

Combination of Anti-Glomerular Basement Membrane Antibodies & Anti-Neutrophil Cytoplasmic Antibodies: A Curious Presentation in a Child- Case Report

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Abstract: Anti-GBM disease is *rare* in all age groups. Available data estimate the annual incidence of anti-GBM disease as one case per million in the general population, and this disorder is even less common in children. It is characterized by the presence of circulating auto antibodies to the GBM and linear deposition of immunoglobulin G (IgG) along the GBM and alveolar basement membrane. Anti-GBM disease is the most *aggressive* form of RPGN and may involve the kidneys alone (Good pasture disease), or be accompanied by pulmonary hemorrhage (Good pasture syndrome). Circulating antibody level in anti-GBM disease correlates with the severity of renal disease and serum creatinine concentrations. Unless the diagnosis is made early and therapy is instituted promptly, anti-GBM disease rapidly progresses to renal failure and end-stage renal disease (ESRD), with a fatal outcome in approximately one-half of all cases. We observed anti-GBM disease in a 13-year-old female child. We present this case of renal failure with anti-GBM and p-ANCA antibodies positive. This patient with dual antibodies is considered to be a vasculitis-variant of anti-GBM antibody nephritis. This patient had a typical presentation, and she presented late to hospital. Recurrence rate is expected to be higher in such patients. We reviewed the literature of cases and studies on crescentic glomerulonephritis with anti-GBM and p-ANCA positive

Keywords: RPGN, anti GBM antibodies, end stage renal disease

1. Introduction

Anti-GBM antibody disease is one of the three major forms of rapidly progressive (or crescentic) glomerulonephritis. Although some patients present with relatively mild renal insufficiency, this disorder is typically associated with severe renal injury that, if untreated, progresses quickly to end-stage renal failure. An important determinant of the response to therapy and long-term prognosis is **early diagnosis** [1, 2]. There is a direct correlation between the initial plasma creatinine concentration and the percent of glomeruli with crescents; in particular, crescents are present in more than 75 percent of glomeruli when the plasma creatinine concentration is above 5 mg/dL (442 micromol/L).

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) and anti-glomerular basement membrane (GBM) disease, the typical autoimmune diseases causing necrotizing crescentic glomerulonephritis (CrGN), have been reported in elderly patients. However, since the establishment of standard assays to screen for serum ANCA and anti-GBM autoantibodies, patients with the two diseases were increasingly identified and studied. [3, 4]. Prevention of end-stage renal disease (ESRD) can usually be achieved

in less severe cases, although some do progress. The proportion of preserved glomeruli and the presence of oligo-anuria may be the best determinants of prognosis. [5]

We report a 13 -year-old female child presenting with double antibody positive crescentic glomerulonephritis, who remained hemodialysis-dependent despite aggressive therapy & was discharged home on renal replacement therapy.

2. Case Summary

A 13-year-old, non-Saudian girl was referred from a local hospital with history of generalized body swelling and oliguria for five days prior to admission. She was healthy till 5 days prior to admission at a local central hospital when she developed generalized body swelling that started in the face and periorbital area, and then progressed to involve the body, became significant in lower limbs and was associated with oliguria. Upon review of medical history, it was remarkable for headache and mild recurrent, self-limited epistaxis that lasted for 2 months. No fever, fatigue, hemoptysis, or diarrhea mentioned by the parents during the course of disease. There was no history of change of urine colour, UTI

infection, joint pain, skin rash, or photosensitivity. No history of previous medical or surgical conditions that required hospitalization & no family history of renal disease.

In that hospital she was found to be edematous, anuric with high blood pressure and acute renal failure (creatinine: 700mmol/L), so, was admitted to pediatric intensive care unit, central line catheter inserted and hemodialysis initiated, given first dose of pulse therapy (methylprednisolone 1 gram IV) as a suspected case of rapidly progressive glomerulonephritis, referred to our hospital as a higher center for further work up and management.

In our centre, patient was assessed, she looked puffy, weak and pale, with an average body built, her weight: 45 kg on 50th centile, height: 149 cm on 25th centile and blood pressure 150/100 above 95th centile. Other vital measurements were unremarkable. She had bilateral lower limb pitting edema and labial edema. Other systemic examination: unremarkable. Urine dipstick test protein +2, RBC +4.

