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LETTER TO THE EDITOR

Fifth kidney transplantation in a patient with focal segmental glomerulosclerosis

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Dear Sirs,

A 40-year-old, HCV- and HBV-positive woman, with 35-year history of FSGS [1] and highly sensitized against the MHC (100% peak historical PRA), presented at our center asking for living donor KTx from her 39-year-old husband. She had already received four KTx and one heart Tx (simultaneously with the fourth KTx) across various countries at the ages of 9, 11, 18, and 32 years. All previous KTx were complicated with early FSGS recurrence and graft failure within 6 months to 9 years; the second KTx was lost within 3 days because of a suspected antibody-mediated rejection (AMR). Because of the ABO blood group incompatibility, we arranged a living donor paired exchange. Virtual donor swap predicted a 3/6 (A-B-DR) MHC-matching and a low-titer donor-specific antibody (DSA) directed against the mismatched DQB1*03:01 (DQ7), with median fluorescence intensity (MFI) of 9000 [2–4].

A desensitization protocol including plasma exchange (PE) with human serum albumin (1.5 volumes on days −7, −5, −4, −3 and −1), rituximab (375 mg/m^2 IV on day −3, +4 and +17) and human intravenous immunoglobulin (IVIg 500 mg/kg on day −1, +1, +2, +3, +4, and +16) was used [5], and both native renal arteries were ligated during surgery [6]. Basiliximab was used as induction therapy and maintenance immunosuppression (given for her heart Tx) remained unchanged (CsA, EC-MPA, and Pred). Angiotensin-converting enzyme and angiotensin-receptor blocker therapy, prescribed several months prior to KTx, was continued after KTx. Serum creatinine decreased to 0.4 mg/dl on postoperative day 3. The highest proteinuria level was 1.28 g/day (80% tubular proteins) on postoperative day 3. The patient was discharged on postoperative day 18 with serum creatinine of 0.7 mg/dl and 24-h proteinuria of 0.224 g. At 1-year follow-up, the patient is in excellent clinical condition, with serum creatinine of 0.9 mg/dl (estimated glomerular filtration rate 85 ml/min/1.73 m^2), urea 44 mg/dl, fasting glycemia 68 mg/dl, LDL-cholesterol 118 mg/dl, normal liver enzymes, serum albumin 3.70 g/l, and no proteinuria (i.e. no proteinuria was detected during all monthly regular visits performed during the first year). Quantitative plasma HCV-PCR is unchanged as compared with pretransplant levels (69.910.652 UI/ml; 6.8 log). Plasma HBV-PCR remained negative throughout follow-up. Plasma and urine polyomavirus (BKV) PCR are negative. CsA trough and C2 levels are, respectively, 93.6 and 519 ng/ml, under 50 mg/bid. EC-MPA dose is 360 mg/bid and Pred of 5 mg/day. Other medications are: adefovir, lamivudine, lisinopril, losartan, simvastatin-ezetimibe, and aspirin. No protocol kidney biopsy was performed because of absence of any clinical or biological sign of recurrence or rejection (see DSA kinetics in Fig. 1; latest MFI measurement was 1.539 on June 2012), aspirin intake and intraperitoneal placement of the KTx. Heart transplant evaluation remained normal throughout follow-up.

In contrast to all four previous KTx, this fifth Tx immediately functioned (no PNF). This immediate graft function could be partially explained by the use of a living kidney; however, this was also the case when she received her first mother's KTx in 1980. This primary KTx was complicated by 1-month PNF and subsequent nephrotic range proteinuria (resistant to high-dose Pred), followed by graft loss on postoperative month six. Two kidney biopsies were compatible with FSGS recurrence. At that time, immunosup-

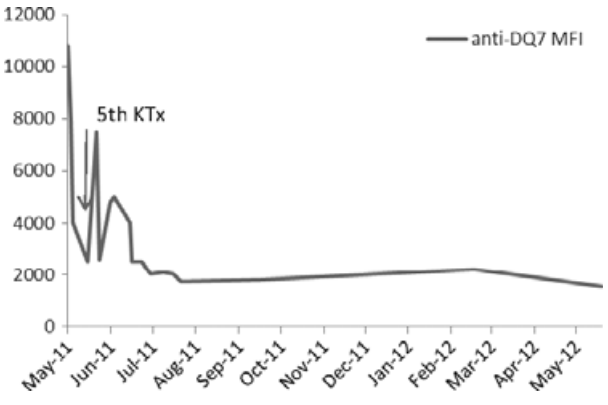

Figure 1 Kinetics of MFI for the anti-DQ7 DSA in recipient's serum.

pression consisted of azathioprine (Aza) and Pred. Her second KTx, performed in 1982 from a cadaver donor, was lost within 72 h; PNF was again observed, followed by graft nephrectomy because of 'graft rupture' (an AMR was suspected). Immunosuppression was again based on Aza and Pred. The third KTx (cadaver donor) was performed in 1989 in the context of persistent CMH-hyperimmunization, with a negative CDC-T-cell CM (B-cell CM was positive) on the day of surgery (both T and B-cell CM were positive with historical sera). Rabbit antithymocyte globulin was given for induction, followed by CsA/Aza/Pred maintenance immunosuppression. PNF was again encountered and massive proteinuria (majority glomerular origin) was diagnosed on postoperative day 12. Despite multiple PE and angiotensin-converting enzyme therapy, proteinuria persisted throughout follow-up although renal function recovered. Near-normal renal function lasted for 9 years, despite persistent, nephrotic range proteinuria. Histology was compatible with FSGS recurrence. Two severe myocardial infarctions required a heart Tx which was combined with a fourth KTx in 2002 (the patient was on dialysis since 4 years). CDC-T and B-cell CM were negative. PNF was again observed despite good cardiac function. Massive proteinuria occurred when urine output recovered on day 10. Histology was again compatible with FSGS recurrence and despite several immunoadsorption and PE cycles, immunosuppression adjustments (CsA, tacrolimus, mycophenolate mofetil, sirolimus, cyclophosphamide, high-dose Pred), and angiotensin-converting enzyme and angiotensin-receptor blocker therapy, dialysis was restarted on 2007. From this two last KTx, one may conclude that CsA immunosuppression, although more efficient than Aza/Pred, is not sufficient to fully prevent recurrence.

The use of rituximab has produced encouraging but inconstant results as rescue therapy in PE-resistant cases of FSGS recurrence [7–11]. Rituximab may act as a direct modulator of podocyte function, similar to what has been reported with CsA, by affecting glomerular filtration barrier via the preservation of sphingolipid-related enzymes that might affect actin cytoskeleton remodeling in podocytes [7,11]. The fifth KTx was performed in May 2011 and for the first time, immediate urine output (7 l within 24 h) was observed with normalization of renal function within 3 days, without glomerular proteinuria at all. Primary function was without doubt related to the absence of recurrence. As this regards, rituximab might be, in association to all other measures, the cornerstone agent used in our protocol to explain so good result in preventing recurrence. Regular monitoring of viral infections, mainly HBV replication, throughout follow-up is necessary among positive patients receiving rituximab. Longer follow-up and larger series will be of interest if confirm the effectiveness and safety of our protocol in preventing FSGS recurrence. If this is the case, patients with FSGS on the waiting list could again hope to be successfully retransplanted even in case of previous failure because of recurrence. Our case could fit the following proverb: 'persevere and you will triumph'.

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Conflict of interest

We declare that we have no conflict of interest related to this manuscript.

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