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BRIEF REPORT

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Double recurrence of FSGS after two renal transplants with complete regression after plasmapheresis and ACE inhibitors

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Abstract A patient who had undergone a first cadaveric donor kidney transplantation for idiopathic focal segmental glomerular sclerosis (FSGS), had an immediate recurrence of a biopsy-proven FSGS that eventually led to graft failure within 5 years from transplantation. The patient underwent a second cadaveric transplantation 10 months later. An immediate recurrence of a biopsy-proven FSGS occurred that was treated with two protracted cycles of plasmapheresis of seven months each, with the addition of an ACE inhibitor from the beginning. A complete and stable remission of FSGS was observed, which continues after more than 6 years from the end of plasmapheresis. The recurrence of FSGS after a second transplantation has a poor prognosis, but prolonged plasmapheresis treatment, by removing circulating factors altering glomerular permselectivity, and the addition of ACE inhibitors, through their potential interference with TGF-β, might be synergistic in obtaining permanent remission.

Key words Recurrence of focal segmental glomerular sclerosis · Kidney transplantation · Plasmapheresis · ACE-inhibitors

Introduction

The recurrence of idiopathic focal segmental glomerular sclerosis (FSGS) after kidney transplantation is an ominous prognostic sign, with a graft loss rate of about 50–85% within 2 years [11]. The prognosis of a second recurrence in a patient who had already lost his first graft due to FSGS recurrence is even more severe. Spontaneous remission of proteinuria is exceptional and long-term management of these patients is difficult, since FSGS can recur in patients under CsA immunosuppression. The use of ACE inhibitors can obtain lasting remission in about 55% of patients [1]. An alternative approach is represented by plasmapheresis, with a response rate of about 29%. However, almost half of the patients who respond to plasma exchange therapy relapse after stopping plasmapheresis.

Case report

In May 1986 a 25-year-old male received a cadaveric renal transplant. He had been under regular dialysis for 15 months for idiopathic focal segmental glomerulosclerosis (FSGS) that progressed to end stage renal disease in about 30 months since the first appearance of proteinuria. After transplantation, he was given cyclosporine (CsA) at a dose of 10 mg/kg per day, then tapered to a maintenance of about 3 mg/kg per day within the 2nd month after transplantation, oral methylprednisolone (MP) (0.2 mg/kg per day, tapered to a maintenance dose of 0.1 mg/kg per day after 1 month) and azathioprine (Aza), 1 mg/kg per day. Graft function promptly recovered, and plasma creatinine reached a nadir of 1.6 mg/dl on the 7th day, ranging thereafter between 1.8 and 2.0 mg/dl. On day 4, a nephrotic proteinuria appeared (more than 10 g/day) and persisted unchanged thereafter. After transplantation, arterial hypertension developed; it was well controlled with Nifedipine 20 mg t.i.d. and Furosemide 25 mg b.i.d. A core renal biopsy performed on day 45 showed a recurrence of FSGS. The only therapeutical measure adopted was the introduction of an ACE inhibitor (captopril, 25 mg/day) which, however, was stopped after 20 days of administration due to a cutaneous reaction. Because of a progressive

increase in plasma creatinine (2.9–3.2 mg/dl), a second core renal biopsy was performed on the 27th month after transplantation. It confirmed the recurrence of FSGS. CsA was increased to 4.6 mg/kg per day at the 30th month. Graft function however progressively worsened, and the patient had to restart dialysis 63 months after renal transplantation.

After 10 months of dialysis, the patient underwent a second cadaveric renal transplant in May 1992. The immunosuppressive schedule was based on MP (0.2 mg/kg per day, tapered to a maintenance dose of 0.1 mg/kg per day within the 6th post-Tx month) and CsA (11 mg/kg per day, tapered to a maintenance dose of 4.4 mg/kg per day within the 2nd post-Tx month). The graft recovered immediately, displaying good function (plasma creatinine 1.4 mg/dl on the 4th day). No rejection was observed. On the 5th day, a nephrotic proteinuria appeared (4.6 g/day), but spontaneously and progressively disappeared by the end of the 1st month. Except for a mild arterial hypertension, easily controlled with a β-blocker, the course was uneventful. The patient remained free from proteinuria until the 12th month, when a nephrotic syndrome (NS) reappeared (proteinuria 4.3 g/day; serum albumin 2.8 g/dl). A core renal biopsy was performed, which showed a focal segmental glomerulosclerosis (FSGS) with extensive effacement of foot processes and no electron dense deposits in the GBM at electron microscopy (EM). No deposits were found at immunofluorescence (IF).

