The Histopathologic Features of Sickle Cell Hepatopathy: A Multi-Institutional Study

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ABSTRACT

Objectives: Recent data on hepatic histopathology in patients with sickle cell disease (SCD) are lacking.

Methods: A total of 39 liver biopsies from SCD patients from 4 medical institutes were systematically evaluated.

Results: The average age of patients was 27 years; 23 were female. The majority of the patients had hemoglobin SS (33), 3 had hemoglobin SC, and 3 sickle cell trait. Elevated liver functional tests and evaluation for cirrhosis were the main indications for biopsy. At the time of biopsy, most had elevated liver transaminases or hepatomegaly. The most common histopathologic abnormalities were Kupffer cell erythrophagocytosis (76.9%), hemosiderosis (74.4%), sinusoidal dilatation (71.8%), and intrasinusoidal sickled red cells (69.3%). Portal inflammation, lobular inflammation, and bile duct injury were mild to minimal and present in a minority of cases. Advanced fibrosis was present in 28.2% of the cases.

Conclusions: The typical histopathologic features seen in patients with SCD include Kupffer cell erythrophagocytosis, hemosiderosis, sinusoidal dilatation, and intrasinusoidal sickled red cells in a pauci-inflammatory or uninflamed background. Necrosis is less common than reported in older literature. Pathologists should be aware that significant portal and lobular inflammation, interface activity, and bile duct injury are unusual and may be suggestive of other etiologies.

INTRODUCTION

Sickle cell disease (SCD) includes a group of inherited disorders resulting from mutations in the gene that encodes hemoglobin subunit β.[1,2] The most common subtype of SCD is sickle cell anemia, which is characterized by the presence of homozygous mutation in hemoglobin β gene.[3] Other SCD mutations include hemoglobin SC and hemoglobin S/β-thalassemia.[1,3] The incidence is approximately 300,000 to 400,000 neonates globally each year. Although it is most prevalent in the Mediterranean and sub-Saharan Africa, global immigration substantially changes the distribution of the disease.[2,4] SCD is a multisystem disorder that affects almost any organ in the body, including the hepatobiliary system.[2,5,6] Sickle cell hepatopathy (SCH) is a general clinical term that

KEY POINTS

- The typical histopathologic features in SCD include Kupffer cell erythrophagocytosis, hemosiderosis, sinusoidal dilatation, and intrasinusoidal sickled red cells.
- Significant portal and lobular inflammation, interface activity, and bile duct injury are unusual and suggestive of other etiologies.
- Liver biopsy is not the routine first-tier diagnostic approach for SCD. It is to exclude other causes, either related or unrelated to SCH.

KEY WORDS

Sickle cell disease; Liver; Sickle cell hepatopathy

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encompasses a broad range of liver dysfunction.[7-10] Liver biopsy is seldom performed in SCD patients with suspected SCH, due to high risk of bleeding, and is contraindicated in the setting of acute hepatic crisis.[11]

The histopathologic evaluation of SCH in medical literature was reported 40 years ago.[12] Since then, advances in early diagnosis and newborn screening have substantially altered the disease course of SCD patients in the United States.[12,13] We hypothesized that the spectrum of hepatic injury may also have changed with advances in detection and therapy. The aim of this multi-institutional study is to (1) update the hepatic histopathology in patients with SCH, and (2) to evaluate the utility of liver biopsy.

MATERIALS AND METHODS

Patients

This is a retrospective multi-institutional observational study. After approval from the institutional review boards, the laboratory information systems of 4 academic institutes (Indiana University, Albert Einstein College of Medicine, Albany Medical College, and University of Michigan) were searched for adequate liver biopsies from SCD patients over a 20-year period from 1998 to 2018. A total of 46 patients were identified. Seven patients suspected to have SCD but without confirmatory hemoglobin electrophoresis were excluded. Therefore, a total of 39 liver biopsies from SCH patients were included in the study.

Histomorphologic Review

All available glass slides were reviewed at the participating sites. In addition, central review was performed by 1 pathologist (J.L.) who evaluated digital images or glass slides of H&E, trichrome, reticulin, and iron special stains for each case. Batts-Ludwig grading and staging system was applied to evaluate the amount of inflammation and fibrosis.[14] Accordingly, the fibrosis was staged as none, portal fibrous expansion, periportal fibrosis, bridging fibrosis, and cirrhosis using trichrome stain. The distribution and severity of other histopathologic features, including cholestasis, sinusoidal dilatation and congestion, zone 3 hepatocyte atrophy, Kupffer cell erythrophagocytosis, necrosis, hepatocyte dropout, and intrasinusoidal sickled red cells were evaluated. Distribution of these findings was classified as focal, patchy, or diffuse. The criteria to define bile duct injury depend on the degree of epithelial atypia. Mild bile duct injury was defined as slight reactive changes of the biliary epithelium, including nuclear disarray and atypia with or without cytoplasmic attenuation. When the epithelia demonstrated prominent atypia or cell dropout, it was considered marked. Moderate bile duct injury fell between mild and marked. Cholestasis was also graded as mild to marked based on the severity. When focal bile plug was observed on high-power magnification, mild cholestasis is considered, whereas marked showed obvious bile pigment evident on low-power magnification involving the majority of the liver biopsy. Moderate cholestasis fell between mild and marked. Iron quantitation was graded by the density of the blue granules on iron stain: 4+ represents intense deposition that can be seen even without microscope, 1+ represents faint staining requiring high magnification (×400) for detection, and 2+ and 3+ falling between.

