

# Sickle Cell Hepatopathy

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Sickle cell hepatopathy encompasses a range of hepatic pathology arising from a wide variety of insults to the liver in patients with sickle cell disease. It occurs predominantly in patients with homozygous sickle cell anemia, and to a lesser extent in patients with sickle cell trait, Hb SC disease and Hb S  $\beta$  thalassemia. The hepatic disease may primarily be caused by the sickling process, but more commonly arises as a consequence of the multiple transfusions that these patients require in their lifetime. The term multitransfusion hepatopathy may therefore be more appropriate for these latter patients.

The direct manifestations of sickle cell disease in the liver relate predominantly to vascular occlusion with acute ischemia, sequestration, and cholestasis, although chronic cholestatic syndromes have also been described. The main hepatic complications of multiple transfusions include acute and chronic infection with hepatitis B and C and iron overload. A further potential consequence of the chronic hemolysis is the development of pigment stones, with consequent cholecystitis and acute and chronic biliary obstruction from choledocholithiasis.

Unfortunately, much of the literature on sickle cell hepatopathy lacks depth, because there are few sizeable or controlled studies, and most studies provide only incomplete information regarding coexisting chronic infection with hepatitis B or C, hepatic iron deposition, and chronic biliary obstruction from choledocholithiasis. It is therefore difficult to evaluate the contributing effects of these various insults in the final pathologic and clinical picture in these patients. As will be discussed subsequently, sickle cell anemia may lead to several unique liver syndromes (Table 1).

## CLINICAL SYNDROMES

Homozygous sickle cell anemia affects 1 in 600 African American babies, and sickle cell trait affects 8% to 10% of the black population.<sup>1</sup> Few American studies have sought to establish the incidence of liver disease in this population. In an autopsy study on 70 patients with sickle cell anemia, sickle C disease, and sickle thalassemia, hepatomegaly was noted in 91% of patients, indicating that some form of liver involvement is relatively common.<sup>2</sup>

Abnormal liver function tests are common in patients with sickle cell anemia, even in the absence of liver disease. Raised bilirubin levels, predominantly unconjugated, are universal in

sickle cell patients due to chronic hemolysis. Total bilirubin concentrations are usually less than 6 mg/dL. Johnson et al. found that 72 of 100 patients with sickle cell anemia had an isolated elevation of bilirubin, with no other clinical or laboratory evidence of liver disease.<sup>3</sup> Bilirubin levels correlate with lactic dehydrogenase levels,<sup>3</sup> suggesting that variable levels found in patients are related to the degree of hemolysis and/or ineffective erythropoiesis rather than to disorders of bilirubin transport or processing. Hemolysis also raises plasma aspartate transaminase (AST) levels, which therefore also correlate with lactic dehydrogenase levels.<sup>3</sup> Plasma alanine transaminase (ALT) levels therefore more accurately reflect hepatocyte injury in sickle cell patients. Elevations in the serum alkaline phosphatase are commonly seen in patients with sickle cell anemia, particularly during pain crises. However, studies suggest that bone alkaline phosphatase is the major enzyme fraction contributing to this increase.<sup>4,5</sup>

## ACUTE SYNDROMES

Patients with sickle cell disease may present with an acute syndrome characterized by right upper quadrant abdominal pain and jaundice. The differential diagnosis includes acute sickle hepatic crises, sickle cell intrahepatic cholestasis, acute viral hepatitis, cholecystitis, and choledocholithiasis with common bile duct obstruction. These can usually be differentiated by a careful history, liver function tests, serologic tests for viral hepatitis, and hepatobiliary imaging studies.

### Acute Sickle Hepatic Crisis

Acute sickle hepatic crisis occurs in approximately 10% of patients with sickle cell anemia.<sup>6-8</sup> Patients commonly present with acute right upper quadrant pain, nausea, low grade fever, tender hepatomegaly, and jaundice. Plasma AST and ALT levels seldom exceed 300 IU/L,<sup>7,8</sup> although levels of 1,000 IU/L or greater have occasionally been reported, presumably because of more severe hepatic hypoxic injury.<sup>9</sup> Serum bilirubin levels are usually less than 15 mg/dL.<sup>7</sup> Liver biopsy performed in 2 patients during hepatic crises showed sinusoidal obstruction by sickle cell thrombi, Kupffer cell hypertrophy, and engorgement with red blood cells. Mild centrilobular necrosis and occasional bile stasis was also noted.<sup>7</sup> The syndrome is self-limited, usually resolving within 3 to 14 days with intravenous hydration and analgesia.

