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CASE REPORT

Immunoadsorbtion and rituximab therapy in a second living-related kidney transplant patient with recurrent focal segmental glomerulosclerosis

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Summary

A 29-year-old patient with focal segmental glomerulosclerosis (FSGS) and recurrence of the disease in a living donor kidney transplant received a second living-related kidney graft. She received pre- and postoperative immunoadsorptions and immunosuppression with tacrolimus, mycophenolate mofetil, basiliximab and steroids. Serum creatinine returned to normal values and only minor proteinuria was detected post-transplant (400 mg/24 h). However, recurrence of proteinuria with up to 3.3 g/24 h occurred 2 months after transplantation and the patient underwent intermediate immunoadsorption sessions with immediate reduction of proteinuria for the following year. She then received three doses of rituximab (600 mg, 375 mg/m^2) that caused immediate reduction of proteinuria with only minimal increase in the following 12 months. Graft function is excellent 2 years after transplantation. These findings suggest that intermittent immunoadsorption combined with B-cell depletion by rituximab treatment induced prolonged reduction of proteinuria in a high-risk patient for recurrence of FSGS in the graft.

Introduction

Primary focal and segmental glomerulosclerosis (FSGS) is a histological diagnosis comprising multiple clinical entities and aetiologies [1]. The disease manifests with steroid-resistant nephrotic syndrome and hypertension and frequently progresses to end-stage renal disease (ESRD, [2]). In children, FSGS is the most frequent kidney disease resulting in ESRD [3]. Consequently, a large number of paediatric and adolescent kidney transplant recipients await kidney transplantation. However, recurrence of FSGS occurs in 30–40% of kidney transplant recipients within hours to days after transplantation [4]. In approximately 50% of the patients with FSGS recurrence in the graft, and especially in adolescent patients, graft survival is significantly reduced [5,6]. In approximately 80% of the patients with loss of their first graft because of recurrence of FSGS, the survival of a subsequent graft is even further reduced [4,7]. Therefore, effective strategies to achieve a favourable graft outcome in this large cohort of patients awaiting kidney transplantation have to be developed.

Identification of patients with a high risk against recurrence is one of the main goals of recent research. Several risk factors for recurrence have been identified: age of onset >6 years, rapid progression to ESRD, native kidney nephrectomy, mesangial hypercellularity or tip lesions in the biopsy, living donor transplants and induction therapy as part of initial immunosuppression [8–12]. The presence of an as-yet-unidentified permeability factor (Palb) was associated with a recurrence rate of 86% in the graft [10]. Patients with FSGS and genetic mutations in the podocin (NPHS2) or *WT1* gene were initially thought to be protected from recurrence in the graft. However, recent reports of patients with these mutations and recurrence in the graft point to a multifactorial origin of this disease [13,14].

Current treatment options against recurrence include plasmapheresis (PP) [15,16] or immunoadsorption [17]

in combination with angiotensin-converting enzyme inhibitors and intensified immunosuppression such as cyclophosphamide [18] or high-dose cyclosporin [19]. In living donor kidney transplantation, pre-operative PP or immunoadsorption can be performed for optimal preparation of the recipient. Pre-operative PP was shown to reduce the risk of recurrence of FSGS after transplantation [15,20]; however, relapse after discontinuation is common [21]. Most recently, rituximab, a genetically engineered, chimeric, immunoglobulin G1κ monoclonal antibody directed against CD20, was shown to be effective in reducing proteinuria in two paediatric patients with recurrence of FSGS and post-transplant lymphoproliferative disease (PTLD) [22,23]. Binding of the antibody to the CD20 antigen results in selective lysis of targeted B cells, but not the haematopoietic stem cells or normal plasma cells through a variety of mechanisms [24]. The use of rituximab for the treatment of FSGS postkidney transplantation has been described in two reports of three cases recently [25,26]. PP and subsequent rituximab therapy were able to induce remission of proteinuria in one patient, but were ineffective in the other. Another patient responded only to rituximab, but not to PP.

We present here a case of a woman with FSGS and recurrence after a first living donor kidney transplant. Preparation for a second living donor kidney transplant included pre- and post-transplant immunoadsorption and, later, rituximab therapy.