Case was admitted to pediatric nephrology ward, managed as acute renal failure. Work up for rapidly progressive glomerulonephritis was requested, CBC result: Hb: 7.3g/dl MCV: 68 fl MCH: 23pg RDW: 24.2 % Reticulocyte count: 1.36 % WBC: $10.32 \times 10^9/L$, PLT: $318 \times 10^9/L$, PT: 14.1 sec, INR: 1.2, PTT: 28.9 sec, S.Ferritin: 165 ng/ml, transferrin saturation 45%. Renal function tests: urea: 21.4 mmol/L, creatinine: 488 umol/L, sodium: 140 mmol/L, potassium: 4.34 mmol/L. Urine protein / creatinine ratio: 305mg/mmol (nephrotic range proteinuria).

Serumcalcium: 2.23 mmol/L, phosphorus: 1.63 mmol/L magnesium: 0.80 mmol/L, ALT: 3.7U/L, AST: 8.4 U/L, serum albumin: 37.4.

Serology lab: C3: 0.957g/L, C4: 0.2g/L: both within normal rang, ASO titer: 148 IU/mL.

Nuclear lab: PTH: 44 pmol/L[high].

Imaging: US abdomen: Mildly increased renal cortical echo pattern, grade I. X-ray left knee & left hand were requested for chronicity of disease: Diffuse decrease of bone density (osteopenic appearance) with exaggerated bone trabeculation. Findings are suggestive of renal osteodystrophy. Echo cardiogram: normal cardiac anatomy and function.

Fluid was restricted as renal regimen (insensible water loss plus urine output), blood pressure was controlled with renal replacement therapy and diuretics, we continued pulse

therapy methylprednisolone 30 mg /kg/dose once per day for five days. Renal biopsy was urgently done on next day. First dose of immunosuppressant drugs (intravenous cyclophosphamide 500 mg /m²) was received on 4th day of admission.

Renal biopsyresult showed:

Gross Description:

The specimen is received in saline, site unstated. It consists of three cores of soft tissue, the largest core measuring 0.1 x 0.1 x 1.5 cm. Portions has been taken for EM and DIF and the remaining tissue is entirely submitted in one cassette.

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Microscopic Description:

The tissue is examined with H&E, PAS, Trichrome, and Jones Silver stains. The biopsy consists of renal cortex and medulla. Seventeen glomeruli are present for evaluation, seven reveal global sclerosis and ten reveal segmental sclerosis. There is mild to moderate interstitial fibrosis and tubular atrophy (20-30% of the cortical tissue), associated with mild interstitial mononuclear inflammatory cell infiltrate admixed with few plasma cells. Arteries show mild intimal fibroelastosis. Arterioles are unremarkable.

Immunofluorescence

Up to five glomeruli are present for evaluation. The glomeruli show linear capillary staining with antiserum specific for IgG (2+). There is no significant glomerular staining with antisera specific for IgA, IgM, C3, C1q, fibrinogen, and Kappa and Lambda light chains. No extraglomerular staining seen.

