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Case report

Successful T-cell engraftment following unconditioned matched unrelated donor transplant in a child with Omenn syndrome and recurrent multidrug-resistant infections: A case report

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Abstract: Omenn syndrome is a rare form of severe combined immunodeficiency characterized by immune dysregulation, recurrent infections, erythroderma, eosinophilia, and failure to thrive. Hematopoietic stem cell transplantation (HSCT) remains the definitive treatment; however, outcomes are particularly challenging in patients with active severe infections before transplantation. Here, we report the case of a female infant who presented with persistent diarrhea and recurrent otitis media at 2 months of age and was diagnosed at 3 months with genetically confirmed Omenn syndrome caused by a homozygous pathogenic RAG1 variant (*c.1187G>A*; p.Arg396His). Her clinical course was complicated by recurrent multidrug-resistant bacterial bloodstream infections, *Candida auris* fungemia, acute kidney injury, disseminated intravascular coagulation, and respiratory failure requiring pediatric intensive care admission. Because she was clinically unstable for conventional conditioning chemotherapy, she underwent unconditioned matched unrelated donor peripheral blood stem cell transplantation at 8 months of age. Despite persistent mixed donor chimerism and absent B-cell engraftment, she demonstrated progressive donor-derived T-cell recovery, normalization of CD4/CD8 ratio, resolution of recurrent infections, and sustained clinical stability. To our knowledge, reports describing unconditioned matched unrelated donor HSCT in genetically confirmed Omenn syndrome complicated by multidrug-resistant bacterial infections and *Candida auris* fungemia remain extremely limited. This case highlights that unconditioned HSCT may provide clinically meaningful immune reconstitution when standard conditioning is not feasible.

Keywords: Omenn syndrome; SCID; unconditioned HSCT; immune reconstitution; Candida *auris*; pediatric bone marrow transplantation

1. Introduction

Omenn syndrome is a distinct phenotype of severe combined immunodeficiency caused most commonly by hypomorphic mutations in RAG1 or RAG2, resulting in impaired V(D)J recombination and restricted T-cell receptor diversity. It is characterized by erythroderma, eosinophilia, elevated IgE levels, lymphadenopathy, hepatosplenomegaly, recurrent infections, and failure to thrive. Hematopoietic stem cell transplantation remains the only established curative therapy.

European Society for Blood and Marrow Transplantation (EBMT) and European Society for Immunodeficiencies (ESID) guidelines generally favor conditioning in Omenn syndrome to optimize donor myeloid and B-cell engraftment. However, transplantation decisions become particularly challenging in critically ill patients with active infections and organ dysfunction.

We report a child with genetically confirmed Omenn syndrome who underwent rescue unconditioned matched unrelated donor HSCT while critically ill with multidrug-resistant bacterial infections and *Candida auris* fungemia. To our knowledge, reports describing unconditioned matched unrelated donor HSCT in Omenn syndrome complicated simultaneously by multidrug-resistant bacterial infections and *Candida auris* fungemia remain exceptionally limited.

2. Case presentation

Our patient, a 24-month-old, full term female, was born to first degree consanguineous parents. She was referred to our institution at 3 months of age for persistent diarrhea, recurrent otitis media, and diffuse scaly erythroderma since she was 2 months of age. Upon presentation, initial laboratory workup showed eosinophilia and elevated serum IgE. Immunological evaluation demonstrated absent $CD19^+$ B cells, markedly reduced $CD8^+$ T cells, and an elevated CD4/CD8 ratio of 11.5. Molecular testing identified a homozygous pathogenic RAG1 mutation (*c.1187G>A;* p.Arg396His), confirming Omenn syndrome. A matched family donor was unavailable; however, a fully matched unrelated donor was identified through the Saudi Stem Cell Donor Registry. The patient was initially planned for conventional conditioned HSCT. Prior to transplantation, however, she developed recurrent multidrug-resistant bloodstream infections, including *Klebsiella pneumoniae*, methicillin-resistant *Staphylococcus aureus*, and *Candida auris* fungemia. Her condition deteriorated further, and she required Pediatric Intensive Care Unit (PICU) admission for acute kidney injury, disseminated intravascular coagulation, and respiratory failure requiring non-invasive ventilation. A multidisciplinary discussion involving a bone marrow transplant (BMT) team, pediatric infectious disease (ID) team, allergy and immunology team, and PICU team concluded that conventional conditioning would carry an increased mortality risk. In addition, delaying transplantation was also considered unsafe because of ongoing uncontrolled infections and severe immune deficiency. Therefore, unconditioned matched unrelated donor peripheral blood stem cell transplantation was pursued at 8 months of age as a rescue strategy. She initially had a Hickman line inserted in preparation for the conditioning transplant; however, due to her deterioration, it was removed, and management was conducted via peripheral venous access, then via jugular venous access, until she was cleared by the ID team for a double-lumen peripherally inserted central catheter (PICC) insertion.

