

LUPUS NEPHRITIS IN CHILDHOOD

*SC PEH MBBS, MRCPPath; *LM LOOI MRCPPath, FRCPA; **KL LAM MBBS, FRCPG and **BH TEH MBBS, MRCP.

Departments of *Pathology and **Paediatrics, Faculty of Medicine, University of Malaya, Kuala Lumpur.

Summary

In the 12-year period between 1974 and 1985, 19 children aged between 8 and 12 years with systemic lupus erythematosus (SLE) were seen in the Department of Paediatrics, University Hospital, Kuala Lumpur. A preponderance of females (M:F = 1:2.8) and ethnic Chinese was evident. Renal biopsies revealed a wide range of renal morphology, including minimal change glomerulonephritis, focal proliferative glomerulonephritis, diffuse proliferative glomerulonephritis with varying degrees of severity and membranous glomerulonephritis. The majority (15) of patients had clinical SLE at the time of renal biopsy, of whom 4 were also grossly nephrotic. In the remaining 4 patients a diagnosis of SLE was made after further investigation for nephrotic syndrome (2) and acute nephritis (2). The pattern of renal pathology in childhood lupus nephritis appears not to differ significantly from adults.

Key words: Systemic lupus erythematosus, glomerulonephritis.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a relatively common disease in Malaysia. Most of the patients are young female adults and a predilection for the ethnic Chinese has been noted.^{1,2} Renal involvement is a well recognised manifestation of the disease. Although the majority of patients with renal involvement present with clinical signs and symptoms indicating renal abnormality, some are asymptomatic and the diagnosis is only made following laboratory investigations. Because renal involvement in SLE often results in significant morbidity and mortality, studies of lupus nephritis are of scientific and clinical interest. Most studies have been based on adult patients, and relatively little is known of lupus nephritis in childhood. This paper presents the glomerular pathology encountered in Malaysian childhood lupus patients.

MATERIALS AND METHODS

In the 12-year period between 1974 and 1985, 19 children with systemic lupus erythematosus were seen at the Department of Paediatrics, University Hospital, Kuala Lumpur. All of these patients underwent percutaneous renal biopsy; 3 of the patients had 2 biopsies done, at intervals ranging from 5 months to 3 years 3 months. Biopsies were repeated to determine the nature of renal pathology which was either not ascertained or in doubt in the

earlier biopsy. For the purpose of this study, only diagnostic biopsies were included in the analysis.

A portion of each renal tissue was fixed in 10% buffered formalin, processed and embedded in paraffin. 2 μ m sections were stained with haematoxylin and eosin, Masson's trichrome, Lendrum's Martius-Scarlet-blue, periodic acid Schiff and periodic acid silver, and examined by light microscopy. In addition, a portion of each biopsy was snap-frozen. Cryostat sections of 4 μ m thickness were examined using the standard direct immunofluorescent method for C3, fibrinogen, human IgG, IgA, IgD, IgE and IgM. Indirect immunofluorescence for HBsAg was also performed. All antisera used were commercial preparations (Hoechst, Behringwerke AG, West Germany). A portion of biopsy was also processed for electron microscopy. After fixation in 4% glutaraldehyde, the tissue was post-fixed in 1% osmium tetroxide prior to embedding in epon. Ultrathin sections were stained with uranyl acetate and examined using a Hitachi HS8 electron microscope operating at 50kV.

All the patients included in this study fulfilled the American Rheumatism Association (ASA) criteria for diagnosis of SLE.^{3,4} The patients' chief complaints, laboratory data on serum urea, creatinine, albumin, urinary protein and microscopy as well as blood pressure at the time of renal biopsy were reviewed.

Address for reprint requests: Dr. S.C. Peh, Department of Pathology, Faculty of Medicine, University of Malaya, 59100 Kuala Lumpur, Malaysia.

RESULTS

General

The age range of these patients was 8 to 12 years. Table 1 shows the sex distribution. The male: female ratio was 1:2.8, indicating a statistically significant female preponderance ($p < 0.01$). 17 patients were Chinese, 1 Malay and 1 Indian (Table 2). The predilection for the Chinese ethnic group was demonstrated to be statistically significant ($p < 0.01$).

