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## Case Report

# “Irony” of managing refractory anemia with transfusional support in hemophagocytic lymphohistiocytosis

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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.

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## 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 > 38.5°C, (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.

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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].

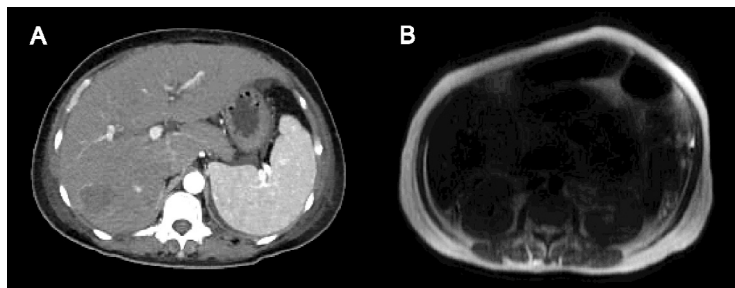
Herein, we report a unique case of a patient with HLH and associated severe refractory anemia who rapidly developed an iron overload state from RBC transfusions. A very high transferrin saturation and aggressive catabolism of transfused RBCs associated with HLH seems to trigger more rapid iron deposition 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

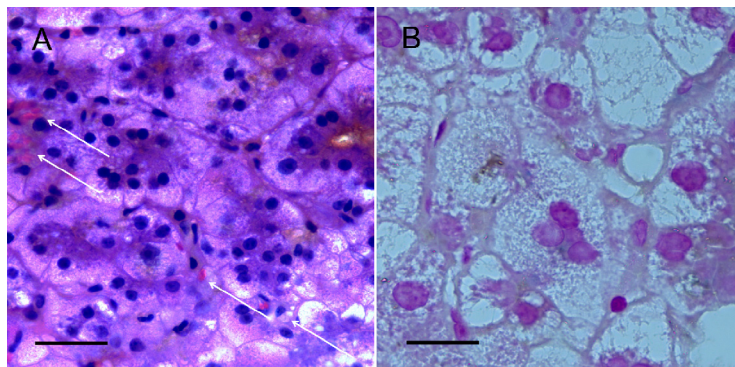
A 44 year-old woman without a significant past medical history presented to the emergency department with two weeks of fatigue, fever, and jaundice. On admission, she was found to be tachycardic to 125/min and febrile to 102.5 F with a blood pressure of 153/73 mmHg. Physical examination revealed severe jaundice and hepatosplenomegaly. A complete blood count showed a white blood cell count of 3800/ $\mu$ L (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/ $\mu$ L. Additional laboratory evaluation revealed iron 138  $\mu$ g/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  $\mu$ m. (B) Negative iron staining at admission (Perl's iron stain). Scale bar = 10  $\mu$ m.

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