Crossing strong antibodies in transplant: Successfully using the surrogate donor crossmatch to find suitable donors for the highly sensitized patient

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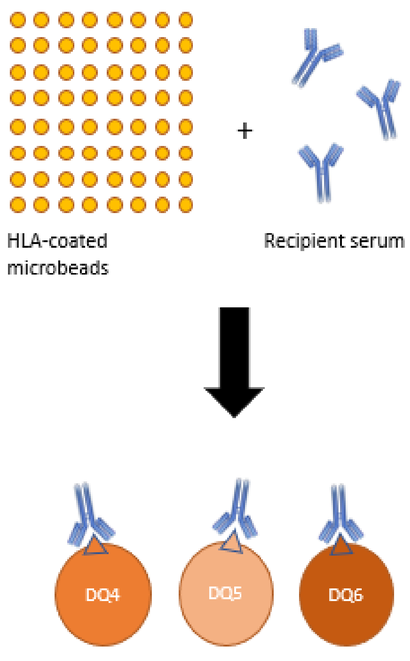
Abstract

Introduction: Sensitized patients wait longer for heart transplantation as human leukocyte antigen (HLA) antibodies limit the donor pool. In the virtual crossmatch, potentially cytotoxic antibodies are identified by solid phase assays in the recipient and corresponding donor antigens are avoided. In broadly sensitized patients, some of these antibodies may not be truly cytotoxic. In the surrogate crossmatch (SXM), the recipient's serum is tested against "surrogate" donors with known HLA specificities to determine whether identified anti-HLA antibodies are truly cytotoxic. We describe our experience in utilizing SXM to identify a donor for successful heart transplantation.

Case Report: The patient is a 42 year-old man with a history of familial cardiomyopathy with prior orthotopic heart transplantation in 2005 complicated by cardiac allograft vasculopathy with restrictive cardiac physiology requiring redo transplantation. In addition, he was found to have cardiac cirrhosis and was sensitized with C1q binding antibodies to DQ4, DQ5 and DQ6 in the high affinity range. Calculated panel reactive antibodies (cPRA) was 64%. He was relisted as status 4 for heart and liver transplantation and waited in a stable clinical condition until he presented in the spring 2018 with decompensated heart failure. Despite upgrading to status 3 listing, the cPRA significantly limited his donor pool. He underwent plasmapheresis and intravenous immunoglobulin infusions without decrease in antibodies. On SXM, only DQ5 and DQ6 antibodies were truly cytotoxic and DQ4 was therefore removed as an unacceptable antigen, reducing his cPRA to 57%. A potential donor with a DQ4 antigen was identified. Based on the results of the SXM, we deemed this donor acceptable for our patient. Both heart and liver transplantation were completed without complication, and he received induction therapy. His retrospective crossmatch showed a borderline B-cell crossmatch and single antigen testing at one week post-transplant demonstrated donor-specific antibody (DSA) against DQ4 as expected, however staining of the donor cells showed a very low level of surface DQ4. The cardiac graft function was uncompromised throughout the post-operative course. The patient was discharged 10 days after transplantation. All subsequent endomyocardial biopsies were negative for cellular or antibody-mediated rejection. HLA studies continued to show strong binding (c1q+) for DQ4. The patient continues to do clinically well.

Summary: SXM may be utilized to expand the donor pool for a successful heart and liver transplantation in a sensitized patient. Although the recipient demonstrated continued c1q binding DSA post-transplant, he maintained normal graft function with no evidence of rejection in the first three months following transplantation.