Case

A now 31-year-old woman had been diagnosed with FSGS in March of 1995 at the age of 21 years. Creatinine clearance was 148 ml/min and total urinary protein was 6.9 g/24 h and serum albumin was 1.7 g/dl. A kidney biopsy showed FSGS with tip-lesions, immunoglobulin M deposition and mild mesangial hypercellularity. The patient had steroid-resistant nephrotic syndrome and cyclophosphamide therapy was started (100 mg/day) resulting in partial remission (1.5 g/24 h albuminuria). Three immunoadsorptions were performed without effect on albuminuria or creatinine clearance. Three years later, end-stage renal failure was reached. The patient received an allogene living kidney transplant from her 71 years-old-father. However, FSGS recurred in the graft immediately after transplantation with 9 g/24 h albuminuria in the first urine. During the following 4 years, serum creatinine values increased constantly, indicating progressive renal disease. A renal biopsy showed focal and segmental sclerosis with complete podocyte foot process effacement, consistent with recurrent disease in the transplanted kidney.

Four years after transplantation, ESRD was reached and dialysis was initiated. Evaluation for a second living donor kidney transplant from her 58-year-old mother was started, despite the high risk for recurrent FSGS in the second transplant. The transplant contained two mismatches ($A = 0$, $B = 1$, DR = 1) and pretransplant HLA antibodies were negative. Prior to transplantation, three immunoadsorptions were performed using a Fresenius extracorporeal immunoadsorption system with Globaffin™ immunoglobulin-binding columns. Thirty gram of pooled immunoglobulins was given 1 day before transplantation because patient IgG was undetectable. Immunosuppression consisted of prednisolone, tacrolimus, mycophenolat-mofetil and induction therapy with basiliximab. Three immunoadsorptions immediately followed transplantation. The kidney showed immediate function with diuresis of 3.5–4.0 l/day. Serum creatinine decreased to normal values and creatinine clearance was 80 ml/min at discharge in June 2005. Protein was detected in the urine in low quantities of 200–400 mg/24 h. Two months after transplantation, albuminuria increased to 1.2 g/24 h (Fig. 1). A renal biopsy was performed, showing minimal change lesions. Immunoadsorptions were performed four times and 10-g of immunoglobulins was substituted once. This treatment decreased albuminuria immediately to 260 mg/24 h. However, in the course of following

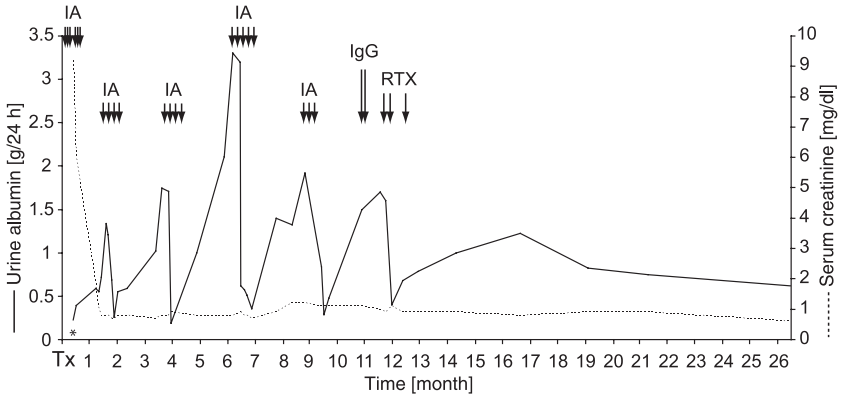

Figure 1 Urine albumin excretion (solid line) and serum creatinine (dashed line) of the patient after her second transplantation (Tx). Immunoadsorption (IA), IgG application without immunoadsorption (IgG), rituximab therapy (600 mg, RTX). To convert serum creatinine in mg/dl to µmol/l, multiply by 88.4.

