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Transduction of a Positive Crossmatch into a Negative Crossmatch through Immunosuppressive Therapy

We report the case of a female prospective recipient of a living donor kidney transplantation where the crossmatch could be changed by means of immunosuppressive therapy.

This is a first case-report demonstrating that caused by immunosuppressive treatment a positive x-match can be converted into a negative x-match successfully. After receiving an immunosuppressive therapy with 500 mg CellCept[®] (MMF) twice a day for 6 months the x-match became negative as was checked 4 times subsequently. The patient's sera prior to transplantectomy showed after DTT-treatment (destruction of IgM antibodies) positive results in T-cell x-match, a reaction obviously caused by destruction of IgM anti-idiotypic antibodies. Anti-idiotypic antibodies (i.e. anti-antibodies) in most cases belong to the IgM-class and are known to suppress anti-HLA-antibodies biologically. Possibly, the graft was surviving for this long period (of about 12 years) because the anti-donor antibodies were suppressed by IgM anti-idiotypic antibodies of the recipient.

However, after the CellCept[®] therapy neither a positive CDC or Flow x-match result, nor a PRA with specific antibodies remained. This could be verified by monthly repeated x-matches between the recipient and the prospective living donor. Interestingly, after destruction of possible IgM-antibody specificities the phenomenon of the preectomy sera was observed again, i. e. due to destruction of IgM anti-idiotypic specificities the serum showed slightly positive x-match results with CD8 + donor T cells.

It was demonstrated that immunosuppressive therapy with CellCept[®] (MMF) made it possible to transfer a positive x-match into a negative current x-match. This transformation of the current x-match is caused by depression of the antibody formation in the B-cell population as indicated by the company producing CellCept.

Key words:

immunosuppression, kidney transplantation, transduction of crossmatch, HLA compatibility, mycophenolate mofetil

Transduktion eines positiven Crossmatches in einen negativen Crossmatch mittels immunsuppressiver Therapie

Mittels Immunsuppression mit einer Kombination von Tacrolimus- und MMF/CellCept-Gabe konnte das x-match-Resultat einer historisch sensibilisierter Lebend-Nierenempfängerin gegen ihre nicht-verwandte Lebendniere spendende von positiv in negativ konvertiert werden. Die Funktion und Akzeptanz der Spenderniere

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durch die Empfängerin verlief bisher erfolgreich. Es ist nicht auszuschliessen, dass in diesem Fall das zusätzliche Auftreten einer Blockierung der transplantatspezifischen Anti-HLA-Antikörper durch anti-idiotypische Antikörper dabei eine wichtige additive Rolle spielt. Die offene Frage bleibt deshalb, ob bei der beschriebenen Konstellation und der präoperativen Therapie mit MMF/CellCept eine Lebendnierentransplantation auch in anderen Fällen erfolgreich sein kann.

Schlüsselwörter:

Nierentransplantation, Immunsuppression, Crossmatch

Introduction

The HLA compatibility between donor and recipient is an important requirement for a potential transplantation of cadaver kidneys (1 - 7). For living donor transplants HLA compatibility is considered not to be a main criterium due to the fact that relatives shared HLA antigens in most cases. Moreover, in case of HLA non compatible related or foreign kidney donors there is no alternative chance to select another donor. Also, our minimum criterium for mismatching in cadaver transplantation (A-B-DR = 2-1-1 or 2-2-0) is unsuitable for a living donation. However, transplantation is excluded if there is a positive crossmatch result (8) and / or a proof of donor specific HLA antibodies of the recipient (9 - 15).

In the present report we demonstrate the case of a female prospective recipient selected for a kidney transplant of a living donor the positive crossmatch result of which could be changed into a negative result by means of immunosuppressive therapy.

Material and Methods

Serologic HLA typing

Anticoagulated blood samples were taken from all test persons. Peripheral blood lymphocytes serving as indicator cells were separated from peripheral blood by density gradient centrifugation (16). Using the micro-lymphocyte toxicity assay (CDC) according to National Institute of Health (NIH) standards the patient and the kidney donor were typed

for their HLA-A, -B, -Cw antigens and for HLA-DR, -DQ following the manufacturer's instruction.