Presentation

At the time of biopsy, the majority (11) of the patients presented with clinical lupus erythematosus (Table 3). Presenting symptoms included rash, fever, arthralgia, arthritis and alopecia. Urine analysis revealed proteinuria in 8, 4 of whom had associated microscopic haematuria. The remaining 3 patients had no urinary abnormalities.

TABLE 1
LUPUS NEPHRITIS IN CHILDHOOD
SEX DISTRIBUTION

Sex	No.	Percentage
Male	5	26.3
Female	14	73.7
Total	19	100.0

Male: Female ratio = 1 : 2.8

TABLE 2
LUPUS NEPHRITIS IN CHILDHOOD
ETHNIC DISTRIBUTION

Ethnic Group	CASE		*Admission (%)
	No.	Percentage	
Malay	1	5.3	26.9
Chinese	17	89.4	46.0
Indian	1	5.3	25.6
Others	0	0.0	1.5
Total	19	100.0	100.0

*Ethnic distribution of all patients \leq 12 years old, excluding Special Care Nursery patients, admitted to the University Hospital between 1974 and 1985.

4 patients (21.1%) had nephrotic syndrome in addition to clinical signs and symptoms of lupus erythematosus. Their serum albumin levels were < 2.5 g/100 mls. The serum cholesterol levels were elevated in all the patients.

2 patients (10.5%) had only nephrotic syndrome at the time of renal biopsy. They were later confirmed to have systemic lupus erythematosus.

2 patients (10.5%) had acute nephritis without clinical evidence of lupus erythematosus at the time of renal biopsy. One of them was in hypertensive crisis, and had raised serum urea level, proteinuria and microscopic haematuria. The other patient had elevated serum levels of urea and creatinine, together with gross haematuria and proteinuria.

Histology

The morphological findings in the biopsies are as shown in Table 4. The commonest histological type was diffuse proliferative glomerulonephritis (47.4%) and another 2 (10.5%) exhibited mesangio-capillary proliferative glomerulonephritis.

Within the group of *diffuse proliferative lupus nephritis* (9), the morphological appearance was polymorphic. Both global and segmental proliferation were seen. Varying degrees of endothelial cell proliferation, associated with varying severity of capillary occlusion, were commonly present. Focal epithelial crescents occasionally complicated the picture. Karyorrhexis, which signified activity, was frequently present (Fig. 1). The wire-loop lesion was a common feature (Fig. 2) and fibrin deposition was sometimes seen. Heavy immune complex deposition was typical and demonstrable as Trichrome-red deposits in the capillary wall and mesangium. Immunofluorescence examination confirmed

TABLE 3
LUPUS NEPHRITIS IN CHILDHOOD
CLINICAL PRESENTATION

Major Presentation	No.	Percentage
Clinical lupus erythematosus	11	57.9
Lupus Erythematosus with Nephrotic Syndrome	3	21.1
Nephrotic Syndrome	2	10.5
Acute Nephritis	-	10.5
Total	19	100.0

the heavy deposition of a wide range of immunoglobulins. Deposition of C3 was often present. Immunoreactivity of deposits for anti-IgB_sAg antisera was observed in 6 cases. Electron microscopy revealed paramyxovirus-like particles in the cytoplasm of the endothelial cells (Fig. 3) and electron dense deposits were characteristically found in the subendothelial region of the capillary loops. 8 of these patients had proteinuria and 7 of them had associated haematuria.

In *mesangio-capillary (membranoproliferative) lupus nephritis* (2), the glomeruli were large, cellular and exhibited lobular accentuation. There was duplication of the basement membrane resulting in a double contour appearance. Both of these patients had severe proteinuria associated with haematuria. One of them developed nephrotic syndrome.

Focal proliferative lupus nephritis was seen in 2 (10.5%) patients. One had mild proteinuria while the other was normal on urinalysis.

