Lupus nephritis

Part II. A clinicopathological correlation and study of outcome

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Summary

A 5-year retrospective study of lupus nephritis at Tygerberg Hospital was performed in an attempt to document the clinical and histological spectrum of the disease and to study the outcome of the illness. Activity and chronicity scores were used in addition to the World Health Organisation classification system. Of 55 biopsies from 51 patients reviewed, 6 were class II, 13 class III, 32 class IV and 4 class V. There were 19 deaths and in 15 of these the histological classification was IV. Renal failure and infections, often with uncommon pathogens, were the most important causes of death. Serum creatinine values and creatinine clearance at the time of biopsy or follow-up, and hypertension at follow-up showed a significant relationship with outcome. WHO class IV was associated with a poor outcome ($P = 0,048$) when compared with the other WHO classes combined. Activity scores showed a significant relationship to the outcome ($P = 0,018$). The anticardiolipin antibodies IgG and IgM were not associated with WHO class or outcome. The study revealed a spectrum of histological results similar to that of other studies, with a high mortality rate, particularly in class IV disease. Poor renal function, persistent hypertension, histological classification IV, and high activity scores were found to be important prognostic indicators.

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Lupus nephritis is an important cause of morbidity and mortality among patients with systemic lupus erythematosus (SLE).[1] Therapeutic regimens remain controversial[2] and controlled trials are confounded by factors such as intercurrent infection, malignant disease and death from non-renal causes.

Although SLE is relatively prevalent in the western Cape, there has been little detailed documentation of lupus nephritis in this region. A retrospective study of lupus nephritis at Tygerberg Hospital was carried out to determine whether there was an association between clinical, laboratory and histological parameters and to document the spectrum and outcome of the disease in this region.

Patients and methods

The records of 51 patients who underwent renal biopsies for clinically significant lupus nephritis from 1983 to 1987 were reviewed. Four patients underwent two biopsies, providing a total of 55 specimens. All patients fulfilled the 1982 American Rheumatism Association (ARA) criteria for SLE.[3]

Forty-seven patients were female (39 coloured, 5 white, 3 black) and 4 were male (2 coloured, 2 white). Mean age at biopsy was 25,7 years (range 14,3 - 53,8 years). Mean duration of follow-up was 1,26 ± 1,29 years. The number of ARA criteria fulfilled by each patient is shown in Fig. 1 and the frequency of the 7 most common ARA criteria in Fig. 2.

The following clinical data were documented at the time of biopsy and at most recent determination: diastolic blood pressure, serum creatinine level, creatinine clearance, 24 h pro-

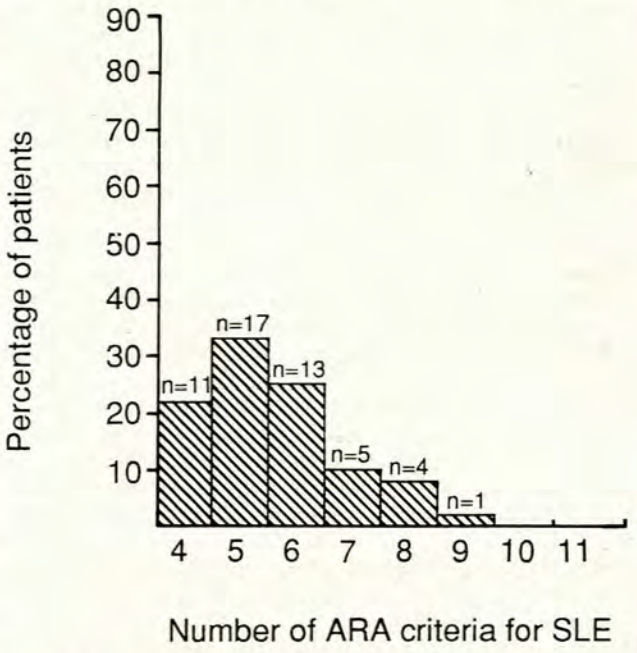

Fig. 1. The number of ARA criteria fulfilled by each study patient.

