Lupus nephritis: clinicopathological study of 162 cases in Thailand

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SUMMARY One hundred and sixty two cases of lupus nephritis biopsied over three years in Thailand were studied. A pattern of clinical and histological renal disease very similar to that seen in the United States or Europe emerged.

The predominant histological type was World Health Organisation class IV (diffuse proliferative; 58.6%). Patients with renal insufficiency (creatinine ≥ 2 mg/100 ml) or hypertension at the time of biopsy had a considerably worse three year survival. Certain features such as sclerotic glomeruli, tubular atrophy, and an interstitial mononuclear cell infiltrate were significantly associated with a worse outcome ($0.05 > p > 0.01$), and patients who died with poor renal function had significantly higher chronicity scores than those in other groups ($p < 0.05$). These findings emphasise the importance of chronic renal damage in the morbidity and mortality of patients with lupus nephritis.

The number of patients with systemic lupus erythematosus registered each year is 150–180, representing 3.3% of the total medical inpatients at the Siriraj Hospital. The renal unit admits 60–80 such patients annually, and during the period covered by this study 162 patients out of 230 had clinical evidence of renal disease.

In the absence of any studies of this condition from Thailand it seemed initially that the degree of concomitant renal disease, both clinically and histologically, was more severe than we had thought. We therefore carried out detailed investigations to establish any clinicopathological or prognostic differences that might be seen when our study was compared with other series^{1–10} from areas of a much lower prevalence.

We report 162 patients with lupus nephritis who attended the renal unit, Siriraj Hospital, Bangkok, who underwent renal biopsy between January 1981 and December 1983, and who were analysed according to the World Health Organisation classification (Table 1).¹¹ (These patients have now become part of a long term follow up study.

Patients and methods

Of 1119 renal biopsies performed between January 1981 and December 1983, 180 were from 173 patients fulfilling four or more of the preliminary¹² or revised,¹³ or both, American Rheumatism Association criteria for the diagnosis of systemic lupus erythematosus. Eleven biopsies were inadequate resulting in 169 from 162 patients (154 new cases and eight repeat biopsies).

The female:male ratio was 154:8 (19:1) and mean age was 26.6 ((SD) 9.8 years) (range 6–66 years) at the time of biopsy.

In each case serological evidence of systemic lupus erythematosus (LE preparation, ANF, anti-ds DNA) was sought as one of the criteria and was obtained in all but one case, in which six other criteria were fulfilled.

There was no obvious geographical bias among the population studied: Siriraj Hospital (750 beds) is one of six teaching hospitals in Bangkok (population 4.5 million) serving a large part of Bangkok as well as provincial cities all over Thailand.

CLINICAL EVALUATION

Renal function was classified by serum creatinine, and a concentration of ≥ 2 mg/dl was categorised as renal insufficiency. Patients were divided into those with

Table 1 Histological patterns, age, sex, and pathological scores in renal biopsies from 162 patients with systemic lupus erythematosus

WHO class ¹¹	Patients			Age at biopsy (years) mean (SD)	Sex F M	Pathological scores (mean (SD))		
	No	Total	%			Activity	Chronicity	Total
Normal glomeruli:								
No immune deposits								
With immune deposits	1	1	0.6	37	1:0	0	0	0
Mesangial:								
Mild cellularity	29	29	17.9	27.6 (11.4)	28:1	1.9 (1.0)	1.1 (1.4)	3.0 (2.2)
Moderate cellularity								
Focal proliferative:								
"Active" lesion	12							
Sclerosing lesion	4	16	9.9	25.5 (8.6)	15:1	4.2 (1.8)	1.9 (1.5)	6.1 (2.5)
"Active" and sclerosing lesion								
Diffuse proliferative:								
Pure proliferation	9							
"Active" lesion	55							
Sclerosing lesion	25	95	58.6	25.9 (9.8)	90:5	8.0 (2.4)	3.1 (1.9)	11.3 (2.9)
"Active" and sclerosing lesion	6							
Membranous:								
Pure	1							
With feature of class II	11							
With feature of class III*	3	21	12.9	27.2 (8.6)	20:1	5.7 (2.1)	2.1 (1.8)	7.8 (3.5)
With feature of class IV*	6							
Total		162	100.0	26.4 ± 9.8	154:8			

*May be classified as class III and IV. In this study if numerous or large subendothelial deposits, or both, or proliferation was severe, the biopsy was classified as class IV.

and without renal insufficiency at the time of biopsy.

