

Brief report

Acute sickle cell hepatopathy represents a potential contraindication for percutaneous liver biopsy

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After several complications following percutaneous liver biopsy in patients with sickle cell disease, we reviewed our experience. We examined 14 patients with sickle cell disease who underwent a percutaneous liver biopsy. Clinicopathologic findings were correlated with outcome. Of 14 patients, 5 (36%) suffered serious hemorrhage; 4 died (80%; 28% of all patients). None of the 9

patients without biopsy complications was in an acute sickling crisis at the time of biopsy; 4 of 5 patients with complications were in acute sickling crisis. Of the 5 patients with complications, 4 underwent biopsy for an emergency indication. Chronic venous outflow obstruction, marked hepatic sequestration of erythrocytes, and sinusoidal dilatation were strongly associated

with complications. Data obtained by biopsy in group 1 were not of substantial value in clinical management, in contrast to group 2 (8/9; 89%). Acute hepatic disease complicating sickle cell anemia represents a newly identified contraindication to percutaneous liver biopsy. (*Blood*. 2003;101:101-103)

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Introduction

Percutaneous liver biopsy remains an invaluable diagnostic tool in the investigation of liver disease. The principal cause of death due to such biopsy is intraperitoneal hemorrhage, with a death rate of 0.11% to 0.33% in district general hospitals in the United Kingdom.¹ Certain conditions, including thrombocytopenia, bleeding diathesis, cirrhosis, ascites, and amyloidosis, are recognized relative or absolute contraindications to biopsy. After encountering serious complications of liver biopsy in 2 patients with sickle cell disease, we reviewed our clinical experience of liver biopsy in this patient group, previously considered as at "neutral risk."²

Study design

Records of all patients with sickle cell disease who in the last 10 years underwent a percutaneous biopsy at King's College Hospital were reviewed. We identified 14 patients (5 female, 9 male; mean age 30 years [range, 8-50 years]). Clinical notes and, where appropriate, autopsy reports and the coroner's death register were examined. We correlated outcome after biopsy with clinical, demographic, and hematologic data (severity of sickle cell disease, sickle cell genotype, evidence of acute sickle cell crisis at time of biopsy, indication for biopsy, known pre-existing liver disease or risk factors [other than sickle cell anemia] for such disease, size of liver biopsy, number of needle passes at biopsy, and prebiopsy platelet count and international normalized ratio [INR]). There were 2 reviewers who independently assessed histopathologic findings in biopsy specimens.

Results and discussion

Outcome

Clinically manifest hemorrhage followed percutaneous liver biopsy in 5 patients (36%), of whom 4 died (80%; 28% of all patients). There were 3 patients who experienced massive intraperitoneal bleeding; although angiographic embolization was successful in 2 patients, multiorgan failure developed and, within 7 days of the biopsy, death supervened. The third patient was too unstable to undergo angiography and died within hours of bleeding. The fourth patient died 35 days after the biopsy and subsequent to embolization of a large hepatic artery pseudoaneurysm, with development of gallbladder necrosis and multiorgan failure. The only patient to survive manifested acute tender hepatomegaly and intermittent upper gastrointestinal tract hemorrhage, owing respectively to bleeding beneath the Glisson capsule and to hemobilia. An arteriovenous fistula was found at angiography 7 days after biopsy and was successfully embolized. The other 9 patients were assessed as complication free.

Clinical and laboratory risk factors

In an attempt to identify factors placing patients with sickle cell disease at risk of adverse outcome of percutaneous liver biopsy, we classed the study population between 2 groups. Group 1 (n = 5) contained the patients who experienced postbiopsy hemorrhage. Group 2 (n = 9) contained the patients who were complication free.

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The baseline liver biochemistry was considerably more deranged at the time of liver biopsy in group 1 (median bilirubin 176 μM [range, 53-626 μM] and aspartate aminotransferase [AST] 190 IU/L [range, 28-283 IU/L]), compared with group 2 (median bilirubin 143 μM [range, 21-332 μM] and AST 56 IU/L [range, 23-159 IU/L]) (Table 1). The laboratory reference range for bilirubin level was 3 μM to 5 μM and AST 10 IU/L to 50 IU/L.

All patients in group 1 were adults (genotype homozygous sickle cell [HbSS]), with clinically more severe sickle cell disease and a longer in-patient hospital stay than that of the patients in group 2 (2 children and 8 adults, HbSS 7 and heterozygous sickle [HbS]/thalassemia 2) (Table 1).

The main indications for liver biopsy in group 1 were significant derangement in liver function (deteriorating rapidly in 4 of 5). Abnormal liver function tests (LFTs) were the sole indication for a liver biopsy in only 3 of 9 patients in group 2, with the remaining 8 patients having evidence of pathology other than sickle cell disease (Table 2).

Histologic risk factors

In liver biopsy specimens from patients in group 1, the main morphologic features were sinusoidal dilatation and chronic venous outflow obstruction (4 of 5 patients). Mild-to-moderate sinusoidal and centrilobular fibrosis was present in both groups. Aggregated, sickled erythrocytes were seen in all group 1 patients (prominent in 3 of 5 cases). In contrast, aggregated, sickled erythrocytes and sinusoidal dilatation were present in only 4 of 9 patients in group 2, and were a prominent feature in only one patient. Changes of chronic venous outflow obstruction were not found in any patients in group 2.

