

Rituximab for the Treatment of Pediatric Double-Positive Small-Vessel Vasculitis



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INTRODUCTION

The syndromes of small-vessel vasculitides (SVV) are rare and potentially life-threatening conditions and can present as a pulmonary renal syndrome. Many such patients have antineutrophil cytoplasmic antibodies (ANCA) directed to either myeloperoxidase (MPO) or proteinase 3 (PR3), although other antigens have been described.¹ Patients with SVV related to ANCA, however, can develop coexisting anti-glomerular basement membrane (GBM) antibodies (Abs),² that is, double positivity, which has been linked to high rates of end-stage renal disease.³ Plasma exchange and immunosuppressive treatment, including the cytotoxic drug cyclophosphamide, for up to 9 months⁴ can prevent end-stage renal disease in approximately 40% of cases.³ Rituximab, an anti-CD20 monoclonal Ab that depletes B lymphocytes, has been proved effective in SVV related to ANCA.^{5,6} At present, no high-quality evidence exists to support a firm recommendation regarding the use of rituximab in patients with anti-GBM Abs.

To the best of our knowledge, 6 cases of SVV linked to ANCA and anti-GBM Abs in patients less than 16 years of age have been described in the English-language literature. We report the first pediatric case, in a patient in whom a sustained remission was induced by rituximab as add-on to a short course of cyclophosphamide as first-line treatment.

CASE REPORT

A 15-year-old girl with no relevant medical history presented at the outpatient clinic with shortness of

breath, cough, and left-sided thoracic pain. Two weeks prior to the presentation, she had symptoms consistent with a mild upper respiratory infection with hemorrhagic blisters on the right elbow and heel as well as the left toe. The review of systems was entirely negative. The patient used oral contraception but no other drugs; she had no history of smoking or illicit drug use. The results of a physical examination were normal. Laboratory investigations showed normal blood counts, C-reactive protein level of 62 mg/l, and D-dimer of 7900 ng/ml. Computed tomographic angiography of the chest showed no vascular abnormalities, although parenchymal consolidations were found in the upper lobes and right lower lobe of the lungs. The patient was admitted, and amoxicillin/clavulanic acid and analgesics were started. New painful hemorrhagic blisters and bloody stools, however, developed.

At day 7, the patient became oliguric, and serum creatinine increased from 57 μ mol/l to 96 μ mol/l. Nonnephrotic proteinuria and red cell casts on urinalysis were found. Systolic and diastolic blood pressures were within the 96th and 79th percentiles, respectively. The kidneys appeared normal on ultrasound, and a diagnosis of rapidly progressive glomerulonephritis was inferred. A kidney biopsy sample showed 11 glomeruli without global sclerosis. Seven glomeruli (64%) showed breaks of the glomerular basement membrane associated with fibrinoid necrosis, karyorrhexis, and cellular crescents, whereas the other glomeruli appeared normal. Interstitial fibrosis, tubular atrophy, and vascular damage were not present, underlining the acute onset of disease. Immunofluorescence microscopy revealed linear deposits of

