EUVAS COURSE

Concise report

IgA Vasculitis and Anti-GBM disease: two ends of a spectrum of immune complex vasculitis

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Key messages:

1. IgAV and anti-GBM vasculitidies cause glomerular crescent formation and may lead to ESRD despite therapy.
2. IgAV may be benign in children but causes increased mortality and morbidity in adults.
3. Clinical trials to define optimal management of IgAV and more rapidly acting therapies in anti-GBM disease are needed.

Abstract:

Two immune complex vasculitidies, IgA vasculitis (IgAV) and anti-GBM disease represent polar extremes with regards our understanding of disease pathogenesis, standardised management protocols and outcomes. This report compares our current approach to these uncommon entities in adults.

Both diseases demonstrate degrees of small vessel necrosis and glomerular crescent formation. IgAV has an antibody response directed against unknown antigens, is often treated conservatively and has poorly studied long term renal outcomes. By contrast, anti-GBM disease presents with rapidly progressive glomerulonephritis and often results in end stage renal failure, despite intensive immunosuppression. Rarely some cases of anti-GBM disease may be IgA predominant and bind other α chains present in the GBM, but their clinical course is as for other anti-GBM disease patients and not IgAV, suggesting that the antigenic target rather than the antibody subclass is the critical factor in determining disease outcome. However, both conditions are associated with increased mortality in adults and result in significant CKD and hypertension.

Introduction

Small vessel vasculitidies have been defined according to the updated Chapel Hill Consensus Criteria[1], which divide the conditions into those that are pauci-immune and generally associated with ANCA or those associated with immune complexes, such as IgA vasculitis(IgAV) (formerly Henoch Schonlein Purpura) or anti-GBM disease. These two immune complex associated vasculitidies share some common renal features such as the predominant capillary involvement, and in those with nephritis varied degrees of crescent formation, and segmental necrotising lesions. However, they are at the two extremes of a spectrum with regards the knowledge of their pathogenesis, how best to manage them and what to expect of their outcomes. While we have great understanding of the molecular basis of anti-GBM disease, we remain mostly ignorant of the processes leading to IgAV.

Pathogenesis

The pathogenic basis of anti-GBM disease has been reviewed in detail recently[2-4]. The disease has strong HLA associations with both susceptibility and resistant genotypes, which are due to presentations of epitopes derived from the NC1 domain of α3 chain of type IV collagen (α3NC1(IV)) promoting inflammatory T helper or regulatory T cell subsets respectively[5]. Disease is rarely

relapsing, unlike other autoimmune diseases, due to re-establishment of a Treg population and possible sequestration of the autoantigen[6, 7]. Autoreactive antibodies directed towards the α3NC1(IV) can be measured in serum and form the basis of diagnostic assays, although peculiarities in presentation have resulted in rare cases of anti-GBM disease without detectable circulating antibodies using such conventional assays[8] and conversely, detectable anti-GBM antibodies that do not bind the native GBM[9], which remain less clearly explained phenomena. In addition, up to a third of patients with anti-GBM disease are ANCA positive, and the reason for this high rate of dual positivity remains uncertain. Finally, rare cases of IgA- anti GBM disease have been reported and these follow a rapidly progressive course, as for IgG- anti – GBM disease. The antigenic target of these molecules does not appear to be the classical α3(IV) NC1, but other α(IV) chain molecules in the GBM[10].

