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Successful treatment of accelerated vascular rejection in a highly immunised renal transplant recipient with immunoadsorption and 15-deoxyspergualin

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Dear Editor,

In 1999, 115 patients within the Eurotransplant Community, awaiting renal transplantation, were designated as being highly immunised to human leukocyte antigens with panel reactive antibody levels (PRA) greater than 85% [1]. These patients have little chance of receiving a crossmatch negative transplant without intervention. Staphylococcal protein A (SPA) immunoadsorption has been proven to be an effective tool to remove low-titre cross-reacting anti-HLA antibodies for successful transplantation [2, 3].

A 29-year-old female patient [HLA-type: A26(10),A28; B35; Bw6; Cw4, Cw6; DRB1*01, DRB1*15; DRB5* positive; DQB1*05, DQB1*06] in end-stage renal failure since 1985, owing to chronic pyelonephritis, received her first kidney transplant [HLA-type: A11, A31; B44(12), B55(22); Bw4, Bw6; Cw3; DR1; DQw1] in 1986 which was rejected in 1988. Thereafter, she developed alloreactive anti-HLA antibodies resulting in PRA levels between 68% and 100%. Although she was repeatedly reported to Eurotransplant Highly Immunised Transplantation protocol, she did not receive a second transplant until March 2000 (cumulative waiting time: 10.4 years). The donor of the second kidney had the following HLA-type: A*02; B*35, B*39; DRB1*04, DRB1*16; DRB4* positive, DRB5* positive (Cw* not tested; DQB1* not tested). The lymphocytotoxic crossmatch performed with DTT, using a fresh and several historical sera of peak reactivity was rated negative. The flow-cytometric crossmatch (FCXM) revealed borderline positive T cell and B cell crossmatches. The patient underwent SPA immunoadsorption treatment (Immunosorba, St. Wendel, Germany) prior to renal transplantation. Immunosuppression consisted of methylprednisolone 100 mg/day for 3 days followed by prednisolone 80 mg/day, cyclosporine A with trough levels between 150 and 200 ng/ml and mycophenolate mofetil 1 g BID. Intravenous basiliximab (Simulect, Novartis, Horsham, UK) was added on day 0 and 5 (Fig. 1). No graft function was noted when, on day 7, the patient complained of fever and increasing pain over the transplantation site. Transplant biopsies on days 7, 12 and 28 revealed collapsing capillary loops with perivascular lymphocyte infiltrates and endothelial thickening. Moderate numbers of lymphocytes and minor signs of tubulointerstitial fibrosis were also noted. Immunhistochemistry including C4d was negative except for fine granular deposition of IgM in the mesangium. The diagnosis of vascular and interstitial rejection was made. The last biopsy still showed partially obliterated blood

vessels and swollen endothelium with mononuclear cell infiltrates. The T-cell and B-cell FCXM were strongly positive. Using the monoclonal antibody-specific immobilisation of platelet antigens (MAIPA) assay, the presence of donor-specific anti-class I antibodies both before and at the time of transplantation could retrospectively be demonstrated (Fig. 1). For this assay, platelets from a blood donor with the HLA-A,B-type A*02; B*39 were used representing the kidney's A,B antigens different from the patient [4]. SPA immunoadsorption was reinstituted again and 5 days later the first urine output was noted. Thirteen immunoadsorptions were performed post transplant with a total of 89.7 l of plasma being processed.

Following completion of the post transplant immunoadsorption treatment antibody resynthesis was suppressed by 15-deoxyspergualin (DSG, Spanidin, Nippon Kayaku, Tokyo) 150 mg intravenously for 7 days, followed by subcutaneous DSG 50 mg once daily for another 10 days. At this time serum creatinine was 0.9 mg/dl (Fig. 1). The FCXM and MAIPA test for donor antigens remained negative throughout the follow-up period (Fig. 1). At the last follow up 2 years later, the patient's creatinine was still 1.1 mg/dl.

In retrospect, this case demonstrates a booster reaction of pre-existing low-titre anti-HLA antibodies by allogeneic renal transplantation resulting in vascular and interstitial rejection. Immunoadsorption onto SPA has previously been shown to effectively eliminate anti-HLA antibodies in renal vascular rejection with good clinical outcomes [5, 6, 7]. Unfortunately, SPA immunoadsorption does not remove anti-HLA antibodies alone; it removes IgG antibodies irrespective of their specificity. Removal of antibodies from the circulation does not inhibit their resynthesis, therefore cytotoxic medications or anti-lymphocyte globulins are generally

