CASE REPORT

Hemosiderosis causing liver cirrhosis in a patient with Hb S/beta thalassemia and no other known causes of hepatic disease

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Abstract

Background: Hemosiderosis in the absence of blood transfusions has been encountered in conditions associated with ineffective erythropoiesis but not in sickle-cell disease (SCD).

Description of the case: We report a case of a 34-year-old Caucasian male, with a history of SCD and beta thalassemia (Hb S/β$^+$-thal) who presented with acute painful crises. Despite never having received regular blood transfusions in the past, the patient demonstrated elevated ferritin levels and transferrin saturation of 83 %. Further evaluation revealed diffuse hepatocellular dysfunction and cirrhosis.

Conclusion: To the best of our knowledge, this is the first patient with Hb S/β$^+$-thal without a prior history of chronic blood transfusions or other predisposing factors for liver disease who developed hemosiderosis and cirrhosis. The pathomechanism, in this case, is thought to be related to increased duodenal iron uptake secondary to premature red cell precursor death. Further studies are required to characterize ineffective intramedullary erythropoiesis and iron metabolism better, and to improve the existing management guidelines of iron overload. The data reported herein suggest that patients with hemoglobinotpathies should be screened for iron overload regardless of transfusion history. HIPPOKRATIA 2017, 21(1): 43-45.

Keywords: Sickle-cell disease, thalassemia, hemosiderosis, Hb S/beta thalassemia, Hb S/β$^+$-thal, cirrhosis

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Introduction

Sickle-cell/β$^+$ thalassemia (Hb S/β$^+$-thal) is a heterozygous condition which is characterized by chronic hemolytic anemia and is associated with acute and chronic complications. Transfusion is a frequently used treatment option of sickle-cell disease (SCD), as it is found to improve disease complications[1]. However, iron overload is a serious and inevitable consequence of the ongoing transfusion therapy. Patients who undergo chronic transfusions and develop iron overload have significantly higher mortality rates than their less transfused counterparts[2]. Moreover, the association between ineffective erythropoiesis and iron overload in the absence of blood transfusions has been evaluated in conditions associated with ineffective erythropoiesis such as thalassemia syndromes, sideroblastic and dyserythropoietic anemias[3-5], but not in sickle-cell variants.

Case report

A 34-year-old Caucasian male, with a history of Hb S/β$^+$-thal, attended the Emergency Department with acute onset of progressive abdominal and thoracic pain. He previously suffered three painful crises of moderate intensity over the preceding nine years and had a history of bilateral arthroplasty due to femoral avascular necrosis. His medication list included 500-1,000 mg hydroxyurea daily. Based on his medical history, he required transfusion with six units of packed red cells in his lifetime. He did not drink alcohol, and his body mass index was normal. On examination, the patient was afebrile and jaundiced. Laboratory evaluation performed on admission revealed a normochromic normocytic anemia, leukocytosis, reticulocytosis and platelets of 207,000/μl. Liver function tests demonstrated elevated levels of bilirubin (conjugated 2.91 mg/dl, unconjugated 5.41 mg/dl), total protein 7 g/dl (normal range: 6.4-8.3 g/dl), albumin 2.5g/dl (normal range: 3.5-5.2 g/dl), aspartate transaminase (AST) 143 U/l (upper normal limit: 34 U/l), alanine transaminase (ALT) 31 U/l (upper normal limit: 55 U/l), and a coagulopathy with an INR of 1.8. Iron studies showed ferritin levels 5,665 ng/ml and transferrin saturation 83 %.

Further evaluation of his impaired liver function was undertaken. Ultrasonography showed a nodular appearance of his liver, while Doppler studies confirmed patency of the splenic, portal, and hepatic veins. To further assess liver function, scintigraphy was performed with evidence of chronic diffuse hepatocellular dysfunction and liver cirrhosis. In contrast to the myocardium,

