-SS-A (Ro) and anti-La (SS-B) antigens were lower in men. Late onset lupus patients (>50 years of age) tended to have more insidious onset of disease, lower female predominance and less frequent complaints of fever, alopecia, arthritis and malar rash at presentation. The causes of death were often treatment related.

Survival studies among 183 SLE patients during theperiodfrom 1970 to 1980 revealed a 5- and 10-year survival rate of 70% and 60%, respectively. Infections and active lupus disease were 2 major causes of death. Research into SLE is targeted at increasing our understanding of the disease process and improving outcome and prognosis

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Key words: Clinical profiles, Genetics, Prevalence, Prognosis, Serology

Introduction

Systemic lupus erythematosus (SLE) or lupus ("wolf" in Latin) in short, is an autoimmune disorder of unknown aetiology(ies) and characterised by diverse clinical manifestations as well as a plethora of autoantibodies in the sera of patients. The clinical features of SLE vary in different population groups. Ethnic and genetic factors may be important in determining the expression and severity of disease. This article takes a comprehensive look at lupus in Singapore through 15 years of research and highlights some differences in the bite of the "wolf" locally.

Prevalence and Genetics

SLE is not a rare disease. In the Tan Tock Seng Hospital, approximately 1000 patients are on long-term follow-up. The estimated prevalence of SLE in Singapore is 3 per 10 000 (1995 to 1996). In Southeast Asia there are few epidemiological studies of SLE. Frank' reported an apparent predisposition to SLE in Chinese in West Malaysia. Eighty-one per cent of Chinese patients were represented in this study compared to Indians or Malays (19%). SLE appears to be the commonest rheumatic disease in patients admitted to one hospital in Thailand.[2] SLE does not occur in the same frequency in different races. There appears to be a higher incidence in black Americans and in Hispanics than in other populations.[3]

Genetic factors in the pathogenesis of SLE are strongly supported by studies in humans and animals in which SLE spontaneously develops. These studies demonstrated increased frequencies of HLA B8, DR2, DR3, DQW1 as well as null alleles of C4A in SLE.[4] However, these HLA associations were not consistently observed from population to population. In an early study in 1981, Chan and co-workers[5] found increased frequencies of HLA B13 in patients with mild SLE and HLA B17 in patients with severe SLE in 75 Chinese SLE patients in Singapore. These increased frequencies could be secondary to an increased frequency in HLA DR2. A more recent study in 1995 showed no significant association between HLA-A, B or DR specificities in 51 Chinese patients.[6] Hawkins and co-workers[7] reported increases in the frequencies of both DR2 and C4-null phenotypes in Southern Chinese patients with lupus in Hong Kong. A similar study of Chinese patients in Malaysia[8] showed that HLA-DRw15 and DQw1 were significantly more frequent in their patients. The C4A gene deletion usually associated with SLE in Caucasoid and black patients was absent in these Chinese patients. Hence, different major histocompatibility complex (MHC) haplotypes

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predispose to lupus in Chinese than in other ethnic groups. There is also suggestion that tumour necrosis factor (TNF) gene may be associated with SLE or certain subsets of SLE.[9] The TNF genes are located between the MHC class I and class II loci and it can induce expression of pro-inflammatory cytokines such as IL-l. A look at the polymorphism of the cytokine gene (TNF-a) in local patients did not reveal any differences between patients and controls.[10]

SLE occurs in families and this predisposition to SLE has been studied in twins. Concordance rates in monozygotic twins are between 30% and 50%.[11] This provides strong evidence of genetic factors. Familial study of SLE by the human genome scan is another powerful tool for identification of disease genes and holds promise of answers concerning susceptibility of disease and pathogenesis of SLE. Progress will be made as we work with others to study our large population of lupus patients.