Membranous glomerulonephritis was a relatively common morphological entity. The glomeruli showed gross thickening of the capillary walls. Silver stains easily demonstrated spiking of the basement membrane as in stage 2 of the classical idiopathic type of

membranous glomerulonephritis. 2 of the 3 patients with membranous lupus nephritis also showed associated albeit mild proliferative change. All these 3 patients had severe proteinuria, 2 of whom were nephrotic.

TABLE 4
LUPUS NEPHRITIS IN CHILDHOOD
HISTOLOGICAL CHANGES SEEN IN
RENAL BIOPSY

Histology	No.	Percentage
No change/minimal change	3	15.8
Membranous	1	5.3
Membranous with minor proliferation	2	10.5
Focal proliferative	2	10.5
Diffuse proliferative	9	47.4
Mesangio-capillary proliferative	2	10.5
Total	19	100.0

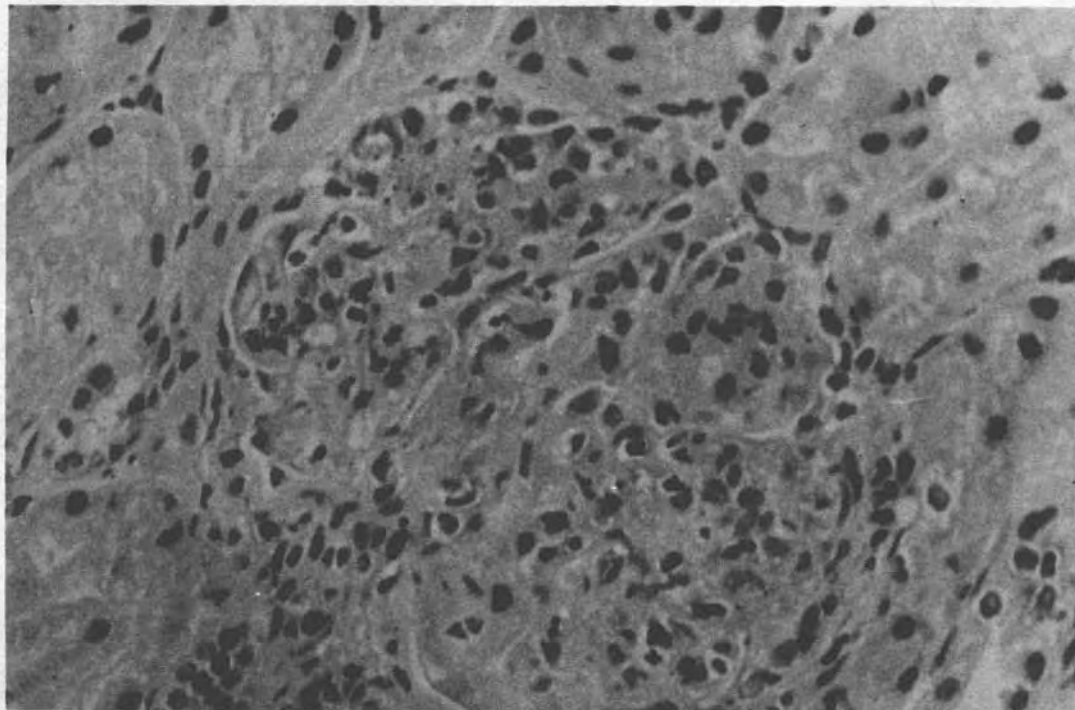


FIG. 1: Proliferation of mesangial cells, partial occlusion of capillary lumen and karyorrhexis. H&F x 400.

