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Case Presentation

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Neurofibromatosis Type I-Related Severe Aplastic Anemia: An Unusual Association with a Complicated Bone Marrow Transplantation Course: A Case Report

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Abstract

Severe Aplastic Anemia (SAA) is a life-threatening condition characterized by bone marrow failure, requiring immunosuppressive therapy or hematopoietic stem cell transplantation (HSCT). Neurofibromatosis type I (NF1) is an autosomal dominant disorder with diverse systemic manifestations. Herein, we report a pediatric patient with unusual coexisting SAA and NF1 who underwent HSCT, facing multiple infectious and hematologic complications. This case highlights the challenges of managing immunosuppression, infections, and engraftment complications in such a rare clinical scenario.

Keywords: Severe aplastic anemia; Neurofibromatosis type I; Hematopoietic stem cell transplantation; Pediatric hematology; Bone marrow failure; Infections; Engraftment complications

Introduction

Neurofibromatosis type 1 (NF1) is the most common inherited tumor predisposition syndrome affecting 1 in 3,000 individuals, with increased risk of malignant and non-malignant tumors [1-4]. The overall risk of

neoplasm development among individuals with NF1 is up to 5-15% higher than in the general population, with an earlier age of onset and worse prognosis [1-4]. In literature, there is an association between NF1 and the following malignancy: gliomas, Malignant Peripheral Nerve Sheath Tumors (MPNSTs), breast cancers, pheochromocytomas, rhabdomyosarcomas, and Gastrointestinal Stromal Tumors (GIST) [1]. In addition, children with NF-1 are at increased risk for malignant myeloid disorders. Primarily Acute Myeloid Leukemia (AML), and Juvenile Myelomonocytic Leukemia (JMML) [2,3]. Severe Aplastic Anemia (SAA) is a disorder characterized by pancytopenia and bone marrow hypocellularity, often requiring Bone Marrow Transplantation (BMT) in refractory cases [2,5-7]. The coexistence of SAA and NF-1presents unique challenges in transplantation and infection management. We present a pediatric case of NF1 with SAA who underwent matched unrelated donor HSCT, experiencing a prolonged and complicated hospital course.

Case Presentation

A previously healthy 11-year-old female who had skin hyper pigmentation and multiple café au lait macules since birth, that have been increasing in size and number, initially presented in May 2022 with febrile neutropenia and progressive pancytopenia. She was diagnosed with NF1 based on clinical criteria and positive genetic testing. Next-Generation Sequencing (NGS) panel for inherited bone marrow failure syndromes came positive for: heterozygous missense likely pathogenic variant on NF1 gene, in addition to coinheritance of multiple germline mutations :heterozygous frame shift that's likely pathogenic CSF3R colony stimulating factor 3 receptor and heterozygous nonsense pathogenic HACE1 Mutation and heterozygous nonsense pathogenic CYP21A2 mutation. Bone marrow evaluation confirmed severe aplastic anemia. She was initially treated with supportive transfusions and infection management. Her hospital course was complicated by recurrent bacterial and fungal infections, including MRSA bacteremia, pulmonary fungal nodules, and disseminated pediculosis and necrotizing lymphadenitis. Hematologic evaluation revealed persistent bone marrow hypocellularity with <10% cellularity. Given the lack of response to supportive care, she underwent Matched Unrelated Donor (MUD) HSCT on October 26, 2022, with a conditioning regimen of cyclophosphamide, fludarabine, and anti-thymocyte globulin; she received 5.4*10^6 per kg of stem cells. GVHD prophylaxis included Mycophenolate Mofetil (MMF) and tacrolimus. The early post-transplant period was complicated by persistent febrile neutropenia, bloodstream infections with Escherichia coli (ESBL) and vancomycin-resistant Enterococcus faecium (VRE), Stenotrophomonas maltophilia as well as neutropenic colitis. Imaging revealed a lung abscess in addition to multiple hepatic and splenic abscesses concerning for fungal infection, requiring prolonged antifungal therapy with posaconazole and amphotericin B. Despite these complications, engraftment was achieved by day +15 post-transplant, with ANC and platelet recovery; she was discharged at day +29 to continue a 3 months course of appropriate antimicrobials, while allowing for lymphocyte recovery. Radiological evolution of infection prior to, during and post bone marrow transplantation is shown in the imaging below **(Figure 1 and 2).** Genetic chimerism analysis at days

30, 60, 180, 1 and 2 years post-HSCT demonstrated sustained donor engraftment (97-100%).

