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Case Report

"Irony" of managing refractory anemia with transfusional support in hemophagocytic lymphohistiocytosis

Sunyoung Lee [a], Ilnaz Salehi [a], Michael Chary [b], Thomas Schiano [c], John O. Mascarenhas [d,*]

[a] Department of Medicine, Elmhurst Hospital Center, Icahn School of Medicine at Mount Sinai, Elmhurst, New York 11373, USA
[b] Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA
[c] Division of Liver Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA
[d] Tisch Cancer Institute, Division of Hematology and Oncology, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening derangement of the immune system in which host macrophages phagocytose the patient's own blood cells. Herein, we present the case of a patient with HLH and associated refractory anemia who developed rapid iron deposition in the liver after transfusion of sixteen units of packed red blood cells (RBCs). Before transfusion, neither a liver biopsy nor computed tomography scan demonstrated iron deposition in the organ parenchyma. After receiving sixteen units of packed RBCs, liver iron concentration rose to 6.7 mg/g dry weight, which is highly unusual in other diseases requiring transfusional support.

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive disorder arising from the uncontrolled activation and derangement of the immune system with dysregulated phagocytosis of blood cells by macrophages [1]. Primary HLH is principally encountered in the pediatric population and associated with specific genetic mutations, while secondary HLH occurs most often as a result of immune system derangement secondary to infections, side effects of immune system-modulating medications, autoimmune diseases, malignancies, or rheumatologic diseases [2,3]. HLH is diagnosed when a patient meets five out of eight criteria [4]: (1) fever > 38.5C, (2) splenomegaly, (3) peripheral blood cytopenias, (4) triglyceride > 265 mg/dL and/or fibrinogen < 150 mg/L, (5) biopsy evidence of hemophagocytosis, (6) low or absent natural killer cell activity, (7) ferritin > 500 ng/mL, and (8) soluble interleukin-2 receptor (CD25) > 2400 U/mL. In particular, patients with HLH have significantly elevated serum ferritin levels and transferrin saturation. It has been reported that a ferritin level > 10,000 ng/mL is 90% sensitive and 96% specific for the diagnosis of HLH. This is likely a consequence of the pathophysiology of HLH involving both a severe degree of inflammation and the release of iron from dysregulated erythrophagocytosis of red blood cells (RBCs) [5–7].

An adult man contains approximately 3–4 g of iron, and a pre-menopausal woman has a lower total iron content due to menstruation; iron is found predominantly in the form of hemoglobin in RBCs [8]. Patients with myelodysplastic syndrome (MDS), leukemias, sickle cell disease, and beta-thalassemia major often depend on chronic RBC transfusions [9]. These patients can require 10–20 units of RBC transfusions a year (each unit contains 200–250 mg of iron) [8], retaining a large amount of iron as the human body lacks a physiological mechanism of removing excess iron [10]. The catabolism of RBCs is mediated by macrophages in the reticuloendothelial system, but macrophages cannot store excreted iron beyond the limit of their own storage capacity.

* Corresponding author. Tisch Cancer Institute, Division of Hematology and Oncology, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. Tel.: +1-212-241-6756; fax: +1-212-876-5276.
E-mail address: john.mascarenhas@mssm.edu (J.O. Mascarenhas).

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At this stage, extra iron termed nontransferrin bound iron (NTBI) starts to deposit and causes complications by generating free radical oxygen species in the liver, heart, and endocrine tissues [11,12].

Herein, we report a unique case of a patient with HLH and associated severe refractory anemia who rapidly developed an iron overload state from RBC transfusions. A very high transferrin saturation and aggressive catabolism of transfused RBCs associated with HLH seems to trigger more rapid iron deposition in the liver and a higher liver iron concentration (LIC) than in other diseases that also require transfusional support. This case demonstrates the irony of managing refractory anemia with transfusional support because patients with HLH seem to be more susceptible to developing a rapid iron overload state.

