LETTER TO THE EDITOR

# Plasma exchange in a patient with primary antiphospholipid syndrome undergoing kidney transplantation

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Early graft thrombosis remains the most frequent cause of renal graft failure in patients with antiphospholipid syndrome (APS) [1–7]. Several authors [2,5–7] have reported that anticoagulation begun before or at the time of kidney transplantation reduces post-transplant thrombosis. Nonetheless, despite anticoagulant therapy, graft thrombosis takes place in 40% of the APS population [7] and the appropriate treatment strategy to utilize in these patients is unclear.

The present study is a case report on a patient with primary APS who, while receiving prophylaxis with plasma exchange (PE) in addition to full anticoagulation therapy, underwent a successful living-donor kidney transplantation.

A 29-year-old Italian woman, scheduled to undergo a living-donor renal transplantation from her 69-year-old father, was referred to us in December 2001. At age 25, she suffered from an idiopathic deep vein thrombosis of the right leg. At that time, renal failure, which would make hemodialysis necessary 2 years later, became apparent. Due to thrombosis, arteriovenous fistula failed four times consecutively. All tests carried out to investigate the thrombophilia were within the normal range except for the antiphospholipid (aPL) assays. Medium titers of IgG anticardiolipin and IgG anti-$\beta$2-glycoprotein I antibodies and positivity for lupus anticoagulants were repeatedly detected. Primary APS was diagnosed and warfarin was prescribed continuously following an international normalized ratio (INR) maintained between 2.5 and 3.5.

Kidney transplantation was planned for March 2002. The treatment protocol foresaw substituting plasma with albumin (PE) to counteract the risk of early graft thrombosis. PE procedures were carried out using a Cobe Spectra (Gambro BCT, Lakewood, CO, USA), a continuous blood cell flow separator, every other day (on days −5, −3, and −1) according to the recently described [8] intensive schedule. At each session, 70–100% plasma volume was exchanged with 4% albumin–saline solution. In addition to full anticoagulation therapy, nadroparin, 0.4 ml two times daily (the patients' body weight was 51 kg) was begun on day −6, to be suspended 12 h before surgery. The surgical procedure was performed without complications and nadroparin was begun again on day +1 at 0.3 ml, two times daily, and from day +3 onwards at 0.4 ml, two times daily. The immunosuppressive regimen consisted of therapy with tacrolimus, mycophenolate mofetil, and methylprednisolone.

After transplantation, renal function slowly recovered until day +6, when (Fig. 1) a sudden decrease in diuresis occurred and the creatinine ceased to fall. A biopsy showed an acute class IB cellular rejection with a negative C4d reaction. Three boluses of 500 mg methylprednisolone were followed by a partial improvement in renal function (creatinine 300 $\mu$mol/l). Another biopsy on day +15 detected an acute class IA cellular rejection with a typical negative C4d reaction, although a spotty C4d deposition was evident. The corticosteroid boluses were repeated followed by antilymphocyte serum.

As creatinine levels and diuresis (Fig. 1) continued to worsen, the immunosuppressive therapy with tacrolimus was discontinued and cyclosporine was attempted on day +29. Renal function slowly improved until day +45, when a rise in lactate dehydrogenase and in D-dimer (Fig. 2) and a 40% decrease in the platelet count indicating thrombotic microangiopathy suddenly occurred. Cyclosporine was immediately substituted with tacrolimus and PE was begun again (three times in 4 days), followed by endovenous immunoglobulin infusions (0.4 g/kg/day for 5 days). The subsequent clinical course was uncomplicated and nadroparin was switched to warfarin on day +53 and on day +71 creatinine reached 159 $\mu$mol/l.

Modifications in the anticardiolipin antibody levels are reported in Fig. 3. In particular, IgG anticardiolipin antibodies decreased from 73.7 to 30.6 GPL (G phospholipid units) following pretransplant-plasma exchange and they shot up to 53.7 GPL during acute rejection. They fell to 20.1 GPL after the corticosteroid boluses and antilymphocyte serum were administered. The titers began to rise again when cyclosporine was administered and reached 69.7 GPL at the first signs of thrombotic microangiopathy. Subsequently, intensive PE reduced the antibody level to 5.3 GPL (cut-off point 8.8 GPL). The patient did not develop antibodies to any of the HLA class I and II donor antigens.

