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IgA mediated anti-glomerular basement membrane disease with associated circulating anti-neutrophil cytoplasm antibodies

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ABSTRACT

Anti-glomerular basement membrane (anti-GBM) disease is an aggressive small vessel vasculitis usually mediated by IgG autoantibodies. We describe the case of a 73-year-old male with rapidly progressive renal failure that was diagnosed with IgA mediated anti-GBM disease associated with circulating anti-neutrophil cytoplasm antibodies (ANCA), where the diagnosis was established on kidney biopsy by detecting linear deposition of IgA along the GBM on immunofluorescence microscopy. Despite an intensive immunosuppressive regimen with plasmapheresis, steroids and oral cyclophosphamide, the disease progressed to end-stage renal failure and the patient was started on hemodialysis.

Case Report

Implication for health policy/practice/research/medical education:
This case-report illustrates the diagnosis and treatment of an IgA mediated form of anti-glomerular basement membrane disease, a rare entity with only 13 cases reported in the literature. Furthermore, this is the first and unique case of IgA-mediated anti-GBM associated with positive circulating ANCA, a novel finding of important clinical value, paired with an education value for nephrology trainees and literature review.

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Introduction

Anti-glomerular basement membrane (anti-GBM) disease is a rare small vessel vasculitis that presents with rapidly progressive glomerulonephritis, sometimes associated with alveolar hemorrhage and histologically characterized by crescentic glomerulonephritis. The hallmark of anti-GBM disease is the presence of circulating and deposited antibodies directed against basement membrane antigens, typically IgG autoantibodies directed against the non-collagenous domain of the α3 chain of type IV collagen (1). Although very rare, variants of anti-GBM disease mediated by different classes of immunoglobulins, like IgA, have been reported in the literature (2). We describe a case of IgA mediated anti-GBM disease in association with circulating anti-neutrophil cytoplasm antibodies (ANCA).

Case Presentation

A 73-year-old white man has presented with progressive fatigue, asthenia and weight loss for one month. The patient's past-medical history included well-controlled hypertension and paroxysmal atrial fibrillation under apixaban. He had no history of kidney disease and an unremarkable family history.

Investigation revealed new-onset acute kidney injury with serum creatinine of 4.49 mg/dL, serum urea of 91 mg/dL, normocytic normochromic anemia (hemoglobin level of 8.5 g/dL, with absence of iron deficiency or other nutritional deficiencies) and elevated erythrocyte sedimentation rate (69 mm/h). Urine examination revealed non-nephrotic proteinuria, hematuria and leukocyturia. Urine culture was negative.

Immunological test results were positive for ANCA anti-

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MPO with a titer of 74.4 UQ and negative for circulating IgG anti-GBM autoantibodies, ANCA anti-PR3 and antinuclear antibodies (ANA). Complement C3 and C4 levels were normal. Serum and urine electrophoresis showed no monoclonal immunoglobulins or light chains. Additionally, HIV, hepatitis B and hepatitis C serologies were negative. Prostate-specific antigen was elevated (11 ng/mL).

Ultrasound examinations revealed normal kidneys. Chest X-ray showed no abnormalities and computed tomography ruled out alveolar hemorrhage or other lesions.

Following renal biopsy, light microscopy identified 14 glomeruli, one with fibrocellular crescents (Figure 1) and two with fibrinoid necrosis lesions (Figure 2), without significant interstitial fibrosis. Indirect immunofluorescence, conducted on frozen tissue sections, showed linear GBM staining for IgA, kappa and lambda. IgG was negative and C3 was weakly positive, but with granular appearance (Figure 3, a-e, respectively).

Based on clinical evolution and laboratory and also radiological findings, the patient was first started on steroids (intravenous methylprednisolone 500 mg/d during three days followed by oral prednisolone 60 mg/d (corresponding to 1 mg/kg) and intravenous cyclophosphamide (500 mg/m^2). However, two weeks later, the renal biopsy results prompted us to alter the initial approach. The patient maintained on oral prednisolone; however, oral cyclophosphamide (2 mg/kg/d) was started. Then we conducted six plasma exchange sessions with 5% human albumin solution in consecutive days.

Despite the implemented therapy, kidney function continued to aggravate and he was started hemodialysis two months after the onset of the disease. According to the immunosuppression related infections and a prostate biopsy later revealing prostatic adenocarcinoma (Gleason score 3+3=6), paired with a lack of improvement in the renal function, we decided to stop immunosuppressive therapy.

