BRIEF REPORT

Fulminant viral myocarditis after rituximab therapy in pediatric nephrotic syndrome

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Abstract

Background We report a 7-year-old boy with high-degree steroid-dependent idiopathic nephrotic syndrome (SDNS) who went into remission with rituximab (RTX) maintenance therapy. *Case-Diagnosis/Treatment* Four months after this patient received his first RTX infusion, there was a progressive and sustained decrease of immunoglobulin (Ig)G and IgM levels. Thirteen months after the initiation of RTX therapy he was in sustained remission without any steroid or oral immunosuppressive therapy; however, B cell depletion was still present. At this time he developed a fulminant myocarditis due to enterovirus. Despite aggressive treatment and the administration of intravenous polyvalent immunoglobulins there was no clinical improvement. He successfully underwent heart transplant surgery.

Conclusions We conclude that B cell depletion with RTX is efficacious in the treatment of paediatric SDNS but that it may be associated with severe infectious complications. Therefore, we recommend a close monitoring of Ig levels in children who have received RTX therapy and a supplementation with intravenous Ig as soon as the Ig levels fall below the lower limit of the normal range

Keywords Idiopathic nephrotic syndrome · Rituximab · B cell depletion · Hypogammaglobulinemia · Fulminant myocarditis

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Introduction

Idiopathic nephrotic syndrome is the most frequent glomerular disease during childhood. Most patients respond to steroids, but a significant number of these will become steroid dependent, with the potential for developing complications associated with long-term steroid exposure, such as growth retardation, bone impairment and metabolic syndrome. B cell depletion with rituximab (RTX), a genetically engineered chimeric murine/human monoclonal immunoglobulin (Ig) G1 kappa antibody directed against the CD20 antigen, is a new therapeutic option in paediatric high-degree steroid-dependent idiopathic nephrotic syndrome (SDNS) [1]. Data from small studies suggest that RTX is usually well tolerated but that some minor adverse events, such as rash, dizziness or fever, may present [2–7]. The increasing use of this drug for a myriad of rheumatologic and immunologic conditions has revealed more severe side effects, namely cytokine release syndrome [8], interstitial pneumonitis [9, 10] and multifocal leukoencephalopathy [11]. Only rarely have infectious complications been reported, among which are a few cases of *Pneumocystis jiroveci* pneumonia [12].

We report here the first case of a paediatric patient with SDNS who developed fulminant myocarditis after B cell depletion due to RTX therapy.

Case report

A 7-year-old boy was diagnosed at the age of 3.5 years with idiopathic nephrotic syndrome that rapidly became steroid dependent. Due to many relapses despite a correct compliance to steroids, adjuvant immunosuppressive therapies with levamisole and subsequently mycophenolate mofetil (MMF) were initiated. His disease was partially controlled with MMF, although he experienced one to four relapses per year that responded well to high doses of prednisone. He further developed significant steroid-related toxicity, and 3.5 years after the initial diagnosis of SNDS, he was started on a 2-week course of RTX at a dose of 375 mg/m^2 per week. RTX infusion was performed during a remission phase of the disease, i.e., in the absence of any proteinuria [proteinuria 0.08 g/l (ratio 10 mg/mmol), serum albumin 34 g/l]. The delay between remission and RTX infusion was 15 days. At the time of the first RTX infusion, renal function was normal (serum creatinine 38 µmol/l). Due to the absence of official authorization allowing RTX use for SNDS in France, the parents were asked and subsequently provided their written informed consent for this procedure. Prior to each RTX treatment, the patient received a premedication with dexchlorpheniramine (2.5–5 mg) and hydrocortisone (0.5 mg/kg). Cotrimoxazole (20 mg/kg; three times a week) as a prophylaxis against pneumocystosis was given during the period of B cell depletion.
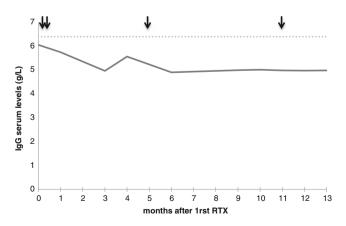
CD19 depletion was monitored by flow cytometry 1 week after the initiation of RTX infusion and then monthly. Our local policy of RTX in SNDS is the following: in case of reappearance of circulating CD19-positive cells (>10/mm^3), a new RTX infusion (375 mg/m^2) is performed in order to achieve a B cell depletion period of 18 months. Ig levels and serum albumin, as well as urinary protein and creatinine were assessed monthly.