Clinical Characteristics

Typical involvement of several organ systems is seen in our patients with SLE. One hundred and eighty Chinese SLE patients were studied between 1970 and 1980.[12] Their ages at diagnosis ranged from 14 to 59 years and the most common age range was 20 to 29 years. The female to male ratio was 9:1. The major initial manifestations were skin and mucous membrane involvement (52%), fever and malaise (48%), and arthritis and arthralgias (44%). Neuropsychiatric manifestations were rare in the initial diagnosis but were seen in 30% of patients on follow up (Table I). The two most frequent manifestations were organic brain syndrome(47%) characterised by impairment of orientation, perception, memory or intellectual function and seizures (24%). Movement disorders (1 1 %), inorganic brain syndrome (7%), peripheral neuropathy (7%) and paralysis (4%) constituted the less common neurological events. Lupus nephritis was diagnosed in 74% of patients (clinical and biopsy results). Diffuse proliferative nephritis was the commonest histologic picture encountered. A 1997study of 155 SLE patients by Fong and co-workers[13] of the initial manifestations and clinical features after 10 years of disease showed that the common clinical features of those with short disease duration (less than one year) were haematological (73%), arthritis (57%), malar rash (43%), renal disorder (31%) and photosensitivity (30%). Renal disorder significantly increased over the years. Hypertension (59%), diabetes mellitus (10%), atherosclerosis (7%) and cataract formation (10%) were evident in those with disease duration of more than 10 years.

TABLE I: INITIAL MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS[12]

Manifestations	London group (Grigor)*	Singapore group n = 183
Arthritis or arthralgia	62%	44%
Skin and mucous membrane	20%	52%
Fever, malaise	4%	48%
Thrombocytopenic purpura	4%	4%
Haemolytic anaemia	4%	3%
Neuropsychiatric	4%	4%
Swelling of face/leg		36%
Lymphadenopathy		8%
Gastrointestinal		7%
Respiratory		7%
Cardiovascular		3%

* Grigor K, Edmonds J, Lewkonia R, Bresnihan B, Hughes G R V. Systemic lupus erythematosus. A prospective analysis. Ann Rheum Dis 1978; 37:121-8.

The neurologic complications of SLE can affect any part of the nervous system. A study[14] of 36 patients who presented with neuropsychiatric (NP) manifestations revealed organic brain syndrome and epilepsy to be the two most commonly observed NP events. There was no pattern of antibody reactivity (including the antiphospholipid antibody) specific for any of the manifestations. Magnetic resonance imaging scans did not contribute more clinically useful information than computed tomographic (CT) scans. A well-defined but uncommon central nervous svstem lesion is transverse myelopathy. Chan and Boey[15] studied 9 patients who developed 14 episodes of transverse myelopathy. Nine episodes of paraperesis, 3 tetraperesis, 1 numbness and 1 neurogenic bladder were reported early in the diagnosis of SLE (median of two years). Urodynamics assessment in 6 patients showed abnormal detrusor behaviour in all. CT scans and myelograms were uninformative and cerebrospinal fluid studies normal. The functional outcomes were good with independent ambulation in all except 3 and improvement of motor scores. Our experience underscores the diagnostic difficulties in NP lupus. There exists, to date, no examination by which central nervous system (CNS) lupus can be identified with certainty.

Pulmonary involvement in SLE may be the first manifestation of lupus. Pleurisy may occur in the course of flares and pleural effusions demonstrated. Lung haemorrhage may complicate severe lupus and is associated with high mortality. A review of 10 local patients who developed pulmonary haemorrhage between 1987 and 1996[16] showed that all had clinical and or laboratory evidence of active lupus disease and 9 patients had a disease duration of two years or less. Fever and lung crepitations were present in 90% of patients while haemoptysis and chest pain occurred in only 3 and 2 patients respectively. Four patients died as a result of pulmonary haemorrhage.

Gastrointestinal abnormalities are observed in SLE.

Symptoms include abdominal pain, vomiting and diarrhoea. Some patients present with an acute surgical abdomen. Analysis of 10 patients[17] showed intra-abdominal sepsis and bleeding peptic ulcer disease constituted two major causes of laparotomies. Lack of definitive diagnostic tests often contribute to the diagnostic dilemma. Early surgical intervention was the single most important factor in the improved mortality of patients in this study.