For evaluation of outcome a change of more than one third of the serum creatinine was considered to be clinically important and on this basis patients were allocated into five groups at the end of the study: A better; B no change; C worse, or death from renal failure, or from another cause, but with a record of deteriorating renal function; D death without a record of deteriorating renal function; E lost to follow up. Patients in group B were reallocated if there had been a change in haematuria, (+ to - or - to +) or by a change in proteinuria of more than 2+.

Clinical definitions used in this study were: clinically important haematuria, >5 red blood cells/high power field; clinically important proteinuria, ≥1 g/24 hours; hypertension, diastolic blood pressure >95 mm Hg on two separate occasions, or a record of anti-hypertensive treatment.

Tissue was divided into three portions for light microscopy with immunoperoxidase staining (an established method),¹⁴ immunofluorescence, and high resolution light microscopy (1 µm).

EVALUATION OF BIOPSIES

All cases had at least five glomeruli in sections embedded in paraffin and epoxy resin. Each biopsy was assessed independently by two observers (PP and NDF) and classified into one of the WHO classes.¹¹ Cases with repeat biopsies were classified by the first one except in the eight cases coming to biopsy before

1981 for which no immunopathological studies were available.

A pathological scoring system⁴ was used, resulting in activity, chronicity, and total scores for each biopsy. Each feature was graded 0 to 3+ (0 = absent, 1+ = <25%, 2+ = 25–75%, 3+ = >75%). There was rarely a difference of greater than 1+ for any feature among the observers. This supports the findings of others.^{6 15}

SEROLOGY

ANF and anti ds-DNA were tested using standard methods.^{16 17} Differences between each WHO class were compared using the Mann-Whitney test. Individual pathological features related to outcome were tested by the χ^2 test and contingency table methods. Survival data were analysed by the life table method¹⁸ and calculated from the time of biopsy.

Results

CLINICAL

Apart from renal disease, the most common presenting signs were skin rash, anaemia, and joint symptoms. Table 2 shows the clinical manifestations throughout the course of follow up. All patients had clinical renal disease, and the most common features were those related to skin and joints. Hypertension and anaemia were common complications, mostly from class IV patients. Disease of the central nervous

Table 2 Clinical manifestations throughout follow up period of 162 patients with systemic lupus erythematosus

	WHO class					Total	
	I	II	III	IV	V	Case	%
No of patients	1	29	16	95	21	162	100.0
Skin rash	1	19	12	59	15	106	65.4
Joint symptoms		18	14	60	11	103	63.6
Hypertension		8	5	57	9	79	48.8
Anaemia		13	6	52	6	77	47.5
Infection		10	4	27	5	46	28.4
Oral ulcer		7	9	19	2	37	22.8
Vasculitis		9	7	14	5	35	21.6
CNS symptoms		3	2	18	4	27	16.7
Serositis		3	1	16	3	23	14.2
Raynaud's phenomenon		4	1	7	3	15	9.3
Ocular signs		1	1	6	1	9	5.6
Avascular necrosis of femur			1	2		3	1.9

system was not a predominant feature in any WHO class. Infections were common and often multiple. There was no clear age difference between patients from WHO classes.

Evidence of renal disease, obtained from referral information, histories, and recorded data at presentation, comprised oedema (72.3%), proteinuria (28.4%), and gross haematuria (14.2%).

PATHOLOGY

Table 1 shows the distribution of age, sex, and pathological scores within each group. Table 3 shows some specific features at the time of biopsy, the most striking of which was the high proportion of patients with haematuria and those in classes IV and V with proteinuria in the nephrotic range.

Mean activity scores between each class, chronicity scores between classes II and V, and total pathological scores between each class except III and V were all significantly different ($p < 0.01$). The remainder were marginally significant ($0.05 > p > 0.01$). Class IV patients had the highest mean scores.