2. Case report

A 44 year-old woman without a significant past medical history presented to the emergency department with two weeks of fatigue, fever, and jaundice. On admission, she was found to be tachycardic to 125/min and febrile to 102.5 F with a blood pressure of 153/73 mmHg. Physical examination revealed severe jaundice and hepatosplenomegaly. A complete blood count showed a white blood cell count of 3800/μL (differential of neutrophils 78%, lymphocytes 12.0%, monocytes 6%, and band cells 4%), hemoglobin of 8.4 g/dL, mean corpuscular volume of 85.0 fL, and platelets of 35,000/μL. Additional laboratory evaluation revealed iron 138 μg/dL, ferritin 4170 ng/mL, and transferrin saturation 93%. Liver chemistry tests demonstrated an aspartate transaminase (AST) 123 U/L, alanine transaminase (ALT) 191 U/L, gamma-glutamyl transpeptidase (GGT) 57 U/L, lactate dehydrogenase (LDH) 1310 U/L, total bilirubin 20.7 U/L, conjugated bilirubin 18.7 U/L, alpha-fetoprotein 88.3 ng/mL, and triglycerides 384 mg/dL. Computerized tomography (CT) of the abdomen and pelvis with intravenous contrast revealed hepatosplenomegaly with a 4.7 cm hemangioma, and there was no specific evidence of iron deposition noted in the liver or pancreas (Fig. 1A).

The patient was admitted and started on broad spectrum antibiotics (vancomycin, cefepime, and metronidazole) to treat an infection of unknown origin. A transjugular liver biopsy was performed and showed the presence of mild hemophagocytosis and a negative staining for copper, iron, and hepatitis B surface and core antigens (Fig. 2A and 2B). Flow cytometry of peripheral blood identified an abnormal population of T cells expressing CD3, CD5 (dim), CD7, CD8, CD38, and CD52. A bone marrow biopsy was performed and revealed a hypercellular marrow (70%) with many CD4, CD68, and CD163-positive histiocytes, hemophagocytosis, and CD3 and CD8-positive T cells within the sinusoids. CD3-positive (CD-4 negative) T cells in bone marrow sinusoids is a typical finding in hepatosplenic T-cell lymphoma [13]. The patient

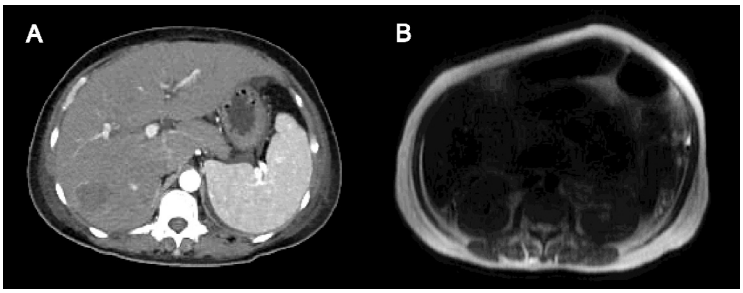

Fig. 1. Abdominal computational tomography (CT) and magnetic resonance imaging (MRI). (A) An abdominal CT image at the early stage of hospital admission, showing splenomegaly and hepatomegaly. (B) An abdominal MRI image after the patient received 16 units of red blood cell transfusional support with diffuse signal dropout due to iron deposition in the liver and pancreas ($T2^* = 5.0$ ms).

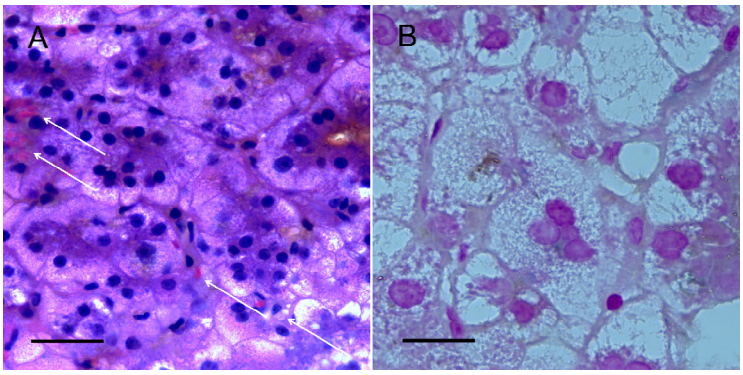

Fig. 2. Liver biopsy with hemophagocytic lymphohistiocytosis. (A) White arrows indicate hemophagocytosis: histiocytes are full of erythroid precursors (hematoxylin and eosin stain). Scale bar = 30 μm. (B) Negative iron staining at admission (Perl's iron stain). Scale bar = 10 μm.

met six of the eight criteria for the diagnosis of secondary HLH: fever, splenomegaly, pancytopenia, elevated triglyceride, elevated ferritin levels, and evidence of hemophagocytosis in the liver and bone marrow biopsy.