Serologic Features

Antinuclear antibodies are hallmarks of SLE. In 1988 10 autoantibodies were assayed in 94 SLE patients.[18] The prevalence of antibodies to the following antigens were as follows: double-stranded (ds) DNA (43%), histone (81%), Sm (26%), nuclear ribonuclear protein (nRNP) (16%), SS-A(Ro) (63%), SS-B(La) (12%), SL/Ki (9%), ribosomal RNP(rRNP)(16%), p70/p80(5%), proliferating cell nuclear antigen (PCNA) (3%) (Fig. 1). Except for a higher prevalence of anti-SS-A(Ro), other autoantibodies were within the range reported from Western countries, indicating a high uniformity of autoantibody profiles in SLE in different countries. Patients with neuropsychiatric manifestations showed a higher plurality of antibodies per patient than patients without neuropsychiatric symptoms, 4.22 versus 2.77. There was no increased prevalence or specific type of autoantibody in those with renal manifestations. Antiphospholipid antibodies comprising anticardiolipin IgG and IgM were found in 53% patients, lupus anticoagulant in 26% and false positive VDRL was present in 17%. Autoimmune haemolytic anaemia in SLE was frequently associated with the presence of thrombocytopenia and anticardiolipin antibodies.[19] The occurrence of autoimmune thrombocytopenic purpura in association with a Coomb's positive haemolytic anaemia is known as Evan's syndrome.

Male Lupus

There is a female preponderance in SLE. The ratio of female to male range from 9 to 12:1. Various reports have highlighted differences between the sexes in SLE.[20-21] These gender differences may play a role in disease expression. A study[22] of 61 male patients showed that arthritis was significantly less common in males. Renal disease was the commonest clinical manifestation and diffuse proliferative glomerulonephritis the dominant finding on renal biopsy. The prevalences of leukopenia and antibodies to extractable nuclear antigens in particular anti-Ro(SS-A) and anti-La(SS-B) were lower in men. Arthritis and serositis were less common in our local Oriental males in contrast to Caucasian patients in many western series (Table II). Hormonal profiles in male lupus patients have been studied. Serum levels of cortisol, estradiol, testosterone, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEA-SO_4), androstenedione and prolactin were assayed in 39 male patients,[23] and in 38 healthy male controls. Serum prolactin levels were significantly elevated in patients with active lupus disease. Prolactin has immuno-modulating effect on T-lymphocytes and may potentially influence disease activity.[24] Depressed androgen level is likely a result of adrenocortical suppression of corticosteroids. The other hormones assayed were normal.

Late Onset Lupus

SLE typically affects female adults between 20 and 50 years of age. A subgroup of the general population of SLE appears during the latter years. This late onset group has been shown to differ from the early onset group in clinical presentations, pattern of organ involvement, severity of disease and prognosis.[25,26] Fifty patients with early (<50 years of age) and 26 with late onset (>50 years) disease were compared.[27] The late onset lupus patients tended to have an insidious onset of disease, lower female predominance and less frequent complaints of fever, alopecia, arthritis and malar rash at presentation (P <0.05). Peripheral neuropathy, myalgias, pancytopenia and elevated liver enzymes were more commonly found in the late onset group during follow up. Major organ involvement was relatively uncommon

