DELAYED HEMOLYTIC TRANSFUSION REACTION IN SICKLE CELL DISEASE

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Abstract

Delayed hemolytic transfusion reactions (DHTR) are potentially life-threatening complications observed in patients with sickle cell disease. We review the clinical features, pathophysiology, laboratory evaluation, and management of this complication. It is important that DHTR be included in the differential diagnosis of acute pain episodes following a red blood cell transfusion in a patient with sickle cell disease.

Keywords

Sickle Cell Disease; Transfusion Reaction; Delayed Hemolytic Transfusion Reaction

Background

Sickle cell disease (SCD), including sickle cell anemia and the various compound heterozygote genotypes, is characterized by the presence of a chronic hemolytic anemia and vaso-occlusive complications. Recently, the clinical manifestations of SCD have been described to fall into two partially overlapping sub-phenotypes: hemolytic and vaso-occlusive sub-phenotypes.[1] As a result of its associated complications, patients with SCD frequently require red blood cell (RBC) transfusion therapy.[2, 3] RBC transfusion therapy is an important treatment modality in patients with SCD. It is generally indicated to increase oxygen carrying capacity or to improve the rheological properties of blood in these patients.[3] Patients may benefit from simple or exchange RBC transfusion to ameliorate or prevent a myriad of SCD-associated complications. Absolute indications for transfusion in SCD are few, and may include new neurologic symptoms including stroke, acute splenic or hepatic sequestration crises, aplastic crises, or hemodynamic/cardiovascular compromise.[3] The hemoglobin concentration, by itself, should not be considered a reason for transfusion.[3] This is because patients with SCD routinely have relatively low hemoglobin values and most of these patients tolerate their anemia quite well.

The exposure to multiple RBC transfusions increases the likelihood of complications of such therapy. In addition to the risks of infectious complications and iron overload, SCD patients may develop delayed hemolytic transition reactions (DHTR) frequently related to alloimmunization,[2, 4] a serious complication due to the development of clinically significant antibodies to RBC antigens. DHTR represents an important and potentially life-threatening complication of RBC transfusion in patients with SCD.

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In this review, we present a synthesis of the current understanding of risk factors for alloimmunization, as well as the clinical presentation, pathophysiology, appropriate laboratory investigation, and clinical management of DHTR in SCD.

Prevalence of Alloimmunization and Risk Factors

Because RBC transfusion in SCD patients is associated with multiple complications, judicious use of transfusion therapy is especially important. A detailed discussion of these complications is beyond the scope of this paper. Among these complications is an increased rate of alloimmunization compared with other chronically transfused populations.[2, 4] The rate of alloimmunization in SCD has been reported to be as high as 19% to 47% in adult patients.[3, 5–7] Antibodies may become rapidly undetectable in a substantial number of patients,[4] which may result in an underestimation of the prevalence of this complication.

Alloimmunization appears to be related to the number of RBC transfusions received, older age at time of first transfusion, and gender, with women having a higher rate than men, in large part due to more frequent transfusions in women.[7] In patients with SCD, racial differences between recipient (predominantly African-Americans) and donor (predominantly Caucasians) expression of RBC antigens are thought to contribute to the increased risk of alloimmunization. [8, 9] In a report comparing red cell phenotypes of African-American patients and blood bank donors, donors had a significantly greater incidence of the antigens E, C, Kell, Fy^a, Fy^b, and Jk^b.[8]

It remains unclear why some patients mount strong alloantibody responses following initial RBC transfusions, while others do not despite multiple transfusions. Associations of HLA types with alloimmunization in multiply transfused SCD patients have been described.[10, 11] More recently, a case-controlled study demonstrated associations of alloimmunization with particular HLA subtypes.[12] The HLA-DRB1*1503 allele was associated with an increased risk of alloimmunization (OR 2.02, p=0.039), while the HLA-DRB1*0901 allele appeared to confer protection from developing alloantibodies (OR 0.13, p=0.008). There is some evidence in murine models that inflammation plays a complex regulatory role in RBC alloimmunization. [13] With the abundant evidence that SCD is characterized by chronic inflammation,[14, 15] it is possible that inflammation may play a role in the high rate of alloimmunization observed in these patients. However, there are, to date, no published data in SCD patients.

