Singapore Med J 2002 Vol 43(12) : 614-616

Clinical Outcomes of Patients with Biopsy-proven Lupus Nephritis in NUH

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ABSTRACT

Objective: To review the clinical outcomes of Systemic Lupus Erythematosus (SLE) patients with biopsy-proven lupus nephritis with regards to the histological features and treatment.

Method: Patients (1) with SLE, (2) had renal biopsy in NUH for lupus nephritis, and (3) on follow-up from the period of January 1998 to April 2001, were reviewed.

Result: Fifty patients were reviewed with female to male ratio of 4:1. Mean age was 35.4 years. Sixty-eight percent had renal involvement at diagnosis of SLE. At least 50% had other major organ systems involvement. Forty-two patients had WHO Class IV lupus nephritis. Biopsy showed crescents in 17 patients, microangiopathy in 19, and vasculitis in two patients. All patients received prednisolone. Forty-one had IV cyclophosphamide, two had oral cyclophosphamide and seven had cyclosporin A. Azathioprine was used in 41 patients, pulse methylprednisolone in eight, IVIG in four, plasma exchange in three and mycophenolate in two patients.

Outcome: Forty-four percent were in complete remission, 26% in partial remission, 34% had relapsed nephritis, 4% had chronic renal failure and 12% progressed to ESRD. There were five deaths.

Conclusion: Renal involvement in SLE occurs early in the disease and is associated with other organ systems involvement. Only 44% were in complete remission. Thirty-four percent had relapsed. Renal survival was 88% in this cohort.

Keywords: lupus nephritis, treatment, outcome.

Singapore Med J 2002 Vol 43(12):614-616

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a common autoimmune disease in Singapore. Kidney is among the commonest organ affected in SLE patients. While studies on SLE in Singapore have been previously published, there has been no study done looking at clinical outcomes of local patients with lupus nephritis.

OBJECTIVE

To review the clinical outcomes of SLE patients with biopsy-proven lupus nephritis with regards to the clinicopathologic features and treatment.

METHOD

Patients (1) with SLE (satisfying the ACR criteria for SLE), (2) had renal biopsy in NUH for lupus nephritis, and (3) on follow-up from the period of January 1998 to April 2001, were reviewed. All the case records were retrieved including the renal histology and relevant data were collected using a standardised form.

RESULT

Demographic characteristics

A total of 50 patients were reviewed with 40 females and 10 males (F:M ratio – 4:1). The age range of the patients was from 18 to 79 years (mean age: 35.4 years). The racial distribution was 84% Chinese, 8% Malay and 8% Indian.

Disease presentation

In terms of renal involvement in relation to the onset of SLE, 68% had renal involvement at diagnosis of SLE, 10% were within one year of diagnosis while 22% were after one year SLE was diagnosed (ranging from one to 11 years).

The renal presenting features were nephrotic syndrome (46%), nephritic syndrome (40%), hypertension (52%)(defined as blood pressure more than 140/90 mmHg), abnormal creatinine clearance (54%)(present when CCT <75 ml/min), and raised serum creatinine (32%)(when serum creatinine >125 umol/l). All patients had proteinuria of >300 mg/day, 74% had hematuria, 68% had pyuria and 80% had urinary casts.

At least 50% had involvement of other major organ systems[1,2]: haematological involvement 52%;

Table I. WHO classification of renal biopsy in SLE.

1st renal biopsy	No. of patients
Class II	2 (4%)
Class III	1 (2%)
Class IV	42 (84%)
Class V	5 (10%)
Repeat renal biopsy	9
Class transformation	
IV → IV	4
IVB → IVC → IVC	1
IV → IV/V mixed → VI	1
IV → V	1
IV → VI	1
V → IV	1

Table II. Outcomes of relapsed Lupus Nephritis.

No. of patients	17 (34%)
No. of relapse	1-4
Time to relapse	1-14 years (mean: 5 years)
Outcome of relapse	No. of patients
Complete Remission	3
Partial Remission	5
Remained in Relapse	2
End-stage Renal Failure	4 (25%)
Death	3

cutaneous 38%; nervous system 24%; musculoskeletal 20%; pulmonary 20%; cardiac 12% and gastrointestinal involvement 8%. Eleven (22%) patients had vasculitis and the same number had secondary antiphospholipid antibody syndrome (APS).

In terms of serological activity, 92% had high anti-dsDNA titres and low C3/C4. Other antibody serology positivity rates were as follows: Ro 24%, Sm 20%, La 18%, RNP 18%, and lupus anticoagulant or anticardiolipin antibody 48%.