A therapeutical cycle of 9 plasma exchanges was started, with removal of 3.0 liters of plasma in each session (separators: Vivacell, Dideco and CS 3000, Baxter) and substitution with 4% albumin. CsA was increased from 300 to 400 mg/day during plasmapheresis. Proteinuria completely disappeared 5 months after the beginning of the plasma exchange. Plasmapheresis was continued with the same technique and at a frequency of 1–2 per week in the subsequent 7 months, and was then stopped. After 7 months from the discontinuation of plasmapheresis, proteinuria reappeared with a progressive increase up to 6 g/day. A further renal biopsy performed about 30 months after transplantation showed a very early stage of recurrence of FSGS with a minor mesangial enlargement due to matrix increase, but no clear-cut cell increase at optical microscopy (OM), a homogeneous thickening of the peripheral basement membrane, and a massive activation and microvilli formation of the podocytes with complete foot process fusion at EM. Plasmapheresis was restarted: 3 sessions per week for 15 days, then 2 per week for 2 months, then one per week for 2 months, then one every fortnight until discontinuation (16 sessions). An ACE inhibitor was simultaneously added (ramipril, 5 mg/day). At the end of a 7-month plasma exchange course, proteinuria was still present (0.52 g/day), but progressively decreased until its complete disappearance on February 1996, 45 months after transplantation. From then on the patient remained without proteinuria until his latest visit in June 1998. His present plasma creatinine is 1.0 mg/dl, blood pressure is 120/80 mmHg. His current immunosuppressive therapy is MP 8 mg/day, and CsA 275 mg/day (body weight 76 kg).

Discussion

Recurrence of idiopathic FSGS after renal transplantation has been reported with a prevalence of 6–60% of cases in various series [2, 4, 7]. About a half of the patients with a recurrence lost their graft. The recurrence rate is particularly high (50–80%) for patients who already had a recurrence in their first transplant [1]. As proteinuria often recurs in the first few days after transplantation, it has been suggested that some circulating factor(s), altering glomerular permselectivity for albumin, may be responsible for this rapid recurrence [8, 10]. This provided a rationale for the use of plasmapheresis or immunoadsorption as a treatment of recurrent FSGS in renal transplant recipients [3, 5]. A reduction of proteinuria has been observed in many patients during plasma exchange treatment, but proteinuria generally increases after discontinuation of plasmapheresis. In some patients, good results may be obtained by the association of plasmapheresis with an increase in immunosuppression, the administration of ACE inhibitors [1, 3] and/or the addition of cyclophosphamide [3, 6]. In the propositus, FSGS recurred after the first transplant and led to graft failure 5 years after transplantation. After undergoing a second transplantation, there was a transient reappearance of proteinuria with a recurrence of a full blown nephrotic syndrome due to FSGS a few months later. Proteinuria completely disappeared after plasmapheresis. A second relapse of NS occurred after plasmapheresis was interrupted. However, a good and persistent response was obtained with a further prolonged course of plasmapheresis plus ACE inhibitors.

While the recurrence of FSGS after undergoing the second transplantation usually has a poor prognosis, our patient is still enjoying his transplant with normal renal function and without proteinuria after more than 6 years. This case is exceptional in that the second recurrence of FSGS in the second transplant completely and permanently disappeared. This confirms the beneficial role of plasmapheresis in recurrent FSGS, which has already been pointed out by previous papers. However, the present experience suggests that prolonged plasmapheresis may obtain stable and consistent results with long-term remission of proteinuria. Thus, patients with recurrent FSGS who obtain a reduction of proteinuira by plasma exchange should receive plasmapheresis for a long period of time in order to prevent renal dysfunction and complications related to the nephrotic state.

Finally, the addition of ACE inhibitors may have an important supportive role in reducing proteinuria. It has been suggested that TGF-β may be involved in the development of mesangial sclerosis and progression of human FSGS [9]. ACE inhibitors, with their potential interference with TGF-β synthesis, might therefore be of help in maintaining remission after this has been achieved with the removal of the putative permeabilizing serum factor by plasmapheresis. The possibility to obtain a complete remission with early and prolonged plasmapheresis treatment, reinforced with the addition of ACE inhibitors, brings new hopes for the management of the recurrence of FSGS after renal transplantation.

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