3. Transplant details

She received peripheral blood stem cells from a fully matched unrelated donor, with a $CD34^+$ dose of 13×10^6 $CD34^+$ cells/kg. A high $CD34^+$ cell dose was selected to reduce the risk of graft failure in the absence of conditioning. No conditioning chemotherapy or serotherapy was administered. Regarding prophylaxis against Graft versus host disease (GVHD), Cyclosporine was initiated before transplant to control erythroderma and lymphocytosis targeting a level of 150–200 ng/mL and later switched to tacrolimus because of nephrotoxicity, aiming at a level of 8–12 ng/mL. Anti-GVHD medications were tapered starting from day +30 and stopped at day +45 post stem cell infusion. The stem cell infusion was done by a pediatric BMT nurse under the supervision of a BMT physician. During her stay in PICU, she remained in a hepa filtered room, while all her care was undertaken by ICU nursing. The BMT team rounded daily on the patient, and all transplant related decisions were taken by the BMT team. In addition, daily discussions among BMT, PICU, and infectious diseases teams took place.

4. Post-transplant course

Five days after receiving stem cells, with the supportive care provided, the patient was switched from PICU to general ward, in a stable condition, on nasal cannula, and discharged initially at day +56 post stem cell infusion after PICC removal. Her early post-HSCT course was marked by repeated admissions for polymicrobial infections, including *Candida auris* fungemia and *Candida haemulonii* from ear and blood, MSSA/MRSA, *Klebsiella pneumoniae*, *Stenotrophomonas maltophilia* bacteremias, Epstein-Barr viremia requiring rituximab, bilateral otomastoiditis, right facial cellulitis, and presumed fungal pneumonia, in addition to provoked left upper limb venous thrombosis, which was PICC related. During her admission to the hospital, she was always placed in a hepa filtered room under strict isolation, as per ID and infection control recommendations. All major infectious complications occurred within the first 150 days following stem cell infusion. During that period, multiple multidisciplinary and family meetings were held to discuss potential conditioned transplantation; however, given the gradual clinical improvement and reduced intensity of the infections, the decision was to observe and wait. Otherwise, she remained on supportive antibacterial, antiviral, and antifungal prophylaxis until 1 year post stem cell infusion and was on subcutaneous immunoglobulin every 2 weeks.

Despite these complications, she remained clinically stable, afebrile, and interactive at follow-up, serial monitoring of her growth parameters. Figure 1A,B shows progressive growth and catching up according to her chronological age. In addition, at the developmental level, her developmental skills approximate those expected for an 18-month-old child.

