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ORIGINAL ARTICLE

Implications of radiologic-pathologic correlation for gallbladder disease in children and young adults with sickle cell disease

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Abstract The purpose of this study is to describe gallbladder imaging findings in patients with sickle cell disease, and to determine how they correspond with occurrence of complications, need for cholecystectomy, and surgical pathology. This study is IRB approved and HIPAA compliant. Informed consent requirements were waived. We reviewed records of 77 children with sickle cell disease ages 0–18 years at the time of their first gallbladder imaging study. Demographics, hospital courses, and radiologic and pathologic reports were collected. Two pediatric radiologists independently and retrospectively reviewed the imaging studies. Statistical analysis was performed using kappa statistic, chi-squared test, and ANOVA *F*-test. Continuous variables were described with mean, median, variance, and range. Patients who underwent cholecystectomy (*N*=25) were more likely than the patients who did not undergo cholecystectomy (*N*=52) to have gallstones or sludge (100 versus 36.5 %, $p=<0.0001$) or other gallbladder or biliary abnormality (70.8 versus 1.9 %, $p=<0.0001$). Patients who did not undergo cholecystectomy more frequently had normal-appearing gallbladders and biliary tracts (63.5 versus 0 %, $p=<0.0001$). Ninety-two percent of patients with cholecystectomy had chronic cholecystitis on pathology, and 96 % had a complication, including chronic cholecystitis and sequelae of biliary obstruction. Young patients with sickle cell disease, cholelithiasis, and any other biliary imaging abnormality will almost certainly require cholecystectomy, and many will experience complications. The most common surgical pathologic diagnosis in this group is chronic cholecystitis, which has a variable radiologic appearance. Our findings support recommendations to perform elective cholecystectomy for children and young adults with sickle cell disease and cholelithiasis or gallbladder sludge.

Keywords Sickle cell disease · Emergency medicine · Gallbladder and biliary tract abnormalities · Pediatric surgery · Ultrasound

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Introduction

Sickle cell disease (SCD) is a group of inherited red blood cell disorders caused by a mutation in both beta chains of hemoglobin (Hb), which causes the red cells to sickle. In homozygous sickle cell anemia, two abnormal sickle genes are present (HbSS), and in the next most common form, a sickle gene and another abnormal hemoglobin called "C" are present (HbSC). Other forms of the disease exist and include HbS beta thalassemia ($HbSB^+$ and $HbSB^0$) [1].

Cholelithiasis and choledocholithiasis are known common complications of SCD, and these patients tend to develop pigment stones resulting from recurrent hemolysis, instead of cholesterol stones more typically seen in individuals

Table 1 Comparison of demographics and follow-up between control and study groups

Characteristic		Overall (*N*=77)	No cholecystectomy (*N*=52)	Cholecystectomy (*N*=25)	*p* value
Gender	Female	38 (49.4 %)	27 (51.9 %)	11 (44 %)	0.51
	Male	39 (50.6 %)	25 (48.1 %)	14 (56 %)	
Race	Black	69 (89.6 %)	46 (88.5 %)	23 (92 %)	0.29
	Hispanic	4 (5.2 %)	4 (7.7 %)	0 (0.0 %)	
	Other	4 (5.2 %)	2 (3.8 %)	2 (8 %)	
Genotype	HbSS	57 (74 %)	39 (75 %)	18 (72 %)	0.19
	HbSC	17 (22.1 %)	12 (23.1 %)	5 (20 %)	
	$HbSB^+$	2 (2.6 %)	0 (0.0 %)	2 (8 %)	
	$HbSB^0$	1 (1.3 %)	1 (1.9 %)	0 (0.0 %)	
Mean age±SD at first study (years)		9.7±5.3	8.5±5.1	12±5.1	*0.006*
Median and range (years)		11 (1–18)	8 (1–18)	13 (2–18)	
No. of radiologic studies/patient		2.8±2.2	2.5±2.3	3.5±1.8	0.061
Median and range		2 (1–12)	2 (1–12)	3 (1–8)	
Mean time±SD to end date (years)		7.4±4.6	5.6±2.5	2.4±2	*<0.0001*
Median and range (years)		6 (0–18)	5 (2–14)	2.8 (0–8)	
Complication		13 (16.9 %)	0 (0.0 %)	13 (52 %)	*<0.0001*

SD standard deviation, *No*. number

Italicized p-values indicate statistically significant difference in outcomes between groups

without hemolytic disease [2]. Cholelithiasis and cholecystectomy have been reported in approximately 20–30 % of children 18 years or younger, and in over 50 % of adult patients with SCD, with higher prevalence in patients with HbSS compared with HbSC [3–10].

According to the Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014, cholecystectomy is indicated for children and adults with SCD and symptomatic cholelithiasis, based on "moderate-quality evidence" [11]. In contradistinction, some studies have concluded that cholecystectomy should be performed for patients with SCD and asymptomatic cholelithiasis [12–14]. At our institution, which is a 496-bed inner city referral hospital, children with SCD, who do not undergo surgical intervention for cholelithiasis until symptomatic, can experience significant morbidity from cholelithiasis and choledocholithiasis. A study from another large referral hospital, which was published in 2013, showed that 28 of 56 (50 %) patients ages 0–22 years with SCD and symptomatic cholelithiasis developed common bile duct (CBD) obstruction within 6 months of initial presentation [15]. The findings published in this study suggest that the management of children and young adults with SCD, cholelithiasis, and/or choledocholithiasis can be improved.