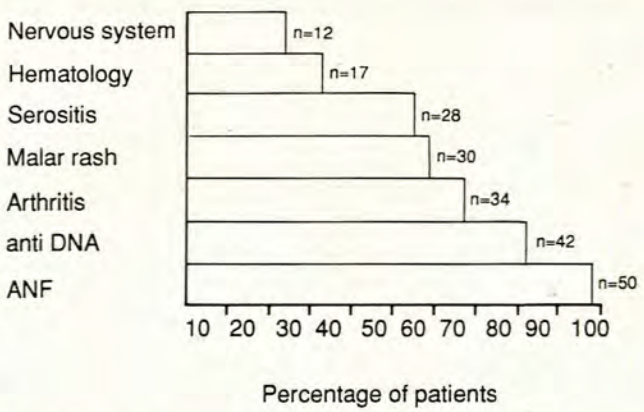

Fig. 2. The frequency of the 7 most common ARA criteria fulfilled by the patients.

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teinuria, and the treatment administered. Treatment protocols were not standardised, and therefore no attempt was made to correlate treatment with outcome. Outcome of the illness as at repeat biopsy or February 1988 was recorded as: death of the patient; alive and maintaining renal function or on long-term dialysis; and lost to follow-up. The following laboratory investigations were performed at the time of biopsy and serially during follow-up: the third and fourth components of complement and total haemolytic complement using a standard nephelometric assay with Behring antisera; an indirect immunofluorescence assay for antinuclear factor (ANF) and anti-double-stranded DNA (anti-dsDNA), using rat liver substrate and *Crithidia lucilliae*, respectively; and anticardiolipin antibodies IgG (aCLG) and IgM (aCLM) using an enzyme-linked immunosorbent assay (ELISA).[4] The anticardiolipin assay has been available at our institution since 1985.

Renal biopsies were classified according to the World Health Organisation classification system[5] and then semiquantitatively scored.[1] These classification systems and the results of the biopsies were fully discussed in part I of this article (see p. 256)

Statistical methods included Student's *t*-test, Fisher's exact test, the χ^2 test and Wilcoxon's two-sample test. Significance levels were adjusted using the Bonferroni procedure.

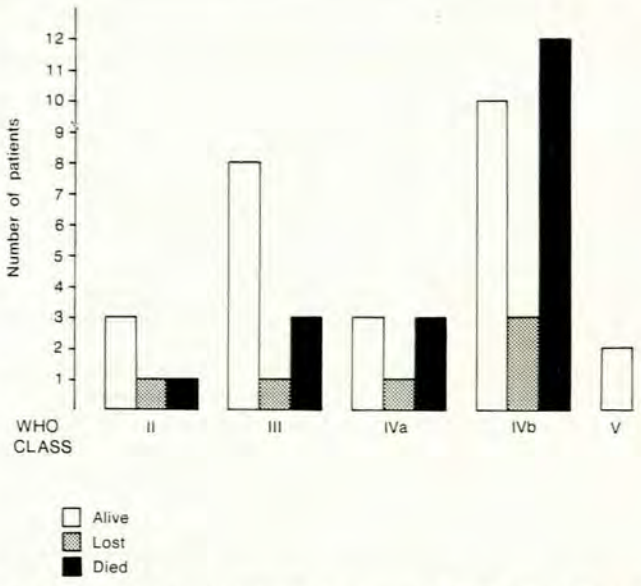

Fig. 3. Outcome of 51 patients in terms of WHO class of most recent kidney biopsy.

