CASE REPORT

ANCA-positive IgA nephropathy without necrotising or crescentic glomerulonephritis: a clinical conundrum

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SUMMARY

IgA nephropathy, the most prevalent form of primary glomerular disease, usually portends a favourable outcome. Antineutrophil cytoplasmic autoantibodies (ANCA) have been reported in association with IgA nephropathy in a small subset of patients, mostly presenting with rapidly progressive glomerulonephritis and necrotising crescentic lesions. Herein, we describe a case of IgA nephropathy, positive serum cytoplasmic and perinuclear ANCA with anti-myeloperoxidase antibody, and preserved renal function without any histological evidence of necrotising or crescentic glomerulonephritis. Based on available mechanistic and clinical data, we opine that such patients could benefit from close monitoring of renal function.

BACKGROUND

IgA nephropathy, the most prevalent form of primary glomerulonephritis worldwide, is characterised by the predominance of IgA deposits either alone or with IgG and IgM in the glomerular mesangium.¹ The mesangial IgA is exclusively of the IgA1 subclass that is deficient in galactose, a biochemical feature thought to play a key role in the pathogenesis of IgA nephropathy.² While IgA nephropathy manifests generally as stable or slowly progressive kidney disease that is associated with good prognosis at long term, a subset of patients with a more progressive course has been identified. These cases often present clinically as rapidly progressive glomerulonephritis, and the histological examination reveals focal or diffuse necrotising crescentic glomerulonephritis.³ A minute proportion of these patients with severe disease can have circulating antineutrophil cytoplasmic autoantibodies (ANCA); it remains unclear whether these antibodies reflect a mere incidental finding or a novel overlap entity with untoward impact on the outcomes.⁴ Herein, we describe an unusual case of a young patient who presented with cytoplasmic ANCA (C-ANCA) and perinuclear ANCA (P-ANCA) positivity with anti-myeloperoxidase (MPO) antibodies in whom renal histology revealed non-crescentic, non-necrotising mild IgA nephropathy.

CASE PRESENTATION

A 29-year-old woman, who was otherwise healthy, referred to nephrology clinic for evaluation of microscopic haematuria in the setting of positive ANCA in the serum. The patient was planning

pregnancy in near future. History was positive for abdominal pain and microscopic haematuria 2 years before her presentation where she received treatment for presumed urinary tract infection. Six months later, she developed a blanchable rash on her leg with no known inciting factor. It was treated with antibiotics for presumed cellulitis and resolved within a few days. Therefore, no skin biopsy was performed. A few months after that episode, she developed haemoptysis; CT of the chest showed non-specific infiltrates. She was treated for pneumonia but continued to have episodes of mild haemoptysis. P-ANCA and anti-MPO were also found to be positive at that time, whereas anti-glomerular basement membrane antibodies were negative. Bronchoscopy was negative for alveolar haemorrhage, and haemoptysis resolved spontaneously. During this period, her renal function was preserved, although with persistent microscopic haematuria; she never experienced gross haematuria, and there was no history of sinusitis, joint pain, facial rash or signs suggestive of serositis.

INVESTIGATIONS

On presentation to the nephrology clinic, her blood pressure was 124/82 mm Hg, and laboratory data are summarised in [table 1](#). Renal ultrasound was normal.

In the context of persistent microscopic haematuria, history of haemoptysis, positive ANCA, anti-MPO antibodies and positive anti-double stranded DNA (anti-dsDNA) antibodies, kidney biopsy was performed. It revealed mild, global increase in mesangial cellularity and matrix, segmental, granular mesangial staining for IgA and small amount of mesangial electron dense immune deposits, all of which were consistent with IgA nephropathy ([figure 1](#)). Cellular crescents or segmental necrosis were not observed. However, 5 out of the 10 glomeruli were globally sclerosed, and there was minimal tubular atrophy and interstitial fibrosis.

TREATMENT

As her renal function was preserved and proteinuria was minimal, we chose not to treat her with immunosuppressive medications and recommended non-specific anti-proteinuric treatment with inhibitors of renin-angiotensin-aldosterone system.

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Table 1 Laboratory data at presentation

Blood	Results	Reference range
White blood cell count (thousand/mm ³)	6	4–10
Haemoglobin (g/dL)	13.7	12–16
Platelets (thousand/mm ³)	279	150–450
Sodium (mmol/L)	139	136–145
Potassium (mmol/L)	4.1	3.4–5.1
Bicarbonate (mmol/L)	26	22–30
Urea nitrogen (mg/dL)	12	6–20
Creatinine (mg/dL)	0.84	0.4–0.9
Calcium (mg/dL)	9.4	8.0–10.6
Phosphate (mg/dL)	3	2.7–4.5
ANA	Positive (titre NA)	Negative
Anti-dsDNA (IU/mL)	13	0–9
P-ANCA	1:320	<1:20
C-ANCA	1:640	<1:20
Anti-MPO (U/mL)	85.8	0–9
Anti-PR3 (U/mL)	<3.5	0–3.5
C3 (mg/dL)	136	82–167
C4 (mg/dL)	32	14–44
Viral hepatitis panel	Negative	Negative
Urine		
Blood	3+	Negative
RBCs (per HPF)	11	<5
Protein/creatinine ratio (mg/g)	336	<150

ANA, anti nuclear antibody; ANCA, antineutrophil cytoplasmic antibody; Anti-dsDNA, anti-double-stranded DNA antibodies; C-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; NA, not available; P-ANCA, perinuclear antineutrophil cytoplasmic antibody; PR3, proteinase 3; RBCs, red blood cells.

