Management of an ABO-Incompatible Lung Transplant

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A 24-year-old woman with cystic fibrosis underwent bilateral sequential lung transplantation and unintentionally received an ABO incompatible graft (blood type A1 graft into a type O recipient). The recipient had a high titer of IgG anti-A antibody (256 by the indirect antiglobulin test). Emergency treatment included antibody removal by plasmapheresis and additional immunosuppression with mycophenolate, rabbit antithymocyte globulin and polyspecific intravenous immunoglobulin. Subsequently, immunoadsorption and the anti-CD20 antibody rituximab were used to remove anti-A antibody and inhibit its resynthesis. Early graft function was good; one episode of rejection at Day 46 responded promptly to treatment with methylprednisolone. Subsequently, graft function continued to improve and anti-A antibody titers remained low. No infectious or other complications were encountered. The treatment regimen that we adopted may prove useful in other cases of unplanned ABO-incompatible organ transplants. The successful outcome suggests that planned ABO-incompatible lung transplants may be possible.

Key words: ABO incompatibility, antibody-mediated rejection, lung transplant

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Introduction

ABO blood-type antigens are expressed in all tissues of the body. Antibodies to these antigens occur naturally in individuals who lack the corresponding antigen, and are present universally after infancy. Exposure of the endothelial cells of an ABO-mismatched allograft to such antibodies may cause complement activation and hyperacute rejection (1,2). Without specific treatment, the majority of ABO incompatible heart and kidney allografts are lost within 30 days of the operation with many of these losses occurring within hours or days of surgery (1,3). The risk of graft rejection is influenced by the nature of the mismatch, with those involving a donor of the A1 subtype carrying a higher risk than those involving A2 or B (1). In renal transplantation, additional therapies have been introduced to allow allografts that involve an ABO-incompatibility to be safely performed between adult patients (4). The success of this approach depends on reducing the titer of antibody to a level where antibody-mediated injury to graft endothelial cells is unlikely to occur (5).

Little is known about the fate of ABO-incompatible lung transplants because they have generally been avoided (1). Catastrophic rejection has been reported after a heart and lung transplant involving an inadvertent ABO-incompatibility (A into O) (6). To our knowledge, only one lung transplant has been reported with an unplanned ABO incompatibility (A1 into B). In that case, the preoperative titer of anti-A antibody was low and additional treatment was given to control the antibody titer after transplantation and so prevent antibody-mediated rejection (2).

Here we report a case of an unplanned ABO-incompatible bilateral sequential lung transplant (A1 into O) where the preoperative antibody titer was high. The mismatch was successfully managed using a modified immunosuppressive regimen that was commenced immediately after the transplant.

Case Report

A 24-year-old woman with cystic fibrosis (CF) underwent bilateral sequential lung transplantation. She had been assessed for transplantation in conjunction with her CF center and had been registered for the transplant as blood type A. The patient had suffered from recurrent Pseudomonas chest infections and had developed respiratory failure requiring home oxygen therapy. In addition, she had noninsulin-dependent diabetes mellitus and required supplemental nutrition via a percutaneous gastrostomy tube; her weight was 50 kg. At the time of the transplant operation her sputum was colonized with Pseudomonas aeruginosa and methicillin-sensitive Staphylococcus aureus, but she did not have signs of an active infection. Pre-operatively, the plasma IgM concentration was 1.3 g/L (normal 0.5–1.9 g/L) and total IgG was 30.2 g/L (6–16 g/L); the increase in IgG was polyclonal
and judged to be consistent with a response to chronic infection.

