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Significance of immunohistochemical findings in Oxford classification of IgA nephropathy: The need for more validation studies

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Oxford classification of IgA nephropathy (IgAN) has been validated as clinically useful tool for prognostication of individual patients with IgAN. The original classification did not address the significance of immunostaining pattern in IgAN. A subsequent study by the same authors found immunostaining data to be potentially useful in predicting some of the morphological variables of Oxford classification. The study under discussion also addresses the potential significance of these ancillary data in refining the individual prognostication in this disease.

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Commentary

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IgA nephropathy (IgAN) is the most common glomerulopathy worldwide (1). The disease is notorious for variable clinical presentation and equally variable histopathological picture on renal biopsies. The prognosis is also variable and end-stage renal disease (ESRD) develops in around one third of cases over 20 years of follow-up (2-4). Numerous studies have been carried out to determine the clinical or histopathological features at the time of presentation that can accurately predict development of ESRD in some but not all of the patients with the disease. Among these, the prognostic value of some clinical and laboratory features such as renal function, level of proteinuria and hypertension, is proved beyond doubt. However, the predictive importance of histopathological features has remained controversial till recent past (5, 6).

The publication of Oxford classification of IgAN in 1999 may be considered a milestone in the prognostic study of this disease. It represented an evidence-based, fairly reproducible and an easy to use classification with proven clinical relevance. All of these attributes of this classification were tested beforehand prior to the final

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promulgation of the classification. This approach has never been applied in diagnostic native renal pathology for any classification (7, 8). Thus, this classification represented a novel approach to classification of a highly variable renal disease with variable outcome. However, as the authors acknowledged that this is not the final classification. Some of the histopathological features were very infrequent in the cohort studied during the development of classification and thus their predictive power could not be tested. The milder and the severe forms of the disease spectrum were not included. The study cohort did not include patients from all over the world and all populations were not represented in the study cohort. Moreover, immunofluorescence (IF) and electron microscopic findings were not evaluated for their potential prognostic importance (9).

Many studies conducted after the publication of this classification scheme have substantiated the independent predictive power of the four variables included in the classification (10-18). Some studies have also found additional morphological features to be of prognostic value as well (19). This further highlights the need for more and more prospective studies of different cohorts of patients with this disease to determine the complete predictive histopathological profile of the disease.

One important aspect of the disease which was not investigated in the initial analysis of the study was the prognostic significance of deposits of immune reactants and their distribution pattern (20-22). A subsequent study from the same group found the deposition pattern of immune reactants to be of some prognostic value (20). They found that the location of glomerular IgA and the presence of IgG correlated with greater histological activity but did not independently predict clinical outcome. However, this study was based on a careful review of the details of written reports available for analysis and did not include a review of the slides (21). Moreover, almost all centers used IF rather than immunohistochemistry (IHC), thus precluding a centralized and uniform review. They were of the view that the data at present do not support the addition of immunostaining pattern to the Oxford classification of IgAN.

Due to these reasons, the authors suggested further validation studies in different cohorts paying careful attention to methodological issues and the confounding variables of immunosuppressive treatment (20).

The study by Nasri et al. in this issue of J Nephropathology is a step forward in the above direction (23). The authors present a review of 114 native renal biopsies in patients with IgAN and correlate IF findings with the demographic, clinical and morphological features identified as prognostically important in Oxford classification of IgAN. This is an interesting study and provides new insights about the role of immune reactants' deposition in the glomeruli with the pathogenesis and progression of IgAN. There is scarcity of information on this topic and this study adds some new information. This study showed that, only C3 deposits had a significant correlation with serum creatinine. Other immune reactant, especially antibodies (IgA, IgM and IgG) had no significant association with serum creatinine. This study also showed that IgA deposition score had significant positive association with endocapillary hypercellularity (E) and segmental scarring (S) variables of Oxford classification. Moreover, IgM deposition score had positive association with the S variable. There was no significant association of IgG deposition score with the four morphologic variables of Oxford classification. There was also a significant association of C3 de-

position score with E and S variables of Oxford classification. The authors conclude that further studies are needed to better define the role of immune reactants' deposition pattern on the clinical behavior and progression of this disease.

Among the strengths of the study are its origin from a racially homogenous population of Iran, consistency in the reporting of histopathological and IF findings by a single nephropathologist with special interest in IgAN and a fairly large number of patients with a variety of histological appearances on the biopsy. No prebiopsy treatment was given in any of the patients. However, the study has certain shortcomings too, the most important of which include a lack of follow-up and outcome data, the origin of the study from a single center and the short duration of study (23). The authors should follow-up the present cohort for a sufficient period of time and then correlate the IF findings with the clinical outcome.

In summary, the authors of the current study have done a nice job and merit congratulations. We hope that they will continue to enlighten us with their interesting findings and results on this important aspect of the disease.

Conflict of interest

The authors declared no competing interests.

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