



Glomerulonephritis

EDITORIAL COMMENT

Rapidly progressive IgA nephropathy: a form of vasculitis or a complement-mediated disease?

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Abstract

A rapidly progressive and crescentic IgA nephropathy (IgAN) is uncommon, but it has a high risk of progression to end-stage renal disease and variable response to immunosuppression. The importance of a positive anti-neutrophil cytoplasmic antibody (ANCA) serology in this group of patients is not fully understood but may have prognostic significance. On the other hand, there is growing evidence of the role of complement in the pathogenesis of IgAN, especially in cases of crescentic IgAN. Therapies directed against the complement system are a potential and rational therapeutic approach. In this issue, two clinical studies of crescentic IgAN are presented. The first work, is a retrospective case-control study describing clinical presentation, histological findings and response to treatment of crescentic IgAN/positive ANCA patients, comparing them with IgAN/negative ANCA patients and ANCA vasculitis patients. The second is a case report showing the effect of eculizumab, a humanized monoclonal antibody that is a terminal cascade complement inhibitor, as salvage therapy for crescentic IgAN resistant to conventional immunosuppression. Both studies broaden our approach to patients with aggressive forms of IgAN.

Key words: ANCA, complement activation, crescentic glomerulonephritis, IgA nephropathy

Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis in the Western world [1, 2]. Gross haematuria bouts preceded by an upper respiratory infection, hypertension and proteinuria and microhaematuria of variable degrees are the most characteristic clinical findings. Dominant or co-dominant mesangial deposits of IgA, with IgG and C3, are the typical findings in renal biopsy immunofluorescence [3]. It is believed that repeated exposure to environmental factors (viruses, bacteria, etc.) causes overstimulation of B-cell subsets in the tonsils, bone marrow and intestinal lymphoid tissue, favouring the production of IgA1 with deficient galactose residues [4]. This circulating abnormally glycosylated IgA1 induces the synthesis

of autoantibodies and the formation of circulating immune complexes, which are deposited in renal mesangium causing local inflammation and the appearance of proteinuria and haematuria [5]. However, many of the mechanisms involved in the abnormal glycosylation of IgA1 or in the different spectrum of clinical manifestations remain unknown. Current guidelines recommend treatment with renin-angiotensin-aldosterone system (RAAS) blockers to reduce proteinuria, and in cases with persistent proteinuria >1 g/day for >4–6 months in spite of optimized RAAS blockade, a cycle of oral corticosteroids is advised. Aggressive immunosuppressive therapy, similar to that used in anti-neutrophil cytoplasmic antibody (ANCA) vasculitis, with corticosteroids and oral or intravenous cyclophosphamide followed by azathioprine has been tried in rapidly progressive, crescentic forms of IgAN [6].

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The rate of IgAN progression is very variable, but after 25 years of follow-up, 30–50% of patients develop end-stage renal disease (ESRD) [7]. The presence of minimal (<500 mg/day) or no proteinuria generally indicates a good long-term prognosis [8], whereas hypertension is a contributing factor for the progression of renal impairment. Acute kidney injury can accompany gross haematuria episodes; renal function recovery is usually observed after the disappearance of macrohaematuria, but it can be incomplete in elderly patients and in those with prolonged macrohaematuria bouts (>10 days) [9, 10].

A particularly rapid progression to ESRD has been reported in a minority of IgAN patients (<10%) [11–13]. Histopathological findings in these patients are in some instances reminiscent of vasculitis, due to the presence of cellular/fibrous crescents, fibrinoid necrosis and arteriolar damage [13, 14]. ANCA, mostly ANCA-myeloperoxidase (MPO), have been found in a minority of IgAN patients [15], even in patients showing no crescents in renal biopsy [16]. Given the relationship of IgAN with Henoch–Schönlein purpura, it has been suggested that crescents in a patient with biopsy-proven IgAN could be interpreted as a limited form of renal vasculitis [17], but the true relevance and significance of ANCA in the pathogenesis and course of ANCA-positive IgAN patients are not yet fully defined.