In this patient, CD19 depletion was obtained 7 days after the first infusion, MMF was discontinued immediately after the second infusion and prednisone was tapered off over 3 months. Because of the reappearance of CD19-positive cells, we performed a new RTX infusion 5 (CD19 270/mm^3) and 11 months (CD19 125/mm^3) after the initial RTX infusion. The urinary protein to creatinine ratio was still <10 mg/mmol before each infusion.
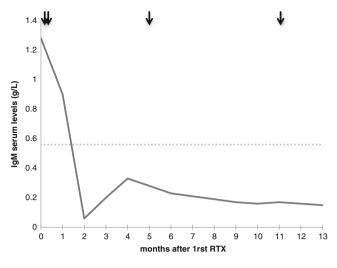
All three RTX infusions were well tolerated; of note, the patient developed a transient neutropenia 7 months after the beginning of RTX; at this time there was no fever or overt infection.

The Ig levels before RTX therapy and during a remission phase of the disease were 6.05 g/l for IgG (normal range 6.33–12.8 g/l), 0.07 g/L for IgA (normal range 0.33–2.02 g/l) and 1.28 g/l for IgM (normal range 0.48–2.07 g/l). After the RTX infusions, he had persisting low IgA levels, while we observed a progressive decrease in the IgG and IgM levels to under 4.6 and 0.3 g/l, respectively, 4 months after the first RTX infusion, as illustrated in Figs. 1 and 2.

Thirteen months after the first RTX infusion, the patient was in sustained remission of SDNS without any steroid or oral immunosuppressive therapy; B cell depletion was still present. At this time he developed a febrile ear pain for which he received oral antibiotics (amoxicillin). Three days later he was admitted to the paediatric intensive care unit, presenting with a cardiogenic shock, a severe left and right ventricular dysfunction and frequent episodes of non-sustained ventricular tachycardia. Myocarditis was diagnosed based on the context of a recent infection, the sudden onset of cardiac dysfunction and both the electrocardiogram and echocardiogram findings. An endomyocardial biopsy was performed which showed an inflammatory infiltrate, vasculitis and myocardial necrosis (Fig. 3); PCR assay of the sample was positive for enterovirus. The patient received intravenous polyvalent immunoglobulins (IVIG) at a dose of 400 mg/kg per day for 5 days in addition to a symptomatic management of cardiac dysfunction [13]. Despite aggressive care, including circulatory and venoarterial extracorporeal membrane oxygenation support, there was no clinical improvement, and 2 months later the patient successfully underwent heart transplant surgery.

At last follow-up (5 months after heart transplant surgery and 19 months after the first RTX infusion), the patient is doing well and receives a standard immunosuppressive regimen with prednisone, cyclosporine A and MMF. The B cell depletion has remained without any relapse of the nephrotic syndrome.

Fig. 1 Evolution of immunoglobulin (*Ig*) G levels after rituximab (*RTX*) treatment. *Arrows* RTX infusion

Fig. 2 Evolution of immunoglobulin (*Ig*) M levels after rituximab (*RTX*) treatment. *Arrows* RTX infusion
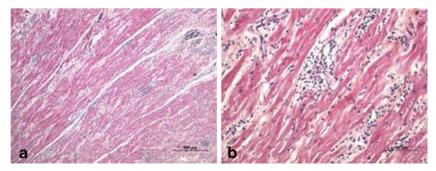
Discussion

Rituximab, a humanized monoclonal antibody approved for the treatment of malignant lymphoma, leukemia and rheumatoid arthritis, is being increasingly and effectively used off label for immune diseases such as SDNS. However, safety data after RTX therapy for nephrotic syndrome are limited.

To date, all published studies on this subject, consisting mainly of case reports and series of cases [1–7], have reported a good tolerance of RTX, with the most commonly described adverse effect being a transient cytokinic reaction. However, severe side effects have been reported when RTX is used to treat SDNS, including a fatal acute respiratory distress syndrome reported by our group [9] or severe ulcerative colitis [14]. Serious infections, such as *Staphylococcus aureus*-related thigh abscess, pneumonia, *Herpes zoster* infection [15], *Pneumocystis carinii* pneumonia [1, 12], severe gastroenteritis and infection due to human herpes virus 6 have also been described [6]. In a series of 70 patients, one case of agranulocytosis with sepsis and two episodes of pneumonia, of which one was due to *Pseudomonas aeruginosa*, have been reported [5]. In all cases, the patients had received concomitant immunosuppressive therapies in addition to RTX, and the extent of the B cell depletion remains uncertain.

