

Case Report

Double-positive Anti-glomerular Basement Membrane Disease in a Child with Crescentic Glomerulonephritis: A Case Report and Review of Literature

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Abstract: ‘Double-positive’ with anti-glomerular basement membrane (anti-GBM) antibody and anti-neutrophil cytoplasmic antibody (ANCA) is an extremely rare cause of small vessel vasculitis in children. Studies have reported a distinct hybrid phenotype in double-positive patients which requires an aggressive treatment approach. The data on double positive children are scarce with few case reports available with varied outcomes. A case of 9-year-old girl from India who had double-positive anti-GBM disease is reported here. The patient presented with complaints of edema, oliguria, gross hematuria with rising creatinine and was diagnosed as rapidly progressive glomerulonephritis (RPGN). Histological examinations of linear immunoglobulin G deposits along with glomerular capillaries were suggestive of anti-GBM disease. The anti-GBM and p-ANCA antibody titers were also high, and the aforementioned findings led to a diagnosis of ‘double-positive’ anti-GBM with RPGN. She was treated with standard plasma exchange therapy along with pulse methyl prednisolone (3 doses of 30 mg/kg/day on Days 1 to 3), oral prednisolone (1.5 mg/kg on Day 4), single intravenous injection of cyclophosphamide (500 mg/m² on Day 5) and mycophenolate mofetil (MMF; 1000 mg/m² on Day 6) followed by maintenance treatment with oral prednisolone (1 mg/kg/day) and MMF (800 mg/m²/day) from Day 7 onwards. Overall, the anti-GBM and p-ANCA levels declined throughout the treatment period but the patient progressed towards end stage renal disease.

Keywords: Anti-GBM, p-ANCA, Double-Positive, Small Vessel Vasculitis, Children

1. Introduction

The anti-glomerular basement membrane (anti-GBM) disease was first described in a patient by Goodpasture as “Goodpasture syndrome” almost a century ago (1919), [1] and different clinical phenotypes have been described since then [2]. The presentation of anti-GBM antibody and anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV), also termed as ‘double-positive’ is a rare phenomenon [3, 4]. An estimated 50% patients with anti-GBM disease have AAV whereas an estimated 10% patients with AAV present with anti-GBM antibody [3].

Furthermore, studies have reported poor prognosis in the double-positive cases versus as reported for individual AAV or anti-GBM diseases [3].

Anti-GBM disease is uncommon in adults and less reported in the pediatric age group. Double-positive cases are extremely rare in children. To our knowledge, only 7 double-positive children aged <16 years have been reported in the literature with crescentic/rapidly-progressive glomerulonephritis (RPGN) (Table 1). We report the first case of a “double-positive” anti-GBM disease with crescentic

glomerulonephritis in a 9-year-old girl.

2. Case Report

2.1. Case Presentation

A 9-year-old girl, a suspected case of acute glomerulonephritis, was referred to Sardar Vallabhbhai Patel Post Graduate Institute of Pediatrics, Cuttack, Orissa, India,

with progressive edema, oliguria, gross hematuria and rising creatinine for the past 10 days. Physical examination revealed pallor, anasarca, hypertension (blood pressure >99th centile) and ascites. She had no relevant past history or history of preceding fever, cough or any drug intake. The provisional diagnoses made were acute nephritic syndrome, nephrotic-nephritic syndrome or acute kidney injury secondary to vasculitis.

Table 1. Clinical characteristics, laboratory parameters, treatment and outcome of 'double-positive' anti-GBM pediatric patients.

