



Crescentic IgA nephropathy; a brief communication to the current evidences

Hamid Nasri*

¹Nickan Research Institute, Isfahan, Iran

Correspondence to

Prof. Hamid Nasri;

Email:

hamidnasri@med.mui.ac.ir

Received 9 January 2016

Accepted 28 January 2016

Published online 29 January 2016

Keywords: IgA nephropathy, Oxford classification, Extracapillary proliferation, Crescent, End-stage renal disease

Abstract

Crescentic immunoglobulin A nephropathy, described as >50% crescentic glomeruli on renal biopsy, is one of the causes of rapidly progressive glomerulonephritis. However, few investigations have considered this condition. It is well known that, if crescentic immunoglobulin A nephropathy is not treated, there will almost predictably be rapid progression to end-stage kidney failure. While, there has been much controversy about the role of extracapillary proliferation as a significant prognostic factor in IgA nephropathy, hence, it is important to re-evaluate extracapillary proliferation in IgA nephropathy patients. Therefore, we suggest further studies on this aspect of IgA nephropathy patients.

Citation:

Nasri H. Crescentic IgA nephropathy; a brief communication to the current evidences. *Immunopathol Persa.* 2016;2(1):e07.



Introduction

Crescentic immunoglobulin A nephropathy, described as >50% crescentic glomeruli on renal biopsy, is one of the causes of rapidly progressive glomerulonephritis (1). However, few investigations have considered this condition. It is well known that, if crescentic immunoglobulin A nephropathy is not treated, there will almost predictably be rapid progression to end-stage kidney failure. IgA nephropathy is an autoimmune disorder and is very common form of primary glomerulonephritis worldwide (1).

Materials and Methods

For this mini-review, we used a variety of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and or their equivalents such as IgA nephropathy, Oxford classification, extracapillary proliferation, chronic kidney disease, crescent, and end-stage renal disease.

Oxford (MEST) classification for IgA nephropathy

The Oxford classification, created in 2009, is a novel method for assessment of morphologic lesions of IgA nephropathy (1,2). This classification has respectable reproducibility and can be used to assess prognosis and response to therapy. This classification,

Key point

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contained of four morphologic lesions detected having prognostic implication. They are (i) mesangial hypercellularity (M), (ii) endocapillary proliferation (E), (iii) segmental glomerulosclerosis (S) and (iv) the proportion of interstitial fibrosis and tubular atrophy; IF/TA (T) named also as MEST classification (1-8). However, crescents (extracapillary proliferations) are not integrated to the Oxford (MEST) classification (1-3). Recently in a group of Japanese patients, Imai et al, studied the long-term outcomes of IgA nephropathy patients with an apparently benign presentation. They evaluated prognostic factors for kidney survival and clinical remission. They studied biopsy-proven IgA nephropathy patients who had an estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73 m² and with a proportion of proteinuria <0.5 g/day at the time of kidney biopsy. The renal biopsies were studied using the MEST classification. They found, the 15-year kidney survival rate was 93.8%.

Clinical remission was observed in nine patients. Baseline proteinuria was the single factor significantly correlated with the absence of clinical remission. They detected that, the long-term prediction of Japanese patients with IgA nephropathy who presents with slight urinary abnormalities and preserved kidney function was good (4).

Extracapillary proliferation in IgA nephropathy

In the study conducted by Walsh et al on 146 patients with IgA nephropathy (median follow-up; 5.8 years), with major outcomes of augmenting serum creatinine, end-stage renal failure or death, they found, the clinical interpreters of outcome were initial creatinine, systolic blood pressure and proteinuria (univariate analysis). However, in multivariate analysis adjusted for clinical characteristics, individual predictors of primary outcome were interstitial fibrosis/tubular atrophy and glomerulosclerosis (5).

