

DOI: 10.21767/2471-8041.100120

Allogeneic ABO-Mismatched Blood for Transfusion of Cold Antibody Autoimmune Hemolytic Anemia: A Case Report and Literature Review

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Received: July 10, 2018; Accepted: August 25, 2018; Published: August 27, 2018

Citation: Fen Ma P, Zhao G, Wang MF, Liang Li L, Yun Zeng P, et al. (2018) Allogeneic ABO-Mismatched Blood for Transfusion of Cold Antibody Autoimmune Hemolytic Anemia: A Case Report and Literature Review. Med Case Rep Vol.4 No.3: 84.

Abstract

Autoimmune hemolytic anemia (AIHA) is defined as the increased destruction of red blood cells (RBCs) in the presence of anti-RBC autoantibodies and/or complement. Here in, we describe the case of a 52-year-old male patient who was admitted to our hospital, and was diagnosed with non-Hodgkin peripheral T-cell lymphoma and cold antibody autoimmune hemolytic anemia (extremely severe). He's hemoglobin decreased progressively after he was admitted, and he developed dyspnea. He also had continuous abdominal discomfort with nausea lasting 20 days. The patient reported abdominal discomfort with no obvious cause starting 20 days before admission, with nausea, vomiting, and poor appetite. In this case report we describe a case of a 52-year-old male patient who had allogeneic ABO-mismatched blood for transfusion of cold antibody autoimmune hemolytic anemia.

Keywords: Cold antibody; Autoimmune hemolytic anemia; Allogeneic blood transfusion; T-cell lymphoma

difficult to find matched blood. High-dose glucocorticoid therapy in combination with gamma globulin did not alleviate the patient's anemic symptoms. According to the 2014 Guideline for Emergency Transfusion under Special Conditions, group O RH positive washed red blood cells that had been heated to around 37°C, all by slow infusion with sodium bicarbonate solution intravenously. In total, the patient received 3 rounds of mismatched blood transfusions. During the process of transfusion and after transfusion, the patient did not exhibit any transfusion-related complications, like chills, fever, rash, lower back pain, dark urine, or other symptoms.

Case Report

A 52-year-old male patient was admitted to our hospital for continuous abdominal discomfort with nausea lasting 20 days. The patient reported abdominal discomfort with no obvious cause starting 20 days before admission, with nausea, vomiting, and poor appetite. The patient said he had no other symptoms such as hematemesis, melena, heartburn, diarrhea, constipation, fever, lower back pain, or hematuria. He reported weight loss of 5 kg over the previous 20 days.

His past history included an injury related to a car accident that required a blood transfusion. The patient was not able to recall the amount of blood he received.

Upon physical examination, the patient's vital signs were normal. No jaundice was noticed, and the palpebral conjunctiva appeared pale. Multiple bilateral enlarged lymph nodes were palpated in the submandibular, cervical, and axillary areas, with medium firmness and no tenderness. The patient's abdomen was flat. No peristalsis or engorged veins were noted. We noted upper abdominal tenderness upon palpation but no rebound tenderness or muscle resistance. No mass was palpated. The liver and spleen were not palpable below the rib cage. Murphy's sign was negative. No percussion tenderness was elicited in the liver or kidney areas. No shifting dullness was observed, and bowel sounds were normal. Laboratory results at admission were white blood cells (WBC)

Introduction

A male patient was diagnosed with non-Hodgkin peripheral T-cell lymphoma and cold antibody autoimmune hemolytic anemia (extremely severe). He's hemoglobin decreased progressively after he was admitted, and he developed dyspnea. Emergency cross matching was ordered, and the patient received 3.5 units of group A RH positive red blood cells. The patient's dyspnea was alleviated after the transfusion. A blood transfusion was planned but multiple cross match tests failed to find a match. The Central Blood Station suggested a diagnosis of cold antibody autoimmune hemolytic anemia. The patient had received a blood transfusion 1 year previously, and these large-volume repeated transfusions can produce irregular antibodies resulting in it