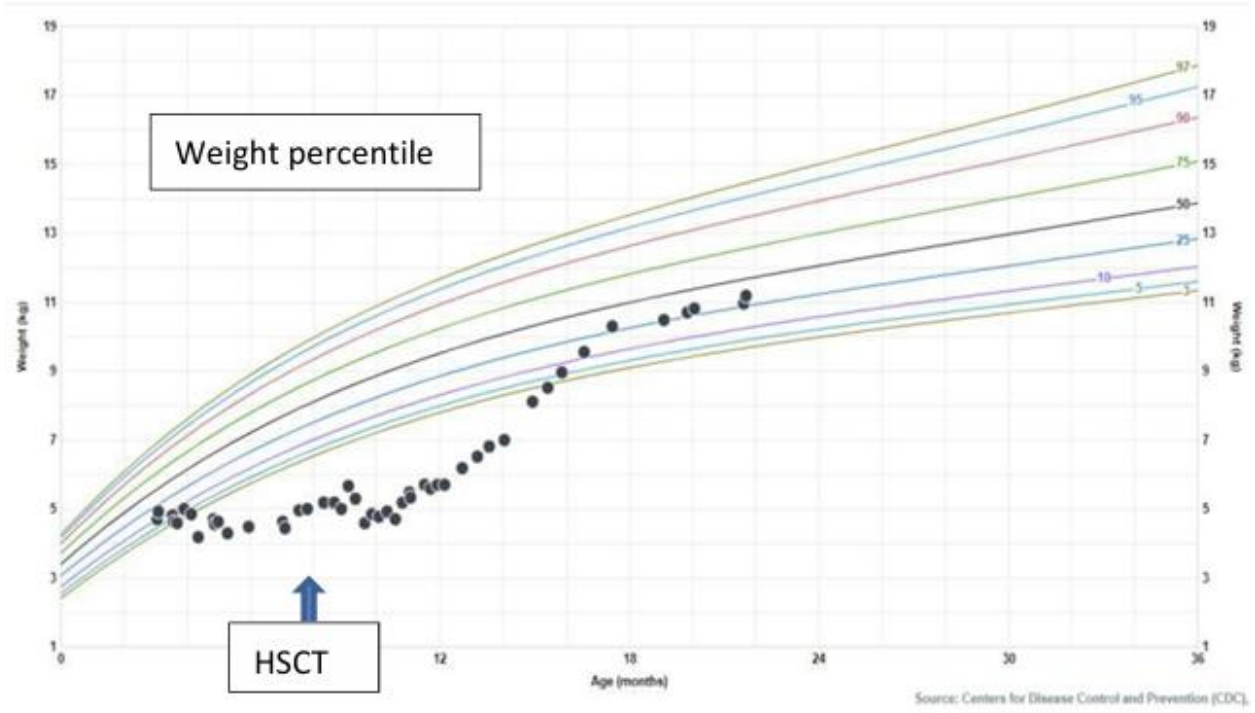

Figure 1A

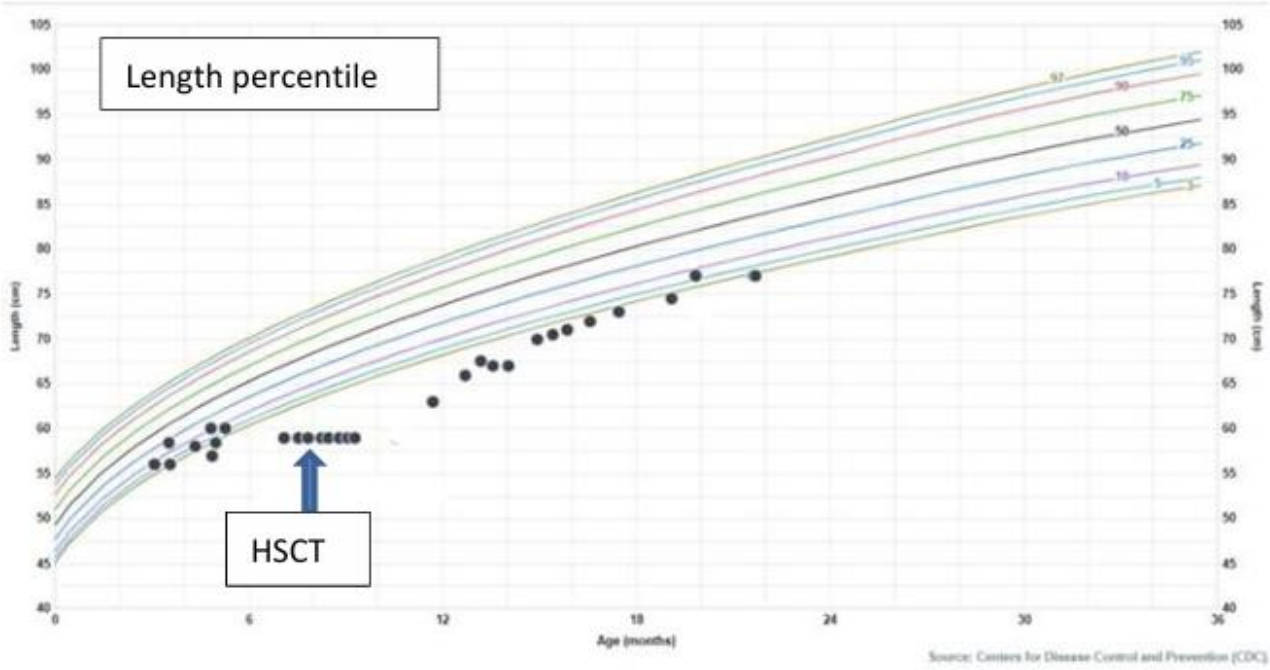

Figure 1B

Figure 1. Growth monitoring of the patient from birth to 24 months. Figure 1A demonstrates weight-for- age percentile trajectory, while Figure 1B shows length-for-age percentile trajectory, based on CDC growth standards. The patient exhibited significant growth delay in early infancy with subsequent catch-up post HSCT.