At our hospital, we noticed that the sonographic appearance of gallbladders in children and young adults with SCD and cholelithiasis was often markedly abnormal, especially in those who eventually underwent cholecystectomy or presented acutely, often to the emergency department, with right upper quadrant (RUQ) pain [16, 17]. We wanted to know what the abnormal appearance of the gallbladders represented and which RUQ imaging abnormalities were most indicative of future complications and need for cholecystectomy.

Materials and methods

Prior approval from our Institutional Review Board was obtained with approval of waiver of informed consent. Health Insurance Portability and Accountability Act (HIPAA) guidelines were followed at all times. This study was performed in two parts: as an observational, retrospective review of patient records, and as a retrospective review of images from prior radiologic studies that evaluated the gallbladder. The images reviewed included those from ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and hepatobiliary ^{99m}Tc-iminodiacetic acid (HIDA) scans. Finally, available pathology reports were reviewed for correlation.

Patients with SCD age 0–18 years at the time of their first abdominal imaging studies, which were performed between January 1999 and December 2011, were identified from our data warehouse, using codes for SCD and abdominal imaging studies. Patients were excluded if pathology reports from cholecystectomy were unavailable, if they transferred care, or if they were lost to follow-up (not seen in >1 year). We included 25 patients in the study (cholecystectomy) group and 52 patients in the control (no cholecystectomy) group.

The patients in the study group were followed from the first radiologic gallbladder imaging date to the date of cholecystectomy, which was considered to be the end date. Additional follow-up was conducted to evaluate for postoperative

Table 2 Gallbladder and biliary imaging findings between control and study groups

Characteristic	Overall (*N*=77)	No cholecystectomy (*N*=52)	Cholecystectomy (*N*=25)	*p* value
Retrospective review				
Mean GB length (cm)	7.1±2.3	6.3±1.9	8.7±2.3	*<0.0001*
Median and range (cm)	7 (2–13)	6 (2–11.5)	8.5 (4–13)	
Mean CBD diameter (mm)	3.4±2.5	2.6±1	5.1±3.6	*<0.0001*
Median and range (mm)	3 (1–14)	2 (1–7)	4 (2–14)	
Normal study	33 (43.4 %)	33 (63.5 %)	0 (0.0 %)	*<0.0001*
Gallstones	34 (44.7 %)	11 (21.2 %)	23 (95.8 %)	*<0.0001*
Sludge	38 (50 %)	17 (32.7 %)	21 (87.5 %)	*<0.0001*
Gallstones and/or sludge	43 (56.6 %)	19 (36.5 %)	24 (100 %)	*<0.0001*
Abnormality besides stones/sludge	18 (23.7 %)	1 (1.9 %)	17 (70.8 %)	*<0.0001*
GB wall abnormality	7 (9.6 %)	0 (0.0 %)	7 (30.4 %)	*<0.0001*
GB wall >3 mm	6 (8.1 %)	0 (0.0 %)	6 (26.1 %)	*0.00014*
GB wall edema	7 (9.6 %)	0 (0.0 %)	7 (30.4 %)	*<0.0001*
Pericholecystic fluid	5 (6.7 %)	0 (0.0 %)	5 (21.7 %)	*0.0005*
Acute cholecystitis	6 (7.9 %)	0 (0.0 %)	6 (25 %)	*0.00017*
Stone(s) in neck	11 (14.5 %)	1 (1.9 %)	10 (41.7 %)	*<0.0001*
Stone(s) in CBD	5 (6.6 %)	0 (0.0 %)	5 (20.8 %)	*0.00066*
Stone(s) in cystic duct	1 (1.3 %)	0 (0.0 %)	1 (4.2 %)	0.14
Biliary ductal dilatation	9 (11.8 %)	0 (0.0 %)	9 (37.5 %)	*<0.0001*
Too collapsed to evaluate wall	4 (5.3 %)	3 (5.8 %)	1 (4.2 %)	*0.77*
Original report				
Normal	38 (49.4 %)	37 (71.2 %)	1 (4 %)	*<0.0001*
Murphy's sign	2 (3 %)	1 (2 %)	1 (5.9 %)	0.43
Gallstones	32 (42.1 %)	9 (17.3 %)	23 (95.8 %)	*<0.0001*
Sludge	15 (19.7 %)	6 (11.5 %)	9 (37.5 %)	*0.0082*
Gallstones and/or sludge	37 (48.7 %)	14 (26.9 %)	23 (95.8 %)	*<0.0001*
Abnormality besides stones/sludge	11 (14.3 %)	2 (3.8 %)	9 (36 %)	*0.00016*
GB wall abnormality	4 (5.3 %)	1 (2 %)	3 (12.5 %)	0.058
Acute cholecystitis	1 (1.3 %)	0 (0.0 %)	1 (4 %)	0.15
Stone(s) in neck	2 (2.6 %)	0 (0.0 %)	2 (8.3 %)	*0.035*
Stone(s) in CBD	1 (1.3 %)	0 (0.0 %)	1 (4.2 %)	0.14
Stone(s) in cystic duct	1 (1.3 %)	0 (0.0 %)	1 (4.2 %)	0.14
CBD dilatation	4 (5.3 %)	0 (0.0 %)	4 (16.7 %)	*0.0025*
Biliary ductal dilatation	3 (3.9 %)	0 (0.0 %)	3 (12.5 %)	*0.0093*

