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ORIGINAL ARTICLE

Unusual post-transplantation recurrence of focal segmental glomerulosclerosis which resolved with cyclosporine but not with sirolimus

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Summary

Recurrence of idiopathic focal segmental glomerulosclerosis (FSGS) is frequent after the first kidney transplantation (KT), but a recurrence that only occurred after the second KT has never been reported. Although cyclosporine reduces proteinuria and prolongs graft survival in patients with recurrent glomerulosclerosis, the effectiveness of sirolimus for this condition is still not known. We report, for the first time as far as we know, the case of a 35-year-old black male patient who experienced a recurrence of FSGS, 10 days after a second KT, although no recurrence had occurred after the first. Cyclosporine treatment led to a decrease in proteinuria, whereas mycophenolate mofetil and angiotensin-converting enzyme inhibitor had no effect. Cyclosporine was replaced by sirolimus as treatment for chronic allograft nephropathy 24 months after KT. Nephrotic syndrome, which reappeared 3 weeks after the switch, was cured by cyclosporine re-introduction. The absence of FSGS recurrence after the first graft does not totally preclude its recurrence after the second. This observation points to the effectiveness of cyclosporine for the recurrence of FSGS and indicates that sirolimus should be given with caution in such cases.

Introduction

Patients transplanted for end stage renal disease because of focal segmental glomerulosclerosis (FSGS) are at a higher risk (20–30%) of a recurrence of nephrotic syndrome (NS) after a renal allograft, leading to a graft loss rate of 40–80% [1]. The risk of a second recurrence in patients who had already lost their first graft because of FSGS recurrence is higher, at 75–100% [2]. However, the recurrence of FSGS after a second renal graft without any recurrence after the first has never been reported. Despite the fact that the effectiveness of cyclosporine in FSGS is not based on randomized study, it is currently used to treat this condition. The effectiveness of mycophenolate mofetil (MMF) and sirolimus in this respect is still not known.

This report describes a case of early FSGS recurrence in the recipient of a second allograft, despite the absence of recurrence after the first. Cyclosporine treatment reduced proteinuria in the two episodes of NS, whereas MMF, angiotenyin converting enzyme (ACE) inhibitors and sirolimus had no effect.

Case report

A 35-year-old black patient received a first cadaveric renal transplant in 1988. His medical history revealed end-stage renal failure secondary to glomerular disease with NS when he was 14 years old, leading to haemodialysis 1 year later. Unfortunately, no renal biopsy was performed at this time. His immunosuppressive regimen after the first transplantation comprised a combination of OKT3,

azathioprine and corticosteroids. Three biopsy-proven acute rejection episodes occurred at day 6, 42 and 102, post-transplant. They were initially treated with corticosteroids alone, and subsequently with corticosteroids plus horse antithymocyte globulin. Despite this treatment, graft function rapidly worsened and the patient had to restart dialysis 8 months after renal transplantation.

The patient had no significant proteinuria and no FSGS lesions were found in the three graft biopsies. After 7 years of dialysis, he underwent a second renal graft from a human leucocyte antigen (HLA) identical brother. The patient's initial immunosuppressive regimen consisted of corticosteroids, azathioprine and rabbit antithymocyte globulin. Acute massive proteinuria (36.5 g/day), quickly followed by NS (hypoalbuminaemia: 24 g/l) occurred 10 days after renal transplantation. Renal biopsy, performed on the 14th day after transplantation, showed podocyte swelling but no acute rejection lesion. These findings were compatible with an early recurrence of FSGS, which had not been diagnosed at end-stage renal failure.

After unsuccessful corticosteroid treatment, cyclosporine was introduced intravenously on day 21 post-transplantation (blood trough levels: 150–250 ng/ml). Proteinuria progressively decreased and NS disappeared by the end of the second month after cyclosporine introduction. However, at 3 months, a protocol biopsy showed typical FSGS lesions and alterations in tubulointerstitial tissue. At that time, serum creatinine was 143 μmol/l and proteinuria, 2.4 g/day.

Mycophenolate mofetil and enalapril were introduced 6 months after transplantation to lower the remaining proteinuria, but were stopped 6 months after their introduction because of ineffectiveness and gastrointestinal symptoms.