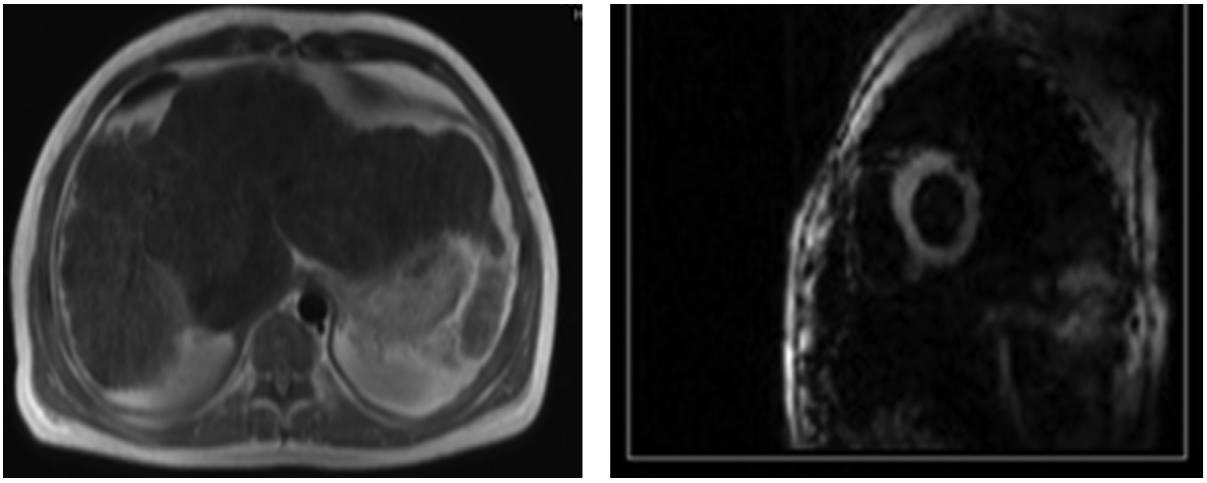

Figure 1: Evaluation of iron load by T2* magnetic resonance imaging: A) T2*-weighted gradient echo axial image demonstrates diffuse abnormal low signal intensity of the liver indicating iron overload. B) Myocardial iron deposition is not observed.

T2*-weighted gradient echo axial imaging demonstrated hepatic iron overload (Figure 1). Serological tests for hepatitis B (HBV), C (HCV), and Epstein-Barr (EBV) viruses, cytomegalovirus (CMV), and parvovirus B19 were negative. Analysis of autoimmune antibodies was performed showing low titers of antinuclear antibodies (1:40). Antimitochondrial antibodies and smooth muscle antibodies were negative, while alpha-fetoprotein (AFP) level was 4.1 ng/ml. Urine copper excretion rate, serum copper, and ceruloplasmin levels were normal, thus excluding Wilsons's disease which was included in the initial differential list. At this point, hemosiderosis-related cirrhosis was suspected. Testing of the human hemochromatosis protein (HFE) gene was performed to rule out primary hemochromatosis. The patient refused liver biopsy and chelation therapy with deferasirox was initiated. Evaluation with endoscopy demonstrated esophageal varices (F1) and the patient was additionally placed on prophylactic therapy with propranolol.

Discussion

SCD can affect any part of the body, including the hepatobiliary system. The hepatobiliary system is affected either directly by the sickling process or indirectly due to chronic hemolysis and multiple blood transfusions. Several manifestations have been reported before, such as cholelithiasis, cholangiopathy, acute hepatic crisis or sequestration crisis, and viral infections[6]. Cirrhosis was demonstrated in 18 % of patients with SCD[7]. The pathogenesis of cirrhosis is generally accepted to be related to viral infection, hypoxic injury, chronic alcohol intake, pigment gallstones, and iron overload secondary to multiple transfusions that these patients require over their lifetime[8]. On the other hand, patients with Hb S/β^+-thal rarely demonstrate hepatic involvement, the severity of which appears to be mild as was shown before in a study of a white Mediterranean population[9]. Samperi et al demonstrated that only two of 142 patients had significantly abnormal liver function tests, while both patients were positive for HBsAg and HCV antibodies, so that their liver disease could be related to the viral infection rather than to the hematological disorder[10].

Moreover, the association between ineffective erythropoiesis and iron overload in the absence of blood transfusions has been examined in thalassemia syndromes[5], sideroblastic anemia[11], and dyserythropoietic anemias[12] but not in SCD. Although ineffective intramedullary erythropoiesis has been supported by *in vivo* studies in SCD patients[13], association with iron overload has not been demonstrated yet. A key difference between SCD and other ineffective erythropoiesis syndromes (i.e., Thalassemia) is the primary site of red blood cell destruction. Ineffective erythropoiesis is predominantly intramedullary. Bone marrow-derived factors such as twisted gastrulation protein homolog 1 (TWSG1)[14] or erythroferrone, suppress hepcidin leading to increased dietary iron absorption. On the other hand, intravascular hemolysis in SCD provides a potential mechanism for excretion of hemoglobin, hemosiderin, and heme through urine or bile resulting in iron elimination[15].

The important point in our case is that our patient with microdrepanocytosis and without a positive history of chronic blood transfusions or other predisposing factors for liver disease developed hemosiderosis and cirrhosis. To our knowledge, there has been only one single report of an SCD presented with iron overload and limited blood transfusions, that was finally attributed to hereditary hemochromatosis[16].

Of importance, this study provides evidence that intramedullary ineffective erythropoiesis is implicated in hemosiderosis in patients with Hb S/β^+-thal. Prospective studies are required to both characterize the mechanism of ineffective erythropoiesis and to explore the correlation between the extent of ineffective erythropoiesis and implications in disease severity in patients with Hb S/β^+-thal. Concurrently, the evidence presented herein suggest that patients with hemoglobinotpathies should be screened for iron overload regardless of transfusion his-

tory. Early screening might allow us to detect the disease early and prevent complications.

Conflict of interest

The authors report no conflicts of interest.

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