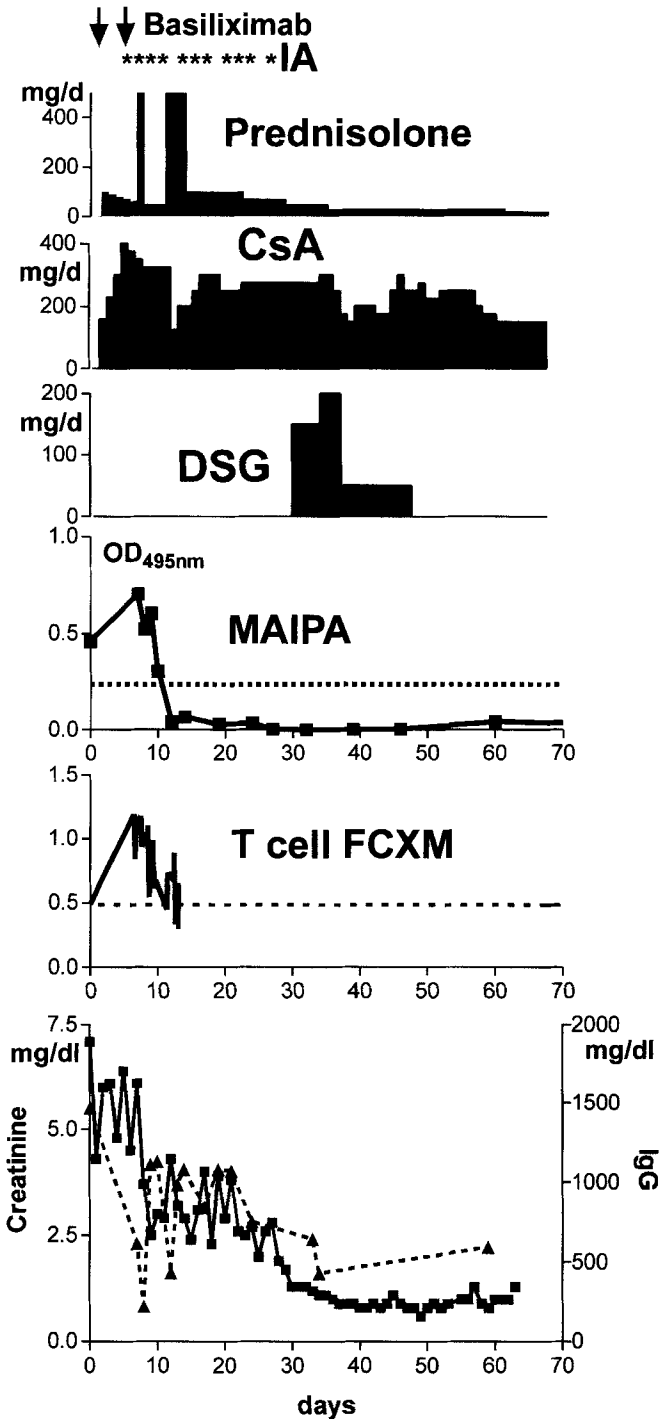

Fig. 1 Therapeutic approach and clinical course to the humoral vascular rejection in a HLA-sensitised kidney transplant recipient. *Bar diagrams* denote immunosuppressive medication in mg/day (DSG = 15-deoxyspergualin, CsA = cyclosporine A). Detection of anti-HLA class I antibodies were measured by the monoclonal antibody-specific immobilisation of platelet antigens (MAIPA) assay. T cell flow cytometry crossmatch (FCXM) results are given as logshift of median fluorescence compared to the autologous crossmatch. Serum creatinine (*straight* line and *squares*; mg/dl) and immunoglobulin G (IgG) levels (*dashed line* and *triangles*; mg/dl) are given in the lower diagram. Asterisks denote immunoadsorption sessions (IA)

used as additive measures. This results in a severe acquired humoral immune deficiency which puts the patient at a high risk of infection with possible life-threatening complications. DSG for the treatment of renal allograft rejection was mainly evaluated in small, mostly non-controlled trials in Japan [8]. On the basis of these data, DSG seemed to be a safe treatment option for renal allograft rejection. Gannedahl et al. [9] reported one renal transplant patient with vascular rejection and another patient with dysfunction of the renal allograft shortly after transplantation, both treated by a combination of plasmapheresis and 5 days of DSG. The patient with vascular rejection showed no change of serum creatinine for more than 14 days despite treatment. In contrast to this report, our patient showed immediate reinstitution of normal graft perfusion and initiation of graft function by immunoadsorption alone. The rapid reconstitution of transplant function after the start of immunoadsorption may be contributed to the immediate removal of antibodies by immunoadsorption, while Gannedahl's patient most likely suffered from quite advanced renal destruction due to prolonged humoral rejection. Intravenous and subcutaneous application of DSG was safely used as maintenance therapy to prevent antibody resynthesis. This was shown by prolonged suppressed total IgG levels and no further detection of anti-HLA antibodies by neither MAIPA nor FCXM.

In conclusion, putative negative standard cytotoxic crossmatch and FCXM might not rule out the presence of pre-formed, very low-titre anti-HLA antibodies, beyond assay detection limits, prior to transplantation. The synthesis of these antibodies could be boosted after transplantation owing to the response of the patient's memory B cells to recall antigens on the graft. Immunoadsorption onto SPA is a highly effective tool for rapid elimination of anti-HLA antibodies and may reinstate normal graft function following a humoral rejection episode. The administration of DSG was shown to be a potent immunoglobulin synthesis inhibitor, of prolonged duration, for the prevention of resynthesis of anti-HLA antibodies following their removal from the peripheral circulation.

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