Cocaine use by sickle cell anemia patients can have potentially disastrous results, precipitating a severe crisis due to synergistic hypoxic injury from cocaine-induced vasospasm and from sickling. Concomitant cocaine hepatotoxicity has been described in a patient with sickle cell crisis, who subsequently developed hepatic failure, coagulopathy, and encephalopathy.<sup>10</sup> ALT elevations were higher (18-fold) than would be expected from a simple sickle hepatic crisis. The patient's bilirubin peaked at 37.5 mg/dL, and prothrombin time at 14.7 seconds. A transjugular liver biopsy showed focal areas of confluent necrosis and large areas of collapse. The patient recovered gradually with supportive care.

### Hepatic Sequestration Crisis/Reverse Sequestration

In patients with sickle cell anemia, the usual site of massive sequestration of red blood cells is in the pulmonary vasculature, and before the advent of hyposplenism, the spleen. Hepatic sequestration may also occur, usually presenting with

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; MRI, magnetic resonance imaging; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; CT, computerized tomography.

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TABLE 1. Hepatobiliary Complications of Sickle Cell Disease

A. Clinical syndromes
Acute sickle hepatic crisis
Hepatic sequestration/reverse sequestration
Sickle cell intrahepatic cholestasis
Acute sickle cell intrahepatic cholestasis
Benign hyperbilirubinemia
Chronic intrahepatic cholestasis
Miscellaneous
Budd-Chiari syndrome
Hepatic infarction
Hepatic abscess
Hepatic biloma
Zinc deficiency with hyperammonemia
B. Complications of chronic hemolysis and multiple transfusions
Cholelithiasis and choledocholithiasis (pigment stones)
Hepatic iron overload
Viral hepatitis B and C (rare in current practice)

right upper quadrant pain, increasing hepatomegaly, and a falling hematocrit.<sup>11,12</sup> Hatton et al. describe 2 cases of hepatic sequestration in patients initially admitted with bone pain. A rapid decrease in the hematocrit in these patients was paralleled by a transient dramatic increase in hepatic size for 3 to 4 days, with little alteration in the liver function tests.<sup>11</sup> Regression of hepatic size to baseline was associated with a rapid increase in hemoglobin from 4.2 to 7.5 g/dL in 1 patient, indicating that not all sequestered cells are destroyed and that some may return to the circulation on resolution of the crisis and relief of sinusoidal obstruction. A case of fatal "reverse sequestration" has been described in which resolution of hepatic and pulmonary sequestration was accompanied by a spontaneous and rapid rise in the hemoglobin, from 5.1 to 12.3 g/dL over 24 hours, presumably from release of viable sequestered cells back into the circulation. Death occurred as a consequence of the resultant hypervolemia, hypertension, heart failure, and intracerebral hemorrhage.<sup>13</sup> Thus, exchange transfusion is probably preferable to partial exchange or additive transfusions in patients experiencing a sequestration crisis.

#### *Sickle Cell Intrahepatic Cholestasis*

This disastrous and often fatal condition may represent a severe variant of sickle hepatic crisis. It occurs as a consequence of widespread sickling within sinusoids with hepatic ischemia. Damage caused by hypoxia may result in ballooning of the hepatocytes with resultant intracanalicular cholestasis. The presentation is similar to sickle hepatic crisis, with right upper quadrant pain, nausea and vomiting, fever, tender hepatomegaly, and leukocytosis. However, striking jaundice then develops, accompanied frequently by renal impairment, a bleeding diathesis, and increasing encephalopathy.

Plasma ALT levels have ranged from 34 to 3,070 IU/L, plasma AST levels from 100 to 6,680 IU/L, and alkaline phosphatase levels have ranged from normal to 860 IU/L. The characteristic finding is that of strikingly high plasma bilirubin concentrations, with a level of 273 mg/dL documented in 1 patient.<sup>14</sup> In most cases the conjugated fraction exceeds 50% of the total bilirubin. The extremely high bilirubin levels are caused by a combination of on-going hemolysis, intrahepatic cholestasis, and renal impairment. Lactic dehydrogenase levels are usually elevated (660-7760 IU/L), and prolongation of

the prothrombin time and partial thromboplastin time is common. Elevations in blood urea, creatinine, and ammonia are also seen. Hypofibrinogenemia, thrombocytopenia, and lactic acidosis may accompany the liver failure.<sup>14</sup>