Parameters	Patient 1[10]	Patient 2[11]	Patient 3[12]	Patient 4[13]	Patient 5[9]	Patient 6[14]	Patient 7[15]	Our patient
Age	12	12	4	8	10	6	15	9
Sex	F	M	F	F	F	F	F	F
Clinical features								
Duration of symptoms (days)	-	-	-	-	-	-	15	10
Pulmonary symptoms	Yes	Yes	No	Yes	Yes	No	Absent	Absent
Hypertension	Yes	Yes	-	-	Yes	Yes	Yes	Yes
Gross hematuria	Yes	Yes	-	-	Yes	No	Yes	Yes
Laboratory parameters								
Hemoglobin (gm/dL)	7.4	10.6	-	2.8	4.4	8.3	-	7.2
Serum creatinine (mg/dL) at presentation	0.5	7.4	2.7	7.7	0.53	8.1	0.6	6.4
Serum creatinine (mg/dL) at follow-up	1.3	2.1	0.8	-	0.66	-	1.09	5.6
Serology								
Anti-GBM titer at presentation (U/mL)	211	-	220	-	-	-	258	>212
p-ANCA	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
c-ANCA	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Renal histopathology								
Crescents (%)	~35	>60	95	83	16	100	64	100
Required RRT at presentation	No	Yes	Yes	Yes	-	Yes	No	Yes
PE sessions	-	10	11	-	-	-	14	21
ISD	MP, CYP	MP, CYP, PRED, MMF	MP, CYP, PRED	Supportive	MP, CYP, PRED, MMF	MP, CYP, PRED	MP, CYP, PRED, RTX	MP, CYP, PRED, MMF
Duration of follow up	Few weeks	18 months	9 months	0 months	10 months	N. A.	24 months	3 months
Renal presentation (RPGN)	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Renal outcome	Normal GFR	CKD (G3)	Normal GFR	-	Normal GFR	ESRD	Normal GFR	ESRD
Outcome	Alive	Alive	Alive	Deceased	Alive	Alive	Alive	Deceased

ANCA, anti-neutrophil cytoplasm antibody; CKD, chronic kidney disease; ESRD, end stage renal disease; F, female; GBM, glomerular basement membrane; GFR, glomerular filtration rate; ISD, immunosuppressive drug; M, male; MMF, mycophenolate mofetil; MP, methylprednisolone; PE, plasma exchange; PRED, prednisolone; RPGN, rapidly progressive glomerulonephritis; RRT, renal replacement therapy.

2.2. Laboratory Investigations

During hospitalization, her laboratory investigations showed moderate anemia (hemoglobin 7.2 g/dL) and high serum creatinine levels (6.4 mg/dL). Urine analysis revealed nephrotic range proteinuria, hematuria and red blood cell (RBC) casts. Serum complement levels of C3 and C4, and antinuclear antibodies (ANA) were within the normal range. Her serum creatinine gradually rose to 8.4 mg/dL and she almost became anuric. The kidneys appeared echogenic in ultrasound. Keeping in view of the serious clinical condition, a diagnosis of RPGN was inferred. Renal biopsy was conducted, and hemodialysis initiated.

2.3. Histologic Investigations

Renal histopathology revealed necrotizing and crescentic glomerulonephritis featuring crescents in all 20 glomeruli; 12 fibrocellular and 8 cellular crescents were seen. There were signs of patchy tubular injury along with focal chronic interstitial inflammation and increased

tubulo-interstitial chronicity (Figure 1). Immunofluorescence microscopy reported IgG deposits in a linear manner along glomerular capillaries (Figure 2) suggestive of anti-GBM disease.

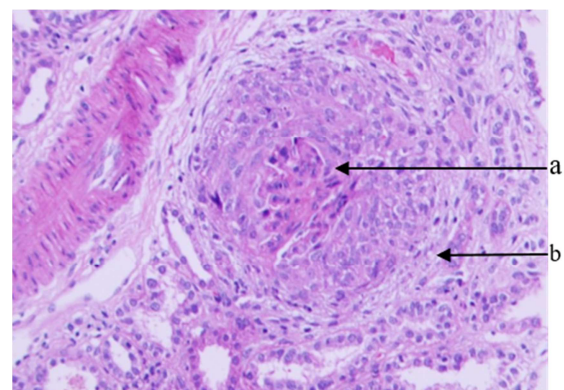


Figure 1. Light microscopy finding on renal biopsy a) fibrinoid necrosis, b) cellular crescent (PASx200).

