ORIGINAL ARTICLE

Mortality in Malaysians with Systemic Lupus Erythematosus

N I J Paton, MRCP*, I Cheong, FRCP**, N C T Kong, FRACP**, M Segasothy, FRCP**,
*Department of Infectious Diseases, St. George's Hospital, Medical School, Tooting, London, United Kingdom, **Department of Medicine, Universiti Kebangsaan Malaysia, 50300 Kuala Lumpur

Summary

One hundred and two patients attending the systemic lupus erythematosus (SLE) clinic of the Department of Medicine, Universiti Kebangsaan Malaysia, were studied retrospectively to determine their survival rates and causes of death. There were 21 deaths. The 1, 5, and 10 year survival rates were 93%, 86% and 70% respectively. There was a bimodal pattern of mortality with more patients dying in the first 2 years or after 5 years of disease. Infection was the direct cause of death in 52% and contributed to a further 19% of deaths. Patients with lupus nephritis had a higher relative risk (RR) of death (RR=4.34, $p<0.02$) although there was no significant increase in risk with any particular histological type on biopsy. Cerebral lupus (RR=3.08, $p<0.001$) and methylprednisolone treatment (RR=6.24, $p<0.001$) were also associated with increased risk of death. Increased awareness of infection and earlier use of antibiotic therapy may improve survival of patients suffering from SLE.

Key Words: Systemic lupus erythematosus, Infection, Methylprednisolone, Lupus nephritis, Mortality in systemic lupus erythematosus

Introduction

Despite steady improvements in survival of patients with SLE in the last 4 decades, the morbidity and mortality from the disease is still appreciable. Studies conducted in North America[1] and Canada[2] have shown that although early deaths from active lupus and infection have decreased, late deaths are common from relapse of previously inactive SLE and cardiovascular disease. Although SLE is a common disease in South East Asia, there are few studies that examined causes of death. Accurate knowledge of factors contributing to mortality is essential for planning management strategies appropriate for this population. We therefore undertook this study to evaluate the causes and risk factors of death in SLE patients in Malaysia.

Patients and Methods

Case records for patients who attended the SLE clinic at Universiti Kebangsaan Malaysia between October 1978 and September 1993 were reviewed. Features of SLE corresponding to the 1982 revised ARA criteria[3] were recorded. Neurological involvement was defined as seizures or psychosis in the absence of offending drugs of known metabolic derangements. Renal involvement was defined as persistent proteinuria greater than 0.5g/day or >3+ (if quantitation not performed), or cellular casts on microscopy.

Information was recorded on sex, race, age at diagnosis, duration of survival (taken from time of diagnosis to last follow-up visit or death), renal biopsy histology, and treatment with azathioprine, oral or intravenous cyclophosphamide or pulse methylprednisolone. Patients were classified into two socio-economic groups: group A were those educated beyond secondary school, or where either the patient or spouse was employed in a skilled or semi-skilled occupation, or if the monthly salary equalled or exceeded 1000 ringgit.

Patients with none of these characteristics were classified as socio-economic group B.

Direct and contributing causes of death were determined after detailed review of the case notes, laboratory results and any post-mortem biopsy findings (no patient underwent a full post-mortem). The direct cause of death was defined as the condition or complication of SLE which was most directly responsible for death. Underlying factors in the patient's death were recorded as contributing causes of death. Disease was recorded as active if there had been marked exacerbation in previous symptoms, and/or clinical or laboratory evidence of rapid progression or new organ system involvement prior to or during the final illness.

Results

Records were available for 153 patients seen at the SLE clinic. Of these, 102 were suitable for analysis. Patients were excluded if they did not fulfill 4 or more ARA criteria, if there was evidence of an overlap syndrome, if the majority of their care took place in another hospital with insufficient communication to determine the course and management, or if they had been seen on one occasion only. Three of the excluded patients were known to have died.

