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An unusual blend; IgA nephropathy and anti GBM disease

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ABSTRACT

Anti-glomerular basement membrane (anti-GBM) disease is a rare illness with a wide spectrum of clinical manifestations. The typical presentation (90% of cases) of anti-GBM is with a rapidly progressive glomerulonephritis (RPGN) in conjunction with pulmonary disease in 25-60% of cases. In its atypical form – seen in 10% of cases, anti GBM disease takes on a chronic form, presenting with long standing renal dysfunction, proteinuria and better renal prognosis when compared to the typical form of the disease. The known associations of anti-GBM disease are with anti-neutrophil cytoplasmic antibody (ANCA)vasculitis and membranous nephropathy. In this case report, a young lady with atypical anti-GBM disease is described with a most unusual association with IgA nephropathy. This association is rare and only described in few case reports worldwide. The possible pathogenesis, clinical features, treatment and outcome of this disease are also elucidated.

Case Report

Implication for health policy/practice/research/medical education:
Anti-glomerular basement membrane (Anti-GBM) disease is commonly associated with anti-neutrophil cytoplasmic antibody (ANCA) vasculitis and membranous nephropathy. It is association with IgA nephropathy is very unconventional. Traditional anti-GBM assays often do not detect the same from plasma since the antibodies are directed against a different antigenic target. The disease is less aggressive and renal prognosis is better than conventional anti-GBM disease.

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Introduction

Anti-glomerular basement membrane (Anti-GBM) disease is a rare disease with an incidence of one per million (1). In this case report we describe a patient with atypical anti-GBM disease in association with IgA nephropathy and review literature of associations between IgA and anti-GBM disease. This combination has been reported in very few cases worldwide.

Case Presentation

A 34-year-old lady presented with gross hematuria for 2 months. There had been no pain, fever, dysuria, calculi in urine or skin rash associated with her symptoms. Her blood pressure was normal. Moreover, urine sediment showed red blood cell (RBC) casts, significant hematuria (urine RBC of 232/hpf) and nephrotic range proteinuria (Tables 1 and 2). Serum creatinine at presentation was 3.4 mg/dL and had remained stable over a 2-month period. Urine culture showed no growth and ultrasound revealed normal sized kidneys and a non-obstructed pelvicalyceal system.

Renal biopsy showed 21 glomeruli, three were sclerosed. There were cellular to fibrocellular crescents in six glomeruli (Figures 1A and 1B). The interstitium showed moderate infiltrates of lymphocytes and plasma cells. Immunofluorescence showed arborizing focal mesangial and capillary wall deposits of IgA3+ and C3+ (Figure 1C), along with linear basement membrane positivity for IgG 3+ (Figure 1D).

There was no pulmonary haemorrhage on computed tomography. Serology for antinuclear antibodies, complements, anti-GBM antibodies were negative. She was diagnosed to have a combination of atypical anti-GBM disease with IgA nephropathy and was started on

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Table 1. Blood evaluation

Lab Parameter	Value in SI units
Hemoglobin	10 g/dL
Total counts	9800/cumm
Platelets	2.34 lakh/cumm
Creatinine	3.5 mg/dL
BUN	48 mg/dL
Sodium	136 mmol/L
Potassium	3.6 mom/L
Bicarbonate	17 mmol/L
Chloride	109 mmol/L
Total bilirubin	0.31 mg/dL
Direct bilirubin	0.05 mg/dL
Total protein	6.9 g/dL
Albumin	3.1 g/dL
SGOT	10 U/L
SGPT	6 U/L
ALP	97 IU/L
ANA (IF)	Negative
C3	95 mg/dL
C4	20 mg/dL
cANCA (Elisa)	10.71 RU/mL (negative)
pANCA (Elisa)	7.02 RU/mL (negative)
Anti-GBM antibody (IF)	1 RU/mL (negative)

BUN, blood urea nitrogen; SGOT, serum glutamic oxaloacetic transaminase; SGPT, Sserum glutamic pyruvic transaminase; ALP, alkaline phosphatase; ANA, antinuclear antibodies.

Table 2. Urine evaluation

Lab Parameter	Value in SI units
Urine RBC	132/hpf
Urine WBC	4/hpf
Urine protein on dipstick	4+
Urine PCR	5.1
Urinary Casts	RBC casts present
Urine Culture	No growth

RBC, Red blood cells; WBC, white blood cell; PCR, polymerase chain reaction.

