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CASE REPORT

Successful treatment of recurrent focal segmental glomerulosclerosis after kidney transplantation by plasmapheresis and rituximab

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Summary

A 22-year-old patient whose primary kidney disease was focal segmental glomerulosclerosis (FSGS) developed severe recurrence of proteinuria (up to 57 g/24 h) immediately after a haploidentic living donor kidney transplantation despite pre-operative plasmapheresis. The immunosuppressive treatment consisted of tacrolimus, mycophenolate mofetil, basiliximab and steroids. He underwent 10 plasmapheresis sessions in the first 3-week post-transplantation. In addition, he received 2 i.v. doses of rituximab (RTX) 600 mg (375 mg/m^2) on days 7 and 15. Proteinuria decreased below nephrotic range at day 14 and serum creatinine returned progressively to normal values. A short course of oral ciclophosphamide (100 mg/j) was administrated between days 22 and 40 and three additional plasmapheresis sessions on days 34, 39 and 49. This strategy allowed obtaining sustained full remission of the nephrotic syndrome (NS) and excellent graft function, which persists over 2 years after transplantation. No notable adverse events related to RTX or plasmapheresis were observed. This case suggests that RTX associated with plasmapheresis may be an effective treatment of recurrent NS because of FSGS.

Introduction

The risk of recurrence of nephrotic syndrome (NS) because of focal segmental glomerulosclerosis (FSGS) after kidney transplantation has been estimated between 15% and 50% in various series. Recurrence usually occurs within the first month after transplantation and is characterized by the appearance of massive proteinuria. It has a poor prognosis as more than 30% of patients progress to end stage renal disease within 5 years [1–2]. There is no consensus for the treatment of recurrence. In most cases, plasmapheresis [1–7] or immunoabsorption [8] are initiated, in combination with angiotensin-converting enzyme (ACE) inhibitors and intensified immunosuppression such as ciclophosphamide [4] or high-dose cyclosporine [5,6]. Both plasma treatment methods were shown to decrease proteinuria significantly but their discontinuation often results in a relapse of proteinuria [7].

Rituximab (RTX) is a chimeric monoclonal antibody directed against the cell surface antigen CD-20 of B-lymphocytes [9]. It is an effective therapy for non-Hodgkin's lymphoma [10] and other B-cell malignancies such as post-transplant lymphoproliferative disorder (PTLD) [11]. In the last years, several reports of successful use of RTX in autoimmune diseases were published, including membranous glomerulonephritis [12], lupus nephritis [13], Wegener granulomatosis [14] and thrombotic thrombocytopenic purpura [15].

Recently, full remission of primary and recurrent NS because of FSGS was reported in two patients treated by RTX for idiopathic thrombocytopenic purpura [16], and PTLD [17].

We report a case of sustained remission of recurrent NS after living-related donor kidney transplantation using plasmapheresis and RTX.

Case report

In June 2004, a 22-year-old male patient received a haploidentic living donor kidney transplant.

At the age of three, he had developed idiopathic NS, which was cortico-dependent. Family history with regard to kidney diseases and a genetic study performed recently were negative. Under corticotherapy, he had frequent relapses and cyclophosphamide treatment (2 mg/kg p.o.) had been unsuccessful. In 1995 after a renal biopsy, showing 'minimal change' disease cyclosporine A was initiated, allowing substantial reduction of steroid doses. However, multiple relapses still occurred, which responded only partially to steroids. In 1999, a second renal biopsy revealed FSGS and cyclosporine toxicity. Mycophenolate mofetil (MMF) and tacrolimus (TAC) had no significant effect on proteinuria and haemodialysis had to be started in August 2003. Renal transplantation with a graft donated by the patient's father was planned. Two plasma-exchanges were performed at days −3 and −1 and immunosuppressive drugs were started 2 days before surgery. Besides TAC (kept at a target trough level >12 ng/ml) and MMF, the postoperative immunosuppressive regimen consisted of two doses of basiliximab at days 0 and 4 and steroids. Graft function rapidly recovered with serum creatinine reaching a nadir of 78 μM at day 3. Nephrotic range proteinuria appeared at day 2 and reached at day 5 8.57 g/mmol creatinine (57 g/24 h), followed by a progressive deterioration of renal function. The clinical course and the degree of proteinuria strongly suggested recurrent initial disease, so that graft biopsy was not performed.

