

Teaching Point
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Rescue of renal function in a 3-year-old girl with Goodpasture's syndrome with a brief review of literature

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Introduction

Goodpasture's syndrome or anti-glomerular basal membrane (anti-GBM) disease is a rare disorder first described by Earnest Goodpasture in 1919 [1]. The disorder is characterized by formation of antibodies against non-collagenous domain of the $\alpha 3$ chain of type IV collagen of the GBM [2,3]. Combination of rapidly progressive glomerulonephritis and pulmonary haemorrhage caused by this anti-GBM formation is known as Goodpasture's syndrome [3]. Pulmonary haemorrhage is present in adult cases, yet children can develop isolated renal disease without pulmonary involvement [4,5]. Pulmonary involvement with Goodpasture's syndrome is therefore less common in younger children [5]. This disease is especially rare in patients under the age of 5 and can lead to poor patient or renal outcome [3,6]. Delay in diagnosis and initiating treatment, together with technical difficulties in treatment, can result in failure to halt the progress of the disease and in permanent loss of renal function [7]. The reverse is true with early diagnosis and prompt, aggressive treatment [4,7].

We describe a case of Goodpasture's syndrome in a 3-year-old child with successful rescue of renal function and amelioration of anti-GBM antibody over the next 3 years with continued mild proteinuria and hypertension from the initial event. According to the literature, only one previous case has been reported with successful renal rescue [5]. To our knowledge, our patient is the youngest to survive isolated Goodpasture's syndrome without permanent loss of renal function but does have adverse prognostic indicators.

Case report

A previously healthy 3-year-old girl was admitted to our hospital with anaemia, gastroenteritis, fever, tiredness and

anasarca for 3 weeks. Her haemoglobin was 6.3 g/dL with a haematocrit of 20.3%, and her serum creatinine was 114.92 $\mu\text{mol/L}$ with serum albumin of 2.7 g/dL. Initial urinalysis showed 1+ albumin, 3+ blood and RBC casts. The chest X-ray was normal. The 24-h catheterized urine collection showed 598 mg of protein and a creatinine clearance of 23 mL/min/1.73 m².

Her C3 was 209 mg/dL, C4 was 35.6 mg/dL and ASO was 400 IU/mL (normal <100 IU/mL). A presumptive diagnosis of glomerulonephritis was made, and as her creatinine continued to rise, a kidney biopsy was performed. The kidney biopsy showed anti-GBM-mediated necrotizing and crescentic glomerulonephritis. Six out of eight glomeruli had severe fibrinoid necrosis and cellular crescent formation (Figure 1). There was no interstitial fibrosis or tubular atrophy, and the vessels were unremarkable with no features of vasculitis. The immunofluorescence examination showed a classical global and bright linear capillary wall staining for IgG (Figure 2).

Her anti-GBM antibody level was 352 AU/mL (normal <19 AU/mL) (Figure 3). The rest of the serology including ANA, anti-DNA and ANCA was negative on multiple occasions. Based on the kidney biopsy and anti-GBM antibody level, a diagnosis of Goodpasture's syndrome was made.

Treatment

She was treated with intravenous (IV) steroid pulse (three doses) and plasmapheresis. Four weeks after admission, when her plasmapheresis was discontinued, her anti-GBM antibody levels rebounded, necessitating ongoing plasmapheresis treatment for a total duration of 7 weeks (Figure 3). At 7 weeks, when her anti-GBM antibody level was 28 AU/mL (normal <19 AU/mL), monthly intravenous infusions of cyclophosphamide treatment was initiated for the next 6 months followed by increasing intervals. Oral prednisolone was continued at 30 mg/day (2 mg/kg/day) for the next 3 months before tapering. It required 4 months of aggressive immunosuppression to rescue and maintain her

