Who is One Locus Mismatched sibling Donor, Who is not?

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Abstract
The most important factor in donor-recipient matching for hematopoietic stem cell transplantation is their HLA typing.
For many patients, we can not find a full-matched donor. In high risk patients, one locus mismatched related donors are suitable alternatives. (1, 2)
Since the matching of patients and their siblings usually is based on low resolution HLA typing, the matching of one locus mismatched siblings is always prone to catastrophic errors.
The following cases clearly demonstrate the possible pitfalls and highlight the importance of the HLA typing of parents in the matching of patients and their full-matched and one locus, mismatched siblings.
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Introduction
Hematopoietic stem cell transplantation is a promising treatment for many malignant and non-malignant diseases.
Improvements in HLA matching techniques and following standard guidelines in donor-recipient matching have had a significant impact on the outcome of transplantation. (3)
In most cases, the matching of HLA identical siblings merely needs a low resolution HLA typing of the patient and his/her family members. (4)
The matching of patients with unrelated donors and other relatives needs high resolution HLA typing. (4, 5)
A borderline situation between the two above mentioned situations is one locus mismatched sibling.
In these cases, we must be cautious of three possible pitfalls:
1- The selection of haploidentical donors with the assumption that they are one locus mismatched.
2- Depriving patients of good available donors and a time- consuming search for matched unrelated donors.
3- Doing unnecessary time-consuming, expensive high resolution HLA typing.

To give an example of the above- mentioned pitfalls, we present three male leukemia cases below:

Cases Report and Discussion
- Case 1:
Patient: A*29, ***A*33***, B*07, B*44, DRB1*03, DRB1*11
Sibling 1: A*29, ***A*03***, B*07, B*44, DRB1*03, DRB1*11
Father: A*24, **A*29**, B*07, **B*07**, DRB1*15, **DRB1*11**
Mother:***A*03, A*33***, **B*44**, B*52, **DRB1*03**, DRB1*07
As you note, the patient and his sibling have inherited A*29, B*07, DRB1*11 haplotype from their father but their maternal haplotype is different in the HLA-A locus.
This is a typical case of a chromosome 6 translocation at the MHC locus.
The HLA typing of other siblings showed that a recombination event had occurred in the sibling 1 maternal gamete. In such cases, we need no further high resolution typing, but an HLA-C typing of the donor, the recipient, and the parent that recombination event had occurred in his/her gamete

is prudent to see whether the HLA-C locus is included in the recombined part or not; if so, there would be two loci mismatches which increases the transplantation risk significantly. (6)

It is important to remember that the rate of crossing over in the MHC locus is about 1% and all of the apparently one locus mismatched siblings should be considered haploidentical unless the HLA typing of other family members clearly shows the recombination event.

Furthermore, since HLA-B and HLA-C loci reside between the HLA-A and HLA-DR loci, within one locus mismatched cases due to translocation, we could have HLA-A or HLA-DR mismatches; single HLA-C or HLA-B mismatched siblings are haploidentical unless high resolution matching proves allele matching in other loci.

- Case 2:

Patient: A*02, A*30, B*13, B*51, DRB1*07, DRB1*04

Siblings: A*02, A*30, B*13, B*51, DRB1*07, DRB1*11

To make a sound judgment about the matching of the patient and his siblings, we requested an HLA typing of their parents:

Father: A*02, A*30, B*13, B*50, DRB1*07, DRB1*12

Mother: A*02, B*51, DRB1*04, DRB1*11

If we split the maternal haplotypes, we would have:

Haplotype 1- A*02, B*51, DRB1*04

Haplotype 2- A*02, B*51, DRB1*11

Based on the above data, we conclude that the patient and his siblings have identical paternal and different maternal haplotypes; thus, they are haploidentical.