Adequate material was available for immunofluorescence or immunoperoxidase studies, or both, in 134 cases. Most were positive for IgG (130), IgA (129), IgM (128), and C3 (131). Sixty eight of 130 patients were positive for fibrinogen and 49 of 60 of those tested were positive for C4. IgG was the predominant immunoglobulin in 97 cases.

Table 3 Renal findings at time of biopsy

	WHO class					Total	
	I	II	III	IV	V	No	%
No of patients	1	29	16	95	21	162	100.0
Hypertension		4	4	51	4	63	38.9
Haematuria (> 5 rbc/hpf)	1	5	9	73	5	93	57.4
Proteinuria 1-3 g/24 hours		1	7	16	4	28	17.3
> 3 g/24 hours		2	3	58	15	78	48.1
24 hour protein (g) (mean (SD))		0.7 (1.4)	1.7 (1.4)	5.28 (3.2)	5.4 (4.3)		
Creatinine mg/100 ml (mean (SD))	0.9	1.0 (0.4)	1.4 (0.7)	2.1 (2.0)	1.3 (0.8)		

SEROLOGY

LE cell preparation, ANF and anti ds-DNA were positive in 55.4%, 91.9%, and 62.1%, respectively, of the patients tested. In all but one of the patients whose test for ANF was negative or not recorded, the LE cell preparation and anti ds-DNA were positive.

FOLLOW UP (TABLE 4)

Fourteen patients were lost to follow up. The remaining 148 were followed up for two to 44 months (mean 14.9 (10.0)) after biopsy. Thirty six (24%) showed no change, 69 (47%) improved, and 19 (13%) deteriorated. Follow up intervals varied widely within each class, and no statistical analysis was attempted.

Twenty four (16%) patients died, 17 of whom were in class IV. Infection was the cause of death in nearly half of them. Renal failure was an important cause of death and occurred only in class IV patients. Survival curves from the time of biopsy seen in Fig. 1 show that class IV patients had the worst three year survival.

REPEAT BIOPSIES

Thirteen cases had more than one adequate biopsy, resulting in 30 biopsies for analysis. Six cases showed no change in WHO class. Three cases changed from class IV to II, two from III to IV, one from II to IV, and one from IV to V.

Fig. 1 Survival of patients in WHO biopsy class II, III, IV, and V.

ANALYSIS

Chronicity scores of the eight patients who died as a result of renal failure (5) or who had renal failure at the time of death from another cause (3) were significantly higher than those of the other outcome groups ($p < 0.05$, Table 4). Division of patients into those with a total pathological score of < 8 and those with > 8 showed only a slightly worse (insignificant) three year survival of the second group (89.6% v 95.1%). Within each WHO class there was no significant difference between the pathological scores of the different outcome groups.

The presence of more than 25% of the following features was associated with a worse outcome: sclerotic glomeruli ($p = 0.014$), tubular atrophy ($p = 0.036$), and interstitial mononuclear cell infiltration ($p = 0.011$). Patients who had "renal insufficiency" (33

cases) or hypertension (63 cases) at the time of biopsy had a significantly poorer three year survival (45.4% v 83.5%, $p < 0.001$; 65.5% v 88.4%, $0.001 < p < 0.01$, respectively) (Figs. 2a and b).

Despite careful searching only two cases with definite capillary fibrin thrombi and one case with vasculitis were found. Haematoxyphil bodies were noted in only six cases (3.6%); four in class IV and two in class III, all in areas of necrosis.

Discussion

Our study shows that systemic lupus erythematosus is unusually common and that a large proportion of the patients seen at this hospital present with renal disease. The preselection of patients for renal biopsy, however, and the fact that this is a referral centre means conclusions drawn about this group do not necessarily apply to all cases of systemic lupus erythematosus in Thailand.

The unusually high female to male ratio (19:1) is, in part, fortuitous. A previous report from Thailand¹⁹ showed a ratio close to that reported in the United States and United Kingdom of 10:1, but the combined figures from 1978–1983 show a ratio of 14:1 (397:28). The reason for this higher preponderance among women is unclear.

Frank²⁰ drew attention to the higher incidence of systemic lupus erythematosus among the Chinese in Malaysia, and two other studies indicated a high prevalence of the disease among Chinese in Hawaii²¹ and a higher mortality among Chinese with systemic lupus erythematosus in the United States.²² It is extremely difficult to analyse the ethnic origin of our patients, but intermarriage between Thai and Chinese is common.