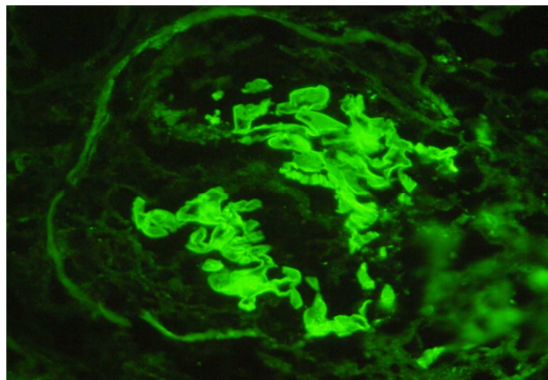


Figure 2. Immunostaining of renal biopsy showed linear pattern along the glomerular capillaries with IgG antibody (x 200).

2.4. Antibody Titers

Circulating anti-GBM antibody titer was 212 U/mL

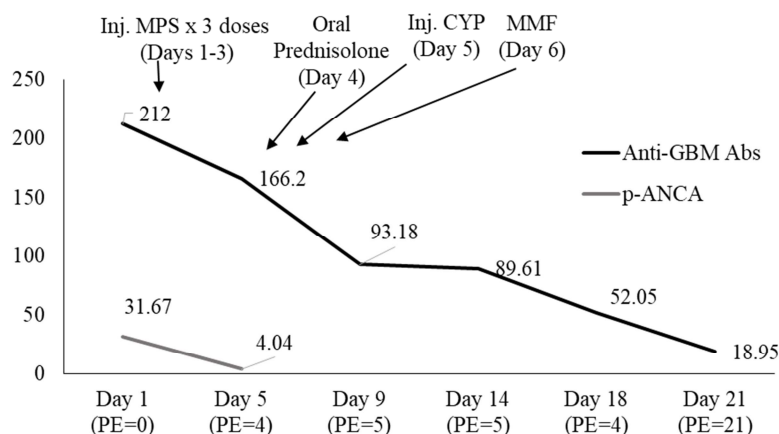


Figure 3. Anti-GBM IgG antibody (by EIA) titers and treatment course during follow-up.

Abs, Antibodies; CYP, cyclophosphamide; EIA, enzyme immune assay; GBM, glomerular basement membrane (normal <20); p-ANCA, anti-neutrophil cytoplasm antibodies by EIA (normal <9.00); PE, plasma exchange; MMF, mycophenolate mofetil; MPS, methylprednisolone.

2.6. Outcomes and Follow-up

Her anti-GBM antibody titers declined gradually (Figure 3). Hence, it was planned to administer one dose of rituximab based on the experience from a recent case report [5]. However, during the course of treatment, she had a hemodialysis catheter associated line infection. Therefore, rituximab was not administered, and she was treated with maintenance therapy comprising oral prednisolone (1 mg/kg/day) and MMF (800 mg/m²/day) from Day 7 onwards. The plasma exchange was continued and stopped when two consecutive anti-GBM antibody titers became negative (<20 U/mL) after 21 days (18.95 on Day 21, and 16.4 on Day 24).

Figure 3 represents the trend of antibody titers in response to plasma exchange and treatment course during hospitalization. Her ANCA values were normalized during the second week of plasma exchange and were not evaluated further. During the follow-up at 2.5 months, though her urine

(reference normal value: <20 U). The p-ANCA (anti-myeloperoxidase) level was also elevated (31.67 U/mL, reference normal value: <9 U/mL) but c-ANCA was within the normal range (2.52 U/mL). All these findings were considered and “double-positive” anti-GBM disease with RPGN was diagnosed.

