Association of Proteinuria with Various Clinical Findings and Morphologic Variables of Oxford Classification in Immunoglobulin A Nephropathy Patients

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Original Article

ABSTRACT

Background: Immunoglobulin A nephropathy (IgAN) with nephrotic syndrome is an uncommon form of IgAN. Clinical and morphological characteristics of proteinuria in IgAN, especially when is in nephrotic range have not yet been fully examined. This study was aimed to correlate morphologic variables of the Oxford classification, and various clinical data with proteinuria in IgAN patients. We also aimed to demonstrate the significance of prevention of proteinuria as one of the important factors in progression of this disease.

Methods: In an observational study conducted on IgAN patients, total of 114 biopsies were entered in the study. IgAN was diagnosed by light and immunofluorescence study.

Results: Of 114 patients 70.2% were male. Mean age of patients was 37.7 ± 13.6 years. The mean of proteinuria was 1742 ± 1324 mg/day. Also mean of serum creatinine (Cr) was 1.6 ± 1.5 mg/dL. Of 114 patients, 11(9.6%) had nephrotic range proteinuria. In this study, there was a positive correlation between proteinuria and serum Cr, peri-glomerular fibrosis or interstitial fibrosis. There was a positive association between proteinuria and totally sclerotic glomeruli too. There was also a positive association between the amount of fibrous crescents and the level of proteinuria. Nephrotic proteinuria could just be seen in male patients. Also, nephrotic syndrome had a positive association with the number of crescents.

Conclusions: Our findings firstly support the prognostic value of crescent due to its association with proteinuria and secondly imply the importance of treatment of proteinuria to prevent progression of IgAN.

Keywords: Crescent, immunoglobulin A nephropathy, nephrotic syndrome, Oxford classification, proteinuria

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is an autoimmune disease and is very common form of primary glomerulonephritis.[1-4] It occurs worldwide with different frequency from 2% to 52% of

all renal diseases in different parts of the world.[1-9] Proteinuria >1.0 g/day, at diagnosis is a well-known indicator of progressive renal disease in patients with IgAN.[9-17] Indeed persistent proteinuria exceeding this amount is an independent predictor of subsequent renal progression in patients with IgAN who have been followed for 10 years or more.[17-21] Nephropathy of IgA with nephrotic syndrome is an uncommon form of IgAN.[3,5,18-20] The clinical and morphological characteristics of this condition have not yet been understood. In IgAN, urinary findings usually consist of mild-to-moderate proteinuria and hematuria, and it rarely presents with a proteinuria in nephrotic range. The prevalence of IgAN with nephrotic syndrome (nephrotic IgAN; nIgAN), varies from 5% to 20%[18-25] The Oxford classification, created in 2009, is a novel method for evaluation of histological findings of IgAN.[23-28] This classification has good reproducibility and can be used to evaluate prognosis and response to therapy. This study was aimed to correlate four morphologic variables of the Oxford classification, and the various clinical data with proteinuria in IgAN patients. We also aimed to demonstrate, the significance of prevention of proteinuria as one of the important factors in progression of this disease.

METHODS

Following popularization of Oxford classification of IgA N on July 2009,[26-28] we applied it in this study for the classification of IgAN.

Definition of IgAN

The pathologic diagnosis of IgAN requires demonstration of IgA-dominant mesangial or mesangial-capillary immune deposits through immune fluorescence(IF) microscopy while there is subdominant, or weak deposit for C_1q. The immune deposits were semi quantified from 0 to 3+positive bright. The definition of IgAN needs the presence of diffuse and global IgA deposits that were graded ≥2+ and weak C_1q deposition.[5,29-31] All renal biopsies, performed at various medical centers (University Hospitals or Private Centers) from July 2009 to July 2012, were sent to a reference laboratory. None of the patients was treated before the biopsy. Biopsies with less than eight glomeruli were excluded from the study. None of the patients was diagnosed as primary IgAN, having a history of collagen vascular diseases, diabetes or liver cirrhosis based on a questionnaire filled at the time of biopsy admission, laboratory data in patients' records and a brief history provided by referee physicians at the time of biopsy admission.

