Successful Simultaneous Pancreas-Kidney Re-transplantation in a Highly Human Leukocyte Antigen–Sensitized Patient

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ABSTRACT

Background. The waiting time for re-transplantation for sensitized patients is greatly prolonged, given the lack of transplants that are available for this group and additional immunologic barriers. We report the case of a successful re-transplantation in a patient with very high levels of panel reactive antibodies ([PRA] >85%).

Methods. A 45-year-old woman had repetitive rejections after simultaneous pancreas-kidney transplantation, with consequent loss of function of both transplanted organs. Because of a symptomatic episode of kidney rejection, additional removal of the transplanted kidney was performed 6 years later. Because our patient had a very high PRA level, she was enrolled in a desensitization protocol. The regimen was based on an initial single dose of rituximab, followed by repetitive plasmapheresis/immune-absorption sessions and intravenous substitution of immunoglobulin. Eight cycles were required, until a cross-match test was negative (PRA level <50%). The protocol included prednisolone and weight-adapted thymoglobulin. The basic immunosuppressive medication consisted of prednisolone, tacrolimus, and mycophenolate mofetil. The patient's postoperative course was uneventful.

Results. Preoperative treatment is essential for sensitized patients. There are no prospective, randomized trials comparing all suggested desensitization protocols. The main tenets of every approach are plasmapheresis and intravenous substitution of immunoglobulin, which appear to have a strong immunomodulatory effect. In the case of re-transplantation, the clinical surgeon not only faces special technical and surgical challenges but also must confront immunologic barriers.

Conclusions. Pancreas-kidney transplantation in patients with high PRA levels is feasible and can be performed successfully with novel desensitization protocols.

SIMULTANEOUS pancreas-kidney transplantation (SPK) is the treatment of choice for selected type 1 diabetic patients with end-stage diabetic nephropathy because it prolongs survival, decreases diabetes-related morbidity, and improves the patient's quality of life. However, the waiting time for re-transplantation for sensitized patients is greatly prolonged given the lack of transplants that are available for this group and additional immunologic barriers. We report the case of an SPK re-transplantation that was successfully performed in a patient with a panel reactive antibody (PRA) level higher than 85%.

Case Report

A 45-year-old female patient underwent an SPK transplantation in our center in 2004 for juvenile diabetes mellitus type I. The pancreas transplant was placed intraperitoneally, and its exocrine drainage was achieved with a 2-layered side-to-side duodenojejunostomy. The portal vein of the pancreas graft was anastomosed to

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the distal inferior vena cava. An end-to-side anastomosis between the donor iliac Y-graft and the right common iliac artery was performed. The kidney transplantation was performed with arterial and venous anastomosis to the recipient's left-sided common iliac vessels. The ureter was implanted into the bladder by use of a standard Lich technique.

Unfortunately, both transplanted organs were repetitively rejected in the years after the transplantation, with consequent loss of function of both transplanted organs in 2009. The patient became insulin-dependent and enrolled in a dialysis program. At that point, she was re-listed in Eurotransplant for a further combined transplantation. Meanwhile, she was highly sensitized (PRA >85%) as the result of a prior delivery, the combined transplantation, and a number of blood transfusions within these years. Additional rejection-related nephritis of the renal transplant led to recurring urinary tract infections, which were difficult to manage and required prolonged treatments in the hospital. Because of a symptomatic renal allograft, a transplant nephrectomy was required in 2010.

According to her immunization status, the patient was ranked quite high on our waiting list and received in priority plenty of primary, center, and rescue offers. Unfortunately, all offers were withdrawn because of the high number of human leukocyte antigen (HLA) antibodies that were pre-formed. Because the PRA level was 85%, and, to increase the possibility of an immune-compatible graft offer, she was enrolled in a desensitization protocol.

