OLGU SUNUMU/CASE REPORT

Red blood cell exchange followed by plasma exchange in patients with intrahepatic cholestasis due to sickle cell disease

Orak hücre hastalığına bağlı intrahepatik kolestazı olan hastalarda eritrosit değişiminin ardından plazma değişimi

Nurhilal Büyükkurt[1], İlknur Kozanoğlu[2], Can Boğa[1], Hakan Özdoğu[1], Mahmut Yeral[1]

[1]Baskent University School of Medicine, Department of Hematology, [2]Department of Physiology Ankara, Turkey

Abstract

Intrahepatic cholestasis, a rare complication of sickle cell anemia, is characterized by marked hyperbilirubinemia, acute hepatic failure, and an often fatal course. In this report, we present patients with homozygous hemoglobin S and one patient with sickle-β thalassemia disease who have intrahepatic cholestasis. Despite automated red blood cell exchange transfusion, which successfully decreased the hemoglobin S level to less than 30% of total hemoglobin level in the peripheral blood, basic biochemical laboratory examination revealed signs of cholestasis with a serum bilirubin level of up to 50 mg/dL in the first case, 30 mg/dL in the second, and 10 mg/dL in the third. The patients underwent plasma exchange, which improved their clinical condition except one. These cases suggest that plasma exchange may have a role in improving the clinical condition of patients with sickle cell disease complicated with intrahepatic cholestasis (SCIC) that fails to respond to automated red blood cell exchange therapy

Key words: Sickle cell disease, intrahepatic cholestasis, red blood cell exchange, plasma exchange.

Öz

İntrahepatik kolestaz, belirgin düzeyde artmış bilüribin ve akut hepatik yetmezlik ile karakterize, orak hücreli aneminin nadir bir komplikasyonu olup sıklıkla ölümcül gidişlidir. Bu raporda, intrahepatik kolestazı olan 2 homozigot hemoglobin S, bir S-β talesemi hastası bildirilmektedir. Otomatize eritrosit değişimi ile başarılı bir şekilde periferik kanda hemoglobin S düzeyi %30'un altına indirilmesine rağmen, kolestazın temel değerlendirme testlerinden olan bilüribin düzeyi birinci hastada 50 mg/dL, ikincisinde 30 mg/dL ve üçüncü hastada 10 mg/dL'nin üzerinde saptandı. Plazma değişimi işlemi uygulanan hastalardan biri dışında diğerlerinde klinik durumlarında iyileşme gözlendi. Bu vakalardan elde edilen veriler intrahepatik kolestazı olan orak hücreli anemi hastalarında eritrosit değişim işlemine yeterli yanıt alınamadığında plazma değişiminin klinik iyileşmede rol oynayabileceğini göstermektedir.

Anahtar kelimeler: Orak hücre hastalığı, intrahepatik kolestaz, eritrosit değişimi, plazma değişimi

INTRODUCTION

Intrahepatic cholestasis, a rare complication of sickle cell disease, is characterized by marked hyperbilirubinemia, acute hepatic failure, and frequently renal dysfunction[1,2]. This entity has been described in patients with sickle cell disease who are homozygous for hemoglobin S (Hb S) as well as in those heterozygous for Hb S and β-thalassemia[1,2]. To our knowledge, fewer than 50 patients with intrahepatic cholestasis have been reported in the literature[3-7].

Intrahepatic cholestasis can be fatal despite aggressive supportive care[6,8]. Automated red blood cell exchange(RBCX) can decrease the Hb S fraction in these patients and diminish intrahepatic sickling, which is considered the primary cause of the disease. Recent advances in automated RBCX transfusion therapy, when coupled with adequate supportive care, can remarkably improve the clinical condition

of patients with sickle cell disease and intrahepatic cholestasis (SCIC).

In this report, we describe 2 patients with homozygous HbS disease and one patients with HbS-β thalassemia who presented with intrahepatic cholestasis. Automated red blood cell exchange procedure, which decreased the Hb S level to less than 30% of the total hemoglobin level in the peripheral blood, was ineffective in improving the biochemical parametres. All received plasma exchange therapy, and the medical condition of 2 of the 3 patients stabilized, and the first died of progressive dysfunction of liver.

CASE 1

A 21-year-old male patient with homozygous Hb S disease was admitted to our hospital because of an oral bleeding, nausea, vomiting, and jaundice. His medical history revealed an intracranial aneurysm that had been surgically repaired 2 years earlier and chronic liver failure caused by hemochromatosis. His hematological and biochemical data was outlined table 1. He had been pretreated with deferoxamine 1 g/d and folic acid 5 mg/d. The peripheral blood smear was notable for varied erythrocyte morphology, including sickle cells and many nucleated red blood cells. Ultrasonographic studies demonstrated patent hepatic vessels and no evidence of choledocholithiasis. Abdominal computed tomography confirmed hepatomegaly, ascites, and hepatic nodularity. The results of cultures from blood, urine, and peritoneal fluid were negative.