A Tc-99m sulfur colloid liver spleen scan done in a single patient showed hepatomegaly with patchy uptake of colloid.<sup>15</sup> Postmortem liver biopsies in 4 patients with sickle intrahepatic cholestasis showed dilated canaliculi with bile plugs.<sup>7,16-18</sup> Scattered bile stained microinfarcts were seen in 1 of these biopsies,<sup>17</sup> while widespread anoxic necrosis with areas of acute and chronic inflammation in addition to the usual findings noted in sickle cell patients were seen in the other 3 biopsies.<sup>7,16,18</sup>

Sixteen probable cases have been reported to date,<sup>7,14-22</sup> and whereas the syndrome proved fatal in 9 early cases, recent reports have described reversal of this process within 48 hours in 7 patients, with vigorous exchange transfusions and correction of coagulopathy with fresh frozen plasma.<sup>14-16,20-22</sup>

The renal impairment in sickle intrahepatic cholestasis has not been well studied, but appears reversible and improves concurrently with hepatic improvement.<sup>16,21</sup> Urine electrolytes were measured in 1 case and suggested acute tubular necrosis,<sup>21</sup> but the investigators attributed this to aminoglycoside therapy administered to the patient. Renal ultrasound done in a single case showed mildly altered corticomedullary differentiation.<sup>14</sup> Multiple focal acute renal infarcts were described on gross examination in a single case postmortem.<sup>7</sup> Renal histology was done in another patient postmortem and showed numerous hemoglobin casts in the distal convoluted tubules.<sup>19</sup> Hemodialysis was instituted in a patient for anuria,<sup>16</sup> and peritoneal dialysis was performed in a further patient for refractory hyperkalemia.<sup>7</sup> Both of these patients succumbed to their illness.

**"Benign" Hyperbilirubinemia.** Marked hyperbilirubinemia of up to 57 mg/dL, in most cases predominantly conjugated with only a mild elevation in ALT levels, has been described by Buchanan et al. in 6 children with minimal or no symptoms.<sup>23</sup> The hyperbilirubinemia resolved spontaneously within 2 to 8 weeks with no subsequent recurrences. Liver biopsy was not performed in these patients. Nine other cases have been previously reported in the literature, again with high bilirubin levels but with only modest elevations in plasma AST, ALT, and alkaline phosphatase levels, and a normal coagulation profile.<sup>3</sup> It is possible that these cases represent a benign variant of intrahepatic cholestasis.

**Chronic Intrahepatic Cholestasis.** A single case report describes a patient with sickle cell anemia and very high bilirubin levels of greater than 88 mg/dL caused by chronic intrahepatic cholestasis. He had no abdominal pain and no hematologic evidence of increased hemolysis. He responded dramatically to an exchange transfusion, with his bilirubin falling to 10 mg/dL. He subsequently developed repeated episodes of hyperbilirubinemia during a 3-year follow-up and required regular exchange transfusions to keep his hemoglobin S levels less than 20% and to prevent intrahepatic cholestasis from redeveloping.<sup>24</sup>

#### *Cholelithiasis in Sickle Cell Anemia Patients*

Cholelithiasis is extremely common in patients with homozygous sickle cell disease, with gallstones being present in up to 58% of patients aged 10 to 65 years versus 17% in patients with Hb SC disease and Hb S  $\beta$  thalassemia.<sup>25</sup> Choledocholithiasis has been noted in around 18% of patients with

sickle cell disease undergoing cholecystectomy. Distinguishing acute cholecystitis in sickle cell patients from sickle hepatic crisis may be difficult because of the similar clinical presentations. Ultrasound imaging is less helpful in making a diagnosis of acute cholecystitis in this patient group, although biliary scintigraphy may be useful in ruling out acute cholecystitis.<sup>26</sup> Because of these diagnostic difficulties, elective cholecystectomy should be considered in patients with symptomatic gallstones and also when there is difficulty in distinguishing gallstone-related symptomatology from sickle hepatic crises.

