Indian Journal of Pediatrics (January 2024) 91(1):73–80
https://doi.org/10.1007/s12098-023-04747-x

GRAND ROUND

Jaundice in a Child with Sickle Cell Anemia: A Case Based Approach

Srinivas Srinidhi Vadlapudi[1] · Anshu Srivastava[1] · Praveer Rai[2] · Rajneesh K. Singh[3] · Moinak Sen Sarma[1] · Ujjal Poddar[1] · Rajanikant R. Yadav[4]

Received: 12 April 2023 / Accepted: 21 June 2023 / Published online: 9 August 2023

Abstract

Sickle cell anemia (SCA) is an autosomal recessive disorder caused by a mutation in beta globin gene. Hepatobiliary system is affected in 10-40% of patients with SCA and has a multifactorial etiology. The authors present a child with SCA and conjugated hyperbilirubinemia due to biliary obstruction. He underwent endoscopic retrograde cholangiopancreatography (ERCP) and biliary stenting, had complications of post sphincterotomy bleed, retroperitoneal hematoma and post laparoscopic cholecystectomy sepsis with acute sickle hepatic crisis. He was managed successfully and is doing well on follow-up. Here authors discuss a stepwise approach in management of jaundice in a patient with SCA. Patients with SCA are prone to develop vaso-occlusive crisis (VOC) during periods of stress. VOC affects the liver as acute sickle hepatic crisis, acute hepatic sequestration or sickle cell intrahepatic cholestasis and is collectively termed as sickle cell hepatopathy. Hemolysis due to sickling results in cholelithiasis with its associated complications. These patients are vulnerable to viral hepatitis and hemochromatosis due to multiple blood transfusions. There may be a concomitant acute viral hepatitis, drug induced liver injury, Budd-Chiari syndrome or other chronic liver diseases. These conditions have considerable clinical overlap and may coexist, making the evaluation more challenging. Detailed history, examination and investigations are required for differentiation of etiology. Periods of stress must be tackled with proper hydration, oxygen supplementation, maintaining hemoglobin >10 g/dL, and a low hemoglobin S fraction. Patients with SCA and conjugated hyperbilirubinemia are "high-risk" and best managed by a multidisciplinary team. Preventive strategies like timely vaccinations, chelation, etc. must be practised.

Keywords Sickle cell anemia · Endoscopic sphincterotomy, Intrahepatic cholestasis · Liver diseases · Hyperbilirubinemia

Introduction

Sickle cell anemia (SCA) is an autosomal recessive disorder caused by a mutation in the beta globin gene. Sickle cell disease (SCD) comprises of patients with SCA as well as other compound heterozygotes who have a sickle cell mutation on one beta globin allele and another mutation such as beta thalassemia or Hemoglobin C (HbC) disease on the other. SCA patients usually present with unconjugated hyperbilirubinemia due to hemolysis. However, the hepatobiliary system may be affected in upto ~40% cases, resulting in conjugated hyperbilirubinemia [1]. Liver related causes account for ~7% of all mortality in patients with SCD [2]. In this review authors will be highlighting a child of SCA with conjugated hyperbilirubinemia due to biliary obstruction and multiple complications who was managed successfully. The stepwise approach to evaluation and management of jaundice in SCD will be discussed.

Case Report

A 13-y-old boy, a resident of Raipur, Chhattisgarh with no significant family history was diagnosed as a case of SCA in infancy. He was on hydroxyurea and maintained a hemoglobin of 9-10 g/dL. There were no episodes suggestive of sickle cell crisis in the past. He presented to authors with 1 mo history of conjugated hyperbilirubinemia. There was history of pain abdomen in the right upper quadrant at the

✉ Anshu Srivastava
avanianshu@yahoo.com

[1] Department of Pediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

[2] Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

[3] Department of Surgical Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

[4] Department of Radiodiagnosis, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226014, India

onset of jaundice which subsided later on. There was no history of pale stools, pruritus, fever or alternative medicine intake. There was no history of hepatic decompensation. On examination he had pallor, deep icterus and a soft non-tender hepatomegaly. The child was hemodynamically stable. The possibilities considered were choledocholithiasis, acute viral hepatitis or acute sickle hepatic crisis.

Basic workup of the patient is shown in Table 1. At admission, he had leukocytosis (29000/mm^3, with 75% neutrophils) and mild anemia (9.4 g/dL). His liver function tests revealed deep jaundice (total/direct bilirubin- 55/32 mg/dL), mild elevation of serum transaminases, normal alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT). A normal GGT does not support the possibility of choledocholithiasis. Coagulation profile and renal functions were normal. Serum procalcitonin (PCT) was negative and blood culture sterile.