5. Immune reconstitution and chimerism

The patient demonstrated sustained and progressive T-cell recovery following unconditioned MUD HSCT. $CD3^+$ T-cell counts rose from 0.36 × 10^9/L pre-transplant to 3.04 × 10^9/L at 3 months, then stabilized around 2.5 × 10^9/L by 12 months. $CD4^+$ helper T cells showed partial but durable reconstitution (0.3 → 1.13 × 10^9/L), while $CD8^+$ cytotoxic T cells expanded significantly (0.026 → 1.24 × 10^9/L), resulting in normalization of the CD4/CD8 ratio (from 11.5 to 0.91). $CD19^+$ B cells remained absent throughout the follow-up period, consistent with failed B-cell engraftment, a common outcome in SCID patients receiving unconditioned grafts. Natural Killer ($CD16^+56^+$) cell numbers remained within acceptable range (Figure 2).

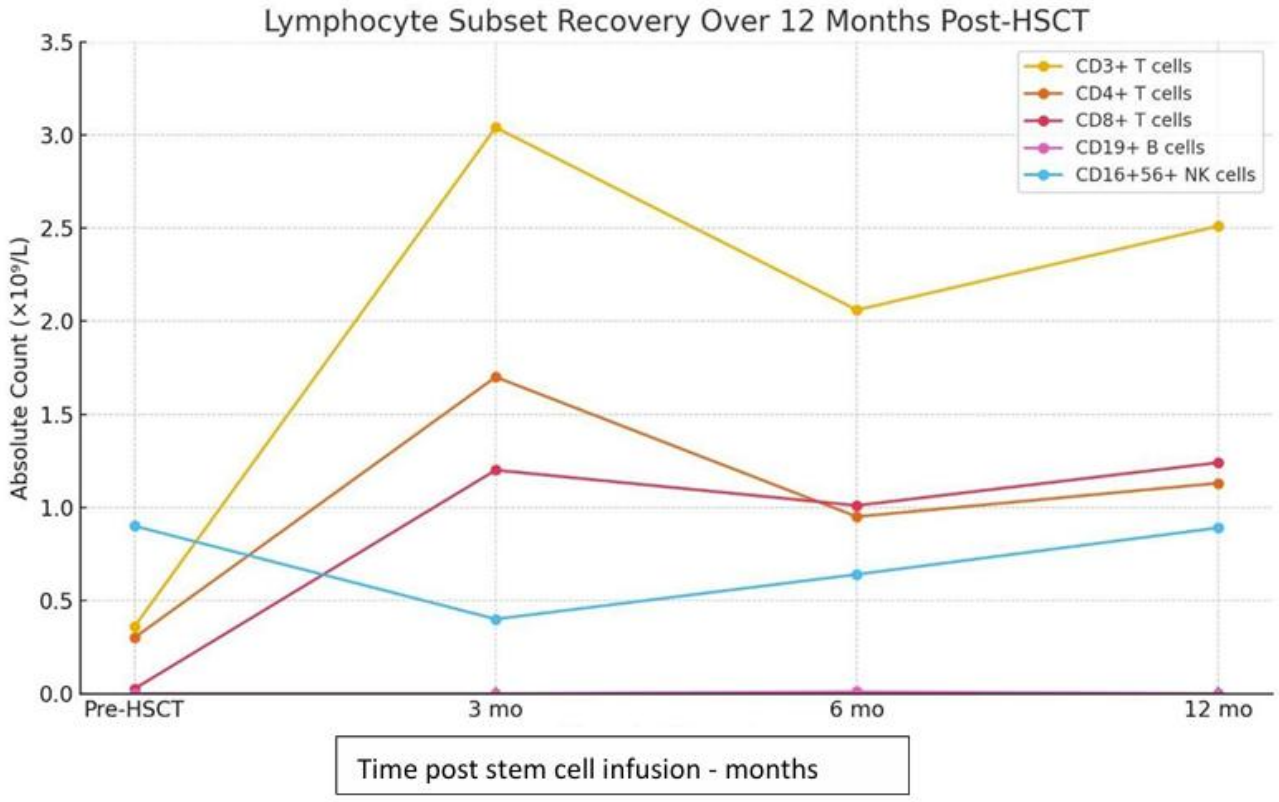

Figure 2. Lymphocyte subset recovery over 12 months following MUD HSCT in Omenn syndrome.

