

Clinical Report

Sustained complete remission of steroid- and cyclophosphamide-resistant minimal-change disease with a single course of rituximab therapy

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Abstract

We report a case of steroid- and cyclophosphamide-resistant nephrotic syndrome secondary to minimal-change disease occurring in an otherwise healthy 19-year-old female, responding rapidly to two doses of rituximab therapy. Complete disease remission has been sustained up to last follow-up (32 months) despite CD19 recovery. Literature review suggests emerging evidence that rituximab may have a role to play in recurrent and/or refractory minimal-change disease.

Keywords: minimal-change disease; nephrotic syndrome; rituximab; steroid resistance

Case report

A 19-year-old female with no significant past medical history or medication use presented to our hospital in April 2010 with severe nephrotic syndrome characterized by marked fluid retention, heavy proteinuria (protein:creatinine ratio of 1244 mg/mmol), hypoalbuminaemia (13 g/L) and elevated total serum cholesterol (9.3 mmol/L). Renal function was preserved with a serum creatinine of 42 µmol/L, and there was no haematuria evident on urine microscopy. Lupus and vasculitis markers, hepatitis serology and serum electrophoresis were negative.

A renal biopsy was performed which revealed normal glomeruli, tubules and interstitium. Immunoperoxidase was negative for immunoglobulin and complement. Electron microscopy was not performed. A diagnosis of minimal-change disease (MCD) was made.

The patient was commenced on prednisolone 50 mg daily (1 mg/kg) in addition to ramipril 5 mg daily, simvastatin 10 mg daily and warfarin therapy. Further increase in ACE inhibitor dose was limited by hypotension.

Complete remission was achieved within 2 months and prednisolone dose was reduced to 25 mg daily. Soon after, and against medical advice, the patient abruptly ceased her prednisolone and within 72 h had a relapse of disease with recurrence of gross peripheral oedema, hypoalbuminaemia of 13 g/L (from 31 g/L) and proteinuria of 1030 mg/mmol (from 0.06 mg/mmol).

Despite recommencing high-dose steroids (60 mg/day), the disease thereafter remained refractory to steroid therapy with persistent gross oedema, nephrotic-range proteinuria and hypoalbuminaemia (albumin of 9 g/L).

After failing to respond to 3 months of high-dose steroids, the patient was commenced on cyclophosphamide. In light

of the patient's history of non-compliance and in an effort to reduce drug exposure and toxicity, pulse intravenous cyclophosphamide was administered in incremental doses of 0.5, 0.75 and 1.0 g/m² 1 month apart. During this period, steroids were gradually weaned. Two months after the third pulse of cyclophosphamide was administered, there was no evidence of disease response with ongoing gross oedema, hypoalbuminaemia (albumin 14 g/L) and heavy proteinuria (1476 mg/mmol).

At this point, it was decided to trial the monoclonal anti-CD20 antibody rituximab (RTX), with two doses of 500 mg given 2 weeks apart. Complete remission was rapidly induced within 1 month of RTX therapy with resolution of oedema, rising albumin to 31 g/L and absent proteinuria (Figure 1). CD19 count fell from 94 to <1/µL consistent with the drug effect.

The patient has remained in complete remission for more than 32 months since the two doses of RTX were administered in February 2011. This is despite recovery of CD19 counts back to normal levels 24 months after treatment.

Discussion

MCD is the most common cause of nephrotic syndrome in children and accounts for 10–25% of cases in adults. Close to 75% of cases will respond initially to a course of high-dose glucocorticosteroids but relapse commonly occurs [1]. Steroid-sparing agents like calcineurin inhibitors and cyclophosphamide are often used for frequently relapsing or steroid-dependent MCD. Besides the significant adverse side effects of these agents, a large proportion of patients relapse after cessation of these medications. While there was some suggestion that oral cyclophosphamide may be

