Paper

The clinico-pathological features of lupus nephritis and the significance of ISN/RPS-2003 Class IV lesions

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Abstract

Background: The ISN/RPS-2003 classification of lupus nephritis should emphasize clinically relevant lesions and encourage uniformity and reproducibility in histopathological reporting.

Objective: To describe the clinico-pathological features of lupus nephritis and discuss the significance of the ISN/RPS-2003 class IV-G and IV-S lesions.

Method: The histopathological features and corresponding clinical data of 75 patients with lupus nephritis were analysed using the International Society of Nephrology/Renal Pathology Society ISN/RPS - 2003 classification. This was a retrospective descriptive study carried out over a period of two and a half years at the Department of Pathology, Faculty of Medicine, Colombo.

Results and conclusions: Lupus nephritis was commoner in females (88%, 66/75), with 52%, (36/75) in the 21-30 year age group. ANA positivity (93%, 70/75) was the commonest ACR (American College of Rheumatology - 1997) criterion to clinically diagnose SLE. Asymptomatic sub-nephrotic proteinuria was found in 47% (35/75), nephrotic syndrome in 21% (16/75) and hypertension in 17% (13/75). Endocapillary proliferation 84% (63/75) and wire-loop lesions 51% (38/75) were found to be the commonest histological features. 79% (59/75) had ISN/RPS class IV lupus nephritis (diffuse lupus nephritis) with the majority 93% (55/75) belonging to class IV-G (predominantly diffuse global lesions) and the remainder to class IV-S (predominantly segmental lesions). The pathogenesis of class IV-G lesions is thought to be immune complex mediated where as class 1V-S lesions are thought to show injury analogous to systemic vasculitides, unrelated to immunologic injury.

Data on the prognostic outcomes of the two groups is conflicting because class IV-G is morphologically heterogenous, with two

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prognostically and pathogenetically distinct subcategories.

Key words: Lupus nephritis, clinico-pathological features, ISN/RPS Classification

Introduction

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease of both children and adults characterised by the formation of immune-complexes, resulting in a wide range of clinical manifestations (1,2,3,4,5). Lupus nephritis, which occurs in approximately 80% of patients, has a range of clinical and morphological expressions from clinically normal to rapidly progressive renal failure. Renal biopsy is used to confirm the diagnosis, evaluate disease activity, determine prognosis and institute appropriate therapy. Renal biopsy reporting systems have been modified and revised, over the years to accommodate clinico-pathological features and pathogenetic mechanisms (6,7).

The first histopathological classification of lupus nephritis was the WHO 1974 Classification which was subsequently modified in 1982 and 1995(7). The ISN/RPS-2003 Classification was introduced for a variety of reasons. Its advantages include preserving the simplicity of the original WHO classification while emphasising clinically relevant lesions and encouraging uniformity and reproducibility in reporting. Like preceding classifications, it was based exclusively on glomerular pathology and required separate reporting of significant tubulo-interstitial pathology.

Objective: To describe the clinico-pathological features of lupus nephritis and discuss the significance of ISN/RPS-2003 Class IV lesions.

Methodology

The renal biopsies of 75 patients diagnosed with SLE in a medical unit at the National Hospital of Sri Lanka, were examined at the Department of pathology, Faculty of medicine Colombo, over the period January 2008 to June 2010. The clinical data of the patients including age, gender, ACR (American College of Rheumatology) criteria for the diagnosis of SLE (Table 1) and the primary clinical presentation (Table 2) were collected from the bed head tickets in the medical record room NHSL by the principal investigator using a data collection sheet.

Renal biopsies stained with haematoxylin and eosin, Periodic Acid Schiff (PAS) and silver methanamine were assessed by the principal investigator and the study supervisor. Only biopsies containing five or more glomeruli were considered ‘adequate’ for the study. In total, 75 biopsies were examined.

All renal biopsies were classified according to the ISN/RPS-2003 criteria and the National Institute of Health classification(8).

Histopathological features documented included endocapillary proliferation, fibrinoid necrosis, glomerulosclerosis, crescents, wire-loop lesions and hyaline thrombi. According to the ISN/RPS Classification, class IV (defined as diffuse lupus nephritis involving 50% or more glomeruli) was subcategorised into class IV-G (diffuse global lupus nephritis) when over 50% of involved glomeruli had global lesions, and class IV-S (diffuse segmental lupus nephritis) when over 50% of involved glomeruli had segmental lesions (7). Data was analysed using an Excel 2007 software package.

Results

Among the 75 patients with lupus nephritis, 88% (66/75) were female. Approximately half 52% (36/75) were in the 21-30 year age group, with the next largest group occurring from 31-40 years (Fig.1). The mean age at the time of diagnosis of SLE was 23 years and the mean age at the time of performing the renal biopsy was 27 years.