Ultrasound doppler of the abdomen revealed gall stones (GS) and dilated common bile duct (CBD, 13 mm) with no features of Budd-Chiari syndrome or chronic liver disease. Magnetic resonance cholangiopancreatography (MRCP) showed a segmental narrowing of the mid CBD over a length of 12 mm with mild proximal dilatation of the CBD and central intrahepatic biliary radical dilatation. However, no filling defect was identified in the CBD. Gall bladder was filled with multiple calculi largest measuring 10 mm in size. Acute viral markers were negative. Sequencing for Gilbert syndrome (UGT1A1 sequencing- $TA_{7/7}$) was positive.

In view of deep jaundice, neutrophilic leukocytosis and abnormal biliary tree at imaging, a diagnosis of biliary obstruction (choledocholithiasis/ ischemic cholangiopathy) with possible cholangitis was considered. Antibiotics (piperacillin-tazobactum) were started and an endoscopic retrograde cholangiopancreatography (ERCP) was done.

At ERCP, the balloon occlusion cholangiogram showed a dilated proximal CBD (15 mm) with a small filling defect and no stricture. However, on balloon sweep only sludge and no stone was retrieved. A check cholangiogram revealed no filling defect. Endoscopic sphincterotomy (ES) was done and a 10 F X 7 cm double pig tail stent was placed into the right hepatic duct. There were no difficulties or apparent complications noticed during the procedure.

Twenty-four hours post ERCP, the child developed melena, postural hypotension and a significant drop in hemoglobin (9.4 g/dL to 6.4 g/dL). Blood transfusion was given. A side viewing endoscopy (SVE) showed oozing of blood from the apex of sphincterotomy site (Fig. 1). Adrenaline injection (1:10000 dilution, in aliquots of 0.5-2 ml) and hemospray application was done and the bleed stopped. However, the child continued to have melena with further drop in hemoglobin to 5.6 g/dL. Computerised tomography (CT) angiography of the abdomen revealed a doubtful arterial blush in the wall of second part of duodenum (suspected pseudoaneurysm/site of active bleed). There was no evidence of perforation in the form of extraluminal air. Digital subtraction angiography (DSA) done after CTA for site of bleed did not identify any abnormality. In view of ongoing bleed, SVE was repeated, which showed continuing oozing from the sphincterotomy site. Hence a 10 mm, 6 cm long fully covered self-expanding metallic stent (FCSEMS, Wallflex, Boston Scientific) was placed. A check SVE done 48 h later showed that there was no further bleed but a bulge

Table 1 Investigations of the patient at admission, hospitalisation and follow-up

Investigation	On admission	At initial bleed post-ERCP	At time of hematoma	Pre LC after successful biliary drainage	Immediate postop	Follow-up after LC
Hb (g/dL)	9.4	6.4*	8.5	9	6.8*	8.6
TLC (/mm^3)	29000	30200	33900	12600	25300	11200
Platelet count (/mm^3)	403000	339000	543000	484000	368000	371000
Bilirubin (T/D) (mg/dL)	55/32	48.9/35.4	23.9/15.6	10.9/0.7	11.9/0.87	4.89
AST/ALT (IU/L)	131/49	156/49	259/112	37/21	69/144	28/24
ALP (IU/L)	238	56	281	194	293	136
GGT (IU/L)	17	17	-	-	-	-
Albumin (g/dL)	3.7	2.9	2.39	4.4	3.3	3.4
INR	1.34	1.68	1.35	1.38	1.42	1.29
Creatinine (mg/dL)	0.4	0.5	0.5	0.5	0.4	0.5

ALP Alkaline phosphatase, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *ERCP* Endoscopic retrograde cholangiopancreatography, *GGT* Gamma glutamyl transpeptidase, *Hb* Hemoglobin, *INR* International normalized ratio, *LC* Laparoscopic cholecystectomy, *T/D* Total/Direct, *TLC* Total leukocyte count

*Blood transfusion given

Normal values: TLC: 4000-11000/mm^3, Platelet count: 150000-400000/mm^3, Bilirubin: 0.1-1.3 mg/dL, AST: 5-40 IU/L, ALT: 5-40 IU/L, ALP: 35-150 IU/L, GGT: 13-86 IU/L, Creatinine- 0.5-1.6 mg/dL