A 2-year protocol biopsy showed grade II chronic rejection according to the Banff 97, cyclosporine toxicity and several FSGS lesions. At that time, serum creatinine was 184 μmol/l and proteinuria, 0.2 g/day. Cyclosporine was switched to sirolimus to avoid calcineurin inhibitor nephrotoxicity. Three weeks after cyclosporine withdrawal, proteinuria started a gradual rise, leading to NS within 2 months (Fig. 1) with proteinuria at 7.6 g/day and albuminaemia at 16 g/l). Sirolimus was stopped 4 months after its introduction and the patient was switched back to cyclosporine. As early as 7 days after cyclosporine reintroduction, a gradual decrease in proteinuria started and NS completely disappeared within 30 days. At the last follow up in June 2002, 66 months after transplantation and 36 months after cyclosporine was restarted, the patient was in complete remission from NS (proteinuria: 0.4 g/day) and renal function remained stable (serum creatinine: 237 μmol/l).

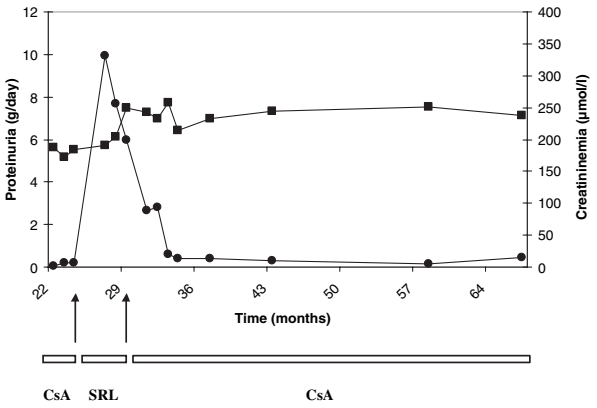

Figure 1 Proteinuria and creatininaemia during immunosuppressive therapy after kidney transplantation. Proteinuria (●) rose 3 weeks after the switch from cyclosporine to sirolimus, but gradually decreased after sirolimus was stopped and cyclosporine re-introduced. Creatininaemia (■) was not affected by the switches.

Discussion

The recurrence rate of FSGS after the second kidney transplantation is particularly high (75–100%) for patients who already had a recurrence after their first [2]. FSGS often appears during the first few days after transplantation [3]. However, to our knowledge, no examples of FSGS recurrence, following a second transplant, have been reported for cases in which no recurrence followed the first. This is why it is believed that if the cause of graft loss after the first transplant was not FSGS recurrence, a second renal transplantation may be considered, possibly with a living related kidney donor. We describe here the case of a man with FSGS, which recurred soon after a second KT, whose first graft loss had been secondary to chronic rejection, but was not followed by a recurrence of FSGS. Absence of both proteinuria and FSGS lesions in the three graft biopsies strongly argues against recurrence of FSGS as the cause of graft loss after the first renal transplantation. No renal biopsy was performed near or after graft loss because it was considered of immunological origin.

Although FSGS had not been diagnosed at the time of chronic renal failure, the original NS, the patient's ethnic origin, the suddenness of the onset of NS a few days after transplantation and the pathological diagnosis of FSGS strongly suggest that the initial glomerulonephritis was indeed FSGS, which might have recurred in the usual way during the second transplantation. Two circumstances may have facilitated this recurrence: first, the second transplant was performed with an identical HLA family donor, which is usually considered as a risk factor for recurrence [4,5]. However, this risk factor is challenged

by a recent study showing that for patients with FSGS who had been grafted with a kidney from an identical HLA family donor, graft survival was better than for those grafted with a kidney from a cadaveric donor or from a living donor with HLA mismatches [6]. Secondly, the patient's ethnic origin might also be a risk factor for recurrence [1,7].

The outcome of this case also confirms the effectiveness of cyclosporine in treating NS secondary to post-transplant FSGS recurrence. Although cyclosporine has indeed been shown to have a beneficial effect in primary corticoresistant FSGS [8], its effectiveness in post-transplant recurrence has not been confirmed by prospective randomized studies. Although here, cyclosporine did reduce proteinuria spectacularly, the presence of FSGS lesions on the 2-year renal biopsy and the recurrence of NS once cyclosporine was stopped suggest that primarily the latter has a beneficial effect on proteinuria rather than on FSGS. Neither the ACE inhibitor, nor MMF had any particular effect on the patient's proteinuria, contrarily to other reports [9]. Sirolimus cannot be incriminated to the resurgence of proteinuria, because it was introduced when cyclosporine was stopped. It has, however, been reported in experimental models that rapamycin and its derivatives can worsen glomerular lesions [10].

Conclusion

The absence of FSGS recurrence after the first KT does not preclude its recurrence after the second. Caution must therefore be exercised in the use of identical HLA living donor grafts for a second transplant in cases of primary FSGS, even in the absence of a recurrence after the first KT. Cyclosporine remains the treatment of choice in case of a relapse in FSGS.

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