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Mitigated Clinical Course of Crescentic Glomerulonephritis with Positive Anti-Glomerular Basement Membrane Antibodies in a 14-Year-Old Girl

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Abstract

Introduction: Anti-glomerular basement membrane (anti-GBM) glomerulonephritis is associated with severe kidney failure and high morbidity and is exceedingly rare in children. The few pediatric studies published about this condition report dependency of kidney replacement therapy at presentation and partial or complete response in kidney function in a minority of cases. ***Case Presentation:*** We describe the case of a 14-year-old girl with crescentic glomerulonephritis based on double positive anti-GBM and myeloperoxidase-antineutrophil cytoplasmic antibodies with a mitigated clinical course presenting with fatigue, anemia, and an estimated glomerular filtration rate range between 34 and 42 mL/min/1.73 m^2. Response to treatment with daily therapeutic plasma exchanges, corticosteroids, and oral cyclophosphamide was prompt. ***Conclusion:*** This ultrarare presentation highlights the need to consider determining anti-GBM antibodies and/or obtaining a kidney biopsy even in children with less severe presentations of unexplained glomerulonephritis and underlines the clinical treatment dilemma in this disease for children due to the potential long-term sequelae.

Introduction

Anti-glomerular basement membrane (anti-GBM) glomerulonephritis is associated with severe kidney failure and high morbidity and is exceedingly rare in children [1, 2]. Comparable to adults, the few pediatric case series and reports published about this condition describe a clinical course that is characterized by rapidly progressive glomerulonephritis, leading to kidney failure and with variable pulmonary involvement [3].

We here report a case of an adolescent girl who presented with decreased estimated glomerular filtration

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rate (eGFR), microscopic hematuria, and proteinuria that, in retrospect, had existed for longer than 6 weeks, and double positive anti-GBM and myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCAs). Histological evaluation indicated a diagnosis of anti-GBM glomerulonephritis, possibly in combination with ANCA-associated vasculitis (AAV). This ultrarare mitigated presentation of anti-GBM glomerulonephritis in a child has important diagnostic and prognostic implications: (1) it attests to the need to consider determining anti-GBM and ANCA antibodies and/or obtaining a kidney biopsy in children presenting with mild to moderate cases of glomerulonephritis, particularly when more common causes such as infection-related glomerulonephritis or systemic lupus erythematosus have been ruled out, and (2) given the potential complications of cyclophosphamide (CPO) treatment on fertility and neutropenia in (post-)pubertal children [4], a 3 months treatment schedule may not be prudent in pediatric patients who are not kidney replacement therapy (KRT)-dependent and show rapid clinical improvement after initiation of treatment.

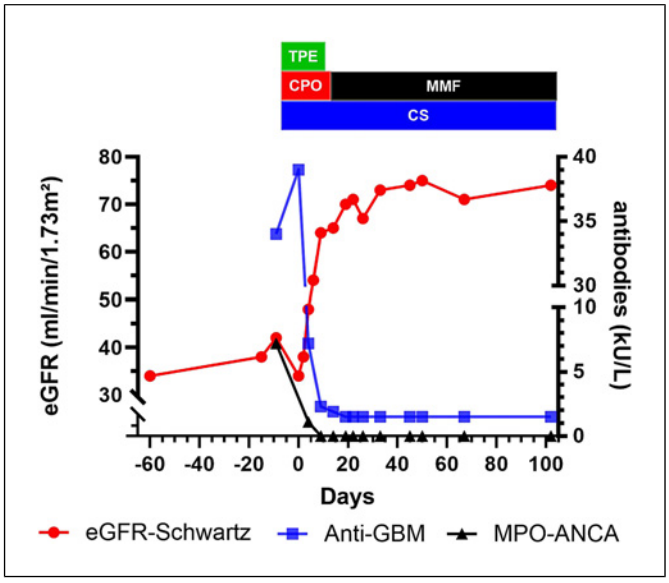

Fig. 1. Course of estimated glomerular filtration rate (eGFR), anti-GBM, and MPO-ANCA antibodies. eGFR is estimated using the Schwartz equation (0.413 × height [cm]/serum creatinine [mg/dL]). Day 0 is the starting day of treatment according to the 2021 KDIGO glomerular diseases guideline (total follow-up time 102 days). Therapeutic plasma exchange (TPE; green) was continued for 2 weeks when anti-GBM and MPO-ANCA antibodies became undetectable. Oral cyclophosphamide (CPO; red) was discontinued after 18 days and switched to oral mycophenolate mofetil (MMF; black; current treatment). Corticosteroids (CS; blue) were given as three pulses of methylprednisolone and continued for 4 weeks of oral prednisolone in a 1 mg/kg daily dosage and then tapered to 0.6 mg/kg (total duration: 2 weeks), 0.5 mg/kg (total duration: 2 weeks), and 0.3 mg/kg (current treatment).

