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Single Case

An Unusual Presentation of Myeloperoxidase-Associated Glomerulonephritis and Suspected IgA-Mediated Anti-Glomerular Basement Membrane Disease: A Case Report

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Keywords

Anti-glomerular basement membrane disease · Antineutrophil cytoplasm antibodies vasculitis · IgA · Glomerulonephritis · Case report

Abstract

Introduction: Anti-glomerular basement membrane (GBM) disease is a rare cause of glomerulonephritis usually mediated by IgG antibodies and is associated with ANCA-associated glomerulonephritis in up to 50% of cases. IgA-mediated anti-GBM disease is extremely rare and presents diagnostic difficulties as circulating IgA antibodies will not be detected by standard serological tests for anti-GBM disease. ***Case Presentation:*** We present the case of a 67-year-old man with rapidly progressive glomerulonephritis requiring haemodialysis at presentation. Serological testing was positive for anti-myeloperoxidase and negative for IgG anti-GBM antibodies. Kidney biopsy revealed necrotizing crescentic glomerulonephritis with linear staining of IgA along the GBM. He was treated with a combination of immunosuppression and plasma exchange and was able to become dialysis-independent. ***Conclusion:*** To our knowledge, this is the first documented "double-positive" IgA anti-GBM disease and ANCA-associated glomerulonephritis.

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Introduction

Glomerulonephritis cases with "double-positive" anti-glomerular basement membrane (anti-GBM) and antineutrophil cytoplasm antibodies (ANCA) have long been described with reported outcomes varying across different case series [1]. Double seropositivity is more common with anti-myeloperoxidase (MPO) antibodies. The pathogenesis remains unclear, though it has been proposed that the development of anti-GBM autoantibodies is an epiphenomenon of vasculitic glomerular injury [2].

Anti-GBM disease is most commonly mediated by IgG antibodies to the non-collagenous (NC1) domain of the α3 chain of type IV collagen. Rarely, there have been cases of IgA and IgM-mediated anti-GBM [3].

In all reported cases of "double-positive" disease so far, anti-GBM antibodies belong to the IgG class and have been identified in patients' serum [4]. To our knowledge, we present the first case of concurrent MPO necrotising vasculitis with IgA anti-GBM disease.

Case Report

A 67-year-old man presented with a 1 month history of malaise, dyspnoea, night sweats, and unintentional 9.5 kg weight loss with no changes in urine output. He had a history of hypertension and bowel cancer treated surgically 9 years prior to admission. He was an ex-smoker with a 50 pack-year history and worked as a bus driver. There was no family history of kidney disease.

On examination, the patient was noted to have tonsillar swelling and exudate. His chest was clear to auscultation, and he had no peripheral oedema. His cardiovascular and abdominal examination was unremarkable. He had no rash or joint swelling. On admission, his serum creatinine was 12 mg/dL (1,063 mmol/L) (creatinine was 0.87 mg/dL [77 mmol/L] 1 year prior to admission), urea 112 mg/dL (40.1 mmol/L), serum albumin 34 g/L. Urinalysis revealed 3+ proteinuria and haematuria. ANCA serology was positive for anti-MPO with titres more than 134 mmol/L. IgG anti-GBM antibodies were not detected by enzyme-linked immunosorbent assay. Complement C3 and C4 levels were within normal range, and no paraprotein was evident on serum electrophoresis. Anti-double-stranded DNA antibodies and antineutrophil antibodies were not detectable. Ultrasound revealed a 12- and 13-cm kidney without hydronephrosis.

Kidney biopsy was performed on day 2 of hospital admission, and he was commenced on haemodialysis. The provisional biopsy report was consistent with crescentic glomerulonephritis. Forty-two glomeruli were present, 32 of which (76%) had cellular crescents, there was some evidence of fibrinoid necrosis, and 2 had associated rupture of Bowman's capsule (shown in Fig. 1). Therefore, the patient was initiated on treatment for ANCA-associated crescentic glomerulonephritis with 3 days of pulsed methylprednisolone followed by intravenous cyclophosphamide according to the CYCLOPS protocol [5].

He received a total of 4 haemodialysis sessions but was not at this stage treated with plasma exchange, before his urine output and chemistry improved with a creatinine of around 5 mg/dL (450 umol/L) and renal replacement therapy was discontinued.

Due to the patient's history of significant weight loss, a CT chest, abdomen, and pelvis was performed to investigate possible malignancy. CT revealed an incidental thrombus in a branch of the left renal vein supplying the upper pole of the kidney. The patient was initially anticoagulated with heparin infusion to manage his renal vein thrombus. While on therapeutic anticoagulation, he had an episode of haemoptysis with ground glass opacities on CT chest suggestive of mild alveolar haemorrhage.

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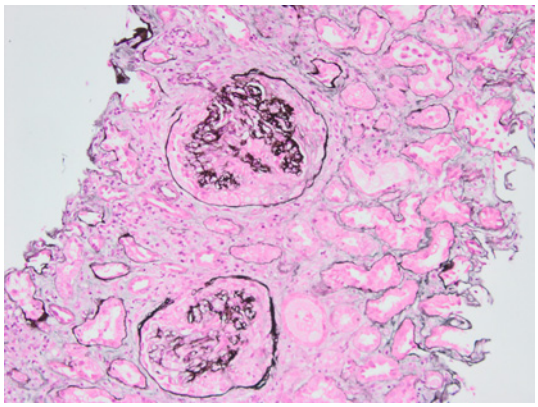

Fig. 1. Silver-stained section showing active cellular circumferential crescents with focal rupture of Bowman's capsule.