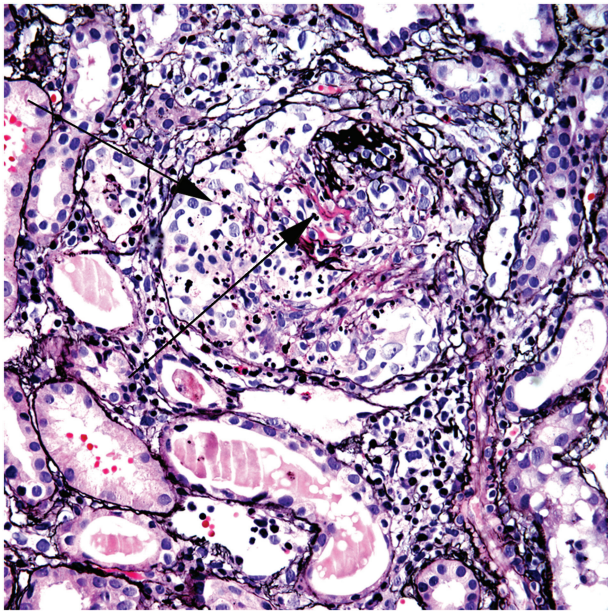


Fig. 1. Light microscopy: kidney biopsy of a 3-year-old girl with anti-GBM disease. Arrows show crescent and fibrinoid necrosis within a glomerulus.

creatinine clearance in the normal range (Figure 3). Her anti-GBM antibody levels were abnormal for 7 months after the onset of disease but were detectable up to a year. As her creatinine clearance improved, she had a spike in proteinuria to 1.8 g/day (Figure 3). She continued to remain hypertensive from the onset of illness for which she was treated with enalapril 3 mg/day (0.2 mg/kg/day).

Ongoing therapy

At 1 year, due to persistent abnormal proteinuria and hypertension, the kidney biopsy was repeated. The biopsy

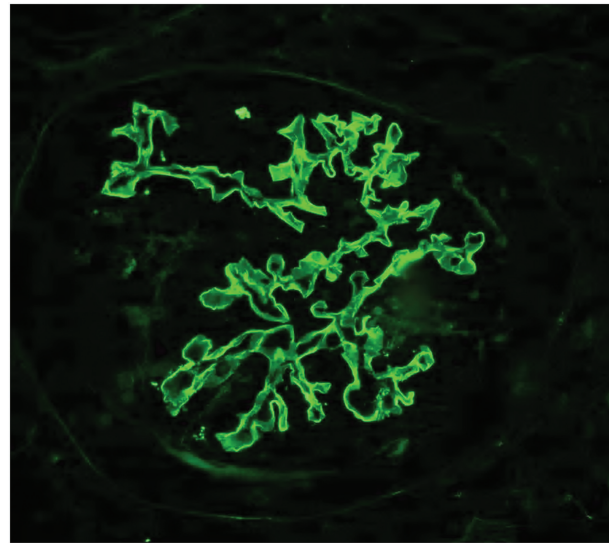


Fig. 2. Immunofluorescence: kidney biopsy of a 3-year-old girl with anti-GBM disease. Linear IgG glomerular basement membrane deposits.

showed anti-GBM-mediated focal sclerosing glomerulonephritis with focal global glomerulosclerosis in 7 of the 64 glomeruli on biopsy. Five of the remaining glomeruli had segmental sclerosis (Figure 4), and the others were unremarkable. There was 10% interstitial fibrosis with tubular atrophy, but the blood vessels were unremarkable. Electron microscopy showed anti-GBM immune deposits (Figure 5).

Following the second kidney biopsy, the decision was made to continue cyclophosphamide infusions at six monthly intervals with the addition of mycophenolate mofetil (MMC) suspension at the dose of 200 mg orally twice a day (20 mg/kg/day). Prednisolone taper and enalapril were continued.