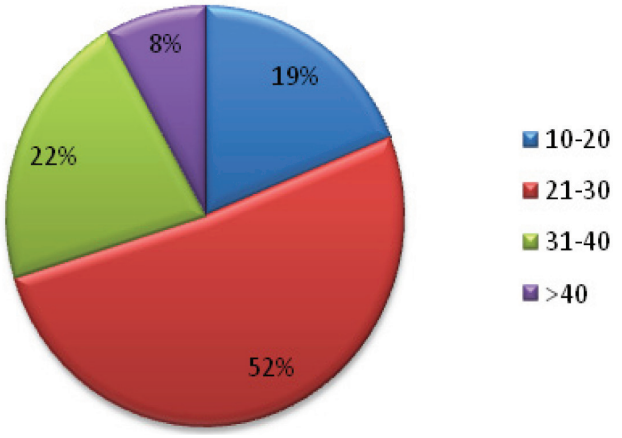

Fig.1. Age distribution of the study population

The diagnosis of SLE was based on the ACR criteria, which includes a minimum of four clinical or serological parameters (8) (Table 1). Of these, the presence of ANA in 93% (70/75) of patients was the commonest finding in the study population. Other features included the presence of ds-DNA in 75% (54/75), oral ulcers in 45% (34/75) and arthritis in 44% (33/75). Neurological disorders were the least common finding in our study amounting to 5% (4/75) (Table 1).

Table 1. ACR criteria for the diagnosis of SLE of our study population

Clinical findings time of renal biopsy	Number of cases (Total=75)	As a % of at total
Asymptomatic proteinuria	35	47
Nephrotic syndrome	16	21
Haematuria	11	15
Nephritic syndrome	10	13
Hypertension	13	17
RPRD*	1	1
CRF+	1	1

RPRD* - Rapidly progressive renal disease. CRF + - Chronic renal failure

Asymptomatic sub-nephrotic proteinuria was the commonest finding at the time of renal biopsy and was recorded in 47% (35/75). Nephrotic syndrome was present in 21% (16/75) and hypertension in 17% (13/75) (Table 2).

Table 2. Clinical findings at the time of renal biopsy

Criteria for the diagnosis of SLE	Number of cases (Total=75)	As a % of total
Malar rash	15	20
Discoid rash	14	19
Photosensitivity	9	12
Oral ulcers	34	45
Arthritis	33	44
Serositis	11	15
Renal disorder	70	93
Neurological disorder	4	5
Haematologic disorder	17	3
Immunologic disorder	56	75
Antinuclear antibodies	70	93

The most frequent glomerular lesion of lupus nephritis was endocapillary proliferation, which occurred in 84% (63/75), followed by wire-loop lesions in 51% (38/75), fibrinoid necrosis in 49% (37/75) and glomerulosclerosis in 45% (34/75). Presence of hyaline thrombi was the least frequent lesion and was found in only 16% (Table 3).

Table 3. Frequency of glomerular lesions in renal biopsies

Glomerular lesions	Number of cases (Total=75)	As a% of total
1. Endocapillary proliferation	63	84
2. Fibrinoid necrosis	37	49
3. Glomerulosclerosis	34	45
4. Crescents	20	27
5. Wire loop lesions	38	59
6. Hyaline thrombi	12	16

When the glomerular lesions were classified according to the ISN/RPS-2003, class IV was found in the majority, 79% (59/75) of our patients. This was significant because the next commonest was class II, found in only 13% (10/75) of patients. A single case of combined class III and V was also found. None had a pure class V lupus nephritis (Table 4). ISN/RPS Class IV was subcategorized into global (G) or segmental (S) categories. The vast majority 93% (55/59) belonged to Class IV-G, with only 7% (4/75) in Class IV-S.

Table 4. Distribution of lesions according to ISN/RPS-2003 Class

ISN/RPS 2003 Class	Number of cases (Total=75)	Number as a % of total
I	0	0
II	10	13
III	3	4
IV	59	79
IV-G	55	93
IV-	4	7
V	0	0
VI	2	3
III+V	1	1

Discussion

Among the 75 patients who underwent renal biopsies in our study, 88% were female. 74% were 20-40 years, with just over half belonging to the 21-30 year age group. These findings were comparable to studies done worldwide over the past ten years (1,4,5,9).

The result of 93% ANA positivity and 75% anti ds-DNA positivity was in concordance with similar studies reiterating the sensitivity of these markers in lupus nephritis (7, 9). A neurological disorder was found in a very small number of our patients, although it has been reported to be commoner in western studies (10, 11).

68% of patients had proteinuria at the time of renal biopsy, with sub-nephrotic proteinuria in 47% and nephrotic range proteinuria in 21%. Hypertension (17%), haematuria (15%) and nephritic syndrome (13%) were less common.