Even elective surgery can be hazardous in sickle cell disease patients, with the acute chest syndrome developing in 10% of patients and pain crises in 5%.<sup>27</sup> Similar complication rates are seen with either aggressive preoperative transfusion regimens designed to decrease the hemoglobin S level to less than 30% or with conservative regimens designed to increase the hemoglobin level to greater than 10 g/dL.<sup>27</sup> Conservative transfusion regimens are therefore recommended.<sup>27,28</sup> Similar complication rates are seen with open and with laparoscopic cholecystectomy, although the hospital stay is shorter with laparoscopic cholecystectomy, which is therefore recommended.<sup>28</sup>

#### MULTITRANSFUSION HEPATOPATHY

Autopsy series indicate a 16% to 29% prevalence of cirrhosis in sickle cell anemia patients.<sup>2,18,29</sup> It is unclear whether chronic hepatic ischemia occurs in these patients or indeed that it contributes to fibrogenesis. Cirrhosis in sickle cell anemia patients is usually secondary to chronic hepatitis B or C infection or because of iron overload.

#### *Hepatic Iron Overload in Sickle Cell Patients*

In patients with sickle cell anemia, serum ferritin levels correlate with the number of units of blood transfused.<sup>30</sup> Increases in serum ferritin occur during painful vaso-occlusive sickle crises,<sup>31</sup> and hence steady-state ferritin levels provide a better estimate of the degree of iron overload.<sup>30</sup> In multitransfused patients, increased deposition of iron occurs within reticuloendothelial cells, including Kupffer cells. Plasma steady-state ferritin levels correlate with hepatic iron stores, as determined by magnetic resonance imaging (MRI) of the liver,<sup>32</sup> and with ALT levels.<sup>30</sup> Iron chelation therapy with intravenous or subcutaneous deferoxamine results in increased urinary and biliary excretion of iron<sup>33</sup> and is associated with significant falls in serum ferritin and plasma ALT levels.<sup>34</sup>

Histologic progression to fibrosis in sickle cell patients with iron overload has been poorly studied. In an autopsy series of 70 patients with sickle cell anemia, sickle C disease, and sickle  $\beta$  thalassemia, 33 patients were found to have variable degrees of parenchymal iron deposition. In 3 of these patients cirrhosis was seen, and parenchymal iron accumulation was felt by the investigators to be severe enough to make a diagnosis of hemochromatosis as the cause for the cirrhosis.<sup>2</sup> However, hepatic iron content was not determined on biopsy, and the data do not rule out other causes contributing to the cirrhosis.

The investigators of another study followed 11 homozygous sickle cell anemia patients over 5 to 10 years. Patients received a mean of 180 units of packed red blood cells during this period together with intravenous deferoxamine 2 g with each transfusion. Despite deferoxamine, 2 patients went on to develop significant hepatic iron overload.<sup>35</sup> Exchange trans-

fusions result in a lower delivered iron load and in slower rises in the serum ferritin compared with conventional blood transfusions<sup>30</sup> and may be the best way to prevent significant iron overload from developing. Erythrocytapheresis, which preferentially removes sickled cells and older erythrocytes has also been shown to retard iron accumulation in sickle cell anemia patients.<sup>36</sup>

There is a single case report of sickle cell disease and purported hereditary hemochromatosis in a 51-year-old black man who had a limited transfusion history, having received only 2 units of packed red blood cells.<sup>37</sup> The diagnosis was based on a high serum iron with high saturation of the iron-binding capacity, and a serum ferritin of 2,450 ng/mL. In addition the patient had A3 and B7 antigens on HLA typing, and his liver biopsy showed iron deposition preferably in parenchymal cells rather than in Kupffer cells, leading the investigators to conclude that he had hereditary hemochromatosis. Of note, family studies were not done and the hepatic iron index was not reported.

#### *Viral Hepatitis in Sickle Cell Anemia Patients*

**Hepatitis A.** No American studies have examined the prevalence of hepatitis A markers in sickle cell populations. In Saudi Arabia, no difference in hepatitis A infection was observed between sickle cell anemia patients and non-sickle cell controls.<sup>38</sup> Yohannan et al. found that 2 of 3 patients developing fulminant hepatic failure over the course of a year were sickle cell anemia patients with acute hepatitis A infection. They propose that the underlying sickle cell disease may have predisposed to the severity of the presentation.<sup>39</sup> All patients with sickle cell anemia and chronic liver disease should be tested for hepatitis A virus antibodies and if negative be vaccinated against hepatitis A.

