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REVIEW

Gastrointestinal and Hepatic Complications of Sickle Cell Disease

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This article has an accompanying continuing medical education activity on page e70. Learning Objectives—At the end of this activity, the learner should be able to identify the main intra-abdominal complications of sickle cell disease and explain the reason for their occurrence.

Sickle cell disease (SCD) is an autosomal recessive abnormality of the β-globin chain of hemoglobin (Hb), resulting in poorly deformable sickled cells that cause microvascular occlusion and hemolytic anemia. The spleen is almost always affected by SCD, with microinfarcts within the first 36 months of life resulting in splenic atrophy. Acute liver disorders causing right-sided abdominal pain include acute vaso-occlusive crisis, liver infarction, and acute hepatic crisis. Chronic liver disease might be due to hemosiderosis and hepatitis and possibly to SCD itself if small, clinically silent microvascular occlusions occur chronically. Black pigment gallstones caused by elevated bilirubin excretion are common. Their small size permits them to travel into the common bile duct but cause only low-grade obstruction, so hyperbilirubinemia rather than bile duct dilatation is typical. Whether cholecystectomy should be done in asymptomatic individuals is controversial. The most common laboratory abnormality is an elevation of unconjugated bilirubin level. Bilirubin and lactate dehydrogenase levels correlate with one another, suggesting that chronic hemolysis and ineffective erythropoiesis, rather than liver disease, are the sources of hyperbilirubinemia. Abdominal pain is very common in SCD and is usually due to sickling, which resolves with supportive care. Computed tomography scans might be ordered for severe or unremitting pain. The liver typically shows sickled erythrocytes and Kupffer cell enlargement acutely and hemosiderosis chronically. The safety of liver biopsies has been questioned, particularly during acute sickling crisis. Treatments include blood transfusions, exchange transfusions, iron-chelating agents, hydroxyurea, and allogeneic stem-cell transplantation.

Keywords: Liver Disease; Gallstones; Abdominal Pain.

Sickle cell disease (SCD) is an autosomal recessive abnormality of the β-globin chain of hemoglobin (Hb) that changes the sixth amino acid from glutamic acid to valine.[1] The resulting Hb S polymerizes reversibly when deoxygenated to form a gelatinous network that stiffens the erythrocyte membrane and increases viscosity, producing the characteristic sickle shape. Such sickled cells lose flexibility needed to traverse small capillaries and have "sticky" membranes that adhere to the endothelium of small venules. These abnormalities result in microvascular occlusion and red blood cell destruction.

The heterozygous sickle trait is found in 8%–10% of the African American population.[1] Less commonly, Hb S combines with either Hb C or β-thalassemia. Fetal Hb F, which accounts for 80% of the Hb concentration at birth, declines to less than 1% by 6 months. It interferes with Hb S polymerization, and its concentration directly correlates with improvement in disease severity and prognosis. Hydroxyurea, which increases the concentration of Hb F, ameliorates the severity of painful crises in SCD.

The Spleen in Sickle Cell Disease

The spleen is almost always involved in SCD (Figure 1). It is usually infarcted within the first 18–36 months of life, paralleling the disappearance of protective Hb F, resulting in hyposplenism or asplenism.[2] Splenic atrophy increases susceptibility to infection with encapsulated bacteria. The onset of functional asplenia is reflected by the appearance of irreversibly sickled cells, anisocytosis, Howell-Jolly bodies, and siderocytes.

Splenic infarction caused by occlusion of the small splenic vessels from sickling is the most common in patients with sickle cell (SC)-Hb C or SC-thalassemia disease.[3] This is due to the near-normal Hb levels that produce a relatively high blood viscosity and to splenomegaly found in a majority of adults with these diseases. It might also occur with SC trait even in nonhypoxic conditions.[4] Splenic infarction presents with left upper quadrant pain, nausea and vomiting, a friction rub over the splenic area, and leukocytosis. With resolution of splenic abscesses or infarcts, pseudocysts might develop.[5]

Sequestration syndrome, or the rapid pooling of blood, usually affects the pulmonary circulation. Before the development of hyposplenism, it can cause rapid splenic enlargement and a drop in Hb.[6] In homozygous SCD, sequestration occurs in infants and children because progressive fibrosis of the spleen

Abbreviations used in this paper: CDL, choledocholithiasis; CT, computed tomography; Hb, hemoglobin; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; SCD, sickle cell disease.