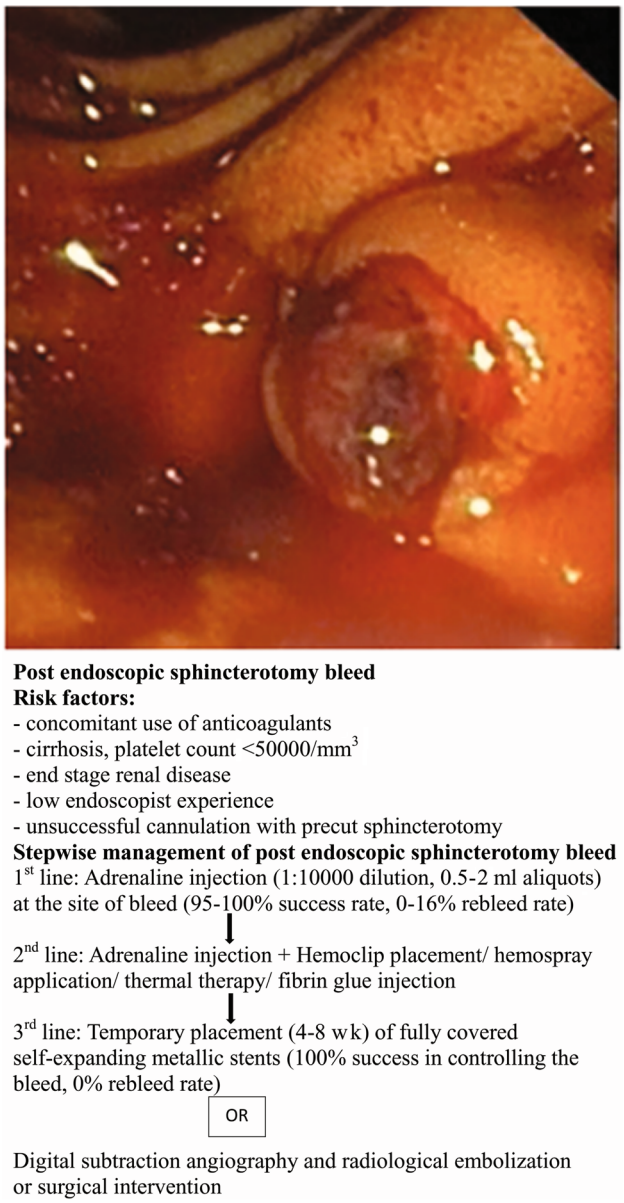


Fig. 1 Side viewing endoscopy showing oozing of blood from the apex of the sphincterotomy site and step-wise management of post endoscopic sphincterotomy bleed

in the duodenum near the papilla was seen (?wall hematoma). There was no further drop in hemoglobin. The child remained well with no abdominal pain, fever or peritoneal signs of free perforation.

Two weeks later the child started having bilious vomiting. CT abdomen (Fig. 2a) showed a large collection (5.1 X 14.1 cm) with hyperdense contents tracking along the C loop of duodenum and causing mass effect. There was no perinephric air or extraluminal leak of oral contrast suggestive of duodenal perforation. Hence, the possibility of a retroperitoneal or duodenal wall hematoma was considered. Percutaneous catheter drainage (PCD, size 10 F) of the collection was done which drained hemorrhagic fluid. The child improved (no vomiting or fever and bilirubin decreased from 55 to 20.7 mg/dL). PCD was removed after 2 wk, and the metallic stent in CBD was replaced by a double pig tail plastic (10 F, 5 cm) stent after 1 mo.

Laparoscopic cholecystectomy (LC) was done six months later. In the immediate post- operative period, he had high grade fever and a small septated collection in gall bladder fossa along with cellulitis at the laparoscopic port site (Fig. 2b). Abdominal sutures were removed, collection was drained and appropriate antibiotics were given. At this time child had a drop in hemoglobin to 6.5 g/dL and required three units of packed red blood cell transfusion. He recovered within a week and continued to be asymptomatic.

Eighteen days post LC, the double pig tail stent was removed. He is asymptomatic over 16 mo of follow-up, and has had no further sickle cell crisis nor required any further transfusions (Table 1).

Discussion

Most patients with SCD (~90%) present with jaundice [3, 4]. However, it is generally unconjugated hyperbilirubinemia secondary to hemolysis of the sickled red blood cells. Hepatobiliary involvement due to multiple etiologies result in conjugated hyperbilirubinemia. The stepwise evaluation and treatment of these cases is detailed in Fig. 3.

