Exceptional Case

Rituximab therapy in early recurrent focal segmental sclerosis after renal transplantation

Terje Apeland¹ and Anders Hartmann²

¹Department of Medicine, Stavanger University Hospital, Stavanger and ²Department of Medicine, Rikshospitalet University Hospital, Oslo, Norway

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Background

Kidney transplants may be lost due to recurrence of the primary disease. In glomerulonephritis, all kinds taken together, 3% of the patients lose their grafts due to recurrence [1]. If, however, a first kidney graft has been lost from recurrence, the rate of failure caused by recurrence in subsequent grafts is ∼48% [1]. Focal segmental glomerulosclerosis (FSGS) in a young patient is associated with the highest rate of recurrence in kidney grafts, i.e. 20–40% of first time kidney recipients [1–3]. With recurrence of childhood FSGS, the 2-year graft survival is poor—∼35% [1]. A circulating factor, which may increase the glomerular permeability to albumin, has been found in some patients with FSGS. Therefore, several trials with plasmapheresis or protein A immunoabsorption have been conducted in patients with recurrent FSGS, but the response appears to be variable and unpredictable [2,3]. Rituximab was first given to a few patients with post-transplant lymphoproliferative disorder and early recurrent FSGS. The lymphoproliferative disorders dissolved, and as a side effect, proteinuria improved [4,5]. Subsequently, rituximab therapy has been reported in several kidney transplants with early recurrent FSGS, but has achieved variable results (Table 1) [6–13]. It is difficult to organize randomized trials in this small patient group. Therefore, we report a case of sustained remission after rituximab in a young patient with resistant early remission of FSGS in his second kidney graft.

Case presentation

A 12-year-old boy presented at our outpatient clinic with nephrotic syndrome. Initially, S-creatinine was 46 μmol/L, S-albumin 16 g/L and proteinuria 15 g/day. The nephrotic syndrome proved to be resistant to high doses of prednisolone. After 2 months, a renal biopsy was performed: bright-field microscopy revealed segmental sclerosis and mesangial expansion with hypercellularity, and by electron microscopy, diffuse fusion of epithelial cell foot processes was evident. A diagnosis of primary FSGS was made. Therapy with prednisolone and cyclosporine A was given for 6 months, without any effect on the nephrotic syndrome. His serum creatinine was steadily increasing, and renal transplantation was planned. The patient received his first kidney graft (one haplotype mismatch) from his father 20 months after the debut of nephrotic syndrome. Bilateral nephrectomy was performed at the same time. As per standard of care, prednisolone and tacrolimus were given. Prior to the transplantation, no plasmapheresis was given. Two days after the transplantation, a nephrotic syndrome presented. Plasmapheresis was initiated on Day 4 after the transplantation, and, on Day 14, a kidney graft biopsy confirmed the recurrence of FSGS. However, proteinuria did not improve, and after 2 months, plasmapheresis was tapered off with a total of 16 treatments. Due to rising S-creatinine, a new graft biopsy was performed 6 months after transplantation; FSGS was still present, but there were no signs of chronic or acute rejection. Mycophenolate mofetil was added to the medication. The kidney function declined gradually and the patient had to start on haemodialysis 3.5 years after the transplantation.

