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Correction

In the Volume 17, number 2 issue of the Turkish Journal of Gastroenterology, the figures related bo the article "Chronic liver disease in a patient with sickle cell anemia" by Akyürek Savaş et al (pp. 123-125) were not published by mistake. We apologize for this and publish the whole manuscript including figures once again.

Chronic liver disease in a patient with sickle cell anemia

Orak hücre anemili bir olguda kronik karaciğer hastalığı

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Various disorders of the hepatobiliary system can occur due to sickling in patients with sickle cell anemia. Pathology and frequency of these disorders are not clearly known. Liver biopsies of these patients show erythrocytosis, erythrophagocytosis, sinusoidal dilatation and hyperplasia in Kupffer cells. We present a 21-year-old male patient diagnosed with sickle cell anemia who developed chronic liver disease, together with a review of the literature.

Key words: Sickle cell anemia, chronic liver disease

Orak hücre anemili olgularda hepatobilier sistemde oraklaşmaya bağlı olarak çeşitli bozukluklar oluşmaktadır. Bu bozuklukların patolojisi ve sıklığı henüz tam olarak bilinmemektedir. Bunların yapılan karaciğer biyopsilerinde eritrositoz, eritrofagositoz, sinozoidal dilatasyon ve Kupffer hücrelerinde hiperplazi görülmektedir. Biz burada orak hücre anemisi tanısı almış 21 yaşında erkek olguda kronik karaciğer hastalığı geliştiğini gözledik ve literatürü gözden geçirerek olguyu sunduk.

Anahtar kelimeler: Orak hücre anemisi, kronik karaciğer hastalığı

INTRODUCTION

Sickle cell anemia is sickling of the erythrocyte membrane due to polymerization and aggregation of HbS molecules inside the erythrocytes. Sickling of erythrocytes is seen clinically as chronic compensated hemolytic anemia, chronic and progressive functional disorders of organs, or acute, painful, vaso-occlusive crisis (1).

Various disorders of the hepatobiliary system can occur in patients with sickle cell anemia. The risk of cholelithiasis, choledocholithiasis and liver failure increases in these patients due to sickling. In addition, viral hepatitis and other hepatobiliary diseases can also occur (2-5). Although there are some theories about frequency and pathophysiology of liver disease in patients with sickle cell disease, they are still not clearly known (6, 7).

Here, we aimed to describe chronic liver disease in a patient with sickle cell anemia and to review the literature.

CASE REPORT

A 21-year-old male patient presented to the Gastroenterology Outpatient Clinic in October 2003 with complaint of yellow discoloration in scleras. His medical background revealed diagnosis of sickle cell anemia when he was five years old. He had no pain crisis since then.

He had no history of smoking or alcohol intake. His complaint started two years previously and he was investigated for upper gastrointestinal bleeding, which showed esophageal varices, and was transfused six units of erythrocyte suspension.

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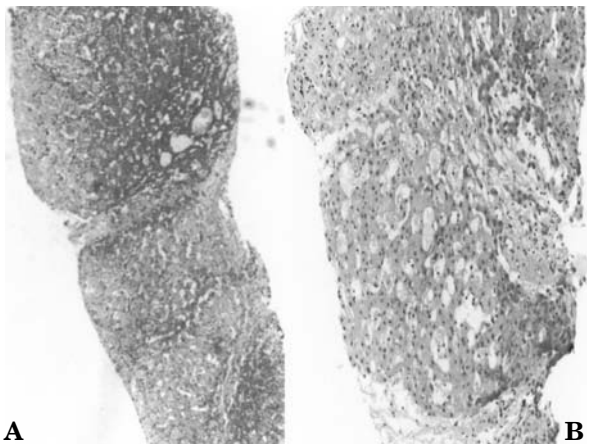
His hemoglobin electrophoresis showed HbF 18% (N:0%), HbS 79% (N: 0%), and HbA2 1.8% (0-3.5%), with positive sickling test. He was hospitalized with diagnosis of sickle cell anemia and portal hypertension.

On physical examination, scleras were icteric and mucosa was pale. There was a mesocardiac 3/6 pansystolic murmur on cardiovascular examination. Liver was palpated 5 cm below right costal margin at midclavicular line. It was non-tender and had a blunt ending; other physical examination findings were in normal limits.