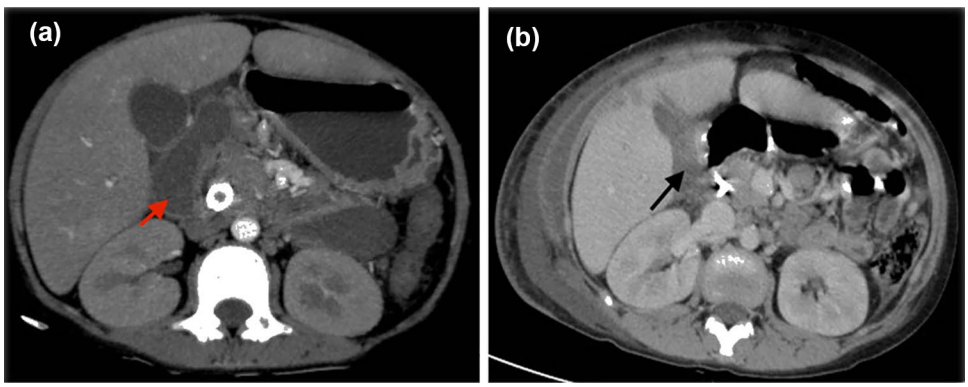
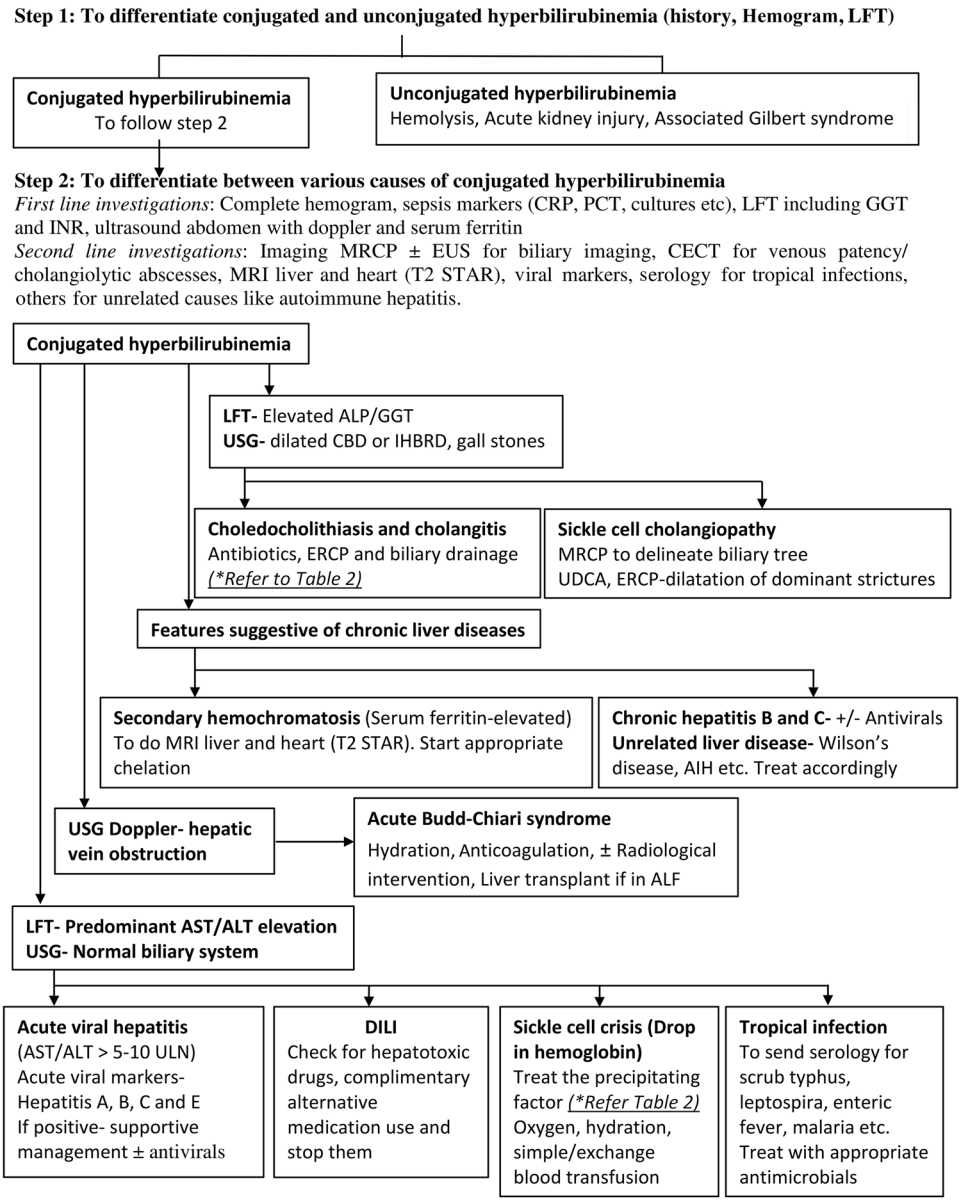


Fig. 2 Contrast enhanced computerised tomography of abdomen showing (**a**) a collection along the C loop of duodenum and compressing it (*Red arrow*). Metallic stent noted in common bile duct and (**b**) a collection in gall bladder fossa (*Black arrow*) and subcutaneous tissue after laparoscopic cholecystectomy



*For details of clinical presentation and differentiation of acute sickle hepatic crisis, acute hepatic sequestration, sickle cell intrahepatic cholestasis and cholangitis please refer to Table 2

Fig. 3 Approach to a case of sickle cell disease with jaundice. *AIH* Autoimmune hepatitis, *ALF* Acute liver failure, *ALP* Alkaline phosphatase, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *CBD* Common bile duct, *CECT* Contrast enhanced computed tomography, *DILI* Drug-induced liver injury, *ERCP* Endoscopic retrograde cholangiopancreatography, *EUS* Endoscopic ultrasound, *GGT* Gamma glutamyl transpeptidase, *IHBRD* Intrahepatic biliary radicle dilatation, *INR* International normalized ratio, *MRCP* Magnetic resonance cholangiopancreatography, *MRI* Magnetic resonance imaging, *PCT* Procalcitonin, *UDCA* Ursodeoxycholic acid, *ULN* Upper limit of normal, *USG* Ultrasonography