Electron Microscopy

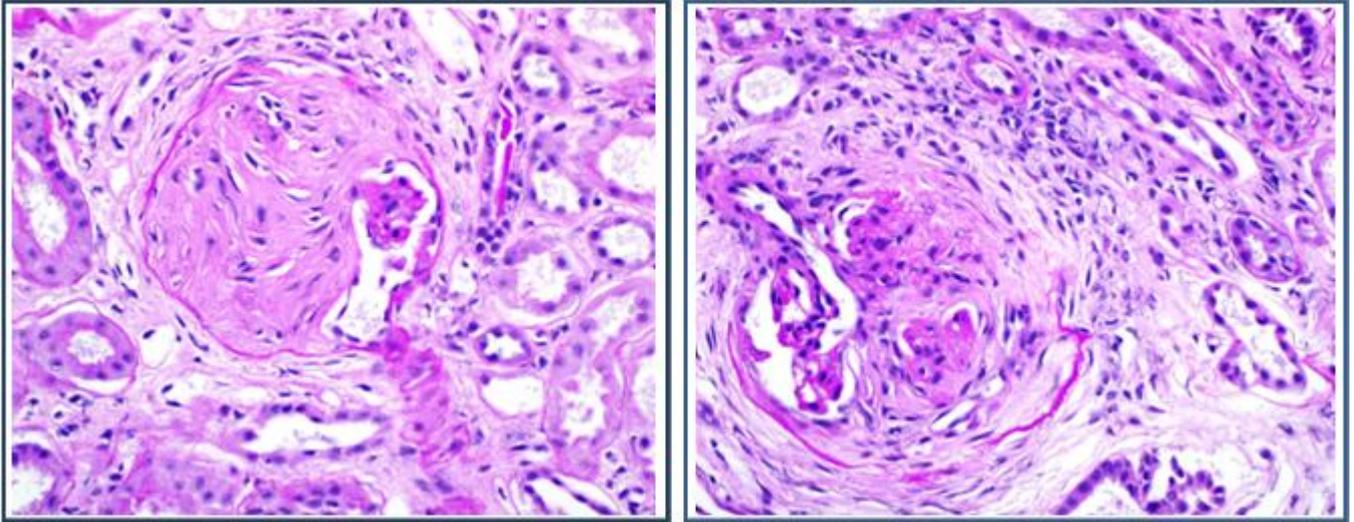
EM18-446

The semi thin sections reveal two glomeruli, one is globally sclerosed and the other is segmentally sclerosed. Ultrastructural examination demonstrates glomerular basement membranes with normal thickness, contour and texture. Mesangial areas are unremarkable. No electron dense deposits are seen. The podocytes show diffuse foot process effacement.

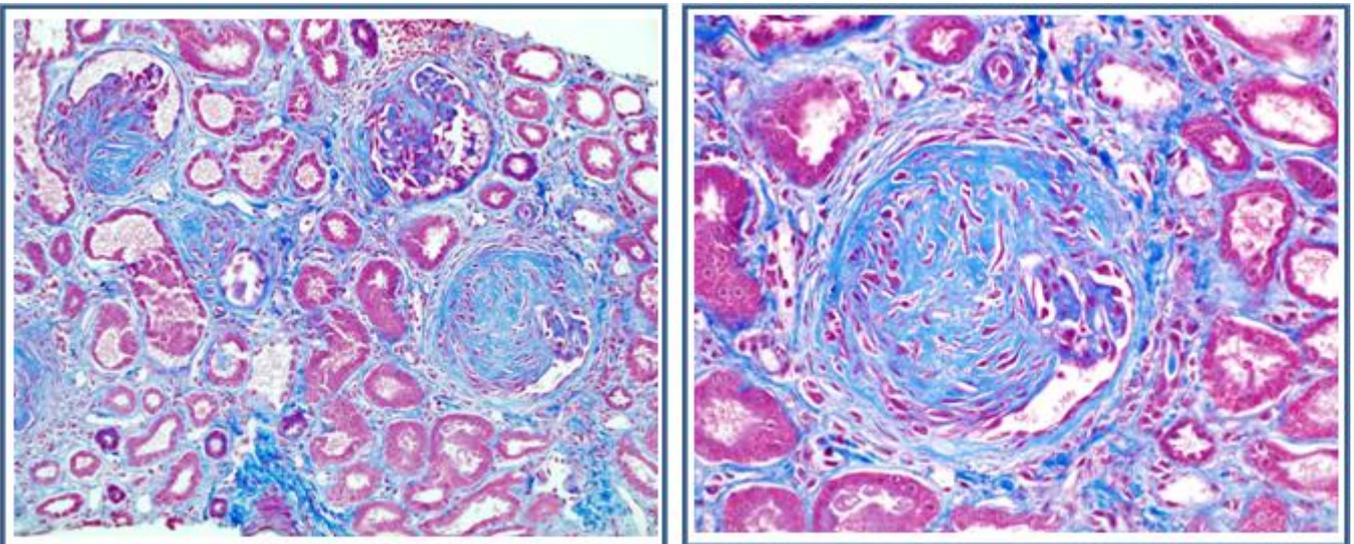
3. Diagnosis

Chronic anti-glomerular basement membrane (Anti-GBM) glomerulonephritis.

