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Prenatal molecular diagnosis and allogeneic hematopoietic stem cell transplantation in an infant with RAG2 deficiency

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ABSTRACT

RAG2 deficiency is a cause of severe combined immunodeficiency (SCID), characterized by a defect in the development of T and B lymphocytes that predisposes patients to life-threatening infections during the first months of life. We present the case of an infant with a prenatal molecular diagnosis of SCID secondary to RAG2 deficiency who underwent allogeneic hematopoietic stem cell transplantation (HSCT) using a human leukocyte antigen-identical sibling donor at 3 months old. The subsequent clinical course was favorable, with successful immune reconstitution. This case highlights the impact of prenatal molecular diagnosis on the implementation of preventive measures, the performance of early HSCT, and the optimization of clinical outcomes in patients with RAG2 deficiency.

Keywords: Hematopoietic stem cell transplantation; Pediatrics; Severe combined immunodeficiency.

INTRODUCTION

Inborn errors of immunity encompass a group of genetic diseases affecting the development or function of the immune system and can manifest with severe or recurrent infections, autoimmunity, inflammation, and malignancies[1,2]. Mutations in the RAG1 and RAG2 genes (recombination-activating genes 1 and 2) cause a wide spectrum of clinical manifestations, ranging from severe combined immunodeficiency (SCID) to milder forms of immunodeficiency and autoimmunity[3,4]. Without treatment, SCID is typically fatal during the first year of life due to opportunistic infections[3].

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment for SCID. Available evidence demonstrates that early diagnosis and performance of HSCT before 3.5 months of age—preferably before the development of infections—are associated with better immunological reconstitution and higher survival[5–7].

We present the case of an infant with a prenatal diagnosis of SCID due to RAG2 deficiency who underwent HSCT with a human leukocyte antigen (HLA)-identical sibling donor at 3 months old, emphasizing the value of prenatal molecular diagnosis for early intervention and the importance of long-term immunological follow-up.

Ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Clinical information confidentiality was preserved, and no data allowing patient identification were included. Written informed consent was obtained from the parents/legal guardians for the publication of the clinical case and corresponding clinical information.

Clinical case

The patient was a 3-month-old male, the fourth child of a non-consanguineous couple with two healthy older children. His family history includes a younger sister (index case) who had died at 6 months of age from sepsis and disseminated aspergillosis. Following her death, an etiological study led to the diagnosis of SCID secondary to RAG2 deficiency. Genetic analysis of the parents showed that both were heterozygous carriers of pathogenic RAG2 variants.

Due to the risk of recurrence, a prenatal genetic diagnosis was performed during a subsequent pregnancy via chorionic villus sampling, identifying compound heterozygous variants p.Asn101Lys and p.Gly451Ala in the RAG2 gene in the fetus, confirming the diagnosis of SCID due to RAG2 deficiency.

The patient was born preterm at 34 weeks of gestation, weighing 2,400 g, and remained hospitalized in the neonatal unit for the first 15 days of life. Due to the prenatal diagnosis, breastfeeding was suspended to prevent postnatal cytomegalovirus (CMV) transmission, the Bacillus Calmette–Guérin (BCG) vaccine and other live vaccines were not administered, and intravenous human immunoglobulin (IVIG) replacement therapy was started every 21 days as a supportive measure until HSCT.

The patient was referred to our institution for HSCT with a matched sibling donor. The donor was his 10-year-old brother, whose immunological evaluation (T, B, and NK lymphocytes, immunoglobulins, and autoimmunity profile) was normal.

At 3 months of age, the patient was admitted weighing 4,800 g to begin conditioning with thymoglobulin (6 mg/kg), fludarabine (160 mg/m^2), and busulfan (10.2 mg/kg, pharmacokinetic monitoring unavailable). Bone marrow was the source (8.36×10^8/kg total nucleated cells, 15.3×10^6/kg CD34+, 2.5×10^8/kg CD3+ cells). Cyclosporine and methotrexate were administered as graft-*versus*-host disease (GVHD) prophylaxis. Complications included neutropenia with an abdominal focus and diarrhea with a negative stool culture, for which empirical treatment with piperacillin-tazobactam and amikacin was administered. The patient presented mild diaper dermatitis and did not require parenteral nutrition. Neutrophil engraftment occurred on post-HSCT day +7, and platelets did not drop below 30,000/mcL. He developed stage 2 lower intestinal GVHD and stage 1 cutaneous GVHD (MAGIC III B), which resolved with systemic and topical steroids, respectively.

IVIG administration was discontinued six months after HSCT, with immunoglobulin G (IgG) levels above 500 mg/dL (Table 1) and normal T, B, and NK lymphocyte values. Subsequently, the vaccination schedule was initiated with an adequate response to vaccine antigens. No infections were recorded after post-HSCT discharge.

Chimerism tests on whole cells ranged from 92% donor on day +30 to 61% at 24 months, but a lineage-specific chimerism test at day +540 showed that CD3+ and CD19+ cells were exclusively donor-specific alleles. Immunological reconstitution is shown in Table 2.

Currently, the patient is at 29 months post-HSCT with age-appropriate growth and development, proper T/B cell function, and no need for immunoglobulin replacement therapy.

