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ANO 2018

CRYPTIC SENSITIZATION AGAINST HLA-DP AND PRIMARY BONE MARROW GRAFT FAILURE A CASE REPORT

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A male patient (Pt), only child, polytransfused, diagnosed with severe aplastic anemia was searching for a bone marrow unrelated donor (URD). The only available URD was HLA-A,-B,-C,-DRB1, -DQB1 identical, but DP typing revealed non-permissive mismatches in the GvH vector according to TCE Algorithm v2.0 (Pt=DPB1*03:01, *13:01; URD=DPB1*04:01, *04:01). Testing for anti-HLA class II antibodies was performed with SAB panel (cutoff>1000) after heat inactivation of sera to overcome prozone effect. Pre-BMT samples of days (D) -36 and -13 showed negative SAB results, therefore, no anti-DPB1*04:01 DSA was uncovered (D-36: MFI=57; D-13: MFI=56). As patient did not show hematologic recovery post-BMT, SAB class II testing was performed on day +24 to search for possible causes of graft failure. Interestingly, DSA specific to DPB1*04:01 (MFI=3126) and also reactivity against DPB1*04:02 (MFI=2389), DP2 (MFI=2371), DP23 (MFI=1425) and DP28 (MFI=1002, 801 and 761) were observed. Under the light of epitopic analysis DSA reactivity could be explained by Eplets 84GGPM (DPB1*04:01/DPB1*04:02/DP2/DP23) and 35FA (DPB1*04:01/DP28). SAB II testing was also performed with anti-IgM secondary antibody to investigate whether the onset of DSA was associated to primary or anamnestic humoral response. No anti-DP antibodies of IgM class were found in the post-BMT sample (MFI <100 for DP4, DP2, DP23 and DP28). This finding taking together with the negative results in pre-BMT samples suggests that the cryptic sensitization led to DSA rebound after infusion of the graft expressing DPB1*04:01 molecules. In order to assess whether DP alpha polymorphic positions 31 and 50 could affect the antigenicity of DP4 target molecule a sample of day +24 was tested using SAB from another manufacturer. This class II panel included five DP4 heterodimers comprised of the same beta chain (DPB1*04:01), but associated to different DP alpha chains. Notably, the heterodimers DPB1*04:01 with α31M/α50Q showed higher reactivity (MFI=8981 and 7847) than heterodimers with α31M/α50R (MFI = 4032) as well as α31Q/α50R (MFI=2976 and 1844) configurations. After the primary graft failure, confirmed by chimerism analysis (0% donor cells on day +28), a salvage haploidentical transplant was performed. The chosen donor was the father against whom patient had no DSA. Hematological engraftment occurred on day +19 and chimerism testing showed 100% of father's cells on day +28 post-second transplant. This case highlights that non-detection of anti-HLA antibodies in pre-transplant peripheral blood samples does not mean absence of immunological memory, especially in individuals with a history of sensitizing events. The findings on this case suggest that DSA anti-DPB1*04:01 may have contributed to the primary graft failure in the first transplant, and further that polymorphisms in the DPα chain can impact the antigenicity of DPβ chain epitopes.

Key words: DSA, HLA-DPB1, BMT, anamnestic response, primary graft failure