Histologic data

All renal biopsies were prepared for light and direct immunofluorescence microscopy. Tissue was fixed in 10% formalin for histologic sectioning. Each kidney biopsy was prepared by cutting paraffin blocks into 3-μm sections and staining two slides with periodic acid Schiff, two slides for hematoxylin and eosin, one slide for Jones methenamine silver and one slide for trichrome. Each slide contained 2-3 sections and nap-frozen in liquid nitrogen was used for IF. Sections (Six-micron in thickness) were stained for immunofluorescence study with IgG, IgM, IgA, C1q, C3, and find 1q.[32-34] IF slides were reported in a scale of 0-3+ positive bright and by a nephropathologist. IF study was performed before reviewing the slides for light microscopy unaware of patients' data. After IF diagnosis of IgAN, histopathology glass slides were reviewed to assess the morphologic variables, which were applied in Oxford classification method. We also assessed the presence of extracapillary proliferation (cellular, fibro-cellular or fibrous crescents). After selection of biopsies having dominant deposition IgA by IF study and in the absence of exclusion criteria, glass slides were reported for the classification of Oxford-MEST.

Definitions of morphologic variables

Total glomeruli and the number of glomeruli with global sclerosis were recorded for each biopsy. The presence of (i) mesangial hypercellularity(M), (ii) endocapillary proliferation(E), (iii) segmental glomerulosclerosis (S) and (iv) the proportion of tubular atrophy and interstitial fibrosis; IF/TA(T) was estimated as published for Oxford classification.[29]

Clinical studies and laboratory data

The medical records of patients were reviewed to obtain various demographic, clinical and laboratory information at the time of biopsy and for follow-up activities. Data gathered at the time of biopsy included race, gender, age, serum creatinine (Cr) and proteinuria (based on a 24 h urine collection).

Statistical analysis

The mean values and standard deviations were calculated, and statistical significance of the differences between groups were evaluated using T and Likelihood Ratio tests. Because of high positive skewness of data, the Spearman's coefficient of correlation was used to check the correlation. A computer program (SPSS version 16.0, Chicago, IL, USA) was used for statistical analysis. $P < 0.05$ was considered as statistically significant.

RESULTS

This observational study was conducted on IgAN patients. A total of 114 biopsies were enrolled to the study. In this trial, out of 114 patients, 70.2% were male. Mean age of patients was 37.7 ± 13.6 years (median = 35 years) (39 ± 14.3 years for male and 35 ± 11.7 years for female patients). Morphologic variables of Oxford classification are summarized in Table 1. The mean of proteinuria was 1742 ± 1324 mg/day (median = 1500 mg/day). The mean number of glomeruli in all renal biopsies was 14.8 ± 7.2 (median = 13 number). In all biopsies, the mean of totally sclerotic glomeruli was 2.4 ± 2.9 (median = 1 number). Furthermore, the mean of serum Cr was 1.6 ± 1.5 mg/dL (median = 1.2 mg/dL). Of 114 patients, 11 (9.6%) had nephrotic range proteinuria. In this study, there was a positive correlation between proteinuria and serum Cr ($P < 0.001$), peri-glomerular fibrosis ($P = 0.013$) or interstitial fibrosis ($P = 0.037$ Figure 1). There was a positive association between proteinuria and totally sclerotic glomeruli ($P = 0.008$). Off our variables of Oxford classification, only M (mesangial proliferation ≥50% of glomeruli) ($P < 0.01$) and T(interstitial fibrosis and tubular atrophy; IF/TA) ($P < 0.007$) had a positive association with proteinuria. There was a positive correlation between the amount of fibrous crescents and the level of proteinuria ($P = 0.028$). None off our deposited immune reactants (IgA, IgG, IgM and C3) had a significant association with proteinuria ($P > 0.05$). Nephrotic range proteinuria was only seen in male patients ($P < 0.05$). Furthermore, nephrotic syndrome had a positive association with the number of crescents ($P < 0.05$).

Table 1: Clinical and histological findings of IgAN patients at the time of renal biopsy

Clinical findings	
Sex (male/female)	80/34
Age (years)	37.7±13.6 (total) (M: 39±14.3, F: 35±11.7)
S-Cr (mg/dl)	1.6±1.5 (total) (M: 1.8±1.7, F: 1.1±0.7)
Histological findings (Oxford classification)	
Mesangial hypercellularity	
M0/M1 (number)	41/73
Endocapillary hypercellularity	
E0/E1 (number)	79/35
Segmental glomerulosclerosis	
S0/S1 (number)	42/72
Interstitial fibrosis/ Tubular atrophy (IF/TA)	
T0/T1/T2 (number)	59/35/20