Table 1. Evolution of serum immunoglobulins before and after hematopoietic stem cell transplantation (HSCT).

Immunoglobulin* (mg/dL)	Pre-HSCT (3 months)	Day +180 (9 months)	Day +360 (15 months)	Day +720 (27 months)
IgA	4	24	26	88
IgG	512	686	690	961
IgM	10	27	128	207

*Results were interpreted using reference values corresponding to the patient's age at each determination. Source: Elaborated by the authors.

Table 2. Evolution of lymphocyte subpopulations before and after hematopoietic stem cell transplantation, performed by peripheral blood flow cytometry.

Cell subtype* (mm³)	Pre-HSCT	Day +60 (4 months)	Day +360 (15 months)
Total white blood cells	3,280	10,520	7,040
Lymphocytes	1,246	4,208	3,308
CD19+	5	2,992	694
CD3+	305	438	2,447
CD4+	262	17	1,323
CD8+	29	14	529
CD56+	880	756	165

*Results were interpreted using reference values corresponding to the patient's age at each determination. Source: Elaborated by the authors.

DISCUSSION

RAG gene mutations in SCID patients were first described in 1996[3]. The incidence of SCID in the United States of America is approximately 1:50,000 live births, with RAG1/2 mutations identified in 28% of cases (1:250,000)[8]. The median age at diagnosis is 6.6 months old, although recurrent infections typically manifest earlier due to the progressive decline of maternal antibodies[4,5]. Without timely diagnosis and treatment, the disease is fatal within the first year of life[3].

In families with a history of SCID, identifying the causal genetic variant allows for prenatal diagnosis or targeted newborn screening, favoring the early implementation of preventive measures and HSCT planning. In an international cohort of RAG-deficient patients, all those diagnosed via family history or newborn screening survived HSCT, highlighting the impact of early diagnosis on clinical outcomes[5,9]. In our case, prenatal molecular diagnosis allowed for early intervention: suspending breastfeeding to avoid CMV transmission, avoiding live-virus vaccines, starting IVIG replacement, and planning HSCT at 3 months of age.

HSCT is the curative treatment for SCID, with overall survival approaching 80% depending on factors such as age at HSCT, donor type, presence of infections, conditioning, and genotype[3,6,7]. In RAG deficiency, survival is 77.5% at one year, but it reaches 100% in those diagnosed via family history or screening[9]. Furthermore, HLA-identical sibling HSCT yield the best results (event-free survival near 90%)[10]. Timing remains the most critical prognostic factor: patients transplanted before 3.5 months of age, prior to developing infections, show better reconstitution and a five-year survival rate of 80–95%[5,6]. Our patient presented with both favorable prognostic factors: prenatal diagnosis and early HSCT from an HLA-identical sibling.

While many SCID patients achieve engraftment without conditioning, its absence is associated with limited B-cell recovery and ongoing immunoglobulin dependence[6]. Conversely, alkylating agents can cause acute and late toxicity[11]. European Society for Blood and Marrow Transplantation/European Society for immunodeficiencies guidelines recommend adjusting busulfan doses via pharmacokinetic monitoring[7]. As this was unavailable at our center, a reduced-intensity regimen was used with favorable clinical evolution.

The quality of immune reconstitution following HSCT is closely related to long-term survival[9]. In our patient, functional recovery of T and B lymphocytes allowed for the discontinuation of immunoglobulins and the initiation of vaccinations. Although global chimerism decreased, lineage-specific analysis confirmed full T and B cell engraftment, highlighting the clinical value of this study during the follow-up of patients with primary immunodeficiencies undergoing HSCT[9].

While HSCT remains the standard treatment, gene therapy represents a promising strategy for patients without suitable donors, showing encouraging preclinical results with lentiviral vectors[12].

As a single-case report, our findings cannot be generalized, but they illustrate the feasibility and potential benefits of prenatal molecular diagnosis and early HSCT.

This case illustrates how prenatal molecular diagnosis changed the natural history of the disease by enabling preventive measures, early referral, and HSCT before infectious complications developed.

CONCLUSION

This case demonstrates that prenatal molecular diagnosis in families with a history of RAG2 deficiency can modify the natural course of the disease by enabling preventive measures and early HSCT with an HLA-identical sibling before the development of serious infections. Adequate immunological reconstitution and follow-up via lineage-specific chimerism support the long-term efficacy of this therapeutic strategy.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Andino MLH, Orozco ML, Suen MV, Spossito L, Mas ME, Basquiera AL, Hollmann CH and Lankester A. **Conception and design:** Andino MLH and Lankester A. **Data acquisition:** Andino MLH and Mas ME. **Data analysis and interpretation:** Lankester A and Basquiera AL. **Technical procedures:** Andino MLH, Orozco ML, Suen MV and Mas ME. **Manuscript preparation:** Andino MLH, Orozco ML, Suen MV, Spossito L, Mas ME and Basquiera AL. **Manuscript writing:** Andino MLH, Orozco ML, Suen MV, Spossito L, Mas ME and Basquiera AL. **Critical revision:** Hollmann CH, Basquiera AL and Lankester A. **Final approval of the version to be published:** Andino MLH.

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DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

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