Letter to the Editor

Post-transplant pediatric autoimmune hemolytic anemia: donor *vs* donor or recipient *vs* self?

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Dear Editor,

We present a case of autoimmune hemolytic anemia (AIHA) following allogeneic hematopoietic stem cell transplantation (HSCT) with an unexpected mechanism of autoimmunity.

AIHA is a well-recognized but uncommon complication post-HSCT, occurring in 2.4 to 6% of patients, particularly in pediatrics[1]. Typically, AIHA post-HSCT is attributed to poor immune reconstitution and loss of tolerance, often manifesting as warm AIHA (wAIHA) mediated by IgG autoantibodies. Most cases are thought to involve donor-*versus*-donor mechanisms, but our case suggests a recipient-*versus*-self phenomenon[2,3].

We report the case of a 7-year-old boy with beta-thalassemia major (blood group O RhD positive: CCDee, kk), who underwent unrelated donor HSCT in July 2019. The donor's blood group was O RhD negative (ccdee, kk). Initial immunohematological workups, including direct and indirect Coombs tests, were negative, with molecular chimerism confirming 98% donor engraftment. However, a decline in donor chimerism to 84% occurred over three months, and the patient was admitted nine months post-transplant with severe AIHA.

Laboratory results showed hemoglobin of 4.4 g/dL, elevated lactate dehydrogenase (LDH) at 1,049 U/L, and bilirubin at 2.4 mg/dL. Direct Coombs testing was positive for IgG1 and C3d, with pan-reactive antibodies and anti-e eluted from the patient's red blood cells, while anti-C and anti-D antibodies were also detected in the serum. Chimerism at this time confirmed 84% donor cells.

The patient was treated with cyclosporine and prednisone, stabilizing hemolysis and reducing antibody titers. Unfortunately, five months post-treatment, he relapsed with a new hemolytic crisis. A direct antiglobulin test (DAT) showed IgG1+IgM+C3d positivity, and chimerism further deteriorated (52% donor cells). The patient remained stable with favorable hemolysis indices until 2023, when another relapse occurred. This was marked by a decrease in donor cells (37%) and an increase in recipient cells (63%), with DAT positive for IgG1+IgG3.

In this case, wAIHA developed nine months post-HSCT with IgG antibodies reactive at 37°C. The AIHA reflects the interplay between the donor's reconstituted immune system and the recipient's residual immune system. Chimerism analysis of sorted cell populations confirmed a predominance of recipient cells: CD3+ 63%, CD19+ 53%, CD56+ 60% and CD14+ 51%. In addition, post-transplant immunologic reconstitution analysis showed a decrease in regulatory T cells and an increase in B lymphocytes associated with hemolytic crises, and worsening chimerism in favor of recipient cell predominance.

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Table I - *Relationship between AIHA and mixed chimerism*

Date	Hb (g/dL)	LDH (U/L)	TBIL (mg/dL)	Chimerism (%)	DAT	IAT
June 2019	9.2	220	0.82	Pre transplantation	negative	negative
July 2019: MUD transplantation						
August 2019	9.9	264	0.31	98 donor	negative	negative
January 2020	11.7	192	0.32	92 donor/8 recipient	negative	negative
February 2020	11.6	192	0.25	90 donor/10 recipient	negative	negative
April 2020	4.4	1,049	2.4	84 donor/16 recipient	IgG1+C3d	1:64
October 2020: 6 months of prednisone therapy						
December 2020	12.2	255	0.5	-	IgG	negative
July 2021	11.5	282	0.9	52 donor/48 recipient	IgG1+IgM+C3d	1:128
September 2023	10.1	400	2.6	37 donor/63 recipient	IgG1+IgG3	1:64

Hb: hemoglobin, LDH: lactate dehydrogenase, TBIL: total bilirubin, DAT: direct antiglobulin test, IAT: indirect antiglobulin test.

Regulatory T cells (Tregs) are crucial in preventing autoimmunity by suppressing autoreactive T and B cells[4,5]. This case is particularly significant due to the Rh mismatch between the recipient (O pos, CCDee) and the donor (O neg, ccdee). Post-transplant, the patient developed pan-reactive antibodies, masking anti-e, anti-C, and anti-D antibodies identified by dilution and adsorption techniques. Chimerism analysis was vital in differentiating these from autoantibodies. Unlike typical post-HSCT AIHA involving donor-*versus*-donor mechanisms, this patient's relapse coincided with a reduction in donor cells and an increase in recipient cells, suggesting a recipient-*versus*-self mechanism (**Table I**).

ETHICAL CONSIDERATION

Considering the retrospective nature of the analysis, the current study did not require the approval of the local ethics committee according to current legislation. Data were retrospectively analyzed in line with personal data protection policies.

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The Authors declare no conflict of interest.

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