HIGH LEVEL DE NOVO ANTIBODIES TO HLA-DPα1 IN A PEDIATRIC PATIENT AFTER HAPLOIDENTICAL HEMATOPOIETIC CELL TRANSPLANTATION

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Background

HLA-DPA1 typing is not required for recipients of hematopoietic cell transplant (HCT) and their related or unrelated donors. However, it is recommended to avoid donors with HLA mismatches targeted by donor-specific antibodies (DSA), including those to alpha chains, as they may lead to engraftment failure. Donor-derived recipient specific antibodies (RSA) to HLA are less well-studied, having been observed in recipients of maternal donor HCT, and reported to associate with increased risk of graft-versus- host disease (GvHD).[1] A 12-year-old male with relapsed acute myeloid leukemia was referred to our institution for haploidentical (haplo) HCT after a 10/10 DP-mismatched unrelated donor (MUD) HCT. HLA typing results for the recipient and donors are shown in Table 1.

Table 1. HLA typing for recipient, matched unrelated donor, and maternal haploidentical donor. HLA typing was performed by next generation sequencing (NGS, AlloSeqTx17, CareDx). Mismatches with the patient are shown in blue. Direction of mismatch is indicated as bidirectional (BiD), graft versus host (GvH), or host versus graft (HvG). DP permissiveness (P) and direction of non-permissive (NP) mismatch was assessed with the DPB1 T-Cell Epitope Algorithm v2.0: www.ebi.ac.uk/ipd/imgt/hla/matching/dpb_v2/. The DPB1 mismatch between Donor 1 and Donor 2 is permissive.

HLA	A*	C*	B*	DRB1*	DRB3/4/5*	DQA1*	DQB1*	DPA1*	DPB1*	DPB1 P/NP
Recipient	11:01	01:02	56:01	01:01	Not Present	01:01	05:01	01:03	06:01	
	02:01	06:02	37:01	10:01	Not Present	01:12	05:01	01:03	02:01	
HCT #1-MUD	11:01	01:02	56:01	01:01	Not Present	Not Tested	05:01	01	13:01P BiD	NP GvH
	02:01	06:02	37:01	10:01	Not Present	Not Tested	05:01	02 HvG	02:01P	
HCT #2-Mother	26:01 BiD	07:02 BiD	08:01 BiD	04:01 BiD	4*01:03 GvH	03:02 BiD	03:02 HvG	01:03	04:01 BiD	NP GvH
	02:01	06:02	37:01	10:01	Not Present	01:12	05:01	01:03	02:01	

Results

Single antigen bead (SAB) testing of recipient serum (Table 2) showed no detectable HLA class I or class II antibodies 127 days prior to the patient's MUD HCT #1 and was positive for one antibody specificity to HLA-Cw9 30 days prior to transplant. After HCT #1 and 28 days prior to haplo HCT #2, patient serum was again negative for antibodies to class I and class II.

One year after the haplo HCT #2, in the context of refractory chronic GvHD, his serum was negative for RSA, but revealed new antibodies to multiple DP antigens, all sharing a DPA1*02 or DPA1*04 allele (Figure 1). Eplet analysis and sequence alignment (Figure 2) suggested serum antibodies were directed towards high exposition 50R, 127P, and/or 160V eplets present on DPA1*02:01, 02:02, and 04:01.[2,3] These immunogenic epitopes were absent in both the patient and maternal donor, but DPA1*02 was present in the first MUD HCT #1 donor (Table 1).

At the time of antibody detection, the patient's bone marrow and blood chimerism was 100% Donor #2: Mother (data not shown), suggesting these antibodies originated from maternal donor cells. It is unknown whether antibody producing cells were present at the time of progenitor cell infusion or if sensitization occurred after infusion in response to residual cells expressing DPA1*02 from the first transplant donor, a possibility given a reduced-intensity conditioning regimen.

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Table 2. Recipient Pre- and Post-Transplant HLA Antibody Identification. Recipient sera was tested for HLA class I and class II antibodies by single antigen bead (SAB) microarray (Luminex, One Lambda, ThermoFisher) prior to and following MUD HCT #1 and haplo HCT #2. Patient serum collected one year after haplo HCT #2 shows new high-level antibodies to alpha chains of HLA-DP.

Sera days pre(-) or post (+)	HCT #	Class I Antibody	Class II Antibody
-127	1	NEG	NEG
-30	1	POS: Cw9	NEG
+258	1	NEG	NEG
-28	2	NEG	NEG
+364	2	NEG	POS: DPA1*02:01, 02:02, 04:01

Figure 1. High Level Antibodies to HLA Class II DP One Year Post Haplo HCT #2. Analysis of SAB testing in Fusion software (One Lambda, ThermoFisher) show the recipient's Class II testing from serum collected 1 year post haplo HCT #2 shows new high-risk antibodies towards multiple DP antigens, all having DPA1*02 or DPA1*04 allele in common.

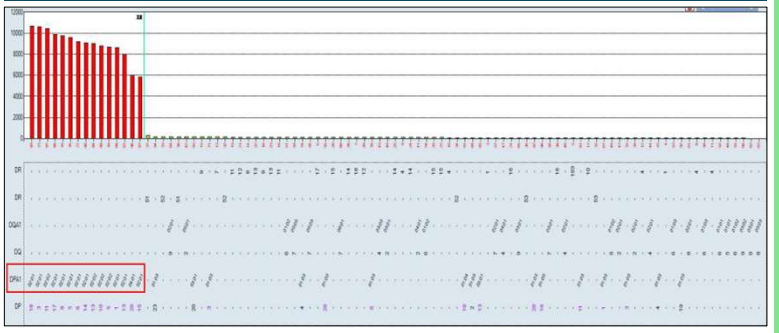
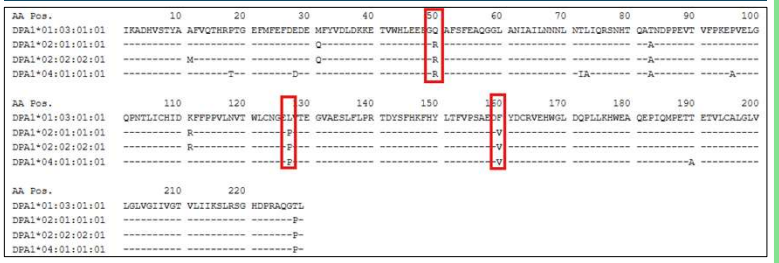


Figure 2. HLA-DPA1 Mature Protein Sequence Alignment[2]



Discussion

Little is known about de-novo HLA antibodies arising in the post-HCT period, especially antibodies toward loci not regularly typed. As the number of HLA-mismatched HCT continues to rise, the presence of donor antibodies against mismatched HLA antigens carries significant implications for transplant recipients.

Assessing donor HLA sensitization and monitoring recipient antibody levels post-transplant may be particularly relevant in pediatric cases, where mothers, who may be sensitized to paternal HLA through pregnancy, commonly serve as donors.

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References

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