Lupus nephritis

Clinicopathological correlation

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ABSTRACT

Objectives: To classify all renal biopsies of lupus nephritis patients presenting in the last 10 years, according to the modified World Health Organization (WHO) classification using the facilities of light, fluorescent, and electron microscopy. To assess the activity and chronicity indices of renal biopsies according to the National Institute of Health protocol, and to correlate the histological findings with the clinical features of the patients presented up to the time of biopsy.

Methods: Seventy-eight patients with lupus nephritis, biopsied over 10 years between January 1995 to December 2005 in King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia were reviewed by 2 histopathologists with the assistance of a nephrologist.

Results: The predominant histological type was WHO class IV. Patients of this class were more commonly associated with microhematuria, elevated proteinuria, and renal insufficiency. Active and chronic lesions were more likely to occur in patients of class III/IV. These patients were also more likely to have evidence of clinical renal disease than patients in class II. There was a significant association between nephrotic syndrome and class V lupus nephritis.

Conclusion: Although the clinical and pathological correlation demonstrated a significant relationship between underlying histopathology and the clinical course of the patient, however, the biopsy findings did not uniformly correlate with the clinical features. Moreover, the status prediction of lupus nephritis patients based on clinical information alone was significantly enhanced by information obtained from renal biopsy.

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Systemic lupus erythematosus (SLE) is a classical prototype of multi-system autoimmune disease with a wide range of clinical manifestations.[1] Renal manifestations of SLE, namely, lupus nephritis are highly pleomorphic with respect to their clinical and morphological expressions.[2,3] They may vary from clinically normal to rapidly progressive renal failure.[4] Due to the varied presentation, renal biopsy specimens may be used to confirm the diagnosis, to evaluate disease activity, to determine prognosis, and to determine appropriate therapy.[5] These biopsies have often been categorized according to different classification systems to provide clinicopathological correlation and prognostic information.[6] However, the role of renal biopsy in SLE remains controversial. On one hand, initial studies suggested that diffuse proliferative lupus nephritis was associated with a poorer prognosis than focal and membranous lesions. These results were supported by more recent studies, which concluded that renal pathological changes contributed to prognosis prediction.[7] Various morphological pictures may contribute to more appropriate choices of therapy. More recently, the usefulness of renal morphology, particularly in terms of activity and chronicity of the lesions on light microscopy, has been noted.[8] Moreover, the additional value of immunofluorescence and electron microscopy has also been appreciated. However, several investigators have challenged the value of renal biopsy and argued that the histological classification of renal biopsy does not add to the predictive value of clinical information, specifically when predicting renal death.[9] In this retrospective study of 10 years, we have taken all lupus nephritis patients presenting to our hospital, to correlate renal histological abnormalities with the clinical features present

at the time of biopsy. This 10 year research work will not only help in understanding the spectrum of lupus cases in this area, but will also enable us to compare our findings with other series, both within the Kingdom and abroad. The objective of the study is to classify all the renal biopsies of lupus nephritis patients in the last 10 years, according to the modified World Health Organization (WHO) classification of lupus nephritis, using facilities of light, fluorescent, and electron microscopy. To assess the activity and chronicity indices of renal biopsies according to the National Institute of Health (NIH) protocol; and lastly, to correlate histological findings with the clinical features of patients presented up to the time of biopsy.

Methods. Renal biopsies taken from patients between January 1995 to December 2005, at King Abdul-Aziz University Hospital were reviewed. Only biopsies containing 5 or more glomeruli were considered adequate for classification. In total, 78 biopsies were found to be appropriate for the study. All biopsy slides were stained with hematoxylin-Eosin, periodic acid-Schiff, trichrome, gomori methanamine silver and Congo red stains for light microscopy. Already performed immunofluorescence for IgG, IgA, IgM, C3 and fibrinogen were considered along with electron microscopy reports. Two histopathologists reviewed the kidney biopsies with the assistance of a nephrologist. All biopsies were classified according to modified WHO classification into 6 classes, namely, normal, mesangial, focal segmental, diffuse proliferative, membranous, and advanced sclerosis. Within each class, the sub groups were also noted. The classification was carried out on the basis of the most prominent lesion. A lesion was considered active if there was cellular infiltrate, karyorrhexis, cellular crescents, fibrinoid necrosis, vasculitis, and interstitial inflammatory infiltrate. Chronicity was judged by glomerular sclerosis and interstitial fibrosis. Patients were assessed according to the lupus protocol, which included complete history, physical examination, and complete laboratory investigations including hematological, biochemical, and serological tests.

