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How did DAT happen? A Coombs Negative Delayed Hemolytic Transfusion Reaction in a Patient with Myelodysplastic Syndrome: A Case Report

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Abstract

Delayed hemolytic transfusion reactions (DHTRs) present significant challenges in diagnosis and management despite advancements in pre-transfusion testing. We report a case of a 76-year-old female with myelodysplastic syndrome (MDS) who developed severe hemolytic anemia following a seemingly compatible blood transfusion and appropriate pretransfusion testing. Evaluation revealed characteristics consistent with DHTR. Diagnostic uncertainty arose due to a negative Direct Antiglobulin Test (DAT) in the setting of a concomitant Vitamin B-12 deficiency. She was supported with prednisone and B12 supplementation. We discuss challenges in diagnosis, including the limitation of DAT, and propose strategies for comprehensive antibody identification. The case underscores the importance of recognizing DHTR and the phenomenon of antibody evanescence, highlighting the need for a national transfusion registry to enhance patient safety. The case underscores the importance of recognizing DHTR and the phenomenon of antibody evanescence, highlighting the need for a national transfusion registry to enhance patient safety.

Keywords

Direct Antiglobulin Test, DAT Negative, Coombs Negative Hemolytic Anemia, Myselodysplastic syndrome, MDS, Coombs Negative Delayed Hemolytic Transfusion Reaction

Conflict of Interest Statement

No conflicts of interest

Cover Page Footnote

Thank you to my partner Diya for her continued support through high school, medical school, and residency - this would not be possible without your encouragement!

CASE REPORT

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Abstract

Delayed hemolytic transfusion reactions (DHTRs) present significant challenges in diagnosis and management despite advancements in pre-transfusion testing. We report a case of a 76-year-old female with myelodysplastic syndrome (MDS) who developed severe hemolytic anemia following a seemingly compatible blood transfusion and appropriate pretransfusion testing. Evaluation revealed characteristics consistent with DHTR. Diagnostic uncertainty arose due to a negative Direct Antiglobulin Test (DAT) in the setting of a concomitant Vitamin B-12 deficiency. She was supported with prednisone and B12 supplementation. We discuss challenges in diagnosis, including the limitation of DAT, and propose strategies for comprehensive antibody identification. The case underscores the importance of recognizing DHTR and the phenomenon of antibody evanescence, highlighting the need for a national transfusion registry to enhance patient safety.

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Keywords: Direct antiglobulin test, DAT negative, Coombs negative hemolytic anemia, Myelodysplastic syndrome, MDS, Coombs negative delayed hemolytic transfusion reaction

1. Introduction

Delayed hemolytic transfusions are amongst the most common complications seen in patients receiving repeated transfusions.[1] Although DHTRs are well described in literature, multiple clinical roadblocks can exist in their appropriate diagnosis and management. Despite considerable advances in cross-matching and pre-transfusion testing, it is still possible to develop these reactions due to fluctuating levels of alloantibodies in the setting of the antibody evanescence.[2] In this report, we explore a case where a patient receives cross-match compatible blood products and develops a delayed hemolytic transfusion reaction. Further, in the setting of a confounder and a negative Direct Antiglobulin test, diagnostic uncertainty arose.

2. Case

This is a 76-year-old woman with a medical history of myelodysplastic syndrome (MDS), iron deficiency anemia, and type 2 diabetes mellitus, who arrived at her outpatient hematology clinic with complaints of worsening dizziness, shortness of breath, and fatigue in the last 2 weeks. Pertinent home medications include Lenalidomide twice a week for MDS, insulin, dulaglutide, metformin, and losartan. She had no history of artificial valves and had no history of liver disease. Family history, social history, and allergy history were non-contributory.