The complement system in IgAN

Recent findings strongly indicate that the complement system has a deep pathogenic influence in IgAN. Studies of genetic susceptibility have described loci that predispose to IgAN, as well as mutations and polymorphisms in genes encoding factor H and factor H-related proteins. Some of these polymorphisms appear to be protective for the development of IgAN [18–20]. Serum levels of C3 are usually normal or slightly decreased in most patients, but deposits of C3 and C4d are found in a substantial proportion of cases, suggesting that the alternative and the mannose–lectin pathways are activated in IgAN [21]. Deposits of C4d in mesangium [22] and C3d in peritubular cells [23] have been associated with a more aggressive form of the disease. Studies in the Japanese population have found that a serum IgA:C3 ratio >3:1 or 4:1 or high serum levels of C4 binding protein could have an impact on prognosis [24, 25]. Toxic and pro-inflammatory substances released by red blood cells in the tubular lumen during gross haematuria episodes activate the complement system, further aggravating tubulointerstitial damage [26, 27]. Taken together, these findings strongly support a role for complement activation in the pathogenesis and progression of IgAN. Figure 1 summarizes the main pathogenic mechanisms involved in renal damage in IgAN.

In this issue of CKJ, two interesting papers regarding aggressive and rare forms of IgAN are presented. In the first, Yang *et al.* [28] describe the clinical and histological features, the response to treatment and the renal outcomes of 20 IgAN patients with positive serology for ANCA (ANCA+). Of 1729 IgAN patients studied between 1997 and 2013 in whom ANCA serology was available, 20 (1.2%) were ANCA+. This low percentage is in accordance with previously published studies [15, 16]. One of the strengths of the study is the comparison of IgAN/ANCA+, IgAN/ANCA– and ANCA-associated vasculitis (AAV) patients. IgAN/ANCA+ patients showed several similarities to AAV patients. Compared with IgAN/ANCA– patients, IgAN/ANCA+ were older and had worse baseline renal function, more lung and systemic involvement and more fibrinoid necrosis in renal histology. IgAN/ANCA+ patients also had a higher frequency of gross haematuria than IgAN/ANCA– and AAV patients. Despite their

more aggressive presentation, IgAN/ANCA+ patients responded better to immunosuppression than IgAN/ANCA– patients, with a higher dialysis withdrawal post-immunosuppression (75 versus 0%, $P = 0.01$) and with a non-significant trend for less ESRD at 6 months (0.77 versus 0.26 events/person/year, $P = 0.09$). At the end of follow-up, no differences in renal outcomes were found.

The study also compared IgAN/ANCA+ and IgAN/ANCA– patients showing crescents in renal biopsy, with a group of crescentic non-IgAN/ANCA+ patients. Again, the number of events (ESRD) at 6 months was lower in patients with crescentic IgAN/ANCA+ when compared with crescentic IgAN/ANCA– patients (0.31 versus 2.94 events/person/year, $P = 0.015$). This poorer response to immunosuppressive therapy in patients with crescentic IgAN/ANCA– had been shown by the same group in a multicentre cohort study, the baseline serum creatinine being the main predictor of renal prognosis [29].

The results of the study by Yang *et al.* suggesting that patients with IgAN/ANCA+ are more responsive to immunosuppression than IgAN/ANCA– patients had already been described in other studies [15]. However, it should be considered that the percentage of glomerular sclerosis was clearly higher in IgAN/ANCA– patients than in the other groups (9.1 versus 3.6% for IgAN/ANCA+ and 0% for AAV, $P = 0.002$), and the finding of extensive glomerulosclerosis could have induced a more restrictive use of immunosuppression in these patients. In fact, IgAN/ANCA– patients received cyclophosphamide and corticoids less frequently (64.9 versus 95% in patients IgA/ANCA+ and 95% for patients with AAV). Proper adjustment by the degree of glomerular sclerosis would have allowed a more proper assessment of the benefits of immunosuppression. Other limitations of the study are the absence of classification according to the type of ANCA (PR3 or MPO) and the lack of information about changes in the levels of ANCA, given that both of these have important prognostic implications [30, 31]. Since gross haematuria was more frequent in IgAN/ANCA+ patients, the recovery of renal function that usually follows the disappearance of gross haematuria may have influenced the apparent better response to immunosuppression in this group. Adjustments according to the degree and duration of haematuria have been desirable.

