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Recent Advances in IgA Nephropathy

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The renal biopsy in IgA nephropathy (IgAN) has three essential functions: diagnosis, prognostication and guiding therapy. In this presentation, I will discuss recent advances in the interpretation and analysis of the renal biopsy in IgAN, focusing on these 3 areas.

1. Diagnosis:
IgAN is defined by the presence of IgA-dominant or co-dominant glomerular deposits in the absence of lupus nephritis. The glomerular deposits in both IgAN (primary and secondary) and IgA vasculitis (IgAV) contain galactose-deficient polymeric IgA1, demonstrated in tissue sections using the monoclonal antibody KM55. The differential diagnosis of IgAN includes infection-related glomerulonephritis (IRGN) with IgA deposits, which is usually secondary to Staph aureus infections, and proliferative glomerulonephritis with monoclonal IgA deposits (PGNMID). Recent studies have demonstrated that KM55 staining is negative in both these conditions and therefore may be of value in distinguishing them from IgAN. Other helpful biopsy features in the identification of IRGN is the presence of neutrophil rich glomerular inflammation (exudative pattern), and the presence of C3 dominant or co-dominant deposits. IgA variant of PGNMID is a frequent consideration as a substantial proportion (10-20%) of IgAN show light chain (LC) restriction of the glomerular deposits, the great majority of these showing lambda LC restriction. Features favoring PGNMID rather than IgAN include a membranoproliferative pattern, kappa light chain restriction, IgA2 heavy chain restriction (in IgAN the deposits comprise mainly IgA1), and negative staining for KM55.

2. Prognosis:
One of the main goals for the development of the Oxford Classification of IgAN was to provide a histological classification that can be used in prognostication and to identify those patients who will develop progressive renal disease in the absence of therapeutic intervention.
In several large international patient cohorts, tubular atrophy/interstitial fibrosis (T score) is found to be consistently the best predictor of renal survival. This is not surprising as T score reflects the stage of disease at the time of biopsy diagnosis; those patients who have already developed substantial irreversible chronic damage show a shorter time to end stage disease. The Oxford Classification study also demonstrated that T score was associated not only with renal survival but with rate of loss of renal function, indicating that the tubulointerstitial changes in IgAN include active lesions.
Tubulointerstitial (TI) inflammation is a potential explanation; recent studies have demonstrated that the number of TI macrophages is related to T score but correlates poorly with glomerular inflammation, and there is evidence that M2 macrophages play an important role in the development of interstitial fibrosis in IgAN.
Endocapillary hypercellularity, the Oxford Classification E score, is a marker of glomerular inflammation, and in retrospective studies predicts disease progression in patients not receiving immunosuppression (IS). One weakness of the E score is its reproducibility; there is poor interobserver agreement between pathologists working in different units. This can be overcome by immunostaining for CD68, a marker of monocyte/macrophages. Quantification of glomerular CD68 positive cells is highly reproducible and correlates closely with E score. CD68 staining might also be helpful in distinguishing inflammatory crescents from pseudocrescents, and in quantifying inflammatory activity in mixed cellular/sclerosing glomerular lesions.
Segmental glomerulosclerosis, the Oxford Classification S score, is a common lesion which is present in approximately 70% of IgAN biopsies. It is heterogenous, the morphology indicating the underlying

cause. Segmental sclerosis can result from organization of necrotizing or crescentic lesions, reflect hyperfiltration injury, or be a manifestation of podocyte injury. In the Oxford Classification cohort, podocytopathic features (podocyte hypertrophy/tip lesions) are associated with an adverse outcome, an observation confirmed recently in the larger VALIGA cohort. Data from these studies support the subclassification of S1 lesions. Hyperfiltration injury, with glomerulomegaly and perihilar sclerosis, plays an important role in disease progression in IgAN; recent studies have demonstrated the prognostic value of measuring glomerular size. This is facilitated by digital pathology and image analysis which have also been used to quantify cellular infiltrates; it is likely that digital techniques and diagnostic algorithms will play an increasing role in the evaluation of IgAN biopsies.

3. Renal histology as a guide to therapy:
Steroid therapy: One of the aims of the Oxford Classification study was to identify histological changes that are associated with a response to IS, and therefore use the renal biopsy to guide therapy. Multiple large retrospective studies have demonstrated an interaction between IS and Oxford Classification E and C scores; patients with these lesions show a benefit from IS. Similarly, podocytopathic segmental sclerosis is associated with improved outcome following steroid therapy. These findings have not been confirmed in randomized control trials (RCTs), but the biopsy component in trials of steroid therapy to date have been underpowered. Scoring of the TESTING study biopsies is currently being performed. A recent retrospective study of response to steroid therapy in patients at risk of progression demonstrated that the number of glomerular macrophages was the single most powerful predictor of response to therapy.
Complement-directed therapy: There is growing evidence that complement plays a central role in glomerular inflammation and injury in IgAN. Recent studies have demonstrated that the intensity of glomerular C3 staining is associated with renal outcome, and that quantification of C3 provides added value to the MEST-C scores. Dysregulation of the alternative pathway is associated with histological markers of disease activity and clinical progression, and glomerular C4d, a marker of lectin pathway activation, also correlates with progressive disease. There are several actively recruiting clinical trials of anti-complement agents in IgAN. These provide an opportunity to determine whether histological markers of complement activation and glomerular inflammation are superior to MEST-C scores in identifying patients who will benefit from complement-directed therapies.

It was always anticipated that the Oxford Classification of IgAN would evolve as new evidence emerged, and with introduction of new therapies. It is likely that in the future, it will incorporate markers of complement activation and inflammation. The use of digital pathology will also expand, not only in assisting in lesion quantification, but the use of machine learning and diagnostic algorithms will identify novel histological markers of prognosis and response to therapy.