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Her physical examination was significant for pallor but was otherwise unremarkable. Her hemoglobin was 7.5 g/ dL, a drop from her baseline of 9g/dL about 6 months prior. Her Iron panel from the previous month showed increased iron stores with Iron 126 mg/dL, ferritin 259 mg/dL, iron saturation 49%, and ferritin 442 mcg/L. Pre-transfusion testing revealed B Rh-positive blood and a positive antibody screen for Anti-Jka, Anti-M, and Anti-S alloantibodies, first noted eight months prior, during a previous trans- fusion. She was transfused with one unit of antigen- negative, crossmatch compatible blood and two weeks later, underwent esophagogastroduodenoscopy (EGD) which showed the presence of small erosions in the gastric antrum without active bleeding. Colonoscopy showed moderate diverticulosis. She was recommended to start PPIs once daily and repeat an EGD in 3 months if her blood counts did not stabilize.

Two days following the procedure, she experienced worsening dizziness, fatigue, and blurring of vision, for which she visited the ED. She denied a history of melena or hematemesis. On arrival, her vital signs were stable and examination was significant for pallor. Laboratory tests showed a hemoglobin of 5.7 g/dL, hematocrit of 17%, MCV of 113 fL, Red Cell Distribution Width (RDW) of 19.5%, Anisocytosis with macrocytosis on peripheral smear, without spherocytes or schistocytes. She had a normal coagulation profile and a normal platelet count. The hemolysis panel showed an increased LDH of 384 U/L, elevated indirect bilirubin, haptoglobin of <1, corrected reticulocyte count of 1.3%, and reticulocyte index of 0.52 (suggestive of hypoproliferation, which would be expected given her MDS). Interestingly, her Direct Antiglobulin Test (DAT) was negative. Vitamin B-12 levels were low-normal at 259 pg/mL. A presumptive diagnosis of Coombs-negative hemolytic anemia was made, thought to be secondary to either DHTR or B-12 deficiency causing intra-medullary hemolysis. She was given appropriate transfusion support throughout the admission, to maintain a hemoglobin of >8 g/dL. Prednisone 20 mg was initiated for the suspected DHTR, and daily 1000 mcg B12 injections were given. Unfortunately, her hematocrit and hemoglobin continued to drop, with worsening LDH; and the prednisone dose was increased to a 60 mg. After a few days of transfusion support, her hemoglobin began to maintain at around 7.5g/dL. She was transitioned to once- weekly B12 shots and discharged without steroid taper, given limited further suspected utility of Prednisone in DHTR. She was advised to undergo extended RBC antigen determination by genotyping. However, since discharge, the patient's hemoglobin levels remained stable, and she did not undergo further testing.

Her hemolysis panels have since been negative, with normalization of LDH and Haptoglobin levels. Bone marrow biopsy showed an unchanged grade of MDS compared to the prior biopsy. She is following up with an MDS specialist and is currently on luspatercept, which has made her less transfusion-dependent. Following this transfer of care, extended RBC antigen determination, which is usually recommended in these situations to identify the causative low-frequency antigen, was deferred for unclear reasons.

3. Discussion

DHTR must be considered in the differential diagnosis when patients present with an acute drop in hemoglobin within 21 days of transfusion.[3] Along with a fall in hematocrit from baseline, markers of hemolysis include an increase in LDH and indirect bilirubin, increased reticulocyte count, and a drop in haptoglobin.[4] The true incidence of DHTR remains unknown, partly due to the lack of mandated reporting of nonfatal transfusion reactions in the US.[5] DHTRs are usually seen in patients who have developed alloantibodies from prior transfusions. The prevalence of alloimmunization among this population is wide and is estimated at a range between 1:800 to 1:11,000. However, these rates have decreased recently, as more sensitive RBC antibody screening assays have become accessible.[6] Despite the decreasing incidence of alloimmunization, DHTR remains among the most common complications seen in patients who receive repeated blood transfusions.[1]

A positive Direct Antiglobulin Test (DAT) or Coombs test is typically expected for immune-mediated hemolytic reactions.[7] However, in our patient, the DAT was negative despite other hemolysis markers. Literature indicates that DAT is positive in only 75% of DHTR cases. A negative DAT does not rule out DHTR.[8] This is thought to be due to the clearance of antibody-coated erythrocytes or antibody levels below the DAT detection threshold.