**Acute Hepatitis B.** Sheehy found that the clinical course and liver function tests in 5 patients with sickle cell anemia who developed acute hepatitis B did not differ from control patients without sickle cell disease.<sup>7</sup> In contrast, Johnson et al.<sup>3</sup> found that their 2 patients who developed acute hepatitis B had a mean peak bilirubin of 47 mg/dL, which is considerably higher than would be expected in patients without sickle cell anemia. The investigators attribute this to the underlying chronic hemolytic state. Sickle cell anemia patients with underlying chronic liver disease and lacking protective antibody against hepatitis B should receive the hepatitis B vaccine. Low-dose intradermal vaccination against hepatitis B is effective and immunogenic in sickle cell patients and may provide a more economical alternative for communities where the cost of vaccination might be considered prohibitive.<sup>40</sup>

**Chronic Hepatitis B.** The prevalence of chronic hepatitis B infection in sickle cell anemia patients has been low in recent fairly large scale studies from the United States, with a 0% to 3.3% seropositivity for hepatitis B surface antigen (HBsAg).<sup>41,42</sup> In parts of the world where hepatitis B is more prevalent, much higher rates of chronic hepatitis B exist in sickle cell patients as also in the general population. A study of 173 patients with sickle cell disease from 4 different regions of Saudi Arabia, indicated that 9.4% to 27.5% of patients were HBsAg positive. Infection rates were high in non-sickle cell controls as well, with 5.8% to 21.3% of controls being positive for HBsAg. Antibodies to delta virus were noted in 0% to 27% of sickle cell patients in the different regions in this study.<sup>43</sup> No data exist on interferon treatment for hepatitis B infection in patients with sickle cell anemia.

**Chronic Hepatitis C.** Not surprisingly, a relatively high prevalence of hepatitis C infection exists in this highly transfused population. Although the prevalence of hepatitis C virus (HCV) antibodies has been evaluated in several studies, confirmation and quantitation of current infection by polymerase chain reaction and genotyping has not been reported. DeVault et al. assayed 121 consecutive patients with sickle cell anemia for HCV antibodies.<sup>42</sup> Twenty-five patients had anti-HCV antibodies (20.7%), 2 of whom were also positive for HBsAg. The risk of HCV infection was related to the number of units of blood transfused; 30.3% of patients who received greater than 10 U transfused blood were positive for HCV antibody, compared with 8.7% of those transfused who received less than 10 U blood. Sixteen of the 25 patients with HCV antibodies had normal liver function tests. Polymerase chain reaction and liver biopsies were not reported in this study. Importantly, of 11 patients overall with a chronically elevated ALT, 9 were positive for HCV and 1 for HBsAg.

Similar results were noted in another study of 99 patients with sickle cell anemia, sickle C disease, and sickle  $\beta$  thalassemia. HCV antibodies were present in 10 patients overall (10.1%) and in 14.7% of previously transfused patients.<sup>41</sup> All patients were negative for HBsAg. HCV antibodies were not present in any of 31 patients who had never been transfused. The likelihood of having antibodies to hepatitis C increased with higher numbers of transfusions, and 23% of patients receiving more than 10 units of PRBCs were positive for HCV antibody, compared with 7.9% of those receiving less than 10 units. Seven patients with HCV antibodies had mild (1.5- to 4-fold) elevations in their plasma AST and ALT levels and underwent liver biopsy. Piecemeal necrosis and cirrhosis were each seen in 1 patient. Portal or lobular lymphocytic infiltration was seen in the remaining 5 patients, with additional focal fibrosis in 2. Four patients had intermediate degrees of siderosis on biopsy (grade 2-3 on a scale of 1-4). Similar HCV antibody prevalences of 17% to 18% have been noted in studies from West Africa<sup>44</sup> and Saudi Arabia.<sup>45</sup>

The natural history of chronic hepatitis C and the rate of progression to cirrhosis in sickle cell anemia patients is not known. Only anecdotal data exist on interferon treatment for hepatitis C infection in patients with sickle cell anemia. A single patient was treated with 3 million units 3 times a week, but therapy was withdrawn at 6 months because of lack of benefit.<sup>46</sup> Interferon use is, however, described in small studies in patients with thalassemia, both as monotherapy<sup>47-51</sup> or in combination with ribavirin,<sup>52</sup> with sustained virologic responses noted in 40% of patients receiving interferon monotherapy<sup>47</sup> and in 45% of patients who were administered combination therapy.<sup>52</sup>

**Hepatitis E.** In a single study from Saudi Arabia, hepatitis E antibodies were found in 18% of children with sickle cell anemia, compared with 5.5% of controls.<sup>53</sup>