Moleculargenetic HLA typing

DNA was isolated from peripheral blood lymphocytes by the salting out technique according to Miller (17). The patient and the kidney donor were additionally DNA-typed in low resolution technique by PCR-SSP. The typing was carried out with commercially available primer test kits according to the manufacturer's instructions.

The quality of the HLA typing methods employed was assured by the regular use of control samples provided by the Institute for Standardization and Documentation in Medical Laboratories e. V: Eurotransplant proficiency testing.

Screening for anti-HLA antibodies

Anti-HLA antibodies were selected by regular screening. The patient's sera were checked by means of CDC according to Terasaki & McClelland (18) and a constant panel (store in LN₂) of CLL(B) cell suspensions with selected HLA-A, B, Cw, DR, DQ, DP type and, thereafter, in a second step by means of CDC with a constant PBL panel consisting of 60 HLA-A, B, Cw typed (stored in LN₂). The CDC was performed at room temperature (+ 23°C, incubator WTB Binder, Tuttlingen, Germany) with extended incubation time (45 min / + C' 90 min) and EBr / AO fluorescence staining. Microscopy was performed with the One Lambda Plus evaluation system. Quality was

shown by participation in the Eurotransplant (ETLR, Leiden, The Netherlands) screening proficiency testing.

Crossmatch

For crossmatch lymphocyte, CD8+ (T) lymphocyte as well as HLA class II + (B) lymphocyte suspensions were isolated by density gradient centrifugation and immunomagnetic beads (Dynabeads, Deutsche Dynal AG, Hamburg, Germany) according to the manufacturer's instructions, respectively, from peripheral blood of the prospective donor and incubated with the historical and current sera of the recipient. The CDC was performed in the same manner as the antibody screening.

The flow cytometric crossmatch was carried out by use of FACScan (Becton Dickenson, Heidelberg, Germany) under adapted conditions (RAINBOW protocol) using the sera of the recipient with and without DTT treatment and donor lymphocytes.

Results

The recipient is a 43-year-old woman who suffered from renal insufficiency probably caused by a reflux illness that had not been treated during her childhood. She had to receive dialysis treatment since 1989. From her autoanamnesis is known an anal atresia which had been surgically corrected in her childhood. Nephrectomy was performed in 1971 on the left and in 1990 on the right hand side. The recipient's mother showed a Mamma-Ca at the anamnesis. The recipient's HLA type was: HLA-A3, 28, B44 (12), 60 (40), DRB1*04,13 (DR4, 6) and further characteristics: Blood group: BD, CMV: positive.

The first renal transplantation was carried out in 1990. The donor was a 15-years-old boy with the following HLA type: HLA-A10, 28, B12, b1 (B44, 45), DR4, 6 (DR13 + 14) and further characteristics: Blood group 0d, CMV: positive. The mismatch degree between donor and recipient was 1-0-0 according to Eurotransplant criteria. Before and after the first allogeneic cadaveric transplant no anti-HLA antibodies could be revealed in the recipient's serum.

Immunaran, Prednisolon and Cyclosporin A were used for immunosuppression. The creatinine value was 118 µmol/l. Due to a chronic rejection developing after 9 years, a treatment switch to Prograf became necessary and a high-dose therapy with Urbason was started simultaneously. There was a paraclinical increase of the creatinine value and urea. A side-to-end UA shunt was created between A. radialis and V. cephalica antebrachii. Moreover, there was histological evidence of a considerable sclerosis of the venous vessel wall.

After 11 years (in June 2001) a chronic transplant failure was started – that was caused by a chronic pyelonephritis which finally led to chronic renal insufficiency and renal hypertonus. Transplant ectomy followed in August 2000. As a result the patient had to be returned to dialysis treatment.

Consequently, starting from November 2001 (see tab. 1) the patient was examined again quarterly a year for panel-reactive antibodies (PRA).