Likewise, Choi et al conducted a study to examine the prognostic relevance of clinical and morphologic features on kidney outcome in patients with IgA nephropathy treated with the combined treatment of angiotensin receptor blockers and steroids (6). Regression analysis revealed that the final urine protein/creatinine excretion ratio and age were critical determinants of slope of the eGFR by both univariate and multivariate analysis. Surprisingly in their study, eGFR, systolic blood pressure, proteinuria, and body mass index at the preliminary appearance were not predictive of slope. They also found that no histological feature, including crescents and predicted slope. They concluded that, reaching to a low urinary protein excretion is the main determinant for the good outcome in individuals treated with combination therapy (6). In contrast to these finding, there was an attempt to correlate crescents in IgA nephropathy with clinical outcomes in various studies, however, they have produced conflicting results. Indeed, IgA nephropathy is a highly heterogeneous disease with variable clinical patterns, morphologic features, long-term kidney progression, and geographic prevalence (1-6). While according to the results of the Oxford cohort study, crescent was not associated with renal disease outcome, however the Oxford study comprised a small number of patients (n=265 patients) (7,8). Therefore, it seems to be necessary to conduct complementary investigations using a larger number of patients from various ethnicities and geographic areas to identify important prognostic morphologic lesions (1-7). Recent studies have demonstrated that crescents may had prognostic significance. To identify risk factors and develop a prediction model, Lv et al assessed data from patients ≥ 14 years old with crescentic IgA nephropathy who were followed ≥ 12 months (9). They examined 52 patients from one renal center, and the validation cohort comprised 61 patients from multiple centers. At biopsy, the mean serum creatinine level was 4.3 (± 3.4) mg/dL, and the mean percentage of crescents was 66.4% ($\pm 15.8\%$). The kidney survival rates at years one, three, and five after biopsy were 57.4% ($\pm 4.7\%$), 45.8% ($\pm 5.1\%$), and 30.4% ($\pm 6.6\%$), respectively. Multivariate Cox regression revealed initial serum creati-

nine level as the only independent risk factor for end-stage renal disease. Notably, the percentage of crescents did not associate independently with end-stage kidney failure. Logistic regression showed that the risk of end-stage kidney failure at one year after biopsy increased rapidly at serum creatinine > 2.7 mg/dL and reached 90% at serum creatinine > 6.8 mg/dL. In both cohorts, patients with serum creatinine > 6.8 mg/dL were less likely to recover from dialysis. In their conclusion, crescentic IgA nephropathy has a poor prognosis and initial serum creatinine concentration may predict renal failure in patients with this disease. Furthermore a recent systematic review and meta-analysis was conducted by Lv et al, on patients with biopsy-proven primary immunoglobulin A nephropathy, by assessing the Oxford classification of IgA nephropathy (4 pathologic lesions as mentioned above). In their review, they defined renal failure as doubling of serum creatinine level, 50% decline in eGFR, or end-stage kidney failure. They considered 16 retrospective cohort investigations with 3893 patients and 570 renal failure events. In a multivariate model, hazard ratios for kidney failure were 0.6, 1.8, and 3.2 for scores of M0 (mesangial hypercellularity score ≤ 0.5), S1 (presence of segmental glomerulosclerosis), and T1/2 ($> 25\%$ tubular atrophy/interstitial fibrosis), respectively, without evidence of heterogeneity (9). They found that, endocapillary proliferation (E) lesions were not associated with renal failure, with evidence of heterogeneity. Interestingly they found that crescent lesions were associated with renal failure, with no evidence of heterogeneity. They finally concluded that, mesangial hypercellularity (M), segmental glomerulosclerosis (S), the proportion of tubular atrophy and interstitial fibrosis (T), and extracapillary proliferation, but not endocapillary proliferation (E) lesions, are associated strongly with progression to renal failure and thus should be included in the Oxford-MEST classification system (10). Previously, Katafuchi et al conducted a study to consider, the significance of pathologic features for progress to end-stage kidney insufficiency by multivariate analysis in 702 individuals with immunoglobulin A nephropathy. They tested, the association of extracapillary proliferation (crescent) with renal survival by univariate analysis in 416 patients who met the Oxford (MEST) criteria and 286 who did not, separately. In a multivariate model, S and T were significantly associated with end-stage renal failure. With addition of extracapillary proliferation, not segmental glomerulosclerosis but extracapillary proliferation was significant for end-stage renal failure. In univariate analysis, kidney survival was significantly lower in patients with extracapillary proliferation (crescent) than in those without, in patients who did not meet the Oxford (MEST) criteria, however such a difference was not found in patients who met it (11). They showed the prognostic significance of extracapillary proliferation (crescent) in their cohort. They suggested that extracapillary proliferation (crescent) be added to the consequent version of the Oxford classification of IgA nephropathy to widen the scope of the classification (11). More recently, we investigated the clinical and morphological significance of extra-