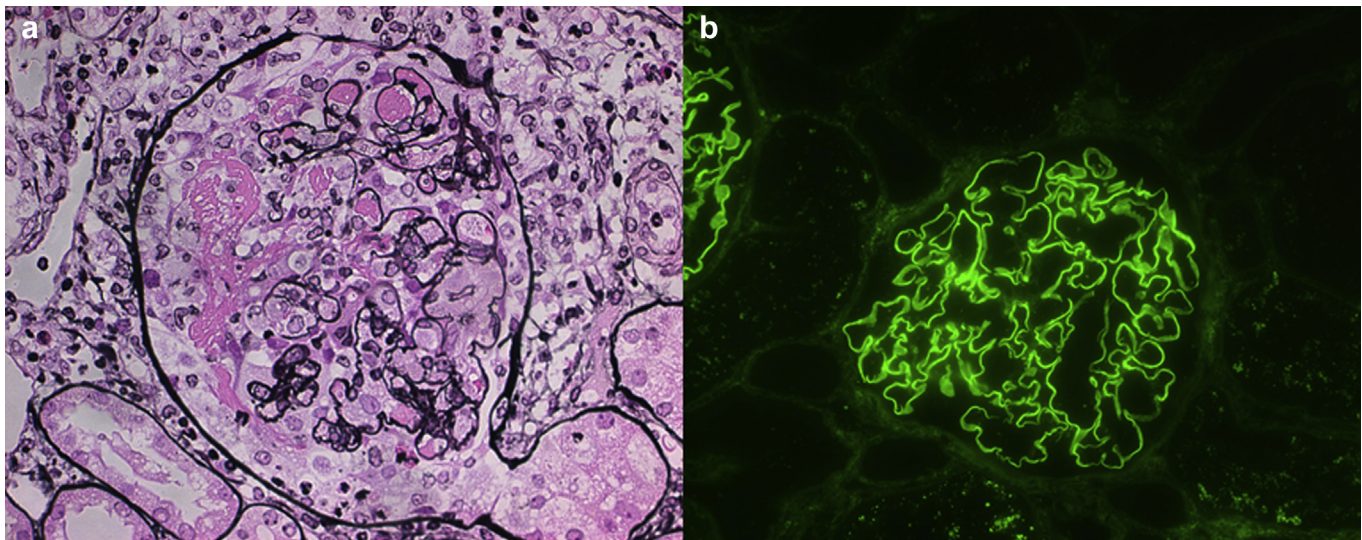


Figure 1. Kidney biopsy findings. (a) Breaks of the glomerular basement membrane can be appreciated with fibrinoid necrosis and crescent formation on light microscopy (Jones methenamine silver, original magnification $\times 400$). (b) Linear deposits of polyclonal IgG (original magnification $\times 400$) and C3c can be found along the glomerular basement membrane on immunofluorescence microscopy.

polyclonal IgG and C3c along the GBM (Figure 1). Indeed, circulating anti-GBM Abs (258 U/ml; reference value, <7 U/ml) and MPO-ANCA (25 IU/ml; reference value, <3.5 IU/ml), confirmed by capture enzyme-linked immunosorbent assay, were detected. Thus, a diagnosis of SVV linked to double positivity was made, with pulmonary and renal involvement.

Plasma exchange was initiated for 14 days and stopped when anti-GBM Abs became undetectable. Methylprednisolone (1000 mg/d for 3 days), prednisolone (60 mg/d tapered over 5 months), cyclophosphamide (150 mg/d for 6 weeks), and rituximab (1000 mg twice) also were started (Figure 2). Six months after the last dose of rituximab, $CD19^{+}$ B lymphocytes reappeared.

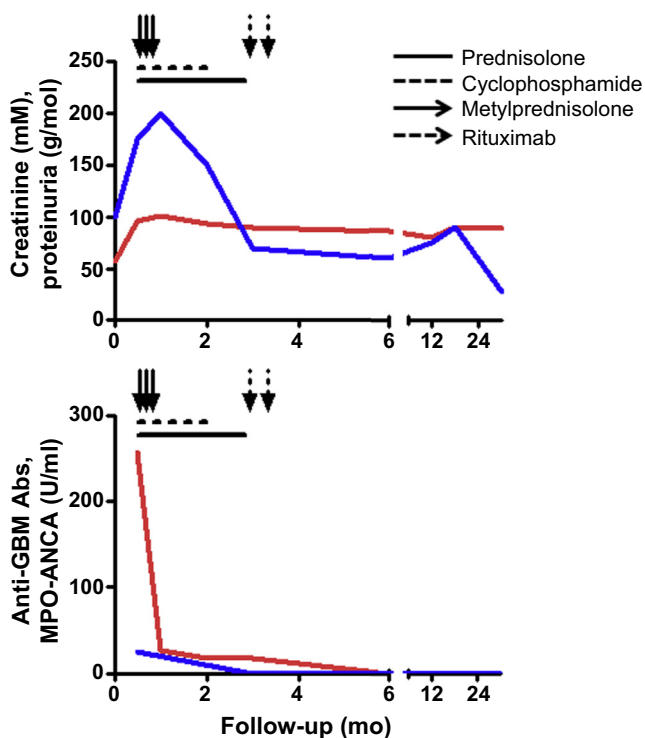


Figure 2. Treatment and follow-up. Red lines represent creatinine and anti-glomerular basement membrane (GBM) antibodies (Abs). Blue lines represent proteinuria and myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA).

The patient's renal function remained stable at an estimated glomerular filtration rate of 84 ml/min per 1.73 m² for 16 months. Nonnephrotic proteinuria (500–1000 mg/d), however, persisted. Focal global glomerulosclerosis ($n/N = 8/36$ glomeruli) and fibrotic crescents ($n/N = 5/36$ glomeruli) were found on repeat kidney biopsy, reflecting structural abnormalities; no significant damage was seen in the tubulointerstitial and vascular compartments. Linear deposits of polyclonal IgG and IgM, however, remained present. Thus, chronic glomerular damage was found with no disease activity. Indeed, neither anti-GBM Abs nor MPO-ANCA have reoccurred since, and the patient's renal function has improved to an estimated glomerular filtration rate of >90 ml/min per 1.73 m². Amenorrhea did not develop.

