Ceylon J. Med. Sci. 33 (No. 2, December) 1990, pp. 79 - 89

RENAL PATHOLOGY IN SYSTEMIC LUPUS ERYTHEMATOSUS: A CLINICO - PATHOLOGICAL STUDY

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Summary: Of 500 renal biopsies performed between January 1990 to December 1990, 32 biopsies were from patients having systemic Lupus Erythematosus (SLE). The male to femelo ratio of SLE patients was 1 :7. The mean age of the males was 34 years, and of the famales 27 years. The histological pattern varied between normal glomeruli to extensive glomerulosclerosis. Each type of glomerulonephritis was classified according to the modified World Health Organization (WHO) Classification.

14% of the patlents had histologically normal glomeruli (WHO Class I), 19% had mesangial nephropathy (WHO Class II), 18% had focal segmental tyge of glomerulonephritis (WHO Class III), 41% had diffuse proliferative glomerulonephritis (WHO Class IV), 4% had membranous nephropathy (WHO Class V), ahd 4% had extensive glomerulosclerosis (WHO Class VI).

Although the value of renal biopsy has been questioned we, conclude that it is a most importan investfgation in the management of lupus nephritis.

Key words: Systemic Lupus Erythematosus, incidence, classification.

INTRODUCTION

Lupus erythematosus is a systemic autoimmune disease that affects both adults and children, and has a wide variety of clinical manifestations. Based on clinical signs of renal disease the incidence of renal involvement in adult patients ranges from 50% to 80% (1). Clinicopathological correlations have demonstrated a significant relationship between the underlying histopathology of renal disease and the subsequent clinical course (2,6). Because of the broad spectrum of lesions that have been seen in patients with lupus erythematosus, the World Health Organization (WHO) proposed a classification of lupus nephritis that included all morphological patterns (1). The modified WHO classification as quoted by Gladman (2) comprises 6 main classes (Table 1). The importance of this classification is that, based on it, a renal biopsy can be used to determine the probable prognosis of an individual in terms of survival and renal function. It also enables the clinician to select the appropriate medication for each case. This is a report of a study of 32 patients clinically confirmed as systemic lupus erythematosus, to ascertain the relationship between the clinical renal manifestations and the histological and immunological findings.

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Table 1. WHO morphological classification of lupus nephrttis (modified)

i. NORMAL GLOMERULI
   (a) Nil by all techniques
   (b) Normal by light, but deposits on electron microscopy or immunofluorescence.

ii. PURE MESANGIAL ALERATIONS (mesangiopathy)
   (a) Mesangial widening and/or mild hypercellularity (+)
   (b) Moderate hypercellularity (++)

iii A FOCAL SEGMENTAL GLOMERULONEPHRITIS
   (a) Active necrotizing lesions
   (b) Active and sclerosing lesions
   (c) Sclerosing lesions

iv. DIFFUSE GLOMERULONEPHRITIS
   (a) Without segmental lesions
   (b) With active necrotizing lesions
   (c) With active and sclerosing lesions
   (d) With sclerosing lesions

v. DIFFUSE MEMBRANOUS GLOMERULONEPHRITIS
   (a) Pure membranous glomerulonephritis
   (b) Associated with lesions of category II
   (c) Associated with lesions of category III
   (d) Associated with lesions of category V

vi. ADVANCED SCLEROSING GLOMERULONEPHRITIS

MATERIALS AND METHODS

The study was conducted on patients having systemic lupus erythematosus uudergoing renal biopsy in the Professorial Unit of Medicine, General Hospital, Colombo from January 1990 to December 1990. All the patients were hospitalized and evaluated clinically by the physicians in the nephrology team. Laboratory investigations for renal disease, including urine culture, routine blood count, ESR, blood for LE cells, antinuclear factor and double stranded DNA antibodies were done.