Etiology of Conjugated Hyperbilirubinemia and Sickle Cell Hepatopathy

Sickle cell hepatopathy (SCH) encompasses the liver diseases encountered in patients of SCD due to intrahepatic sickling. It includes acute sickle hepatic crisis, acute hepatic sequestration and sickle cell intrahepatic cholestasis [5]. SCH is precipitated by stress, infections, hypovolemia etc. In patients with SCD admitted with vaso-occlusive crisis, liver is reportedly affected in 10-39% of the cases [5, 6]. The degree of sickling increases from mild in acute sickle hepatic crisis to moderately-severe in acute hepatic sequestration and very-severe in sickle cell intrahepatic cholestasis. In the latter two forms of SCH there is sinusoidal dilatation while in sickle cell intrahepatic cholestasis there is also ischemia of the hepatocytes leading to liver failure. The differences between the three forms of SCH are detailed in Table 2 [7, 8].

Apart from SCH, there is an increased risk of transfusion related viral hepatitis or iron overload, hemolysis associated cholelithiasis and its complications, acute Budd-Chiari syndrome and ischemic cholangiopathy. In addition, acute viral hepatitis, drug-induced liver injury (DILI), tropical infections etc also occur in these patients, similar to the general population (Table 2 and Fig. 3).

Table 2 Comparison of clinical and investigative findings in different causes of acute conjugated hyperbilirubinemia in patients with sickle cell disease

Features	Acute sickle hepatic crisis	Acute hepatic sequestration	Sickle cell intrahepatic cholestasis	Cholangitis	Acute viral hepatitis
Fever	+	+	+	++	-*
Jaundice	+	+	++	+	+
RUQ pain	+	+	+	+	-*
Pale stool	-	-	-	+	-**
Prodrome	-	-	-	-	+
Tender hepatomegaly	+	++	++	+/-	+/-
Hemoglobin	Mild drop[a]	Significant drop[a]	Significant drop[a]	Normal	Normal
Conjugated bilirubin	<15 mg/dL	<30 mg/dL	>30 mg/dL	Variable	Variable
Transaminases	Mild elevation, <3 ULN	Mild elevation	Moderate to severe elevation (>5-10 ULN)	Mild elevation	Moderate to severe elevation (>5-10 ULN)
Coagulopathy	No	+/-	++	+/-	- + (If in ALF)
Treatment	Hydration, oxygenation	Simple/exchange blood transfusion	Exchange blood transfusion	Antibiotics and biliary drainage	Supportive ± antivirals

ALF Acute liver failure, *RUQ* Right upper quadrant, *ULN* Upper limit of normal

* as part of prodrome

** in cholestasis phase of AVH

[a]Mild drop: Settles with oxygenation and hydration and generally doesn't require blood transfusion. Significant drop: >2 g/dL, requires simple/exchange blood transfusion

As discussed previously the index patient had GS with biliary obstruction. However, due to very high bilirubin authors evaluated and confirmed the presence of concomitant Gilbert syndrome in him. Gilbert syndrome is an autosomal recessive disorder caused by a mutation (increased dinucleotide repeats $[TA]_7$ or $[TA]_8$) in the promotor region of UGT1A1 which causes decreased production of the enzyme uridine diphosphoglucuronate-glucuronosyltransferase 1A1 that is required for bilirubin conjugation. Patients of SCD with concomitant Gilbert syndrome tend to have higher bilirubin levels and a greater prevalence of GS [9].

Cholelithiasis in Sickle Cell Disease

Hemolysis of the irreversibly sickled erythrocytes results in unconjugated hyperbilirubinemia. Unconjugated bilirubin precipitates on contact with calcium in the lumen of gall bladder and results in pigment stone formation. The prevalence of GS in SCD increases progressively with age: 14% at the age of 10 y, 36% at 15-18 y, 50% above 22 y of age and 70% above 30 y of age [10]. In addition, they are more likely to develop symptoms due to GS. In a study, 70% of the patients with SCD and incidentally detected cholelithiasis developed symptoms (biliary colic, acute cholecystitis and/or conjugated jaundice) after a median follow-up of 38 (range: 12-80) mo [11].

Patients with SCD and GS are also at a higher risk of having choledocholithiasis than the general population with GS (18-30% vs. 5-15%) [12]. Patients with choledocholithiasis and cholangitis require antibiotics and ERCP for biliary drainage, as done in present case.

Sickle Cell Cholangiopathy (SCC)

SCC is an ischemic cholangiopathy where sickling of erythrocytes in the end arteries of the bile ducts results in hypoxia of bile ducts, which leads to ischemia and stricturing of the bile ducts [7]. In a series of 616 children with SCD, 0.8% of them had features of SCC [1]. In another study of patients with SCD and conjugated hyperbilirubinemia, 24.6% of them had SCC [13]. Treatment of SCC includes ursodeoxycholic acid, endoscopic dilatation of dominant strictures and liver transplantation in advanced cases [7, 14]. MRCP, endoscopic ultrasound (EUS) and ERCP will help in evaluation of these cases.