Case Presentation

A 14-year-old girl was referred to the Department of Pediatric Nephrology of our university children's hospital with an eGFR of 38 mL/min/1.73 m^2, microscopic hematuria, and sub-nephrotic range proteinuria. She had not been feeling well for almost 2.5 months, with intermittent nausea, vomiting, and extreme fatigue. One month before the start of her complaints, she had suffered a rupture of her right semimembranosus muscle during exercise. She initially had been taking ibuprofen following this injury for 2 weeks, but this was discontinued after. She was diagnosed with profound anemia (hemoglobin 7.0 g/dL) with normal cell indices, LDH, and iron status, and low reticulocyte counts, initially attributed to her muscular hematoma but persisting after recovery. She had been prescribed iron and folic acid supplements by her general practitioner with little therapeutic effect. She did not report having respiratory symptoms, skin rash, or arthritis. She did not smoke (electronic) cigarettes and had had a sore throat 6 weeks prior to developing complaints. Her medical history included recurrent urinary tract infections between the ages of 5 and 10 years, which had been ascribed to dysfunctional voiding after kidney ultrasound and nuclear imaging studies had revealed no abnormalities. Family history included her father having an unclassified auto-inflammatory syndrome, with recurrent episodes of fever, arthralgia, skin involvement, and splenomegaly but without kidney involvement, for which he was taking oral prednisolone as maintenance treatment at the time of presentation. A targeted exome panel for primary immunodeficiency in 2021 did not yield a genetic diagnosis in the father.

At presentation, she had lost 2.5 kg of weight, and her blood pressure was 116/72 mm Hg. Further physical examination was unremarkable. A kidney ultrasound and chest X-ray were normal. Her serum creatinine was 1.7 mg/dL (eGFR: 42 mL/min/1.73 m^2). In hindsight, extensive evaluation of her anemia by her general practitioner 6 weeks before had already shown kidney failure (serum creatinine 2.1 mg/dL; eGFR 34 mL/min/1.73 m^2) (Fig. 1). Serum electrolytes were within normal ranges. Urinary analysis revealed hematuria, leukocyturia, and proteinuria (urinary protein to creatinine ratio: 160 mg/mmol [albumin-fraction 78%]).

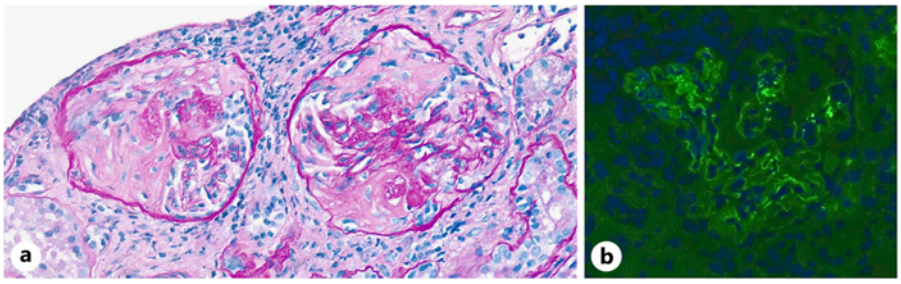

Fig. 2. Histological images of the kidney biopsy. **a** Representative microphotograph (PAS staining; original magnification ×20) of two glomeruli, with segmental destruction of the capillary tuft by fibrocellular crescents. The surrounding parenchyma shows interstitial fibrosis and interstitial inflammation. **b** Immune fluorescence image (IgG staining, DAPI background staining; magnification ×20), showing weak-to-moderate linear staining of IgG.

Additional examinations with a broad differential diagnosis for glomerulonephritis demonstrated positive antinuclear antibodies (titer: 1:3,200, homogeneous pattern) but without elevation of anti-double-stranded DNA antibodies and negative anti-extractable nuclear antigen antibodies. Anti-streptolysin O titer was 1,600 IU/mL, which indicated a recent *Streptococcal* infection, yet with serum complement C3 and C4 levels within normal ranges. A broad screening for recent viral infections was negative (including HIV, hepatitis B/C, hanta, Epstein-Barr, and cytomegaloviruses). Surprisingly, anti-GBM antibodies were positive (34 kU/L, normal range: 1–10 kU/L) in two different assays, and MPO-ANCA antibodies were detectable just above normal range (7.2 kU/L, normal range: 0–5 kU/L) (Fig. 1). Additional human leukocyte antigen (HLA) class II determination showed heterozygosity for HLA *DRB1*15:01*.