Discussion

Anti-GBM disease is a rare disease, with an incidence of one per million population/year in European populations (1). IgA mediated forms of this disease are even rarer, with only 13 cases reported in the literature (Table 1) (2–15).

IgA-mediated anti-GBM disease, similarly to the classical form of the disease, is characterized by a pulmonary-renal syndrome. All of the cases described in the literature presented with features of rapidly progressive

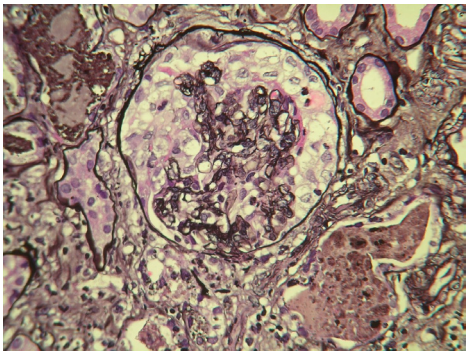

Figure 1. Renal biopsy showing one fibrocellular crescent (methenamine silver, ×400).

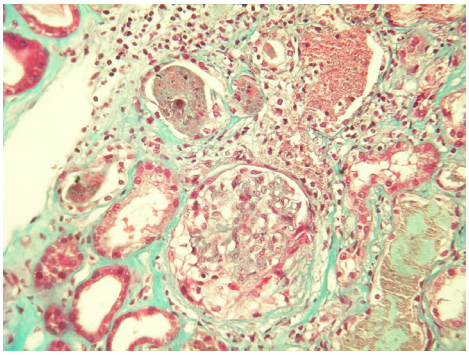

Figure 2. Renal biopsy showing fibrinoid necrosis lesions (Masson's trichrome, ×200).

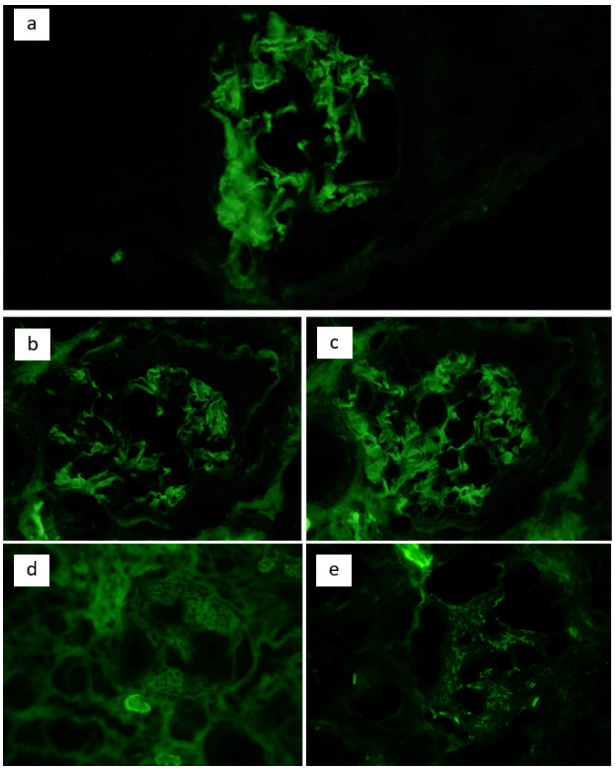

Figure 3. Immunofluorescence x400, showing linear glomerular basement membrane staining for IgA (a), kappa (b) and lambda (c). IgG was negative (d) and C3 was weakly positive with granular appearance (e).

Table 1. Published cases in the literature

Reference	Age/Gender	Serum creatinine	Alveolar hemorrhage	Initial Treatment	Outcome
Present case	73/M	4.49	No	CS, CYC, PE (6)	HD
Antonelou et al 2019	37/M	12.53	No	CS, MMF, PE	HD → KT with no recurrence
Bacalja et al 2018	67/M	3.54	No	CS, CYC, PE (12)	HD
Wen et al 2013	65/M	2.8	Yes	CS, CYC, PE (2)	HD
Ke et al 2012	70/M	4.0	Yes	CS, CYC, PE	HD
Moulis et al 2012	49/M	6.1	No	CS, CYC, PE	HD → KT with no recurrence
Ho et al 2008	74/F	1.25	No	CS, CYC	Persistent kidney dysfunction
Shaer et al 2003	35/M	20	No	CS, PE	Death
Ghohestani et al 2003	72/M	5.6	No	CS, CYC, PE	PD
Carreras et al 2002	69/M	3.8	Yes	CS, IVIg	Death (after 2 days)
Maes et al 1999	67/M	3.0	No	CS, CYC	Death (after 1 month)
Fervenza et al 1999 + Borzaet al 2005	54/M	1.2	Yes	CS, CYC, PE	KT with recurrence after 2 years
Gris et al 1991	62/M	9.0	No	CS, AZA	HD
Border et al 1991	55/M	Unknown	Yes	CS, AZA	Death