The main conclusion of our study is that the pattern of renal disease and clinical presentation is

Table 4 Follow up data

	WHO class					Total	Pathological score		
	I	II	III	IV	V		Activity	Chronicity	Total
No of patients:	1	28	16	84	19	148			
Interval (biopsy to end of study in months) (mean (SD))	18	19.1 (17.3)	15.1 (10.6)	16.3 (13.5)	11.5 (7.5)				
Outcome:									
Improvement		13	7	39	10	69	6.2 (3.3)	2.4 (1.8)	8.6 (4.3)
No change	1	8	4	20	3	36	5.9 (3.5)	2.1 (1.6)	8.0 (4.6)
Deterioration		5	3	8	3	19	5.1 (3.1)	2.5 (2.1)	7.6 (4.4)
Death from:									
i Renal failure				5		5			
ii Heart failure				1 (1)*		1 (1)*			
iii Infection		1	1	7 (2)*	2	11 (2)*			
iv CNS					1	1			
v Unknown		1	1	4		6			
Deaths due to and associated with renal failure				8		8	7.4 (2.1)	5 (3.2)	12.4 (3.6)

*Numbers in parentheses indicate No of patients who had renal failure at the time of death but whose death was not caused by renal failure.

Fig. 2 Survival of patients: i) with (a) and without (b) renal insufficiency; ii) with (a) and without (b) hypertension; iii) with crescents of more (a) and less (b) than 25% of the glomeruli; and iv) with (a) and without (b) hyaline thrombi.

very similar to that seen in the United States or United Kingdom. We found a 10% higher proportion of patients in WHO class IV and a 9% lower proportion of patients in class II and III combined, when compared with combined data presented by Hill;²³ these differences are not significant, which is of importance in the light of a recent report²⁴ in which 27 Korean patients were found to have a significantly higher percentage of class IV (77.8%) and fewer class VII cases. This apparent discrepancy could be due to the relatively small number of Korean patients, or it could reflect a difference in the pattern of renal disease in Thailand and Korea. Compared with other

series^{1 3 5 7} our cases show similar age distribution, clinical manifestations of systemic lupus erythematosus, renal presentation, and prevalence of hypertension.

Our follow up period was short, but causes of death are similar to those discussed in previous reports,⁵⁻⁷ with infections being the commonest and renal failure the second commonest cause. Our three year survival rates were close to those of Appel *et al*¹ in all classes; class IV patients showed the worst survival, which supports the view that histological class is prognostically important.

Using the scoring system, we found class IV

patients had significantly higher mean pathological scores (activity, chronicity, and total) as did Balow *et al*⁴ and Austin *et al*,⁵ but the overlap of scores between classes meant that the score alone was not a good predictor of class or survival.

Our findings, although not directly comparable, do not support Kaslow's²² findings of higher mortality in oriental patients with systemic lupus erythematosus. Our follow up period was short, however, and we only looked at patients with lupus nephropathy, while Kaslow's data were taken from death certificate records.

Assessing indicators of outcome, we found that renal insufficiency and hypertension at the time of biopsy were associated with a worse three year survival, and a clinically important presence of sclerotic glomeruli: tubular atrophy, and an interstitial mononuclear cell infiltrate were associated with a worse outcome. In addition, patients who died with deteriorating renal function had a considerably higher chronicity score than other outcome groups. These findings emphasise the importance of chronic renal damage in lupus nephritis.

The total pathological score was not associated with deteriorating renal function or development of renal failure, unlike Balow's study,⁴ and important differences between scores of each outcome group within each class were not found.

In view of previous authors weighting their scoring systems⁸⁻²⁵ for cellular crescents we were surprised to find no association between crescents and a worse outcome and no important difference in the three year survival between these patients. It will be interesting to see if longer term follow up shows any such association, as patients may have an initially good response to aggressive treatment, which may delay the decline in renal function for as much as three or four years. A recent paper by Austin *et al*²⁶ reported that after four years of follow up cellular crescents predicted a decline in renal function: a further report²⁷ identified crescentic glomerulonephritis as the most common underlying pathology of acute deterioration in renal function.

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