

Case Report

Cholelithiasis Diagnosis and Management in Thalassemia

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Abstract:

Background: Cholelithiasis, while infrequently found in children, carries a significant risk for those with underlying conditions like thalassemia compared to the general population. This study aimed to describe the manifestations of cholelithiasis in thalassemic children.

Case: A 12-year-old girl with beta-thalassemia major presented with recurrent right upper quadrant abdominal pain and vomiting. Imaging revealed cholelithiasis and choledocholithiasis. Due to complications related to her thalassemia, she underwent endoscopic retrograde cholangiopancreatography (ERCP) for gallstone removal followed by laparoscopic cholecystectomy. Post-operative management addressed post-ERCP pancreatitis and bleeding concerns. The patient recovered well and is scheduled for follow-up.

Discussion: Increased bilirubin production, iron overload, and altered bile properties in beta-thalassemia contribute to cholelithiasis risk. The patient presented with typical symptoms and underwent successful laparoscopic cholecystectomy after initial management with ERCP, which led to post-ERCP pancreatitis.

Conclusion: This case underscores the elevated risk of cholelithiasis in thalassemic children and the importance of early diagnosis and intervention for optimal outcomes.

Keywords: beta-thalassemia major, cholecystectomy, cholelithiasis, endoscopic retrograde cholangiopancreatography

Introduction

Cholelithiasis, also known as gallstones, is uncommon in children. The prevalence between boys and girls during pre-puberty ranged similarly at 0.13% and 0.2%, respectively.¹ However, the increased use of ultrasound imaging since 2000 has led to a higher detection rate of cholelithiasis compared to previous years.¹

Risk factors of cholelithiasis in children differs from adults. In children, the most common cause of cholelithiasis is thalassemia (20 – 30%), followed by factors such as obesity, total parenteral nutrition, ileal resection, congenital hepatobiliary disease, antibiotic use (e.g., ceftriaxone), metabolic syndrome, progressive familial intrahepatic cholestasis (PFIC), choledochal cysts, and idiopathic causes.¹ Children with thalassemia showed a 10 – 20% higher risk of cholelithiasis compared to the general population. However, it often remains asymptomatic for many years.²

Management for non-thalassemic patients with cholelithiasis is usually conservative unless signs of cholecystitis or cholangitis were found. However, due to the increased risk of complications, a tailored approach is required for managing cholelithiasis in thalassemia patients.² This case report illustrated the manifestations of cholelithiasis presenting in a thalassemic child, with the aim to increase the recognition of cholestasis signs and symptoms in children.

Case

Case Illustrations

A 12-year-old girl with beta-thalassemia major presented to the emergency department with a chief complaint of severe, stabbing pain in the right upper quadrant of her abdomen for three days. The pain was constant, radiated to her back, and worsened after consuming fatty foods. She also reported vomiting more than five times a day. Her appetite significantly decreased, resulting in a 3 kg weight loss. Presence of fever, cough, abnormal bowel habit, or dark-colored urine were denied.

The patient had experienced recurrent abdominal pain for two years prior to this presentation. Previous abdominal ultrasound performed two years earlier revealed small gallstones, which were deemed not to require surgery at that moment. She was treated with pain medication and discharged for follow-up. Four months before admission, the pain intensity worsened. Re-evaluation using ultrasound was subsequently performed, revealing cholelithiasis with multiple, sand-like stones, signs of cholecystitis, common bile duct dilation containing multiple stones and splenomegaly. Due to limited resources, patient was referred to tertiary hospital for definitive management.

Patient was diagnosed with beta-thalassemia major at one year of age. She currently receives regular blood transfusions (every 2-3 weeks) and iron chelation therapy. There was no significant family history of similar conditions, but both her brother and sister are asymptomatic carriers of the thalassemia trait. Her development was with her age, and she had not yet begun menstruating.

Upon physical examination, she appeared generally ill with Cooley facies. Her anthropometric status indicated underweight with normal stature. Her abdominal examination displayed tenderness in the right upper quadrant (positive Murphy's sign) with a significant pain score (VAS 6-7). The liver was palpable (5 cm below costal margin) and the spleen mildly enlarged (Schuffner's grade 1-2), indicating complications related to the thalassemia. Vital signs and other examination were within normal limits, except for pale conjunctiva.

Laboratory workup revealed microcytic anemia (hemoglobin 9.6 g/dL, hematocrit 26.7%) and elevated ferritin (4515.37 ng/mL). Magnetic Resonance Cholangiopancreatography (MRCP) with intravenous contrast performed prior to admission demonstrated cholecystolithiasis with choledocholithiasis and dilation of the common bile duct and common hepatic duct, mild dilation of the right and left hepatic ducts and narrowing of the distal common bile duct. The results suggested a stricture due to passing gallstones in the distal common bile duct, bile sludge, decreased liver parenchymal homogeneity (which might also caused by hemosiderosis), and splenomegaly. Abdominal ultrasound results confirmed cholecystolithiasis, cholelithiasis, and choledocholithiasis, with dilation of the common bile duct, common hepatic duct, cystic duct, and right and left hepatic ducts. The ultrasound findings are shown in **Figure 1**.