By contrast the pathologic basis of IgA vasculitis is less clear-cut. Genetic studies have demonstrated susceptible HLA alleles and cytokines [11], some of which overlap with those implicated in IgA nephropathy. It is believed that there are additional similarities with IgA nephropathy in the susceptibility to disease due to an hypo-galactosylated hinge region of IgA_1 that act as neo- or cross reactive-epitopes allowing IgG anti-IgA antibodies to bind and promote immune complex deposition. In addition, these galactose deficient IgA_1 molecules may bind soluble Fcα receptor, forming immune complexes whose levels correlate with more progressive kidney disease. However, there are differences in size of immune complexes between IgAN and IgAV as well as their composition(for example containing fibronectin), and there are higher levels of circulating IgE antibodies in IgAV, which may promote greater IL-8 production and neutrophil recruitment – leading to the endothelial damage[12]. Galactose deficient IgA_1 molecules are found in glomeruli in IgA nephropathy and IgAV but not other glomerulonephritidies [13]. The subendothelial localisation of the IgG-IgA complexes permits aberrant leucocyte activation, GBM damage and ultimately capillary loop rupture with crescent formation. The targets of the IgA1 antibodies are uncertain. Abnormal T cell populations in IgAV have also been identified, such as CXCR3-expressing T cells which accumulate in the kidney and whose numbers correlate with renal damage assessed by proteinuria[14], as well as expanded T follicular helper cells and augmented levels of T cell cytokines such as IL17 and IL-4[15]. The renal pathological features in IgAV, classical- and IgA-mediated- anti-GBM disease are summarised in Table 2.

Diagnosis

Establishing an early diagnosis of anti-GBM disease is not always straightforward, as there are often no or few preceding symptoms. Patients may present with non-specific symptoms of advanced renal failure or are found to have abnormal renal function or urinary abnormalities, and due to the rare nature of the condition, physicians often do not consider it as a diagnostic possibility, leading to frequent delays in diagnosis. Once considered, testing serum for the presence of anti-GBM antibodies is straightforward, but should always be considered an urgent test, as there are almost no situations (unless considered likely to be a false positive test , for example in the context of acute viral infection) where anti-GBM antibodies do not necessitate immediate treatment initiation. It should be remembered that the modern tests use recombinant α3(IV) antigen and test for IgG subclasses only, so detecting rare variants that have antibodies directed to α1(IV) or an IgA subclass or lack circulating antibodies would require renal biopsy.

IgA vasculitis may often present with a purpuric rash, which, in children, may lead to a clinical diagnosis, while in adults the wide differential diagnosis may require skin or renal biopsy to confirm the presence of deposited IgA. The presence of vasculitic lesions, on the skin or in the renal biopsy

suggests that this is IgAV rather than IgA nephropathy, although there is a degree of overlap, for example in cases of IgA nephropathy with crescents, but no cutaneous manifestations. The updated Chapel Hill consensus acknowledges that IgAV may, in some cases, be renal limited[1]. Perhaps the lower incidence of IgAV in adults compared to children leads to some diagnostic delay, as many primary care physicians may not consider a diagnosis of IgAV in adults. When it has been analysed there is good concordance in IgA between deposited Ig A in the skin and kidney[16].

Management

In view of the dysregulated autoimmune response to a self-antigen in anti-GBM disease, the basis of management is early institution of immunosuppression, to stop autoantibody production, attenuate autoreactive T cell responses and inhibit the glomerular-targeted innate immune responses that arise secondary to the autoantibody deposition (Table 1). This is achieved with high dose glucocorticoids and cyclophosphamide, although recent reports suggest benefit with rituximab and MMF in selected cases[17, 18]. Additional intensive plasmapheresis is used to rapidly eliminate autoantibodies and pro-inflammatory mediators, such as complement, and clotting factors known to promote endothelial damage. Despite these measures, and possibly as a result of the late presentation of disease, or the time taken for treatment to translate into halting leucocyte glomerular damage, up to 75% of patients in recent series present with end stage renal disease[19], requiring renal replacement therapy. Novel approaches using streptococcal enzymes cleaving of GBM-binding IgG currently in clinical trial, will test the theory that more immediate dissociation of IgG-mediated leucocyte activation may promote improved renal outcomes.

Although protocols based on these principles have been established for a number of years, they have not been subjected to more than one randomised trials of only 17 patients[20], and the ongoing IDES trial is testament to how a network of investigators can introduce new strategies in rare diseases.

