Immunoglobulin A nephropathy

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Introduction

There are three classes of IgA nephropathy defined morphologically by the presence of predominant or co-dominant mesangial IgA deposits. In idiopathic IgA nephropathy, an aetiology agent is not identified and the patients may be thus rendered a diagnosis of Berger’s disease honouring the French physician who first described it. Secondary IgA nephropathy may accompany hepatobiliary, autoimmune diseases, bacterial/viral infections, or neoplasia. The third category is the vasculitic form of the disease, Henoch–Schönlein Purpura (HSP). The diagnostic hallmark of all three IgA nephropathies is diffuse IgA mesangial deposits detected by immunofluorescence (IF).

Pathology

In classic IgA nephropathy, mesangial matrix/cellular increase on H+E or PAS is highly suggestive of the diagnosis, but histologic features may range from minimal to focal segmental mesangial cell proliferation to diffusely proliferative glomerulonephritis (GN). Thus, IF is essentially the best tool for diagnosis. In most biopsies IgA deposits predominate over IgG, IgM, or complement. C3 specifically tends to be weaker than IgA or absent, particularly in stable disease. Mesangial IgM deposits are often present in variable amounts. IgG deposits may be as intense as the IgA deposits, making distinction from lupus GN difficult, specifically in biopsies with fibrinoid necrosis or crescents. In IgA nephropathy crescents are rarely seen, with the exception of biopsies taken immediately after an episode of macroscopic haematuria. Electron microscopy is merely confirmatory, demonstrating the location of the deposits primarily in the mesangium. Paramesangial or subendothelial deposits are common and may be confluent, particularly in biopsies of patients with symptoms of HSP. Large, bell-shaped deposits (humps), similar to subepithelial deposits seen in post-infectious GN, are on occasion identified in active IgA or HSP. In fact, subepithelial and/or subendothelial deposits in addition to mesangial, correlate with poor outcome in HSP. Lastly, an association between IgA and thin basement membranes is described, but whether this is simply a coincidence, is irresolute. HSP and IgA nephropathy may be histologically similar, but in our experience, some HSP features are rarely seen in IgA nephropathy. Segmental or diffuse GBM duplication, crescents, glomerular or interstitial neutrophils, fibrin thrombi, and vascular degeneration or thrombosis, favour HSP. However, one may state that any lesion may be seen in IgA nephropathy making light microscopic appearance as variable as the course of this disease and distinction from HSP impossible based solely on pathology.

Clinicopathologic correlations

IgA was initially thought to be a benign disease, but the experience of the last three decades indicates that a subset of patients develop end-stage renal disease (ESRD). Histologic classification according to the WHO format were devised aiming to guide prognosis and or therapy, following the paradigm of lupus nephritis. Five classes are devised as follows. Class I, with minimal lesions, class II, with focal segmental hypercellularity or sclerosis, class III, focal proliferative GN in <50% of glomeruli, with or without crescents, class IV, diffuse proliferative in >50% with or no crescents and class V >40% globally sclerosed glomeruli and >40% tubular atrophy. Ninety per cent of patients with IgA class I or II have a 10-year survival rate, dropping to 50% in class III, and 20% in class IV and V. The predictive value of this scheme is supported by independent studies, which using multivariate analysis, find that glomerular
sclerosis is the best independent predictor of adverse outcome and renal failure [4]. Other independent predictors were: increased serum creatinine at the time of biopsy and younger age [4]. Additional bad prognostic indicators include body weight, hypertension and presence of HLA-B35 [3]. HLA-B35 appears to predispose patients to recurrent disease. Notably, mesangial hypercellularity did not correlate with renal failure or presence of proteinuria in these series [4]. In contrast, there is significant correlation between interstitial inflammation and renal function at the time of biopsy, but not with long-term prognosis. Glomerular capillary wall deposits, when present correlate with bad prognosis.