Clinical, Radiographic, and Laboratory Data

Relevant clinical, radiographic, and laboratory data were collected retrospectively. Data collected included age, sex, sickle cell type, indication for the liver biopsy, episode of sickle cell crises, treatment regimens, treatment location (inpatient vs outpatient), presence of hepatomegaly (confirmed by imaging), liver enzymes, and viral and autoimmune serologies.

Statistical Analysis

The Statistical Package for Social Science (SPSS version 26) was used to analyze the data. Univariate analysis was done to assess the associations between histologic features, presence or absence of hepatomegaly, and treatment location. Pearson χ^2 or Fisher exact test was performed and $P < .05$ was considered significant.

RESULTS

Demographics and Clinical Data of the Patients With Sickle Cell Hepatopathy

The average age of the SCH patients was 27 years (range, 3-64 years). Slightly more than half of the patients were female (23, 59%) with a female to male ratio of 1.4:1. The majority of the patients had hemoglobin SS (33, 85%), 3 had hemoglobin SC, and 3 sickle cell trait.

TABLE 1 The Demographics, Radiographic, and Laboratory Features of the Patients With Sickle Cell Hepatopathy

Feature	No. (%)
Imaging (n = 27)	
Hepatomegaly	9 (33.3)
Not enlarged	18 (66.7)
Viral serology (n = 37)	
HBV	2 (5.4)
HCV	4 (10.8)
Negative serology	31 (83.8)
AST (n = 35)	
Normal	6 (17.2)
Elevated	29 (82.8)
ALT (n = 35)	
Normal	10 (28.6)
Elevated	25 (71.4)
ALP (n = 35)	
Normal	14 (40.0)
Elevated	21 (60.0)
TBIL (n = 35)	
Normal	8 (22. 9)
Elevated	27 (77.1)
Treatment location (n = 37)	
Inpatient	20 (54.1)
Outpatient	17 (45.9)

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; TBIL, total bilirubin.

TABLE 2 Clinical, Laboratory, and Radiographic Features of 39 Patients With Sickle Cell Hepatopathy

Patient	Age, y/Sex	LFT	Virus	Image	Indication for Liver Biopsy	Sickle Cell Crises	Treatment
1	12/F	+	–	NA	Evaluation for cirrhosis	Yes, multiple	Transfusion/iron chelation/supportive
2	23/M	+	–	NA	Evaluation for cirrhosis/suspicion for HPS	Yes, multiple	Transfusion/iron chelation/hydroxyurea/supportive
3	18/M	+	HCV	NA	Evaluation for cirrhosis/acute liver failure	Yes	Unknown
4	55/M	+	–	+	Elevated LFTs	No	Unknown
5	12/F	+	–	NA	Elevated LFTs/cholecystectomy	Yes, multiple	Hydroxyurea/supportive
6	22/F	+	HBV	NA	Acute liver failure	Yes	Supportive
7	56/M	–	HCV	–	Evaluation for cirrhosis/elevated LFTs	Yes, multiple	Supportive
8	29/F	–	HBV	–	Elevated LFTs	Yes, multiple	Hydroxyurea/supportive
9	19/F	–	–	NA	Transplant workup/acute liver failure	Unknown	Unknown
10	15/M	+	–	–	Evaluation for possible liver sequestration crisis	Yes, multiple	Supportive
11	29/F	+	–	–	Evaluation for cirrhosis	Yes, multiple	Transfusion/iron chelation/supportive
12	53/F	+	–	–	Elevated LFTs	Yes, multiple	Transfusion/supportive
13	20/F	+	HCV	–	Abnormal liver at time of cholecystectomy	Yes, multiple	Supportive
14	11/M	+	–	–	Evaluation for cirrhosis	Yes, multiple	Transfusion/iron chelation
15	27/F	+	–	–	Enlarged liver SCD vs sarcoidosis	Yes, multiple	Iron chelation/hydroxyurea/supportive
16	35/M	+	–	–	Evaluation for cirrhosis	Unknown	Supportive
17	45/F	+	–	–	Elevated LFTs	Yes, multiple	Transfusion/iron chelation/supportive
18	24/M	+	–	+	Elevated LFTs	Yes	Supportive
19	19/F	+	–	NA	Elevated LFTs	No	Supportive
20	30/F	+	–	+	Evaluation for cirrhosis	Yes	Transfusion/supportive
21	20/F	+	–	+	Elevated LFTs	Yes	Transfusion/iron chelation/hydroxyurea/supportive
22	21/F	+	–	–	Evaluation for cirrhosis	Yes	Transfusion/iron chelation/supportive
23	6/F	+	–	+	Elevated LFTs/acute liver failure	Yes	Hydroxyurea/supportive
24	48/F	+	–	–	Evaluation for cirrhosis	Yes, multiple	Transfusion
25	17/M	+	–	NA	Elevated LFTs	Yes, multiple	Transfusion
26	10/F	+	–	–	Evaluation for cirrhosis/iron overload assessment	Yes, multiple	Transfusion/iron chelation/hydroxyurea/supportive
27	43/M	+	–	+	Not provided	Yes, multiple	Transfusion/iron chelation
28	16/M	+	–	+	Abnormal liver at time of cholecystectomy	Yes, one	Iron chelation
29	64/F	–	HCV	–	Elevated LFTs	Yes, multiple	Supportive
30	3/M	–	–	+	Biopsy for clinical trial	No	Transfusion/iron chelation
31	33/M	–	–	NA	Iron overload assessment	Yes, multiple	None
32	23/F	+	–	NA	Elevated LFTs/positive autoimmune serology	Yes, multiple	Transfusion
33	17/M	–	–	NA	Elevated LFTs	Unknown	Hydroxyurea
34	56/F	+	–	–	Elevated LFTs	No	Unknown
35	13/F	+	–	–	Iron overload assessment	Yes	Hydroxyurea
36	11/M	+	–	–	Iron overload assessment	Yes, one	Transfusion
37	48/M	+	–	NA	Iron overload assessment	Yes, one	Transfusion/iron chelation/supportive
38	17/F	+	NA	–	Iron overload assessment	Yes, multiple	Transfusion/iron chelation/hydroxyurea/supportive
39	23/F	+	NA	+	Elevated LFTs	Yes, one	None