When the immunochemistry biopsy results became available, linear IgA staining of the glomerular capillary walls was demonstrated (shown in Fig. 2), suspicious of concurrent IgA anti-GBM disease; all other routine stains, including C3, were negative. In light of this and presence of alveolar haemorrhage, and despite the absence of a laboratory test to enable detection of possible circulating anti-GBM IgA, a decision was made to empirically treat for anti-GBM disease with 10 cycles of plasma exchange.

On day 16, the patient was able to be discharged from hospital with a creatinine of 3.54 mg/dL (313 mmol/L). He was followed up in Nephrology Clinic and following completion of induction treatment with a total of 6 doses of intravenous cyclophosphamide, he received maintenance azathioprine therapy and a reducing dose of prednisolone. At 6 months, his renal function had stabilised with an estimated glomerular filtration rate of 33 mL/min, and MPO remained low-level positive without any manifestations of active disease.

Nevertheless, at 7 months, he was admitted overtly septic to hospital with bilateral pneumonia and type 1 respiratory failure. COVID PCR was negative on 3 consecutive occasions, and an opportunistic infection was suspected, but no pathogen was identified. The patient was admitted to intensive care, where he sadly died a few days later. Of note, the CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538973).

Discussion

Anti-GBM disease is a rare small vessel vasculitis, with an incidence of approximately 1 per million per year. It is usually mediated by IgG antibodies targeting the non-collagenous domain of α3 chain of type IV collagen. Anti-GBM disease mediated by IgA is even less common with only a few cases documented in the literature [6–16]. To the best of our knowledge, this is the first case ever reported of dual positive IgA anti-GBM and ANCA MPO vasculitis.

Among patients with standard (IgG) anti-GBM disease, 10–50% have also positive ANCA serology, most commonly MPO, and may also present signs of a systemic vasculitis [1, 17]. It appears that renal prognosis is relatively better in double-positive ANCA and anti-GBM disease than single anti-GBM but possibly worse than those with severe single ANCA vasculitis; however, overall survival does not seem to differ. It is recommended that in double-positive cases, following induction treatment for anti-GBM, maintenance treatment is administered to prevent an ANCA relapse [18]. The mechanism of association between ANCA

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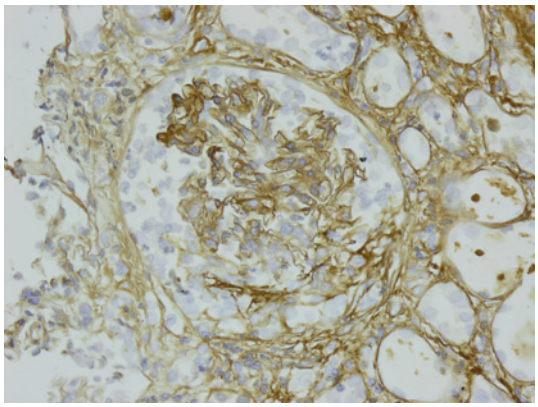

Fig. 2. IgA immunoperoxidase stain section showing linear IgA staining of the glomerular capillary walls (×200 magnification).

and anti-GBM disease remains unclear, but some studies have suggested that the ANCA positivity predates the anti-GBM disease, and therefore the ANCA-associated vasculitis could act as a trigger for anti-GBM disease. One possible mechanism is inflammatory damage to the GBM during ANCA-positive glomerulonephritis exposing epitopes resulting in development of anti-GBM antibodies [12].

Of the reported IgA anti-GBM cases, the majority are male, and age at presentation ranges from 35 to 74 years old [6–16]. Most commonly, patients present with rapidly progressive glomerulonephritis, and variable degrees of crescents are noted on renal biopsy. Overall, renal and survival outcomes are poor, and, though direct comparisons are limited by small number of cases, overall prognosis appears worse than in IgG anti-GBM disease [13].

IgA anti-GBM disease presents diagnostic challenges as standard serology will only detect IgG anti-GBM antibodies and can result in delays to treatment while awaiting biopsy and immunofluorescence in patients with seronegative with rapidly progressive glomerulonephritis. In other reported cases, attempts to detect IgA anti-GBM antibody in serum have been successful, but there were no means for such an attempt with our patient.

Our patient presented with 1 month of symptoms consistent with a systemic inflammatory response in keeping with ANCA-associated vasculitis. The biopsy showed linear IgA staining on GBM, but in the absence of positive serology, anti-GBM disease can only be speculated. At presentation, despite severe renal impairment, urine output was maintained, and haemodialysis discontinued after 4 sessions. At 6 months from diagnosis, his renal function had substantially improved and stabilised; his renal outcome censored at 6 months appeared better than reported in the literature for IgA anti-GBM. The patient also had a mild alveolar haemorrhage that could be the result of either disease process. His death was most likely driven by infection secondary to intense immunosuppression highlighting the constant need to balance the risk of disease against the risk of treatment in these patients.

To the best of our knowledge, this is the first documented “double-positive” case involving IgA anti-GBM disease. Strikingly, this case is the only documented recovery of renal function in IgA anti-GBM disease requiring renal replacement therapy on presentation. However, treatment complications may have contributed to his death. Such cases highlight the continued need to understand better the exact pathological sequence and contribution of ANCA and anti-GBM antibodies in double-positive cases but also the challenge to establish an accurate and timely diagnosis of IgA anti-GBM disease in the absence of a widely available serological test.

Statement of Ethics

This case report study did not require ethical approval according to local guidance. Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying image.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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No funding was received for this study.

Author Contributions

C.T.B. collected data of case and drafted the manuscript; S.S., K.V., K.B., and C.H. reviewed, edited, and approved the manuscript; and E.L. designed work, reviewed, edited, and approved the manuscript.

Data Availability Statement

The data that support this study are not publicly available due to patient confidentiality but can become available from Dr. Eirini Lioudaki upon reasonable request.

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