Initial management consisted of the administration of intravenous saline, vitamin K, and broad-spectrum antibiotics. Automated RBCX was initiated within 12 hours of the patient's admission because of his multiorgan failure, particularly hepatopathy. Six units of packed red blood cells were exchanged in 1 session by using an automated system (COBE Spectra 7.0, Lakewood, Co, and USA). Pre-exchange and post-exchange hemoglobin electrophoresis showed a decline in the level of hemoglobin S from 82% to less than 30%, but the patient's total bilirubin value remained constant at about 50 mg/dL.

At that time, we performed 1 plasma volume exchange with fresh-frozen plasma of the patient's blood type (Cobe Spectra 7.0). Despite an initial clinical improvement involving a decreased level of

Hb S, the patient's condition continued to deteriorate. He received aggressive supportive care, including mechanical ventilation, in the intensive care unit. Two days after his initial admission, however, he died of progressive dysfunction of liver.

CASE 2

A 46-year-old male patient with homozygous Hb S was admitted to our hospital because of abdominal discomfort, confusion, vomiting, and jaundice. He had a history of chronic liver failure. The patient had been pretreated with deferoxamine 1 g/d and folic acid 5 mg/d. His hematologic and biochemical profile was shown in table 1. Analysis of the peripheral blood smear was notable for varied erythrocyte morphology that included sickle cells, and many nucleated red blood cells. Ultrasonographic studies showed patent hepatic vessels and no evidence of choledocholithiasis. The results of abdominal computed tomography confirmed hepatomegaly, ascites, and hepatic nodularity. The results of cultures from blood and peritoneal fluid were negative.

Initial management consisted of the administration of intravenous saline, vitamin K, packed red blood cells, and fresh-frozen plasma. Automated RBCX was initiated within 24 hours of the patient's admission. Five units of packed red blood cells were exchanged in 1 session by using an automated system (Cobe Spectra 7.0). Pre-exchange and post-exchange transfusion hemoglobin electrophoresis showed a decline in the hemoglobin S level from 65% to less than 30%. Despite having undergone red blood cell exchange, the patient's total bilirubin level remained unchanged at around 30 mg/dL. The day after we performed 1 plasma volume exchange with fresh-frozen plasma of the patient's blood type (Cobe Spectra 7.0), his clinical condition was stabilized. His conjugated bilirubin level was regressed up to 20 mg/dL and he was discharged from the clinic.

CASE 3

A 17-year-old male patient with Hb S/ β-thalassemia was admitted to our hospital because of abdominal discomfort, nausea, vomiting, and jaundice. He had a history of chronic liver failure. His hematologic and biochemical profile was shown in table 1. The results of analysis of a peripheral

blood smear were notable for varied erythrocyte morphology, including sickle cells, many nucleated red blood cells, and Howell-Jolly bodies. Ultrasonographic studies demonstrated patent hepatic vessels and no evidence of choledocholithiasis. Abdominal computed tomography showed hepatomegaly, ascites, and hepatic nodularity. The results of cultures from blood and peritoneal fluid were negative.

Initial management consisted of the administration of intravenous saline, vitamin K, packed red blood cells, and fresh-frozen plasma. The patient was treated empirically with broad-spectrum antibiotics. Automated red blood cell exchange was initiated within 12 hours of his admission because of multiorgan failure, particularly hepatopathy. Six units of packed red blood cells were exchanged in 1 session (Cobe Spectra 7.0). Pre-exchange and post-exchange transfusion hemoglobin electrophoresis showed a decline in the hemoglobin S level from 62% to less than 15%. Despite having undergone red blood cell exchange, the patient's total bilirubin level remained constant at around 10 mg/dL. The day after we performed 1 plasma volume exchange with fresh-frozen plasma of the patient's blood type (Cobe Spectra 7.0), his clinical status was stablized. His conjugated bilirubin level was regressed up to normal level and he was discharged from the clinic.

DISCUSSION

Intrahepatic cholestasis has been identified as a rare and potentially fatal complication of sickle cell disease. Right upper quadrant pain, progressive hepatomegaly, coagulopathy with hemorrhage, and extreme hyperbilirubinemia are the main features of intrahepatic cholestasis[1,2,4,8]. The diagnosis of that disorder is usually established by characteristic clinical and laboratory findings in the absence of choledocholithiasis affecting the biliary tract[1,2,4].

Although the pathogenesis of intrahepatic cholestasis has not been definitively established, sickled erythrocytes in the sinusoids, vascular stasis, and ballooning of hepatocytes are considered the primary etiologic factors[1-4,7]. İntrahepatic cholestasis can occur during the course of chronic liver parenchymal cell damage[3,9]. All 3 patients described in this report had evidence of chronic liver disease. However, possible predisposing factors for intrahepatic cholestasis in patients with sickle cell disease include concomitant hepatic disease, medical therapies, genetic factors, and iron overload.

The association of hepatotropic viruses with intrahepatic cholestasis has been reported in literature. Among such viruses, hepatitis B virus, hepatitis C virus, and cytomegalovirus can increase the risk of intrahepatic cholestasis[10]. However, our patients demonstrated no evidence of viral infection, and all denied hepatotoxic drug use during the month before their admission to the hospital. We therefore focused on genetic factors and iron overload as causes of intrahepatic cholestasis in our patients.