#### MISCELLANEOUS LIVER CONDITIONS RELATED TO THE SICKLE CELL STATE

Hepatic infarction may occur as a consequence of a severe hepatic sickle crisis with vaso-occlusion.<sup>54</sup> Pyogenic liver abscesses may develop in patients with sickle cell anemia, at times at the site of prior hepatic infarction.<sup>55-58</sup> Hepatic abscess should be considered in sickle cell patients who develop fever and right upper quadrant pain. An expanding hepatic bile-filled cyst (biloma), presumably a consequence of hepatic infarction, has been described in a patient presenting with

right upper quadrant pain, fever, and jaundice.<sup>59</sup> The Budd-Chiari syndrome with both hepatic vein thrombosis<sup>60</sup> and inferior vena cava thrombosis<sup>61</sup> has been described in patients with sickle cell disease. Extensive thrombosis involving the hepatic, portal, superior mesenteric and splenic veins has also been described in a 13-year-old boy with sickle cell anemia.<sup>62</sup>

#### HYPERAMMONEMIA CAUSED BY ZINC DEFICIENCY

Patients with sickle cell anemia have hyperzincuria and systemic zinc deficiency caused by increased renal loss of zinc,<sup>63,64</sup> which may lead to zinc deficiency. Deferoxamine therapy may also increase fecal losses of zinc.<sup>34</sup> A recent study of 104 patients with sickle cell disease indicated that 44% had low plasma levels of zinc.<sup>65</sup> Zinc is a cofactor for ornithine transcarbamylase, a urea cycle enzyme,<sup>66</sup> and inhibition of the urea cycle with resultant hyperammonemia may occur with zinc deficiency.<sup>67</sup> The hyperammonemia may theoretically contribute to encephalopathy in cirrhotic patients with sickle cell anemia. The hyperammonemia of sickle cell anemia patients is reversible and can be corrected by zinc therapy.<sup>68</sup> Zinc therapy also appears to significantly decrease the number of sickle/pain crises in treated patients,<sup>69,70</sup> and zinc deficiency should therefore be corrected if present. Zinc may also regulate copper absorption from the gastrointestinal tract, and enhanced copper absorption and increased ceruloplasmin levels may also be seen with zinc deficiency.<sup>67,71</sup>

#### SICKLE CELL HEPATOPATHY IN WHITE POPULATIONS

An American survey of 65,751 naval recruits indicated a 0.045% prevalence of sickle cell trait in white recruits.<sup>72</sup> The prevalence of liver disease has not been studied in this population. In white Mediterranean populations the course of sickle cell anemia/trait is often milder than in African Americans, and few patients require regular transfusions.<sup>73</sup> In an Italian study of patients with sickle cell anemia, sickle cell trait and sickle  $\beta$  thalassemia, only 2 of 142 patients had significantly abnormal liver function tests, with only marginal abnormalities being seen in the rest.<sup>74</sup> Three- to 4-fold elevations were seen in the ALT in these 2 patients, with serum bilirubin levels between 10 to 14 mg/dL. Both patients were positive for HBsAg and for HCV antibody, and the abnormalities in their liver function tests may be explained on this basis.

#### ABDOMINAL IMAGING IN THE SICKLE CELL PATIENT

Given the significant overlap in the clinical presentation of the various hepatobiliary syndromes in sickle cell patients, imaging studies are commonly performed and may help elucidate the specific or dominant pathophysiologic process.

##### *Abdominal Ultrasound*

Abdominal ultrasound in patients with sickle cell anemia may reveal gallstones and increased echogenicity of the liver and pancreas caused by iron deposition.<sup>75</sup> Ultrasound examination is less useful for evaluating left upper quadrant pain due to the frequent presence of artifact from splenic calcifications, and computerized tomography (CT) is the preferred mode of imaging in this situation.

##### *CT of the Abdomen*

CT scanning in homozygous patients with sickle cell anemia usually reveals diffuse hepatomegaly, possibly a reflection

of expansion of the hepatic reticuloendothelial system. Only 2 studies, both from the same group, have sought to examine the use of abdominal CT in sickle cell disease patients with acute abdominal pain and/or fever.<sup>76,77</sup> CT provided a diagnosis which affected management in 17 of 30 patients. Hepatic infarction with wedge-shaped areas of low attenuation, hepatic abscess (irregular low attenuation area with peripheral enhancement and air/fluid levels), iron overload, and retained common bile duct stones after cholecystectomy were among the noted abnormalities.