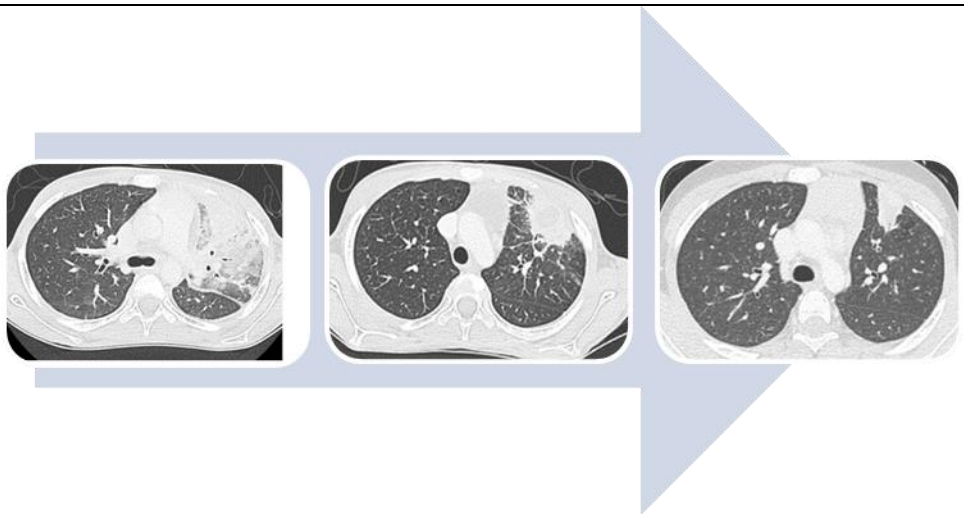

Figure 1: Chest CT changes pre, during and 8 months' post-transplant.

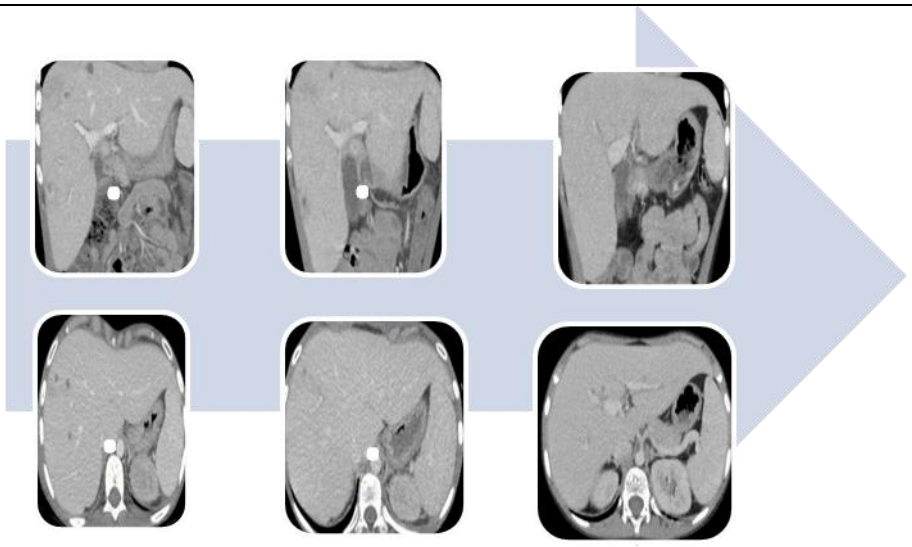

Figure 2: Liver/abdominal CT changes pre, during and 8 months' post-transplant.

Discussion

This case underscores the challenges associated with HSCT in patients with SAA and NF1. The combination of immunosuppressive therapy and pre-existing immune dysfunction increased the patient's susceptibility to severe infections, necessitating prolonged antimicrobial coverage. NF1 has been linked to hematologic abnormalities, yet its impact on HSCT outcomes remains poorly understood. Our patient's complications, including recurrent bacterial and fungal infections, neutropenic colitis, and persistent abscess formation, highlight the

importance of close multidisciplinary management. Given the successful engraftment and infection resolution, this case adds valuable insights into the post-transplant course in patients with coexisting NF1 and SAA.

Conclusion

To the best of our knowledge This the first reported case of NF I -Related Severe Aplastic Anemia,highlights the complexities of managing HSCT in a patient with NF1 and SAA, emphasizing the need for vigilant infection monitoring and tailored immunosuppression strategies. Further studies are warranted to explore the impact of NF1 on hematologic disorders and transplant outcomes.

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