Clinical features

The clinical presentation of a DHTR in SCD may be quite similar to that of a sickle cell pain crisis, with or without features of an "aplastic crisis." [6, 16–18] As a result, the diagnosis of a DHTR may be delayed because the anemia and pain are attributed to a pain crisis with "hyperhemolysis." Indeed, the components of the sickle cell hemolytic transfusion reaction syndrome have been described (Table 1).[19] In addition to the manifestations of acute or delayed hemolysis, patients typically exhibit symptoms of a pain crisis, marked reticulocytopenia (a decrease from the patient's usual absolute reticulocyte count), and may develop a more severe anemia following transfusion than was present before.

In light of these clinical features, it is important to include DHTR in the differential diagnosis of any SCD patient presenting with features of a typical or atypical pain episode and to inquire about recent transfusion history, particularly in patients who were recently hospitalized. Although patients often have multiple RBC alloantibodies or autoantibodies making it difficult to find compatible RBC units, occasionally no alloantibodies may be detected and serologic studies may not provide an explanation for the DHTR. As patients recover, they exhibit a reticulocytosis and improvement in hemoglobin.[19]

Pathophysiology

The mechanism of the worsening anemia that occurs following RBC transfusion remains controversial (Table 2). By performing a hemoglobin electrophoresis, it is easy to show that donor RBCs are often completely destroyed. The reason for this is obvious when new antibodies directed against the transfused units are observed. However, alloantibodies may not be detected at the time of the DHTR, may become detected later, or may never be detected.[6] The worsening anemia probably represents a combination of hemolysis of transfused cells, hyperhemolysis related to the immunologic response, and suppression of erythropoesis.[19–22]

The so-called "bystander hemolysis" may be a major mechanism in DHTR in SCD. In this situation, one observes immune hemolysis of RBCs that are negative for the antigen against which the relevant antibody is directed.[21] Bystander hemolysis during DHTR may occur following activation of complement as a result of the reaction of alloantibodies with transfused RBCs or other antibody reactions with transfused foreign antigens, leading to the attachment of activated complement components to autologous RBCs.[6]

The suppression of erythropoeisis that accompanies transfusion may also contribute to the increased anemia observed following a DHTR.[19] Marked reticulocytopenia is not always a feature of DHTR,[18, 23] although many patients have reticulocyte counts that are lower than their baseline values. As patients with SCD have a shortened RBC survival, suppression of erythropoiesis has a profound effect on hemoglobin concentration compared to patients with normal red cell lifespan. Based on the finding of erythroid hyperplasia on a bone marrow aspirate during a DHTR, a more recent case report suggests that the observed reticulocytopenia during the course of a DHTR is not due to suppression of erythropoiesis, but rather is likely due to peripheral consumption.[22] While no experimental data were provided, the authors postulated that the increased RBC destruction and reticulocytopenia during DHTR may be due to the hyperactivity of macrophages.

The exposure of phosphatidylserine (PS) in RBC has recently been reported to be significantly increased following the incubation of donor RBC with pre-transfusion plasma samples from SCD patients who develop DHTR compared to other SCD patients who do not develop this complication.[24] Furthermore, the exposure of PS in RBC progressively increased in patients with DHTR, particularly when donor erythrocytes were completely destroyed. As PS exposure is a signal for apoptosis, this increased RBC PS exposure may contribute to the increased hemolysis observed during DHTR.[25] The role of PS in RBC adhesion to endothelium may also, at least in part, explain the severe pain episodes observed during DHTR.[26]

Diagnosis

The diagnosis of DHTR is based on an appropriate history and laboratory testing. A DHTR should always be in the differential diagnosis whenever a patient with SCD presents with symptoms consistent with a pain crisis and decreasing hemoglobin approximately 5–10 days following a transfusion of RBC. In addition to a complete blood count with reticulocyte count, laboratory evaluation should include an antibody screen (indirect antiglobulin test) and direct antiglobulin test to detect new RBC alloantibodies and/or autoantibodies, chemistries such as serum bilirubin (total and indirect) and lactate dehydrogenase to assess for increased hemolysis, and a urine sample to evaluate for hemoglobinuria. Inability to identify a new antibody does not exclude the diagnosis of a DHTR, and in many cases, the antibody screen remains negative. [20] A hemoglobin electrophoresis is also helpful in establishing the diagnosis of a DHTR. Hemoglobin electrophoresis often demonstrates total or near total destruction of donor erythrocytes, indicated by a lack of hemoglobin A in the specimen.[6]

Management

There are no controlled studies that define the optimal treatment for DHTR in SCD. Whenever a DHTR is suspected, further RBC transfusion should be withheld unless absolutely necessary, as it may precipitate acceleration of the hemolytic reaction. The volume and frequency of blood draws should be minimized. High dose steroids appear to be important [20] and for complicated cases, IVIG should be considered, usually with the supervision of a hematologist. We have also used high doses of erythropoietin, although baseline levels are likely to be elevated in patients with normal renal function. Pain episodes and other complications associated with DHTR should be treated as required.