Small atrophic splens with dense calcification were usually seen in homozygotes in these studies. Heterozygotes uniformly had splenomegaly. Other splenic findings in heterozygotes included infarcts, splenic rupture from extensive infarction and necrosis, hemorrhage, abscess, and acute splenomegaly caused by sequestration. A CT scan of the abdomen may also incidentally reveal basal pulmonary pathology presenting as abdominal pain. CT is therefore the preferred modality for the investigation of upper abdominal pain in patients with sickle cell disease.

#### MRI

MRI provides a qualitative assessment of hepatic iron overload in transfusion-dependent patients, showing a decreased signal intensity in the liver, pancreas, and spleen before atrophy, caused by iron deposition.<sup>75,78,79</sup> MRI can also provide a limited quantitative assessment of hepatic iron overload, being able to effectively separate patients with hepatic iron levels greater than 100  $\mu\text{g}/\text{mg}$  from those with levels less than 100  $\mu\text{g}/\text{mg}$ . However, it is unable to differentiate between iron levels in the 100- to 400- $\mu\text{g}/\text{mg}$  range.<sup>80</sup>

#### Biliary Scintigraphy

Because of the high morbidity and mortality of emergent cholecystectomy in sickle cell patients during a sickle crisis, excluding acute cholecystitis is of paramount importance in patients with right upper quadrant pain and fever. The use of scintigraphy with technetium-99m-diisopropyl-IDA (Tc-99m DISIDA) was investigated by D'Alonzo and Heyman, in a series of 9 patients with sickle cell disease (7 with documented cholelithiasis) presenting with acute right upper quadrant abdominal pain.<sup>26</sup> They were able to rule out acute cholecystitis in 7 of the 9 patients. The most common finding in these 7 patients was delayed gallbladder visualization, consistent with chronic cholecystitis.<sup>26</sup> Only 1 of the 9 patients had prolonged nonvisualization of the gallbladder consistent with acute cholecystitis. However, this patient was managed conservatively, hence the accuracy of this modality in establishing a positive diagnosis remains unclear.

#### Liver Spleen Scan

Liver spleen scans using 99m Tc-sulfur colloid may show absence of splenic activity due to splenic atrophy.<sup>81,82</sup> Occasionally rounded areas of functional spleen may persist and cause confusion with splenic abscesses on CT or ultrasound studies.<sup>83</sup> The distinction can be made using the liver-spleen scan, which should show uptake of Tc-99m sulfur colloid within these areas.<sup>83</sup> In patients with mild forms of disease and relative splenic preservation, such as sickle C disease, splenic sequestration crises are associated with a rapid increase in splenic size with diminished splenic function, indicated by diminished uptake of radioisotope.<sup>84,85</sup> Splenic up-

take returns to normal on resolution of the sequestration crises.<sup>85</sup> Uptake of 99mTc-diphosphonate has been reported in calcified areas of the atrophic spleen in patients undergoing bone scans for bone pain.<sup>81,82,86,87</sup> Care must be taken not to confuse appearances with abnormal bony lesions or an abnormal left upper quadrant mass.

#### LIVER BIOPSY FINDINGS

Pathologic changes caused by concurrent chronic hepatitis B or C including portal triaditis, chronic interface hepatitis, or cirrhosis, and changes caused by cholestasis from common bile duct stones may be seen in sickle cell patients.

Findings primarily caused by sickle cell anemia, which have been reaffirmed in several studies, include intrasinusoidal sickling with Kupffer cell hyperplasia with erythrophagocytosis, proximal sinusoidal dilatation, and hemosiderosis.<sup>2,9,29,88,89</sup> The largest postmortem series of 70 patients with sickle cell anemia noted Kupffer cell erythrophagocytosis in 91% of cases, sinusoidal red blood cell distension in 71% of cases, and iron deposition in 47% of cases.<sup>2</sup> Additional changes noted in this study included focal necrosis in 35% of cases, portal fibrosis in 20% of cases, regenerative nodules in 20% of cases, and cirrhosis in 16% of cases.

No correlation has been seen between the degree of intrasinusoidal sickling and plasma ALT and AST levels.<sup>3,89,90</sup> Incubation with formaldehyde was found to increase the sickled cell count from a mean of 12% to 48%,<sup>3</sup> and therefore some degree of intrasinusoidal sickling noted on histopathology may be due to fixation artifact. Omata et al. argue against the concept of anoxia contributing to liver damage in sickle cell patients, because their biopsy series in sickle cell patients showed no evidence of shrunken hepatocytes or perivenular necrosis (findings usually associated with anoxic damage).<sup>89</sup> The only patient in their series with zonal coagulative necrosis in perivenular areas had been in septic shock prior to undergoing liver biopsy. In contrast, ischemic necrosis was seen in 43.8% of liver specimens studied at autopsy in sickle cell patients in their series, which they attribute to agonal anoxia. However, in the series of 26 patients described by Charlotte et al., ischemic necrosis was seen in 5 patients, and hepatocellular atrophy in 14.<sup>91</sup>