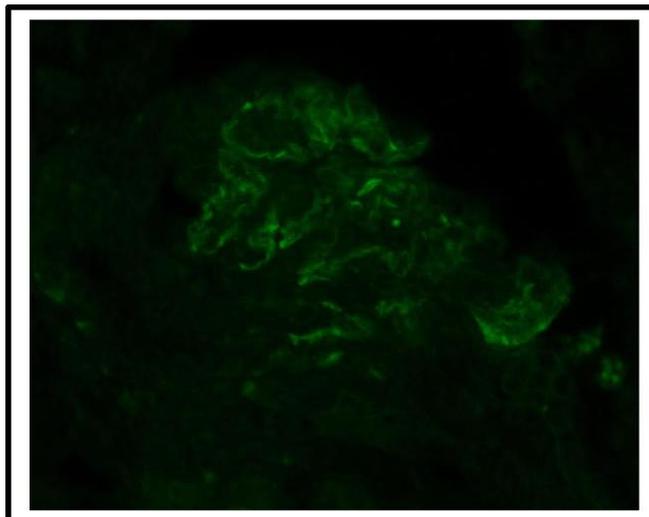
Interstitial fibrosis and tubular atrophy, mild to moderate Arteriosclerosis, mild.



PAS stain showed (A) Global glomerular sclerosis (B) Segmental sclerosis with fibrous crescents



Tri chrome stain showed: mild to moderate interstitial fibrosis and tubular atrophy



The glomeruli show linear capillary staining with antiserum specific for IgG (2+)

Result of Anti-GBM antibodies came **high 191.2 units** (Ref. Range ≤ 20), **p-ANCA =27.1 units** (Ref. Range 0.0- 20.9). She was diagnosed as anti-GBM disease with p-ANCA positivity. Patient was admitted to PICU for 5 sessions of plasmapheresis.

Hospital Course

She received 8 doses of pulse therapy methylprednisolone 1 gram intravenous once per day, then continued on prednisolone 60 mg PO once per day.

Anti hypertensive medication: Lasix 1 mg /kg /dose every 6 hours and calcium channel blocker amlodipine 10 mg PO once per day.

Fluid intake as her maintenance and depends on renal regimen (insensible water loss+ urine output)

Third day of admission, she received first dose of cyclophosphamide 500mg/m², as mentioned.

On day 7 of admission, results of p-ANCA & anti-GBM were completed and showed double positivity of them, patient was immediately admitted to pediatric intensive care unit for plasma exchange.

Hemodialysis was performed as needed, depending on clinical condition and correlated with fluid status, electrolytes and kidney function tests.

Patient in PICU, received seven cycles of plasma exchange, urine output improved (she was anuric 0.1 – 0.3 ml per kg per hour, then reached 1 ml per kg per hour), but renal insult was still there, renal function was almost same and hemodialysis requirement as well.

After 7 cycles of plasmapheresis, patient was shifted to pediatric nephrology ward. Unfortunately, her renal function did not recover after management, and she remained hemodialysis-dependent & was discharged home on renal replacement therapy.

4. Discussion

Anti-GBM disease remains a very uncommon condition in the pediatric population. Only 23 cases were identified as published in English literature over a 25-year span [6]. Anti-GBM disease has an estimated frequency of 0.5–1 case per million /year [7, 8].

Symptoms of nephritis often exhibit a clinical picture of rapidly progressive glomerulonephritis; however, to date, several cases of anti-GBM disease with normal kidney function have been reported. [9]. Systemic symptoms (i.e., malaise, fever, or weight loss) were less common in patients with normal renal function than in those with renal impairment. Circulating anti-GBM antibodies were detected less often and at lower levels in individuals with normal renal function than in those with renal impairment. The histological abnormalities were not as less marked in patients with normal renal function compared to those with renal impairment [10]

