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Case Report

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High cut-off haemodialysis induces remission of recurrent idiopathic focal segmental glomerulosclerosis after renal transplantation but is no alternative to plasmapheresis

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Abstract
A 26-year-old male experienced a recurrence of idiopathic focal segmental glomerulosclerosis (iFSGS) after his second renal transplant. Reduction of proteinuria was rapidly induced by plasmapheresis (PP) and the patient has remained in remission with a once-weekly PP regimen, which has now been continued for >3½ years. We were also able to induce remission of iFSGS in this patient by treatment with high cut-off haemodialysis using the Theralite™ dialyser. This observation lends support for the pathophysiological role of an as yet unknown, circulating glomerular filtration barrier permeability factor with an estimated weight of between 30 and 50 kDa.

Keywords: focal segmental glomerulosclerosis; plasmapheresis; proteinuria; transplantation

Background

Idiopathic focal segmental glomerulosclerosis (iFSGS) recurs after renal transplantation in ~20% of cases and the chance of recurrence after a second renal transplant exceeds 80% [1,2]. The pathogenesis of iFSGS is unknown but there is evidence that the disease is caused by an incompletely characterized circulating glomerular filtration barrier permeability factor [3,4]. Plasmapheresis (PP) is effective in treating recurrent iFSGS after transplantation, possibly by removing this unknown permeability factor [3,5]. Therefore, early treatment of recurrent iFSGS with PP is recommended but detailed descriptions of treatment regimens are lacking [6–8]. Recently, high cut-off (HCO) dialysers have become available which allow for the removal of molecules with a molecular weight of up to 45 kDa. HCO-dialysers have been used successfully to remove light chain immunoglobulins in patients with myeloma cast nephropathy [9,10].

We describe a patient who achieved a sustained remission of recurrent iFSGS after receiving a second renal transplant with long-term maintenance PP and HCO-haemodialysis.

Case history

A 26-year-old male patient received a second, three human leucocyte antigen (HLA) mismatched (A, B and DR) kidney transplant from a living-related donor in January 2007. Immunosuppression consisted of tacrolimus, mycophenolate mofetil and prednisolone without induction therapy. He had been diagnosed with steroid-resistant iFSGS of the native kidneys when he was 19 years old. Renal failure developed within 3 years and haemodialysis was initiated. His first living-related HLA-identical kidney transplantation in 2004 was complicated by a rapid recurrence of iFSGS. Symptomatic therapy with angiotensin-converting enzyme (ACE)-inhibitors was started and 1½ years after transplantation, his graft failed, necessitating haemodialysis. Prior to his second transplantation, a transplant nephrectomy was performed. Hereafter, the patient became anuric and therefore the native kidneys were left *in situ*. The donor of the second transplant (his mother) had a normal renal function without hypoalbuminaemia or proteinuria at the time of donation and remains in good clinical condition with a normal renal function some 3 years after donation. His second renal transplantation was complicated by a biopsy-proven vascular and tubulointerstitial rejection on Day 3 (acute rejection Type IIA, t1v1g0i0 according to the Banff criteria), which was treated successfully with high-dose steroids and rabbit anti-thymocyte globulin (rATG). When renal function improved, proteinuria developed. Electron microscopic examination of the transplant biopsy taken on Day 3 after transplantation showed podocyte foot effacement. Recurrent iFSGS was diagnosed. Daily PP treatment was initiated at a dose of 2.4 L plasma volume exchange with fresh frozen plasma as substitution fluid (Figure 1). In addition, the patient was treated with ACE-inhibition (fosinopril 20 mg twice daily) and an angiotensin receptor blocker (losartan 50 mg twice daily). Remission of proteinuria was swift but returned within 2 weeks after cessation of PP. After another two cycles of PP, urinary protein excretion was again significantly reduced. Because anecdotal reports have suggested that anti-CD20 immunotherapy may be effective in treating post-transplant

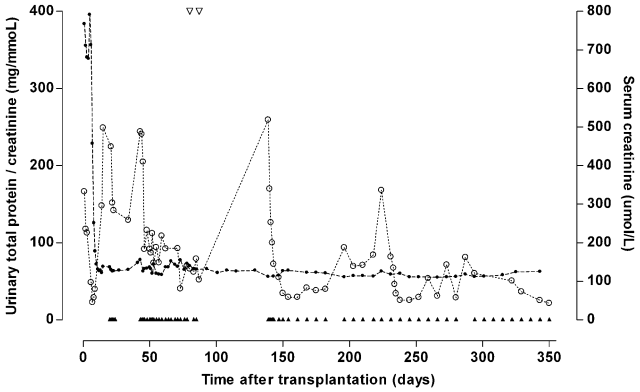

Fig. 1. Evolution of serum creatinine (filled circles) and proteinuria (open circles) after transplantation. The filled triangles represent single PP treatments. The two open triangles represent the two doses of rituximab (375 mg/m^2 each).

