MedPress
Case Reports and Clinical Images

Aplastic Anemia on a Background of HELLP Syndrome in Identical Twins – Diagnosis and Management

Case Report

Running Title: SAA and HELLP in syngeneic twins

Lipton JH*

* Princes Margaret Cancer Centre, University of Toronto, Canada

***Corresponding author**
Lipton JH,
Princes Margaret Cancer Centre,
University of Toronto, Toronto,
Canada, Tel: +416-946-2267;
Fax: +416-946-6585,
Email: jeff.lipton@uhn.ca

Article Information
Received: 27 Jan 2025;
Accepted: 07 Feb 2025;
Published: 10 Feb 2025.

Abstract

Syngeneic twins presented at different times with HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets) Syndrome and in both cases a post-pregnancy with severe aplastic anemia. Both were managed with matched related donor bone marrow transplant, again at different times, from a third sister and are doing well more 15 years later. Management of aplastic anemia is discussed.

Keywords: Aplastic anemia, HELLP syndrome, Bone marrow transplant

Introduction

Acquired Aplastic Anemia (AA) is a bone marrow failure syndrome characterized by pancytopenia and symptoms related to reduced blood cell numbers [1,2]. The etiology in the western world is often not known and the disease often is thus described as idiopathic. Viral infection is suspected but not proven in most cases, but it can also be due to inflammatory disease, certain medications, autoimmunity and proven viral illness especially parvovirus. In the developing world, hepatitis B is felt to be the most common cause. The disease varies in severity from mild requiring observation to severe (SAA) or very severe (VSAA) which are life threatening and require aggressive intervention. Aplastic anemia can occur during pregnancy [3-5].

For mild AA requiring intervention, utilization of oral immunosuppressive agents such as cyclosporine or tacrolimus can be all that is necessary to correct or stabilize blood counts. As the disease increases in severity, supportive care becomes necessary with blood product transfusion and antibiotic therapy. Definitive therapy is variable and depends on a number of things, including patient age, stem cell donor availability, and availability of a center to perform the bone marrow allograft or provide the intensive immunosuppression. Generally and with some controversy, the dogma has been that if the patient is under the age of 40 and has a fully matched sibling donor, the transplant is the treatment of choice. Other opinions would allow the upper age of allograft to be around 60, matched unrelated donors to be considered and even mismatched or haploidentical donors in the case where immunosuppressive therapy has failed [6,7].

Intensive immunosuppressive therapy generally consists of antithymocyte globulin, rabbit preferred over horse, plus cyclosporine or tacrolimus, and in some cases adding corticosteroid and growth factor. The issue with this form of therapy is that it may take up to 6 months to see a response and during this time, transfusion support continues and there are risks of bleeding and/or infection. A successful allograft can reconstitute blood counts in as little as a month, limiting the risk of these problems, albeit with the risk of transplant related complications. Delaying an allograft also increases the risk of blood cell alloimmunization and transfusion refractoriness [8,9].

In this report, the cases of identical twin sisters who develop SAA under similar unusual circumstances but not at the same time, and are treated in the same way with a sibling allograft is reported.

Case 1

In 2008, this 28 year old woman, presented at around 36 weeks gestation with first pregnancy, with hypertension, mild elevation in hepatic enzymes, slight elevation of creatinine, occasional red cell fragments on blood film and mild thrombocytopenia. A diagnosis of HELLP syndrome was made. Management was conservative with bed rest, hydration and delivery at 38 weeks after induced labor. There were no complications at delivery and mother and infant were discharged with no issues. Other than mild anemia, blood counts had normalized. Two months post delivery, patient presented with epistaxis and bloodwork revealed pancytopenia and after bone marrow was performed, a diagnosis of severe aplastic anemia was made. In 2008, few tests were available to characterize further the etiology. Cytogenetics were normal. Hepatitis and HIV serology, ESR, rheumatoid factor were all negative. There was no molecular testing and available done at that period of time. She became platelet transfusion dependent and was referred to this center.