HBV, hepatitis B virus; HCV, hepatitis C virus; HPS, hepatopulmonary syndrome; Image +, liver enlarged; Image –, liver not enlarged; LFT, liver function test (+, elevation of liver enzymes, –, normal); NA, not available.

As shown in TABLE 1 and TABLE 2, most SCH patients had either elevated liver enzymes or hepatomegaly at the time of liver biopsy. Liver enzyme values were available in 35 patients. Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) were elevated in most patients. At the time of liver biopsies, 82.8% of the patients had elevated AST (average 215.9 units/L), 71.4% had elevated ALT (average 186 units/L), and 60% had elevated ALP (average 219.8 units/L). Total bilirubin was elevated in 27 patients (77.1%, average 8.4 g/L). Nine of 27 SCH patients with available clinical data had hepatomegaly (33.3%) confirmed by imaging.

Viral serology was performed and available in 37 patients. Four were positive for hepatitis C virus (HCV) infection and 2 were positive for hepatitis B virus (HBV) infection. No patients in our cohort

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had an evidence of autoimmune hepatitis, alcoholic liver disease, or nonalcoholic fatty liver disease. Drug-induced liver injury had also been excluded clinically. Less than half of the patients were treated as outpatients (17, 45.9%).

Indications for the liver biopsies were variable in our study and some had more than 1 indication. Elevated liver functional tests (38.5%) and evaluation for cirrhosis (28.2%) were the most common indications. The others included evaluation for iron overload (15.4%), acute liver failure (12.8%), abnormal liver during cholecystectomy (7.7%), pretransplant evaluation (2.7%), SCD crisis (2.7%), hepatopulmonary syndrome (2.7%), clinical trial (2.7%), or no indication provided (2.7%). At least 82.1% of the patients had recorded episodes of sickle cell crises and many had multiple. Treatment regimens were widely viable. At least 46.2% of patients received exchange transfusion, 35.9% had iron chelation, 25.6% had hydroxyurea, and 59.0% had supportive treatment. Two patients had no recorded treatment. Two patients' treatment documents were not available. Detailed clinical data are provided in TABLE 2.

Histopathologic Features of Sickle Cell Hepatopathy

As shown in TABLE 3, TABLE 4, and FIGURE 1, the most common histopathologic patterns in SCH were Kupffer cell erythrophagocytosis (76.9%, FIGURE 1A), hemosiderosis (74.4%, FIGURE 1B), sinusoidal dilatation (71.8%, FIGURE 1C), and intrasinusoidal sickled red cells (69.3%, FIGURE 1D). Hemosiderosis was severe in 38.5% of the cases. Although sinusoidal dilatation is common, central vein recanalization, as shown in FIGURE 2, is rare. There was no confluent hepatocyte necrosis identified in the study cohort, although zone 3 hepatocyte atrophy and dropout were present in 35.9% and 17.9% of the cases, respectively FIGURE 1B. Among 14 biopsies with hepatocyte atrophy, 4 showed diffuse involvement. Portal inflammation, lobular inflammation, and bile duct injury were mild to none FIGURE 1B and FIGURE 1C, present only in a minority of cases (30.8%, 15.4%, and 12.8%, respectively).

Advanced fibrosis (bridging or cirrhosis) was present in 11 (28.2%, FIGURE 2C) cases; among them, none had positive viral serology. Interestingly, beyond the conventional staging for fibrosis, we observed that zone 3 perisinusoidal fibrosis was common (69.2%) in our study cohort, including those with more advanced fibrosis. It could be either focal delicate FIGURE 2A or diffuse prominent FIGURE 2B. Only 1 biopsy (2.6%) showed cholestasis (moderate). Other minor histologic changes included rare tiny noncaseating granulomas (2 cases).