Results

The mean diastolic blood pressure at biopsy was 87 ± 17 mmHg and at follow-up 85 ± 17 mmHg. The diastolic blood pressure at follow-up showed an association with the outcome ($P = 0{,}023$). The mean serum creatinine value at biopsy and follow-up was 133 ± 19 μmol/l and 245 ± 266 μmol/l, respectively. There was an association between serum creatinine level and outcome both at biopsy ($P < 0{,}001$) and at follow-up ($P < 0{,}001$). The mean creatinine clearance at biopsy and follow-up was 67 ± 33 ml/min and 62 ± 52 ml/min, respectively. There was an association between creatinine clearance and outcome both at biopsy ($P < 0{,}001$) and at follow-up ($P = 0{,}037$). The mean 24-hour urinary protein excretion at biopsy and follow-up was 2,2 ± 3,1 g and 2,13 ± 2,7 g, respectively. Neither of these values was associated with the outcome.

The causes of death in 19 patients are noted in Table I. The mean age at death was 27,6 years (range 14,7 - 55,8 years). Fourteen of the patients were under 30 years of age. Autopsies were performed on 9 patients. Two patients with end-stage renal failure were successfully entered onto long-term dialysis during the study period, 1 of whom died of staphylococcal septicaemia (patient 8).

Figs 3 and 4 show the outcome of the illness and the treatment administered according to WHO class, respectively. WHO class IV was associated with a poor outcome ($P = 0{,}048$) compared with the other WHO classes combined; however, WHO class IVb alone did not show an association with outcome compared with the other WHO classes combined. There was no significant relationship between chronicity scores and outcome, or chronicity scores and creatinine clearance at biopsy or follow-up. The association between activity scores and outcome is shown in Table II. There was a significant relationship between activity scores and outcome ($P = 0{,}018$).

There was no significant relationship between complement components or total haemolytic complement and WHO class. There was no significant relationship between ANF and WHO class, or anti-dsDNA and WHO class. Boxplots of the distribution of anticardiolipin antibodies according to WHO class are shown in Fig. 5. Serial determinations over 36 months were analysed to produce this composite picture. No determinations were available on patients with class V histology, 2 of whom transformed to class IVb before 1985. There was no

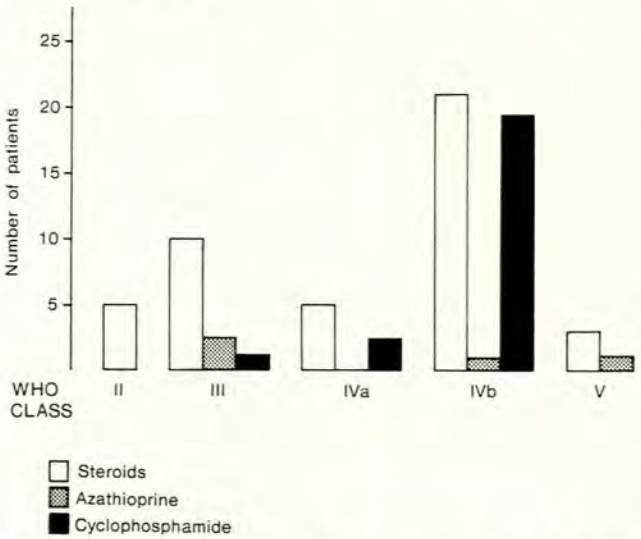

Fig. 4. Treatment of 51 patients in terms of WHO class of most recent kidney biopsy.

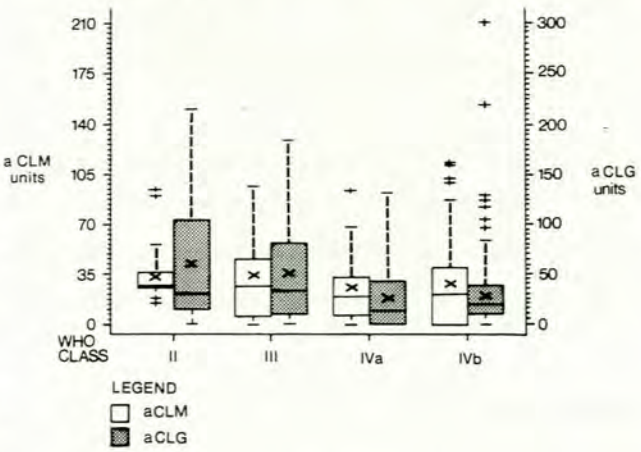

Fig. 5. Boxplots showing the distribution of anticardiolipin antibodies IgM (aCLM) and IgG (aCLG) according to WHO class. X is the mean value (normal value of aCLM = 0-37 units; normal value of aCLG = 0-34 units).