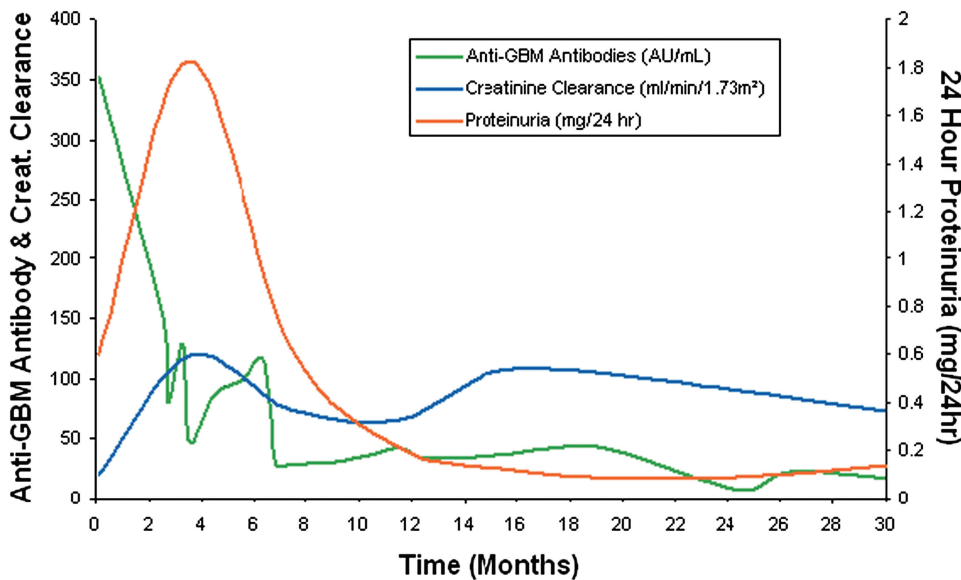


Fig. 3. The levels of anti-glomerular basement membrane antibody, urinary protein excretion rate and renal function (creatinine clearance) in a 3-year-old girl with Goodpasture's syndrome for initial 30 weeks.

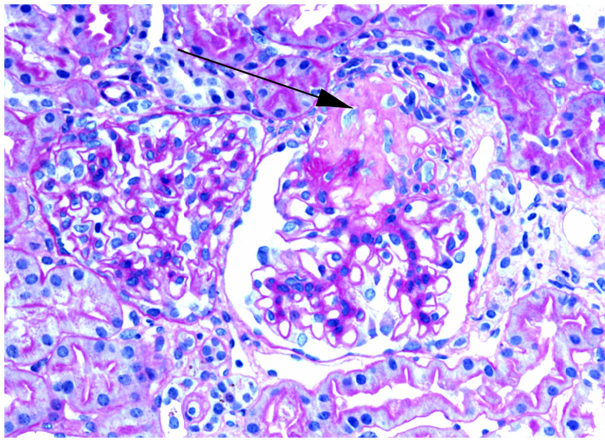


Fig. 4. Light microscopy of repeat kidney biopsy a year after presentation of anti-GBM disease. Arrow shows segmental sclerosis within a glomerulus.

Follow-up

At 3 years after initial presentation, the patient is asymptomatic but has controlled hypertension and proteinuria. Her creatinine clearance is 88.4 mL/min/1.73 m², proteinuria is 408 mg/day and anti-GBM antibody is still undetectable. Enalapril and MMC are continued, adjusted for her body weight. Prednisolone and cyclophosphamide were discontinued. Her renal prognosis remains guarded.

Discussion

We report a unique case of Goodpasture's syndrome in a young child in whom we successfully rescued renal function with aggressive immunosuppression. Her ongoing mild proteinuria, hypertension and development of focal

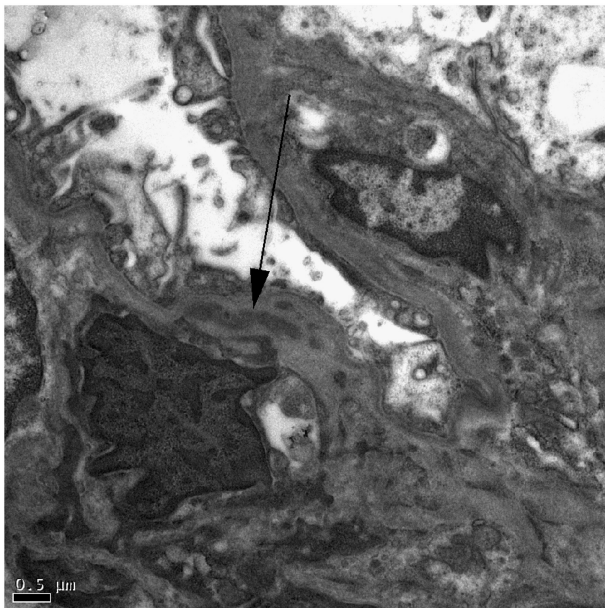


Fig. 5. Electron microscopy of repeat kidney biopsy a year after presentation of anti-GBM disease. Arrow shows immune deposits.

sclerosing glomerulonephritis in subsequent kidney biopsy a year later forebode a guarded prognosis. At 3 years, since the onset of the disease, she has near normal renal function.