The histopathologic features (hemosiderosis, sinusoidal dilatation, congestion, zone 3 hepatocyte atrophy, and advanced fibrosis) were correlated with treatment location and the presence of hepatomegaly by imaging. None were statistically significant.

DISCUSSION

SCH is an umbrella term that comprises a diverse range of hepatobiliary complications in SCD.[6,9,15,16] The prevalence of liver dysfunction in adults with SCD is estimated to be approximately 10%.[6,9] In a large retrospective study on more than 600 children with SCD, nearly 40% had a history of hepatobiliary manifestations.[6] Generally speaking, the hepatobiliary complications of SCD can be divided into acute (acute sickle cell hepatic crisis, acute hepatic sequestration, and acute intrahepatic cholestasis) and chronic (cholelithiasis/choledocholithiasis, iron overload, viral hepatitis, and sickle cell cholangiopathy).[6] Hepatobiliary complications are the result of multiple complex mechanisms including vascular occlusion and hyperbilirubinemia caused by the disease itself, as well as iron overload and viral hepatitis due to the repeated blood transfusions that are often needed in those patients.[6,8]

The literature on hepatic histopathology in SCH would benefit from updates to reflect the advances in the management of SCD over the decades. Forty years ago, Bauer and colleagues described the histopathologic spectrum of liver disorder in a series of 70 autopsies from patient who had SCH. Kupffer cell erythrophagocytosis, sinusoidal dilatation, and hemosiderosis were the most common histologic abnormalities.[12] These findings were verified by other colleagues.[13,17] We sought to add to the available data on hepatic histopathology of SCH by evaluating liver biopsies from SCH patients performed in the era of modern screening and therapy. Kupffer cell erythrophagocytosis, sinusoidal dilatation, and intrasinusoidal sickled red cells remained common findings in our cohort. These features are pathognomonic for SCH itself. SCD patients accumulate iron in their liver secondary to a multitude of pathophysiologic derangements including repeated blood transfusions, increased gastrointestinal absorption, and continuous hemolysis.[18] In our study, hemosiderosis was a common pathologic finding in SCH patients. The frequency of hemosiderosis detected on histopathologic examination varies from 8%[19] to 47%[12] in the published literature. A possible explanation of the high frequency (74.4%) of hemosiderosis in our study is that the advances in management and longer life expectancy potentially expose the patients to the increased risk of repeated transfusions.

Necrosis has been commonly observed in the past studies of SCH. In 1957, an autopsy study described that all SCD patients had some degree of hepatic necrosis; among them, 6 had massive necrosis.[20] Another study performed in 1986 showed that necrosis was seen in almost half of the autopsy and 5% of biopsy specimens[13]; most of the SCD patients with hepatic necrosis in this study had shock and critical illness preceding death. In 2007, Berry and colleagues[19] reported that 2 of 40 SCD patients had significant hepatic necrosis, and 1 of them died. In contrast to these studies, no significant necrosis was identified in our cohort, although negligible hepatocyte dropout was seen in 17.9% of the cases. The difference is probably attributed to the improved management, immediate fluid therapy, and delayed biopsies until patients became clinically stabilized.

Song and colleagues[20] reported that cirrhosis was detected in almost 30% of SCH patients in their autopsy study that was carried out more than 60 years ago. The frequencies were found to be 16% to 18% in the later studies.[12,19] Pinto and colleagues[5] in 2017 described that 19% of SCH patients had advanced fibrosis by noninvasive imaging studies. In our study, cirrhosis was found in 15.4% of the cases. The prevalence of advanced fibrosis in sickle cell patents is compared and shows less in the current studies.

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TABLE 3 Pathologic Features of 39 Patients With Sickle Cell Hepatopathy