Complications of ERCP in SCD and Post Sphincterotomy Bleed

Biliary obstruction and cholangitis is a significant stress for patients with SCD and it can precipitate SCH and increase the risk of complications during interventions. The index

child had post-sphincterotomy bleed which first required adrenaline injection and hemospray followed by placement of FCSEMS to control the bleed.

Post endoscopic sphincterotomy (ES) bleed complicates 0.3-9.6% of ERCP procedures [15]. Other complications being post ERCP pancreatitis (3.5-9.7%), cholangitis (0.5-3%), bleeding (0.3-9.6%), duodenal perforation (0.08-0.6%) and sedation related events (upto 24.6%) [15].

The index child had delayed (occurs after the procedure is completed) and severe bleed as it resulted in prolonged hospitalisation (>10 d) including ICU stay (>1 d) [15]. Post-procedure at the time of bleed, authors noted that the child had mild coagulopathy (INR- 1.7), most likely due to sickle cell crisis precipitated by the stress of ERCP and acute cholangitis.

Stepwise management of post-ES bleed has been detailed in Fig. 1 [15]. Initial moderate-severe bleed and serum bilirubin >10 mg/dL are independent risk factors for rebleed [16]. Both of which were present in index patient. Although a sickle cell crisis can complicate the outcome of invasive procedures like ERCP, in a series of 240 ERCP procedures done in 224 patients, only 4 (1.7%) had mild post ES bleed and 8 (3.3%) had mild acute pancreatitis [13]. Hence, ERCP is safe if done only when indicated and by experts.

The index child also had a retroperitoneal hematoma which was symptomatic with bilious vomiting and required percutaneous drainage. The differentials being a retroperitoneal or a duodenal wall hematoma. These two entities are sometimes difficult to differentiate, especially when large as in present case. The absence of clinical and imaging evidence of perforation (extraluminal air or oral contrast), tracking of the hematoma along the C loop of the duodenum, and the timing of hematoma formation favour the possibility of duodenal wall hematoma. The duodenum is a likely location for hematoma formation due to its fixed, retroperitoneal nature, rich submucosal arterial supply and formation of a closed loop between pylorus and ligament of Treitz. Trauma due to the endoscope or instruments can result in rupture of the vessels [17–19].

However, one cannot exclude totally the possibility of a small duodenal perforation which got sealed by the FCSEMS placed for the management of the post ES-bleed [20].

Fortunately, the management of both these conditions is similar and requires drainage (percutaneous or surgical) when symptomatic as was done in index patient [17, 18, 21].

Controversies in Management of Patients with Sickle Cell Disease

1. Laparoscopic cholecystectomy (Elective vs. emergent; Symptomatic vs. asymptomatic)

   Although the index patient had symptomatic cholelithiasis which requires cholecystectomy, there is an ongoing debate whether to subject the asymptomatic GS patients to an elective cholecystectomy or wait for symptoms to develop and then perform the same. Elective LC may be preferred as the symptoms of biliary complications may overlap with that of vaso-occlusive crisis or a vaso-occlusive crisis may be triggered because of cholangitis, resulting in a more complicated situation. On the other hand, surgery in an asymptomatic patient is an additional stress and risks the development of a vaso-occlusive crisis.

   Curro et al. found that patients of SCD undergoing LC when asymptomatic (n = 16) had a shorter post-operative stay (3 vs. 7.4 d, $p = 0.001$) and fewer complications (12.5% vs. 80%, $p = 0.03$) as compared to patients who were symptomatic (n = 10) at the time of LC [11]. Al-Mulhim et al. also showed a higher need of conversion to open cholecystectomy (9.5% vs. 12%) and greater number of complications (0 vs. 18%) in symptomatic patients [22]. However, Muroni et al. found that although elective LC patients fared better, there was no significant difference in number of complications (11.5% vs. 22.5%), need for conversion to open cholecystectomy (2% vs. 10%) and duration of hospital stay (5.8 vs. 7.96 d, $p = 0.56$) among patients undergoing LC with incidentally detected GS (n = 52) vs. those with symptomatic GS (n = 51) [23].

   Goodwin et al. (n = 191) compared sickle cell patients undergoing elective asymptomatic vs. elective symptomatic vs. emergent cholecystectomy and found that the length of hospital stay was lesser in patients undergoing elective cholecystectomy in asymptomatic patients (2.9 vs. 4.5 vs. 7.2 d, $p = 0.02$) [24]. Al-Salem et al. (n = 87) compared LC with open cholecystectomy (OC) and found lower complication rate (7.7% vs. 22.9%) and hospital stay (4.5 vs. 7.5 d, $p < 0.001$) in the LC group [25]. None of the studies have reported mortality due to surgery.

   In view of these findings, most centres practice elective LC when GS are identified on screening even if asymptomatic.