DISCUSSION

In IgA nephropathy, absence of clinical and histological features of severe glomerular disease in the presence of ANCAs is very rare; to the best of our knowledge, it has been reported only once previously.⁵ On the other hand, there have been a few reports of ANCA positivity in the setting of IgA

nephropathy that presented with nephritic sediment, histological picture of crescentic glomerulonephritis and rapidly worsening renal function.^{4–8} Bantis *et al* studied the clinical and histological features of eight patients with ANCA-positive crescentic IgA nephropathy and their response to treatment in comparison to 26 patients with ANCA-negative crescentic IgA nephropathy. Of these, five had anti-MPO, and three had anti-proteinase 3 (PR3) antibodies. All patients presented with clinical syndrome of rapid progressive glomerulonephritis and reached a peak serum creatinine level of 4.2+2.2 mg/dL within the first 3 months as opposed to 2.5+1.9 mg/dL in ANCA-negative patients. Moreover, ANCA-positive patients had a higher percentage of crescentic glomeruli (54.3% vs 34.5%) than those without ANCA. Interestingly, ANCA-positive patients treated with immunosuppressive medications (ie, cyclophosphamide and corticosteroid) experienced significant improvement in kidney function, while ANCA-negative patients did not. Because it is very rare for patients with IgA nephropathy to present with ANCA without any clinical or histological features of crescentic glomerular disease, it remains unclear whether this entity represents a mere coincidence without any pertinent impact on the clinical course or should be regarded as a risk marker for experiencing a less benign course in the future. The finding of significant number of globally sclerotic glomeruli in this young patient with no significant history also raises the question whether the current mildly active processes are indeed the remnants of undetected more severe pathological insults to the kidney in the past.

There are a few additional teaching points embedded in this case. First, the positivity of both P-ANCA and C-ANCA in the presence of anti-MPO antibodies and negative PR3 could reflect the well-known high sensitivity and low specificity of indirect immunofluorescence that could lead to cross reactivity or detection of antibodies against other cytoplasmic antigens apart from MPO and PR3. We recently reported a case of C-ANCA positive with anti-MPO who presented with crescentic glomerulonephritis.⁹ In the current case, it is conceivable that the positivity of both C-ANCA and P-ANCA could also reflect the abundance of other yet undetected auto-antibodies as evidenced by simultaneous positivity of ANA and anti-dsDNA antibodies. Second, ANCAs do not need to

Figure 1 Renal biopsy findings. (A) Light microscopy showing increased mesangial cellularity and matrix. (B) Immunofluorescence showing segmental, granular mesangial staining for IgA. (C, D) Electron microscopy demonstrating small electron dense mesangial and para-mesangial deposits (arrows).

Learning points

- ▶ A minute proportion of patients with IgA nephropathy have circulating antineutrophil cytoplasmic autoantibodies (ANCAs). Whether the presence of these antibodies represents a novel overlap entity or merely a coincidence is not known.
- ▶ Most patients with ANCA-positive IgA nephropathy tend to present with severe disease, that is, rapidly deteriorating renal function and histological picture of crescentic glomerulonephritis.
- ▶ Patients with severe disease respond to treatment with cyclophosphamide and corticosteroids.
- ▶ It remains a clinical dilemma whether to treat patients with stable renal function with immunosuppressive therapy or manage conservatively. In our opinion, these patients should be treated with supportive care and periodic monitoring of metabolic panel and urinalysis. One should have low threshold for repeat renal biopsy and immunosuppressive therapy if they present with acute glomerulonephritis.

be always present at the time of active IgA glomerulonephritis; they could appear later.¹⁰ Thus, it may be worthwhile to periodically monitor the titres of these antibodies especially if there is an unexpected change in the course of the disease. Close monitoring of renal function is of utmost importance if this young woman becomes pregnant, as she has been planning to; patients with even mild degrees of kidney disease or recovered acute kidney injury are at higher risk for adverse pregnancy outcomes due to loss of renal functional reserve.¹¹ In summary, this case is about an unusual presentation of IgA nephropathy with challenging aspects from a mechanistic standpoint and reflects the uncertainties surrounding its long-term monitoring and therapeutic approach. Despite lack of biologic and clinical plausibility for a benefit from immunosuppressive therapy at the present time, it would be prudent to closely monitor her renal function and antibody titres as she could conceivably be at higher risk for adverse renal outcomes.

Contributors AbK: attending nephrologist who treated the patient; drafted the initial version of manuscript. XZ: attending pathologist who provided the images and input on pathological findings. AmK: senior nephrologist who provided input on the management decisions; reviewed and revised the manuscript for critically important intellectual content.

Competing interests None declared.

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