Patient	KCE	Iron	SD deg/ dis	SRC /dis	SC deg/dis	Z3HA deg/dis	Fibrosis	PI	Z3HD deg/dis	LI	BD Injury	Chole
1	+	4+	–	–	–	–	–	–	–	–	–	–
2	+	2+	–	–	–	–	–	–	–	–	–	–
3	+	4+	–	–	–	–	±	–	–	–	–	–
4	+	4+	–	+/++	–	–	±/+++	+	–	–	–	–
5	+	2+	++/++	+/+	+/+	+/+	±	–	–	–	–	–
6	+	–	+/+++	+/+	+/+++	–	±	++	–	+	–	–
7	+	2+	+++/+++	+/++	++/+++	++/++	±	–	–	–	–	–
8	+	–	+++/+++	+/++	+++/ +++	–	±	–	–	–	–	–
9	+	4+	+/+	+/+	+/+	–	–	–	–	–	–	–
10	–	4+	+/+++	+/++	+/+++	–	±	–	–	–	–	–
11	–	4+	–	+/++	–	–	+++	+	–	–	–	++
12	–	2+	++/++	–	+/+	+/+	±	–	–	–	–	–
13	+	1+	+/+++	+/+	+/+++	–	±	++	–	–	–	–
14	+	4+	+/+	+/+	+/+	–	±	–	–	–	–	–
15	–	3+	–	–	–	–	±	–	–	–	–	–
16	–	1+	++/++	+/++	–	++/++	±/++	++	+/+	+	++	–
17	+	–	+++/+++	–	–	++/+++	±/+++	++	+/+	–	–	–
18	+	4+	+++/++	+/++	+++/++	++/+++	±	–	–	–	–	–
19	+	4+	+/++	+/++	+/++	–	±/+	–	–	–	–	–
20	+	4+	++/+	+/+	–	+/+	++	–	–	–	–	–
21	–	3+	+++/+++	+/+	+/+	++/++	±	–	–	–	–	–
22	+	–	–	–	–	–	–	–	–	–	–	–
23	+	–	+/+++	+/++	–	–	±	+	–	+	+	–
24	+	4+	+++/+++	+/++	+++/+++	+++/+++	–	–	+++/+++	–	–	–
25	+	3+	++/+++	+/+	++/+++	+/++	±/+	–	–	–	–	–
26	+	–	–	+/+	+/+	–	+++	+	++/ ++	–	+	–
27	+	–	–	–	–	–	+++	+	–	+	+	–
28	+	2+	+++/+++	+/++	+++/+++	–	±	+	–	+	–	–
29	+	1+	+/++	–	–	+/+	±	+	+/+	–	+	–
30	+	3+	+/+	–	–	–	–	+	–	–	–	–
31	+	1+	+++/+++	+/+	+++/+++	+/+++	±/++	–	–	–	–	–
32	+	4+	+/+	+/+	+/+	–	±/+	–	–	–	–	–
33	+	4+	+/++	+/+	+/++	–	±	–	–	–	–	–
34	–	–	++/++	+/+	++/++	++/++	–	–	+/++	–	–	–
35	+	2+	+++/+++	+/++	+++/+++	++/++	±/++	–	–	–	–	–
36	–	–	++/++	+/+	++/++	–	–	–	–	–	–	–
37	–	4+	–	–	–	–	±/+++	–	–	–	–	–
38	+	4+	–	–	–	–	±/++	–	–	–	–	–
39	+	–	+++/+++	+/++	+++/+++	–	±	–	+/ +	+	–	–

BD injury, bile duct injury (–, absent; +, mild; ++, moderate); Chole, cholestasis (+, mild; ++, moderate; +++, marked); Fibrosis (–, absent; ±, perisinusoidal fibrosis; +, periportal fibrosis; ++, bridging fibrosis; +++, cirrhosis); Iron, iron deposition (graded from –, absent to 4+, marked); KCE, Kupffer cell erythrophagocytosis (+, present; –, absent); LI, lobular inflammation (–, absent; +, minimal; ++, mild; +++, moderate; ++++, severe); PI, portal inflammation (–, absent; +, minimal; ++, mild; +++, moderate; ++++, severe); SC deg/dis, sinusoidal congestion degree/distribution (–, absent; +, mild; ++, moderate; +++, marked/ +, focal; ++, patchy; +++, diffuse); SD deg/dis, sinusoidal dilatation degree/distribution (–, absent; +, mild; ++, moderate; +++, marked/ +, focal; ++, patchy; +++, diffuse); SRC/dis, sickled red cells presence/distribution (+, present; – absent/+, focal; ++, patchy; +++, diffuse); Z3HA deg/dis, zone 3 hepatocytes atrophy degree/distribution (–, absent; +, mild; ++, moderate; +++, marked/ +, focal; ++, patchy; +++, diffuse); Z3HD deg/dis, zone 3 hepatocytes dropout degree/distribution (+, mild; ++, moderate; +++, marked/ +, focal; ++, patchy; +++, diffuse).

This is mostly ascribed to improved therapy for SCD. However, a possible role that HCV played in the older cases cannot be completely excluded because of the unavailability of the tests 60 years ago. Several studies attempted to identify associated risk factors for advanced fibrosis and cirrhosis in SCH, but to no avail.[12,20] An autopsy study in 2006 found that 43.8% of cirrhotic SCH patients had iron overload compared to 2.4% in noncirrhotic patients.[21] We did not find significant association between the presence of advanced fibrosis and hemosiderosis or viral infection. Although hemosiderosis and secondary viral infection could theoretically

TABLE 4 Summary of the Histopathologic Features of Sickle Cell Hepatopathy (n = 39)