The racial composition of the cohort was 47% Chinese, 46% Malay and 7% Indian. Female patients made up 93% of the group and 24% were classified as being in socio-economic group A. The mean age at diagnosis of SLE was 26.4 years (range 8.6 to 61 years) and the mean duration of follow up was 5.7 years. The mean number of ARA criteria satisfied was 5.2 (range 4 to 9). Lupus nephritis was present in 69% of patients and CNS lupus in 20%.

One or more renal biopsy were performed in 52 patients. Membranous glomerulonephritis was found in 40%, diffuse proliferative glomerulonephritis in 40%, focal proliferative glomerulonephritis in 19% and mesangial proliferative glomerulonephritis in 12%.

Survival and causes of death

There were twenty-one recorded deaths among the 102 patients. The mean age at death was 28 years (range 15.1 to 43.1 years). The mean duration of illness to death was 3.3 years (range 0.1 to 10.2 years). The 1, 5, and 10 year survival rates were 93%, 86% and 70% respectively. There was a bimodal pattern of mortality with most deaths occurring in the first two years and after five years from the time of diagnosis of SLE (Fig. 1).

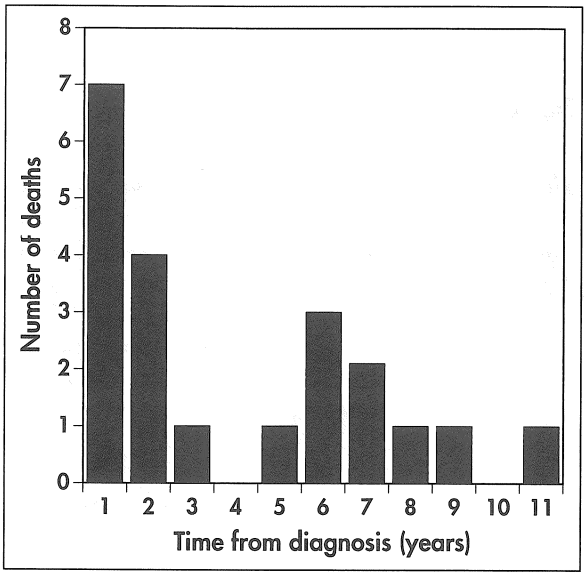

Fig. 1: Mortality of 21 patients following diagnosis of SLE

The causes of death are shown in Table I. Infection was implicated in 71% of deaths, being the direct cause in 11 patients (52%) and a contributing cause in a further 4 patients (19%). The organisms responsible for infection-related deaths are listed in Table II. Active SLE directly caused 4 deaths (19%) and contributed to the demise of another 9 patients (43%). Renal failure was the cause of death in 3 patients (14%) and contributed to 8 deaths (38%). Disseminated intravascular coagulation occurred in 6 patients during the final illness; this was associated with infection and active SLE in 4 patients, septicaemia alone in 1 patient and florid SLE in the remaining patient.

Active disease and infection were implicated in 77% and 62% of early deaths (before 5 years) and 37% and 87% of late deaths (after 5 years) respectively.

Table I
Causes of death of patients with SLE

Direct cause of death	Number of cases
Infection	
septicaemia	8
pneumonia	2
tuberculosis	1
Active SLE	
renal lupus	3
florid multisystem disease	1
Intracranial bleed	3
Bleeding oesophageal varices + renal failure	1
Pulmonary embolism	1
Unexplained sudden death in sepsis	1
Contributing cause of death	
Infection	
septicaemia	3
pneumonia	1
Active SLE	
renal lupus	4
renal + cerebral lupus	2
renal lupus + intestinal vasculitis	1
renal lupus + TTP* + haemolytic anaemia	1
cutaneous vasculitis	1
Inactive cerebral lupus	1
Renal failure (not due to active lupus)	1
Disseminated intravascular coagulation	6
Gastrointestinal bleed	1

* *thrombotic thrombocytopenia purpura*

Risk factors for death

The relative risk (RR) of death at any time during the study was not significantly different between males and females, races, socio-economical groups or the renal histological types. However, the relative risk of death was higher in patients with lupus nephritis (RR=4.34, $p<0.02$) or with cerebral lupus (RR=3.08, $p<0.001$). Treatment with methylprednisolone was associated with a significant risk of death (RR=6.24, $p<0.001$) but treatment with azathioprine, oral or intravenous cyclophosphamide were not.