Despite its simplicity, the aforementioned classification scheme has not gained the popularity of the lupus nephritis WHO scheme, perhaps because of absence of defined treatment modalities dependent on histology. The fact that the published series show statistical significance in large cohorts but are weak on individual patients may be a discouraging factor to utilize this classification rigorously. Prognostic parameters tend to be safe statements for patients at the two ends of the spectrum, those with mild disease and those with glomerulosclerosis. Other findings, such as complement deposition and or interstitial damage, are not necessarily accounted for in the WHO classification. Recent studies suggest that complement C3 activation occurs in relationship to progressive disease, but not in stable disease [5].

Two classification schemes are devised for HSP, one similar to the IgA scheme above, with an additional class (VI), which describes an MPGN pattern of injury [3]. This scheme emphasizes the presence of crescents and leukocytes as they affect long-term outcome [3]. None of the two schemes is routinely practiced. Vasculitis is very rarely present in the kidney in association with any of the three IgA diseases. Chronic vascular disease on the other hand, may be common, found to be equal to glomerular sclerosis in predicting progressive disease in IgA nephropathy. In children as well as in adults, proteinuria exceeding 1 g/day or renal insufficiency at the time of biopsy significantly increases the risk of developing ESRD to about 20%. Most patients with IgA nephropathy have recurrent macroscopic haematuria. Nephrotic syndrome may, however, be the presenting symptom and in these cases renal biopsy invariably shows diffuse fusion of foot processes in addition to IgA deposits. Response to steroids is followed by recovery of the podocyte injury, but IgA deposits remain, indicating the primary underlying disease vs dual disease (e.g. IgA and minimal change). Rarely, nephrotic syndrome may be the presenting symptom of IgA myeloma. Also rarely, the presenting symptom may be acute renal failure. Acute tubular necrosis with tubular lumina filled with red blood cells is pronounced in renal biopsies in such cases. Rapidly progressive GN is reported but is a very rare occurrence. Finally, renal scarring is invariably found in biopsies of patients with long standing disease complicated by hypertension, proteinuria, and renal failure. Notably, IgA deposits are consistently present even at late stages, uncovering the aetiology of ESRD in such patients. Dual disease, for example IgA and diabetic GN, is not rare.

Transplantation

IgA nephropathy recurs in the transplant in more than 50% of patients known to have IgA. Mesangial deposits may be identified in the allograft biopsy as early as days post-transplantation, but graft failure and hypertension are delayed up to 5 years. A few cadaveric kidneys from patients with IgA have been grafted to recipients without IgA, but the deposits disappeared in the graft, suggesting of a systemic deregulation of the IgA immune system and not kidney-based disease. Similarly, HSP recurrence in the allograft is high (about 35%), but clinical manifestations are mild despite histologic recurrence [3].

Pathogenesis

IgA nephropathy is considered an immune complex mediated disease, characterized by primarily polymeric IgA (pIgA) deposits in the skin, gastrointestinal capillaries and glomeruli. IgA normally produced by mucosal plasma cells circulates in low amounts in the blood. In both IgA and HSP, serum IgA levels are high, suggesting that the two entities represent a spectrum of clinical manifestations of the same or similar causative agent, but increased serum IgA alone is not sufficient to induce kidney deposits. Abnormal IgA1 O-glycosylation is currently proposed to trigger mesangial cell receptor and local complement activation, leading to mesangial deposition of IgA [5].

Conclusions

Histologic parameters which negatively affect prognosis in IgA nephropathy, include glomerular sclerosis, capillary wall IgA deposits and vascular and tubulo-interstitial fibrosis. In HSP, additional bad indicators include number of crescents present, and subepithelial/subendothelial deposits. Clinical markers with strong correlation to ESRD in IgA nephropathy are: older age, severity of proteinuria, hypertension, and obesity. Recurrent macrohaematuria per se is of good prognosis, while serum IgA levels and gender appear to have no impact on prognosis. In the majority of patients the disease course is prolonged besides worrisome histology in both IgA and HSP. Histologic evidence of disease in the allograft kidney does not indicate early loss of the graft.