Feature	No. (%)
Kupffer cell erythrophagocytosis	
Present	30 (76.9)
Absent	9 (23.1)
Hemosiderosis	
None	10 (25.6)
Mild, 1+	4 (10.3)
Moderate, 2+	6 (15.4)
Marked, 3+	4 (10.3)
Severe, 4+	15 (38.5)
Degree of sinusoidal dilation	
None	11 (28.2)
Mild	11 (28.2)
Moderate	7 (17.9)
Marked	10 (25.6)
Distribution of sinusoidal dilation	
None	11 (28.2)
Focal	5 (12.8)
Patchy	9 (23.1)
Diffuse	14 (35.9)
Intrasinusoidal sickling	
Present	27 (69.3)
Absent	12 (30.7)
Distribution of intrasinusoidal sickling	
None	12 (30.8)
Focal	14 (35.9)
Patchy	13 (33.3)
Diffuse	0 (0)
Degree of sinusoidal congestion	
None	16 (41.0)
Mild	12 (30.8)
Moderate	4 (10.3)
Marked	7 (17.9)
Distribution of sinusoidal congestion	
None	16 (41.0)
Focal	7 (17.9)
Patchy	5 (12.8)
Diffuse	11 (28.2)
Degree of zone 3 hepatocyte atrophy	
None	25 (64.1)
Mild	6 (15.4)
Moderate	7 (17.9)
Marked	1 (2.6)
Distribution of zone 3 hepatocyte atrophy	
None	25 (64.1)
Focal	4 (10.3)
Patchy	6 (15.4)
Diffuse	4 (10.3)
Fibrosis	
None	8 (20.5)
Perisinusoidal fibrosis	17 (43.6)
Periportal fibrosis	3 (7.7)
Bridging fibrosis	5 (12.8)
Cirrhosis	6 (15.4)
Portal inflammation	
None	27 (69.2)
Minimal	8 (20.5)
Mild	4 (10.3)
Moderate	0 (0)
Severe	0 (0)
Degree of hepatocyte drop out	
None	32 (82.1)
Mild	5 (12.8)
Moderate	1 (2.6)
Marked	1 (2.6)
Distribution of hepatocyte drop out	
None	32 (82.1)
Focal	4 (10.3)
Patchy	2 (5.1)
Diffuse	1 (2.6)
Lobular inflammation	
None	33 (84.6)
Minimal	6 (15.4)
Mild	0 (0)
Moderate	0 (0)
Severe	0 (0)
Bile duct injury	
None	34 (87.2)
Mild	4 (10.3)
Moderate	1 (2.5)
Marked	0 (0)
Cholestasis	
None	38 (97.4)
Mild	0 (0)
Moderate	1 (2.6)
Marked	0 (0)

contribute to cirrhosis, our statistical analysis does not support such relationship in the modern era. Our study suggests that SCH itself may be the main insult that leads to cirrhosis, maybe through repeated episodes of impaired intrahepatic circulation. As demonstrated, zone 3 perisinusoidal fibrosis is a common finding in our study, which might represent an intrinsic pattern of fibrosis particular to SCH. The evidence to support this speculation includes the SCH-associated pathognomonic features, including Kupffer cell erythrophagocytosis, sinusoidal dilatation, and intrasinusoidal

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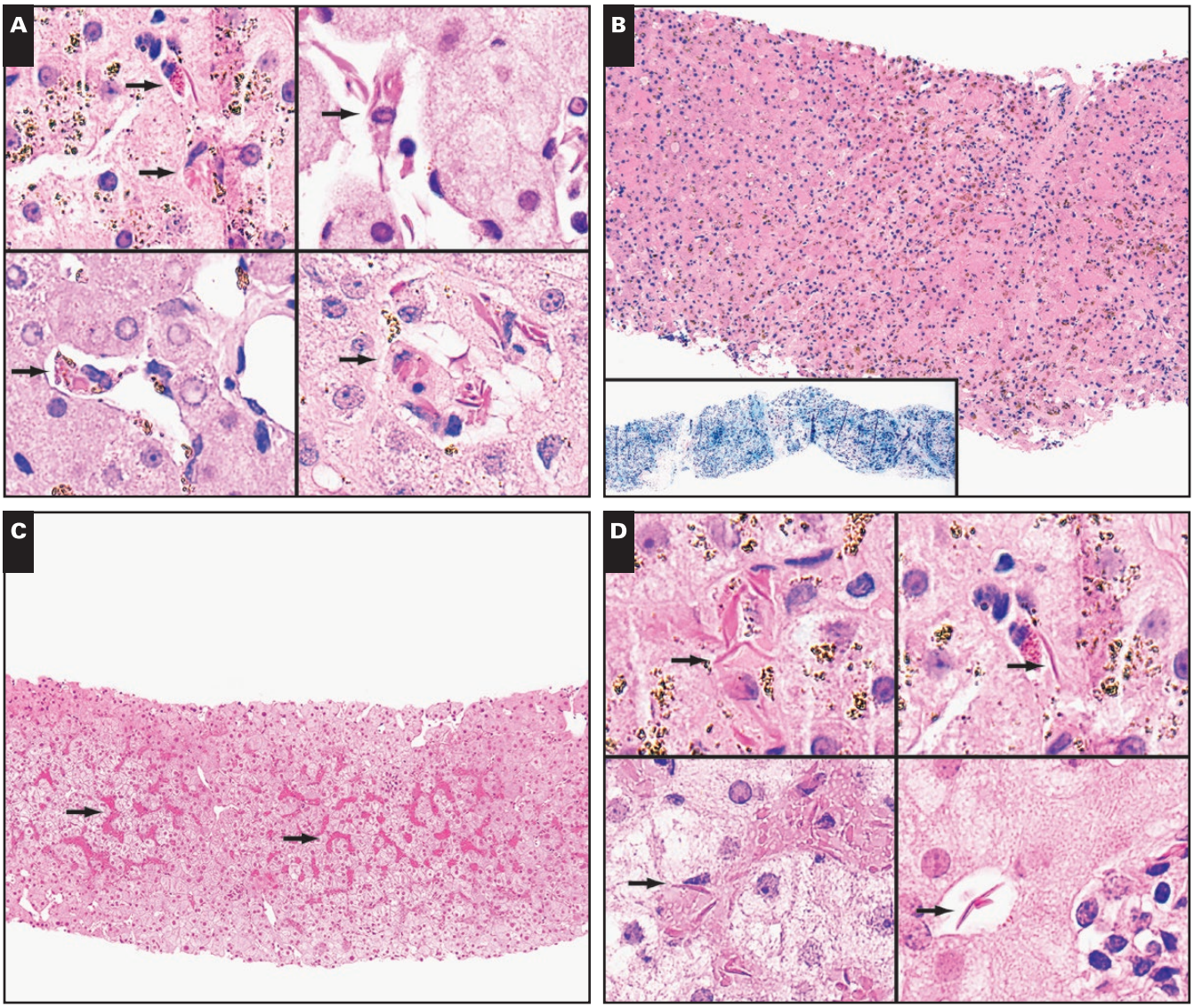