Renal histopathology

All patients underwent renal biopsy. Diffuse proliferative lupus nephritis was the most common histological pattern seen followed by membranous lupus nephritis. Renal biopsies according to WHO classification[3] were: Class II (2), Class III (1), Class IV (42) (84%), and Class V (5). Nine had repeat biopsy and the class transformation is shown in Table I.

Renal histological features of crescents formation were seen in 17 patients (34%), microangiopathy in 24 patients (48%) and vasculitis in two patients (4%). The patients with renal biopsy showing microangiopathy were found to have positive lupus anticoagulant or anticardiolipin antibody.

Immunosuppressive therapy

Corticosteroids are the backbone of treatment of SLE. All patients received prednisolone (usually started at 1mg/kg per day and is tapered over the first six months to a maintenance dose of 5 to 10 mg/day). Forty-one (82%) had pulse intravenous cyclophosphamide (i.e. monthly for six months then every three months for a total treatment period of two years with the initial dose of 0.5g/m^2 and the dose is increased gradually to a maximum of 1g/m^2 unless patients develop leukopenia or other side effects), two had oral cyclophosphamide and seven had cyclosporin A. Azathioprine was used in 41 patients, hydroxychloroquine in 19 patients, pulse methylprednisolone in 13 patients, IVIG in four patients, plasma exchange in three patients and mycophenolate mofetil in two patients. Forty percent of patients received antiplatelet agents while 18% were given anticoagulation for APS.

Outcome

The duration of follow-up of the 50 patients from time of diagnosis to the outcome varied from one to 20 years (mean: 4.5 years). At the time of assessment, 22 (44%) were in complete remission (i.e. inactive urinary sediment, proteinuria <1 g/day, inactive lupus serologies) and 13 (26%) in partial remission. Seventeen (34%) had relapsed nephritis (defined as renewed clinical activity manifested by an active urine sediment, increasing proteinuria and a rise in serum creatinine). The outcomes of those who had relapsed are shown in Table II. Two were in chronic renal failure while six had progressed to end-stage renal disease.

There were five deaths (10%) in the cohort. The causes of death were as followes: One from active SLE, one from active SLE and sepsis and three from sepsis related to cyclophosphamide induced neutropenia.

Influence of renal histology on outcome

The renal histology had a significant bearing on the outcome[4,5,6]. The presence of cellular crescents and renal microangiopathy has additional prognostic information[7,8]. Twelve out of 17 patients (70%) who relapsed had evidence of crescents formation and/or microangiopathy.

The complete remission rate for those who were positive for the histological features of crescents formation or microangiopathy was only 30% versus 50% for those negative for both features.

Table III. Comparative Studies of 2 other Lupus Nephritis Cohorts with the NUH Cohort.

	Mok CC et al AJKD 99	Huong et al Medicine 99	Chan et al Med J Mal 2000	NUH 2001
Patient No.	183	180	85	50
Sex ratio F:M	5.8:1	4.5:1	8.4:1	4:1
Renal disease at onset of SLE	49.2%	63%	–	68%
Nephrotic syndrome	34%	19.4%	–	46%
Abnormal CCT	28%	17.7%	20%	54%
+ve Anti-dsDNA	69%	78%	–	92%
Low C3	74%	75%	–	92%
Class III	25%	20%	4.7%	2%
Class IV	55%	29%	89.4%	82%
Complete remission	53% (at 1 year)	–	–	44%
Relapse	23.5%	–	–	34%
ESRF	14% (24% of Class IV)	8%	6%	12%
Death rate	–	14%	22%	10%

For those who had both histological features of crescents formation and microangiopathy, the complete remission rate was only 23%. Both patients with renal vasculitis on biopsy presented with end-stage renal failure.

COMPARATIVE STUDY

A comparative study is made with three other similar cohorts of SLE patients from Hong Kong, France and Malaysia[9-11]. Our cohort of patients tended to be more severe in terms of SLE activity and the majority were Class IV nephritis compared to the Hong Kong series[9] (55%) and the French series[10] (29%). There was also a higher relapse rate in our series but the ESRD and death rates were fairly similar (See Table III).

CONCLUSIONS

Renal involvement in SLE occurs early in the disease in our study cohort and is associated with involvement of other organ systems.

The renal involvement tended to be severe compared to other series published.

Based on current treatment with monthly pulse cyclophosphamide and steroids, only 44% were in complete remission, 34% had relapsed and renal survival was 88% in this cohort.

Newer therapies (e.g. Mycophenolate mofetil) need to be explored to improve the outcome of our SLE patients with lupus nephritis.

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