Immune-modulating medications provide an exciting possibility for new modalities of prevention for DHTR. Although clinical trials are lacking, a case report presented a patient with three prior episodes of DHTR for whom rituximab, a monoclonal antibody that targets B cells by binding CD20, allowed successful transfusion.[27] This will likely be an active area of research in upcoming years.

Minimizing RBC transfusion and the use of more extensive phenotypic matching of blood, particularly the Rh and Kell blood group systems,[28] when transfusion is required are essential to decrease the risk of alloimmunization.[7, 29] Although this is costly, transfused patients should receive at the minimum, leukocyte-reduced RBC units that are E-, C-, and Kell-negative.[2, 3, 28, 30]

RBC transfusion can increase blood viscosity to a greater degree in patients with SCD than in normal patients, thereby paradoxically decreasing the oxygen-carrying capacity at some levels. [2] As a result, every effort should be made to ensure that post-transfusion hemoglobin levels do not exceed 10–11g/dL. Finally, patients should be educated about DHTR, providing them with a letter (or card) that explains this complication and listing any known alloantibodies, so that unnecessary transfusions are avoided by medical providers who are otherwise not familiar with the patient's medical history.

Conclusions

DHTR is an important complication of transfusions in SCD and should be considered whenever a patient with SCD presents approximately 5–10 days after a transfusion with a decreasing hemoglobin level and symptoms consistent with a pain crisis. It appears to result from a destruction of transfused cells, suppression of erythropoiesis, and destruction of autologous red cells. Further research on genetic associations with DHTR will likely provide considerable help in elucidating risk factors, and perhaps information on the pathogenesis, of this syndrome. The early identification of patients likely to develop alloantibodies could lead to focused, cost-effective transfusion strategies by limiting the use of phenotypically matched RBCs to those at greatest risk. Once a DHTR is suspected, further RBC transfusion should be withheld, unless absolutely necessary. The optimal treatment for DHTR is not defined. However, many patients appear to respond to treatment with high-dose steroids, with or without intravenous immunoglobulin. More studies are needed to define the optimal treatment for this life-threatening complication in SCD.

Acknowledgments

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Table 1

Components of Delayed Hemolytic Tranfusion Reactions[*]

Clinical Presentation

Manifestations of an acute or delayed hemolytic transfusion reaction

Symptoms suggestive of a sickle cell pain crisis associated with the hemolytic transfusion reaction

Diagnosis

Reticulocytopenia/fall from the patient's baseline reticulocyte count

Development of a more severe anemia after transfusion than was present before it.

Serologies may not provide an explanation for the hemolytic reaction (i.e., no mismatch of blood products or new alloantibody may be demonstrated)

Clinical Management

Further transfusion can worsen the anemia

Finding compatible units of RBCs may be challenging because of multiple alloantibodies or coexisting autoantibodies. Some patients do not have demonstrable alloantibodies or are easy to crossmatch.

Recovery of reticulocytosis and increasing RBC counts may only occur if transfusion is withheld. Steroids are important therapies in some patients.

Follow-up/Future Management

After recovery, further transfusion may cause recurrence of delayed hemolytic transfusion reaction.

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[*] Adapted from Petz L, Calhoun L, Shulman I, et al. The sickle cell hemolytic transfusion reaction syndrome. *Transfusion*. 1997;37:382–392.

Table 2

Proposed Mechanisms for Development of More Severe Anemia Following Transfusion

Proposed Mechanism	Reference
1. Suppression of erythropoiesis	Petz et al, 1997
2. Immune-mediated destruction of autologous red cells ("bystander hemolysis)	King et al, 1997
3. Destruction by hyperactivated macrophages	Win et al, 2001
4. Increased RBC exposure of phosphatidylserine	Lang et al, 2005