Two cores of renal biopsies were obtained from all patients. One core of tissue was fixed in Duboscq Brazil Solution (Modified Boin's Sloution) for light microscopy and the other in 10% formal saline for immunohistochemical studies. Electron microscopic studies were not perfomed as gluteraldehyde fixed renal tissue was not available.

LIGHT MICROSCOPY

Paraffin sections were made from tissue fixed in Duboscq Brazil Solution (DBS). Sections were stained with Haematoxylin and Eosin (H & E), Periodic Acid Schiff (PAS) and Silver Methanamine. Depending on the histological features, they were classified according to the modified WHO classification of lupus nephritis (2).

IMMUNOHISTOCHEMISTRY

The biopsies fixed in formal saline were used for immunohistochemical studies. Paraffin sections were made at 2-3 mμ thick. Immunohistochemical (IHC) staining was performed using the Avidine Biotin Complex (ABC) method (3, 4). All primary antisera were obtained commercially from Hoechst Behring Laboratories. Secondary Antibody and ABC were obtained from Dakopats, Denmark. Trypsin was obtained commercially from Sigma Chemicals. Reagent activity was confirmed with known positive and negative biopsies as controls

All sections were deparaffinised in xylene and brought to alcohol. Endogenous peroxidase activity was inhibited by reacting with hydrogen peroxide and methanol. The sections were then trypsinised for 15 minutes, washed with phosphate buffer and nonspecific proteins were blocked by adding 10% egg white solution, because normal swine serum was not available. The sections were then incubated at room temperature for 30 minutes with primary antisera; IgG, 1/800 dilution, IgA 1/600 dilution, IgM 1/500 dilution, C 3 1/300 dilution and fibrinogen 1/600 dilution, After washing with buffer solution biotinylated second antibody was added. ABC complex was added and after washing with the buffer solution the colour was developed with Diamino Benzidine (DAB). The stained sections were examined under the light microscope to identify the presence of immunocomplexes indicated by a brown stain.

RESULTS

Out of 32 patients, 8 presented with Nephritic Syndrome. Another 10 patients presented with mild proteinuria and haematuria. Two of them also had mild oedema. 8 patients had only proteinuria, 4 had nephrotic syndrome, and the other 2 patients presented with rapidly progressive renal failure.

Table 2. Clinical Presentation of WHO Classes

WHO Classification	No. of Patients	Clinical Presentation
Class I	3	Proteinuria
	1	Proteinuria/Haematuria
Class II	2	Nephrotic Syndroma
	3	Proteinuria
	2	Proteinuria/Haematuria
Class III	3	Nephritic Syndrome
	2	Proteinuria/Haematuria
	1	Proteinuria/Haematuria with oedema
Class IV	1	Nephrotic Syndrome
	2	Proteinuria
	1	Proteinuria/Haematuria/ oedema
	3	Proteinuria/Haematuria
	1	Rapidly progressive
	5	Nephritic Syndrome
Class V	1	Nephrotic Syndrome
Class VI	1	Rapidly progressive renal failure

Under the light microscope 4 patients (14%) had normal glomeruli (Fig.1). The capillary basement membranes were thin and regular. The tuft cellularity was normal. There was no tubulointerstitial disease. The WHO classification of these patients is shown in Table 2. 7 patients (19%) had pure mesangial alterations (Fig. 2). The PAS positive mesangial matrix was very prominent, but the rest of the glomerular tufts were within normal histological limits. Another 6 patients (18%) had focal segmental glomerulonephritis (Fig. 3). One segment of the glomerular tuft showed proliferation of mesangial cells and endothelial cells with fibrinoid necrosis. Some glomeruli were spared. 13 patients (41%) had diffuse proliferative glomerular nephritis (Fig. 4). In these biopsies all glomeruli were involved and enlarged. The tuft cellularity was increased due to proliferation of mesangial endothelial cells. Fibrinoid material and inflammatory exudate were also seen within the tufts.

