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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