After 5 months on haemodialysis, at the age of 18 years, the patient was transplanted for the second time with an HLA A = 1, B = 1, DR = 1 mismatch kidney from a deceased donor. As per standard of care, immunosuppression with prednisolone, tacrolimus and mycophenolate mofetil was given, with basiliximab induction. Plasmapheresis was not given before the transplantation. However, 4 days after transplantation, the nephrotic syndrome recurred with biopsy-proven FSGS (Figure 1). Treatment with plasmapheresis was started on Day 7. The plasmapheresis induced a partial remission of the nephrotic syndrome. However, we considered him plasmapheresis-dependent and weekly maintenance treatment was given. After 6 months, treatment intervals were increased to 2 weeks, and after this, proteinuria became worse. However, S-creatinine remained
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>FSGS</th>
<th>Immunosuppression</th>
<th>Plasma exchange</th>
<th>Rituximab dose</th>
<th>Outcome after rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>[6]</td>
<td>One 48-year-old woman</td>
<td>Recurred 1 month after kidney-Tx</td>
<td>Tacro, MMF, Pred</td>
<td>Yes, stopped prior to rituximab</td>
<td>375 mg/m² × 6, 3 months after Tx</td>
<td>No response</td>
</tr>
<tr>
<td>[13]</td>
<td>One man and three women, 41, 43, 41 and 47 years old</td>
<td>Two early recurrences in kidney grafts, two after 1 and 2 months</td>
<td>Three on Tacro, MMF, Pred; One on CyA, MMF</td>
<td>Yes, two treatments given concomitantly and two stopped 1 and 2 months prior to rituximab</td>
<td>375–1000 mg × 2–6; given at 7, 5, and 11 months after Tx</td>
<td>Remission in the 41-year-old man No response in the three women</td>
</tr>
<tr>
<td>[9]</td>
<td>Two men, 25 and 46 years old</td>
<td>Early recurrence in kidney graft</td>
<td>CyA, MMF, Pred</td>
<td>Yes, concomitantly to 25-year-old patient, and stopped 1 month prior to rituximab in 47 years</td>
<td>375 mg/m² × 2–4, at first week to 25-year-old patient, and, at Month 7 to 47 years</td>
<td>Remission only in the younger man</td>
</tr>
<tr>
<td>[12]</td>
<td>Two girls, 10 and 12 years old</td>
<td>Native kidneys, steroid resistant</td>
<td>CyA, Pred, Cph, Mizorbin</td>
<td>Yes, stopped prior to rituximab</td>
<td>375 mg/m² × 1–2</td>
<td>Remission</td>
</tr>
<tr>
<td>[7]</td>
<td>One 48-year-old woman</td>
<td>Early recurrence in kidney graft</td>
<td>Tacro, MMF, Pred</td>
<td>Yes, concomitantly</td>
<td>375 mg/m² × 2, 4 months after Tx</td>
<td>Remission of the nephrotic syndrome</td>
</tr>
<tr>
<td>[11]</td>
<td>One 29-year-old woman</td>
<td>Recurred 2 months after kidney-Tx</td>
<td>Tacro, MMF, Pred</td>
<td>Yes, five courses of immunoabsorption</td>
<td>375 mg/m² × 3, 12 months after Tx</td>
<td>Remission of the nephrotic syndrome</td>
</tr>
<tr>
<td>[10]</td>
<td>Two boys, 6 and 10 years old</td>
<td>Early recurrence in kidney graft</td>
<td>Tacro, Pred, Cph and Tacro, MMF, Pred</td>
<td>Yes, one concomitantly, the other stopped 3 months prior to rituximab</td>
<td>375 mg/m² × 4 and 750 mg/m² × 2 at 3 and 9 months</td>
<td>No response</td>
</tr>
<tr>
<td>[8]</td>
<td>One 22-year-old man</td>
<td>Early recurrence in kidney graft</td>
<td>Tacro, MMF, Pred, Cph</td>
<td>Yes, concomitantly</td>
<td>375 mg/m² × 2 given 1 week after Tx</td>
<td>Remission of the nephrotic syndrome</td>
</tr>
<tr>
<td>[5]</td>
<td>One 7-year-old boy</td>
<td>Early recurrence in kidney graft, PTLD appeared 5 months after Tx</td>
<td>Tacro, MMF, Pred</td>
<td>Yes, stopped 3 months prior to rituximab</td>
<td>375 mg/m² × 6, given 5 months after Tx</td>
<td>Remission of the nephrotic syndrome and the PTLD</td>
</tr>
<tr>
<td>[4]</td>
<td>One 12-year-old boy</td>
<td>Early recurrence in kidney graft, PTLD appeared 4 months after Tx</td>
<td>CyA, Pred</td>
<td>None</td>
<td>375 mg/m² × 4, given 6 months after Tx</td>
<td>Remission of the nephrotic syndrome and the PTLD</td>
</tr>
</tbody>
</table>

Tx, transplantation; Early recurrence, during the first 2 weeks after Tx; PTLD, post-transplant lymphoproliferative disease; Pred, prednisolone; MMF, mycophenolate mofetil; CyA, cyclosporine A; Tacro, tacrolimus; Cph, cyclophosphamide.
with rituximab (375 mg/m²) was given. Plasmapheresis was started at 26 months post-transplantation, with a total of 86 treatments (Figure 1). At this time, serum albumin had risen to 38 g/L and the urine protein/creatinine ratio was 146 mg/mmol.

Presently, the patient is on therapy with prednisolone 5 mg, tacrolimus 5 mg and mycophenolate mofetil 500 mg per day. The last serum albumin was 43 g/L and urine protein/creatinine ratio was 88 mg/mmol. The trough whole blood concentrations of tacrolimus and mycophenolate mofetil have been ~7 µmol/L and 0.7 mmol/L, respectively. The patient is short for his age: at the age of 17.5 years, he was 144.5 cm tall (4 SD below average), with a bone age of 14 years (Greulich and Pyle). During the 36 months after the second kidney graft, the patient increased in height from 155 to 160 cm, and his body weight increased from 43 to 52 kg. Kidney graft function has remained stable with S-creatinine at 51 µmol/L, at the time of transplantation, and 76 µmol/L at 33 months post-transplantation. We plan a fourth, and last, rituximab infusion at Month 37, provided there are normal CD20+ leukocyte counts in the blood and negative BK-virus PCR in the urine.