Figure 1: Single Bead Antigen Solid Phase Assay



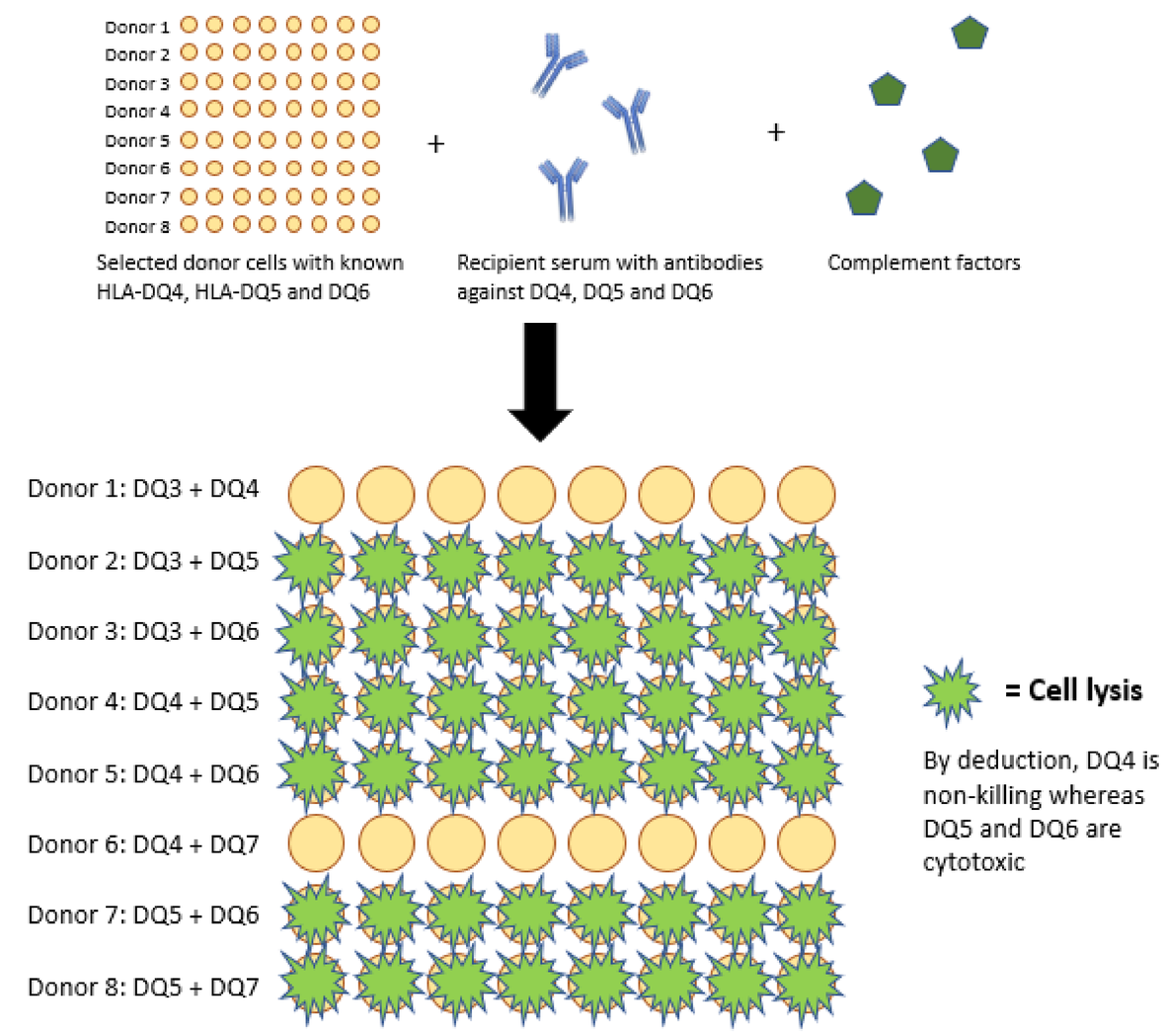
Background

Allosensitization limits the donor pool for sensitized patients and a high calculated panel reactive antibody (cPRA) panel is associated with increased wait list mortality. There are several methods to optimize HLA compatibility in highly sensitized patients. In the virtual crossmatch, potentially cytotoxic antibodies are identified by solid phase assays in the recipient and corresponding donor antigens are avoided (**Figure 1**). However as some of these may be auto-antibodies in broadly sensitized patients, some of the identified antibodies may not be cytotoxic. The surrogate crossmatch tests the recipient's serum against "surrogate" donors with known HLA specificities to identify cytotoxic anti-HLA antibodies.

Patient Presentation

- 42 year-old man with prior orthotopic heart transplantation in 2005 complicated by cardiac allograft vasculopathy, requiring redo transplantation.
- Sensitized high-affinity antibodies to DQ4, DQ5 and DQ6. Desensitization therapy did not decrease his antibodies.

Figure 2: Surrogate (CDC) Crossmatch



Use of The Surrogate Crossmatch

In order to increase the likelihood of transplantation, we explored the surrogate crossmatch, which is a complement dependent cytoxicity (CDC) test. A mix of donor cells with known HLA-DQ4, HLA-DQ5 and HLA-DQ6 antigens are mixed with the recipient serum prior to transplant (**Figure 2**). True cytotoxicity is assessed by cell lysis. By deduction, we found that recipient antibodies against donor cells with HLA-DQ4 were not killing and therefore more likely to be a result of non-specific autoantibodies. Based on the results of the surrogate crossmatch, we deemed a potential donor with a DQ4 antigen acceptable for our patient.

After transplant, donor-specific antibody (DSA) against DQ4 was identified, however donor cell staining showed a very low level of surface DQ4 protein. The patient did clinically well and was discharged on post-operative day 10. He has maintained normal graft function with no evidence of rejection in the first six months following transplantation.

Conclusion

- Highly sensitized patients have a severe limited donor pool and alternative methods are needed to increase their likelihood of transplantation.
- We described a case where the surrogate crossmatch was successfully utilized to expand the donor pool for heart and liver transplantation in a sensitized patient.
- Although C1q binding donor specific antibodies were found after transplant, our patient maintained normal graft function with no evidence of rejection. This indicates that these antibodies are not truly cytotoxic as demonstrated by the surrogate crossmatch.