Unraveling the Consequences of Stem Cell Transplant with ABO Major Mismatch and High Titer Anti-A Antibodies with the Development of Pure Red Cell Aplasia in a Patient with Therapy-Related Acute Myeloid Leukemia

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BACKGROUND/ CASE STUDY

A 63-year-old male, with blood type O Rh-positive, was diagnosed with bladder cancer in 2012 and underwent irradiation and surgery with neobladder. He has a history of deep venous thrombosis and pulmonary embolism. In July 2023, he received a sibling-allogenic stem cell transplant (SCT) to treat therapy-related acute myeloid leukemia (AML). Since then, he has been diagnosed with severe anemia, specifically pure red cell aplasia (PRCA), which is characterized by normocytic, normochromic anemia and reticulocytopenia with an absolute reticulocyte count of zero from 10/10/23 to date. Disease surveillance has been negative for measurable residual disease and he has full donor chimerism in blood and bone marrow. He is currently on transfusion support, Daratumumab with Aranesp (Darbepoietin) support, and a tyrosine kinase inhibitor (Ibrutinib) to manage chronic Graft vs. Host Disease (GVHD). Recently, he was admitted to the hospital due to a septic prosthetic joint infection of the right knee and associated bacteremia with Klebsiella. He underwent surgical washout with hardware removal and placement of an antibiotic spacer on 3/27/2024. He was discharged on IV antibiotics.

STUDY DESIGN/ METHODS

In April 2023, the patient experienced breathlessness and was found to be pancytopenic. A bone marrow biopsy revealed that he had AML with 80% myeloblasts. Additionally, FISH identified the deletion of 5q31 (EGR1), gain of RUNX1T1, deletion of CBFB, and deletion of TP53. After two cycles of chemotherapy induction, he achieved clinical remission. The therapy was consolidated with a sibling allogeneic SCT with D0=7/17/2023. The transplant has been complicated by PRCA, which has required frequent RBC transfusions and donor lymphocyte infusions (DLIs). Nearly 9 months after the sibling-allogeneic SCT, he remains RBC transfusion dependent with a reticulocyte percentage of 0.1%.

Anti A Titers: The patient originally typed as O, Rh-positive and his stem cell donor was A, Rh-positive. For this reason, anti-A titers were initially measured before D0 and continue to be followed.

RESULTS

At the time of SCT, the patient faced a high risk of acute graft rejection and delayed red cell engraftment, which could have potentially led to PRCA. To mitigate the risk, the patient underwent therapeutic plasma exchange (TPE) for three days prior to the scheduled SCT on July 14th, 15th, and 17th, 2023 (day of transplant). After D0, despite receiving three DLIs with the aim of potentially treating complications, including the PRCA, through enhanced graft-vs-plasma cell effect and preventing relapse through the graft-vs-leukemia effect, he continues to have PRCA. The patient also completed immunosuppressive therapy (with taper) on November 4th, 2023 and was started on Aranesp. In addition, the patient has received Daratumumab, which has shown efficacy in treating PRCA post-allo transplant due to recipient anti-A/B antibodies, with continued unmeasurably low reticulocyte counts. The clinical team continues to monitor the patient's condition and explore further treatment options to ensure the best possible outcome for the patient and the patient remains transfusion dependent

CONCLUSION

PRCA was first identified in 1922 by Kaznelson who distinguished it from aplastic anemia, which causes pancytopenia. The congenital form of PRCA was first described by Joseph in 1936 and by Diamond and Blackfan in 1938. Congenital PRCA is a lifelong disorder and is often associated with physical abnormalities. PRCA can also be temporary and reversible. For example, transient erythroblastopenia of childhood (TEC) can occur after viral infections. Similarly, PRCA caused by medications and infections is often reversible.

Matching HLA antigens has been proven to be of the utmost importance when choosing a stem cell donor, but using ABO major mismatched donors can result in the development of target-specific antibodies, which can cause delayed engraftment of erythroid precursors. In this setting, PRCA is a rare condition that causes a halt in the development of red blood cells due to residual antibodies from the recipient that attack donor RBCs. This results in a lack of erythroblasts in the bone marrow while white blood cell and platelet production remain normal. The anemia caused by PRCA is typically normocytic but can also be macrocytic. PRCA seen after SCT is associated with high titers of isohemagglutinins directed against the donor RBCs. To avoid this complication, the titer of the offending antibody is lowered prior to the infusion of stem cells by immune suppression and TPE. There is no specific titer that has been determined to be safe, but a value generally less than 64 is often recommended. Sometimes, as seen in this case, suppressing the isohemagglutinins is not enough to avoid PRCA.

TABLE AND GRAPH

Date	IgG	IgM
06/22/2023	1:8192	1:64
08/09/2023	1:1024	1:512
09/26/2023	1:1024	1:256
10/13/2023	1:1024	1:512
11/10/2023	1:1024	1:1024
12/11/2023	1:1024	1:256
12/27/2023	1:1024	1:512
01/31/2024	1:1024	1:512
02/26/2024	1:1024	1:256
04/08/2024	1:1024	1:128

Table with each row represents a different date, and the columns represent the IgG and IgM values respectively. Note the consistently elevated Anti-A IgG. These values fluctuate even with TPE and immunosuppressive therapy, they do not fall down to a value under 1:128 (IgM) & 1:1024 for IgG. These high titres play a crucial role in delayed engraftment and are responsible for development of PCRA

Underlaying is a graphical representation of the peripheral blood indices including hemoglobin in pink ranging between 5.8 to 13.1 gm % over the span of 1 year (2023-24) on a scale of 5-13.2 gm % with continued transfusion support represented by crests following transfusions of 1-2 pRBCs. Also, nucleated RBCs in purple as representation of the reticulocytes that have consistently remained at zero over a 1-year period demonstrating PCRA. . In this clinical scenario, the progression of the disease (AML) with myeloablation , conditioning and SCT may explain the low erythrocytosis during the initial period. However, the continued progression to PCRA with no evidence of AML (in remission) with reticulocyte percentage of 0.1%. Is consistent with PCRA.