As the patient had high risk leukemia, we performed additional low resolution HLA-C and high resolution HLA- A and HLA-B typing to evaluate the allele level matching of those loci. Unfortunately, there was no allele level matching in the tested loci:

Haplotype 1- A*02**04**, CW*16, B*51**01**, DRB1*04 (patient's maternal haplotype)

Haplotype 2- A*02**34**, CW*04, B*51**05**, DRB1*11 (siblings' maternal haplotype)

Now, assume that a recombination event occurs in the maternal haplotypes between the HLA-B and HLA-DR loci; then we would have:

Recombined haplotype 1- **A*0204, CW*16, B*5101**, DRB1*11

Recombined haplotype 2- A*0234, CW*04, B*5105, **DRB1*04**

If two siblings have an identical paternal haplotype but one of them has an intact haplotype 1 and the other one a recombined haplotype 1, they would be one locus mismatched:

Haplotype 1- A*0204, CW*16, B*5101, DRB1*04 (sibling 1)

Recombined haplotype 1- A*0204, CW*16, B*5101, DRB1*11 (sibling 2)

Again, assume that sibling 1 has an intact haplotype 1 and sibling 2 has a recombined haplotype 2:

Haplotype 1- A*0204, CW*16, B*5101, DRB1*04 (sibling 1)

Recombined haplotype 2- A*0234, CW*04, B*5105, DRB1*04 (sibling 2)

As can be seen, in this situation, sibling 1 and sibling 2 have three mismatches; two at the allele level and one at the antigen level. If we perform low resolution HLA typing, we would have only one HLA-C mismatch. If we had not performed the HLA-C typing, it would be assumed that the two siblings were full-matched:

Haplotype 1- **A*02**, CW*16, **B*51, DRB1*04** (sibling 1)

Recombined haplotype 2- **A*02**, CW*04, **B*51, DRB1*04** (sibling 2)

In conclusion, for this case, if one of the **parents** was apparently homozygous on one of the MHC loci (that is, had a blank in the HLA typing), we have to request additional low and/or high resolution tests to make a proper decision about the matching of **siblings**.

- Case 3:

Patient: A1/**A9**/B15/B51/DRB1*13/**DRB1*15**

Sibling 1: A1/A9/B15/B51/DRB1*13/**DRB1*11**

Sibling 2: A1/**A2**/B15/B51/DRB1*13/DRB1*15

As can be seen, two of the patient's siblings apparently have one locus mismatch with him; one of them in the HLA-A locus and the other one in the HLA-DRB1. Which of them is the real one locus mismatch?

We requested further HLA typing by the PCR method to detect A9 subtypes and the HLA-C alleles:

Patient: A*01, A*24, CW*07, CW*07, B*15, B*51, DRB1*13/DRB1*15

Sibling 1: A*01, A*24, CW*07, **CW*15**, B*15, B*51, DRB1*13/**DRB1*11**

Sibling 2: A*01, **A*02**, CW*07, CW*07, B*15, B*51, DRB1*13/DRB1*15

As will be noticed, the patient has 2 loci mismatches with sibling 1 and one locus mismatch with sibling 2 at a low resolution level.
We requested HLA typing of other family members to have a clear image of the HLA inheritance of the whole family:
Mother: A1/**A9**/B15/**B21**/DRB1*11/DRB1*13 (the father was dead)
5 of siblings: A2/**A9**/**B21**/B51
3 of siblings: **A1**/A2/**B15**/B51
Thus maternal haplotypes are A1/B51 and A9/B21 and one of the paternal haplotypes is A2/B51.
By inclusion of sibling 1 and sibling 2 HLA typing, we conclude:
Maternal haplotypes: A*01, CW*07, B*15, DRB1*13
A9/B21/DRB1*11
Paternal haplotypes: **A*02**, CW*07, B*51, DRB1*15 (Sibling 2 haplotype)
A*24, **CW*15**, B*51, **DRB1*11** (Sibling 1 haplotype)

To summarize, a recombination event had occurred in the paternal haplotypes between the HLA-A and the HLA-C loci; the patient harbors an A*02 to A*24 translocation and is one locus mismatched with sibling 2 and haploidentical with sibling 1.

Conclusion

The three cases which have been discussed clearly demonstrate the importance of family HLA typing in the matching of patients with sibling donors. If we ignore this important rule that is included in the ASHI and EFI standards in the field of hematopoietic stem cell transplantation (4) , our patients will be exposed to the risk of the selection of mismatched or haploidentical siblings with the assumption of them being fully-matched or a one locus mismatched donor.

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