count $16.33 \times 10^9/L$, neutrophil (NE) levels 86%, lymphocyte levels 7%, red cell count (RBC) $2.72 \times 10^{12}/L$, hemoglobin (Hb) 88 g/L, hematocrit (Hct) 0.263 L/L, and platelets (PLT) $169 \times 10^9/L$; fecal occult blood was weakly positive. Liver function tests showed direct bilirubin 13.2 $\mu\text{mol}/L$, indirect bilirubin 8.8 $\mu\text{mol}/L$, and albumin 36.4 g/L. Ferritin was 1294.00 ng/ml (normal range is 30–400 ng/ml), folic acid 1.85 ng/ml (normal range is 3.1–17.5 ng/ml), and vitamin B-12 195.60 pg/ml (normal range: 243–894 pg/ml). Abdominal CT revealed the following: 1. Bilateral pleural effusion; 2. multiple nodules around abdominal aorta suggesting enlarged lymph nodes; 3. multiple hypodense lesions in the spleen suggested splenic infarction; 4. peritoneal effusion. Portal vein phase CT revealed 1. bilateral pleural effusion, incomplete atelectasis in the lower lobes of both lungs; 2. multiple enlarged lymph nodes in portal, mesenteric and retroperitoneal area; 3. splenomegaly and splenic infarction; and we suspected lymphoma. Abdominal ultrasound revealed enlarged lymph nodes that were shown as multiple hypoechoic area around the pancreatic head; splenomegaly; and peritoneal effusion. Neck ultrasound suggested multiple bilateral enlarged lymph nodes as indicated by multiple hypoechoic areas in the parotid and submandibular glands on both sides. Lower limb ultrasound revealed multiple bilateral inguinal lymph node enlargements. Gastroscopy, colonoscopy, and cardiac and renal ultrasound were normal. The patient received lymph node biopsy because his CT and ultrasound reports revealed multiple lymph node enlargements. The patient's hemoglobin decreased progressively to 52 g/L after he was admitted. On November 24, 2016, the patient developed dyspnea. His hematological values were RBC $1.19 \times 10^{12}/L$, Hb 40 g/L, and Hct 0.118 L/L. Emergency cross matching was ordered and the patient received 3.5 units of group A RH positive red blood cells. The patient's dyspnea was alleviated after the transfusion. Another hematological test was performed the next day and revealed RBC $1.55 \times 10^{12}/L$, Hb 53 g/L, and hematocrit 0.158 L/L. A blood transfusion was planned but multiple crossmatch tests failed to find a match. Therefore, a crossmatch test was requested to be done by the Central Blood Station of Gansu Province. The results were as follows: in the major crossmatch test of the blood samples from the patient and donors, early agglutination occurred during the saline phase, while no agglutination or hemolysis occurred during the antihuman globulin phase. This suggested a diagnosis of cold antibody autoimmune hemolytic anemia (AIHA) and the Central Blood Station recommended that blood transfusion be avoided because it might trigger life-threatening, severe hemolysis.

For this reason, the patient was treated with high-dose glucocorticoid therapy in combination with human immunoglobulin. Comprehensive examinations were also performed to establish the causes of AIHA. During the immunologic test, only cANCA and PR3 were found to be positive, and they had low titers. Bone marrow aspiration indicated acute hematopoietic stagnation. Lymph node biopsy results showed complete destruction of the lymph node structure; subcortical proliferation and cortical invasion of atypical lymphocytes of different sizes; increased numbers of small blood vessels and various inflammatory cells in the