A kidney biopsy was performed, which revealed a crescentic glomerulonephritis characterized by fibrinoid necrosis, fibrocellular and fibrous crescents in ~50% of glomeruli, and mild interstitial fibrosis and tubular atrophy (IFTA) (Fig. 2). Approximately 20% of glomeruli were globally sclerosed. Immunofluorescence staining showed linear staining of IgG (weak-to-moderate), kappa (weak), and lambda (weak), as well as granular and segmental linear staining of C3c (weak-to-moderate). IgM and C1q were negative. Electron microscopy did not show electron-dense depositions, arguing against a diagnosis of immune-complex or complement-mediated glomerulonephritis. A histological diagnosis of crescentic glomerulonephritis with extensive segmental glomerular sclerosis was made, best classified as anti-GBM glomerulonephritis, possibly combined with AAV given the abovementioned antibody profile. With the working diagnosis of anti-GBM glomerulonephritis, we started treatment according to the 2021 KDIGO guidelines [5], which includes 3 intravenous pulses of methylprednisolone (750 mg/dose) followed by a 6-month tapering schedule of oral prednisolone, daily therapeutic plasma exchanges (TPEs; 40 mL/kg per session [6]) until anti-GBM antibodies fell below the threshold of assay sensitivity (total duration of treatment: 14 days), and oral CPO (2 mg/kg per day in once daily dosage). Given the mitigated presentation, we aimed to reduce the cumulative dosage of CPO after discontinuation of TPE by switching to mycophenolate mofetil (MMF; 1,200 mg/m^2 body surface area) when anti-GBM/MPO-ACNA titers remained negative, eGFR had stabilized and hematuria normalized (total duration of CPO treatment: 18 days). At the current follow-up (102 days after the start of treatment), the patient is on oral prednisolone in a tapered schedule (currently 0.3 mg/kg for 4 weeks), MMF (750 mg twice daily dosage), and lisinopril (15 mg once daily to treat remnant proteinuria). eGFR is 74 mL/min/1.73 m^2 with both anti-GBM and MPO/ANCA levels below the assay sensitivity threshold.

Discussion

Detectable anti-GBM IgG antibodies that target collagen type IV within the glomerular and alveolar basement membrane typically lead to rapidly progressive glomerulonephritis with or without pulmonary hemorrhage in adults and children [3, 7]. As of now, it is unknown what causes the formation of anti-GBM antibodies, but a genetic predisposition by HLA haplotypes *HLA DRB1*15:01* and *DRB1*04:03*, as well as immunological and environmental exposures (e.g., infections and cigarette smoking or hydrocarbon toxicity, respectively), have been proposed to

play a pivotal role [3]. Secondary anti-GBM glomerulonephritis may occur in children after kidney transplantation in patients with Alport syndrome due to pathogenic *COL4A3-5* variants.

The total number of pediatric cases with primary anti-GBM glomerulonephritis reported in the literature over the past 15 years is smaller than 50 cases, underscoring the extreme rarity of this disease [3]. In a recent review, Dowsett and Oni showed that all but 1 of these pediatric patients presented with chronic kidney disease (CKD) stage 5 and KRT-dependency [3]. Bayat and colleagues reported on a girl with a history of tetralogy of Fallot and cigarette smoking who presented with pulmonary symptoms and an eGFR of 60 mL/min/1.73 m^2, microscopic hematuria, and proteinuria (<0.5 g/day) due to positive anti-GBM antibodies [8]. After treatment with TPE (4 sessions of single volume), methylprednisolone, and prednisolone and 6 months of intravenous CPO, recovery was complete. Although the clinical outcome of many other reported pediatric cases was not consistently recorded, complete and partial (i.e., CKD stage <5) responses have been reported in 4/13 (31%) and 4/13 (31%) of children, respectively [8–16].

In our case, initial presentation was strikingly different than from what has been previously reported in the literature. The patient was found to have anti-GBM and MPO-ANCA antibodies both in serum and linear immunofluorescent staining of IgG in the kidney biopsy, but she did not require KRT at presentation. On the contrary, it appeared that the deterioration of GFR had already been present for more than 6 weeks, indicating a much more prolonged clinical course. The biopsy also showed signs of chronicity, as evidenced by global and segmental glomerulosclerosis and IFTA. When compared to previous positive measurements (n = 4) of anti-GBM antibodies in our immunology laboratory (median (range) 585 [98–1,960] kU/L), the titer in our patient was markedly lower (34 kU/L). The relatively weak linear IgG staining by immunofluorescence, which is unusual in anti-GBM glomerulonephritis, may have been the result of this low anti-GBM antibody titer. Although florid anti-GBM glomerulonephritis with kidney and pulmonary symptoms has been described in adult patients with anti-GBM levels comparable to those in our patient [17], we hypothesize that the mitigated clinical course may be explained by this relatively low titer.