HLA-typing was done on the patient and two sibling matches 6/6 were identified – an identical twin sister and a second

sister. Although the etiology of the SAA was thought be due to pregnancy/HELLP, nothing could be confirmed and given the possibility of a genetic basis, bone transplant was done from the non-syngeneic sister. Discussions pre-transplant raised the balance between a genetic issue making the non-twin safer, but also the possibility of graft versus host disease and the patient agreed on the donor choice. Conditioning was cyclophosphamide/TBI and GVH prophylaxis was cyclosporine/MTX with the cyclosporine continued for 6 months. Mild chronic GVHD developed two months post CSA discontinuation and it responded to a short course of prednisone. Patient is well and has had two successful pregnancies. Both children have been diagnosed with ryanopathy (RYR-1), but this has not been found in cousins, or tracked to their mother, or has any reported relationship to either HELLP or SAA.

Case 2

In 2009, 14 months after the patient in Case 1 was diagnosed, her identical twin sister presented at 37 weeks gestation with first pregnancy with exactly the same symptom profile as her sister. Again, a diagnosis of HELLP Syndrome was made. As symptoms were slightly milder, she was managed with observation and bed rest and delivered without complications, a healthy infant at 39 weeks. Again, other than mild anemia, blood work was unremarkable.

Without any symptoms, routine bloodwork at three months post delivery revealed severe pancytopenia. Work up as for her sister confirmed a diagnosis of severe aplastic anemia with unknown etiology. Again, it was presumed to possibly be due to pregnancy/HELLP. With donor status already identified and again with the same caveats for GVHD risk, a bone marrow transplant was done from the same non-twin sister using the same conditioning and GVHD prophylaxis. No significant GVHD developed after immunosuppression discontinuation and the patient is well 15 years later and has had one successful pregnancy.

Case 3

24-year old sibling donor for both her sisters was worked up on two occasions pre bone marrow collection. Health history was unremarkable and all blood work and a diagnostic bone marrow prior to the first harvest were normal. Has had successful pregnancy post stem cell donation with no evidence of either HELLP or aplastic anemia.

All three sisters gave verbal consent to describe the cases in a publication.

Discussion

This report presents two unusual presentations. The first is the development of SAA in identical twins, although not at the same time point. Cases of this are not reported in the literature, where in fact the use of an identical twin as a stem cell donor in the case of aplastic anemia is considered a plus, as syngeneic GVHD is a very rare event and only seen in the case of immunosuppression withdrawal scenarios. Some GVHD which is associated with a graft-versus-leukemia (tumor) effect (GVL) is a wanted outcome when allografts are done for malignancy, but in the case of SAA, there is no such need.

The second is the issue of HELLP syndrome and whether there is any relationship to the SAA. HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets) is considered a preeclampsia variant that occurs in late pregnancy and can be life-threatening. It is a syndrome that occurs in an inflammatory milieu and is associated with thrombocytopenia very similar to TTP, but has not been associated with SAA [10-12]. Not available at the time when these patients were affected and better characterized since then, molecular testing suggests complement alternative pathway dysfunction. Currently available tests were not an option 15 years ago [13,14].

The fact that syngeneic twins developed two problems, HELLP and SAA, under similar circumstances and that a third sibling who was HLA-matched did not, suggests some other genetic susceptibility that has hot been identified. Another possibility is some remote external exposure to the twins that was not seen in the donor sister. Since “inflammation” can be involved in both HELLP and SAA, was this a response to a similar milieu, i.e. pregnancy? [1,2,15].