M: Male, F: Female, CS; Corticosteroids, CYC; Cyclophosphamide, PE; Plasma exchange, MMF; Mycophenolate mofetil, IVIg; Intravenous immune globulin, AZA; Azathioprine, HD; Hemodialysis, PD; Peritoneal dialysis, KT; Kidney transplant.

glomerulonephritis, with alveolar hemorrhage present in 5 of the 12 cases (6,9,10,14,15). In all cases, the histology was consistent with crescentic glomerulonephritis and demonstrated linear GBM staining with IgA, similar to our case.

The pathophysiology of IgA-mediated GBM disease is not entirely understood. In contrast with IgG-mediated anti-GBM disease, the autoantigen may be more heterogeneous and directed towards different epitopes, although the specificity of IgA anti-GBM antibodies has seldom been characterized in the published cases. Standard assays for anti-GBM antibodies can only detect IgG antibodies, failing to detect other classes of immunoglobulins, thus, the recognition of this disease depends on detecting linear staining of IgA on GBMs using immunofluorescence microscopy on the kidney biopsy, making the biopsy an essential step. There is however a drawback in relying on the kidney biopsy results to make the right diagnosis, the results may take several days, delaying the diagnosis and adequate therapy with possible prognostic implications.

Comparing to the IgG-mediated anti-GBM disease, IgA-mediated anti-GBM disease has a poorer prognosis, with persistent renal dysfunction in all the described cases, most of them leading to end-stage renal failure, despite immunosuppressive therapy. IgA-mediated anti-GBM disease is treated similarly to the classic form of the disease, with a triple regimen of plasmapheresis, steroids and oral cyclophosphamide. However, with only a few published cases and with all of them developing end stage renal disease, it is possible that this variant of anti-GBM disease may require a different and more specific approach. In our case, the initial treatment was directed towards a suspected ANCA-associated vasculitis, given the positive ANCA anti-MPO. However, after the immunofluorescence findings, we adjusted the immunosuppressive regimen to the above-mentioned triple regimen. Unfortunately, the outcome of our patient did not differ from the ones reported in the literature, with our patient starting hemodialysis two months after the onset of the disease. Kidney transplantation is a treatment option for patients who develop end-stage renal disease caused by anti-GBM disease, with most centers recommending a period of at least six months of sustained seronegativity for GBM antibody before undertaking transplantation, in order to reduce the risk of recurrence in the allograft (1). In IgA mediated anti-GBM disease, this constitutes a challenge in itself because monitoring of IgA GBM antibody is not possible by standard assays. In the literature, three patients with IgA-mediated anti-GBM disease underwent renal transplantation (2-4), with one of them (4) recurring two years after transplantation.

Co-presentation with other kidney diseases such as ANCA-associated vasculitis is well established for the classical form of anti-GBM disease, in some series, almost half of patients with GBM disease have detectable ANCA.

The mechanism of this association is unclear, although it has been hypothesized that ANCA-induced glomerular inflammation may be a trigger for the development of an anti-GBM response, possibly by exposing GBMs epitopes that are usually sequestered (1). To our knowledge, we describe the first documented case of a "double-positive" patient for IgA anti-GBM antibodies and ANCA. It is possible that this patient may have the characteristics of the typical "double-positive" patients: the early morbidity and mortality of anti-GBM disease requiring aggressive immunosuppressive therapy combined with the higher risk of relapse of ANCA-associated vasculitis warranting more careful long-term follow-up and maintenance immunosuppression.

Conclusion

IgA-mediated anti-GBM is extremely rare and presents as a challenge for diagnosis and for therapeutic approach, with very poor renal prognosis despite intensive immunosuppressive therapy. To our knowledge, this is also the first case of IgA-mediated anti-GBM associated with positive circulating ANCA, the implications of such are yet to be known.

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All authors have seen this version and approve of the submission.

Authors' contribution

PA was the principal investigator of the study, responsible for conceptualization, methodology, investigation and writing of the original draft. MG, TP, DC and FN participated in the review and editing of the final draft of the manuscript, as well as visualization, supervision and project administration. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This case report was conducted in accord with the World Medical Association Declaration of Helsinki. The patient has given us a written informed consent for publication as a case report. Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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