

## Case Report

# Successful kidney transplantation with a well-matched donor despite a positive crossmatch; detection and management of sensitization secondary to an alternate allelic variant of ‘self’ HLA

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### Abstract

Under current UK standards of deceased donor typing, the formation by the recipient of HLA antibody against an allelic variant of a ‘self’ antigen creates a particular problem for organ allocation. In the reported case, the decision to transplant was taken in the situation of a positive flow crossmatch result attributed to allelic antibody. The potential that target antigen density contributed to this patient’s subsequent good outcome is discussed.

**Keywords:** allelic; antibody; antigen; crossmatch

### Background

Avoidance of donor HLA mismatches against which a recipient has formed an antibody is standard practice [1]. As a consequence, HLA-sensitized patients are disadvantaged in terms of transplant opportunity. Under the UK deceased donor organ allocation scheme, low resolution HLA-A, B, Cw, DR and DQ typing of donor and recipient provides the basis upon which sharing occurs. In this scheme a problem is encountered in progressing a sensitized patient to transplantation when their profile of HLA specificity includes antibodies against ‘self’ antigen. This situation can occur because of the development of antibodies against allelic level variants of antigens represented within the patient’s type. In the circumstance that the patient then receives an apparently well-matched ‘offer’, a risk for a positive crossmatch exists through recipient reactivity against the non-self allelic variant of antigenic ‘self’ present in the donor.

### Case report

The recipient was a 51-year-old female relisted for transplantation following failure of a mismatched graft after 15 years. The patient was sensitized with an HLA antibody profile that precluded receipt of offers from 80% of the donor population. After 7 years of waiting, an HLA fully matched offer was

accepted for the patient. While the lymphocytotoxic crossmatch was fully negative (compatible), the flow cross match was strongly T- and B-cell positive. A review of the patient’s serum screening history was performed. It had previously been noted that the patient had formed antibodies to self HLA-A2, characterized upon single-antigen bead testing (One Lambda) as being limited to the HLA-A\*0201/03/06 allelic variants. It had been decided not to list HLA-A2 as an antibody defined unacceptable antigen because of the patient’s already broad sensitization and the impact on her ‘matchability’. Flow crossmatch positivity was therefore presumed due to non-self HLA-A\*02 allelic antibody. Following discussion, the decision was taken to progress with the transplant with a risk-adjusted post-transplant management plan. The transplant operation was uneventful. Immediate renal function was obtained and the patient’s serum creatinine level declined to 130 by 2 days post-transplant. Immunosuppression comprised tacrolimus (trough levels 9–14 µg/L), mycophenolate mofetil 750 mg twice a day and prednisolone 20 mg daily. Three elective post-transplant plasma exchanges were performed. Follow-up investigations confirmed the patient’s HLA-A2 allelic level type as HLA-A\*0220 and the donor as HLA-A\*0201. Structural analysis of these types identified just one amino acid difference (asp to lys) at position 66 creating a single eplet [2] mismatch in the donor. Screening of the patient’s time-of-offer serum sample confirmed the presence of HLA-A\*0201 antibodies at a moderate level (MFI = 5245). HLA-A\*0201 antibodies remained detectable in the Day 3 post-transplant pre-plasmapheresis sample (MFI = 4225). At 57 days post-transplant, the patient continues to do well, despite persistence of HLA-A\*0201 antibodies (MFI = 4953), with a serum creatinine level of 120 µmol/L.

### Discussion

Under the current UK deceased donor kidney allocation scheme, reporting requirements for donors are for low-resolution HLA-A, B, Cw, DR and DQ typing. Under

these arrangements, the presence of allele-specific antibodies in the recipient represents a problem for allocation when the patient's own HLA type includes an alternate allelic variant of the same antigen. The number of allelic-level variants of some HLA can be well in excess of 100 [3] providing considerable scope for intra-allelic group sensitization. Constraints imposed by organ ischaemia time together with the logistics of cadaveric organ allocation make the suggestion that allocation should take allelic-level matching into account impracticable. Under the existing UK scheme, available remedies include revising the patient type to avoid offers matched for the relevant antigen or to accept offers which include the antigen and then evaluate risks of transplantation based on results of compatibility tests. Where the extent of patient sensitization is limited, the former approach is arguably most valid, as it would reduce the risk of a positive crossmatch and the need for reallocation. However, in circumstances where the patient is extensively sensitized and the transplant 'chance' small, a case can be made for the latter approach. This decision must be informed as a result of time-of-crossmatch discussions between the laboratory and clinical teams and requires patient workup to have included high-confidence serum-specificity analysis.

As IgG can accommodate a span of only 9–15 nm [4] between antigen recognition sites, it is tempting to speculate that the clinical risk of transplanting across the allelic incompatibility in the present case was reduced by the low target epitope valency on the renal endothelium. This may have had the effect that target epitopes were too widely separated to be bridged by bivalent antibodies with

inference for stability of antibody binding, as has been demonstrated in *in vitro* systems [5], and efficient initiation of processes such as complement and leucocyte activation.

A high degree of clinical interest exists in regard to transplantation in the face of donor-specific HLA antibodies and the optimal approach to the problem has yet to be defined. In exploring this issue, focus has been on the influence of the antibody level and class, and while these considerations apply to the current case, it is speculated that the issue of target epitope valency is equally worthy of consideration. Further investigation is now called for.

*Conflict of interest statement.* None declared.

## References

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