There have been case reports on anti-GBM disease following lithotripsy and ureteric obstruction, suggesting that antigens released from a mechanically damaged kidney may initiate the disease in susceptible individuals [11, 12]. Anti-GBM antibody levels must be monitored frequently until their disappearance, and then every 6 months to confirm sustained remission in the absence of clinical signs of recurrence. Prognosis of the disease is strongly associated with its initial presentation. Survival rates are related to the degree of renal compromise at onset of the disease. [13, 14]

Although the hypothesis that endogenous basement membrane components induce anti-GBM antibodies in patients with ANCA is plausible, there is no direct evidence to support it. Double-positive patients have a hybrid disease phenotype, requiring aggressive early treatment for anti-GBM disease, and careful long-term follow-up and consideration for maintenance immunosuppression for AAV. [15, 16]

We report a pediatric case with coexistence of p-ANCA and anti-GBM antibodies. Anti-glomerular basement membrane (anti-GBM) disease and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis in our patient caused rapidly progressive glomerulonephritis. The coexistence of ANCAs and anti-GBM antibodies was known as “double positive,” which was extremely rare in children.

To the best of our knowledge, this is the tenth case report of the coexistence of anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) and anti-glomerular basement membrane (GBM) disease in a child. Ninth pediatric case reported with anti-GBM and ANCAs was published in July 2015 by Zhao Cui et al, she presented with similar condition but renal biopsy showed 100% of large crescent formation in all glomeruli. Unfortunately, her renal function did not recover after management as they described, and she remained hemodialysis-dependent although she presented earlier than our case [17]. They mentioned that, only 8 cases were reported before their case in children and the therapy strategy was formulated based on the studies from adults.[18]

The outcome of reported eight pediatric cases was not different from that in adults: two patients died at presentation from massive pulmonary hemorrhage; two patients, both dialysis dependent at presentation, remained in end-stage renal disease (ESRD); one patient, whose treatment was delayed for 5 months after clinical onset, had improved renal function; three patients, had normal renal function several weeks to 10 months after onset of disease [18].

Close relationship between the immune characteristics of autoantibodies and the clinical phenotypes of anti-GBM disease and ANCA-associated vasculitis has been revealed in many studies. As our case had chronic anti-glomerular basement membrane (Anti-GBM) glomerulonephritis, associated with interstitial fibrosis and tubular atrophy, in addition to arteriosclerosis; so, it was unexpected to resume normal kidney function to that patient, especially that there was a delay of seeking medical advice by the parents.

5. Conclusion

We herein describe a case who presented with rapidly progressive glomerulonephritis due to anti-glomerular basement membrane antibodies associated with anti-neutrophil cytoplasmic antibodies as a rare case in children that led to severe form of RPGN that led to irreversible kidney damage. We think that the accumulation of similar cases will help elucidate the pathology of anti-GBM disease in children. Clinical phenotype-based studies may reveal the pathogenic mechanism of the autoantibodies, which may provide useful information to improve the clinical

management of these patients in the near future. Since double-positivity appears in younger age, further work is required to define the underlying mechanisms of this association and define optimum treatment strategies. Patients with either ANCA-related disease or anti GBM disease, should be tested for the second antibody.

Rapid institution of plasmapheresis and aggressive immunosuppressive therapy can induce remission and preserve renal function in dual positive patients. Renal prognosis depends on the extent of kidney injury at diagnosis and appropriate treatment

We recommend that patients suspected with RPGN should be checked for anti-GBM and p-ANCA antibodies, should undergo renal biopsy and should have close long term follow up to watch for recurrence.

6. Consent

Written informed consent was obtained from the parents of this patient for publication of this case report. A copy of the written consent is available for review by the editor of this journal.

7. Conflict of interest

None

8. Acknowledgements

None

9. Abbreviations

AAV: ANCA associated vasculitis
ANCA: Antineutrophil cytoplasmic antibodies
CrGn: crescentic glomerulonephritis
DIF: direct immunofluorescence
EM: electron microscopy
ESRD: end stage renal disease
GBM: glomerular basement membrane
IgG: immunoglobulin G
p-ANCA: perinuclearantineutrophil cytoplasmic antibodies
RPGN: rapidly progressive glomerulonephritis
UTI: urinary tract infection
VUR: vesico-urteric reflux

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