The transplant donor was a 29-year-old patient who had sustained a head injury; the donor had blood type A. Both donor and recipient had tested negative for antibodies to cytomegalovirus (CMV). Pre-operatively, cyclosporine and azathioprine were administered orally to the recipient. A bilateral sequential lung transplant was performed using cardiopulmonary bypass. The surgery proceeded routinely but during the operation it was discovered that the recipient’s blood type was O. At this stage the donor lungs had already been transplanted and the patient had been weaned off cardiopulmonary bypass without difficulty; 20 mg/kg of methylprednisolone had been administered. Once the error became known, the patient was immediately treated by plasmapheresis. A 2-L (40 mL/kg body weight) exchange was performed using a Gambro PF1000N filter and a Gambro AK10 hemofiltration machine (Gambro-Hospat, Huntingdon, Cambridgeshire UK); volume replacement was given using a mixture of fresh-frozen plasma (blood type AB) and 4.5% human albumin solution. The planned immunosuppression protocol of cyclosporine, azathioprine and prednisolone was changed by substituting mycophenolate for azathioprine. In addition, rabbit antithymocyte globulin (RATG; Thymoglobuline, Imtix Sangstat, Lyon, France) was given as induction therapy (2 mg/kg daily for 3 days). The first dose of RATG was administered as soon as the plasmapheresis had been completed. Further investigation confirmed the donor blood type to be A1 and the recipient to be group O. The recipient’s total IgM and IgG anti-A level was measured by titrating untreated serum by the indirect antiglobulin test using doubling dilutions; the anti-A IgG component was measured similarly by testing serum treated with dithiothreitol. Pre-operatively, both total (IgM + IgG) and IgG titers were 256. After the initial plasmapheresis the total Ig titer was 32 and IgG titer 16 (Figure 1). Plasmapheresis was repeated on both the first and second postoperative days (Days 1 and 2).

After the third exchange (Day 2), 0.4 g/kg of pooled polyspecific immunoglobulin (Flebogamma 5%, Grifols, Cambridge, UK) was given by intravenous infusion (i.v. Ig). Subsequently immunoadsorption was performed on Days 3, 4, 6, 9 and 12 using the PlasmaSelect Life 18 system with Ig-TheraSorb columns (PlasmaSelect AG, Teterow, Germany, distributed by Meltenyi Biotec, Bisley, UK). This avoided the need to replace albumin and coagulation factors. Following the RATG induction therapy the T-cell count was \(0.134 \times 10^9/L\) and B-cell count \(0.151 \times 10^9/L\). Rituximab (11 mg/kg) was administered on Days 3 and 11; on Day 12 the B-cell count was \(0.05 \times 10^9/L\) and the T-cell count was \(1.654 \times 10^9/L\). I.v. Ig was administered again on Days 4 and 12. On Day 10, IgM (< 0.3 g/L) and IgG (2.1 g/L) concentrations were low but by Day 16 the IgG level had normalized (7.5 g/L) although IgM remained low (0.3 g/L). All therapeutic antibodies (RATG, i.v. Ig and rituximab) were administered immediately after plasmapheresis or immunoadsorption to prevent the therapeutic antibodies being removed by those treatments.

Background immunosuppression was maintained with cyclosporine (12-h trough level, 250 ng/mL in whole blood by mass spectrometry), mycophenolate 1.5 g BID (subsequently reduced to 1 g BID to maintain a total white cell count >3.5 \(\times 10^9\) \(L^{-1}\)) and corticosteroids. Because of our concern about an increased risk of infection, the prednisolone was rapidly tapered from the initial dose of 1 mg/kg/day to zero by Day 14. Dalteparin (50 u/kg daily) was administered as prophylaxis against thromboembolism from Day 1 to Day 14.

The patient’s postoperative recovery followed the pattern expected after uncomplicated lung transplantation. Lung function was good and she was extubated on the second postoperative day. Antibiotic treatment was administered in accordance with the sensitivities of the \(Staphylococcus\) and \(Pseudomonas\) isolated from her sputum preoperatively (intravenous flucloxacillin, aztreonam, and chloramphenicol together with nebulized colistin). Her subsequent respiratory function and anti-A IgG titers are shown in Figure 1. Anti-infective prophylaxis after discharge included nebulized colistin, oral cotrimoxazole and itraconazole.
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On Day 46, she was readmitted to the hospital because of a fall in her spirometry (Figure 1). Bronchoscopy, bronchoalveolar lavage and transbronchial biopsy were performed. The lavage did not yield any bacterial or fungal growth and the test for CMV antigen in the blood was negative. The transbronchial biopsy showed normal lung histology. The anti-A antibody titer had not increased (Figure 1). A presumptive diagnosis of cell-mediated acute rejection was made. She was treated with intravenous methylprednisolone followed by a tapering course of oral prednisolone. The lung function improved promptly and she has subsequently been maintained on prednisolone 0.2 mg/kg/day; cyclosporine and mycophenolate were continued. Subsequently, her lung function continued to improve and at the latest follow up (Day 128), she was well and planning to resume her college studies. At that stage, the T-cell count in peripheral blood was $1.352 \times 10^9 \text{ l}^{-1}$ and the B-cell count was $\leq 0.05 \times 10^9 \text{ l}^{-1}$. The immunoglobulin concentrations were in the normal range; IgG 11.1 g/L and IgM 0.7 g/L, but the IgG anti-A antibody titers remained low at 16. Preoperatively, the titer of IgG anti-B was 32; this fell to 4 after the first plasma exchange and remained 4 on Day 128.