Our patient did not have any known environmental hazard exposure but was a heterozygous carrier of the risk haplotype of HLA *DRB1*15* and had suffered from a recent *Streptococcal* infection. Furthermore, our team was not able to identify a connection between her disease and the medical history of her father that includes an unexplained auto-inflammatory disease. As is the case in approximately 30% of patients with anti-GBM antibodies, our patient was found to also have detectable MPO-ANCA antibodies [5]. The double seropositivity has been associated with a more prolonged disease course and warrants continuation of immunosuppressive treatment beyond the duration of treatment advised for patients positive for anti-GBM antibodies alone [5].

Our case additionally raises important questions regarding the treatment of anti-GBM glomerulonephritis in children. Given the rarity of this disease in children, treatment is based on the 2021 KDIGO guideline for adults and has not been specifically tailored to children. This guideline advises treatment with daily TPE for 2 weeks or until anti-GBM are no longer detectable, corticosteroids for 6 months in a tapered dosage schedule, and oral CPO for 3 months [5]. Particularly the use of CPO in children merits careful consideration given its well-known complications of, amongst others, neutropenia and particularly gonadotoxicity, possibly resulting in infertility in both males and females. Infertility in young females due to premature ovarian failure has been reported to ensue in cases with a cumulative dose of 10–15 g/m^2 and over, but has been proven unpredictable [4]. Furthermore, there is an association of CPO exposure and malignancies in long-term follow-up studies [18]. At the end of the recommended 3-month CPO treatment, our patient would have received a cumulative CPO dose of 5.6 g/m^2, which is below the reported risk threshold for fertility, but uncertainty regarding this complication still poses a dilemma in treatment choice for affected children.

As the clinical course in our case was relatively mild and the kidney biopsy showed profound crescentic glomerulonephritis and instigation of IFTA without any other lead points for disease, our team decided to start treatment according to the 2021 KDIGO guideline to preserve as much kidney function as possible. Besides the fact that poor outcomes of successful pregnancies have been described [4], current fertility-preserving methods before the start of treatment with CPO were not desirable due to time sensitivity to start treatment. However, we aimed to shorten the use of CPO after rapid improvement in eGFR and urine sediment analyses to keep the total cumulative dose of CPO as low as possible. After successful cessation of TPE, we therefore switched CPO after 18 days of treatment (total cumulative dose 1.4 g/m^2) to MMF (1,200 mg/m^2, dosage adjusted based on trough levels) in combination with prednisolone 1 mg/kg daily dosage for 4 weeks in order to prevent the reformation of anti-GBM and MPO-ANCA antibodies.

Switching from CPO to MMF treatment in children with non-KRT-dependent anti-GBM glomerulonephritis is in line with a recent publication by Klaus and colleagues, who primarily investigated the efficacy of rituximab treatment in a nationwide case series of pediatric patients [19]. Interestingly, only one out of five adolescent patients with anti-GBM glomerulonephritis in this retrospective case series presented with an impaired eGFR (median 124 mL/min/1.73 m^2). Four (80%) patients were successfully and safely treated with TPE ($n = 5$) and MMF ($n = 5$) with or without rituximab ($n = 4$ and $n = 1$, respectively) [19]. Currently, our patient has stable CKD stage 2 (eGFR 65–75 mL/min/1.73 m^2) and sub-nephrotic range proteinuria, which is treated by angiotensin-converting enzyme inhibition.

In conclusion, our case presentation shows an unusual and mitigated course of crescentic glomerulonephritis best classified as an anti-GBM glomerulonephritis, possibly in combination with AAV, in an adolescent girl who did not require KRT. This case has important diagnostic and prognostic implications for an early determination of anti-GBM antibodies and MPO-ANCA antibodies in (post-)pubertal children with unexplained glomerulonephritis, even when kidney function is less severely affected, and KRT-dependency is absent. A fast diagnosis of anti-GBM glomerulonephritis may provide a crucial window for therapy to not only improve the long-term clinical outcome but also to mitigate the potential severe complications of therapy, specifically in children with this ultrarare but detrimental disease.

Acknowledgments

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Statement of Ethics

Ethical approval is not required for this case report in accordance with local or national guidelines. Written informed consent was obtained prospectively from the patient and parent/legal guardian of the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

R.W. is a board member of the Working Group on CAKUT, Urinary Tract Infection, and Bladder Dysfunction of the European Society of Pediatric Nephrology (ESPN). R.W. and M.J.S.O. are members of the NL Research Consortium "Kidnie," which is supported by the Dutch Kidney Foundation. R.W. and M.J.S.O. are working in the reference center of the European Reference Kidney Network (ERKNet).

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Author Contributions

Conceptualization: N.M.M., M.J.S.O., R.W. Writing and editing of the manuscript and final review: N.M.M., M.J.S.O., E.M.M.L., M.S.W.Q., J.J.T.H.R., and R.W.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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