GB gallbladder, *CBD* common bile duct

Italicized p-values indicate statistically significant difference in outcomes between groups

complications in the study group. The patients in the control group were followed from first radiologic gallbladder imaging date to their most recent visit as of the chart review date (May 20, 2014), and the most recent visit was considered to be the end date for the control group.

Data collection

A single reviewer collected data from the electronic medical records, including demographic information, histories from the emergency department and clinic visits, and hospital courses from discharge summaries and surgical dictations. This reviewer and two additional reviewers collected imaging findings from the original radiology reports, so that two reviewers checked each report.

Two board-certified radiologists reviewed all US, CT, MRI, and HIDA studies independently. Both radiologists are fellowship-trained in pediatric radiology with 7 and 4 years of clinical experience in pediatric radiology at the time of image review. For all radiologic examinations, each of the two radiologists indicated the presence or absence of the following imaging characteristics: adequate distension of the gallbladder, sludge, gallstones, stones in the gallbladder neck, choledocholithiasis, gallbladder wall thickening (≥3 mm),

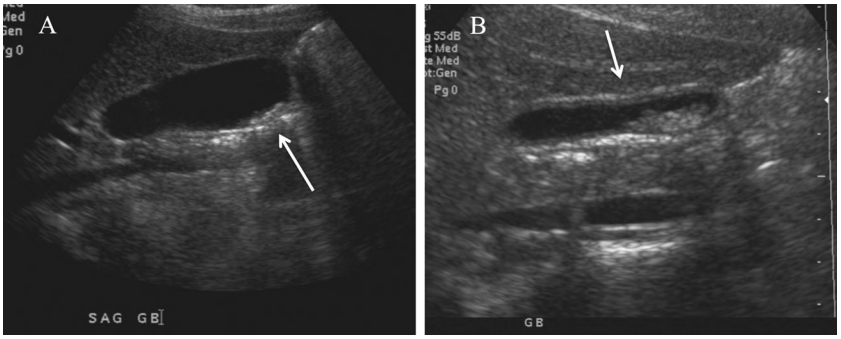

Fig. 1 Seventeen-year-old girl with HbSS and multiple visits for right upper quadrant pain. The first US showed cholelithiasis (*arrow*), as did an abdominal CT performed 5 days later (not shown) (**a**). An ultrasound performed 6 months later revealed gallbladder wall thickening (≥3 mm) and edema (*arrow*) (**b**). The patient underwent cholecystectomy the following day. Pathology demonstrated chronic cholecystitis

gallbladder wall edema, pericholecystic fluid, presence or absence of acute cholecystitis (subjective based on gallbladder imaging appearance), and degree of biliary ductal dilation (0= none, 1=mild, 2=moderate, and 3=severe). The results were compared, and a consensus session between the two radiologists was held to resolve discrepant findings. Both radiologists recorded the CBD diameter, and these results were averaged between reviewers. One of the pediatric radiologists recorded the gallbladder length for each study.

Statistical methods

Statistical analysis was performed to compare the findings from the patients' final ultrasound before end date between the control and study groups. Binary variables were described with frequencies and percentages. Agreement between retrospective review and original reports were summarized using kappa statistic and 95 % confidence intervals. Continuous variables were described with mean, median, variance, and range. Categorical variables were compared between risk groups using chi-squared test, while continuous variables were compared using ANOVA *F*-test. All analyses were performed using SAS version 9.3 statistical software (SAS Institute Inc. Cary, NC).

Results

Subjects

The study population was comprised of 77 children and young adults with a mean age (±SD) of 9.7±5.3 years (range 1–18 years) at the time of the first gallbladder imaging study. Thirty-nine patients were male and 38 were female. Patient genotypes included HbSS, HbSC, $HbSB^+$ thalassemia, and $HbSB^0$ thalassemia.