All nonapproved treatment was provided on a ‘compassionate use’ basis; the patient’s written consent has been obtained for the publication of this report.

Discussion

To our knowledge, this is the first report of a successful transplant of an A\(_1\) lung into an O recipient; only one previous case of a successful ABO-incompatible lung transplant (A\(_1\) into B) has been reported (2). However, in that case the preoperative titer of anti-A antibody was low whereas the titer in the case reported here was high. In both our case and the one previously reported, modifications were made to the immunosuppressive regimen to avoid antibody-mediated rejection.

Conventional immunosuppressive protocols primarily affect the T-cell-mediated immune response to the allograft (7). This will inhibit the de novo formation of antibodies directed towards the allograft by reducing T-cell help to B cells. However such treatment does not prevent rejection caused by natural antibodies against blood-type antigens or other preformed antibodies. A variety of methods have been used to prevent or treat antibody-mediated rejection (8–14) and combination therapy has usually been required (Table 1).

Once the ABO-incompatibility became apparent, our priority was to quickly reduce the antibody titer so as to prevent hyperacute or humoral rejection (1,5,15). We initially aimed for a titer of 8 (16), which was achieved by Day 2; subsequently we determined treatment in the light of graft function as well as the antibody titer. Owing to the emergency nature of the situation, we used plasmapheresis that could be implemented immediately. As more information became available, it became clear that there was a serious risk of antibody-mediated rejection because the donor had the subtype A\(_1\) (the commonest subtype of A and a strong expression of the A antigen). Additionally, the recipient had a high baseline titer of anti-A antibody. Although plasmapheresis reduced the titer of anti-A antibody, we subsequently used immunoadsorption because of its ability to selectively remove immunoglobulin without depleting albumin and coagulation factors. We used nonspecific adsorption with a column containing antihuman immunoglobulin, which removed all classes of antibody regardless of their specificity (10,17). Other systems are available for immunoadsorption; nonspecific adsorption using protein-A columns, which principally adsorb IgG (17), or selective adsorption which only removes antibodies directed against antigens that have been incorporated into the column (2).

We administered intravenous polyspecific immunoglobulin (i.v. Ig) for two reasons. First, replacing immunoglobulin reduced the risk of infection caused by immunoglobulin deficiency, which would have occurred as a result of nonspecific adsorption (18); second, i.v. Ig has immunomodulatory activity and has been used to treat a number of autoimmune disorders as well as antibody-mediated rejection in HLA-sensitized patients undergoing transplantation (11,19,20).

We also modified our usual protocol for immunosuppression by substituting mycophenolate mofetil for azathioprine and also by the addition of induction therapy with RATG. Mycophenolate is a more potent immunosuppressant than azathioprine (21), has direct effects on B cells, reduces the incidence of antibody formation after transplantation (13). Rabbit antithymocyte globulin increased the intensity of the initial immunosuppression and, because it contains some antibodies directed against B cells, it may have helped to control the antibody response (14). Subsequently we used the chimeric anti-CD20 antibody rituximab which has been effective in treating a number of