Recently, many investigators have examined the nonglobin genetic modifiers of sickle cell disease. Phenotypic heterogeneity causes the course of sickle cell disease to range from a mild to a very severe presentation with organ damage[11]. Genes related to cellular proliferation, growth and maintenance, DNA repair, DNA replication, cell cycle progression, and inflammation have been reported to be expressed at significantly higher levels in patients with sickle cell disease as opposed to controls[12]. For example, the greater expression of genes in the TNF, MAPK, and NFkB pathways, which is associated with an inflammatory state, has been noted[13]. It has also been reported that many complications of sickle cell disease are associated with a variation of the genes in the TGF-beta super family, the genes that have a role in vascular reactivity, and apoptosis.

Iron overload has never been implicated in the development of intrahepatic cholestasis in people with sickle cell disease. The liver contains most of the body's iron stores. In general, the primary causes for intrahepatic cholestasis in the ductular phase are endotoxins and immunotoxins. During iron overload, iron accumulates within the parenchymal cells of the liver and possibly within the ductular cells, where (in both sites) it causes significant oxidative damage[14]. A clear association of iron overload with the risk of hepatocarcinoma has been established, at least in patients with thalassemia[15]. Chelation with iron-chelating drugs such as deferoxamine leads to the excretion of iron via the bile. Perhaps in that way, the chronic administration of deferoxamine may interfere with the cellular contact of iron with the ductular cells, which results in ductular cell damage and delay in excretion from hepatocytes to bile ducts. The results of liver biopsy and the analysis of specimens obtained at autopsy

from afflicted patients usually show dilated intrahepatic canalicules[7]. Sickle cell thrombi, sinusoidal engorgement, scattered bile stained microinfarcts, and hypertrophy of Kupffer cells have also been reported[1,2-4]. The results of liver biopsy in our patients could have provided a semiquantitative evaluation of iron load, the effects of iron damage, and possible information about independent factors such as the presence of viral hepatitis or steatosis. However, we did not perform liver biopsies because liver biopsy can induce severe procedure-related complications[16]. Magnetic susceptometry, which is a noninvasive method for the quantitative estimation of iron overload, could have been used, but we had no such system functioning. Further studies are needed to define the role of iron in intrahepatic cholestasis in patients with sickle cell disease.

The goals of the erythrocyte exchange procedure are to decrease the concentration of hemoglobin S to a value below 30% of the total hemoglobin level in the peripheral blood and to lower the levels of erythrocyte-expressed integrin $a4\beta1$ and surface glycoprotein IV (thrombospondin receptor, CD36) to prevent interaction between erythrocytes, endothelial cells, and platelets[17,18]. Maintaining HbS levels at, 20% to 30% has been proposed, but this is based on praf matism rather than evidence. Future work must explore the natural history of SCİC in order to identify which patients are at rist of disease progression and which would benefit from regular erythrocyte exchange programe.

Plasma exchange conducted by new-generation machines is rapid and safe, although an experienced team must perform that procedure. With an automated system that separates cells from plasma by means of continuous blood flow, 60% to 70% of a patient's plasma can be exchanged for donor plasma during a single procedure[19]. In a brief report on plasma exchange in patients with SCD, Svarch and colleagues observed a dramatic improvement in a child with SCD in whom acute cholestasis and a neurologic syndrome developed after a plasma exchange[20]. These patients were admitted to our clinic while they were in an acute decompensation of chronic period of intrahepatic cholestatis, so we first preferred automated erythrocyte exchange. We performed plasma exchange due to that procedure failed to improve the patient's clinical condition, Sickle hepatopathy is covering in wide variety pathologies, both acute and chronic. In the severe

acute liver dysfunction syndromes, and progressive liver cholestatis, anecdotal experience is accruing for the use of RBCX transfusion, although this has not been cautiously evaluated. There are several case reports demonstrating that acute SCIC can be reversed with prompt RBCX3,4,6. With progressive disease, it is not clear when RBCX should be commenced or what the aims of treatment should be. There are few examples in the literature of the use of a program of RBCX to manage chronic SCIC in the nontransplant setting[9,21,22].

Our data suggest that in some patients with SCD whose clinical condition is critical, extremely complicated with progressive intrahepatic cholestatsis, plasma exchange exerts a cumulative effect on erythrocyte exchange and restores microcirculation to deteriorated tissue. Plasma exchange can help to eliminate plasma components that can contribute vaso-occlusive episodes. Furtermore plazma exchange may be a tool to save time for another treatment option as either hematopoietic or liver transplantation in patients with sickle cell intrahepatic cholestatis. In conclusion, intrahepatic cholestasis can be highly fatal in patients with sickle cell disease.

Our case report indicates that a worse response to automated exchange transfusion may be expected in patients with intrahepatic cholestasis and either iron overload or prior hepatic disease, such as chronic liver disease. Our findings indicate that plasma exchange may play a role in the recovery of critically ill patients with sickle cell disease who have not benefitted from automated red blood cell exchange.

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