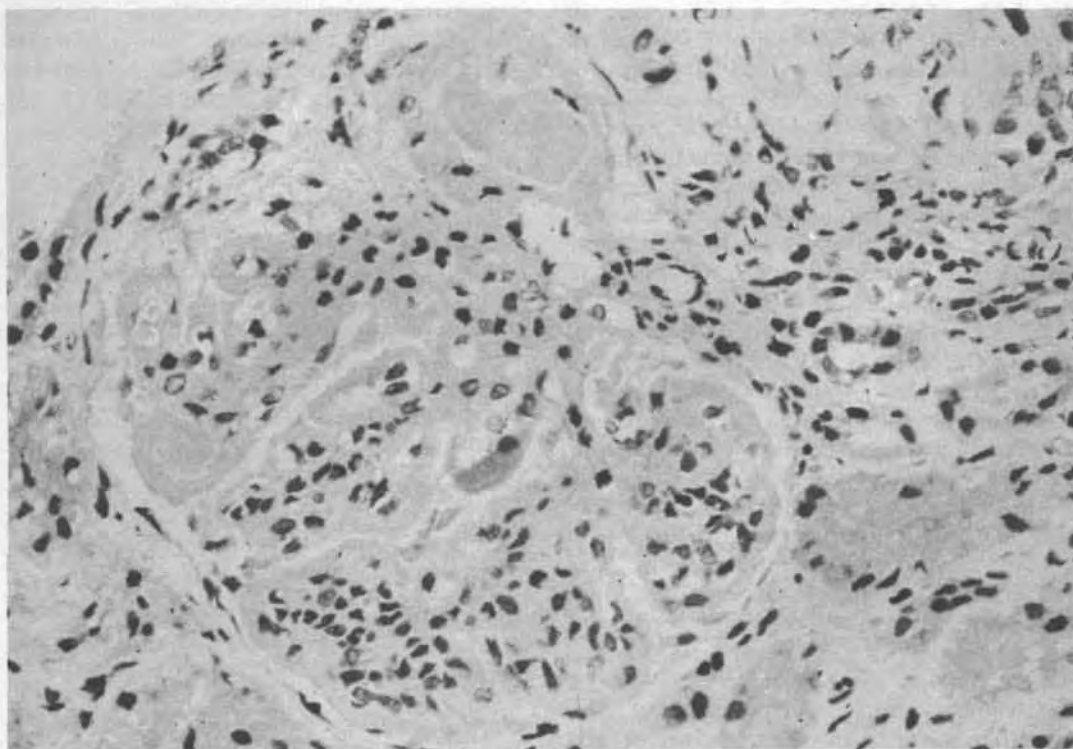


FIG. 2: Hyaline thickening of the capillary walls resulting in characteristic wire-loop lesions. H&E x 400.