interstitium; and incomplete follicular dendritic network. Immunohistochemistry showed tumor cells to be CD3+, CD43+, CD20-, CD79a-, CKpan-, and Ki67>70%; histocytes were CD68+ and CD21+. The patient was then diagnosed with non-Hodgkin peripheral T-cell lymphoma (not otherwise specified). After the aforementioned treatment, the patient's anemia persisted without significant improvement. Blood tests revealed RBC $0.57 \times 10^{12}/L$, Hb 23 g/L, Hct 0.061 L/L, PLT $133 \times 10^9/L$. Cross-matching blood was not observed, even after multiple crossmatch tests. On December 8, 2016, the emergency transfusion protocol had to be implemented due to the patient's critical condition. The patient's blood type was type A, RH-positive. After dexamethasone was administered, 1.5 u of group O, RH-positive washed red blood cells prewarmed to 37°C were slowly transfused into the patient with sodium bicarbonate solution intravenously. The transfusion went smoothly and did not trigger chills, fever, rash, lower back pain, dark urine, or other symptoms. After the patient received the transfusion, his shortness of breath was alleviated. He received COP chemotherapy the next day, and his blood test returned RBC $1.02 \times 10^{12}/L$, Hb 35 g/L, and Hct 0.103 L/L. On December 10, 2016, the patient presented with drowsiness, confused speech, and urinary and fecal incontinence. He was again transfused with 1.5 u group O, RH-positive washed red blood cells without complications. On December 11, 2016, the hematologic test results were RBC $0.65 \times 10^{12}/L$, Hb 30 g/L, and Hct 0.065 L/L. The patient was then given another 1.5 u group O, RH-positive washed red blood cells. The patient's symptoms continuously grew worse. The patient decided, along with his family, to forego further treatment due to financial difficulties and was then discharged. He died on December 18, 2016. In total, the patient received 3 rounds of mismatched blood transfusions; that is, a total of 4.5 u group O, RH-positive washed red blood cells. During the process of transfusion and after transfusion, the patient did not exhibit any transfusion-related complications, like acute hemolysis.

Diagnosis and Treatment

The diagnosis of the patient is clear:

1. Non-Hodgkin peripheral T-cell lymphoma (not otherwise specified);
2. Acute hematopoietic stagnation;
3. Cold antibody AIHA (extremely severe).

Diseases of the immune system were not considered to be the cause of AIHA even though cANCA and PR3 tests were positive, because the antibody titers were low. The patient had received a blood transfusion 1 year previously, and this large-volume blood transfusion may be related to AIHA. The diagnosis of lymphoma was clear and the AIHA was principally attributed to lymphoma. High-dose glucocorticoid therapy in combination with gamma globulin, a treatment targeting AIHA, did not alleviate the patient's anemic symptoms. A prewarmed mismatched blood transfusion was then performed due to the patient's critical condition and went on smoothly without triggering any transfusion related complications.

Discussion

Autoimmune hemolytic anemia (AIHA) is a group of hemolytic conditions caused by autoimmune dysfunction in which the body produces autoantibodies against erythrocytes or complements, resulting in accelerated red blood cell destruction. The incidence of AIHA is 0.8%–3.0% with a mortality rate of 11% [1]. AIHA is classified as either primary or secondary based on the identification of a secondary cause. Common causes of secondary AIHA include connective tissue disease, lymphoproliferative disease, and infection [2]. According to the thermal range of the antibodies, AIHA is divided into warm, cold, and mixed antibody types. Cold antibody AIHA includes cold hemagglutinin syndrome (CAS) and paroxysmal cold hemoglobinuria (PCH). Cold antibody AIHA is relatively rare, accounting for approximately 10% to 20% of AIHA [3].

CAS is commonly secondary to malignancies and infections, of which lymphoma is the most common malignancy and mycoplasma pneumoniae infection is the most common infectious disease. Chronic lymphocytic leukemia/small lymphocyte lymphoma (CLL/SLL) and vascular immunoblastic T cell lymphoma (AITL) are common causes of secondary AIHA. Follicular lymphoma, marginal zone lymphoma, lymphoblastic lymphoma, diffuse large B-cell lymphoma, and interstitial large cell lymphoma have also been reported [4-8]. Studies show that AIHA is related to the abnormal proliferation and apoptosis of clonal B cells with CD5 expression [9]. Recent clinical research has indicated that T cell dysfunction may play more important roles in AIHA pathogenesis. One recent work observed 5 cases positive under the Coombs test among 40 ATL patients [10]. Palla et al. found that 7 out of 78 T cell lymphoma patients developed AIHA, which indicated that T cell lymphoma patients are more prone to developing AIHA than the general population [11]. In this case study, the patient's diagnosis of non-Hodgkin peripheral T cell lymphoma is clear. The patient's RBC count progressively decreased during his hospital stay. The diagnosis of cold antibody AIHA is also clear. Based on the examinations results, infection and immune system diseases were excluded and the patient's AIHA was attributed to T cell lymphoma.