The study group consisted of 25 patients who underwent cholecystectomy, and the control group consisted of 52 patients who had not undergone cholecystectomy. Comparison of demographics between the study and control groups is included in Table 1. For those who underwent cholecystectomy, the average age at surgery was 14.8±5.2 years (range 3–

Table 3 Inter-observer agreement between retrospective reviewers and original reporter

Characteristic	Kappa	95 % lower confidence limit	95 % upper confidence limit
Normal	*0.86*	0.79	0.94
Gallstones	*0.94*	0.89	0.99
Sludge	0.21	0.11	0.31
Gallstones and/or sludge	*0.88*	0.81	0.94
Abnormality besides stones/sludge	0.28	0.15	0.42
GB wall abnormality	0.43	0.18	0.69
Acute cholecystitis	0.30	−0.02	0.61
Stone(s) in neck	0.11	−0.02	0.24
Stone(s) in CBD	0.25	−0.04	0.54
Stone(s) in cystic duct	*1.00*	1.00	1.00
Biliary ductal dilatation	0.34	0.08	0.59

GB gallbladder, *CBD* common bile duct

Italicized Kappa values indicate strong correlation between retrospective reviewers and original reporter

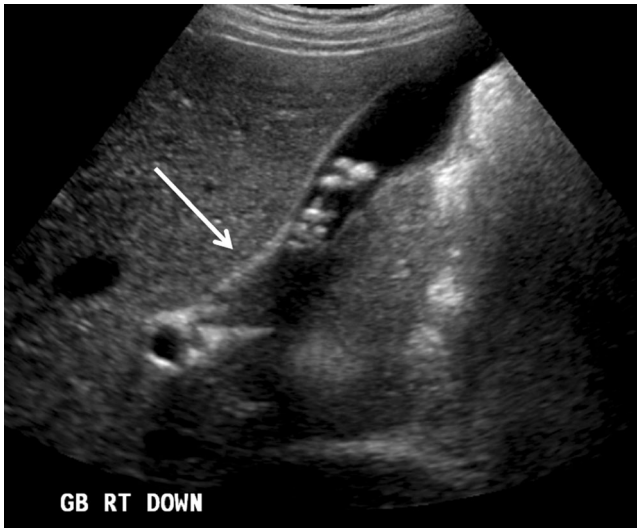

Fig. 2 Eighteen-year-old woman with $HbSB^{+}$ and right upper quadrant pain. The US showed cholelithiasis and stones in the gallbladder neck (*arrow*). She presented with clinical diagnosis of gallstone pancreatitis 3 years later, for which she underwent laparoscopic cholecystectomy during her admission at age 21 years. Pathology demonstrated chronic cholecystitis

25 years). One patient in the study group underwent splenectomy at the same time as cholecystectomy, and four additional patients in the study group underwent splenectomy at a different time. Seven patients in the control groups have undergone surgical splenectomy.

Number and type of imaging studies

The 77 children and young adults included in this study had a total of 216 imaging studies with gallbladder evaluation by our institution's radiology department prior to the end date. These studies included 181 USs, 19 CTs, 15 MRIs, and 1 HIDA scan. In addition, these patients had a total of six ERCPs performed in the gastroenterology department before the end date. The patients may also have had additional studies at other hospitals, but we did not have documentation or access to these and did not include them in this study.

For all patients, the average number (±SD) of radiologic imaging studies (excluding ERCP) at our hospital was 2.8± 2.2, ranging 1–12. Between control and study groups, there was no difference in the number of imaging studies per patient (p=0.061) (Table 1).

Comparison of imaging findings between groups

There were five patients for which one or more of the previously mentioned imaging characteristics could not be evaluated on retrospective review. In 4 of the 77 final studies, the gallbladder was decompressed, and therefore the wall was not well evaluated, but the remaining imaging findings were documented. For one patient, the final study before cholecystectomy was a HIDA scan, and therefore, the only applicable gallbladder/biliary characteristic to be evaluated was "acute cholecystitis."

Per retrospective imaging review, the patients who underwent cholecystectomy were more likely to have a longer gallbladder, larger CBD diameter, gallstones and/or sludge, or other gallbladder or biliary abnormality (Table 2, Fig. 1). Patients in the control group were more likely to have a completely normal appearance of the gallbladder and biliary tract (63.5 versus 0 %, p=<0.0001). In the control group, 36.5 % of patients had gallstones and/or sludge, while 100 % of the patients in the cholecystectomy group had gallstones and/or sludge (p=<0.0001). Only one patient (1.9 %) in the control group had a gallbladder or biliary abnormality other than gallstones and/or sludge, which was gallstones within the neck of the gallbladder, while 17 (70.8 %) of the patients in the cholecystectomy group had a gallbladder or

