Gastrointestinal Pathology in Sickle Cell Disease*†

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ABSTRACT

The literature was reviewed to investigate the existence of unique gastrointestinal (GI) pathological lesions in sickle-cell disease (SCD). Chole- and choledocholithiasis have long been recognized, but bilirubin gallstones can occur in any chronic hemolytic anemia. Acute pancreatitis has been reported as a possible ischemic consequence of sickling. It is unclear if the hepatic lesions of SCD differ from those of any chronically transfused population. Hepatic failure has been associated with massive sickling and hyperviscous bile ("sludge") has been linked to SCD. Elevated 5'-nucleotidase in the presence of elevated aminotransferase may suggest both hepatic and biliary tree involvement in a subgroup of patients with SCD. Low levels of the hepatically produced coagulation inhibitors, Protein S and Protein C, have been identified in SCD, but their precise relation to thrombosis in this instance remains unclear. Finally, a syndrome of intracanalicular cholestasis, sinusoidal dilation, Kupffer cell hyperplasia, and erythrophagocytosis has been linked to SCD. It has been suggested that the use of exchange transfusion prior to liver biopsy in this group of pediatric SCD patients may mask the pathophysiological role of sickled red blood cells in hepatic dysfunction. With the exception of some of the situations cited, it is concluded that most GI lesions in SCD are common to a heavily transfused population with chronic hemolytic anemia.

Introduction

Sickle-cell disease (SCD) is a heterogeneous group of conditions associated with the substitution of valine for glutamic acid at the sixth position of the hemoglobin beta-chain. This abnormality causes hemoglobin to polymerize when the oxygen saturation is lowered, resulting in red blood cell (RBC) deformity, vaso-occlusion, ischemia, infarction, and chronic hemolysis, most closely associated with homozygous HbS disease. Patients with SCD have a variety of gastrointestinal (GI) conditions including gallstones, hepatitis, biliary sludge, hepatomegaly, painful crisis, and cirrhosis of various etiologies. These entities and other

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related GI states in SCD are reviewed with emphasis upon their morphological and biochemical attributes.

**Review of the Literature**

**Gallbladder**

Pigmented gallstones are a frequent and long recognized complication of SCD as well as other chronic hemolytic anemias. In one ultrasonographic study in the United Kingdom, over half of the homozygous HbS patients aged 10 to 65 years had gallstones, whereas, a much lower incidence of cholelithiasis existed in HbSC and HbS-beta thalassemia patients. A similar study in Jamaica, limited to a 5 to 13 year old population, found an incidence of only 13 percent for cholelithiasis in this group. Another sonographic study identified a 28.9 percent incidence of cholelithiasis in 90 Africans 15 years and over. Ware et al recognized the limitations of ultrasonography for the detection of common bile duct stones; however, in patients with sickle hemoglobin an etiological relationship of biliary sludge to gallstones has not been proven. Moreover, the clinical significance of and appropriate therapy for biliary sludge in the absence of cholelithiasis remains indeterminate.

Bile can be collected after cholecystokinin (CCK) stimulation and examined for calcium-bilirubin crystals. Also, dynamic nuclear scan with CCK stimulation can identify dyskinesia associated with bilirubinate crystals, cholesterol crystals, adenosis, and cholesterosis. Salmonella has also been identified using this technique. In childhood, gallstones might serve as a focus for infection, as reflected by increased hospitalizations and ambulatory visits. Also, there is one case report of a cholecystectomized adult with a Candidal fungal ball demonstrated by endoscopic retrograde cholangiography, possibly reflecting a similar phenomenon.

Laparoscopic cholecystectomy has been increasingly used for treatment of cholelithiasis. Gholson et al noted that serum aminotransferase and alkaline phosphatase were poor predictors of choledocholithiasis but that choledocholithiasis was relatively common in patients with SCD and cholelithiasis with increased baseline hyperbilirubinemia.

Others have touted the salutary effect of preoperative transfusions in this situation. Still, other groups have confirmed the value of laparoscopic cholecystectomy in SCD with cholelithiasis. One group, however, citing perioperative complications, did not recommend laparoscopic cholecystectomy in SCD preferring elective cholecystectomy instead.

**Pancreas & GI Tract**

Pancreatic symptoms associated with veno-occlusive etiology have been reported in patients with sickle hemoglobinopathies and should be considered in the differential diagnosis of abdominal pain in SCD. An 18-year-old woman died of a massive upper GI hemorrhage which the autopsy identified as pyloroduodenal ulcer with pancreaticoduodenal artery erosion. Duodenal ulcer symptomatology can be confused with abdominal pain crisis. Patients with SCD with duodenal ulcer do not appear to have high acid output suggestive of a different duodenal ulcer etiology in this population. Pseudomembranous colitis not associated with C. difficile has been associated with SCD. Fatal small bowel necrosis in SCD has occurred with vasodilators and hypotension. Finally, abnormal hydrogen breath tests possibly reflecting disordered GI motility or abnormalities of the intestinal microflora have been reported.