The patient underwent 10 plasma-exchanges from days 2 to 22. Per session, a mean of 1.5 l of plasma was substituted by human albumine and fresh frozen plasma. No change in proteinuria was observed after the first four sessions. We therefore decided to use RTX in an attempt to achieve further immunomodulation. Two i.v. doses of RTX (Mabthera®; Roche Laboratories, Basel, Switzerland) 600 mg (375 mg/m^2) were given at days 7 and 15. Proteinuria decreased below the nephrotic range after day 14 and renal function normalized. ACE inhibitors, which had been stopped during the acute deterioration of renal function, were reintroduced.

In an attempt to consolidate this favourable evolution, the patient received cyclophosphamide 100 mg/day between days 22 and 40 and three additional plasmapheresis sessions on days 34, 39 and 49. Proteinuria decreased continuously and complete remission was achieved after day 87 (Fig. 1).

One year after transplantation, the patient had excellent graft function and no significant proteinuria. His immunosupression associated TAC, MMF and low-dose prednisone. He had no major infectious episodes during this period.

A graft biopsy made 1 year after transplantation did not show any glomerular abnormalities or any immunological deposits. At 24 months after transplantation, renal function is stable with a serum creatinine of 128 μM and no microalbuminuria. Steroids have been withdrawn.

Discussion

Recurrence is a major problem in renal transplantation for patients with FSGS. If untreated, serious complications and graft loss can occur.

In the present case, despite pre-emptive plasmapheresis and pre-operative introduction of immunosuppression, massive proteinuria appeared immediately after transplantation leading to rapid deterioration of renal function. We added RTX followed by cyclophosphamide to plasmapheresis in an attempt to inhibit putative B-cell clones responsible for the production of glomerular permeability factors. Under this combined therapy, full remission of the NS was obtained.

As plasmapheresis could not avoid immediate recurrence of proteinuria and cyclophosphamide used in the past had revealed its lack of efficacy, we believe that it was the addition of RTX, which played the principal role in achieving full remission of NS.

To our knowledge, there are only two published cases in which RTX treatment induced remission of proteinuria in patients with recurrent FSGS after kidney transplantation. In both cases, RTX was administrated for PTLD and resolution of proteinuria was a favourable side-effect [17,18]. Our case is the first in which RTX was used in a patient who had no concomitant lymphocyte disorder.

The mechanism by which RTX might influence the course of recurrent FSGS remains elusive as is the physiopathology of this disease. The occurrence of immediate relapse after transplantation and the possibility to induce proteinuria in rats injected with plasma fractions obtained from FSGS patients [19] suggest the presence of a circulating glomerular permeability factor. The exact nature of this factor and the cells involved in its production remain unknown.

A primary T-cell dysfunction was suspected, following the reports that T-cell hybridomas from nephrotic