The treatment regimen included a single dose of rituximab (375 mg/m^2, 650 mg), followed by 5 repetitive treatments of plasmapheresis/immune-adsorption and intravenous substitution of immunoglobulin (IVIG) in a 14-day rhythm. The course of PRA levels is shown in Fig 1. Eight cycles were required until a negative cross-match test was achieved. The HLA (A/B/DR) mismatch to the accepted grafts was 0-1-0 (locus HLA B40). The simultaneous pancreas-kidney re-transplantation was performed in 2013, whereas the pancreas had been drained systemic venous to the inferior vena cava and enteric exocrine to the ileum via a side-to-side duodenoileostomy. The small, fibrotic, and asymptomatic pancreas graft was left in place. Kidney re-transplantation was performed through the use of a fresh anastomosis to the recipient's left external iliac vessels. The patient underwent an additional plasmapheresis treatment immediately before surgery. Induction immunosuppression was performed with the use of 1000 mg prednisolone and daily administration of weight-adapted thymoglobulin (1.5 mg/kg/body weight) within the first 4 days after surgery. The basic immunosuppressive medication was started on the first postoperative day and consisted of prednisolone, tacrolimus (target trough level, 10–15 mg/mL), and mycophenolate mofetil (1000 mg bid). The patient received cytomegalovirus prophylaxis with ganciclovir, followed later by valganciclovir for 3 months. *Pneumocystis jirovecii* prophylaxis was performed with the use of trimethoprim/sulfamethoxazole also for 3 months in total. Perioperative antibiotic prophylaxis was performed with the use of ceftriaxone/metronidazole and fluconazole.

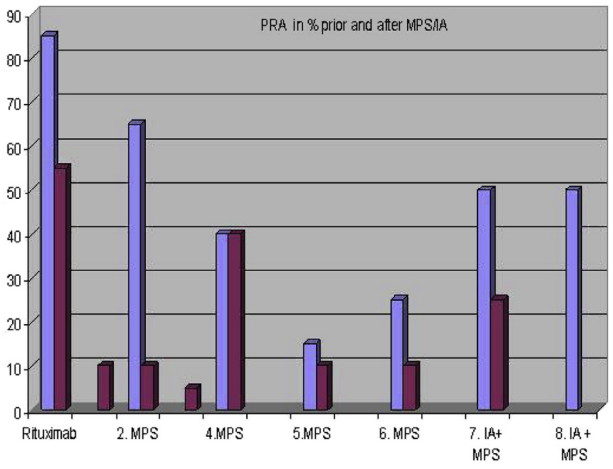

Fig 1. Pre- and post-treatment courses of PRA levels. The purple and red bars represent the PRA in % prior and after MPS/IA, respectively. Abbreviations: PRA, panel reactive antibody; MPS, membrane plasma separation; IA, immune adsorption.

Both transplanted organs showed early primary function during an uneventful postoperative course. Two months after the patient's admission and during her follow-up, the patient's retention values (blood urea nitrogen/creatinine) were measured and found to be elevated. In contrast, the serum levels of glucose, hemoglobin A1c, and c-peptide were normal. After excluding urinary tract infection and an elevated tacrolimus level as potential causes, a biopsy of the kidney was performed. The histologic analysis revealed a borderline cellular rejection (BANFF 97 classification), which was successfully treated with steroid pulse therapy for 3 days. The HLA antibodies were estimated at that time, whereby no donor-specific antibodies were detected. Since then and for an observation period longer than 4 years, the function of both allografts remained stable. The dialysis fistula in the patient's left arm was meanwhile ligated.

DISCUSSION

The PRA score represents the proportion of the population to which the pre-formed anti-human antibodies of a "sensitized" patient's blood will react. The waiting time for re-transplantation for highly sensitized patients is prolonged because suitable grafts cannot be found easily. The risk is that an appropriate offer often comes too late in the course of the underlying disease. This has a negative impact on patient morbidity and mortality rates because these patients cannot be considered suitable for transplantation unless the PRA levels have first been reduced through desensitization protocols.

The two basic treatment policies include high-dose IVIG alone or a combination of plasmapheresis with low-dose IVIG. Splenectomy, which aims to remove lymphocytes, was initially incorporated in several desensitization protocols or even in the treatment of a severe antibody-mediated rejection [1,2]. On the other hand, and, because of its permanent effect on the immune system, splenectomy is associated with a life-long risk of severe complications. In our opinion, this approach has no more place in the new era of immunosuppressive therapy because its usefulness has been widely replaced with the use of a B-cell–depleting agent.

Jordan et al [3] reported desensitization action in high-dose human IVIG (2 g/kg) and published encouraging results on the treatment of acute humoral rejection in renal transplant recipients (Cedars-Sinai protocol). The strong immunomodulatory effect of IVIG consists of both inhibition of lymphotoxicity and reduction of anti-HLA antibodies in human recipients. The combined inhibition