One patient (4%) had membranous nephropathy. The capillary basement membranes were uniformly thickened and the silver stain showed basement membrane spikes characteristic of this lesion (Fig. 5). There was no proliferation of the glomerular tuft.

One patient (4%) had end-stage renal disease with extensive glomerulosclerosis. There was marked tubulointerstitial disease with fibrosis. Blood vessels were markedly thickened,

Out of 32 biopsies stained by the ABC method, 2 were overstained and the results were not recorded. Out of the other 30 remaining biopsies 3 did not contain any immune complexes, C_3 or fibrinogen (Table 3). Histologically these biopsies showed normal glomeruli, Another biopsy which showed. normal glomeruli histologically revealed IgG immunocomplexes

IgG, IgM, and C_3 were seen in patients having histological pattern of focal segmental and diffuse proliferative type of glomerulonephritis.

IgG and C_3 was seen in membranous nephropathy. One biopsy which showed glomerulosclerosis had IgG, IgM. IgA immunomplexes and C_3.

Table 3: The Results of Immunohistochemical Stains.

No. of Biopsies	Histological Diagnosts	WHO Class	Immune Complexes Present				
			IgG	IgM	IgA	C3	Fibr-inogen
13	Diffuse Proliferative	IV	+	+	—	+	+
6	Focal Segmental	III	+	+	—	+	+
5	Mesangial Proliferative	II	—	+	+	+	—
3	Minimal	I	—	—	—	—	—
1	Minimal	1	+	—	—	—	—
1	Membranous	V	+	—	—	+	—
1	Glomerulo Sclerosis	VI	+	+	+	+	—

DISCUSSION

Lupus Nephritis affects both children and adults. In our study there were 2 female children, aged 6 and 10 years, and the others (30) were adults. The commonest clinical symptoms in our study were proteinuria and haematuria, which were seen in 10 patients. Out of these ten patients 40% had Class IV lesions, 30% had Class III lesions, 20% had Class II and 10% had Class I lesions,

Normal glomeruli or Class I lesions are very rare (5), although there were 4 patients in the study (14%). Since electron microscopic studies were not performed, they cannot be definitely categorised as Class I or Class II. However, out of the four one had IgG immunocomplexes in the mesangium and should therefore be classified either as Class I B or Clas II A.

Diffuse proliferative glomerulonephritits is the most serious of the renal lesions in SLE, occuring in 45% or 50% of the patients who are

biopsied (5). In the study 41% of patients showed this type of glomerulonephritis or Class IV lesions. The prognosis in this category of lesion is bad (6, 7). One patient presented with a rapidly progressive type of renal failure.

In patients with normal glomeruli (WHO Class I), mild mesangial hypercellularity (WHO Class II) and with membranous nephropathy (WHO Class V), renal function is preserved for long periods, although patients with the membranous lesion commonly exhibit heavy proteinuria and the nephrotic syndrome.

In our study 12 of the 32 patients (35%) belonged to this category of non-proliferative lesions. The other 65% had proliferative lesions like focal, segmental or diffuse proliferative and end stage renal disease.

Active or proliferative and chronic lesions on biopsy have been shown to be an indicator for poor renal outcome (6).

Immunocomplexes are present in large amounts in proliferative lesions. However in this study all 5 patients with mesangial nephropathy contained IgM, IgA and C_3. Another striking feature was that, in Class VI lesions, IgG, IgM, IgA immunocomplexes were present along with C_3. Immunocomplexes which are deposited in the glomerular tufts are either dissolved or absorbed with time. Therefore the patient who had extensive glomerulosclerosis may not be in a very late stage of the lesion, but probably had extensive proliferative lesions which caused sclerosis of the glomeruli.

All 32 patients in the study had clinical signs of renal involvement and it is necessary to evaluate renal morphology in these patients in order to decide on the form of treatment, and to predict the long term prognosis.