Results. This study included 78 SLE patients, 67 females, and 11 males who presented with renal disease. The female to male ratio was 6.5:1 The youngest patient was 7 years, and the oldest was 52 years at the time of biopsy. The most common presenting signs of these renal patients were skin rash, anemia, and joint symptoms. Hypertension and anemia were the common complications, mostly from class IV patients. Disease of the central nervous system was not a predominant feature. There was no clear age difference between patients from various WHO classes. Evidence of renal disease, obtained from referral information, histories, and recorded data at presentation comprised edema, proteinuria, and gross hematuria. By percentage, the most common clinical manifestations of these patients were skin rash (64.5%), joint symptoms (62.3%), hypertension (47.2%), anemia (46.4%), infection (26.2%), and CNS symptoms (14.2%). Other nonspecific manifestations included fever with fatigue (38.3%), and lymphadenopathy (17.4%). The results of renal biopsies according to the modified WHO classification are shown in **Table 1**. Active lesions occurred primarily among patients with class III and IV disease. In addition to the active necrotizing lesions, these patients had cellular crescents, karyorrhexis and interstitial inflammation. Chronic lesions were more common in class II and IV disease. Patients in class III and IV disease showed significant sclerosing lesions. Clinical and pathological correlation demonstrated a significant relationship between underlying histopathology and the patient's clinical course. At the time of biopsy, proteinuria was observed in all the 78 cases. Patients with class II lupus nephritis had non-nephrotic proteinuria, whereas nephritic syndrome and renal insufficiency were absent. The patients of class II and class V showed relatively preserved renal function for a longer period. The most common presentation was diffuse proliferative glomerulonephritis (class IV), which represented 49 cases. These patients were most likely to have an elevated serum creatinine, proteinuria, microscopic hematuria, and low serum C3 and C4

Table 1 - Results of renal biopsies according to the modified World Health Organization classification.

Class	n
I. Normal glomeruli	Nil
A. Nil by all techniques	
B. Normal by light microscopy but deposits seen by electron or immunofluorescence microscopy	
II. Pure mesangial alterations (mesangiopathy)	16
A. Mesangial widening and mild hypercellularity (+)	11
B. Moderate hypercellularity (++)	05
III. Focal segmental glomerulonephritis	06
A. Active' necrotizing lesions	05
B. Active' and sclerosing lesions	01
C. Sclerosing lesions	Nil
IV. Diffuse glomerulonephritis	49
A. Without segmental lesions	Nil
B. With active necrotizing lesions	38
C. With active and sclerosing lesions	11
D. With sclerosing lesions	Nil
V. Diffuse membranous gloemrulonephritis	07
A. Pure membranous glomerulonephritis	Nil
B. Associated with lesions of category II (A or B)	07
VI. Advanced sclerosing glomerulonephritis	Nil

levels. Patients of class III and IV had relatively rapidly progressive clinical course. However, the patients with focal lesion, namely, class III had more preserved renal function as compared to class IV. Nephrotic syndrome has a significant association with class V lupus nephritis.

Discussion. Lupus nephritis usually presents after the age of 10 years, and rarely before 5 years. In a recent study carried out by Khoo et al,[10] 85.2% of children presented with lupus nephritis after the age of 10 years. In our study, the youngest age of presentation was 7 years. One female developed the disease at 9 years of age. Other cases presented after the age of 12 years. Lupus nephritis is more common in females as compared to males.[3] In our study, the female to male ratio was 6.5:1, similar to other published reports.[10-13] As has been reported previously,[10,11,13] we observed that class IV lupus nephritis was the most common class, and it was more commonly associated with microhematuria, elevated proteinuria, and renal insufficiency. The NIH activity index of these patients was correlated with proteinuria, hematuria, and renal insufficiency. This finding is in accordance with other reports that the presence of hematuria and proteinuria correlates with disease activity.[4] We also noted the finding that the chronicity index correlates with renal function, microhematuria, and presence of hypertension. Most of our patients with mesangial lesions had some clinical evidence of renal disease, including elevated creatinine levels. One patient of class III had no clinical evidence of renal disease, but had a significant lesion on biopsy.

In conclusion, we observed that prediction of the status of lupus nephritis patients based on clinical information alone, is significantly enhanced by information obtained from renal biopsy.[3] The biopsy certainly helps to identify patients at risk of developing progressive renal disease, and who therefore require progressive therapeutic intervention.[3] Similarly, it also avoids unnecessary aggressive management in some other cases.[10,11]

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