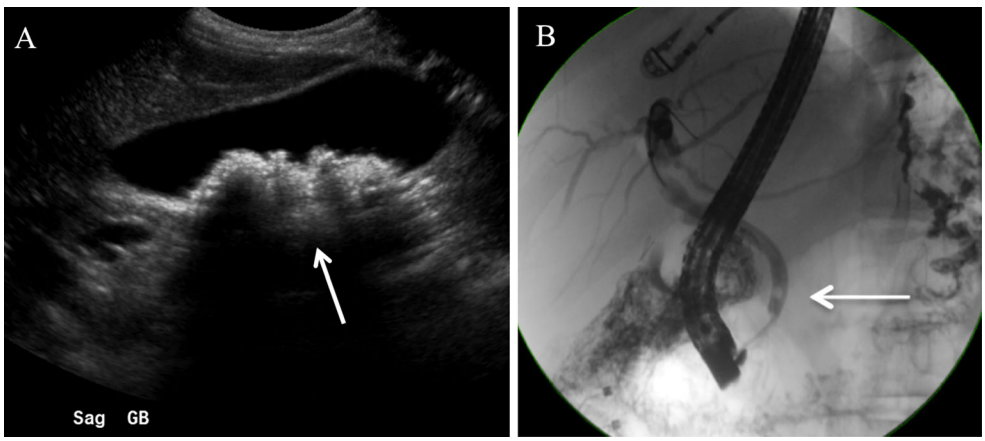

Fig. 3 Twelve-year-old boy with HbSS presented multiple times with right upper quadrant pain and had five USs between ages 12 and 17 years, which all showed cholelithiasis (*arrow*) (**a**). The patient underwent elective cholecystectomy, and he presented again within 1 month after the operation with jaundice and right upper quadrant pain. HIDA scan was negative for leak. ERCP was positive for choledocholithiasis (*arrow*) (**b**), and the patient underwent stone retrieval and sphincterotomy. Gallbladder pathology demonstrated chronic cholecystitis

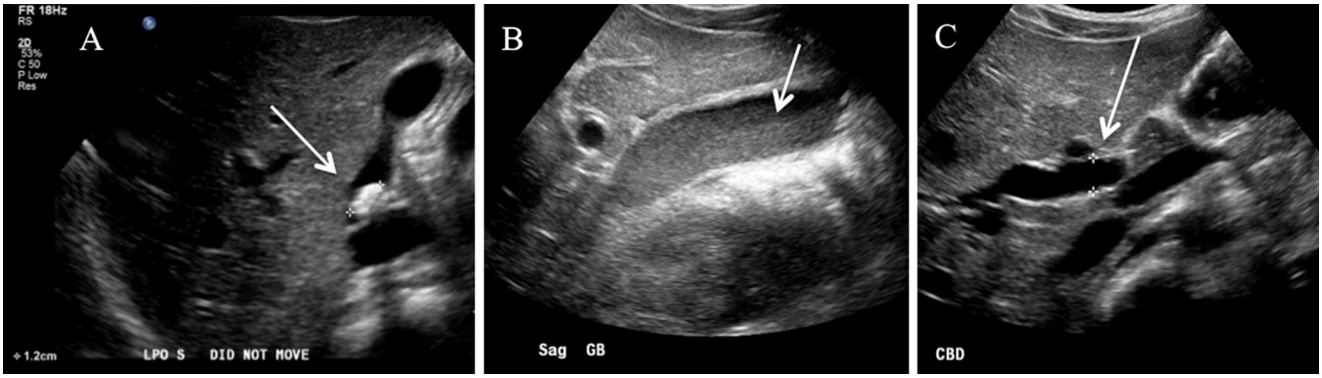

Fig. 4 Twelve-year-old boy with HbSS presented three times in 3 years for right upper quadrant pain. The first US reported only sludge (images were not available for review). The second US showed cholelithiasis with a 1.2 cm stone in the gallbladder neck (*arrow*), gallbladder length of 5 cm, and CBD diameter of 4 mm (**a**). The third US showed cholelithiasis, sludge (*arrow*), gallbladder distension (11 cm), wall thickening (>3 mm), and pericholecystic fluid (**b**). There was also biliary ductal dilation and CBD dilation of 10 mm (*arrow*) (**c**). The patient underwent cholecystectomy 12 days later. Pathology demonstrated chronic cholecystitis

biliary abnormality other than gallstones and/or sludge (p=<0.0001). Differences in findings per original report between the control and study groups are also listed in Table 2.

Inter-observer agreement between retrospective reviewers and original reporter was analyzed, and the results are presented in Table 3. Agreement was best when determining if the gallbladder and biliary tract were normal (κ=0.86), if there were gallstones (κ=0.94), and if there were gallstones and/or sludge (κ=0.88). Inter-observer agreement appears strong for the evaluation of stone(s) in the cystic duct (κ=1), but there was only one patient with this finding.

Complications

Per retrospective chart and image review, 13 of the 25 patients (52 %) with cholecystectomy had at least one complication from cholelithiasis (Figs. 2, 3, 4, 5, and 6). The complications included evidence of biliary obstruction on retrospective imaging review (N=7) (moderate-to-severe intrahepatic biliary ductal dilation, CBD diameter increase by ≥4 mm between two exams, or CBD diameter ≥10 mm), choledocholithiasis (N=4, with three patients requiring sphincterotomy and stone retrieval), gallstone pancreatitis (N=4), jaundice (N=2), pathology-proven acute cholecystitis (N=1), dropped stone with abscess formation (N=1), and/or biliary dyskinesia (N=1). All patients with one or more of the above complications were in the study group (p<0.0001) (Table 1). Eleven of the 13 patients had a complication before cholecystectomy, and the remaining two patients had a complication after cholecystectomy (choledocholithiasis requiring sphincterotomy and stone retrieval, and dropped stone with abscess formation).

The patients with complications underwent cholecystectomy at an older age compared with patients without a complication (17±3.1 versus 12.4±6.1 years, p=0.025). There was no difference in age at first study, total number of radiologic studies, or time to end date between patients without or with a complication (p=0.091, p=0.78, and p=0.24, respectively).

