Successful living donor kidney transplantation across HLA and ABO incompatibilities

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A 56-year-old white female presented for evaluation for kidney transplantation in November 2003. Her end-stage renal disease (ESRD) was presumed due to medullary sponge kidney associated with stones and infection and she had started haemodialysis in April 2003. Other medical history included hypertension and anaemia. She was otherwise well. She had had four pregnancies and had received blood transfusions. Examination was unremarkable.

Initial tests showed blood group ABO-O. Her current panel reactive antibody (PRA) was 64% by the complement-dependent cytotoxicity (CDC) method and the peak PRA, 5 months prior to that, was 100%. Flow PRA screening confirmed IgG antibodies against class I and II human leukocyte antigens (HLA). The cause of the sensitization to HLA antigens was presumed to be the pregnancies and transfusions. Examination was unremarkable.

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Because of her high sensitization to HLA antigens, the idea of a transplant across the HLA and ABO barrier was discussed with the patient. She was advised to wait several months to see if her PRA or crossmatch titres fell with rituximab therapy. She was vaccinated against pneumococcus and meningococcus in the event that a splenectomy would be included in her immunosuppressive protocol. She received rituximab 375 mg/m² in March and April of 2004. However, the crossmatch remained strongly positive and the PRA remained high (Table 1). After detailed discussion of the risks vs benefits, the patient and son gave informed consent to proceed with transplantation of a kidney from the son to the mother.

Before 4 weeks of the transplant, she began receiving thrice-weekly plasmapheresis and daily tacrolimus plus mycophenolate mofetil (MMF). She was given 10 g of IgG intravenously after each plasmapheresis session. The anti-microbial prophylaxis was sulfamethoxazole-trimethoprim (SMX-TMP) and acyclovir. On 20 December 2004, the T-cell and B-cell crossmatch against her donor were negative and the anti-A titre (IgG titer by enhanced anti-globulin assay) was 1:2 (Figure 1). A third dose of rituximab was given, and she underwent kidney transplantation the next day. A laparoscopic hand-assisted splenectomy was also performed. There were no intra-operative complications and the allograft produced urine immediately. She received five more sessions of plasmapheresis in the first 10 post-operative days, to maintain anti-A titres ≤ 1:4.

The patient was discharged 1 week after surgery with a plasma creatinine of 63 μmol/l. Immunosuppression was now tacrolimus, MMF and prednisone. After 2 weeks of the transplant, the creatinine rose to 141 μmol/l, and an urgent allograft biopsy was performed. The anti-A titre was 1:4 and the crossmatch was positive against donor T- and B-cells by flow cytometry. The biopsy showed mild focal neutrophil capillaritis, acute tubular injury and intraluminal calcifications. There was diffuse staining for C4d in the peritubular capillaries. Interestingly, she had started p.o. phosphate 1–2 days prior to the elevation in plasma creatinine. The possibility of acute calcium—phosphate precipitation in the allograft [1] was, therefore, entertained and the phosphate was stopped. The presumed acute antibody-mediated rejection was treated with four sessions of plasmapheresis over 10 days (followed by 10 g IgG) and pulse IV methylprednisolone. The plasma creatinine fell quickly to 71 μmol/l. A repeat flow cytometry crossmatch against donor T- and B-cells was negative.

The patient was continued on immunosuppression with tacrolimus, MMF and prednisone. No further
plasmapheresis was prescribed, as the anti-A titres remained low (Figure 1) and the plasma creatinine remained at 80–106 μmol/l. A further flow cytometry crossmatch, at 4 months post-transplant, was negative against donor T-cells and weakly positive against donor B-cells. No changes in treatment were instituted, however, as she was doing well. Valganciclovir was stopped 6 months post-transplant and SMX-TMP was continued indefinitely, because she had undergone splenectomy.

In November 2006, she was admitted with a urinary tract infection, diarrhoea (of unclear cause), hypovolaemia and plasma creatinine 141 μmol/l. The creatinine fell quickly to 114 μmol/l with IV fluids. A protocol biopsy was performed in January 2006. There was no capillaritis, and the C4d stain was negative. There was no evidence of transplant glomerulopathy. Her immunosuppression was continued as prednisone 5 mg daily, MMF 1.5 g daily and tacrolimus with troughs of 5–8 ng/ml.