During this period antibodies against the cross-reacting HLA antigens B35, B5, B15, B18 were revealed which the patient formed as a consequence of an immunization by blood transfusions as well as antibodies against the incompatible antigen HLA-A10 of the first rejected kidney graft. The anti-HLA-B35 antibodies were specific against a HLA-B antigen of the prospective non-related living kidney donor with the HLA type: HLA-A3, bl, B35, 41, DRB1*03, 13 (DR3, 6) making the transplantation impossible. The mismatch degree between donor and recipient was 0-2-1 according to Eurotransplant criteria.

As expected the crossmatch of this recipient's serum with CD8 + donor lymphocytes was positive with DTT and without DTT treatment of the serum (table 1, figure 1 on the top). Therefore, the recipient received two times a day 500 mg MMF (mycophenolate mofetil) in order to destroy the anti-donor specific anti-HLA-B35 antibodies.

As a consequence of the MMF (CellCept®) treatment the development of anti-HLA antibodies active in the crossmatch could be successfully suppressed after a 3 month. Finally, the subsequent serum samples of the recipient (03/01/2003, 20/01/2003 and 25/03/2003) therefore showed the desired negative crossmatch result without of DTT treatment. However, after DTT treatment for destruction of possibly disturbing IgM auto-antibodies the result became again positive against the CD8-positive donor lymphocytes. An additional flow-cytometric crossmatch confirmed this effect (tab. 1, fig. 1 on the bottom).

The course of treatment after the living donor transplant operation

Because of the negative x-match achieved the patient could receive the kidney transplant of the living donor having the incompatible antigen HLA-35. Prograf, MMF (Mykophenolate Mofetil) and Urbason were applied as immunosuppressing agents. Due to the historical antibodies and the fact that it was the second transplantation the patient received ATG for 7 days. Two preoperative and four postoperative dialysis courses were performed. The

kidney graft started to work only with delay, and beginning with a daily diuresis between 24 and 52 ml over a p.o. period of 8 days reached 2400 ml. A renal biopsy obtained on the 7th p.o. day uncovered the following histologic diagnosis: renal tissue without indication of rejection, no relevant pathomorphological findings, glomerulus without of any evidence of a capillary thrombus, no transplant glomerulitis (ET-No.: 6077/03). The examination for anti-HLA antibodies revealed no donor-specific antibodies on the 2nd, 5th, 8th and 12th days after transplantation and a PRA value of 10%. The donor-specific antibody specificity against the HLA-A26 (A10) incompatibility of the formerly rejected cadaveric kidney was not donor-specific against the new kidney transplant. Obviously, its production remained untouched by the application of MMF (CellCept®).

At the moment a retention-effective excretion of 2,2 l daily can be observed (current urea value 29,8 mmol/l, creatinine 264 µmol/l, with initial values of 12,5 and 708, respectively). The recipient's state is subjectively well. There is no clinical, paraclinical or immunological indication of an acute or chronic rejection or an increased risk of infection. The CRP value in the urine was 21,5 mg/l at the time of transplantation and at the moment it is < 0,16 mg/l. IgC was then 490 mg/l and is now 14,5 mg/l. AAP was 61 U/l at the time of transplantation and is 21,8 U/l at present.

Tab. 1: The development of anti-HLA antibodies and PRA-value and of the cross-match result between donor and recipient of a prospective recipient of a live kidney after treatment with MMF / CellCept.

serum from	11/2001	01/2002	04/2002	10/2002	03/01/2003	20/01/2003	25/03/2003
PRA(%)	0	13	18	37	57	10	10
anti-HLA specificity	-	-	-	A26+ B35+5+	-	A26	A26
crossmatch vs. CD8+ cells	-	negative	negativ	positive	negative	negative	negative
crossmatch (DTT) vs. CD8+ cells	-	negative	negative	positive	positive	positive	positive
treatment with CellCept	no	no	no	no	yes	yes	yes