2. Role of ERCP in patients with cholelithiasis with or without choledocholithiasis

   In the era of OC, intraoperative cholangiogram (IOC) to look for CBD stones used to be done routinely. CBD exploration was done in patients with IOC suggestive of CBD stones. However, at present in the era of LC and easy availability of ERCP, IOC is used sparingly. Issa et al. had shown that among 242 ERCP procedures in patients with SCD, CBD stones were detected in 88 (39.3%) including 18 (18.6%) cases with normal CBD on ultrasound and conjugated hyperbilirubinemia. Therefore, USG is not a good modality for evaluation of CBD stones in these cases [12, 13]. They opined that ERCP should be performed prior to cholecystectomy if the patient with SCD has CBD stones on imaging,

complications like acute cholangitis or pancreatitis, deep jaundice (bilirubin >50 mg/L) or elevated alkaline phosphatase. In patients of SCD with cholelithiasis and conjugated hyperbilirubinemia, it may be better to perform an MRCP or EUS to identify CBD stones [12, 13]. This will help to better select patients for ERCP and decrease the rate of negative ERCP.

Post LC, the index child developed a significant fall in hemoglobin along with a collection in gall bladder fossa and port site cellulitis. Even though there was no documented conjugated hyperbilirubinemia, a significant fall in hemoglobin is likely due to sickle cell crisis due to the stress of surgery and infection.

The present patient highlights two important aspects of managing children with SCD and jaundice. One is that these patients are prone to unexpected complications and need a multidisciplinary team of interventional radiologist, endoscopist, surgeon and hepatologist for a good outcome. Second that these patients may have multiple factors contributing to the conjugated hyperbilirubinemia at the same time which are difficult to differentiate like biliary obstruction causing infection and also precipitating SCH. This calls for extreme vigilance while managing these "high-risk" individuals.

Preventive Strategies for Patients with Sickle Cell Disease

Patients with SCD encounter transfusion related viral hepatitis (hepatitis B and C) or iron overload. Regular screening for hepatitis B, C, HIV and signs of iron overload (serum ferritin, MRI liver and heart in cases with suspected iron-overload) must be done [26–28]. Hepatitis A and B vaccine should be given. As patients are at risk of auto-splenectomy they must be vaccinated against capsulated organisms (*Pneumococcus, meningococcus* and *Haemophilus influenza B*) and influenza (yearly vaccine). Iron overload can occur even in transfusion independent patients as they undergo continuous hemolysis. Adequate chelation must be offered as and when required.

These patients need screening for GS, and elective cholecystectomy before development of GS related complications. Invasive procedures like liver biopsy should be avoided as much as possible, especially in emergency setting. A study reported a mortality of 28% and hemorrhagic complications in 36% after liver biopsy. These patients were in sickle cell crisis at the time of biopsy which predisposed them to an adverse outcome [29].

To prevent sickle cell crisis, a HbS of at least <50% and preferably <30% and Hb >10 g/dL should be maintained by use of hydroxyurea, packed red cell transfusion or exchange transfusion [8, 11, 30]. Stressful conditions/infections should be avoided and if present, treated urgently by hydration, antipyretics and antibiotics.

The patients and parents need to be educated about their disease, need of regular follow-up and urgent medical attention during illness.

In conclusion, hepatobiliary involvement is an important problem in patients with SCD with a multifactorial etiology. Targeted step-wise management by experts results in a good outcome.

Authors' Contributions SSV contributed to acquisition, analysis and interpretation of the data and drafting the article; AS conceptualized and designed the study and contributed to acquisition, analysis and interpretation of the data and co-drafting the article; PR contributed to acquisition, analysis and interpretation of the data, co-drafting the article; RKS, MSS, UP and RRY contributed to acquisition, analysis and interpretation of the data and critical revisions of the manuscript. All the authors approved the final version of the manuscript. AS will act as the guarantor for this manuscript.

Declarations

Conflict of Interest None.

References

1. Allali S, de Montalembert M, Brousse V, et al. Hepatobiliary complications in children with sickle cell disease: a retrospective review of medical records from 616 patients. J Clin Med. 2019;8:1481–96.
2. Kyrana E, Rees D, Lacaille F, et al. Clinical management of sickle cell liver disease in children and young adults. Arch Dis Child. 2021;106:315–20.
3. Aloni MN, Tshimanga BK, Ekulu PM, Ehungu JLG, Ngiyulu RM. Malaria, clinical features and acute crisis in children suffering from sickle cell disease in resource-limited settings: a retrospective description of 90 cases. Pathog Glob Health. 2013;107:198–201.
4. Yadav R, Lazarus M, Ghanghoria P, et al. Sickle cell disease in Madhya Pradesh, Central India: a comparison of clinical profile of sickle cell homozygote vs. sickle-beta thalassaemia individuals. Hematology. 2016;21:558–63.
5. Shah R, Taborda C, Chawla S. Acute and chronic hepatobiliary manifestations of sickle cell disease: a review. World J Gastrointest Pathophysiol. 2017;8:108–16.
6. Koskinas J, Manesis EK, Zacharakis GH, Galiatsatos N, Sevastos N, Archimandritis AJ. Liver involvement in acute vaso-occlusive crisis of sickle cell disease: prevalence and predisposing factors. Scand J Gastroenterol. 2007;42:499–507.
7. Lacaille F, Allali S, de Montalembert M. The liver in sickle cell disease. J Pediatr Gastroenterol Nutr. 2021;72:5–10.
8. Ahn H, Li CS, Wang W. Sickle cell hepatopathy: clinical presentation, treatment, and outcome in pediatric and adult patients. Pediatr Blood Cancer. 2005;45:184–90.
9. Batista JVGF, Arcanjo GS, Batista THC, et al. Influence of UGT1A1 promoter polymorphism, α-thalassemia and β^s haplotype in bilirubin levels and cholelithiasis in a large sickle cell anemia cohort. Ann Hematol. 2021;100:903–11.
10. Suell MN, Horton TM, Dishop MK, Mahoney DH, Olutoye OO, Mueller BU. Outcomes for children with gallbladder abnormalities and sickle cell disease. J Pediatr. 2004;145:617–21.