ACKNOWLEDGEMENTS

We wish to thank Professor Rezvi Sheriff for giving permission to study these patients and for providing renal biopsies, Miss J. L. Padmani for her technical assistance and Miss Sandya Nanayakkara for secretarial assistance.

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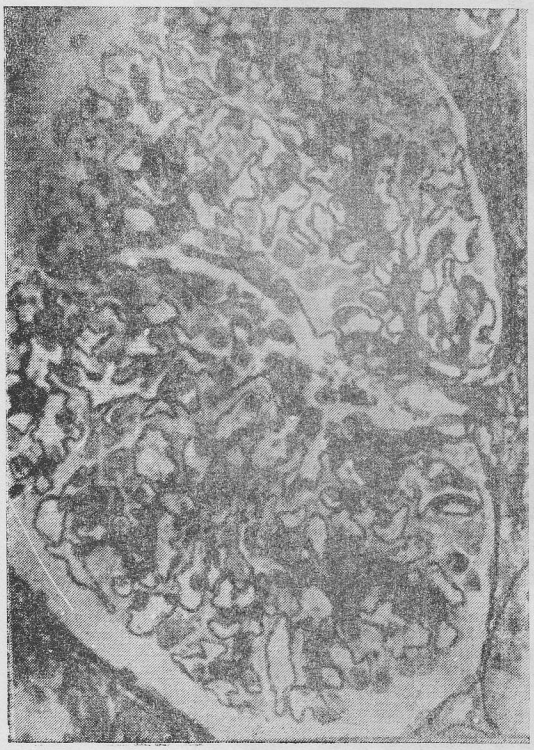

Fig. 1. Section of glomerulus stained with silver methanamine, showing normal capillary loops and basement membranes (X 400).

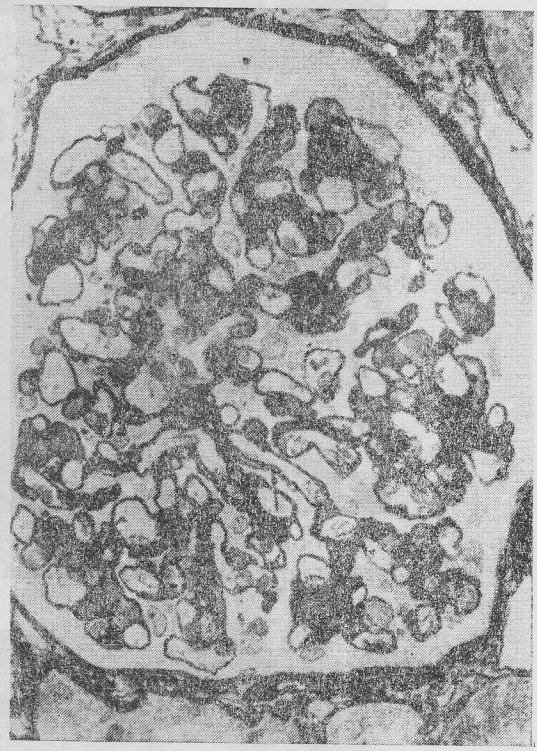

Fig. 2. Sections of glomerulus stained with PAS / Silvermenthanamine showing prominent mesangial matrix (X 400).