Laboratory workup revealed hemoglobin: 8 g/dl, white blood cells: 10900/mm^3, platelet count: 150000/mm^3, and reticulocytes: 11% (N:0-1.2%); sickle cells; target cells, and anisopoikilocytosis were present on peripheral blood smear. HbSS was shown in hemoglobin electrophoresis. Total serum bilirubin level was 8 mg/dl, AST 73 U/L, ALT 53 U/L, GGT 93 U/L, ALP 374 U/L, and LDH 892 U/L. Serum Fe level was 141 µg/dl (N: 65-175 mg/dl), serum iron binding capacity 239 µg/dl (N:250-450 µg/dl), serum ferritin 653 ng/ml (N:23-336 ng/ml), vitamin B_{12} level 248.00 pg/ml (N:145-980 pg/ml), and folic acid level 12.00 ng/ml (N:>5.21 pg/ml). Prothrombin time was 15 sec, aPTT 33 sec, and fibrinogen 2.88 mg/dl. Viral hepatitis markers of the patient were negative. Copper level in 24-hour collected urine and blood ceruloplasmin levels were within normal ranges.

With these results, abdominal ultrasonography, liver biopsy, upper gastrointestinal system endoscopy, and echocardiography were planned. On abdominal ultrasonography, liver parenchyma was seen as heterogeneous, and left lobe angle was blunted. Portal vein width was 14.6 mm, and there were 2 lymphadenopathies with 8-9 mm diameters on portal hilus. Intrahepatic biliary ducts and choledoch were normal. There was minimal edema on gall bladder wall. Craniocaudal size of spleen was 125 mm. Upper gastrointestinal system endoscopy showed grade 2-3/4 esophageal varices, fundal varices, diffuse gastropathy and duodenitis. Echocardiography was normal.

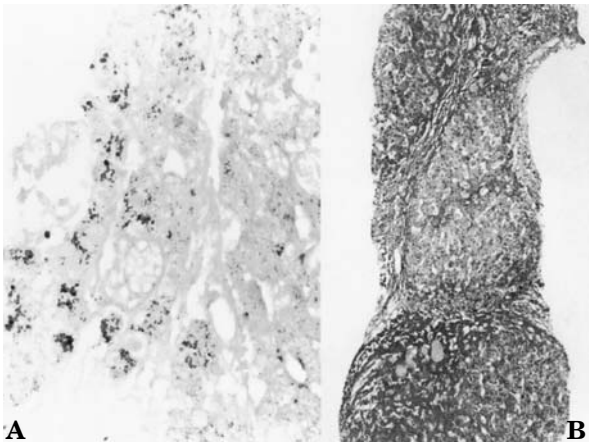
On portal venous system color Doppler ultrasonography, portal vein and its branches, splenic vein, inferior vena cava and hepatic veins were patent; color and filling were normal and no thrombus was found. Portal flow was hepatopedal, and no significant collaterals were found.



A **B**

Figure 1. A-B) Notable dilatation on sinusoids and significance of kupffer cells **B)** 10x magnified

Liver biopsy was planned in order to determine the etiology of portal hypertension. On liver biopsy, lobule order was lost occasionally, with notable dilatation on sinusoids, significant Kupffer cells, rare spotty necrosis, and mild cholestasis on parenchyma. There was mild mononuclear cell infiltration and dilatation due to fibrosis on portal regions, areas of porto-portal fibrosis and nodular appearance were seen, and mild piecemeal necrosis was recorded on some portal regions. On iron histochemical stain, presence of hemosiderin was shown in Kupffer cells on two periportal regions (Figures 1, 2). Histomorphology of Wilson disease was not found. Dry copper level of liver was measured as 216 mcg/g. Laboratory tests for autoimmune hepatitis as anti-nuclear anti-core (ANA), anti-smooth muscle antigen (SMA), anti-liver/kid-



A **B**

Figure 2. A) Presence of hemosiderin in kupffer cells on periportal area **B)** Fibrozis on periportal area

ney microsome (LKM) antigen, anti-double stranded DNA (ds-DNA), and antithyroid anticore were ordered and all were negative. Immunglobulin levels within normal limits. With these findings, autoimmune hepatitis was excluded and the patient was diagnosed according to his liver histology as chronic liver disease occurring due to his primary disease, sickle cell anemia. Hydroxyurea was started in order to decrease the severity of hemolysis.