Fig. 1. The urine protein/creatinine ratio and serum albumine during the first 3 years after the second kidney transplantation.

stable, and at 8 months, we decided to go back to weekly plasmapheresis. Despite this, the nephrotic syndrome persisted, with increasing oedema. Eventually, we informed the patient about experimental therapy with rituximab. The patient gave his consent, and 13 months after transplantation, the plasmapheresis interval was increased to 14 days (Figure 1). In peripheral blood, the percent of CD20+ leukocytes fell from 6.3 to 0.2%. Over the following months, proteinuria declined gradually (Figure 1). Otherwise, the clinical course was uneventful, except for an acute appendicitis with appendectomy and removal of the old graft at 20 months post-transplantation. Seventeen months after transplantation, the nephrotic syndrome was worsening; however, the present observations do not allow for any conclusions. Previously, there have been 10 case reports published on FSGS treated with rituximab (Table 1). Nine patients responded with sustained remission of the nephrotic syndrome, and seven did not (Table 1). It is possible that one of the non-responders had FSGS secondary to incomplete to maintenance plasmapheresis and triple immunosuppression. The nephrotic syndrome was worsening and we were expecting gradually declining kidney function, when rituximab was first given. This was a turning point, and thereafter, the condition improved steadily. Otherwise, the plasmapheresis schedule and immunosuppressive drugs were kept unchanged during the 3 months preceding rituximab therapy and the following 4 months. After Month 17, plasmapheresis was gradually tapered off and stopped at Month 26; concurrently, we were able to lower the doses of immunosuppressive drugs. Thus, it appears that rituximab had a significant beneficial effect on the recurrent FSGS in this patient.

Rituximab treatment leads to depletion of CD20+ B-lymphocytes, and treatment with this monoclonal antibody may be beneficial in various immune-related diseases [15]. The drug appears to be reasonably safe in kidney transplant patients and is routinely used for ABO-incompatible transplantations [16]. The reduction in number of CD20+ cells may last for 6–12 months. Rituximab appears to have a time-limited effect on disease activity in patients with rheumatoid arthritis and Wegener granulomatosis [17,18]. However, there is no consensus as to how rituximab should be given. We wanted to avoid a new recurrence of the nephrotic syndrome in our patient. Thus, we chose to spread out the four rituximab infusions, although there is little evidence to support this specific treatment schedule.

The effect of rituximab in our patient may be convincing; however, the present observations do not allow for any conclusions. Previously, there have been 10 case reports published on FSGS treated with rituximab (Table 1). Nine patients responded with sustained remission of the nephrotic syndrome, and seven did not (Table 1). It is possible that one of the non-responders had FSGS secondary...

Discussion

This patient belongs to a subgroup of FSGS patients with a high risk of recurrence of the primary disease post-transplantation. They have an aggressive form of FSGS with rapid deterioration of native renal function; time from onset of disease to uraemia is often <3 years. These patients tend to be <20 years of age and may have mesangial hypercellularity on the biopsy of the native kidney [1,14]. As would be expected, our patient had an early recurrent nephrotic syndrome with his first kidney graft, and despite treatment, he went on maintenance dialysis after 3.5 years. The recurrent disease in his second kidney graft apparently responded incompletely to maintenance plasmapheresis and triple immunosuppression. The nephrotic syndrome was worsening and we were expecting gradually declining kidney function, when rituximab was first given. This was a turning point, and thereafter, the condition improved steadily. Otherwise, the plasmapheresis schedule and immunosuppressive drugs were kept unchanged during the 3 months preceding rituximab therapy and the following 4 months. After Month 17, plasmapheresis was gradually tapered off and stopped at Month 26; concurrently, we were able to lower the doses of immunosuppressive drugs. Thus, it appears that rituximab had a significant beneficial effect on the recurrent FSGS in this patient.

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to obesity [13]. It may appear that younger patients with primary FSGS and normal serum creatinine have a greater probability of success (Table 1).

The possible therapeutic effect of rituximab in primary FSGS points to an immunologic pathogenesis, at least in a subgroup of these patients. The exact role of B-lymphocytes in primary FSGS remains unclear, and the relationship to the previously described ‘circulating factor’ is an open question.

In conclusion, rituximab may be an alternative in recurrent FSGS not responding to plasmapheresis, but randomized studies are required to establish such a therapy.

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References


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