This study is the first to report the high risks of hemorrhage (36%) and death (28%) in a group of patients with sickle cell disease who underwent percutaneous liver biopsy. We have identified clinical and histologic associations with adverse outcome. These may explain why our experience with liver biopsy in such patients differs from that previously reported.

The Institute for Liver Studies at King's College Hospital, where these patients received care, is a tertiary referral unit. Less gravely ill patients may not be referred here, with the clinical spectrum encountered at King's skewed toward severe disease. This is perhaps reflected in these patients by long histories of

Table 2. Clinical indications for liver biopsy and histopathologic diagnosis

Clinical indication for liver biopsy	Histopathologic diagnosis
Group 1	
1 Abnormal LFT	Acute sickle cell hepatopathy/probable cirrhosis
2 Abnormal LFT	Acute sickle cell hepatopathy
3 High ferritin/HSM	Acute sickle cell hepatopathy
4 Abnormal LFT/HCV RNA+ve	Acute sickle cell hepatopathy/mild HCV hepatitis
5 Abnormal LFT/HSM	Chronic sickle cell hepatopathy
Group 2	
1 HCV RNA positive	HCV-related hepatitis/mild focal sickling
2 Drug-induced hepatitis	TB granulomas/severe siderosis
3 Raised ACE levels/HSM	Severe sarcoid granulomatous hepatitis
4 HCV RNA positive	Severe fibrosis, siderosis, and cholangiolitis
5 Abnormal LFT	Granulomatous hepatitis
6 Abnormal LFT, hepatomegaly	Grade 3 siderosis and focal sickling
7 Suspicion of liver infiltration	Flourid granulomatous hepatitis
8 Assessment of iron deposition	Grade 2-3 siderosis and minimal fibrosis
9 Abnormal LFT	Steatohepatitis/Wilson disease

LFT indicates liver function tests; HSM, hepatosplenomegaly; HCV RNA, hepatitis C virus RNA; and ACE, angiotensin converting enzyme.

illness, marked abnormalities in laboratory test results, and the presence of histologic findings.

In a recent publication that reported no significant complications of percutaneous liver biopsy in patients with sickle cell disease, the group studied regularly received blood transfusions.³ Elective liver biopsy in these patients was conducted primarily to assess transfusional hemosiderosis rather than to investigate acutely manifest or worsening liver disease. Laboratory test evidence of liver disease was less in this group (eg, mean serum concentration of alanine aminotransferase activity, 27 ± 15 U/L). In addition, none of the electively studied patients examined in this report had evidence of acute sickling crisis at the time of liver biopsy.

The histologic findings in our patient group may in part explain why so many of them bled. Hepatic venous congestion confers an increased risk of postbiopsy hemorrhage,³ and dilated sinusoids with centrilobular fibrosis and parenchymal loss (changes of chronic venous outflow obstruction) were seen in material from all the patients who died. In addition, a high degree of red cell aggregation, suggestive of hypoxemia with sickling and sludging, was associated with poor outcome. These histologic features, together with Kupffer cell enlargement owing to erythrophagocytosis,⁴ are thought to contribute to intrahepatic obstruction to blood flow and to hepatocellular hypoxia.^{5,6} Hepatocellular dysfunction (a consequence of hypoxia) and hepatic fibrosis may be postulated to diminish liver reserve, explaining why our patients tolerated the insults of hemorrhage and hypotension poorly.

The rapid worsening in results of liver function tests seen in 4 of the 5 patients in group 1 was in retrospect caused by an episode of acute sickle cell hepatic crises. In a recent review of sickle cell hepatopathy, Banerjee et al⁷ described 3 acute syndromes directly attributed to the effect of sickle anemia in the liver (acute hepatic cell crisis, acute hepatic sequestration crisis, and sickle cell intrahepatic cholestasis). Acute sickle cell hepatic crises occurs in 10% of patients with sickle cell anemia,^{8,9} commonly presenting with tender hepatomegaly, jaundice, and low-grade fever. AST and bilirubin rarely exceed 300 IU/L and 255 μM , respectively,

Table 1. Baseline clinical and laboratory parameters in the 2 groups examined

	Group 1 (n = 5), hemorrhagic complications	Group 2 (n = 9), complication free
Demographics		
Age, years (range)	32 (20-39)	31 (8-50)
Sex, M/F	5/0	5/7
Disease severity		
Genotype (HbSS/HbS-Thal)	5/0	7/2
Hospital admissions in the year, in days (range)	69 (40-365)	3 (0-30)
Patients in sickle cell crisis at time of biopsy	4	1
Laboratory indices		
Bilirubin level, μM	176 (53-626)	143 (10-332)
AST level, IU/L (range)	190 (28-283)	56 (23-159)
INR (range)	1.23 (1-2.2*)	1.09 (0.86-1.8*)
Platelet count, $\times 10^9/\text{L}$ (range)	109 (69†-573)	154 (56†-865)

*Before fresh frozen plasma transfusion.

†Before platelet transfusion.

although higher levels have been reported. This syndrome is usually self-limiting, resolving within 3 to 14 days with supportive treatment.

It is to be regretted that the information gained through liver

biopsy in our group 1 patients did not contribute significantly to clinical management. Histologic findings contributed substantially to clinical management, however, in 8 of 9 group 2 patients, who paradoxically experienced no complications (Table 2).

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