FIGURE 1 Histopathologic findings in sickle cell hepatopathy. **A**, High-power view showing multiple examples of Kupffer cell erythrophagocytosis (arrows, ×600). Coarse brown to yellow pigmented hemosiderin granules are also noted. **B**, Intermediate-power view showing marked hemosiderin deposition in both hepatocytes and sinusoids with marked zone 3 hepatocyte atrophy and dropout (×100). The inflammation is minimal. Inset, iron stain showing marked and diffuse hemosiderin deposition (×12.5). **C**, Intermediate-power view showing zone 3 sinusoidal dilatation and congestion (arrows, ×100). There is no inflammation in hepatic parenchyma. **D**, High-power view showing multiple examples of intrasinusoidal sickled red cells (arrows, ×600).

sickled red cells, which could all be related to intrahepatic circulation. Although no thrombosis or embolism is clearly observed in our study, the presence of central vein recanalization is evident. Although it is a rare finding, it unambiguously represents an adaptive alteration owing to circulatory abnormality. This observation is in line with the postulated hypothesis of impaired intrahepatic circulation caused by intrasinusoidal sickled red cells as a direct cause of liver injury.[12,13,19,22]

The diagnosis of SCH can be clinically challenging, as presentation ranges from mild abdominal pain, self-limited jaundice, and asymptomatic transaminase elevation to life-threatening acute liver failure. The initial diagnostic tools for SCH include hemoglobin electrophoresis, liver enzymes, and imaging studies (ultrasound/computed tomography/magnetic resonance imaging). Examination of the liver by biopsy may provide valuable insight in diagnosis and subsequent management. However, liver biopsy is not the routine first-tier diagnostic approach for SCD patients with suspected SCH, because of potential bleeding complication.[11] Viral hepatitis was the most common liver disease superimposed on SCH with a prevalence of 21% in the previous report[13] and 16.2% in our current study. No patients in our cohort had evidence of autoimmune hepatitis or steatohepatitis.

The diagnosis of SCH is mainly based on biochemistry and radiology. On the basis of our series, it appears that liver biopsy is rarely necessary in patients with SCD because most cases showed only changes attributable to the disease itself. We would advocate for liver biopsy only when there is clinical suspicion for a superimposed disease, such as viral hepatitis or autoimmune hepatitis, or