 

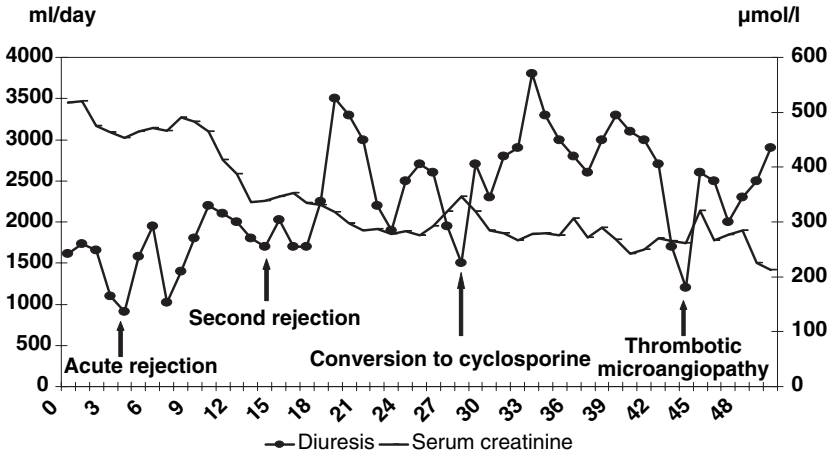


**Figure 1** Creatinine and diuresis values after kidney transplantation.

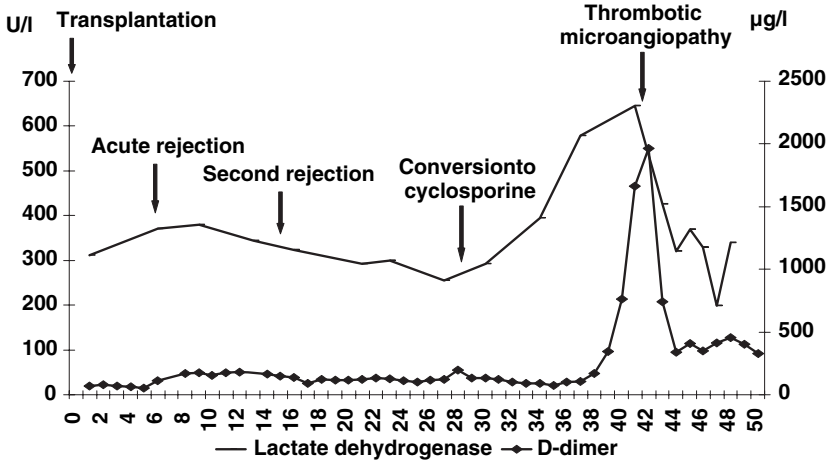


**Figure 2** Lactate dehydrogenase and D-dimer levels after kidney transplantation.

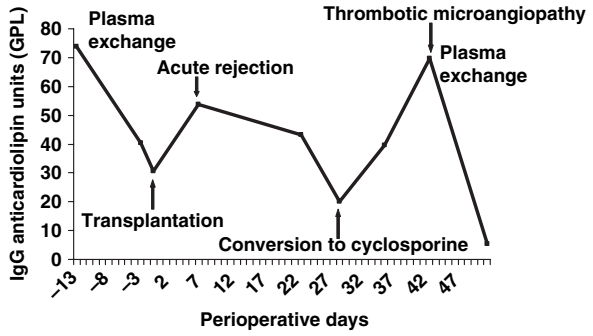


**Figure 3** The trend of the IgG anticardiolipin antibody titers before and after kidney transplantation.

Now, 4 years post-transplant, the patient presents stable renal function (creatinine 160 $\mu$mol/l). Her antibody profile shows a medium titer of IgG anticardiolipin and IgG/IgM anti-$\beta$2-glycoprotein I antibodies. During the follow-up period, the patient had an important menorrhagia, and as a consequence INR anticoaguation range was decreased from 2.5–3.5 to 2–3, following no thrombotic or hemorrhagic events.