2.5. Treatment

Plasma exchange was initiated and immunosuppressive medications (3 days of treatment with pulse methylprednisolone 30 mg/kg/day and then a single dose intravenous cyclophosphamide 500 mg/m² on Day 5) were administered. On Day 4, she was administered oral prednisolone 1.5 mg/kg and on Day 6, she was administered mycophenolate mofetil (MMF) 1000 mg/m² (Figure 3).

output improved, she was still oliguric (urine output: >350 mL/day), hemodialysis dependent (3 times per week) and hypertensive (on two antihypertensive medications). Later, the renal functions further deteriorated with end stage renal disease (ESRD) and the patient succumbed following 3 months of follow-up due to hypertensive encephalopathy.

3. Discussion

The anti-GBM disease is characterized with small vessel vasculitis caused due to the development of anti-GBM antibodies resulting in RPGN and/or pulmonary hemorrhage [3]. There are three different anti-GBM phenotypes reported including single positive (only anti-GBM antibody is positive), double-positive (coexistence of ANCA and anti-GBM antibodies) and atypical anti-GBM diseases (negative circulating anti-GBM antibodies but with evidence of IgG immunofluorescence staining from renal biopsies) [6].

Anti-GBM and ANCA double positive is a rare disease (estimated incidence rate: 0.47 case/1,000,000 people/year) [4]. Reported small case studies in adults have described conflicting clinical outcomes. A study by Levy et al., in 27 double positive adult patients demonstrated poor renal outcomes despite immunosuppressive therapies, [7] whereas Segelmark observed good prognosis in single-positive patients with anti-GBM disease [8]. However, single-anti-GBM disease usually does not relapse, whereas about half of the double-positive patients develop recurrent disease [3].

Though the standard treatment for double-positive disease is not established, the most common treatments include plasma exchange with immunosuppressive therapies, cyclophosphamide and corticosteroids [3]. Also, rituximab has been used in young female patients in whom cyclophosphamide needs to be avoided to preserve fertility [5]. Our exceptional case, of a girl aged 9 years, having a double-positive disease 'anti-GBM with RPGN' responded with decrease in the titers for anti-GBM and p-ANCA antibodies after treatment with corticosteroids and MMF. She was also administered one injection of cyclophosphamide which was stopped later, and rituximab treatment advocated. However, due to the development of a line infection, rituximab was not administered. The girl was treated with prednisolone and MMF.

The renal histopathology of our patient revealed 100% crescents with signs of patchy acute tubular injury along with focal chronic interstitial inflammation and increased tubulo-interstitial chronicity. These findings were suggestive of a late-stage renal disease. Studies have reported improved renal functions after treatment in double-positive patients, however, poor renal prognosis is also reported in recent reports with 35%-100% presence of crescents, and higher creatinine levels (up to 8.1 mg/dL) [9-15]. Similarly, our patient remained hemodialysis dependent even after treatment and there were no marked improvements seen in the renal functions. Later, the renal functions of our patient severely deteriorated, which resulted in ESRD. The patient died at 3 months of follow-up due to hypertensive encephalopathy and difficulty in getting hemodialysis at her hometown during the prevailing Covid-19 pandemic.

Overall, the anti-GBM and p-ANCA levels declined throughout the treatment period in our patient.

4. Conclusion

In conclusion, double-positive anti-GBM antibodies in children are rare, however, may exist with renal injury and has poor prognosis. An early diagnosis and immunosuppressive therapeutic strategies may help prevent the progression of the disease. However, best therapeutic strategies are not known.

Declarations

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Conflict of Interest

The authors have no potential conflicts of interest to declare with respect to the research, authorship, and publication of this article.

Patient Consent for Publication

Signed informed consent document was obtained from the patient for the publication of this case report.

Author Contributions

Both SKP and SN participated in study design, data collection, and writing of the case report. All authors meet ICMJE criteria and all those who fulfilled those criteria are listed as authors.

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