In spite of the retrospective nature of the study and the relatively small number of patients, the adjusted comparison by the presence of crescents, the two control groups (IgAN/ANCA– and AAV) and the comparison between subgroups of patients with crescents strengthen the interest of the study in comparison with the anecdotal case reports and small series of patients previously published [14]. If the coexistence of ANCA in IgAN patients represents overactivation of certain types of autoantibody-producing B-cells, or a second independent disease, cannot be elucidated in this type of study.

In another study, Ring *et al.* [32] described the case of a young man with a Schönlein–Henoch purpura with crescents and deposits of IgA, C3 and C4 in the renal biopsy, who presented as a rapidly progressive glomerulonephritis (RPGN) resistant to therapy with cyclophosphamide, steroids and plasmapheresis. As rescue therapy, despite the lack of evidence of serological or genetic abnormalities in the complement system, treatment with eculizumab was initiated (4 weekly doses of 900 mg and a final dose of 1200 mg). An improvement in renal function was rapidly observed and cyclophosphamide was substituted by azathioprine. A control biopsy at 11 months showed initial signs of chronicity and some cellular crescents.

Due to the role of complement in the pathogenesis of IgAN, anti-complement therapies could have a place in the treatment of IgAN, particularly in aggressive cases resistant to currently

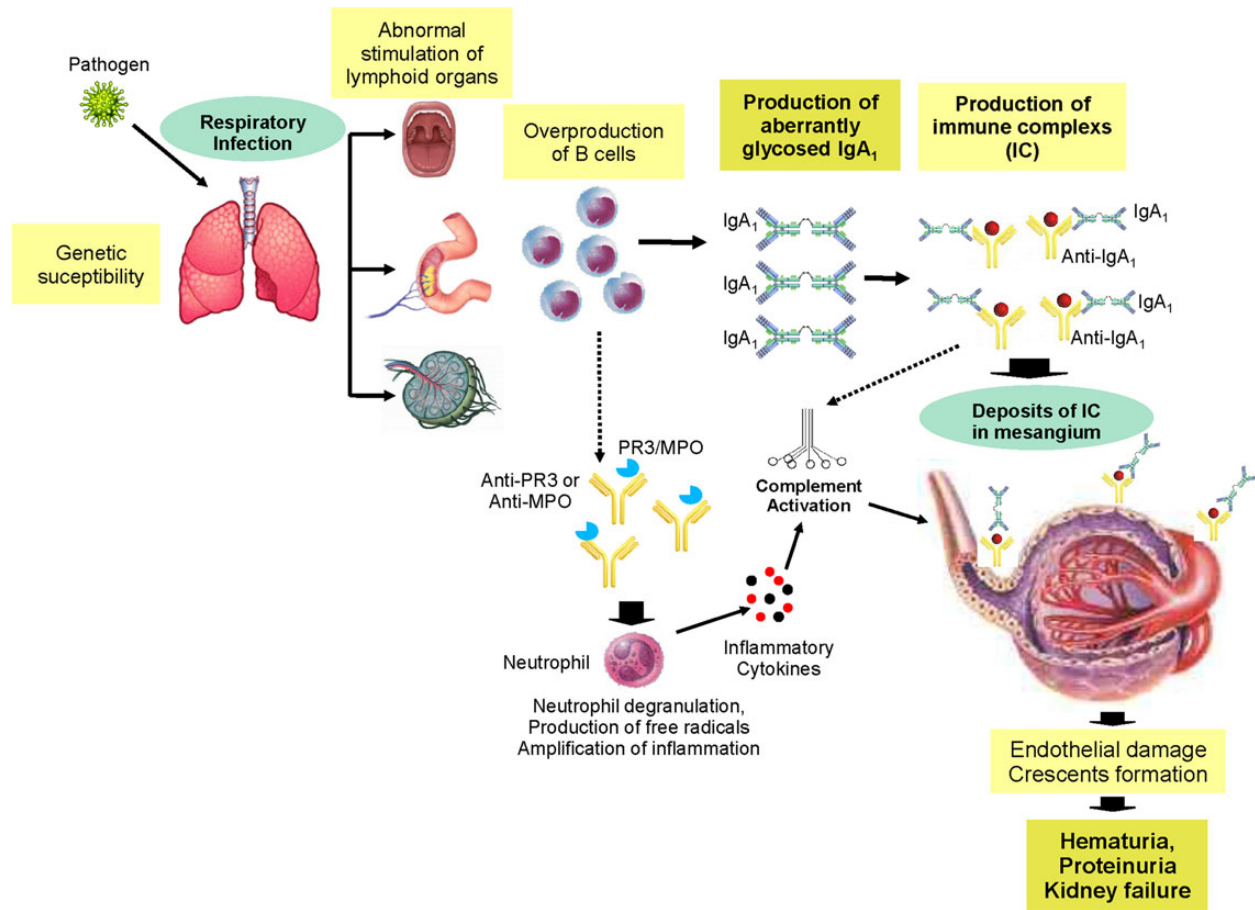


Fig. 1. Main pathogenic mechanisms involved in renal damage in IgA nephropathy. IgA, immunoglobulin A; IC, immune complex; PR3, proteinase-3; MPO, myeloperoxidase.

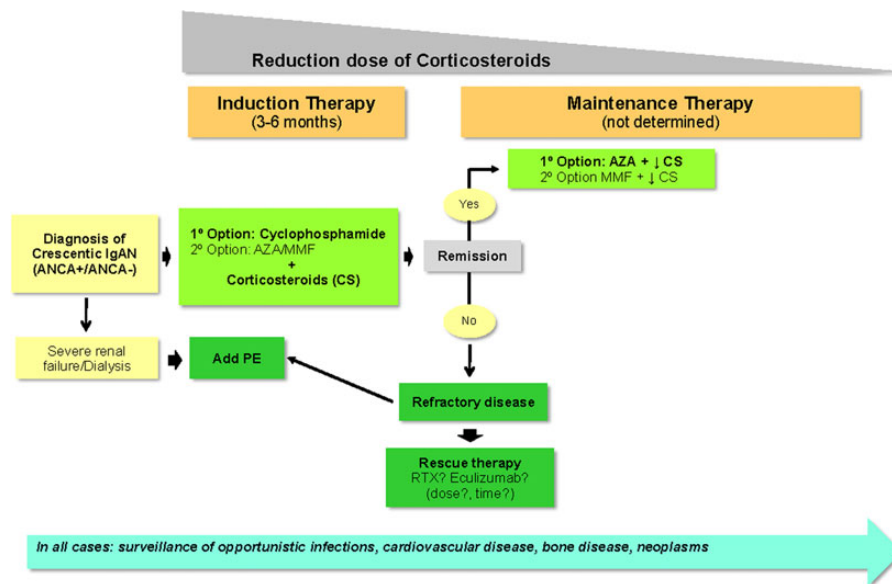


