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Original Article

Correlates of hematuria on glomerular histology and electron microscopy in IgA nephropathy

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ABSTRACT

Background: Hematuria is the most important clinical manifestation of IgA nephropathy. This study was undertaken with the objective to describe the spectrum of histological changes with reference to the Oxford classification and the ultrastructural changes in the glomerular basement membrane and to correlate them with hematuria.

Methods: 66 patients who underwent renal biopsy for IgA nephropathy were evaluated histologically by the Oxford system and also subject to electron microscopic examination for glomerular immune deposits, as well as alterations in the glomerular basement membrane.

Results: On comparing the histological scores generated by the Oxford classification with degree of hematuria, it was found that the status of 'endocapillary proliferation' and the status of 'tubular atrophy and interstitial fibrosis showed a significant correlation. Correlation of hematuria with location of the deposits, i.e. mesangial only, and mesangial with capillary wall deposits (subendothelial and subepithelial) did not show any association. Other alterations of the GBM were seen in 12 cases. The changes included thinning alone in 4 cases, thinning and lamellar splitting in 5 cases, and lamellar splitting alone in 2 cases.

Conclusion: At presentation, endocapillary proliferation is one histological parameter which shows close association with hematuria.

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Introduction

IgA nephropathy is known to be the most common form of primary glomerulonephritis in the entire world.[1] It is an immune complex mediated disease defined by the presence of either dominant or co-dominant deposits of IgA, predominantly in the glomerular mesangium. In India, the prevalence has been estimated to be between 12 and 15% of all renal biopsies.[2] The classical presentation of the disease is with hematuria, although purely proteinuric presentations are also not unknown. Histological evaluation of the disease is now done according to the Oxford system of classification which generates a score based on four histological parameters.[3] Electron microscopic examination in this disease has been mostly limited to evaluation for presence of immune complex type of electron dense deposits which may be seen in the mesangium, as well as the glomerular capillary walls. Alterations in the glomerular basement membrane have been often described, though poorly characterized.[4] They have usually been considered to be rare. However, thinning of the glomerular basement membrane has been reported upon earlier to occur with some frequency.[5] This study was undertaken with the objective to describe the spectrum of histological changes with reference to the Oxford classification and the ultrastructural changes in the glomerular basement membrane and to correlate them with hematuria.

Materials and methods

A total of 98 cases who underwent renal biopsy and were reported as IgA nephropathy were included in the study. The sample size was calculated at $\alpha = 95\%$ and prevalence of 14.3%[2] with a precision of 10%. Out of the total 98 cases, 22 cases had not undergone an electron microscopic examination and were excluded from the study. Cases with IgA nephropathy, but with sclerosed glomeruli were also excluded from the study. The remaining 66 cases were evaluated further for presence and degree of hematuria, light microscopic findings based on the Oxford system of classification, direct immunofluorescence findings, and electron microscopy. Degree of hematuria was classified as microscopic and gross. The gold standard for diagnosis of IgA nephropathy was considered to be dominant or codominant glomerular staining for IgA on IF. In all cases, the biopsy was fixed in formalin and routinely processed 3 μm serial sections were studied with H&E, PAS, and Massons Trichrome stains. Tissue for Immunofluorescence was transported in Michels medium and frozen sections were stained with FITC conjugated antibodies to IgG, IgA, IgM, C3, Kappa, Lambda, and C1q. Tissue for EM was routinely processed and stained with uranyl acetate and lead citrate.

On light microscopy, the cases were categorized as per the Oxford system[3,6] and the four histological variables studied were mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), and the proportion of tubular atrophy and interstitial fibrosis, IF/TA(T). On electron microscopy, the changes looked for were the location and nature of immune complex type of electron dense deposits, and thinning, thickening, lamellar splitting, or rarefaction of the glomerular basement membrane. The clinical parameter studied was hematuria. Chi square test was used for analysis with SPSS 19.

Results

Of the 66 cases finally included in the study, 51 patients were males and 15 were females. The age ranged from 8 to 66 years with a mean of 37 years. Histologically, as per the Oxford classification, out of the 66 cases, 61 cases showed the presence of mesangial proliferation (M1) (Fig. 1(a)), 13 showed endocapillary proliferation (E1) (Fig. 1(b)), 32 showed segmental sclerosis (S1) (Fig. 1(c)), 36 showed mild tubular atrophy and interstitial fibrosis (T1) (Fig. 1(d)), while 7 showed severe tubular atrophy and interstitial fibrosis (T2).

On comparing the MEST scores with degree of hematuria, it was found that the status of E (endocapillary proliferation) and the status of T (degree of tubular atrophy and interstitial fibrosis) showed a significant correlation (Table 1). The degree of mesangial expansion and segmental sclerosis had no significant correlation with hematuria. Combined scoring of E and T lesions was attempted with microscopic and gross hematuria, but we could not demonstrate any association due to an insufficient number of cases falling into the E1T2 group.

In addition to hematuria, proteinuria was also noted in 45 cases which ranged from trace to subnephrotic.

In addition to mesangial immune complex type of electron dense deposits which were seen in all cases, glomerular basement membrane deposits were seen in 47/66 cases (71.2%). Of these 47 cases, 43 cases (68.1%) showed mesangial and subendothelial deposits and 4 cases showed mesangial, subendothelial, and subepithelial deposits. Correlation of hematuria with location of the deposits, i.e. mesangial only, and mesangial with capillary wall deposits (subendothelial and subepithelial) did not show any association (Table 2).

Other alterations of the GBM were seen in 12 cases. The changes included thinning alone in 4 cases, thinning and lamellar splitting in 5 cases, and lamellar splitting alone in 2 cases (Fig. 2).

Discussion

In the present study, we have attempted to describe the correlation of hematuria with renal histology as per the MEST score and ultrastructural changes in the glomerular basement membrane. IgA nephropathy has traditionally been considered to be a disease affecting males more than females. The male:female ratio ranged from less than 2:1 in Japan to as high as 6:1 in northern Europe and the United States.[7] Our study showed the prevalence of the disease to be more in males (77.2%). This is against the findings of Chandrika[2] who reported the ratio to be 1.5:1 in a study from south India.

With the publication of the Oxford classification, various studies have been carried out over the years to study the significance of the four variables under consideration. We tried to correlate them with hematuria at presentation.