Antiphospholipid syndrome in patients with end-stage renal disease constitutes a supplementary risk for the development of thrombosis shortly after transplant [1–7]. To our knowledge, PE has been used, until now, in patients with primary APS undergoing kidney transplantation only by Chew *et al.* [4]. Prescribed by these investigators only after transplantation to treat thrombotic complications, PE was related to a partial recovery in renal function [4]. In our patient, it was utilized after transplantation to help the kidney recover from thrombotic microangiopathy, and before surgery to prevent aPL-related thrombotic injury by removing the offending autoantibodies. Prevention of thrombosis is fundamental for graft survival [7]. In fact, once the thrombotic process starts, there is no effective therapy available to lyse the clot and to recover the graft [7].

The role of aPL in the pathogenesis of kidney rejection is controversial [9]. However, the rise in IgG anticardiolipin levels observed in our patient at the time of acute rejection

(Fig. 3) seems to implicate their involvement. The spotty C4d deposition evident on kidney histological sections along with the absence of antibodies to the HLA class I and II donor antigens is in accordance with this hypothesis.

Cyclosporine seems to be linked to a predisposition for thrombotic microangiopathy [10,11]. The fact that it occurred in the present case and in some APS patients after therapy [1,2,4] indicates that other immunosuppressive agents should be prescribed after kidney transplantation in these patients. The important increase in IgG anticardiolipin titers in our patient after it was introduced (Fig. 3) would seem to support the hypothesis that cyclosporine together with aPL are related to the thrombotic microangiopathy.

What prophylaxis of thrombosis to utilize in APS patients undergoing kidney transplantation, especially if they are living-donor recipients, is unclear. Some authors [1] in fact question the eligibility of APS patients for kidney transplantation and others [4] would limit it to cadaveric grafts. On the basis of these findings in a single case, it is impossible to conclude that PE and heparin are useful as prophylaxis for thrombosis in APS patients undergoing renal transplantation. Further studies are of course warranted.

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## References

1. Mondragón-Ramírez G, Bochicchio T, García-Torres R, *et al.* Recurrent renal thrombotic angiopathy after kidney transplantation in two patients with primary antiphospholipid syndrome (PAPS). *Clin Transplant* 1994; **8**: 93.
2. Knight RJ, Schanzer H, Rand JH, Burrows L. Renal allograft thrombosis associated with the antiphospholipid antibody syndrome. *Transplantation* 1995; **60**: 614.
3. Vaidya S, Wang CC, Gugliuzza K, *et al.* Relative risk of post transplant renal thrombosis in patients with antiphospholipid antibodies. *Clin Transplant* 1998; **12**: 439.
4. Chew CG, Bannister KM, Mathew TH, Russ G, Seymour A. Thrombotic microangiopathy related to anticardiolipin antibody in a renal allograft. *Nephrol Dial Transplant* 1999; **14**: 436.
5. Vaidya S, Sellers R, Kimball P, *et al.* Frequency, potential risk and therapeutic intervention in end-stage renal disease patients with antiphospholipid antibody syndrome. *Transplantation* 2000; **69**: 1348.
6. Wullstein C, Woeste G, Zapletal C, Dette K, Bechstein WO. Simultaneous pancreas–kidney transplantation in patients with antiphospholipid syndrome. *Transplantation* 2003; **75**: 562.
7. Vaidya S, Gugliuzza K, Daller JA. Efficacy of anticoagulation therapy in end-stage renal disease patients with antiphospholipid antibody syndrome. *Transplantation* 2004; **77**: 1046.
8. Ruffatti A, Marson P, Pengo V, *et al.* Plasma exchange in the management of high risk pregnant patients with primary antiphospholipid syndrome. A report of 9 cases and a review of the literature. *Autoimmun Rev* 2006; (in press).
9. McIntyre JA, Wagenknecht DR. Antiphospholipid antibodies. Risk assessments for solid organ, bone marrow, and tissue transplantation. *Rheum Dis Clin North Am* 2001; **27**: 611.
10. Rigotti P, Flechner SM, Van Buren CT, Payne WT, Kahan BD. Increased incidence of renal allograft thrombosis under cyclosporine immunosuppression. *Int Surg* 1986; **71**: 38.
11. Imbasciati E, Bucci R, Barbisoni F, *et al.* Acute renal failure and thrombotic microangiopathy (TM). *G Ital Nefrol* 2003; **20**: 285.

 