Fig. 2. Current therapeutic alternatives for crescentic IgA nephropathy. ANCA, anti-neutrophil cytoplasmic antibody; AZA, azathioprine; CS, corticosteroids; IgA, immunoglobulin A nephropathy; MMF, mycophenolate mofetil; PE, plasma exchange; RTX, rituximab.

recommended therapies [6]. Positive responses to eculizumab have been reported in complement-mediated glomerulonephritis [33, 34], and the effectiveness of blocking C5a receptors in ANCA vasculitis is now being evaluated by clinical trials [35]. In all these diseases, abnormal activation of complement plays an important role as initiator and amplifier of kidney damage [36–38]. Serum levels of C5b-9 complex, a promising biomarker to monitor complement activation and the response to eculizumab in atypical haemolytic uremic syndrome cases [39], were not measured in this case. Whether the improvement in renal function may have been more complete and sustained with longer eculizumab treatment and if measurement of serum C5b-9 levels could contribute to monitor both disease activity and response to therapy are interesting questions that need further studies. However, the high cost of eculizumab therapy is an important factor to be considered. Larger series of patients with longer follow-up and, ideally, controlled clinical trials comparing eculizumab with other therapies in aggressive types of IgAN are needed. Only such studies may offer solid conclusions about the possible role of eculizumab in rapidly progressive IgAN. Figure 2 shows the current therapeutic alternatives for crescentic IgAN.

(See related articles by Yang *et al.* Clinical features of IgA nephropathy with serum ANCA positivity: a retrospective case–control study. *Clin Kidney J* (2015) 8: 482–488 and by Ring *et al.* Use of eculizumab in crescentic IgA nephropathy: proof of principle and conundrum? *Clin Kidney J* (2015) 8: 489–491.)

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