DISCUSSION

We present the first pediatric case of SVV that developed on the background of anti-GBM Abs and MPO-ANCA, in a patient in whom a sustained remission was achieved upon Abs depletion and rituximab in addition to a short course of cyclophosphamide as first-line treatment.

SVV related to ANCA is extremely rare among children (Table 1), with an estimated incidence

Table 1. Teaching points

Patients with pulmonary renal syndrome should be tested for anti-GBM Abs and ANCA, as these antibodies can coexist, having an impact on treatment and prognosis.

The initial presentation and follow-up of double-positive small-vessel vasculitis reflect anti-GBM disease and ANCA disease activity, respectively.

Rituximab appears to be safe and may be used as add-on for the treatment of small-vessel vasculitis in double-positive patients.

ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

of <1 per 100,000 children per year.⁷ In the adult population, up to 10% of cases with SVV related to ANCA present with coexisting anti-GBM Abs^{2,3}; to date, double positivity also has been described in 6 pediatric cases (Supplementary Table S1). In line with our case, most of these patients present with significant kidney disease and alveolar hemorrhage, indicating that the phenotype at presentation resembles anti-GBM disease rather than ANCA-related disease (Table 1).

The pathogenicity of both MPO-ANCA⁸ and anti-GBM Abs⁹ have been demonstrated in animal models. Rutgers *et al.* demonstrated that MPO-ANCA develops prior to anti-GBM Abs.² The GBM in its native form, however, consists of a network of type IV collagen molecules of $\alpha 3$, $\alpha 4$, and $\alpha 5$ chains, preventing exposure of the Goodpasture antigen within the non-collagenous domains of these α chains. It has been postulated that patients with double positivity have smoldering glomerular inflammation related to ANCA, inducing a conformational change of the Goodpasture antigen, anti-GBM Abs formation via epitope spreading,^{S1} and fulminant SVV. Pathologic studies underline this hypothesis, as various stages of disease can be found on kidney tissue sections from patients with double positivity. In contrast, synchronous crescent formation can be found in most cases of pure anti-GBM disease.^{2,3}

The patient's kidney biopsy showed necrotizing crescentic glomerulonephritis with no evidence of chronic damage in the tubulointerstitial and vascular compartments, indicating early disease. Also, unaffected glomeruli were found, indicating a favorable prognosis.^{S2,S3} Many of such patients will be treated with plasma exchange and a cyclophosphamide-based immunosuppressive regimen.^{3,4} Jones *et al.* showed that a rituximab-based immunosuppressive regimen can safely be used to induce a sustained remission in patients with severe SVV related to ANCA.⁶ In the present case, we induced a sustained remission with add-on rituximab; Touzot *et al.* corroborated our observation in a series of 8 patients with severe and/or refractory anti-GBM disease.^{S4} These clinical observations suggest that rituximab may be used in patients with SVV and double positivity (Table 1).

Relapses are common among patients with SVV related to ANCA, either with anti-GBM Abs³ or without it,^{S5} indicating that the long-term course of disease can be linked to ANCA. Patients with double positivity therefore require maintenance treatment, in contrast to those with pure anti-GBM disease, who have a low risk of relapse. Rituximab can be used for remission maintenance following sustained remission in SVV related to ANCA, although the optimal use has to be established yet. Monitoring of ANCA levels and circulating CD19⁺ B lymphocytes may guide rituximab treatment.^{S6} The patient's CD19⁺ B lymphocytes reappeared after 6 months, whereas ANCA test results remained negative, indicating quiescent immunologic disease. Furthermore, negative ANCA test results after the induction of a sustained remission and initial MPO specificity have been linked to a lower risk of relapse. Rituximab has therefore not been reinfused.

In conclusion, SVV and double positivity are extremely rare in the pediatric population and warrant immunosuppressive treatment. Rituximab appeared safe and may be used as add-on treatment for remission induction. Future trials therefore should focus on rituximab for the treatment of SVV linked to double positivity. CD19⁺ B lymphocytes and Abs levels may guide maintenance treatment.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Table S1. Clinical and laboratory data of pediatric patients with SVV and double positivity.

Supplementary References.

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