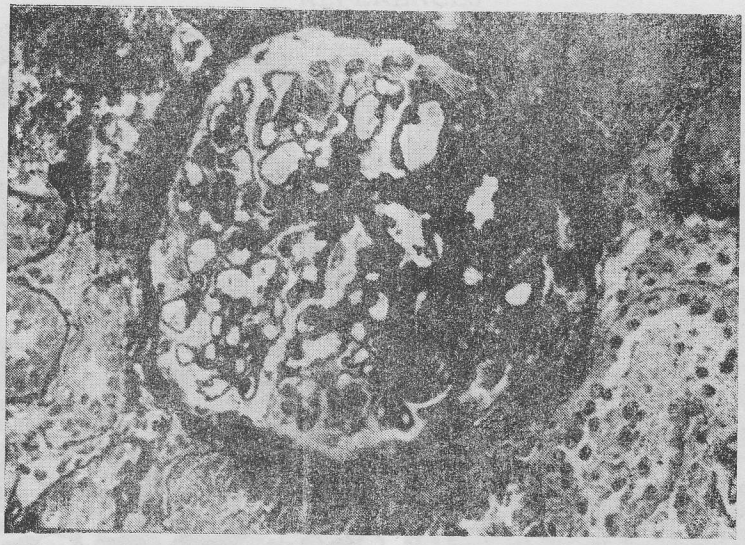

Fig. 3. Section of glomerulus stained with PAS/Silvermethanamine showing focal segmental glomerulo nephritis (X 400).

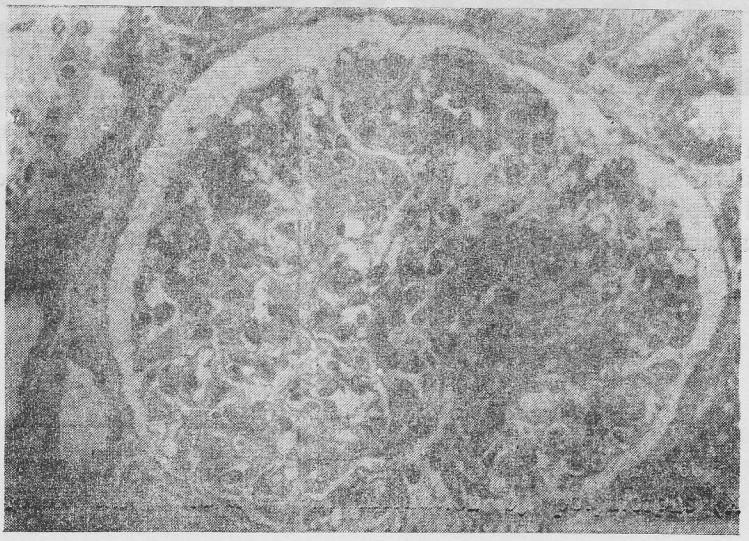

Fig. 4. Section of glomerulus stained with haematoxylin and eosin showing increased tuft cellularity and infiltration by polymorphs (X 400).

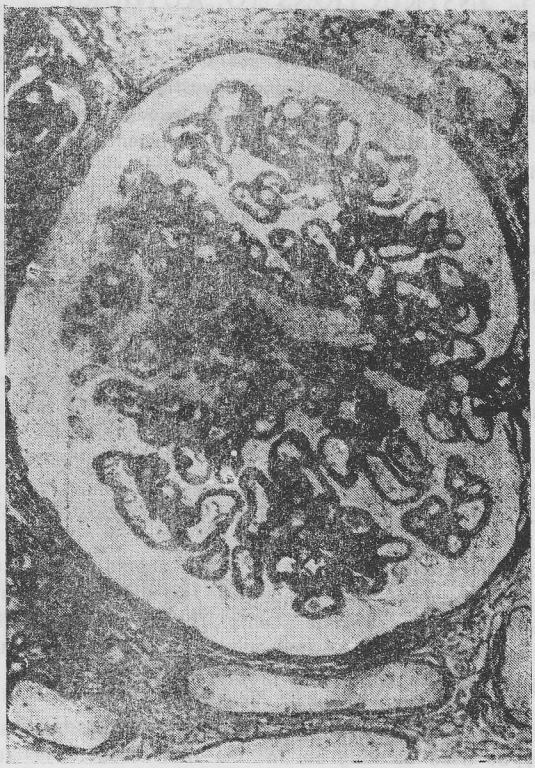

Fig.. 5. Section of glomerulus stained with silvermethanamine showing thickened capillary basement membranes with "spikes" (X 400).

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