Mild centrilobular necrosis has also been described in patients with sickle hepatic crises,<sup>7</sup> and widespread anoxic necrosis has been noted in 2 postmortem biopsies in patients with sickle cell intrahepatic cholestasis.<sup>7,16</sup> Other findings that may be seen on liver biopsy include perisinusoidal fibrosis, peliosis hepatis,<sup>91</sup> and extramedullary erythropoiesis in the liver.<sup>92</sup>

#### TREATMENT OF SICKLE CELL ANEMIA: EFFECTS ON THE LIVER

##### Androgenic Steroids

Androgenic steroids have been used in the past as therapy for sickle cell disease with severe anemia. Reversible hepatic toxicity, with hyperbilirubinemia exceeding 50 mg/100 mL, has been reported after treatment with oxymetolone.<sup>93</sup>

##### Hydroxyurea

Hydroxyurea increases HbF levels and has been shown to decrease the frequency of pain crises and the acute chest syndrome as well as transfusion requirements in patients with sickle cell anemia.<sup>94-97</sup> However, no difference was noted in

the frequency of hepatic sequestration crises compared with untreated controls,<sup>94</sup> which may also occur during hydroxyurea therapy.<sup>98</sup> Hydroxyurea treatment may result in a return of splenic function, with revisualization of the spleen on 99m Tc-sulfur colloid liver-spleen scans.<sup>99</sup>

#### Bone Marrow Transplantation

The main current indication for treatment with bone marrow or peripheral blood progenitor cell transplantation in pediatric populations with sickle cell anemia is a history of stroke.<sup>100</sup> The main gastrointestinal complications after transplantation include acute and chronic graft-versus-host disease and veno-occlusive disease of the liver.<sup>100-104</sup>

#### Liver Transplantation in Patients With Sickle Cell Anemia

Three cadaveric liver transplantations and 1 living-related donor transplantation have been reported in patients with sickle cell anemia and liver failure.<sup>46,105-107</sup> Successful liver transplantation was initially described in a 12-year-old child with sickle cell anemia and end-stage biliary cirrhosis by Lang et al.<sup>105</sup> Regular blood transfusions were used to maintain HbS levels at less than 20% for the first 6 months posttransplantation to minimize damage to the graft from sickle cell anemia. A 46-year-old woman with sickle cell anemia and liver failure caused by hepatitis C underwent transplantation,<sup>46</sup> with perioperative transfusions to decrease HbS levels to less than 25%. Mild elevations in plasma ALT levels and liver biopsy changes of sinusoidal congestion with sludging by sickled cells, and focal hepatocyte necrosis were noted postoperatively on day 39. Although her postoperative recovery was complicated by the development of an intracerebral hemorrhage, transplantation was otherwise successful. A patient with sickle  $\beta$  thalassemia and cryptogenic cirrhosis undergoing transplantation has also recently been reported.<sup>106</sup> Perioperative transfusions were used to keep hemoglobin S levels low. Despite this, early graft function was poor with very low levels of factor V at days 1 and 5. Severe cholestasis developed, with the bilirubin peaking at 44 mg/dL at day 7. Hydroxyurea was subsequently used to decrease the incidence of sickle crises posttransplantation. At 6 months posttransplantation, transient allograft dysfunction was noted caused by a sickle crisis leading to multiple hepatic infarcts, but subsequent graft function was satisfactory.

A single living-related liver transplantation has been performed in a child with acute liver failure caused by sickle cell intrahepatic cholestasis syndrome. However, outflow obstruction prompted retransplantation 3 months later. The child eventually succumbed to vascular complications related to sickle cell disease.<sup>107</sup>

#### CONCLUSION

The clinical spectrum of sickle cell disease ranges from mild liver function test abnormalities in asymptomatic patients, to dramatic clinical crises with marked hyperbilirubinemia and liver failure. Multiple factors may contribute to the etiology of the liver disease, including ischemia, transfusion related viral hepatitis, iron overload, and gallstones. Clarifying the dominant etiologic consideration during a crisis requires a thorough understanding of the various syndromes unique to this disorder and a comprehensive workup, including serologic testing and abdominal imaging.

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