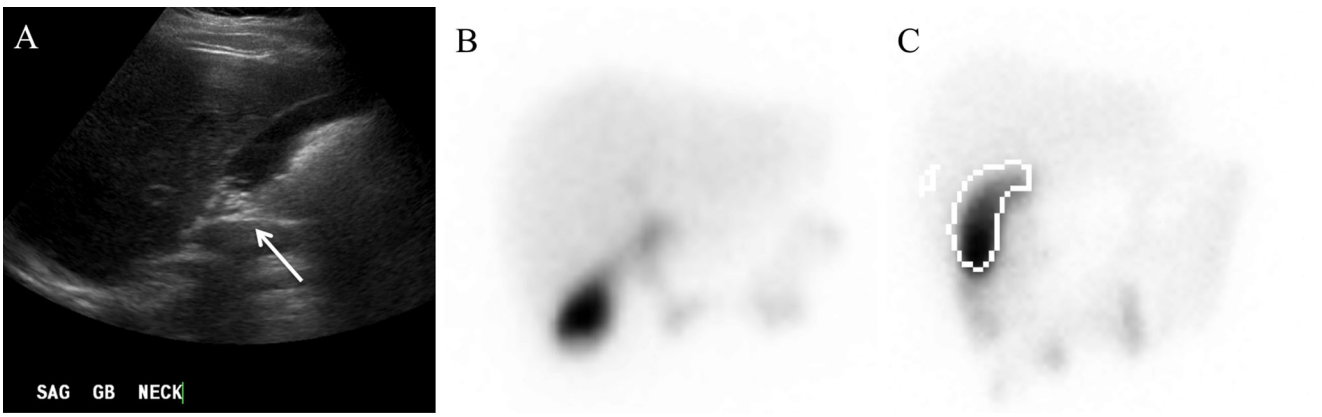

Fig. 5 Thirteen-year-old girl with HbSC and right upper quadrant pain had three USs in 2 years, all demonstrating cholelithiasis. The third US showed cholelithiasis and stones in the gallbladder neck (*arrow*) (**a**). The patient had a HIDA scan demonstrating biliary dyskinesia: ejection fraction was 9 % after 40 min (expected >35 %) (**b** and **c**). The patient underwent elective cholecystectomy 3 months later. Pathology demonstrated chronic cholecystitis

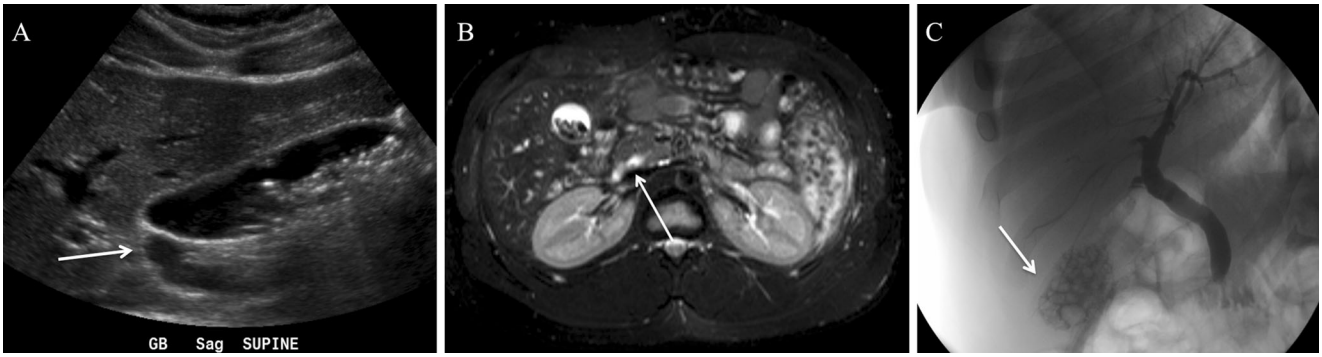

Fig. 6 Seventeen-year-old boy with HbSC presented with abdominal pain. Abdominal US showed gallstones and sludge (not shown). The patient returned at age 25 years with right upper quadrant pain and nausea, and the US showed gallstones, sludge, and a dilated CBD measuring 9 mm (*arrow*) (**a**). MRCP performed the next day showed cholelithiasis and choledocholithiasis (filling defect in distal CBD marked with *arrow*) (**b**). ERCP performed 3 days later revealed cholelithiasis (*arrow*) and biliary sludge (**c**). Sphincterotomy and extraction were performed. Elective cholecystectomy was performed 4 months later and pathology revealed acute-on-chronic cholecystitis

Per retrospective imaging review, the patients who had a complication were more likely to have a longer gallbladder, larger CBD diameter, or sign of biliary obstruction compared to patients without a complication (Table 4). Per original report, patients with complications were more likely to have CBD dilatation (p= 0.028).