Chimerism: Day 30 CD3 cells were 51% donor DNA; increased to 83% on day +60, dropped to 70% on day +180, and stabilized afterward between 69–79% donor DNA.

Detailed functional immune studies, including TREC analysis, naïve/memory T-cell subsets, and proliferation assays, were unavailable.

Clinical immune recovery was therefore assessed through infection control, lymphocyte recovery, and overall clinical stability.

6. Discussion

Severe combined immunodeficiency (SCID) remains a pediatric emergency due to its high mortality

without early intervention by definitive therapy. Hematopoietic stem cell transplantation (HSCT) has been the cornerstone of curative treatment for decades, with evolving strategies aimed at improving survival and immune reconstitution outcomes. Early HSCT before severe infection remains the strongest predictor of survival in SCID [1–4]. Our patient underwent transplantation under exceptionally high-risk circumstances, including active multidrug-resistant bacteremia, invasive fungal infection, multiorgan dysfunction, and intensive care admission.

The 50-year experience from the Center for International Blood and Marrow Transplant Research (CIBMTR) underscores improved survival particularly with early transplantation, ideally before 3.5 months of age and in the absence of active infection [5]. In addition, EBMT/ESID recommendations generally favor conditioning in Omenn syndrome because of improved B-cell and myeloid engraftment. However, this approach was not feasible in our patient as she was in a setting of a complex infectious course, including fungal and multidrug-resistant bacterial infections, factors consistently associated with increased transplant-related morbidity and mortality [2,6,7].

The immune reconstitution trajectory post-HSCT varies significantly. In the SCID cohort studied by Heimall et al., sustained T-cell recovery was the primary predictor of survival, regardless of donor type or conditioning regimen. Moreover, Slack et al. demonstrated that functional T-cell recovery not full donor chimerism was more critical in achieving long-term immune competence [8]. This aligns with our patient's evolving T-cell numbers despite mixed chimerism and absent B-cell recovery, further reinforcing the principle that immune function may supersede lineage-specific engraftment in predicting clinical stability.

Infection risk remains high post-transplant, particularly in patients colonized or infected with carbapenem-resistant Enterobacteriaceae (CRE) or invasive fungal pathogens. These organisms are notoriously difficult to eradicate and are associated with poor outcomes in immunocompromised hosts [6–9]. Our patient's recurrent CRE infections may reflect environmental exposure and impaired mucosal or neutrophil barrier defenses, while the persistent candidemia underlines the vulnerability of SCID patients post-HSCT even under antifungal prophylaxis.

This case highlights the intricacies of managing SCID patients undergoing HSCT in the presence of significant infectious burden and mixed immune reconstitution. While full donor chimerism was not achieved, the gradual recovery of T-cell subsets supports the notion that immune function, not absolute engraftment, is paramount [8,10].

Reports describing unconditioned matched unrelated donor transplantation in Omenn syndrome complicated by multidrug-resistant bacterial infections and *Candida auris* remain exceptionally rare. Persistent B-cell aplasia remains an expected limitation of unconditioned transplantation and requires ongoing immunoglobulin replacement [1–4,8].

This case highlights the importance of individualized transplant strategies in critically ill children with primary immunodeficiencies when standard approaches are not feasible.

7. Limitations

This report is limited by the absence of detailed functional immune studies, including TREC analysis, naïve versus memory T-cell assessment, T-cell proliferation studies, and T-cell receptor repertoire analysis. In addition, long-term immune competence requires continued follow-up.

8. Conclusion

Unconditioned matched unrelated donor HSCT may serve as a life-saving rescue strategy in critically ill children with Omenn syndrome who cannot tolerate conventional conditioning. Clinically meaningful immune recovery may occur despite mixed donor chimerism and absent B-cell engraftment. However, long-term follow-up remains essential.

Use of AI tools declaration

The authors state that they have not utilized Artificial Intelligence (AI) tools when creating this article, except for language editing.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

FM: Data collection, primary draft and final draft; IS: Primary draft and review; FA: Data approval and draft revision; MAlzahrani: Data approval and draft revision; MAlsultan: Final revision of the manuscript prior to submission.

Ethics approval of research

The study was exempted from IRB approval because it's a single case report. Written informed consent for publication was obtained from the patient's legal guardians and is retained in the institutional medical records.

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