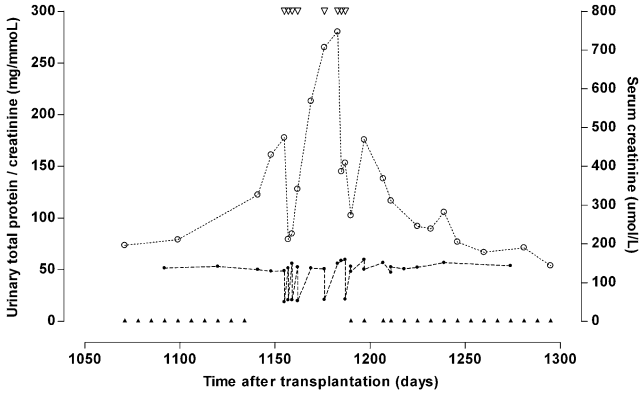

Fig. 2. Effect of HCO-haemodialysis with the Theralite™ dialyser on proteinuria. The urine protein to creatinine ratio is depicted by the open circles. The filled circles represent the serum creatinine. The filled triangles represent single PP treatments, whereas the open triangles represent dialysis treatments with the HCO dialyser.

iFSGS, the patient was given rituximab twice at a dose of 375 mg/m^2 [11]. Thereafter, circulating B cells were completely depleted but to no apparent effect on proteinuria. We decided to continue PP after inducing remission of the proteinuria by daily PP, in once-weekly sessions exchanging plasma volume with 4 L of a 4% albumin solution. This regimen kept the proteinuria at 0.5 g/24 h. Reducing the frequency of PP to once every 2 weeks (at Day 182 post-transplantation) led to an increase of proteinuria necessitating a short interval of intensified PP treatment. The PP sessions were all tolerated well.

Some 2½ years after transplantation, a second renal biopsy was performed because of a slowly deteriorating renal function and slight increase in proteinuria. The histological findings were consistent with recurrent FSGS, cellular variant. In addition, moderate calcineurin inhibitor nephrotoxicity was present (arteriolar hyalinosis and isometric tubular vacuolization). The tacrolimus dose was reduced aiming for predose concentrations of 5–6 ng/mL rather than 8 ng/mL.

In March 2010, after ~200 PP sessions, we started treating the patient with HCO-haemodialysis by use of the Theralite™ HCO dialyser (Gambro®, Zaventem, Belgium) in an attempt to reduce the intensity of his treatment. At this time, his medication consisted of tacrolimus, prednisolone and fosinopril. Treatment with mycophenolate mofetil had been stopped 2 years previously because of pancytopenia. HCO-haemodialysis was started 2 weeks after the last PP during which time his proteinuria increased from 0.5 g to >2 g/day (Figure 2). Initially, HCO-haemodialysis was performed every other day for 4 h, which led to a rapid reduction of proteinuria. However, reduction of the HCO-haemodialysis frequency to once a week led to an increase of proteinuria. More intensive HCO-haemodialysis was initiated, again followed by a rapid and very good partial response, which was comparable to that seen during treatment with PP. A second attempt to reduce the treatment interval to once a week, once more led to an increase of urinary protein excretion. Hereafter, because of the intensity of the HCO-haemodialysis regimen, we restarted once-weekly PP. Ever since, the patient has remained in remission with once-weekly PP and is in an excellent clinical condition. During HCO-haemodialysis plasma–albumin levels decreased slightly below the normal range (with a nadir of 31 g/L) but otherwise no serious adverse effects, such as allergic reactions or infections, were noted.

Discussion

The patient reported herein remained in sustained remission with once-weekly PP for a period of >3½ years after recurrence of iFSGS following a second renal transplant. Our findings support the pathophysiological role of an unknown circulating permeability factor [3,4]. Firstly, the patient remained in remission independently of the substitution fluid used, suggesting that the removal rather than the substitution of an unknown circulating factor is of importance. Secondly, the amount of proteinuria (and its recurrence) in response to PP fully matches a first-order kinetics of elimination and implies a direct and rapidly reversible effect of a circulating factor on glomerular filtration barrier permeability. Thirdly, HCO-haemodialysis was successfully used to induce remission after PP was temporarily discontinued. The HCO Theralite™ filter allows removal of molecules with a molecular weight of 45 kDa, whereas the as yet unknown circulating permeability factor in iFSGS presumably has a molecular weight of 30–50 kDa [3,4,7]. Our observations are therefore in line with the presumed pathophysiological role of the circulating permeability factor. Recently, by use of proteomic techniques, McCarthy *et al.* [12] proposed cardiotrophin-like cytokine-1 and soluble urokinase receptor as active factors in iFSGS.

Due to ethical considerations, we did not attempt to dialyse our patient with a standard low cut-off filter. If dialysis using a low cut-off filter would have been unsuccessful in inducing remission, this would have provided additional evidence for the proposed molecular weight of the permeability factor of 30–50 kDa rather than a smaller molecule. In addition, although HCO-haemodialysis was used

successfully, an intensive regimen was necessary to maintain the level of proteinuria <1 g/L. Because of the relatively low effectiveness of our HCO-haemodialysis regimen as compared with once-weekly PP, the size of the unknown permeability factor is likely to be near the 45 kDa cut-off of the Theralite™ dialyser. Possibly, we might have achieved a higher clearance if we had dialysed our patient for 6–8 h rather than 4 h, as was described by Hutchinson *et al.* [9,10] for the treatment of light chain disease. The reason we did not was that our patient refused to be treated with longer dialysis sessions. Finally, the costs of the HCO-haemodialysis regimen we used were about four times higher than that of regular once-weekly PP. Therefore, our observations show that HCO-haemodialysis is effective in inducing remission of recurrent iFSGS after transplantation (the proof of principle) but that it is not a realistic alternative to once-weekly PP.

In conclusion, we report the long-term efficacy of once-weekly PP for recurrent iFSGS after renal transplantation. Evidence for the pathophysiological role of an unknown 30–50 kDa permeability factor was strengthened by the demonstration of the effectiveness of HCO-haemodialysis to induce remission. The value of this protocol needs to be established in a larger group of patients with recurrent iFSGS after renal transplantation.

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Conflict of interest statement. Dr I.N., Dr M.W. and Dr M.G.H.B. declare to have no conflicts of interest to disclose.

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