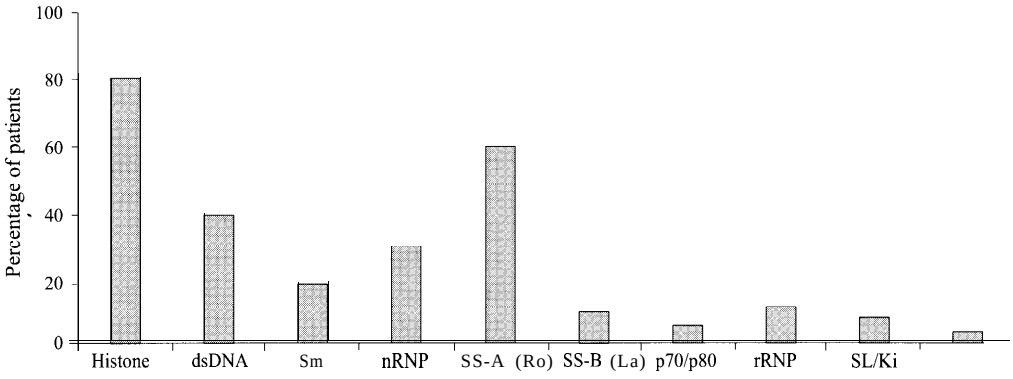

Fig. 1. Autoantibody profile in 94 patients with systemic lupus erythematosus.

TABLE II: CLINICAL AND LABORATORY FEATURES IN LUPUS PATIENTS[22]

Manifestation	Male		Female		*P* value
	No. (61)	(%)	No. (86)	(%)	
Malar rash	34/61	(55.7)	59/86	(68.6)	ns
Discoid rash	9/61	(14.8)	8/86	(9.3)	ns
Photosensitivity	18161	(29.5)	16/86	(18.6)	ns
Oral ulcers	1l/61	(18.0)	14/86	(16.3)	ns
Arthritis	33/61	(54.1)	62/86	(72.1)	0.04
Pleuritis	5/61	(8.2)	7/86	(8.1)	ns
Pericarditis	4/61	(6.6)	7/86	(8.1)	ns
Renal disease	44/61	(72.1)	64/86	(74.4)	ns
Neuropsychiatric	15/61	(24.6)	34/86	(39.5)	ns
Haemolytic anaemia	6/61	(9.8)	13/86	(15.1)	ns
Leukopenia	22/61	(36.1)	49/86	(57.0)	0.02
Lymphopenia	15/61	(24.6)	34/86	(39.5)	ns
Thrombocytopenia	22/61	(36.1)	42/86	(48.8)	ns
Anti-DsDNA	56/61	(91.8)	74/86	(86.1)	ns
ANA	56/61	(91.8)	83/86	(96.5)	ns
False VDRL	6/31	(19.4)	10/51	(19.6)	ns
LE cells	15/25	(60.0)	60/78	(76.9)	ns
Anti-Sm	4/41	(9.8)	23/86	(26.7)	ns
Anti-Ro	9/43	(20.9)	58/86	(67.4)	<0.00001
Anti-La	0/22	(0.0)	14/86	(16.3)	
Anti-nRNP	7/39	(18.0)	27/86	(3 1.4)	ns

ns: not significant; Anti-DsDNA: anti double-stranded deoxyribonuclei acid antibodies; ANA: antinuclear antibody; VDRL: venereal disease research laboratory; LE: lupus erythematosus

in the late onset patients. No sex-related differences could be demonstrated with respect to the mean age of onset of disease and clinical manifestations. No significant serological differences were detected between the two groups (Table III). Two of the 3 deaths in the late onset group were treatment related and were from pneumonia and gastrointestinal bleeding.

TABLEIII: LABORATORY FINDINGS BETWEEN EARLY AND LATE ONSET LUPUS[27]

Laboratory tests	Early onset n = 50 (%)	Late onset n = 26 (%)	*P* value
Haemolytic anaemia	18	11.5	ns
Leukopenia	50	26.9	ns
Thrombocytopenia	44	23.1	ns
Pancytopenia	6	26.9	<0.05
Elevated liver enzymes	0	15.4	<0.05
ANA	100	96.2	ns
anti-dsDNA ab	97.7	84.6	ns
anti-Ro ab	38.9	34.8	ns
anti-La ab	5.7	7.7	ns
anti-Sm ab	32.5	21.7	ns
anti-RNP ab	16.7	17.4	ns
VDRL	36.4	22.2	ns
RF	27.3	23.5	ns
Hypocomplementemia	100	78.3	ns