TABLE I. MAJOR CAUSE OF DEATH, HISTOLOGY AND TREATMENT IN 19 PATIENTS

Patient	Cause of death	WHO class	Immunosuppressive therapy
	Infection		
1	Miliary tuberculosis; defaulted	IVa	Prednisone
2	Cryptococcal meningitis	III	Prednisone, cyclophosphamide
3	Fulminant endocarditis	IVb	Prednisone, cyclophosphamide
4	Cytomegalovirus pneumonitis, gastro-intestinal haemorrhage	IVb	Prednisone, cyclophosphamide
5	Meningococcal septicaemia, end-stage renal failure — not accepted for chronic haemodialysis	IVb	Nil
6	Streptococcal septicaemia	IVb	Prednisone, cyclophosphamide
7	Staphylococcal septicaemia, acute renal failure — on dialysis	IVb	Nil
8	Staphylococcal septicaemia, end-stage renal failure — on peritoneal dialysis	III	Prednisone, azathioprine
	Haemorrhage/thrombosis		
9	Disseminated intravascular coagulation, pancreatitis, intracerebral haemorrhage	IVb	Prednisone, cyclophosphamide
10	Mesenteric artery occlusion, septic arthritis; anticardio-lipin antibodies present	II	Prednisone
	Renal failure		
11	Acute renal failure — on haemodialysis, bronchopneumonia	IVa	Prednisone
12	Acute renal failure, hypertensive encephalopathy; defaulted	IVb	Prednisone, cyclophosphamide
13	Acute renal failure, sepsis	IVb	Prednisone, cyclophosphamide
14	End-stage renal failure — not accepted for chronic haemodialysis, recurrent endocarditis	IVb	Nil
15	End-stage renal failure — not accepted for chronic haemodialysis	IVb	Prednisone, cyclophosphamide
16	End-stage renal failure, patient refused treatment	IVb	Nil
17	End-stage renal failure — not accepted for chronic haemodialysis	IVb	Prednisone
18	End-stage renal failure, psychosis	IVb	Prednisone, cyclophosphamide
	Unknown		
19	Patient transferred elsewhere	III	Prednisone, azathioprine

association between anticardiolipin antibodies and WHO class or outcome.

The details of 4 patients who underwent second renal biopsies are shown in Table III.

Discussion

Lupus nephritis in southern Africa has been reported in a number of publications, as part of a larger study of SLE in most cases.[6-9] None of these reports has studied the role of clinical, laboratory or histological features in predicting the

TABLE II. ASSOCIATION OF OUTCOME WITH ACTIVITY SCORES

Outcome	Activity 0	Activity 1-10	Activity > 10	Total
Alive†	8	16	6	30
Dead	0	9	9	18
Lost*	0	3	3	6
Total	8	28	18	54

χ^2: $P = 0.018$.

* Those lost to follow-up were excluded from the statistical analysis.

† Initial activity scores in 4 patients who underwent repeat biopsies were included under 'Alive'.

TABLE III. PROTEIN EXCRETION, WHO CLASS, ACTIVITY AND CHRONICITY SCORES IN 4 PATIENTS WHO UNDERWENT FOLLOW-UP BIOPSIES

Biopsy	Proteinuria g/24 h	Treatment	WHO class	Activity	Chronicity
1	1,0	Steroids,	V	0	0
2	11,9	cyclophos-phamide	IVb	12	1
1	Unknown	Steroids	V	0	0
2	1,4		IVb	14	1
1	1,1	Steroids	III	5	2
2	7,5		IVa	8	1
1	0,03	Steroids	II	0	0
2	0,02		III	5	1

outcome of the disease. Activity and chronicity scores have been shown to predict the outcome of lupus nephritis more accurately than WHO scores alone.[2] Activity scores predict decreased survival and are reported to be responsive to corticosteroid therapy.[1,10] Chronicity scores reflect glomerular sclerosis and correlate with diminishing renal function. In a 15-year study of lupus nephritis, patients with chronicity scores of 2 or 3 were shown to develop progressive renal scarring with renal failure if treated with steroids alone.[2] The activity and chronicity scores thus assist in identification of patients who will benefit from immunosuppressive therapy.