11. Curro G, Meo A, Ippolito D, Pusiol A, Cucinotta E. Asymptomatic cholelithiasis in children with sickle cell disease: early or delayed cholecystectomy? Ann Surg. 2007;245:126–9.
12. Issa H. Role of ERCP in the era of laparoscopic cholecystectomy for the evaluation of choledocholithiasis in sickle cell anemia. World J Gastroenterol. 2011;17:1844–7.
13. Issa H, Al-Haddad A, Al-Salem A. Sickle cell cholangiopathy: an endoscopic retrograde cholangiopancreatography evaluation. World J Gastroenterol. 2009;15:5316–20.
14. Ahmed M, Dick M, Mieli-Vergani G, Harrison P, Karani J, Dhawan A. Ischaemic cholangiopathy and sickle cell disease. Eur J Pediatr. 2006;165:112–3.
15. Dumonceau JM, Kapral C, Aabakken L, et al. ERCP-related adverse events: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2020;52:127–49.
16. Lee MH, Tsou YK, Lin CH, et al. Predictors of re-bleeding after endoscopic hemostasis for delayed post-endoscopic sphincterotomy bleeding. World J Gastroenterol. 2016;22:3196–201.
17. Samra M, Al-Mouradi T, Berkelhammer C. Gastric outlet obstruction due to intramural duodenal hematoma after endoscopic biopsy: possible therapeutic role of endoscopic dilation. Case Rep Gastroenterol. 2018;12:692–8.
18. Pan YM. Endoscopic drainage for duodenal hematoma following endoscopic retrograde cholangiopancreatography: a case report. World J Gastroenterol. 2013;19:2118–21.
19. Weiss E, Tadley M, Leung PS, Kaplan M. Ruptured dissecting intramural duodenal hematoma following endoscopic retrograde cholangiopancreatography. ACG Case Rep J. 2017;4:e70-2.
20. Kumbhari V, Sinha A, Reddy A, et al. Algorithm for the management of ERCP-related perforations. Gastrointest Endosc. 2016;83:934–43.
21. Theopistos V, Theocharis G, Konstantakis C, et al. Non-operative management of type 2 ERCP-Related retroperitoneal duodenal perforations: a 9-year experience from a single center. Gastroenterol Res. 2018;11:207–12.
22. Al-Mulhim A, Abdulatif M, Ali A. Laparoscopic cholecystectomy in children with sickle cell disease. Saudi J Gastroenterol. 2006;12:130–4.
23. Muroni M, Loi V, Lionnet F, Girot R, Houry S. Prophylactic laparoscopic cholecystectomy in adult sickle cell disease patients with cholelithiasis: a prospective cohort study. Int J Surg. 2015;22:62–6.
24. Goodwin EF, Partain PI, Lebensburger JD, Fineberg NS, Howard TH. Elective cholecystectomy reduces morbidity of cholelithiasis in pediatric sickle cell disease. Pediatr Blood Cancer. 2017;64:113–20.
25. Al-Salem AH, Issa H. Laparoscopic cholecystectomy in children with sickle cell anemia and the role of ERCP. Surg Laparosc Endosc Percutan Tech. 2012;22:139–42.
26. Ebert EC, Nagar M, Hagspiel KD. Gastrointestinal and hepatic complications of sickle cell disease. Clin Gastroenterol Hepatol. 2010;8:483–9.
27. Theocharidou E, Suddle AR. The liver in sickle cell disease. Clin Liver Dis. 2019;23:177–89.
28. Praharaj DL, Anand AC. Sickle hepatopathy. J Clin Exp Hepatol. 2021;11:82–96.
29. Zakaria N, Knisely A, Portmann B, et al. Acute sickle cell hepatopathy represents a potential contraindication for percutaneous liver biopsy. Blood. 2003;101:101–3.
30. Kliegman R, Behman RE, Nelson WE. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Elsevier; 2016.