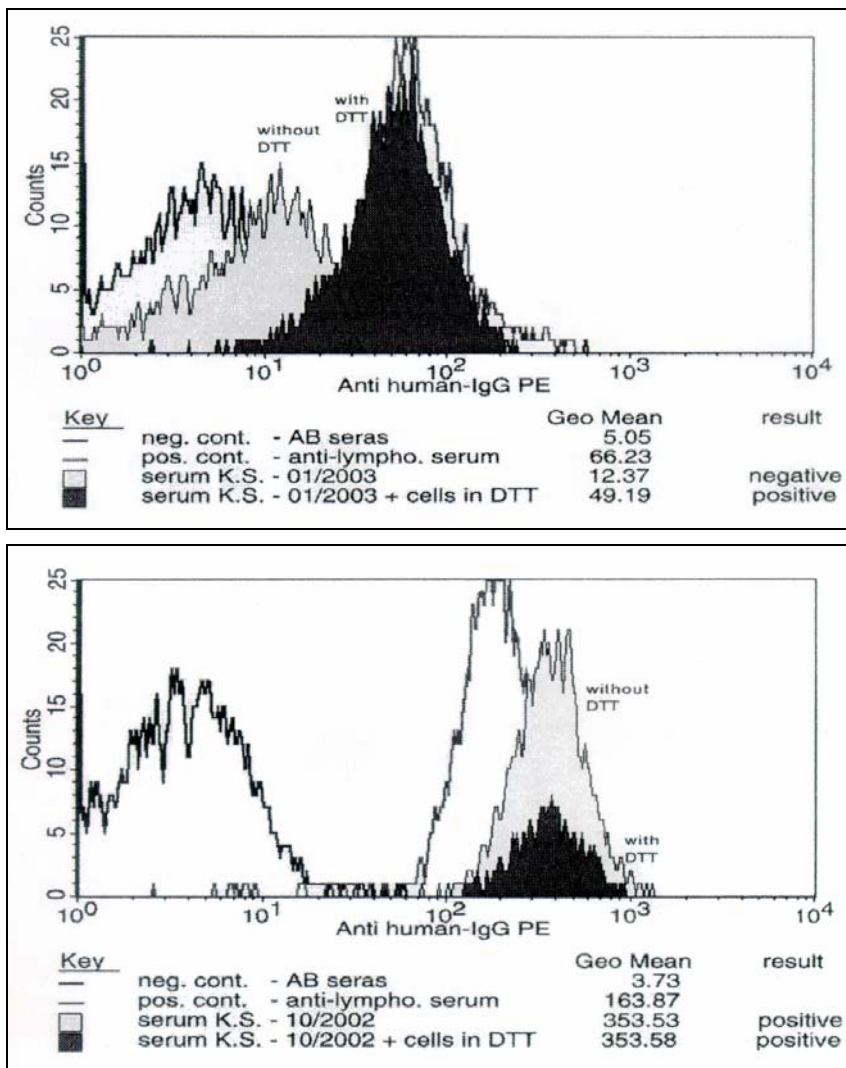


Fig. 1: Flowcytometric detection on transduction of a positive crossmatch (upper figure shows serum of the recipient in 10/2002) in a negative crossmatch (lower figure shown serum of the recipient in 1/2003) by Prograf / MMF therapy

Discussion

As reported in the present case a transduction of the crossmatch with a positive result into a negative result is possible by a successful immunosuppressive treatment. That the negative crossmatch became again positive after destruction of IgM by dithiotreitol (DDT) can be explained as idiotypic effect in the sera of recipients as suggested in previous findings (19, 20). Obviously, in the present case anti-idiotypic antibodies of the IgM class occur that inhibit the anti-HLA antibodies of the IgG class. Beside the suggested IgM autoantibodies in parallel, DTT treatment destroys these anti-idiotypic IgM molecules and thus their blocking effect on the IgG anti-

HLA antibodies. Anyway, in vivo this suppressing effect by anti-idiotypic antibodies (anti-antibodies) may be desirable because it fights additionally the anti-donor specific anti-HLA antibodies.

Beside cellular mechanisms of tissue destruction donor-specific antibodies (DAS) play an important role for the mechanism of renal allograft rejection. The identification of the complement component C4d as a specific marker for humoral rejection in peritubular capillaries in renal allograft biopsies has contributed to the characterization of this syndrome and the definition of acute humoral (AHR) and chronic (CHR) humoral rejection (21, 22).