The case reported here is the first case of viral acute myocarditis in a child with SDNS in which the patient required a heart transplant after RTX therapy. The causal relationship between RTX use and the onset of a severe viral infection appears to be more likely than in the other cases, especially since all other immunosuppressive therapies had been stopped for several months. After the start of RTX therapy and before the development of fulminant myocarditis, our patient did not present any significant infectious episode, except for a transient neutropenia, which is a classical side effect of RTX [16]. The myocarditis occurred after 12 months of B cell depletion while the patient displayed a global hypogammaglobulinemia involving the main isotypes IgG, A and M. As illustrated in Figs. 1 and 2, we observed a progressive decrease of IgG and IgM levels after the initial RTX infusions and re-injections. At the time of the viral myocarditis, the IgM levels were undetectable, which might explain this increased sensitivity to an enterovirus otherwise considered to be 'banal' during childhood. As a matter of fact, enteroviral myocarditis is a classical presentation of Bruton's agammaglobulinemia and immune deficiency.

There are very little data in the literature on the evolution of Ig levels after RTX treatment. As haematopoietic progenitor cells and only a fraction of differentiated plasma cells express CD20, the effect of RTX on immune function appears to be minimal. The expression of CD20 begins at the pre-B cell stage (before IgM expression) and is lost before these cells differentiate into immunoglobulin-secreting plasma cells [17]. Immunoglobulin levels do not fall below normal levels in the majority of patients treated with one course of RTX [18]. However, the proportion of patients with hypogammaglobulinemia has been found to increase with repeated doses, which may be required in relapsing/remitting diseases [8, 19], and hypogammaglobulinemia can persist for several years after RTX infusion associated with a persistent memory B cell

Fig. 3 Endomyocardial biopsy showing inflammatory infiltrate, vasculitis and myocardial necrosis. (**a**) low amplification showing diffuse inflammatory infiltrate and myocardial necrosis (*bar* = 500 μm) (**b**) higher amplification showing active vasculitis with enhanced density of the inflammatory infiltrate around dilated blood vessels (*bar* = 100 μm)

reduction [20–23]. It may also occur more commonly in children, who have an immature immune system, and in patients with underlying T cell abnormalities [24]. It has also recently been noted that IgM levels fall more than IgG levels, with the former dropping by 10 % after the first course, 19 % after the second and 24 % after the third course; these results are based on the largest study of patients with active rheumatoid arthritis carried out to date [8]. In contrast, in this same study, IgG and IgA levels only fell by 2 and 4 %, respectively, although in a few cases, they fell below normal levels. However, serious infection rates in these patients (5.6 and 4.8 per 100 patient-years in patients with low IgM and IgG levels, respectively) were comparable with those observed in patients with Ig levels above the normal range (4.7 per 100 patient-years). In this study no patient received IVIG replacement.

Besada et al. reported two cases of prolonged low levels of IgM and IgG in patients with severe infections who were on RTX maintenance therapy; these patients were successfully treated with monthly IVIG [25]. In another study, the authors recommend the use of prophylactic IVIG when IgG levels fall below normal, but there has not been any prospective trials focusing specifically on this question [26]. However, given the severity of the infection that developed in our young patient, we believe that in the case of low IgG and IgM levels, the use of IVIG would have been beneficial.

In conclusion, B cell depletion with RTX is efficacious in the treatment of paediatric SDNS, but it might be associated with severe infectious complications. The age of our patient as well as the low IgG and IgM levels may have played a role in the severity of the presentation. Lower doses of RTX (100 mg/m^2 instead of 375 mg/m^2) could be considered to be one approach by which to reduce the duration of each CD19 depletion period. Therefore, before larger studies are performed, we suggest that Ig levels in children who have received RTX therapy should be closely monitored and that supplementation with IVIG should be initiated as soon as these levels fall below the lower limit of the normal range.

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