Another confounding factor was the patient's[8-10] borderline Vitamin B-12 level of 259 pg/mL, as B-12 deficiency can cause intramedullary hemolysis. While a Vitamin B-12 level below 200 pg/mL has a high sensitivity for diagnosing true deficiency, levels between 200 and 300 pg/mL are less definitive and should not confirm a diagnosis without symptoms or a high pre-test probability.[11-14] In this case, the lack of glossitis, neuropathy, and megaloblasts in bone marrow studies, alongside a normal peripheral smear, suggested that B-12 deficiency was not the cause of hemolysis.

Given the likely DHTR diagnosis, treatment options for DHTRs are broadly classified into supportive care including appropriate blood transfusions, erythropoiesis optimization through agents like erythropoietin, immunomodulator therapies like corticosteroids and rituximab, and minimizing future transfusions if possible.[15] In this case, transfusion support was used to maintain hemoglobin levels of >7 g/dL. Although specific guidelines for DHTR treatment in the context of myelodysplastic syndromes (MDS) do not exist, hematology consultation and potential immunosuppressant use are advised. However, evidence supporting immunosuppression in DHTR management is weak, despite its established role in autoimmune hemolytic anemia.[15]

The development of an immune-mediated hemolytic reaction despite receiving crossmatch-compatible blood raises questions. Alloantibody screens before transfusion aim to detect alloantibodies, but these antibodies can fluctuate, sometimes becoming undetectable -a phenomenon known as evanescence.[16] Our patient likely had alloantibodies that evaded detection. In these situations, the patient is usually advised to undergo extended antibody identification with a low-frequency antigen RBC panel.[17] As this testing was deferred in this patient for unclear reasons, the culprit alloantibody is yet to be identified. Once identified, antibodies persist in the recipient's blood for life, necessitating the selection of donor blood free of these antigens regardless of current pretransfusion testing results.[18] One report showed that 81% of patients with known alloantibodies, had at least one undetectable antibody, which was later detected by RBC elution methods. Therefore, if a unit of blood is transfused in a facility unaware of the patient's antibody history, it puts the patient at risk of developing a life-threatening transfusion reaction. This underlines the need for a national registry for alloantibodies, as is present in other countries, wherein this data would be freely available, and tied to the patient's chart.[19] Countries like the Netherlands, which have successfully implemented such a registry, can do so as they work in conjunction with private blood banking companies that supply a large number of hospitals. Proposals for such registries are in place in the United States and are receiving strong national support for their establishment.[20]

4. Conclusion

DAT can often be negative in patients with DHTR, and a negative DAT cannot be used to exclude a diagnosis of immune-mediated hemolytic anemia. Antibody identification with a low-frequency antigen RBC panel must be performed in patients who develop an immune-mediated hemolytic reaction despite transfusion of appropriately cross-matched blood products. The phenomenon of evanescence and evasion of antibody detection in pretransfusion testing underlies the need for a national transfusion registry wherein antibody data for patients would be updated and available.

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Author contributions

Conception and design: Aniket Vijay Rao, Nagesh Jadhav. (II) Administrative support: Nagesh Jadhav, Basil Verghese. (III) Provision of study materials or patients: Aniket Vijay Rao. (IV) Collection and assembly of data: Aniket Vijay Rao, Aditya Sanjeevi, Daniel Jose Idoate Domench, Himal Kharel. (V) Data analysis and interpretation: Aniket Vijay Rao, Aditya Sanjeevi, Daniel Jose Idoate Domench, Himal Kharel. (VI) Manuscript writing: All authors. (VII) Final approval of manuscript: All authors.

Conflicts of interest

None.

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