Discussion

There are two reports of survival rates and causes of death of Chinese patients with SLE from this region. In a study from Singapore covering the period 1970 to 1980, the five and ten year survival rates were 70% and 60% respectively[4]. A second study from Hong Kong, which evaluated patients seen between 1985 to 1989, the five year survival was 76%[5]. In an earlier report at the University Hospital, Petaling Jaya, the 5 years survival for 419 patients with SLE (Chinese 63%; Malays 28%; Indians 9%) was 83% at 5 years and 80% 10 years.[6] The survival rates of our patients at 5 and 10 years were 86% and 70% respectively. Differences in survival figures may be due to referral bias, differences in patient compliance to treatment and socio-economic conditions. SLE appears to follow a more severe course in Chinese patients[7,8] and the higher mortality in these previous studies might therefore be attributed to the greater proportion of Chinese patients compared with our cohort. However, we found no significant difference in survival between the racial groups in our study.

Infection was the major cause of death in our patients, being the direct or contributing factor in 71% of deaths. A similar finding has been reported in other SLE populations, accounting for 37% of deaths in Hong Kong[5], 20% in Singapore[7], 33% in Jamaica[9], 27% in Canada[2], and 49% in the largest study from America[1]. We have reported that infection related deaths most often occurred in the setting of active SLE[10]. In fact, active lupus was the second most important cause of death, playing a role in 62% of deaths.

In contrast to the findings of Cohen and Li[5], none of our patients died of active cardiopulmonary disease (myocarditis, pericarditis od pneumonitis). However, comparison of causes of death between studies in S.E. Asian countries and the West is limited by the lack of post-mortem examinations in the former (usually due to cultural and religious reasons) to ascertain definitive causes of death. This limitation is unlikely to be overcome in future studies and hence conclusion of causes of death in patients from this region will always be more speculative than comparable studies in Europe and USA where autopsy data is more frequently available.

Table II
Infections resulting in death in patients with SLE

Site	Organism(s)	
Septicaemia (11 cases)	Pseudomonas aeroginosa	1
	Pseudomonas aeroginosa + Staph aureus	1
	MRSA	1
	Staphylococcus epidermidis	1
	E. coli	1
	E. coli + Klebsiella + Acinetobacter	1
	No organism	4
Pneumonia (4 cases)	Mycobacterium tuberculosis	1
	Pseudomonas aeroginosa	2
	No organism	1

Rubin and colleagues[2] also reported a bimodal pattern of mortality in SLE with most patients dying either within two years of diagnosis from active disease or after five years from infection and cardiovascular disease, mainly artherosclerotic coronary heart disease. Death from cardiovascular disease is uncommon in studies with a large population of non-white patients[1] (as in our study), suggesting that mortality from cardiovascular disease is mainly a Caucasian manifestation of SLE.

We found that patients with lupus nephritis and cerebral lupus had a significantly higher risk of death than those without. This finding is not surprising and consistent with the findings of the Lupus Survival Study Group in American patients with SLE[1]. In addition, we also found the use of intravenous bolus methylprednisolone therapy strongly associated with a higher risk of death (RR=6.24, $p<0.001$). This may be due to the dramatic increase in infection rate following methylprednisolone therapy in our patients[10] or may be due to the association of this form of treatment with patients who have more severe disease. The administration of high dose methylprednisolone is advocated as a final therapeutic manoeuvre to save very ill patients and may have created an artefactual association of this form of treatment with death.

In conclusion, our study on Malaysian SLE patients supports previous finding that infection is a major cause of mortality in patients with SLE. Although much has already been achieved, further improvement in survival is likely to be gained by earlier recognition and therapy of infections in addition to the continually improving treatment for active disease.

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