Table 1: Therapeutic approaches to prevent or treat antibody-mediated rejection

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<th>Antibody removal</th>
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<tr>
<td>Plasmapheresis (8,9)</td>
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<tr>
<td>Non-specific immunoadsorption (10)</td>
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<td>Immunoadsorption of specific antibodies (2)</td>
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<td>Immunomodulation</td>
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<td>Intravenous polyspecific immunoglobulin (11)</td>
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<td>Reduced antibody synthesis</td>
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<td>Cyclophosphamide (12)</td>
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<td>Mycophenolate mofetil (13)</td>
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<td>Antithymocyte globulin (14)</td>
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<td>Rituximab (anti-CD20) (4,22)</td>
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<td>Splenectomy (4)</td>
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<td>Inhibition of antibody-induced complement activation</td>
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<td>Recombinant soluble complement receptor type 1 (2)</td>
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autoimmune conditions as well as in treatment of antibody-mediated rejection (22).

Our approach differed from that used by Pierson et al. (2). Although the principles of treatment (removing the anti-A antibody and inhibiting its resynthesis) were the same in both cases, we did not use cyclophosphamide, phototherapy or an inhibitor of complement. Their patient had a low initial titer of anti-A antibody and they waited until the titer began to rise before initiating immunoadsorption therapy. We commenced treatment immediately and continued it once it had been confirmed that our patient’s initial anti-A antibody titer had been high. Despite our patient’s preoperative colonization with Pseudomonas and Staphylococcus, she did not experience any post-transplant infection, whereas the previous patient experienced several infections (2). However, this difference may have been owing to factors other than the immunosuppression used, such as our patient’s younger age and her lack of exposure to CMV.

We are unable to determine from a single case study which components of the treatment were necessary or to know what the outcome would have been without the additional therapy. Because of the complexity of immunological processes, we cannot be certain that our protocol would be successful in other cases of ABO-incompatible lung transplantation. Treatment reduced the high titer of anti-A antibody to a level that has been found to be safe in ABO-incompatible renal transplantation (1,5) and has kept it there for at least 4 months despite a recovery in immunoglobulin concentrations to within the normal range. The initial fall in the antibody titer may not have been solely owing to the plasmapheresis because some antibody would also have become bound to the graft during that period. However, the protocol used resulted in good graft function, which was maintained despite one episode of clinically defined acute rejection. Although the biopsy did not confirm cellular rejection we believe that this was the most likely mechanism because it occurred at a time when the number of circulating T cells had increased and the episode responded promptly to treatment with methylprednisolone alone. Although humoral rejection was not excluded by immunohistochemistry, this appears unlikely because the episode was not associated with any increase in the anti-A antibody titer.

In heart transplantation, it has been possible to deliberately cross the ABO barrier in infants who have not yet formed isoagglutinins (23). Subsequently, the infants may fail to form antibodies to the blood-type antigens present in the graft while producing antibodies to blood-type antigens that are absent in the graft, demonstrating that infants can develop a specific B-cell tolerance to ABO antigens. We cannot conclude that tolerance to the blood-type A antigen occurred in the patient presented here because antibody titers to the blood-type B antigen, which was not present in the graft, were also reduced. We do not yet know the long-term outcome of this transplant but experience from other types of organ transplant suggests that, even if the titer of anti-A antibody gradually rises, the clinical course will now be no different from that expected in an ABO-matched allograft (1). This is probably owing to adaptive changes that occur in the endothelium of the graft, a process known as accommodation (24). The purpose of reporting our experience at this stage is to provide information that will be of use if an unplanned ABO-incompatible lung transplant should occur elsewhere.

Unplanned ABO-incompatible transplants are potentially avoidable accidents. A full investigation has been conducted into the circumstances that led to the error in the case reported here; changes in the assessment process have been made to reduce the risk of a recurrence. However, human error cannot be prevented completely and it is important to have a recovery plan available when such accidents do occur. The case reported here, and that reported by Pierson et al., suggest that many such incidents could be managed successfully provided treatment is started early, so that emergency retransplantation, with its attendant risks, can be avoided. Such observations also raise the possibility that lung transplants which deliberately cross the ABO barrier could be successful. This may be particularly important in cases where the choice of donor is limited, as in live-related pulmonary lobe transplantation (25), or where a clinically urgent lung transplant is needed and, perhaps, in regions where the waiting time for transplantation in blood type O patients is particularly long.

References