IF=Interstitial fibrosis, TA=Tubular atrophy, IgAN=Immunoglobulin A nephropathy

DISCUSSION

After publication of IgAN classification (Oxford) on July 2009,[29-31] the various studies were conducted to better find the clinical significance of each of four variables. In this study, we aimed to correlate proteinuria, especially in the nephrotic range, with Oxford classification. The present investigation showed that off our variables of Oxford classification only M variable (mesangial proliferation ≥50% of glmeruli) and T (interstitial fibrosis and tubular atrophy; IF/TA) had a positive association with

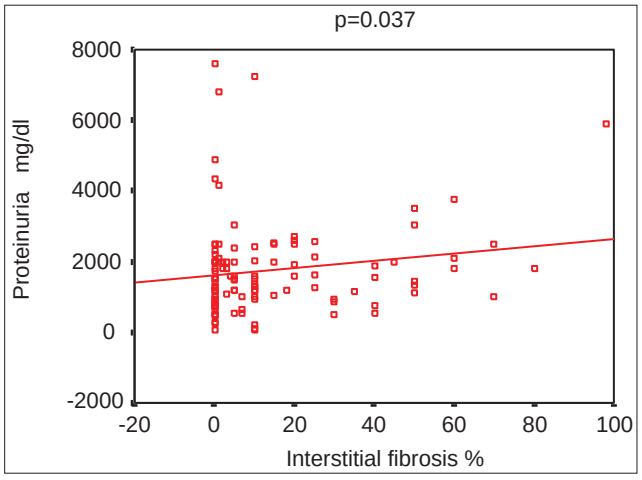

Figure 1: Positive association of proteinuria with interstitial fibrosis

proteinuria. There was not any significant association between four deposited immune reactants (IgA, IgG, IgM, and C3) and the level of proteinuria. Study on patients who had nephrotic range proteinuria showed that, this amount of proteinuria was only seen in male patients. We also found a positive association between nephrotic range proteinuria and T variable of Oxford classification. At the time of renal biopsy for diagnosis of glomerular disease, proteinuria is a well-known indicator of progressive renal disease invarious renal diseases[35-45] as well as in patients with IgAN.[14] In a study conducted by Donadio *et al.* on 154 IgAN patients, they found that 24-h urine protein was a good predictor for subsequent end-stage renal failure.[10] Kobayashi et al. also reported that persistent proteinuria more than 1 g/day was the most reliable, independent predictor of long-term prognosis in Japanese patients with IgAN followed for 10 years or more.[14] Our study was consistent with the results of these reports. Furthermore, it strengthens its importance because this study showed the highest correlation with various pathologic variables that to the best of our knowledge were not reported, yet. We found a positive association between proteinuria and peri-glomerular fibrosis or totally sclerotic glomeruli. We also found a positive correlation between proteinuria and the number of crescents. Specially, among cellular, fibro-cellular and fibrous crescents, only fibrous crescents had an association with proteinuria. In clinical point of view, we found nephrotic range proteinuria (nephrotic syndrome) in only male patients, which further support that, male gender is a risk factor for IgAN.[3-5] Similarly, Hwang *et al.* in a study on 125 biopsy-proven primary IgAN patients who had more than 1.0 g/day proteinuria at the first assessment and underwent anti-proteinuric treatment, found that achievement of less than 1.0 g/day proteinuria was important for limiting the loss of renal function, and relapse of proteinuria should be closely monitored in proteinuric IgAN.[46] The various studies have described that the natural courses and prognostic factors for IgAN patients are progressed to end-stage renal disease.[17,46-50] In these studies, the worst prognosis for nephropathy of IgA was overt proteinuria, renal impairment and high grades of histological classification. However, of these prognostic factors, proteinuria is the most important factor requiring the treatment in IgAN patients.[17,46-50] This finding suggests that reducing these verity of proteinuria in the longterm seems to be the most important for limiting the loss of renal function in proteinuric IgAN.[17-21,51-55] Kim *et al.* conducted amulti center observational study on 1076 patients with biopsy-proven IgAN from four medical centers in Korea. Of 1076 patients, 100 presented with nephrotic syndrome. They showed that the prognosis of nephrotic syndrome in IgAN was not favorable.[56] In the present study, we showed a positive association between proteinuria and M as well as T variables of the Oxford classification in IgAN. Furthermore, out off our variables, we also showed a positive association between proteinuria and the number of crescents especially fibrous crescent.[57-61] Our findings firstly support the prognostic value of crescent due to its association with proteinuria and secondly imply the importance of treatment of proteinuria to prevent progression of IgAN.

Limitation of the study

We cannot follow the patients.

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