Current treatment for cold antibody AIHA is unsatisfactory. The common strategies include keeping the patient warm, corticosteroids, immunosuppressive drugs, intravenous globulin, plasma exchange, and rituximab [12]. For CAS secondary to malignancies or infectious disease, no evidence-based therapy is currently available. In general, treatment of underlying diseases is accompanied by improved hemolysis, especially in patients with lymphoproliferative diseases and mycoplasma pneumonia [13]. Because most cold AIHA patients only present with chronic mild hemolysis and the antibody is highly reactive to human RBC at 0–5°C, they normally do not need to drug or other treatment except for taking measures to keep warm so as to avoid cold-triggered enhanced autoantibody responses [3]. When the patient is in serious condition, rituximab-based treatment is the main first-line treatment and it can reach an efficacy of 50% to 60%. However, glucocorticoid and immunosuppressive drugs are

less effective for cold-antibody AIHA than for warm-antibody AIHA, and they are only effective in a small number of patients [14]. Plasma exchange exerts only temporary effects and does not generate long-lived efficacy [15]. Because, in cold antibody AIHA, the red blood cell clearance is complement-conditioned and first occurs in the liver. Splenectomy is usually considered an ineffective treatment for cold antibody AIHA [16]. Only limited data are available regarding the use of intravenous immunoglobulin for CAS. At present, immunoglobulin is considered ineffective for cold antibody AIHA.

In general, blood transfusions are not recommended for AIHA patients. If severe anemia persists in spite of other active regimens, blood transfusion may be given. But repeated blood transfusions pose a great obstacle to later treatment because repeated transfusions can produce irregular antibodies. Influenced by the serological characteristics of blood groups, these irregular antibodies can be easily disguised by autoantibodies and escape detection, resulting in hemolytic transfusion reaction. Meanwhile, the existence of autoantibodies and irregular antibodies can also affect crossmatch testing and make it difficult to find matched blood. Washed red blood cells should be used for transfusion to reduce the possibility of reaction. The red blood cells should be infused slowly, if possible, at a rate of less than 1 ml/kg/h. Glucocorticoid can be infused at the same time. Blood should be warmed up to 37°C before infusion to patients with cold AIHA [3,15].

To date, several research groups have reported using allogeneic mismatched blood transfusion to treat emergent and critical patients. When crossmatch tests fail to find a matching donor in the event of an emergency, the emergency blood transfusion protocol can be implemented, and the patient can be given allogeneic mismatched blood components. Research has shown that using allogeneic mismatched blood transfusions to treat critical patients during special circumstances is practical in clinical settings [17,18].

There are currently no reports about using mismatched blood to treat cold antibody AIHA. In our case, the patient displayed progressive decreases in red cell count after admission. His first crossmatch test was negative, and he received blood-type-matched red blood cells. However, all following crossmatch tests came back positive. We think this is because of his previous history of large-volume blood transfusions: The patient produced a great deal of auto antibodies in his blood.

Conclusion

Based on the test results, we concluded that the patient's anemia was caused by cold antibody AIHA and decided that replenishing his red blood cells via blood transfusion would not be suitable. We instead administered glucocorticoid in combination with immunoglobulin, but the patient's symptoms did not improve. His Hb still decreased progressively. According to the 2014 Guideline for Emergency Transfusion under Special Conditions, group O cells should be given to patients whose crossmatch tests come back positive.

In our case, the patient received intravenous infusion of 2 g sodium bicarbonate dissolved in 120 ml sodium chloride, and Group O RH positive washed red blood cells that had been heated to around 37°C, all by slow infusion. Dexamethasone was also administered before infusion to prevent allergic reaction. The transfusion went on smoothly without triggering any transfusion reaction symptoms like chills, fever, rash, lower back pain, or dark urine. The following mismatched blood transfusions also did not trigger any obvious transfusion reactions. This observation suggests that strategic allogeneic mismatched blood transfusion can be used for cold antibody AIHA patients whose crossmatch tests are positive. This is because, in cold antibody AIHA patients, the optimal temperature for the antibody to react with human red cells ranges from 0–5°C, and prewarming blood products before infusion can reduce the incidence of hemolysis induced by autoantibodies. To reduce the renal damage caused by hemolysis, clinicians should also consider using alkalized blood products.

Acknowledgements

We express our heartfelt thanks for the strong support of all the medical staff from department of hematology and the Second Hospital of Lanzhou University.

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