Advancing decision strategies when crossmatch positivity defies donor specific HLA antibodies

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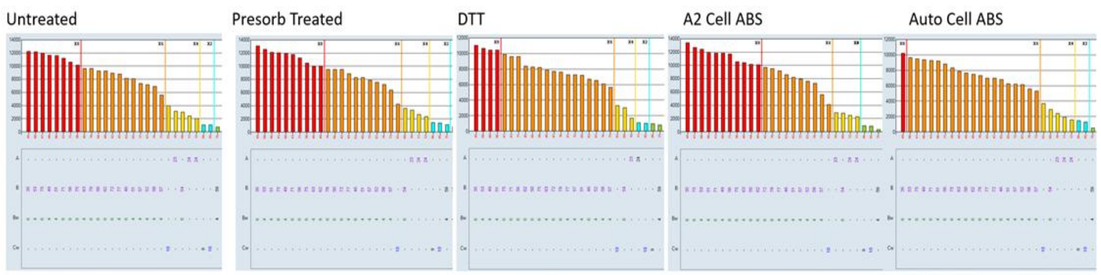
Background

A 60-year-old highly sensitized woman with end-stage renal disease secondary to biopsy-confirmed IgA nephropathy (IgAN) was referred to the National Kidney Registry (NKR) for paired kidney exchange along with her HLA-incompatible daughter. NKR is currently the largest and most active kidney exchange program in the United States, facilitating most paired kidney donations. It is designed to increase access to compatible donors for sensitized and hard-to-match patients by creating chains of transplants that link multiple donor-recipient pairs.
A proposed match through NKR demonstrated excellent clinical and immunologic compatibility, with no detectable donor-specific antibodies (DSA) by single-antigen bead (SAB) testing. However, the final T- and B-cell flow cytometry crossmatches (FCXM) were unexpectedly positive, resulting in termination of the chain. In the NKR system, a single chain break has cascading consequences: it can halt multiple downstream transplants, jeopardize trust in the program, and lead to missed opportunities for other patients awaiting transplantation. Because of the magnitude of this impact, every unexplained break requires careful investigation. Lessons learned from such cases are critical for improving allocation safety, refining immunologic risk assessment, and protecting the integrity of kidney paired donation programs.

Investigation

A detailed investigation was undertaken: 1)Detailed patient's history review; 2)Reevaluate HLA antibody profile and strength using new serum samples; 3)Treated the serum to identify and eliminate interferences: EDTA (routine); DTT; autologous cell adsorption; and adsorption with donor cells that has cross-reactive group HLA antigens; 4)Perform surrogate FCXMs using treated samples against random donor cells with known HLA profiles.

HLA Class I SAB Profile



Results

- The history review revealed that the patient had received multiple vaccinations in the weeks preceding serum draw for NKR final FCXM.
- Repeat SAB assay showed no significant changes in HLA antibody specificity or strength.
- Cell adsorption, auto and allo, did not alter SAB profile and FCXM pattern.
- Overall FCXMs were weaker in the current sample.
- Surrogate FCXMs with donor and autologous cells, using both adsorbed and non-adsorbed sera, confirmed persistent allo-positive but auto-negative reactivity.

These findings support the conclusion of a non-HLA antibody-mediated mechanism, which was elevated by vaccination. And the immune dysregulation inherent to IgAN may predispose patients to develop allo-directed, non-HLA antibodies, such as anti-endothelial or anti-AT1R antibodies, that bind to epitopes present on donor but not self-cells.

FCXM-T cell no pronase/B cell with pronase

FCXM#	Cell ID	Sample ID	T X-Median Delta shift	Result	DSA	B X-Median Delta shift	Result
1	Auto-Blood	25HLA-097HL0020	33	Neg	None	94	Neg
2	Donor 1-Blood	25HLA-097HL0020	553	Pos	None	1292	Pos
3	Donor 1-repeat	25HLA-097HL0020	551	Pos	None	1036	Pos
4	Donor 2-Blood	25HLA-097HL0020	476	Pos	None	1247	Pos
5	Donor 2-Blood	25hla-106HL0030	10	Neg	None	549	Borderline
		25HLA-106HL0030_auto adsorb	101	Neg	None	937	Pos
6	Donor 3-Blood	25hla-106HL0030	80	Neg	None	391	Neg
		25HLA-106HL0030_auto adsorb	112	Neg	None	471	Borderline
7	Donor 4-Spleen	25HLA-097HL0020	4342	Pos	A24	14011	Pos
		25HLA-097HL0020_PRESORB	3856	Pos	B51	10112	Pos

Conclusions

This case underscores four critical points:

1. When chain break occurs due to unexpected FCXM positivity, systematic investigation is essential to potentially save current chain or prepare for future matching attempts.
2. IgAN patients may be susceptible to non-HLA antibody formation, leading to auto-negative but allo-positive FCXM results.
3. Avoid or delay vaccinations-patients actively listed with NKR should be advised to consult their transplant team before immunization. High level of non-HLA antibodies can impact long term graft survival.
4. Under defined circumstances, weak FCXM positivity may be acceptable for transplantation if determined to be non-HLA in origin and not associated with DSA.