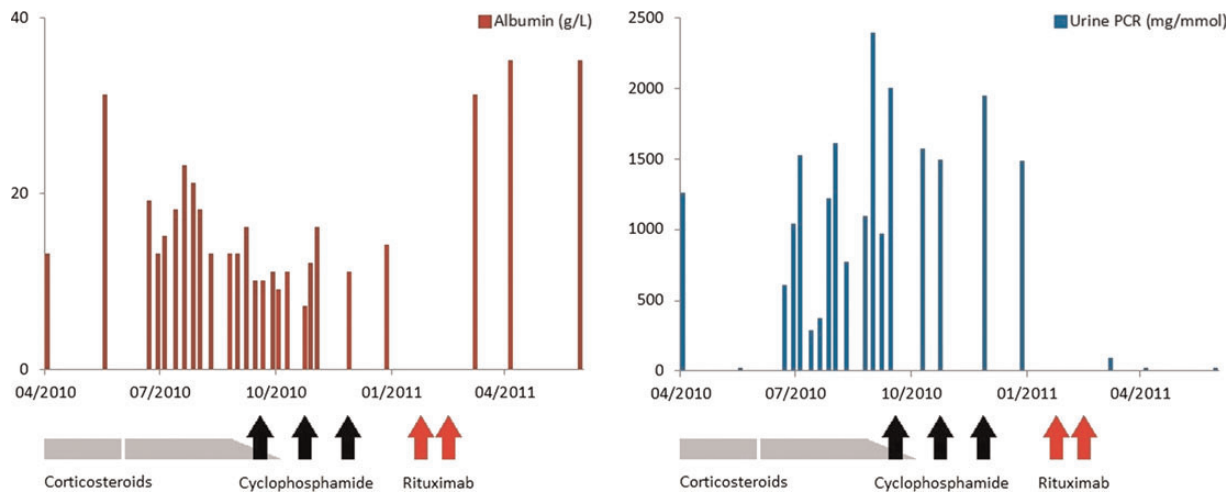


Fig. 1. Changes in serum albumin (g/L) and urine protein:creatinine ratio (mg/mmol) over time, relative to treatment modality.

more successful than IV cyclophosphamide in achieving disease remission in refractory MCD [2], larger clinical trials have suggested that both forms of therapy are equivocal with respect to relapse rates and toxicity [3].

There are an increasing number of reports of success of RTX therapy for steroid- and cyclosporine (CsA)-dependent nephrotic syndrome in paediatric populations [4, 5]. A single RTX infusion also appeared to improve response to CsA therapy and had significant steroid-sparing effects in children with steroid-'dependent' nephrotic syndrome (SDNS) who had developed secondary resistance to CsA [6].

In a long-term follow-up study of 37 children who received RTX for SDNS, 26 patients remained in remission after 12 months and 7 remained in remission after 24 months without further maintenance immunosuppression [7].

However, response to RTX has been mixed in cases of steroid-'resistant' nephrotic syndrome (SRNS) in children. Bagga *et al.* [8] reported the successful use of rituximab in five patients with SRNS, two of which had MCD. Prytuła *et al.* [9] carried out a multi-centre questionnaire-based study in which the response rate in children with SRNS was as high as 44%. In another case series of four children with SRNS, including one case of MCD, all children failed to achieve sustained remission after a single dose of rituximab, despite complete B-cell depletion [10].

In adults, the first case report of the efficacy of RTX in multi-relapsing MCD was published in 2007 [11]. Since then there have been a number of reports of success with rituximab in steroid-dependent MCD [12, 13]. Munyentwali *et al.* [14] analysed the outcome of 17 adult patients who were treated with RTX for steroid-dependent MCD over a mean follow-up period of 29.5 months. After the first course of RTX, 11 patients (65%) did not relapse after a mean follow-up of 26.7 months. Four of them received a second course of RTX because of CD19 cell recovery. Twelve of the 17 patients (70%) were free of any immunosuppressant drugs at last follow-up.

There are minimal data available regarding the use of RTX in steroid-resistant MCD in adults. The first case report, published in 2008, describes an adult patient with steroid- and mycophenolate mofetil-resistant MCD who remained in complete remission 1 year after initiation of RTX therapy [15]. A further case report was of a 23-year-old patient with steroid- and CsA-resistant MCD treated with two doses of RTX with sustained complete remission

at the end of 1 year. The second dose of RTX was given at 6 months in response to a recovery of B-cell counts [16].

A long-term follow-up study was published recently by Bruchfeld *et al.* [17] on 16 adult patients with biopsy-proven MCD of which 13 were steroid dependent, 2 multi-relapsing and 1 steroid and multi-drug resistant. In this study, the RTX dose varied from 1000 to 2800 mg. Complete remission was achieved after initial RTX treatment in 13 patients. In the remaining cases, partial remission was achieved in all except the patient with steroid- and multi-drug-resistant disease.

Relapses can often occur after the reappearance of CD19 cells, although this is not always the case [12, 14]. Guignon *et al.* [5] found a consistent association between relapses (3 of 22 paediatric patients) and an increase in CD19 cells which occurred at a median time of 11 months (range 8–39 months). However, nine sustained remissions were achieved despite the reappearance of CD19 cells.

Sellier-Leclerc *et al.* [18] evaluated disease outcome after a minimum CD19 depletion period of 15 months obtained by repeated RTX infusion and found that it induced long-term remission even after definitive CD19 recovery in almost two thirds of the paediatric patients without the use of maintenance oral immunosuppressive drugs.

The RTX dosing has varied greatly in various reports including a single dose, doses of 500 or 1000 mg given at one or two time-points and 375 mg/m² once weekly for 4 weeks. In the study by Munyentwali *et al.* [14], no correlation was found between RTX dose used and relapses.

We report a unique case of steroid- and cyclophosphamide-resistant MCD responding rapidly to two doses of RTX at 500 mg each, with sustained complete remission even after CD19 recovery. As discussed, RTX has been shown to be efficacious in a growing number of small case series in steroid-sensitive and steroid-dependent MCD; however, reported success of its use in multi-drug-resistant disease, particularly in adults, remains limited. In our case, the drug was well tolerated with nil reported side effects.

Clearly, a well-conducted multi-centred clinical trial of RTX for MCD is warranted either as a first-line agent or in cases of steroid-dependent and/or -resistant disease.

Conflict of interest statement. None declared. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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