Exceptional Case

Antibody-mediated rejection following transplantation from an HLA-identical sibling

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Abstract

Putative antibody-mediated rejection (AMR) in HLA-identical sibling transplantation has rarely been reported and occurred before routine calcineurin inhibitor use. A 29-year-old male developed allograft dysfunction following an HLA-identical renal transplant from his sibling. A pretransplant panel-reactive antibody (PRA) was elevated, pre-transplant crossmatch was negative and no donor-specific antibody (DSA) was identified. Induction with alemtuzumab was followed by maintenance immunosuppression with corticosteroids, tacrolimus and mycophenolate. A biopsy for allograft dysfunction suggested AMR, but DSA could not be detected. Treatment for rejection was transiently successful. Undetectable minor histocompatibility antibodies may have contributed.

Keywords: acute allograft dysfunction; alemtuzumab; limitations of testing; living kidney donor; minor histocompatibility antigens

Introduction

Transplants from HLA-identical siblings usually result in favourable outcomes [1]. We present a case of allograft failure attributed to antibody-mediated rejection (AMR) following transplantation from an HLA-identical sibling. Although the allograft pathology was consistent with AMR, no donor-specific antibody (DSA) was identified. The patient in this case received his transplant and much of his care at another medical centre but was referred to our institution due to persistent allograft dysfunction.

Case

A 29-year-old man with a history of an undefined renal disease who had progressed over 10 years to end-stage disease received a kidney from his sister, an ABO-compatible, HLA-identical sibling. Prior to transplant, the panel-reactive antibody (PRA) was 95% for HLA class I and 14% for class II, B- and T-cell flow cytometric crossmatch testing was negative and DSA was undetectable. He received a standard dose immunosuppression regimen consisting of intraoperative alemtuzumab followed by corticosteroids, tacrolimus and mycophenolate sodium for maintenance. Five years before, he received a transplant from his mother that failed within 1 year, reportedly due to Banff type III acute rejection. No mention of a DSA or positive C4d staining in the allograft at that time was in the records that were available to us.

Although the patient felt well after transplant and did not need dialysis, his renal function did not improve as quickly as expected. On post-operative Day 7, his creatinine was 2.4 mg/dl. A biopsy was performed and surprisingly showed margined mononuclear cells and neutrophils in peritubular and glomerular capillaries, acute tubular injury and diffuse, bright staining of peritubular capillaries for C4d by immunofluorescence (Figure 1). Repeat flow cytometric T- and B-cell crossmatch testing was found to be positive. The findings were consistent with AMR.

Initial treatment for AMR consisted of pulse methylprednisolone, five sessions of plasmapheresis followed by 10 mg/kg intravenous immunoglobulin (IVIG) (Days 9–11) and two doses of rituximab (Days 13 and 30). A repeat biopsy (Day 38) demonstrated mild improvement. Persistent C4d staining prompted the administration of two treatments with 2 g/kg IVIG (Days 45–46). A biopsy performed 10 weeks following transplantation was again compatible with AMR, leading to rituximab treatment and repeat plasmapheresis and IVIG (2 g/kg). Additionally, oral cyclophosphamide replaced mycophenolate sodium.

Two months later, his renal function continued to be poor (creatinine 3.0 mg/dl). The repeat biopsy suggested persistent AMR. This puzzling situation prompted his transfer to our hospital for management. The biopsy findings were unchanged. Cyclophosphamide was replaced with mycophenolate mofetil because of leucopaenia. We confirmed
that the donor and recipient were matched at HLA-DP, DQ and C loci, and high resolution typing did not demonstrate any discrepancy. The referring institution had arranged for testing for antibodies against phospholipids, the angiotensin receptor, vimentin, red blood cell antigens and random platelet antigens were negative. Testing for antibodies against major-histocompatibility-complex class I-related chain A (MICA) was borderline positive but not donor specific. Monocyte crossmatch performed by another medical centre was reported as inconclusive. The patient was ultimately dismissed from our hospital with improved and stable allograft function (creatinine 2.1 mg/dl) and on standard dose immunosuppression regimen with tacrolimus, mycophenolate mofetil and prednisone. His primary transplant nephrologist resumed care and his immunosuppressive regimen remained the same. Unfortunately, within 3 months, his creatinine increased to 6.7 mg/dl. Histologic evidence of AMR with borderline changes for cellular rejection with patchy interstitial inflammation was demonstrated, but DSA was never detected. He was again treated for AMR, but ultimately maintenance dialysis was needed. Before immunosuppression was tapered, a biopsy was done and revealed severe changes of AMR, with arterial fibrinoid necrosis, diffuse and global mesangiolysis, glomerular and peritubular capillary neutrophils and mononuclear cells. Immunofluorescence demonstrated bright, diffuse C4d staining (Figure 2).