The etiology or risks for both problems in these sisters is not known and whether there is even a common cause or this is just two unfortunate unrelated problems that developed. Fortunately, delivery of the infants solved the first and bone marrow transplant the second in both cases and other than the RYR-1 disorder in one set of children, all are doing well more than 15 years later. Management of the HELLP syndrome will not be commented on here as I am not an obstetrician and it was done elsewhere. In terms of the SAA however, these cases confirm the advantage of moving quickly with a bone marrow, not a peripheral blood stem cell transplant with a higher risk of GVHD, to resolve the problem and reduce the high risks associated with severe pancytopenia.

Disclosure

No funding was received for this publication. Patient consent was obtained in all cases. The author has no conflicts to declare.

Reference

1. Gale RP, Hinterberger W, Young NS, Gennery AR, Dvorak CC, et al. (2023). What causes aplastic anaemia? Leukemia. 37: 1191-1193.
2. Patel BA, Giudice V, Young NS. (2021). Immunologic effects on the haematopoietic stem cell in marrow failure. Best Pract Res Clin Haematol. 34: 101276.
3. McGowan KE, Malinowski AK, Schuh AC, Whittle W, Shehata N. (2019). Aplastic anaemia in pregnancy - a single centre, North American series. Br J Haematol. 184: 436-439.
4. Perolla A, Cela B, Semanaj V, Dedej-Kurti T, Caja T. (2024). Aplastic Anaemia in Pregnancy: A Case-Based Comprehensive Review of the Literature. Cureus. 16: e58365.
5. Bortolotti M, Trikha R, Salter S, Large J, Vlachodimitropoulou E, et al. (2024). Pregnancy in acquired bone marrow failure syndromes: Antenatal management and maternal and fetal outcomes. Am J Hematol. 99: 1647-1650.
6. Storb R. (2024). Allogeneic bone marrow transplantation for aplastic anemia. Int J Hematol. 119: 220-230.
7. Vo PT, Pantin J, Ramos C, Cook L, Cho E, et al. (2015). Conditioning with rabbit versus horse ATG dramatically alters clinical outcomes in identical twins with severe aplastic anemia transplanted with the same allogeneic donor. J Hematol Oncol. 8: 78.
8. Piekarska A, Pawelec K, Szmigielska-Kapłon A, Ussowicz M. (2024). The state of the art in the treatment of severe aplastic anemia: immunotherapy and hematopoietic cell transplantation in children and adults. Front Immunol. 15: 1378432.

9. Scheinberg P. (2024). Progress in medical therapy in aplastic anemia: why it took so long? Int J Hematol. 119: 248-254.
10. Kappler S, Ronan-Bentle S, Graham A. (2017). Thrombotic Microangiopathies (TTP, HUS, HELLP). Hematol Oncol Clin North Am. 31: 1081-1103.
11. Frimat M, Gnemmi V, Stichelbout M, Provôt F, Fakhouri F. (2024). Pregnancy as a susceptible state for thrombotic microangiopathies. Front Med (Lausanne). 11: 1343060.
12. Petca A, Miron BC, Pacu I, Dumitrașcu MC, Mehedințu C, et al. (2022). HELLP Syndrome-Holistic Insight into Pathophysiology. Medicina (Kaunas). 58: 326.
13. Gardikioti A, Venou TM, Gavriilaki E, Vetsiou E, Mavrikou I, et al. (2022). Molecular Advances in Preeclampsia and HELLP Syndrome. Int J Mol Sci. 23: 3851.
14. Vaught AJ, Braunstein E, Chaturvedi S, Blakemore K, Brodsky RA. (2022). A review of the alternative pathway of complement and its relation to HELLP syndrome: is it time to consider HELLP syndrome a disease of the alternative pathway. J Matern Fetal Neonatal Med. 35: 1392-1400.
15. Stojanovska V, Zenclussen AC. (2020). Innate and Adaptive Immune Responses in HELLP Syndrome. Front Immunol. 11: 667.

Citation: Lipton JH; Aplastic Anemia on a Background of HELLP Syndrome in Identical Twins – Diagnosis and Management. Medp Case Rep Clin Image. 2025; 3(1): mpcrci–202501001.