Pathology

All 25 patients who underwent cholecystectomy had pathology reports available for review. Pathologic evaluation demonstrated chronic cholecystitis in 23 patients (92 %), acute-on-chronic cholecystitis in one patient (4 %), and a normal-appearing gallbladder without

Table 4 Gallbladder and biliary imaging findings between patients without and with complication(s)

Characteristic per retrospective review	Overall (N=25)	No complication (N=12)	Complication (N=13)	p value
Mean GB length (cm)	8.7±2.3	7.7±2.5	9.6±1.7	*0.044*
Median and range (cm)	8.5 (4–13)	7 (4–12)	9.5 (7–13)	
Mean CBD diameter (mm)	5.1±3.6	3.3±1.1	7±4.3	*0.0073*
Median and range (mm)	4 (2–14)	3.5 (2–5)	6.5 (2–14)	
Normal study	0 (0 %)	0 (0 %)	0 (0 %)	1
Gallstones	23 (95.8 %)	11 (91.7 %)	12 (100 %)	0.31
Sludge	21 (87.5 %)	10 (83.3 %)	11 (91.7 %)	0.54
Gallstones and/or sludge	24 (100 %)	12 (100 %)	12 (100 %)	0.54
Abnormality besides stones/sludge	17 (70.8 %)	7 (58.3 %)	10 (83.3 %)	0.18
GB wall abnormality	7 (30.4 %)	3 (27.3 %)	4 (33.3 %)	0.75
GB wall >3 mm	6 (26.1 %)	2 (18.2 %)	4 (33.3 %)	0.41
GB wall edema	7 (30.4 %)	3 (27.3 %)	4 (33.3 %)	0.75
Pericholecystic fluid	5 (21.7 %)	2 (18.2 %)	3 (25 %)	0.69
Acute cholecystitis	6 (25 %)	3 (25 %)	3 (25 %)	1
Stone(s) in neck	10 (41.7 %)	3 (25 %)	7 (58.3 %)	0.098
Stone(s) in CBD	5 (20.8 %)	0 (0.0 %)	5 (41.7 %)	*0.012*
Stone(s) in cystic duct	1 (4.2 %)	0 (0.0 %)	1 (8.3 %)	0.31
Biliary ductal dilatation	9 (37.5 %)	2 (16.7 %)	7 (58.3 %)	*0.035*
Too collapsed to evaluate wall	1 (4.2 %)	1 (8.3 %)	0 (0.0 %)	0.31
Stone(s) in cystic duct	1 (4.2 %)	0 (0.0 %)	1 (8.3 %)	0.31
CBD dilatation	4 (16.7 %)	0 (0.0 %)	4 (33.3 %)	*0.028*
Biliary ductal dilatation	3 (12.5 %)	0 (0.0 %)	3 (25 %)	0.064

GB gallbladder, *CBD* common bile duct

Italicized p-values indicate statistically significant difference in outcomes between groups

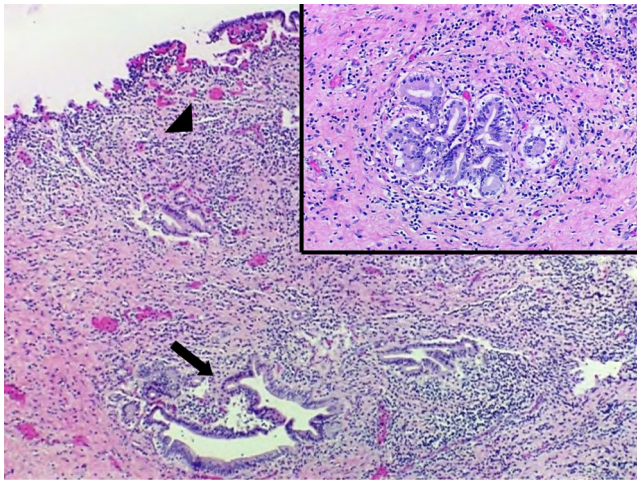

Fig. 7 Twenty-year-old woman with HbSS and chronic cholecystitis: The biliary submucosa shows lymphocytic infiltration and numerous small capillaries (vascular congestion-*arrowhead*); magnification ×20, Hematoxylin and eosin stain. Columnar epithelium lined Rokitansky-Aschoff sinuses (mucosal diverticulum—*arrow* and *inlet figure*) are present and are surrounded by dense fibrous proliferation and lymphocytes; magnification ×200, Hematoxylin and eosin stain

stones or sludge in one patient (4 %). Pathologically, patients with acute cholecystitis have gallbladders with thick, edematous walls, with red discoloration, infiltration of the wall with neutrophils, and epithelial necrosis. Patients with chronic cholecystitis have thick-walled gallbladders and Rokitansky-Aschoff sinuses within the muscularis (Fig. 7) [18].

Radiology/pathology correlation

For the 25 patients with cholecystectomy, six had an imaging diagnosis of "acute cholecystitis" per retrospective radiologic review, and one of these patients had acute cholecystitis per the original radiology report. All six patients with radiologic acute cholecystitis had chronic cholecystitis on pathologic analysis. Per retrospective radiologic review, none of the gallbladders of the patients with cholecystectomy were normal, and only one was normal per pathologic review, as mentioned above.

Twenty-two of the 23 patients with pathologic chronic cholecystitis were compared with the retrospective sonographic findings (the remaining patient had a HIDA scan for their final study). All 22 patients (100 %) with pathologic cholecystitis had stones and/or sludge per radiologic review. Sixteen patients (72.7 %) had another imaging abnormality, including seven patients (31.8 %) with an abnormal-appearing gallbladder wall, nine (40.9 %) with a stone in the gallbladder neck, five (22.7 %) with a stone in the CBD or cystic duct, and eight (36.4 %) with biliary dilatation.