There are only a handful of cases of anti-GBM disease developing in extremely young children. One possibility may be the difficulty of diagnosing mild cases which can be mistaken for post-streptococcal glomerulonephritis (PSGN) that classically occurs at a similar age [7]. There are distinguishing characteristics such as low C3, normal C4 and absence of rapidly progressive glomerulonephritis that distinguish PSGN from anti-GBM antibody disease [7].

In our case, the patient had exposure to streptococci based on positive ASO, but because of normal C3 and C4, and rising creatinine, we performed a kidney biopsy early in the illness and were able to successfully diagnose and ultimately rescue renal function. On the second kidney biopsy, the patient developed focal sclerosing glomerulonephritis presumably due to anti-GBM disease, which has not been reported in younger children. Despite aggressive immunosuppression and normalization of anti-GBM antibody in the serum 6 months after the onset of the disease, the kidney biopsy showed deposition of anti-GBM antibody a year after the onset of the disease.

A 6-year-old boy has been described in literature to have presented with an anti-GBM-mediated crescentic glomerulonephritis, and following plasmapheresis and immunosuppressant therapy had a favourable outcome with normal renal function two and a half years later [5]. However, the patient was left with 30% fibrous crescents [5]. Most cases of anti-GBM disease in paediatric patients have acute presentations with diffuse glomerular disease and severe fibrinoid necrosis along with cellular crescent formation with subsequent glomerular scarring and severe chronic disease leading to end-stage renal disease [4]. Being that there is direct antibody formation to the non-collagen domain of type IV collagen, the involvement is typically diffuse, with all glomerular lesions being of the same age. An 11-month-old child with anti-GBM disease showed diffuse glomerular involvement with necrosis and cellular crescent formation [8]. Despite plasmapheresis and extensive immunosuppressive therapy, the renal disease worsened leading to kidney transplantation 12 months later [8]. The development of diffuse involvement of glomeruli with necrosis and cellular crescent formation due to anti-GBM disease in older children, teenagers and young adults from ages 8–24 years has been described in literature [2,6,9–12]. Renal outcome in these series of papers has been often unfavourable despite aggressive immunosuppression.

Even though our patient presented with anti-GBM glomerulonephritis with diffuse glomerular necrosis and crescent formation, on repeat kidney biopsy, she had focal glomerular sclerosis with mild chronic tubulointerstitial injury. The recovery of renal function with aggressive immunosuppression was consistent with mild chronicity on follow-up biopsy. The rescue of renal function is highly atypical for her age group.

It had been hypothesized that full basement membrane expression of type IV collagen does not occur until 3 years of age and that the full expression of the $\alpha 3$ antigen is at 3 years of age and beyond [8]. Some researchers

have argued that between the ages of 3 months and 3 years, the $\alpha 3$ antigen is in a transition period that may lead to decreased anti-genicity prior to age 3 years [2]. In Alport syndrome, the lack of $\alpha 3$ antigen protects the kidney from developing anti-GBM disease [2]. The lack of full expression of $\alpha 3$ antigen prior to age 3 years could potentially lead to milder anti-GBM disease that can be mistaken for PSGN as mentioned above [5,8]. However, subsequent research has shown that $\alpha 3$ antigen is well expressed at birth [13]. Others have postulated that young patients that develop anti-GBM glomerulonephritis might have precocious development of mature basement membrane formation or an autoimmune response to an unknown basement membrane antigen that is not age-dependent [8,14].

The initiating stimulus (antigen) that leads to the development of anti-GBM antibodies is unknown. However, hypotheses include exposure to viral and bacterial infections [5], unknown toxins [7], or induced glomerular trauma such as in lithotripsy [8]. HLA type DR15 and DR4 are common in patients with anti-GBM disease with or without pulmonary involvement [8].

In conclusion, anti-GBM disease, even in the absence of pulmonary involvement, should be considered in the differential diagnosis of rapidly progressive glomerulonephritis even at a young age. Unfavourable renal outcome is not uniform, and early diagnosis with aggressive long-term immunosuppression can lead to favourable renal outcome.

Conflict of interest statement. None declared.

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