The patient was last seen in October 2006 and was feeling very well. The creatinine at that time was 97 μmol/l and the anti-A titre was 1:2.

### Table 1. Crossmatch titres and PRA of recipient before and on the day of transplantation

<table>
<thead>
<tr>
<th>Date</th>
<th>Titre at which CDC crossmatch* against donor T-cells was negative</th>
<th>Titre at which CDC crossmatch against donor B-cells was negative</th>
<th>PRA to class I HLA antigens by CDC method</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/12/03</td>
<td>Titres not done (strongly positive with neat serum)</td>
<td>Titres not done (strongly positive with neat serum)</td>
<td>64%</td>
</tr>
<tr>
<td>15/06/04</td>
<td>1: 64</td>
<td>1: 256</td>
<td>50%</td>
</tr>
<tr>
<td>03/08/04</td>
<td>1: 512</td>
<td>1: 512</td>
<td>72%</td>
</tr>
<tr>
<td>20/12/04</td>
<td>Neat</td>
<td>Neat</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Anti-human globulin method.

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**Discussion**

Until recently, transplant options for ESRD patients who were highly sensitized to HLA antigens (often defined as a PRA >50%) were limited. Such patients wait much longer for a deceased donor kidney transplant; many never receive an allograft. Transplantation from a deceased or living donor across a positive CDC T-cell crossmatch was considered very high risk for severe antibody-mediated rejection and allograft loss. Fortunately, a number of options now do exist for highly sensitized patients. These include acceptable mismatch programmes, exchange programmes, desensitization using high-dose IgG and desensitization using plasmapheresis protocols [2–4].

With the increase in living kidney donation in many countries, ABO-incompatibility has become an important barrier to living kidney donation. It is estimated that, based on the distribution of blood groups in the USA, there is a 35% chance that any two individuals will be ABO-incompatible [5]. Options for an ABO-incompatible donor–recipient pair now include
exchange programmes and transplantation across the ABO barrier (the latter using protocols involving plasmapheresis or immunoabsorption to remove the noxious antibody) [3,6,7]. In general, exchange programmes are preferable to plasmapheresis/immunoabsorption protocols as the former—by definition—circumvent the problem of ABO-incompatibility, and ultimately this means less immunosuppression and a lower risk of antibody-mediated rejection. However, exchange programmes are more difficult—although not impossible—if the recipient is also highly sensitized to HLA antigens, as was the case with our patient.

Fortunately, a plasmapheresis-based protocol is effective in removing both anti-HLA and anti-ABO antibodies. Our patient had baseline CDC crossmatches that were very highly positive against donor T- and B-cells and her anti-A titres were of intermediate strength. Hence we prescribed a high total dose of immunosuppression, including splenectomy. Fortunately, there have been no major complications of the immunosuppression, to date.

Transplant across the ‘double-barrier’ of HLA and ABO-incompatibility has, to our knowledge, only been described by two other groups. Warren et al. [5] described a series of three patients, all of whom underwent splenectomy; outcomes were excellent at times of latest follow-up (9–11 months). Rituximab had been given to 1 of the recipients in the peritransplant period. Kayler et al. [8] described a case wherein splenectomy was also performed: creatinine at 9 months post-transplant was 150 μmol/l. Rituximab was not administered. Interestingly, no serious infections were reported in any of these four patients.

Our case has the longest reported follow-up after ‘double-barrier’ incompatible kidney transplantation and confirms that short and medium term outcomes in these immunologically complicated cases can be excellent. One can speculate as to whether the combination of rituximab and splenectomy (as we used here) is excessive therapy, even in the setting of dual ABO and HLA incompatibility. However, our case had stronger baseline CDC crossmatches against donor T- and B-cells than the cases described earlier—perhaps justifying our aggressive approach.

In conclusion, we report an excellent outcome in a patient transplanted across what were traditionally considered incompatible ABO and HLA barriers. This strategy does involve intense immunosuppression, but may be useful for a small number of patients who have explored other transplant options without success. Our case also illustrates the fact that even patients with very strongly positive CDC crossmatches against their ABO incompatible donor can be successfully transplanted.

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Conflict of interest statement. None declared.

References

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