Discussion

In children and young adults with SCD and cholelithiasis, it has been shown that delay in surgical intervention can lead to serious morbidity, either from recurrent symptoms or obstructing choledocholithiasis [19, 20]. When these patients seek medical attention for RUQ or generalized abdominal pain, often acutely in the emergency department, a sonogram is the initial imaging choice. Due to frequent hospital visits of individuals in this group, the radiologist will often have longitudinal imaging data readily available, which can help guide interpretation. The radiologist should be familiar with the clinical implications of cholelithiasis in patients with SCD, and with the indications for elective surgery, which can be coordinated during the visit [16]. In this study, we sought to determine the gallbladder imaging abnormalities that correspond to the occurrence of complications and need for cholecystectomy. To improve accurate interpretation of sonographic imaging findings in this group of patients with primarily pigment stones, we correlated imaging findings with patient outcomes and with pathologic diagnoses in those who underwent cholecystectomy.

For the 77 children and young adults with SCD and gallbladder imaging included in this study, the patients who required cholecystectomy were more likely to have gallstones and/or sludge (100 versus 36.5 %, p=<0.0001) or any other gallbladder or biliary abnormality (70.8 versus 1.9 %, p=<0.0001) than the patients who did not require cholecystectomy. Patients who had not undergone cholecystectomy were more likely to have a completely normal appearance of the gallbladder and biliary tract (63.5 versus 0 %, p=<0.0001). There was a high complication rate in the cholecystectomy group (52 %), and complications included choledocholithiasis and/or biliary obstruction, gallstone pancreatitis, acute cholecystitis, dropped stone with abscess formation, and biliary dyskinesia. If we include chronic cholecystitis as a complication, the rate increases to 96 %. Therefore, including chronic cholecystitis as a complication, and considering both the cholecystectomy and control groups, 24 of 43 patients (55.8 %) with gallstones and/or sludge had a complication.

Although it may be expected for patients with cholelithiasis and right upper quadrant pain to have acute cholecystitis, the overwhelmingly most common surgical pathologic diagnosis in the study group was chronic cholecystitis (92 %). We found that 100 % of the patients with pathologic chronic cholecystitis had an ultrasound showing gallstones and/or sludge. We therefore hypothesize that either the pigment stones cause chronic cholecystitis, or that the pigment stones are a biomarker of more severe sickle cell disease, hemolysis, and vaso-occlusive episodes, which result in both pigment stones and ischemia-induced chronic cholecystitis. We found that pathologic chronic cholecystitis had a variable radiologic appearance and was associated with sonographic gallbladder wall

abnormalities in 31.8 % of cases and with biliary dilatation in 36.4 % of cases. In 27.3 % of cases of chronic cholecystitis, there was no other sonographic abnormality other than stones or sludge.

Within the literature, there is a case report of a 7-year-old boy with SCD who had cholelithiasis and pathology-proven "cholecystitis ossificans," which was characterized by fibrous proliferation and osseous metaplasia in the gallbladder wall [21]. We did not observe this entity in our study, but it may be within the spectrum of chronic cholecystitis according to the report. To our knowledge, there is no other radiologic-pathologic correlation of gallbladders in patients with SCD.

Limitations of our study include sample size (77 children and young adults) and retrospective methodology. Although a larger study group including all imaging studies performed at outside hospitals would be preferred, this study does provide a foundation for future radiologic research. The radiologists were not entirely blinded to whether or not each patient underwent surgery, but they were blinded to complications. There is, therefore, potential for bias, which would lead to over-calling imaging findings related to gallbladder wall abnormalities, or evidence of biliary obstruction in patients who underwent cholecystectomy. We do not feel that over-calling either of these is a limitation, since we are recommending surgical intervention with or without these findings. Over- or under-calling cholelithiasis or sludge could be problematic, since the presence or absence of gallstones/sludge is the basis for our surgical recommendation. We held a consensus session to resolve all discrepancies between the two reviewers, and we believe that the assessment for cholelithiasis and sludge was accurate.

To summarize our findings, ultrasound is the primary imaging modality for the evaluation of children and young adults with SCD and RUQ pain. In keeping with our initial anecdotal observation that RUQ sonograms in this patient population are often markedly abnormal, we found that all patients who underwent cholecystectomy had gallstones or sludge on ultrasound, and that 70.8 % had another abnormality such as gallbladder wall thickening/edema or biliary dilatation. Surgical pathologic analysis demonstrated chronic cholecystitis in 92 % of cases. All observed biliary imaging abnormalities were more common in the cholecystectomy group, and patients with complications had longer gallbladders and were more likely to show evidence of biliary obstruction. When considering both the study and control groups together, 55.8 % of patients with gallstones and/or sludge had a complication. Our study therefore supports recommendations for elective cholecystectomy in patients with SCD and cholelithiasis, even without symptoms or other sonographic abnormalities.

Conflict of interest The authors declare that they have no conflict of interest.

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