8-months, albuminuria increased repeatedly to maximal 3.3 g/24 h and immunoadsorption sessions were performed as indicated in Fig. 1. In May 2006, albuminuria again reached 1.5 g/24 h and the patient received 60 g of pooled immunoglobulins with 100 mg of prednisolone over 3 days but without immunoadsorptions. This treatment did not decrease albuminuria (1.7 g/24 h at the follow-up visit). Thereafter, the anti-CD20 antibody rituximab was administered after consent to off-label use of rituximab three times in weekly intervals at a dose of 375 mg/m^2 body surface combined with 100 mg of prednisolone. This treatment reduced B cells to 28/μl (1%) and albuminuria to 400 mg/24 h. In the following 6 months, albuminuria increased slowly to a maximum of 1228 mg/24 h and decreased thereafter without additional treatment. Two years after transplantation, renal function is stable with a serum creatinine of 0.9 mg/dl (79.6 μmol/l), creatinine clearance of 97 ml/min and albuminuria of 622 mg/24 h.

Discussion

This is the first reported case of a patient with biopsy-proven recurrent idiopathic FSGS, receiving two living donor transplants, who was successfully treated with immunoadsorptions and rituximab. The patient had most known risk factors for recurrence in the first graft [27]. Therefore, the second transplantation was combined with pre- and post-transplant immunoadsorptions to reduce the risk of immediate recurrence and indeed proteinuria was low for 2 months after transplantation. Thereafter, albuminuria increased and minimal change lesions were present in a transplant biopsy consistent with recurrence of FSGS. Subsequent repeated immunoadsorptions were initiated as soon as proteinuria reached a level of above 1 g/24 h to prevent tubular damage from proteinuria. Immunoadsorptions were able to reduce albuminuria to levels of approximately 400 mg/24 h with increases to 3300 mg urine albumin/24 h in between. We believe that, without this intervention, proteinuria would have increased to much higher values. The effect of rituximab on albumin excretion was immediate and sustained. The fact that albuminuria remained at a level of around 800 mg/day suggested that only some, but not all, permeability activity was affected by this treatment.

Before rituximab treatment, the patient also received corticosteroids together with pooled immunoglobulins (IgG in Fig. 1) in May 2006 to avoid infections. However, this treatment had no effect on the amount of proteinuria. Therefore, corticosteroids or immunoglobulins were not likely to have contributed to the prolonged reduction of the proteinuria. However, in the presented case, concomitant institution of corticosteroid and rituximab therapy probably contributed to the clinical response.

Tacrolimus was used as initial immunosuppression because the patient received a second living-related graft. The use of cyclosporin has been shown to reduce proteinuria in recurrent FSGS as well as primary FSGS and has been shown to reduce Palb activity in patients with FSGS, but did not prevent recurrence [28,29]. So far, there is no comparison available for FSGS recurrence under immunosuppression with cyclosporin, tacrolimus or mTOR inhibitors. However, recent studies preferred tacrolimus to cyclosporin [15].

Plasmapheresis or immunoadsorption can significantly reduce protein excretion or induce complete remission in patients with recurrent FSGS [16,17,30,31]. Both treatments work best when applied immediately after recurrence and may have a transient effect with relapse when discontinued [20]. However, all available reports were uncontrolled, small-sized and with short-term follow-up evaluation. The long-term prognosis of patients with complete remission after PP or immunoadsorption is not clear. The major advantage of immunoadsorption is the increased selectivity compared with standard plasma exchange and a reduction of infection risks. Gohh studied the outcome of pre-emptive PP and recurrence of FSGS in high-risk renal transplant recipients. Pre-emptive PP reduced recurrent FSGS to 30%, but those patients with recurrence showed rapid deterioration of renal function despite PP [15].

A functional assay in isolated rat glomeruli is used to measure the capacity of patient serum to increase albumin permeability Palb *in vitro* [10]. Approximately, 30% of all patients with FSGS have a Palb > 0.5 including nearly all patients with recurrent FSGS in the transplant [15,32]. The albumin permeability was not measured in our patient, but we think that it is very likely that our patient would have had increased Palb. The fact that immunoadsorption with a protein A column is highly effective in reducing proteinuria in recurrent FSGS [33] suggests that immunoglobulins or co-precipitated substances mediate the disease, i.e. they are the permeability factors. However, immunoglobulins have never been identified as a permeability factor in various approaches [34]. Instead, permeability activity seems to be carried by small, highly glycosylated, hydrophobic proteins or peptides. Therefore, normal plasma is proposed to contain substances capable of blocking or inactivating the FSGS permeability factor [35].