capillary proliferation (crescent) in a group of IgA nephropathy patients with regard to the Oxford classification (12). Our study was an observational investigation conducted on immunoglobulin A nephropathy patients. We collected a total of 114 (70.2%; male) biopsies. We diagnosed immunoglobulin A nephropathy by light and immunofluorescence for all patients. The mean age of the patients was 37.7 (\pm 13.6) years. The mean serum creatinine was 1.6 (\pm 1.5) mg/dL. Twenty-five (21.9%) of patients had extracapillary proliferation. We found a significant positive association between the proportion of crescents and serum creatinine ($P < 0.001$). Additionally, we observed a positive correlation between the nephrotic range proteinuria and the total number of crescents ($P < 0.05$). Furthermore, a significant positive association between the proportion of globally sclerotic glomeruli and extracapillary proliferation ($P = 0.028$). These findings attest that extracapillary proliferation has a significant correlation with proteinuria and proportion of globally sclerotic glomeruli (12). Similarly, Lee et al, on a total of 430 patients with biopsy-proven in immunoglobulin A nephropathy between January 2000 and December 2009, examined the morphologic variables of the Oxford classification (MEST) and the presence of crescents were assessed too (13). They found that, 18.8% had an extracapillary proliferation. During a mean follow-up of 61 months, the primary outcome occurred in 23.5% of patients with crescents compared with 11.5% patients without crescents. The 10-year kidney survival rate was meaningfully lower in individuals with crescents than patients without crescents (extracapillary proliferation). However, in a multivariable Cox analysis which comprised clinical items and the Oxford classification, extracapillary proliferation was not significantly associated with an increased risk of developing the primary outcome. They interpreted that, including extracapillary proliferation to the Oxford (MEST) classification did not progress the discriminative capability for the estimation of kidney outcomes. They concluded that extracapillary proliferation was not an independent prognostic factor, suggesting that extracapillary proliferation have limited value in predicting renal outcomes of IgA nephropathy (13). More recently, Kaneko et al, retrospectively examined the relevance of extracapillary proliferation consisting cellular and fibrocellular crescents on the long-term outcome of kidney function. They studied 314 patients who were diagnosed having IgA nephropathy, with 12 months or more of follow-up period. They found that, in univariate analysis, the renal survival rate was significantly lower in patients with crescent if urine protein ≥ 0.5 g/day. Similarly in the multivariate model including pathological parameters, crescent was an independent risk factor for kidney outcome if urine protein ≥ 0.5 g/day. Additionally in patients who treated with RAS-blocker or treated before initiation of methylprednisolone pulse therapy, crescent was the only independent risk factor. They concluded that, extracapillary proliferation would be associated with the kidney outcome of the patients with urine protein ≥ 0.5 g/day (14).

Conclusion

While, there has been much controversy about the role of extracapillary proliferation as a significant prognostic factor in IgA nephropathy, hence, it is important to re-evaluate extracapillary proliferation in IgA nephropathy patients. Therefore, we suggest further studies on this aspect of IgA nephropathy patients (15-19).

Author's contribution

HN is the single author of the paper.

Conflicts of interest

The author declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Funding/Support

None.

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