ANA: antinuclear antibody; VDRL: venereal disease research laboratory; RF: rheumatoid factor; ns: not significant

Pregnancy

SLE affects women of childbearing age. Thus, issues concerning pregnancy, fertility and contraception arise during the patient's disease course. Between May 1987 and June 1989, 23 pregnant SLE patients were studied.[28] The mean age was 30.4 years. Spontaneous abortion rate of 19% was observed. IgG and IgM anticardiopin antibodies were present in 45% and 18% of patients, respectively. There was no intra-uterine foetal death. This was attributed to improved antenatal surveillance with ultrasound assessment of foetal growth and blood flow patterns. Improved neonatal support gave confidence for pre-term intervention. There was a significantly lower mean crude birth weight amongst babies born to mothers with SLE. This could be due to a shorter mean gestational age of the infants or intra-uterine growth failure. One pregnancy was complicated by complete heart block in the neonate. Anti-Ro(SS-A) antibody was present in the child at the age of 10 months. Corticosteroid dose was adjusted appropriately during pregnancy and it did not adversely affect the outcome of the pregnancy nor the foetus. The study highlights the importance of team management of these high-risk pregnancies of lupus patients by rheumatologists, obstetricians, neonatologists and paediatricians.

Prognosis

Prognosis in SLE has improved since the 1950s. Five-

year survival rates of between 90% and 98% have been reported in some series.[29,30] This has been attributed to early detection and treatment of the disease and better patient education. The judicious use of existing therapies contributes to improved survival. Besides corticosteroids, immunosuppressives such as cyclophosphamide, azathioprine and methotrexate have been used to control the disease. Plasmapheresis and intravenous immunoglobulin infusion are other modalities of treatment for severe and life-threatening disease manifestations such as pulmonary haemorrhage and severe thrombocytopenia. In Singapore, the overall estimated survival rate of patients in the study period between 1970 and 1980 was 70% and 60% at 5 years and 10 years, respectively (Fig. 2).[12] The major causes of death then were renal (36%), central nervous system involvement (26%) and infection (20%). A reappraisal of the causes of death from 1976 to 1984[31] revealed that infection was the leading cause of death (48%) (Table IV). Organisms implicated include Pseudomonas *aeruginosa, Klebsiella, Escherichia coli, Cryptococcus neoformans* and *Candida albicans* (Table V). Infections were shown to be significantly associated with the peakcorticosteroid received.[32] Death from active lupus disease remain substantial. Central nervous system disease and pulmonary haemorrhage were the two commonest manifestations of active disease that resulted in death. Late deaths from vascular complications were infrequent.

Morbidity and mortality rates are greatly influenced by the socio-economic status of the patient population.“” The availability of health education, the reliance of alternative medicine and psychosocial well-being are factors which have a direct bearing on morbidity and mortality. In a case-controlled, cross-cultural study of the psychiatric morbidity of SLE, Lim and co-workers[34] found that patients in the Singapore sample experienced greater social support, more psychiatric morbidity (53%) than did the London patients (40%). Psychiatric morbidity was significantly correlated with patient perception of the illness and disease activity. Significant stressors in the study were poor relationships of patients with spouses and poor social life. In 1997, a further attempt to measure outcome of the disease was made. A quality of life assessment using the Short Form (SF) 36 questionnaire was used in 36 lupus patients and 76 controls.[35] Lupus patients had lower mean scale scores than controls for physical functioning, bodily pain, physical role functioning and general health. Mean scores for vitality, social and emotional role function and mental health were similar in both groups (Table VI). This data suggest that the SF-36 health survey may be able to measure differences in the quality of life between lupus patients and healthy controls in Singapore.