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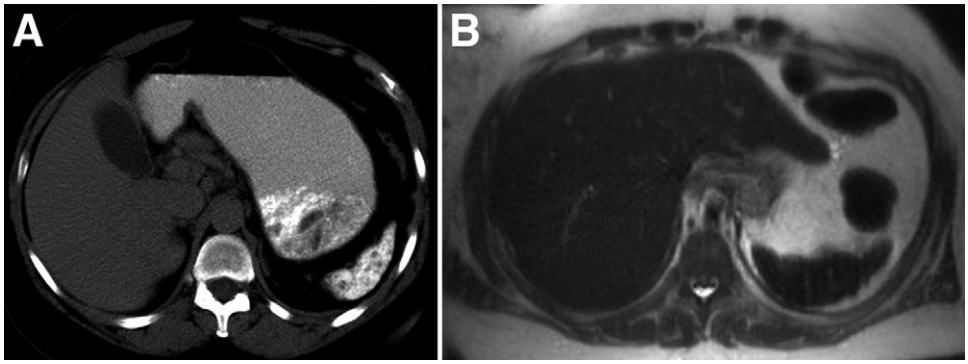

Figure 1. A 47-year-old woman with SCD and history of autosplenectomy. Unenhanced CT of the abdomen (*A*) shows increased density of the small spleen. On MRI (*B*) the spleen is also small and diffusely hypointense on all sequences, consistent with findings of dense calcification on CT. The calcifications and small size make detection of the spleen difficult on ultrasound.

impairs its ability to sequester blood. In SC-thalassemia, on the other hand, sequestration might occur at any age because the spleen is chronically enlarged. Hypovolemic shock and death might occur within hours if not prevented by transfusions. Occasionally, the organ might rupture. Splenomegaly might also be due to extramedullary hematopoiesis or to hemosiderosis.[5]

The Liver in Sickle Cell Disease

Acute Processes

There are several causes of right upper quadrant pain as it specifically relates to SCD. In patients admitted for acute vaso-occlusive crisis (severe pain in chest, abdomen, and joints), the liver is involved in about 39% of cases.[7] These patients present with abdominal meteorism, right upper quadrant pain, or acute painful hepatomegaly. The type of liver injury is usually cholestatic or mixed rather than purely hepatocellular, usually with normal synthetic function.

Liver infarction in SCD has been observed in 34% of autopsies.[8] In half of these cases, an associated cause of infarction (cardiac dysfunction or sepsis) is present. The resulting high blood viscosity predisposes to infarction despite the dual blood supply of the liver. Infarction might also occur in those with SC trait[9] or SC-Hb C disease.[10]

Acute sickle hepatic crisis affects about 10% of patients admitted for painful crisis.[11] It simulates acute cholecystitis with right upper quadrant pain, fever, leukocytosis, and variable increases in serum transaminases and bilirubin levels. The AST and ALT levels are usually 1–3 times normal,[12] although levels of greater than 1000 IU/L have been reported.[13] Unlike cholecystitis, the liver is usually enlarged and tender.

An uncommon complication is acute hepatic sequestration with jaundice and right upper quadrant pain associated with an enlarged liver and a drop in hematocrit accompanied by an appropriate reticulocytosis.[14,15] This is thought to be due to obstruction of sinusoidal flow by masses of sickled erythrocytes, trapping them in the liver. With resolution of the sinusoidal obstruction, erythrocytes might return to the circulation, causing a rapid rise in Hb; this suggests that not all sequestered cells are destroyed. The result can be death as a result of hypervolemia, heart failure, and intracerebral hemorrhage.[16]

A rare but potentially fatal complication known as SC intrahepatic cholestasis is thought to represent an unusually severe form of hepatic crisis.[17,18] There is widespread sickling in the sinusoids, resulting in hepatic ischemia. It is characterized by right upper quadrant pain, nausea, vomiting, tender hepatomegaly, and leukocytosis. There is extreme hyperbilirubinemia (from hemolysis, intrahepatic cholestasis, and renal impairment), with the conjugated fraction exceeding 50% of the total. In addition, there is a modest elevation of transaminase levels and coagulopathy. Patients die of liver failure and/or a hemorrhagic diathesis.

Rarely, liver abscesses occur as a result of diminished removal of bacteria from the bloodstream as a result of functional asplenism and reduced IgG antibodies to polysaccharide antigens.[19] It should be considered in a patient with fever and right upper quadrant pain and might represent a secondarily infected hepatic infarct.[20] Rarely, the liver abscess is due to *Yersinia enterocolitica* because iron overload and desferrioxamine therapy increase susceptibility to this organism.[21]

The clinical course of acute hepatitis B in patients with SCD might be the same as in control patients[22] or marked by higher bilirubin levels.[11] Seropositivity for hepatitis B surface antigen in SC patients is up to 3.3% of the population in the United States.[23] Vaccination against hepatitis B has been shown to be effective in SC patients.[24]

A hepatic bile-filled cyst (biloma), presumably the result of a hepatic infarction, has been described in a patient with right upper quadrant pain, fever, and jaundice.[25] Cocaine hepatotoxicity has been described in a patient in SC crisis.[26] The patient subsequently developed hepatic failure, which is rare in SCD. Occasionally, large vessel obstruction of the hepatic or portal veins[27,28] has been encountered in SCD.

Chronic Processes

Chronic liver disease in SCD might be due to hemosiderosis and hepatitis. It is possible that repeated small, clinically silent microvascular occlusions occur throughout the life of an SCD patient, eventually leading to liver fibrosis, superimposed on other causes of chronic liver disease. The high rate of liver cirrhosis of 18% among young patients with SCD, causing death in 11% of cases, supports this view.[29,30]

With increased longevity of patients with SCD, iron overload has become an issue. It stems from accumulation of transfused iron, increased gastrointestinal absorption as a result of intensive erythropoiesis, and iron deposition as a result of continu-