Discussion

Renal transplantation from an HLA-identical sibling donor usually results in favourable long-term outcomes [1]. Our patient had an HLA-identical sibling donor, but developed AMR soon after transplant. According to the Banff '07 schema, definitive diagnosis of acute AMR requires histologic features of tissue injury, immunopathologic evidence of antibody (e.g. C4d positivity) and serologic evidence of DSA [2]. Banff criteria for AMR were not met in this case.
DSA is sometimes not initially identified because testing for antibodies against HLA-DR, DQ and C loci is not routinely performed. These antibodies do not often result in rejection, but it has been reported [7]. In true HLA-identical kidney transplant this should not be a cause. Additionally, the level of antibody may be too low for detection or is absorbed in the allograft and only identified when an allograft nephrectomy is performed [8]. The patient in this case did not have an allograft nephrectomy. We also do not have tissue or serum from the time of his first kidney transplant to look for DSA. Another possibility is the presence of an antibody that we do not have a ligand to.

In HLA-identical sibling organ transplantation, graft rejection more often occurs when recipients have increased parity, prior blood transfusions or previous transplants. Furthermore, these transplants fail more frequently among recipients who have a high PRA suggesting that antibodies against mHA may contribute to rejection [9]. If only HLA-reactive antibodies were important, the PRA would be irrelevant in these transplants. Antibodies to mHA or EC may occur together with anti-HLA resulting in rejection [9]. Interestingly, the recipient in this case had a high PRA.

Putative AMR in HLA-identical sibling transplantation has rarely been reported and occurred before calcineurin inhibitor use. Collins et al. found diffusely positive C4d staining of peritubular capillaries with evidence of tissue injury in 2 of 17 HLA-identical grafts (HLA-A, -B and -C loci) [10]. Serologic analysis was unavailable, but mixed lymphocyte reaction was nonreactive pre transplant.

This case highlights several points. Antibody-mediated damage occurs in HLA-identical sibling organ transplantation receiving a calcineurin inhibitor. The responsible antibodies are presumably against non-HLA antigens and were not detected. Because a subset of DSA is not necessarily detected by current techniques, clinicians should consider AMR if the renal pathology is suggestive even if DSA is not detected. Lastly, false-positive crossmatch testing is possible after using chimeric or humanized monoclonal antibodies.

Conflict of interest statement. None declared.

References

Acute antibody-mediated rejection after ABO-incompatible kidney transplantation treated successfully with antigen-specific immunoadsorption

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Abstract
ABO-incompatible kidney transplantation is possible after pre-treatment with rituximab, intravenous immunoglobulin and basiliximab combined with tacrolimus, mycophenolate mofetil and prednisolone. We report on the first patient treated with this protocol who developed acute antibody-mediated rejection (Banff grade II with IgG deposits) caused by ABO antibodies (anti-B). Anti-rejection treatment with anti-B-specific immunoadsorption, intravenous immunoglobulin and methylprednisolone efficiently cleared deposited IgG from the kidney allograft and re-established normal kidney function. We suggest that ABO-incompatible kidney transplantation complicated by acute antibody-mediated rejection, caused by ABO antibodies, may successfully be treated with this regime.

Keywords: ABO-incompatible kidney transplantation; acute antibody-mediated rejection; antigen-specific immunoadsorption

Introduction
Acute antibody-mediated rejection (aAMR) after ABO-incompatible (ABOi) kidney transplantation caused by ABO blood group antibodies is characterized by elevation of the anti-A or anti-B titre combined with graft dysfunction [1]. A standardized rescue treatment regime of aAMR after ABOi transplantation has not been established. Treatment protocols for aAMR typically comprises intravenous immunoglobulin (IVIG) in combination with modalities for antibody removal such as immunoadsorption (IA), plasma exchange or double filtration [2–4].

ABOi kidney transplantation in our department is performed in accordance with Tydén et al. [5]. The principals of this protocol are (1) reduced immunoglobulin synthesis following anti-CD20 treatment (rituximab), (2) pre-transplant removal of ABO blood group antibodies by repeated ABO antigen-specific IA, (3) induction therapy with IVIG and (4) triple immunosuppression with tacrolimus, mycophenolate mofetil and prednisolone.

Case report
A 54-year-old Caucasian male with nephrosclerosis and treated with peritoneal dialysis was transplanted with an ABOi kidney (blood group B to O, HLA-A,B,-DR mismatch 2:1, no donor-specific HLA class I or II antibodies).

The patient was medically treated according to the Tydén protocol [5]. However, on the day of rituximab treatment (Day −42), the IgG anti-B titre had increased (1:512), and 24 h after the infusion, the patient developed sterile peritonitis. After 30 days, just before the first IA (glycosorb B), the IgG anti-B titre was 1000 (Day −12) and after three IA’s