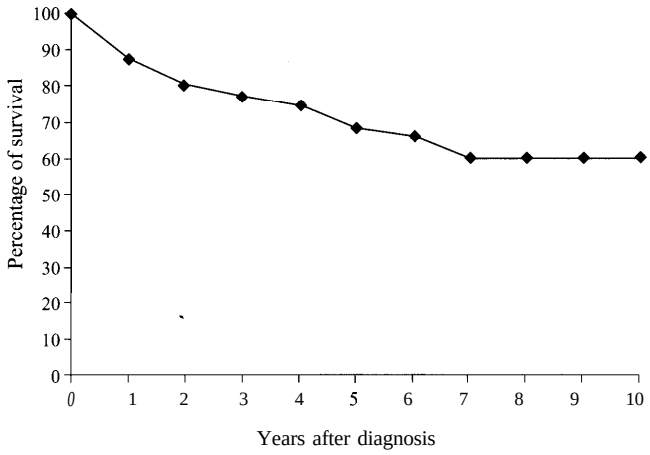

Fig. 2. The estimated percentage of survival after diagnosis of systemic lupus erythematosus in 183 Chinese patients.

Conclusion

SLE in Singapore has marked clinical similarities when compared to SLE reported elsewhere in the world. Differences may lie in disease severity, genetics and

TABLE IV: CAUSE OF DEATH IN 50 PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)[31]

Primary cause of death	No. of patients
Active SLE specific organ involvement	20
Renal	7
CNS	5
Haematologic	2
Cardiac	1
Infection	24
With active SLE	18
SLE inactive	6
Vascular events	1
Pulmonary embolism	1
Myocardial infarct	1
Cerebrovascular accident	4
Unrelated	1
Unknown	4

CNS: central nervous system

TABLE V: INFECTIONS AS PRIMARY CAUSE OF DEATH[31]

No. of patients	Organism	Involvement	Cytotoxic drugs received
3	*Pseudomonas aeruginosa*	Septicaemia	*No*
3	*Cryptococcus neoformans*	Meningitis	Azathioprine
2	*Candida albicans*	Pneumonia	No
2	*Klebsiella*	Septicaemia, peritonitis	No
1	Tubercle bacilli	Pneumonia	*No*
1	*Escherichia coli*	Septicaemia	Azathioprine
1	Salmonella D	Septicaemia	No
1	β-haemolytic streptococcus	Septicaemia	Azathioprine
1	Cytomegalovirus	Viraemia	No

TABLE VI: MEAN SHORT FORM-36 SCORES FOR LUPUS PATIENTS CONTROLS[35]

Domain	Lupus patients n = 36 Chinese females (ages between 20 and 60 years)*	Controls n = 76 Chinese females (ages between 20 and 60 years)*	*P* value
Physical	73.0 (10 to 100)	89.7 (15 to 100)	0.0027
Functioning	55.7 (0 to 100)	89.5 (0 to 100)	0.0001
Role-Physical	71.0 (22 to 100)	81.4 (22 to 100)	0.027
Bodily pain	47.4 (15 to 62)	5 1.8 (30 to 72)	0.05
General health	43.8 (20 to 60)	44.8 (20 to 60)	0.61
Vitality	45.9 (12.5 to 75)	45.8 (12.5 to 75)	0.95
Social functioning	71.4 (0 to 100)	74.7 (0 to 100)	0.67
Role-Emotional	55.1 (28 to 72)	56.3 (24 to 72)	0.54
Mental health			

* Range of SF-36 scores in brackets

Mean age of lupus patients (outpatients or inpatients) = 3 1.9 years (range 2 1 to 53 years)

Mean age of controls (healthy individuals) = 29.0 years (range 21 to 53 years)

Activity of disease assessed by British Isles Lupus Assessment Group (BILAG) index. Mean BILAG score of patients = 2 (range 0 to 14)

outcomes. Appropriate medications and health education, which are cornerstones of management, are readily available to our patients. Whilst progress has been made in early diagnosis, health education and support via patient support groups, the greatest challenge remains in reducing morbidity and mortality of the disease. Our participation and progress in research not only contributes to the understanding of the pathogenesis and treatment of this complex disease but gives hope of cure to all our patients with SLE.

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