Our study found hypertension, which persisted at the most recent follow-up, to be associated with a poor outcome, as was poor renal function both at biopsy and follow-up. Leaker *et al.*[1] found that survival in lupus nephritis is unaffected by age, sex, nephrotic syndrome or hypertension. Elevated serum creatinine levels at presentation were, however, associated with a poorer prognosis in their study and that of Ginzler *et al.*[11] WHO class IV histology was associated with a poor outcome in our study, despite previous reports that have queried the prognostic value of the WHO system.[12] The activity index was helpful in predicting the clinical outcome; however, the chronicity index proved disappointing in predicting renal impairment or outcome. The frequent early mortality from non-renal causes and the short period of follow-up may have obscured the true value of the chronicity index.

Serial renal biopsies provide valuable insight into the frequent and complex histological transitions that take place in lupus nephritis.[13] Despite therapy, the 4 patients who were rebiopsied progressed to more proliferative forms of the disease, reflected by increased activity and chronicity scores and clinical deterioration. This supports the contention that a biopsy should be regarded as but one point in a dynamic process[14] and that a repeat biopsy is indicated should the clinical picture change significantly.

Anticardiolipin antibodies are associated with thrombotic complications in SLE and with major organ involvement, particularly of the central nervous system.[15] It is unknown whether anticardiolipin antibodies are associated with more severe renal disease, particularly in view of the thrombotic nature of activity features such as hyalin thrombi. We were unable to demonstrate a correlation between levels of aCLG or aCLM and WHO class using values at biopsy (data not shown) or serial determinations over a period of time. There was no association between anticardiolipin antibodies and outcome.

The prognosis for lupus nephritis has improved since the advent of immunosuppressive drugs, and some centres claim to be able completely to prevent progression to end-stage renal failure with adequate therapy in these patients.[1] The outlook for patients in less advanced countries, however, appears to be less promising. Low socio-economic status and race other than white are reported to be independent predictors of a poor prognosis.[16] Harris *et al.*[17] recently found SLE to be an important cause of death in young hospitalised Jamaicans. The mean age of onset of SLE was 25,7 years and mean age of death 30,5 years. Overwhelming infection, often complicating immunosuppressive therapy, was the most common cause of death, followed by renal failure, haemorrhagic complications and cerebral lupus.

Our study demonstrated a high mortality from both renal and non-renal causes. A wide range of infections, including the opportunistic organisms *Cryptococcus* and cytomegalovirus, were encountered. A 15-year-old patient died within 24 hours of final admission to hospital of fulminant infective endocarditis involving all four heart valves. Four patients died from acute deterioration in renal function, despite intensive immunosuppressive therapy, plasmapheresis, and in 2 instances acute haemodialysis. The fulminant course of the disease and young age of many of our patients is reminiscent of the Jamaican experience[17] rather than that reported from North America and Australia.[1,16]

We have documented the spectrum and outcome of lupus nephritis in a group of patients followed up at a major teaching hospital. Of the study group 63% had WHO class IV histology, which was associated with a poor outcome. Standardised treatment protocols were not uniformly applied, thus the role of immunosuppressive therapy could not be addressed. However, progression to more active, severe disease despite therapy was demonstrated in 4 repeat biopsies, suggesting that lupus nephritis in the western Cape is an aggressive disease, often unresponsive to therapy.

Late presentation, poor compliance, inadequate facilities for long-term haemodialysis and death from non-renal causes are important factors contributing to the high mortality rate in this study. Controlled therapeutic trials of treatment for lupus nephritis in this region are urgently needed.

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