DISCUSSION

Etiology and pathological features of chronic liver disease occurring in sickle cell anemia are under debate. Green et al, (8) in 1953 first described the hepatopathy developing in patients with sickle cell anemia in autopsy studies. They reported that hyperplasia of Kupffer cells, sinusoidal dilatation and erythrophagocytosis occur due to accumulation of sickled erythrocytes, which may lead to hypoxia, necrosis and cirrhosis in late stages. Later, Bauer et al, (9) reported autopsies of patients with sickle cell disease, which revealed that 91% of cases had erythrocytosis in Kuppfer cells and 71% had sinusoidal dilatation, and they explained the etiology of chronic liver disease with microvascular stasis.

Chronic liver disease can also occur due to blood transfusions in patients with sickle cell disease (3-5). In a study of Comer et al (10), sinusoidal dilatation and erythrophagocytosis were found in liver biopsies of nine patients who formerly received blood transfusions. They reported that all patients had hemosiderosis but only two developed liver cirrhosis. They suggested that transfusion-related complications could play a role in chronic liver disease development in patients with sickle cell anemia.

Our case was diagnosed as sickle cell anemia when he was five years old, and a year previously he had upper gastrointestinal system bleeding due to esophageal varices, at which time he received only six units of blood transfusion. This amount of blood transfusion is considered low for causing hemosiderosis. In our opinion, our case developed liver cirrhosis before he received the blood transfusion. As a result, we do not think that our case developed liver cirrhosis due to hemosiderosis or blood transfusion.

Excessive iron load in sickle cell anemia is believed to occur in patients receiving multiple blood transfusions, and mortality and morbidity due to excessive iron load is not a well-studied subject (11).

Peronne et al, (12) examined the causes of death retrospectively in patients with sickle cell anemia in England and France. They classified causes of death as: 1. Vaso-occlusion due to acute sickling, 2. Chronic liver disease due to sickle cell anemia, 3. Infections, and 4. Other causes. They reported that 10 of a total of 61 deaths (19%) were due to chronic terminal organ failure due to sickle cell anemia, and the main cause was liver cirrhosis (6 deaths). They also reported that three of these six cases received blood transfusions and developed hemosiderosis; they also had concurrent hepatitis C and liver cirrhosis as a result (12).

Viral hepatitis markers of our case were negative. The liver cirrhosis that developed in our patient was not due to viral hepatitis. Abdominal Doppler ultrasonography was found normal.

Histological changes in patients with sickle cell anemia are intrasinusoidal distortion due to sickled erythrocytes and erythrophagocytosis in Kupffer cells. Obstruction of intrahepatic blood flow leading to anoxia causes disturbances in liver functions (3, 6, 8). These morphological features are suggested to be specific for sickle cell anemia and are the basic pathophysiological condition explaining the hepatic dysfunction (3, 4, 13).

In studies of Omata and friends (13) and Barrett–Connor (14), no correlation was reported with grade of intrahepatic sickling and transaminase levels. Rosenblate et al, (6) performed liver biopsies in 12 patients with sickle cell disease. Although symptoms and liver enzyme levels were different, they found sinusoidal dilatation, Kupffer cell hyperplasia and erythrophagocytosis in liver biopsies of all patients. On electron microscopy, they showed increased collagen in basal membrane of Disse's space (6). In autopsy series, similar changes in liver biopsies have been confirmed (8, 9, 14).

Causes of liver cirrhosis in sickle cell disease can be determined as: 1. Hypoxic injury due to sickling, 2. Hepatitis, 3. Gall stones, 4. Right heart failure, 5. Iron overload, and 6. Chronic alcohol intake or chronic use of other drugs (2).

Our patient did not have viral hepatitis, Wilson disease, gall stones, iron overload, or history of chronic alcohol intake or medication. He did not describe any previous pain crisis. The cause of liver cirrhosis in our patient is thought to be progressive liver injury secondary to sickle cell anemia.

There are many causes for liver disease development in sickle cell disease. Diagnosis and treatment are difficult based on clinical features and

laboratory findings. 10% of autopsy cases had associated sickle cell disease and otherwise unexplained liver cirrhosis. Abnormalities in liver function tests are also frequent in asymptomatic patients. These findings are described as chronic hepatopathy in sickle cell anemia (2-4).

In conclusion, it should be kept in mind that chronic liver disease can develop secondary to primary disease in patients with sickle cell anemia.

Further studies are needed to understand the pathophysiology and progression of liver disease in sickle cell anemia.

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