Table 3. Trajectory of creatinine over time

Month	Creatinine value in mg/DL
July 2021	3.4
September 10	3.5
September 24	2.4
October	1.5
December 2021	1.1

immunosuppression along with plasma exchange. A total of five plasma volumes were exchanged over 10 days with albumin and fresh frozen plasma (FFP) replacement. She was given 60 mg of prednisolone (1 mg/kg body weight) and 120 mg of cyclophosphamide (2 mg/kg) for three months. She showed clinical improvement with no further episodes of gross hematuria. Her creatinine and proteinuria showed a declining trend with decrease in protein creatinine ratio (PCR) from 5.1 to 3.2 over three months (Table 3).

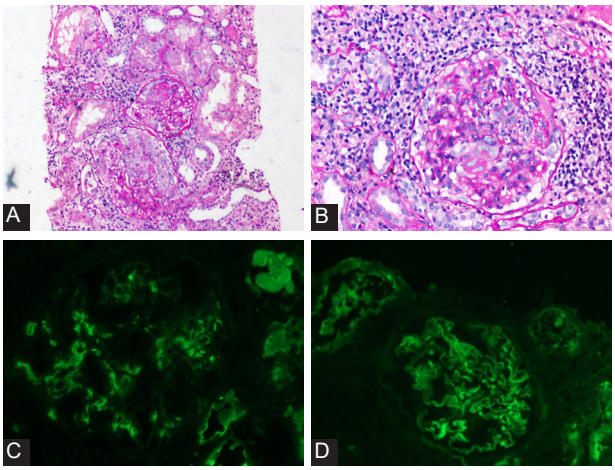

Figure 2. (A) Light microscopy view with PAS stain 100× magnifications showing proliferative glomerulonephritis with segmental necrotizing lesions and segmental cellular crescents variably compressing the underlying glomerular capillary tuft. **(B)** Light microscopy with PAS stain at high power 400× showing proliferative glomerulonephritis with segmental necrotizing lesions. **(C)** Immunofluorescence staining of slide with IgA showing arborizing deposits of IgA 3+ within the capillary walls and mesangium. **(D)** Immunofluorescence staining of slide with IgG stain showing linear deposits of IgG 3+ along the glomerular basement membrane in the pattern pathognomic of anti-GBM disease.

Discussion

This patient had definitive evidence of IgA nephropathy on immunofluorescence of the renal biopsy. Recurrent episodes of gross hematuria and the mesangial proliferation on the renal biopsy further confirm the diagnosis of IgA nephropathy. Recent studies have established certain new prognostic markers in IgA nephropathy such as an increased serum IgA/C3 ratio (2) or low IgG levels (3).

Anti-GBM disease refers to a pulmonary –renal syndrome caused by antibodies to α3 Col 4 directed at the GBM. The pathognomonic finding in anti-GBM disease is the linear deposition of IgG along the basement membrane (4). Although the clinical presentation of anti-GBM disease is typically that of a rapidly progressive glomerulonephritis (RPGN), this patient had a more indolent course with stable renal function over two months, heavy proteinuria and normal urine output. There was no pulmonary involvement also. These findings suggested an atypical anti-GBM disease (5).

The combination of IgA and anti-GBM disease is rare and reported in only a handful of cases worldwide (6). Anti-GBM has been linked with ANCA vasculitis in 21-47% of cases and also with membranous nephropathy

in literature (7). Review of literature divulges that IgA in combination with anti-GBM disease usually does not have pulmonary involvement or oliguria and has better renal prognosis than isolated anti-GBM disease. Crescents are seen on the renal biopsy in only 59% of cases – less often than in typical anti-GBM disease. In 60% of cases there is improvement in renal function with only 30% being dialysis dependant after treatment (8).

The proposed pathogenesis is that structural changes inflicted on the GBM by the immune complex deposits of IgA, leave the GBM antigens exposed. These previously sequestered antigens then act as triggers for development of anti-GBM antibodies. This is similar to the suggested pathogenesis of ANCA with anti-GBM disease (9).

In IgA mediated Goodpasture's syndrome, the antibodies to anti-GBM are IgA and directed against different anti-GBM antigens (α5, α2, α4). Serology is often negative for typical anti-GBM antigens since assays are not geared to detecting the different antigenic target (10).

Conclusion

IgA with anti-GBM is rare entity. The clinical course is indolent when compared with isolated anti-GBM disease and the combination disease portends a better prognosis than isolated anti-GBM disease. The standard of care in these cases is not known. Most patients are treated with immunosuppression and plasma exchange.

Authors' contribution

Conceptualisation: EI, MJ.
Methodology: All authors.
Validation: NJ, EI.
Investigation: NJ, EI, MB, SSR.
Resources: NJ, MB, SSR, MJ.
Data curation: All authors.
Writing: NJ, SSR.
Writing reviewing and editing: all authors.
Visualization: NJ, EI, MB, MJ.
Supervision: EI, MJ.
Project administration: EI.

Conflicts of interest

The authors declare there is no conflict of interest.

Ethical issues

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

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