While we believe that the basis of IgAV is also a dysregulated autoimmune response, with autoreactive T cells and the formation of IgA-IgG immune complexes, unlike other immune complex vasculitidies there is a paucity of evidence for short or long term benefits of immunosuppression, like in IgA nephropathy. Perhaps this is because therapeutic trials have been carried out mostly in children and there are few trials in adult patients, where the disease is associated with more renal damage. Despite a lack of convincing trial evidence, many physicians still use colchicine, glucocorticoids alone or in combination with immunosuppressants (including cyclophosphamide, azathioprine, and MMF) in the management of IgAV, although we remain uncertain if these provide additional benefit over conservative measures such as renin-angiotensin blockade. In the small trials that have been carried out addition of immunosuppressants (cyclophosphamide or MMF) to glucocorticoids provides no extra benefit with regards remission induction[21, 22], however, they appear to be superior to colchicine therapy alone[23]. In children, there are data suggesting glucocorticoid use results in a more rapid resolution of abdominal symptoms or arthropathy, and these are therefore often reserved for more symptomatic patients. In addition, in cohort studies of children and adults, plasmapheresis has been shown to be of benefit in treatment of IgAV[24, 25]. Recent data has demonstrated a resolution of symptoms with rituximab therapy, allowing a more rapid tapering of glucocorticoids[26]. A critical question that needs to be answered is, if IgAV is indeed responsive to immunosuppressive therapy and what the optimal protocol for its management is. This needs to be addressed in a randomised trial. Current KDIGO guidelines (Table 1) suggest treatment of IgAV in adults should be as for children, with renin-angiotensin blockade for

those with proteinuria >0.5g/day and immunosuppression with glucocorticoids alone or with cyclophosphamide reserved for those with persistent proteinuria>1g/day and crescentic (>50% glomeruli crescents) respectively.

Outcomes

Renal function

Renal outcomes in anti-GBM disease are generally poor unless disease is treated early while the patients still retain significant urine output. Anuric patients and those requiring dialysis at presentation are less likely to recover renal function[27]. However, in those that maintain urine output even in the presence of dialysis requirement there may be significant renal recovery.

In IgAV recent data suggest that the risk of developing ESRD is higher in older patients and our own data demonstrate that older patients present with more advanced renal disease but in those not requiring dialysis at presentation rates of renal decline are equal across all age groups(Staneway unpublished).

Future areas for investigation

It is clear that renal outcomes can be poor in adults with either condition, and earlier diagnosis maybe helpful, especially in anti-GBM disease. The use of AKI alert systems which trigger a request for anti-GBM antibodies may provide a more rapid exclusion of this rare condition and rely less on the consideration of the physicians who may come to the diagnosis only when more advanced renal failure is achieved. The relation between IgAV and IgA nephropathy needs to be better investigated and the nature of the antigen(s) may be important in defining the pathogenesis of disease, especially given the HLA susceptibility, implicating T cell mediated B cell help. More interestingly, the basis for resolution or failure of progression of glomerular necrosis and crescents in IgAV contrasting with the progressive damage and lack of reversibility in anti-GBM disease may provide some better insights into mechanisms of glomerular inflammation.

Table 1. Current recommended management strategies

IgAV	Anti-GBM disease	
Conservative care with analgesics and hydration in mild cases	Prophylaxis for bone, infection and gastric protection(bisphosphonates, calcium/D3; Co-trimoxazole; PPI or H2 blockade)	
Proteinuria>0.5 g/day start ACEi or ARB Persistent proteinuria > 1 g/day start glucocorticoids Crescentic glomerulonephritis consider addition of cyclophosphamide to glucocorticoids	Plasmapheresis 60 mls/Kg daily until anti-GBM titre normalises High dose glucocorticoids (1 mg/Kg/day; max 60 mg); tapering and stopping after 6 months Oral cyclophosphamide 2-3 mg /Kg, for three months	

Table 2. Comparison of renal pathology in IgAV, classical anti-GBM disease and IgA anti-GBM disease

IgAV	Anti-GBM disease(IgG)	IgA anti-GBM
Mesangial, capillary loop and perivascular galactose-deficient IgA1 deposition Endocapillary and mesangial proliferation Fibrin deposition Variable crescent count	Linear GBM deposition of IgG and C3 Fibrin deposition High glomerular crescent count , of similar ages	Linear GBM deposition of IgA and C3 Bowman's capsule staining Fibrin deposition High glomerular crescent score Concurrent IgAV reported

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