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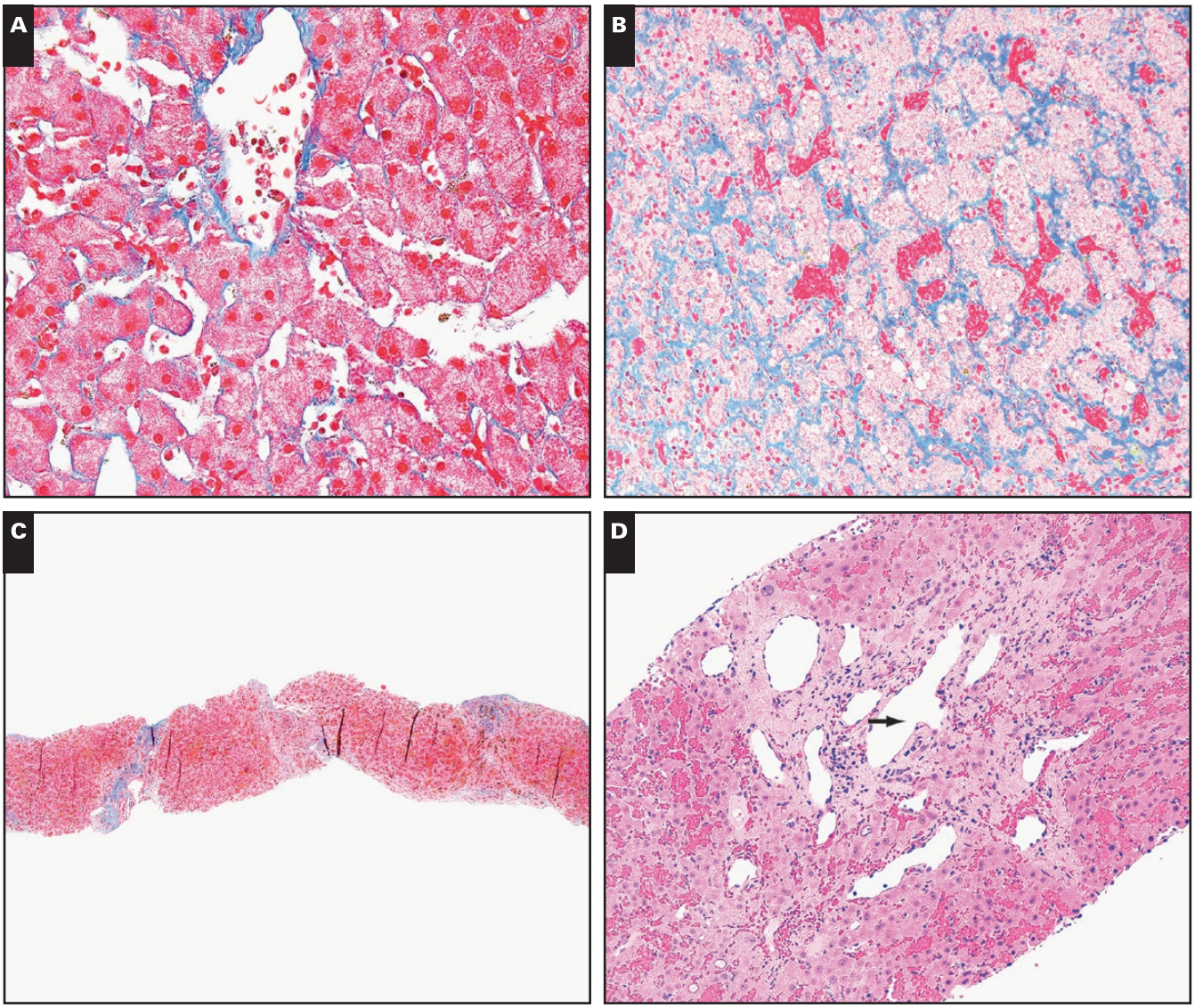

FIGURE 2 Fibrosis in sickle cell hepatopathy. **A**, Trichrome stain highlights delicate zone 3 perisinusoidal fibrosis (×400). **B**, Trichrome stain shows diffuse zone 3 perisinusoidal fibrosis (×400). **C**, Trichrome stain shows a cirrhotic liver (×12.5). **D**, Intermediate-power view showing prominent central vein dilation and recanalization. Zone 3 sinusoidal dilatation and congestion are also noted (arrow indicates central vein, ×200).

to ascertain the degree of fibrosis in situations where noninvasive testing results are not reliable. Similarly, in cases where cirrhosis is suspected on clinical and radiologic grounds, liver biopsy may be useful to qualify candidates for potential liver transplantation.

Most prior studies on SCH relied on clinical data; the limited pathologic studies on SCH are either based on autopsy specimens or small series.[12,13,20,22] Although some previous studies included more patients, the number of patients who had liver biopsies was small. The advantage of our study is that we reviewed the clinical, laboratory, radiographic, and histopathologic features of 39 liver biopsies from living SCH patients, especially given its rarity and the fact that liver biopsy is seldom performed. To our knowledge, this is the largest biopsy series in SCH patients from multiple medical institutions. Another contribution of our study is that we updated the hepatic histopathology in SCH over the decades. Key differences that we identified from historical series include a decreased incidence of hepatocellular necrosis and cirrhosis. The former likely reflects earlier interventions in patients with sickle cell crises, whereas the latter reflects improved management. Some of these findings have been documented in recent radiology literature on this subject but, to date, none has provided histologic correlation. Our study is limited by its retrospective nature and not all data points were available in all cases. As mentioned, indication for liver biopsies was variable in our study. For most cases it was to evaluate elevated liver functional tests or to exclude cirrhosis, which could introduce selection bias.

In summary, the comparison between our and the past studies emphasizes that Kupffer cell erythrophagocytosis, hemosiderosis, sinusoidal dilatation, and intrasinusoidal sickled red cells in a less-inflamed background are the characteristic features of SCH. Necrosis is a rare pathologic finding currently in contrast to the past, and cirrhosis is still common, although decreased compared

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to historical series. Pathologists should be aware that significant portal and lobular inflammation, interface activity, and bile duct injury are not typical, and thus suggestive of additional etiologies. The value of liver biopsy is to exclude other causes, either related or unrelated to SCH, and to provide evidence to prompt effective treatment.

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