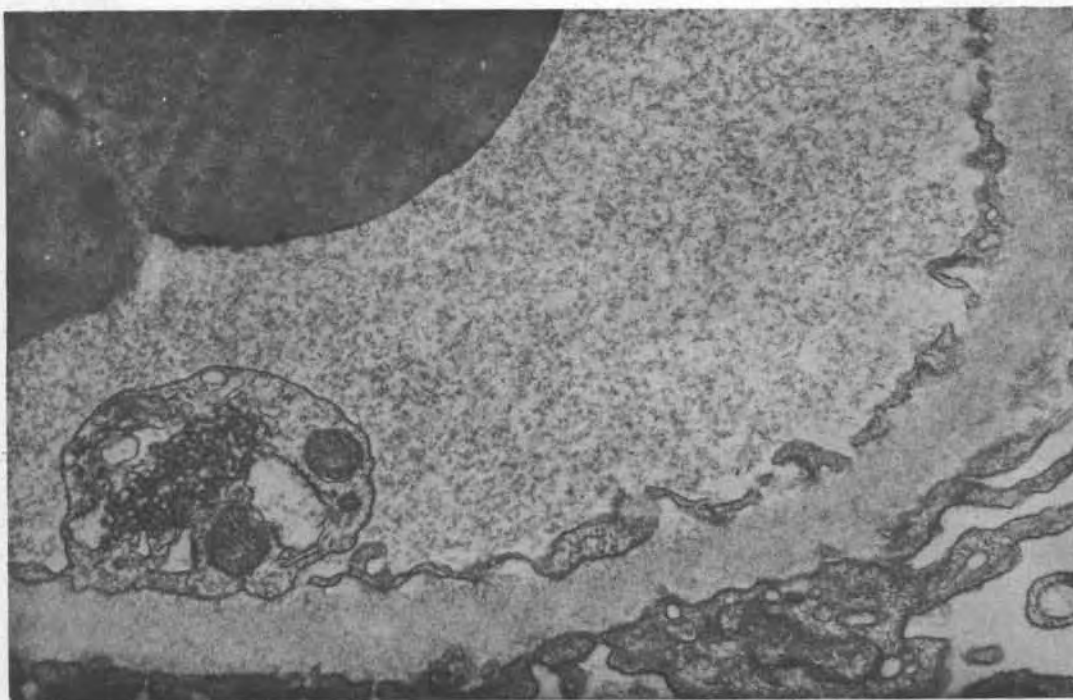


FIG. 3: Electron microscopy exhibiting paramyxovirus-like particles in the cytoplasm of endothelial cell. x 15000.

In 3 patients, renal biopsy revealed *minimal* or no *change* in the glomeruli on light microscopy. 2 of the patients had proteinuria without haematuria. The remaining 1 had no evidence of any renal abnormalities both clinically and on urinalysis.

The renal pathology of the 3 SLE patients who had no obvious urinary abnormalities include minimal change glomerulonephritis (1), focal proliferative glomerulonephritis (1) and diffuse proliferative glomerulonephritis (1).

DISCUSSION

A wide range of renal pathology was seen in our patients. They included minimal change glomerulonephritis, focal proliferative glomerulonephritis, varying degrees of diffuse proliferative glomerulonephritis including mesangio-capillary glomerulonephritis and membranous glomerulonephritis with or without associated proliferative change. The findings are similar to those seen in our adult lupus patients.² This is not surprising as the pathogenesis of the disease in both children and adults are expected to be the same. However, because this series is small, a proper comparison of the prevalence of the various types of glomerulonephritis in children and adults cannot be made. It seems reasonable to expect some difference in evolution of glomerular pathology between these two groups of patients in view of differences in the physiology of prepubertal and adult individuals.

Involvement of the kidney in SLE is known to be a serious complication and remains as one of the leading causes of death in this disease.¹ Hence, studying its renal pathology is likely to contribute to a better understanding of the pathogenesis of SLE. Urinary abnormalities were present in 16 (84.2%) of our patients as compared to 50% in some other studies.⁶ Proteinuria appears to be the commonest abnormality. In 6 (31.5%) of the patients with proteinuria, it was severe enough to result in nephrotic syndrome. On the other hand, a previous study on patients with nephrotic syndrome in the University Hospital, Kuala Lumpur, revealed that only 6.3% of the cases had SLE.⁷

There was generally no good correlation between the renal lesions and the clinical presentation or the degree of proteinuria. However, haematuria, be it microscopic or

gross, tends not to occur in lupus patients who have mild renal pathology, such as focal segmental proliferative glomerulonephritis and minimal change glomerulonephritis. Certain renal lesions such as membranous lupus glomerulonephritis with proliferation have been shown to be associated with severe disease and poorer outcome.^{8,9} However, we are unable to demonstrate this in our study due to the small number of patients with membranous lupus nephritis. It is also known that lupus nephritis can show transformation from one histological type to another. This means that morphological typing at just one point in time is unreliable as a prognostic indicator."¹¹ Repeat biopsies during the course of the disease is often necessary. Besides the histological type, it is probably important to consider whether other microscopical features such as proliferative changes in the glomeruli, leucocyte exudation, karyorrhexis, fibrinoid necrosis, cellular crescents, hyaline deposits and interstitial inflammation can be correlated to prognosis. As these features signify activity, they may be useful in predicting severity of renal damage and subsequent risk of progression to end stage disease.¹²

Much in the aetiology and pathogenesis of SLE remains to be clarified. It is believed that both environmental and genetic factors play important roles.^{3,14} Our study of childhood lupus patients shows a predilection for Chinese females, a finding which concurs with the observations on our adult patients.^{1,2} The racial predilection suggests that there is genetic predisposition to this disease. This notion is not without support as other studies have shown a predilection for American blacks.^{4,15} The female preponderance observed in this study is expected as it is well-recognised in SLE.