The diagnosis of HLH secondary to hepatosplenic T-cell lymphoma was made, and the patient was started on methylprednisolone, pentostatin, and alemtuzumab. Etoposide was held because of the extremely high bilirubin level. Magnetic resonance imaging (MRI, average T2* relaxation time of 5 ms) of the abdomen on day 23 of hospitalization revealed a high degree of iron deposition in the liver and pancreas (Fig. 1B), which was performed after the patient received sixteen units of RBC transfusion for persistent, transfusion-refractory anemia. Five days after initiation of HLH-directed therapy, the patient expired from respiratory failure secondary to overwhelming pneumonia.

3. Discussion

Initial liver imaging and biopsy did not reveal iron deposition in the liver. However, after receiving 16 units of RBC transfusions, MRI of the abdomen revealed extensive iron deposition in the liver and pancreas. Wood et al described a method to estimate the liver iron concentration (LIC) on MRI, based on T1, T2, and T2* relaxation times. Pixels of this patient's MRI were averaged together, and T2* = 5.0 ms. The corresponding estimated LIC is calculated 6.7 mg/g dry weight (LIC = 0.03/T2* + 0.7, where the unit of T2* is seconds) [14,15]. It has been shown previously that patients with sickle cell disease who had serum ferritin > 1000 ng/mL and received 12–19 units RBC transfusions showed a mean LIC of 2.1–2.3 mg/g dry weight [16]. Transfusion-dependent patients with MDS showed MRI detectable hepatic iron (T2* < 6.3 ms) when receiving at least 24 units of RBC transfusions [17]. One patient with MDS, who received 16 units of RBC transfusions, did not show MRI detectable hepatic iron overload [18]. Other than sickle cell disease and MDS as discussed above, no other clinical scenarios have been reported in which this degree of iron overload has been documented after a limited amount of RBC transfusions.

The estimation of LIC on MRI and previously reported studies imply that patients with HLH could reach an iron overload state more rapidly than those with other diseases requiring transfusional support. This is likely a consequence of the pathophysiology of HLH: excessive iron from the catabolism of RBCs by aggressive macrophages is released, resulting in a very high transferrin saturation. Therefore, the reticuloendothelial system in the setting of HLH has a reduced capacity to store iron associated with RBC transfusions required to support the refractory anemia. LIC is reportedly more strongly associated with the total units of transfusion, rather than the rate of transfusion for other diseases requiring transfusional support [16]. This is supported by the lack of a physiologic mechanism of removing excess iron from the body [10,16]. However, this is not likely the case in HLH, in particular during an acute stage of HLH. Extra iron from RBC transfusion in MDS or other diseases would be released slowly because the life span of RBCs is around 120 days [19]. However, RBCs transfused for refractory anemia in HLH are destroyed rapidly, and excess iron would be released at a faster rate, which is superimposed with an elevated transferrin saturation.

4. Conclusion

Patients with HLH require RBC transfusions to counteract immune-mediated destruction of RBCs. Patients with HLH are also more prone to rapidly develop iron overload due to elevated transferrin saturation even before receipt of RBC transfusions, as well as active destruction of transfused RBCs. Therapeutic phlebotomy is commonly used to manage iron overload, but refractory anemia prevents venesection for the management of iron overload in HLH. Clinicians should recognize this unique feature of HLH and "ironic" complications leading to organ damage that can rapidly occur when refractory anemia is managed with transfusional support.

5. Contributors

SL planned the study and wrote the manuscript. IS and MC performed clinical work and wrote the manuscript. TS and JOM supervised the study and wrote the manuscript.

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