We utilized the standard lymphoma treatment regimen for rituximab, which is a weekly dosing schedule and was shown to be effective also in anti-neutrophil cytoplasmic antibodies-associated vasculitis [36]. Weekly dosing was preferred to monthly application because of a wide

individual variability in drug half-life and to avoid underdosing. One weekly dose was not given because of a urinary tract infection. At the time of transplantation, *ad hoc* therapy with rituximab was not intended because of the lack of data on this issue. Anti-CD25 antibody treatment (basiliximab) was included in our standard induction therapy regimen for high-risk transplantations are similar to regimens in many other institutions. Only after the failure of this conventional induction therapy and immunoadsorptions, a rescue therapy with rituximab was initiated.

In humans, serum immunoglobulin levels are maintained after rituximab therapy and acquired humoral immunity is preserved confirming that plasma cells responsible for the production of IgG are not depleted by rituximab. In our patient, the depletion of immunoglobulins by immunoadsorption was not able to produce a prolonged reduction of proteinuria. The proposed mechanism of rituximab therapy in recurrent FSGS would therefore be unrelated to antibody depletion, but may be due to reduced B-cell mediated activation of T cells. Rituximab influences T-cell activation by an unexplained mechanism. One possibility would be the reduced presentation of antigens by B cells also reducing T-cell activation. However, induction therapy with anti-thymocyte antibody, depleting CD3 positive T cells, has not been associated with a better outcome or less proteinuria in recurrent FSGS [9,11].

To date, there are nine reported cases of rituximab therapy in recurrent FSGS in the transplant. In two paediatric cases with recurrent FSGS and PTLD, one PP-resistant and one without PP, rituximab was given [22,23]. Both patients showed resolution of both PTLD and proteinuria after rituximab treatment. In the third case, rituximab was administered after repeated successful PP and achieved persistent resolution of the nephrotic syndrome [37]. In another report, one out of two cases responded to immediate rituximab therapy after recurrence in the transplant. The other patient received rituximab 13 months after transplantation and did not respond to either PP or rituximab [25]. In another patient, PP was unable to reduce proteinuria, but rituximab induced immediate remission of biopsy-proven FSGS in the transplant [26]. However, in two recent case reports, rituximab did not induce remission of proteinuria in three patients with FSGS that were successfully treated with PP [38,39]. It is therefore interesting to note that the response to immunoadsorption or PP cannot predict the efficacy of later rituximab treatment, and future studies are clearly needed to address this point.

Whereas in our case the immediate effect of rituximab on proteinuria was striking, proteinuria increased slowly in 6 months after administration of rituximab and later regressed to stable values. This time course contrasts the prolonged effect of rituximab in the other cases studied. One possibility for the subsequent increase is that reduction of a specific a B-cell clone lasted only for this period of time. However, a secondary effect of B-cell depletion with decreased helper T-cell activation has also been described [40]. Therefore, helper T-cell activity could increase again, independent of B-cell number.

There has been a recent concern about the role of rituximab in the development of unusual infections, such as progressive multifocal leukoencephalopathy (PML) following the reports of two cases of PML resulting in death in patients who received rituximab for treatment of systemic lupus erythematosus [41]. PML is a rare, progressive, demyelinating disease of the central nervous system caused by activation of latent polyomavirus (JC virus) that typically causes PML only in immunocompromised patients. PML has been reported in immunosuppressed HIV or cancer patients, organ transplant recipients and patients with different autoimmune disease who were not receiving rituximab. This suggests that the overall immunosuppression, and not a specific agent such as rituximab, is responsible for the development of PML. However, the complete side-effect profile of rituximab in FSGS and post-transplantation is not completely understood, and remains subject matter for further future trials.

In conclusion, there are two reported patients, and now our patient, who responded to PP or immunoadsorption and rituximab therapy with a significant reduction of proteinuria. Clinical trials that compare the therapeutic options for patients with recurrent FSGS in the graft are very much needed. In our patient, renal function remains within normal limits 2 years after transplantation and the patient has resumed her career.

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Authorship

TNM collected the data and wrote the paper. FT and RAKS were responsible for treatment and follow-up of the patient.

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