Whether viruses play a role in the aetiology or pathogenesis of SLE is a question that has been raised time and again.¹⁶ The presence of paramyxovirus-like particles in the cytoplasm of endothelial cells on electron microscopy, as demonstrated in our patients, is characteristic of SLE.¹⁷ Although previously thought to be actual viral particles, these are now known to be tubular contortions. Some of our patients showed immunoreactivity for anti HBsAg antisera. The significance of this is unclear but nevertheless raises the questions of an association between the hepatitis B virus and SLE.⁸

REFERENCES

1. Frank AO. Apparent predisposition to systemic lupus erythematosus in Chinese patients in West Malaysia. *Ann Rheum Dis* 1980; 39: 266-9.
2. Prathap K, Looi LM. Morphological Patterns of Glomerular Disease in Renal Biopsies from 1000 Malaysian Patients. *Ann Acad Med Singapore* 1982; 11: 52-6.
3. Anonymous. The Arthritis Foundation. Preliminary Criteria for the classification of Systemic Lupus Erythematosus. *Bull Rheum Dis* 1971; 21: 643-8.
4. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7.
5. Dunnill MS. Systemic Lupus Erythematosus. In: *Pathological Basis of Renal Disease*. 2nd ed. London: W.B. Saunders, 1984: 149-77.
6. O'Dell JR, Hays RC, Guggenheim SJ, Steigerwald JC. Systemic lupus erythematosus without clinical renal abnormalities: renal biopsy findings and clinical course. *Ann Rheum Dis* 1985; 44: 415-9.
7. Prathap K, Looi LM, Lam KL, Wang F, Chua CT. The Pathology of the nephrotic syndrome in Malaysians. *Malays J Pathol* 1983; 6: 39-49.
8. Wang F, Looi LM. Systemic lupus erythematosus with membranous lupus nephropathy in Malaysian patients. *Q J Med* 1984; 210: 209-26.
9. Williams WW, Shah DJ, Morgan AG, Alleyne GAO. Membranous glomerulonephropathy with crescents in systemic lupus erythematosus. *Am J Nephrol* 1985; 5: 158-62.
10. Dumas R. Lupus nephritis: Collaborative study by the French Society of Paediatric Nephrology. *Arch Dis Child* 1985; 60: 126-8.
11. Lee HS, Mujais SK, Kasinath BS, Spargo BH, Katz AI. Course of Renal pathology in patients with systemic lupus erythematosus. *Am J Med* 1984; 77: 612-20.
12. Austin HA, Muenz LR, Joyce KM, Antonovych TT, Balow JE. Diffuse proliferative lupus nephritis: Identification of specific pathologic features affecting renal outcome. *Kidney Int* 1984; 25: 689-95.
13. Decker JL, Steinberg AD, Reinertsen JL, et al. Systemic lupus erythematosus: evolving concepts. *Ann Intern Med* 1979; 91: 587-604.
14. Siegel M, Lee SL. The epidemiology of systemic lupus erythematosus. *Semin Arthritis Rheum* 1973; 3: 1-54.
15. Lee HS, Spargo BH. A renal biopsy study of Lupus Nephropathy in the United States and Korea. *Am J Kidney Dis* 1985; 5: 242-50.
16. Hollinger FS, Sharp JT, Lidsky MD, Rawls WE. Antibodies to viral antigens in systemic lupus erythematosus. *Arthritis Rheum* 1971; 14: 1-11.
17. Grausz H, Earley LE, Stephen BG, Lee JC, Hopper J Jr. Diagnostic import of virus-like particles in the glomerular epithelium of patients with systemic lupus erythematosus. *N Engl J Med* 1970; 283: 506-11.
18. Looi LM, Prathap K. Hepatitis B virus surface antigen in glomerular immune complex deposits of patients with systemic lupus erythematosus. *Histopathology* 1982; 6: 141-7.