Classification of renal biopsies according to the ISN/RPS-2003, yielded interesting results. The vast majority (79%) of patients in our study were found to have ISN/RPS class IV glomerulonephritis, designated ‘diffuse lupus nephritis’ and defined as segmental or global lesions involving 50% or more glomeruli (7). This particular group is important because of its prognostic and therapeutic outcome. In 1989, Schwartz et al of the Lupus Nephritis Collaborative study group used the term ‘severe lupus nephritis’ (SLN) to define active glomerular inflammation involving > 50% of the glomeruli that have either a segmental or global distribution including coexisting membranous lesions (12, 13). It was found to be a more aggressive form of the disease with poorer prognosis, which showed an overall improvement by early diagnosis and treatment with immunosuppression.

In the 1995 WHO classification, SLN was defined as either severe focal segmental glomerulonephritis (WHO III> 50%) or diffuse global glomerulonephritis (WHO IV) (12).

In the ISN/RPS Classification, SLN was defined as diffuse lupus nephritis (class IV), with diffuse segmental IV-S and diffuse global IV-G subcategories.

Ninety-three percent of our class IV patients belonged to class IV-G. Whether Classes IV-G and IV-S are distinct or two ends of a continuous spectrum is currently uncertain (14). The differences in pathogenesis, likelihood of entering a remission and probability of progression to renal failure have been the subject of much study. The results have often been varied and frequently conflicting (15, 16, 17).

Data has suggested that Class IV-G lesions behave as an immune complex disease, having a positive correlation with the extent of immune deposits and a negative correlation with serum complement levels, the model traditionally assumed for lupus nephritis as a whole. However in Class IV-S lesions, the presence of proportionally greater glomerular fibrinoid necrosis with karyorrhexis and the paucity of immune deposits suggest that these lesions have a different pathogenesis with mechanisms of glomerular injury analogous to those occurring in the systemic vasculitides, unrelated to immunologic injury (6, 13, 15, 17).

Regarding the likelihood of entering a remission following immunotherapy the results have been varied. A study done in 42 patients in Korea in 2008 concluded that the number of patients with complete remission following intravenous cyclophosphamide were significantly higher in IV-S than IV-G lesions (16). However, a collaborative study done at Harvard Medical School on seventy patients did not find a significant difference in the outcome although they had identified some drawbacks in their study (17).

Which of the lesions were likely to progress to end stage renal failure? Two studies in 2004 by Yokohama et al and Mittal et al found that a higher percentage of patients with IV-S tended to have a poorer prognosis and a lower median renal survival than IV-G (6, 11, 12). However, Hill et al found no difference in the prognosis of these two groups on short term follow up, but observed a ‘dramatic difference’ in the long term (10 year) survival with IV-G being worse than IV-S (12, 15).

Several studies of the ISN/RPS classification (6, 15, 17) have not shown different outcomes between patients with IV-S and IV-G glomerular lesions, implying that morphological differences between severe segmental and diffuse global SLE GN are clinically irrelevant and of neither prognostic nor therapeutic import.

A reason for the conflicting results regarding the outcomes of classes IV-G and IV-S has been given by Schwartz (13). Application of the ISN/RPS criteria to the study cases resulted in the removal of some from the WHO severe segmental GN class (WHO III ≥50%) and inclusion into the diffuse global GN class of the ISN/RPS (IV-G.).

The ISN/RPS classification switches cases of segmental GN in which ≥50% of the glomeruli have lesions involving >50% of the glomerular surface area, from the severe segmental class in the WHO classification (III ≥50%) to ISN/RPS class IV-G. The switched cases represent biopsies with the most extensive segmental glomerular lesions.

Schwartz claims that ISN/RPS Class IV-G thus becomes heterogenous and comprises two morphologically distinct classes of renal biopsies, one group with diffuse global lesions (WHO class IV) and the other with widespread segmental lesions (WHO class III > 50%). ISN/RPS class IV-S comprises less widespread segmental lesions (WHO class III< 50%). Many of the severe cases of segmental glomerulonephritis have also been assigned to the IV-G category and have significant morphological, serological and prognostic differences from the WHO class IV cases that make up the majority of Class IV-G. The end result is that Class 1V-G ends up containing two prognostically and pathogenetically distinct subcategories.

Both the WHO and ISN/RPS Classifications are used in Sri Lanka. It is important that we understand the relevance of clinical and pathogenetic categories, if attempts at reclassification are made. The WHO (1982) and ISN/RPS-2003 Classifications reflect radically different diagnostic approaches (13). In the former, the diagnosis is an interpretation based on the pathologist's observations and understanding of the degree of inflammation and glomerulonephritis in a renal biopsy. In contrast, the ISN/RPS Classification reflects the belief that the severity and prognosis of lupus nephritis are a function of the proportion of cross-sectional involvement of each glomerulus,

and therefore the distinction between IV-S and IV-G becomes dependant upon the proportion of glomerular surface area involved.

The query that Schwartz et al raised regarding the presence of two prognostically and pathogenetically distinct subcategories in class IV-G of the ISN/RPS is valid and needs further consideration. This will enable differences in the prognostic outcome between IV-G and IV-S to become clearer.

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