AHR is to be expected in 7,7 % of cases during the first 3 months after renal

transplantation. Specific anamnestic humoral responses to donor HLA antigens play an important role in the pathogenesis of AHR (23 - 25). In 60 % of all histological findings with the criteria for a chronic rejection C4d deposits were found in the peritubular capillaries (26). At the same time donor-specific antibodies (DAS) were found in these patients' sera.

Previous studies reported that the allo-antibody production can be suppressed by pretransplant plasmapheresis and treatment with a combination of intravenous immunoglobulin, rituximab and splenectomy (27) or treatment with a combination of MMF + tacrolimus + corticosteroids (28-34). The suppression of allo-antibodies was obviously caused by the ability of MMF (CellCept®) to bind to inosine monophosphate hydrogenase (IMPDH) representing the key enzyme for guanosine (purin) synthesis and necessary for division and proliferation of the antibody producing B lymphocyte clones.

As a consequence the circulating donor-specific antibodies (DAS) could be reduced for patients with AHR by application of MMF over a period of 3 to 6 weeks. In that way hyperacute and acute rejections of kidney grafts could be avoided. Moreover, this observation has also been used to control the humoral response for patients with CHR. It was also found that recipients with CHR showed a stable function of the renal allotransplant after MMF or TAC therapy. In the present case, in the period before the transplantation the suppression of allo-antibodies against the donor's unacceptable mismatch HLA-B35 was caused by the ability of MMF to suppress antibody producing B cells supported by inhibition of T cells by tacrolimus. The present findings led to the conclusion that the suppression of allo-antibody production is possible in certain cases by the combination of MMF with tacrolimus and that a negative crossmatch result between donor and recipient can be achieved on this way. It has to be pointed out that in spite of the donor-specific sensitization of the recipient in the present case of a living kidney transplant after converting the crossmatch from a positive into a negative result neither a hyperacute, nor an acute rejection has taken place. Hence, the successful kidney graft outcome after converting the crossmatch result that has been recently reported by

Gloor et al. (2003) can be now confirmed by the MMF + tacrolimus treatment. The present case report is demonstrating that there is not only an improved long-term outcome of kidney grafts in recipients treated early with MMF (35), but also a chance in removing the barrier of a positive crossmatch result by MMF + tacrolimus treatment with sufficient outcome of transplantation.

In the future the treatment with the combination of MMF and tacrolimus could thus be assumed to be also successful in further similar cases.

Summary

The crossmatch result of a historically sensitized recipient against a non-related living kidney donor could be converted from a positive into a negative one by means of immunosuppression with a combination of tacrolimus and MMF. The function and acceptance of the kidney graft were demonstrated to be successful so far. Additionally, the possibility that the transplant-specific anti-HLA antibodies were blocked by anti-idiotypal antibodies could play an important supplementary role in the present case.

Nevertheless, finally the question still remains to be answered whether a living donor kidney transplant in a constellation which is similar to the presented case report can also be successfully treated with preoperative MMF + tacrolimus therapy in further cases.

Conclusions

In case of one patient it was demonstrated that an immunosuppressive therapy with CellCept® (MMF) made it possible to transfer a positive x-match into a negative current x-match. This transformation of the current x-match is caused by depression of the antibody formation in the B-cell population as indicated by the company producing CellCept®. We conclude that the depletion of specific PRA against a cell panel and the positive reaction of the recipient's current serum in the x-match against donor PBL and CD8 + T cells make it possible to perform the transplantation of the kidney of the living donor.

Despite the originally shown donor specific antibodies by depleting the formation of donor specific antibodies in the B-lymphocytes there is not further cause for a hyperacute rejection.

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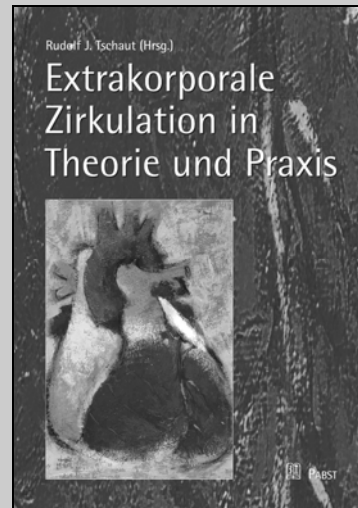
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