**Liver**

Much has been written concerning the hepatic pathological complications of SCD. Charlotte et al suggest that hepatic histologic lesions in SCD are primarily vascular—including sinusoidal dilatation, perisinusoidal fibrosis, and acute ischemic necrosis. Yeomans et al examined 40 women who received multiple RBC transfusions during pregnancy and found hepatic iron deposition without necrosis or fibrosis and concluded that the risk of irre-
GASTROINTESTINAL PATHOLOGY IN SICKLE CELL DISEASE

Versatile hepatic damage from transfusions during one pregnancy was minimal.\(^{26}\) Mills et al concluded that, with the rare exceptions of Budd-Chiari syndrome (hepatic vein occlusion) and chronic biliary sludge, the changes observed in the SCD liver are those to be expected in a heavily transfused chronically hemolytic population with a high incidence of cholelithiasis.\(^{27}\) Autopsy examination of 58 SCD patients aged 3 to 45 years identified sinusoidal distention, hemosiderosis and erythrophagocytosis, portal triaditis, cholestasis, focal necrosis, and fibrosis, and, uncommonly, extramedullary erythropoiesis. Among older patients aged 30 to 45 years, severe hemosiderosis, chronic inflammation, pigment stones, and fatty change were observed.\(^{28}\)

Comer et al studied the medical records and liver biopsies of 9 multiple transfused SCD patients and concluded that transfusion related etiologies were the most significant pathologic finding and were the most common cause of chronic liver disease in SCD.\(^{29}\) Among the viral causes of hepatic disease, both hepatitis B and C have been identified with increased incidence in SCD, and their prevalence is directly related to the number of transfusions received.\(^{30,31}\)

Acute and chronic intrahepatic cholestasis also have been associated with SCD. Clinical features include hepatomegaly, extremely elevated serum total bilirubin, coagulopathy, and liver failure.\(^{32}\) Therapy for this syndrome can include apheresis as well as correction of the coagulopathy.\(^{32,33,34}\) Mallouh and Asha, as opposed to others, concluded that acute cholestatic jaundice in SCD children was a relatively benign process.\(^{35}\)

Massive hepatic sickling leading to sequestration of RBCs in the liver has been postulated as a cause of acute hepatic failure with hepatomegaly amenable to apheresis.\(^{36,37}\) One group found a 72 percent hepatitis A incidence in acute fulminant childhood hepatic failure in SCD.\(^{38}\) Interestingly, a study of white Sicilian SCD patients revealed an extremely low incidence of liver disease owing to the more benign form of SCD associated with beta + thalassemia prevalent there.\(^{39}\) Omata et al compared liver biopsy to post-mortem hepatic histopathology and found an increased incidence of ischemic necrosis in post-mortem material as well as an almost universal prevalence of intrahepatic sickling and erythrophagocytosis not correlated with liver function test data leading them to conclude that these histologic features did not reflect the pathogenesis of liver disease in these patients.\(^{40}\)

Certain biochemical parameters are abnormal in SCD. Johnson et al concluded that the liver becomes the primary site of RBC destruction in SCD in the absence of splenic function. They identified a trimodal distribution of total bilirubin (TB) and lactic acid dehydrogenase (LDH) levels in SCD patients without liver disease and identified significant differences in various liver function test levels between SCD patients with and without hepatic disease.\(^{41}\)

This trimodal distribution reflected low, intermediate, and high TB and LDH level means and standard deviations of 1.4 ± 0.4, 3.1 ± 0.5, and 7.1 ± 2.5 mg/dl and 895 ± 266, 1152 ± 455, and 1700 ± 923 U/L, respectively, in a group of 78 patients. The TB was primarily indirect in all 3 subgroups; therefore, the TB and LDH levels most likely directly reflect 3 degrees of severity (mild, moderate, severe) of chronic hemolysis in SCD. The hepatically synthesized coagulation factor inhibitors, protein C and protein S, have been shown to be decreased in SCD, although the relevance of these observations to any presumed thrombotic tendency in SCD is unclear.\(^{42,43}\) The serum 5‘ nucleotidase has been shown to be elevated in SCD and correlated well with the gammaglutamyl transferase as opposed to the alkaline phosphatase values.\(^{44}\)

The recent identification of cocaine hepatotoxicity complicates the diagnosis of acute liver failure in cocaine abusers with SCD.\(^{45}\) El Younis et al noted a patient with autoimmune hepatitis which was ameliorated by corticosteroids and azathioprine.\(^{46}\) Furthermore, benign hepatic portal venous gas has been associated with endoscopic sphincterotomy.\(^{47}\) Hepatitis C associated cirrhosis has been treated by orthotopic liver transplantation in SCD.\(^{48}\)


Discussion

Owing to the polymerization of deoxygenated hemoglobin S causing RBC shape distortion and reduced deformability, SCD has protean manifestations.49 Virtually all the gut organs can be affected by SCD. The spectrum of GI disease associated with SCD can vary from hepatic sequestration, iron deposition, and cirrhosis to cholelithiasis. Liver function tests in SCD can be elevated in steady state SCD patients and can further increase owing to concomitant liver disease.

The differential diagnosis of abdominal pain in SCD is complicated by the possibility of conditions such as urinary tract infection or appendicitis, which are not directly related to SCD, as well as conditions such as renal infarction or hepatic sequestration which are more closely related to SCD.50 Finally, theoretical considerations involving the effect of hypoplasmin on GI disease need to be considered.51 Are SCD patients predisposed to GI disease owing to decreased splenic function? When considering this information in its entirety, it is difficult to conclude that there are unique GI lesions in SCD. However, it is our belief that a constellation of these findings can be characteristic of SCD. Moreover, the study by Johnson et al41 citing elevated liver function tests in steady-state SCD patients supports the need for using reference values oriented to the individual patient in SCD. Here, as an alternative to determining a reference interval for a group of subjects, a single subject’s previous values can be used as a reference for future values; this reference interval is referred to as a subject-based prediction interval.52 Furthermore, certain liver function tests such as the LDH and TB are affected by the chronic hemolysis which occurs in SCD. Finally, the trimodal LDH and TB distribution, identified by Johnson et al, can reflect the effect of alpha-thalassemia genes and beta-globin cluster genetic polymorphisms upon fetal hemoglobin synthesis and the severity hemolysis in SCD.

References