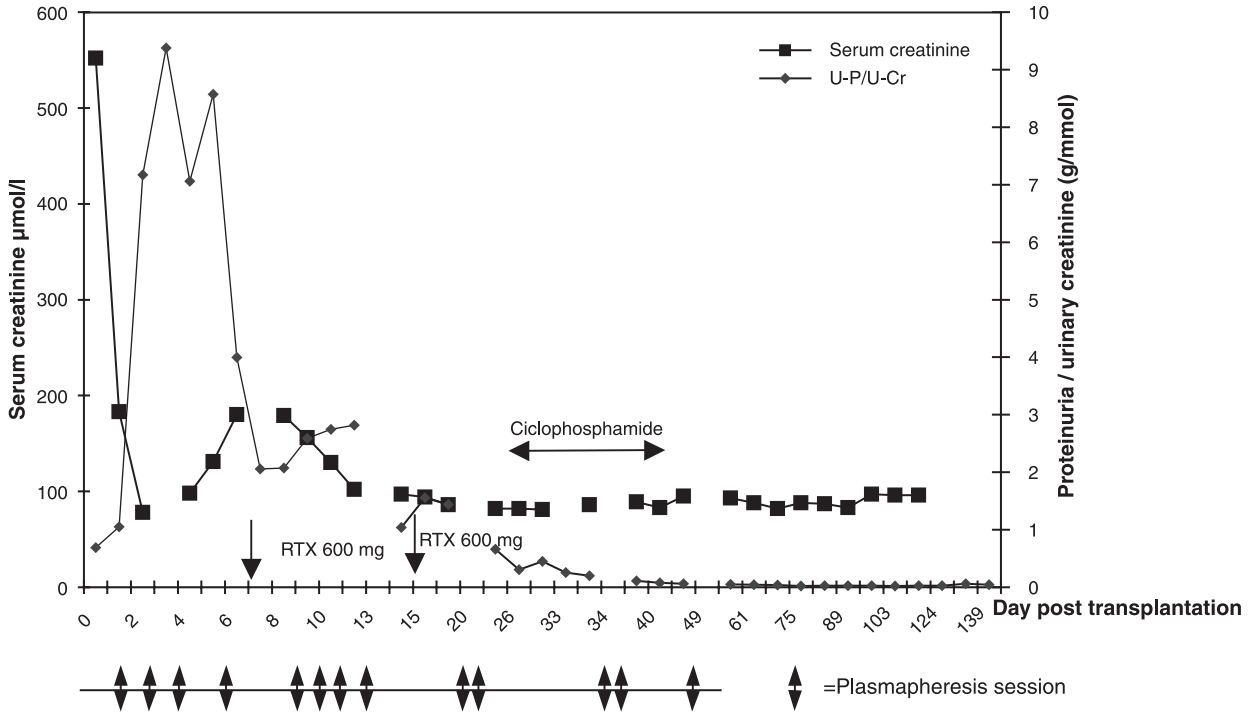

Figure 1 Clinical course in terms of serum creatinine and ratio of urinary protein to urinary creatinine.

patients synthesize a factor that rises glomerular permeability in rats [20]. The cytokine profile found during FSGS relapse, characterized by increased levels of interleukin-4 [21] and interleukin-13 [22], suggests the predominance of the Th2 subtype of lymphocytes. Nevertheless, the link between these anomalies and proteinuria is unknown.

The role of B-cells in the pathogenesis of FSGS is more controversial and less explored. Abnormalities in the gammaglobuline subclasses (increased IgE [23], depressed IgG1 and IgG2 [24]) are common in FSGS. Both B- and T-cell activation markers are increased during relapse of idiopathic NS [25]. Involvement of B-cells is also supported by the observation that some patients with B-cell proliferative disorders develop NS and B-cell depletion therapy, even if it does not include steroids, induces remission [26]. Another argument for the implication of immunoglobulines and B-cells is the capacity of immunoabsorption using a protein A or an anti-IgG column to temporarily remove the proteinuric activity of sera from nephrotic patients [8]. Finally, the involvement of B cells in autoimmune diseases goes beyond the production of auto-antibodies and a role in regulating T cells may be of importance [27].

Thus, it can be hypothesized that RTX depletes B cells, which directly or by their interaction with other cell lines influence the production of the glomerular permeability factors.

Our combined therapy makes it difficult to assess the precise role of RTX in this case. Indeed, cyclophosphamide might as well have contributed to achieve the remission. Nevertheless, in the past, it had revealed its lack of efficacy and the decrease in proteinuria began before the introduction of this drug.

Similarly, we cannot exclude that plasmapheresis alone or in combination with TAC and MMF has contributed to obtain sustained remission of NS. Plasma exchanges have been shown capable to reduce proteinuria in recurrent FSGS. However, in the majority of patients treated by plasmapheresis or immunoadsorption, proteinuria reappears after cessation of these treatments [7]. Our patient, who had a severe form of FSGS, which was resistant to the standard therapeutic regimens, remains in full remission 24 months after the initial disease's recurrence. It is probable that the combined treatment strategy which included RTX has achieved this long-term remission.

No acute adverse events related to RTX were observed. Common side-effects related to a cytokine release syndrome can usually be reduced by premedication with corticoids and histamine blockers. There is an increased rate of infection because of the profound B-cell depletion in the months following the RTX treatment, but they are rarely severe and do not require hospitalization [27]. No serious infectious event occurred in our patient during the first 2 years after transplantation.

This case suggests that treating post-transplant recurrent FSGS by plasmapheresis and RTX can induce sustained full remission. More cases and prospective trials are needed to confirm the benefit of RTX treatment in this disorder. If efficacy of RTX will be demonstrated, it might reveal new pathophysiological mechanisms of this disease.

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