Case Management

Based on clinical findings, the patient was diagnosed with multiple cholelithiasis, cholecystolithiasis, and beta-thalassemia major with hemosiderosis. Initial management included paracetamol for pain control, supplemented with ketoprofen as needed. Additionally, ursodeoxycholic acid and a red blood cell transfusion were given. Deferiprone was administered as iron chelation therapy due to concerns of hemosiderosis.

The patient was referred to gastroenterology for endoscopic retrograde cholangiopancreatography (ERCP) and pediatric surgery for a planned cholecystectomy. Due to the repeated episodes of severe pain (VAS 6-7) despite the administration of analgesics, patient was also referred to the pain management team. The regimen was adjusted to include ketorolac and increased-dose paracetamol. This effectively reduced pain, with a VAS score of 2-3.

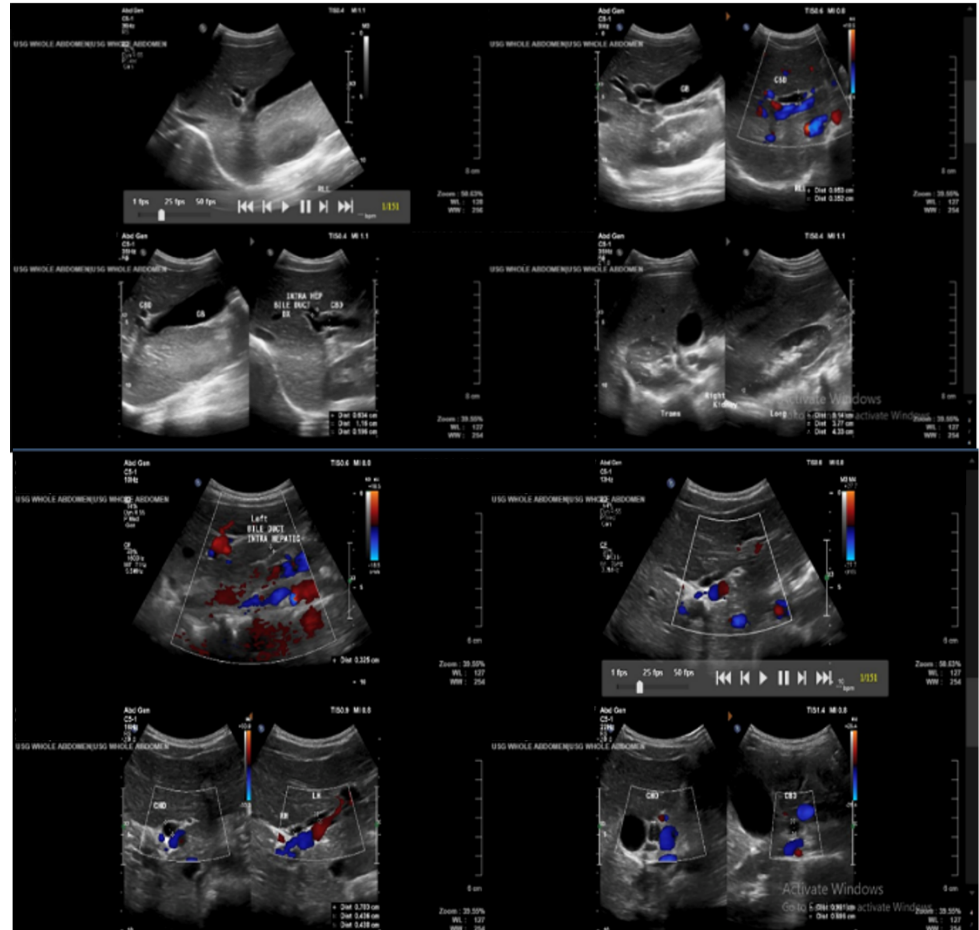


Figure 1. Abdominal ultrasound findings

On the 8th day, ERCP were conducted and revealed multiple mobile gallstones within the common hepatic duct. A successful gallstone extraction and biliary duct cleansing procedure were also performed (results shown in **Figure 2**).

Following ERCP procedure, the patient was placed on nil per os (NPO) status and received intravenous fluids. A prophylactic antibiotic regimen of cefoperazone-sulbactam was administered for seven days.

Additionally, she received vitamin K, tranexamic acid for bleeding prophylaxis, omeprazole for gastric acid suppression, sucralfate syrup for gastrointestinal protection, and ketoprofen suppositories for pain management. Somatostatin was administered as a bolus followed by a continuous infusion for five days to prevent post-ERCP pancreatitis. Frozen blood plasma was also administered. Six hours after ERCP, the patient developed severe right upper quadrant pain radiating to her back (VAS 6-7) with nausea and vomiting, which were managed with increased-dose of

paracetamol. Elevated amylase (954 U/L) and lipase (1378 U/L) confirmed post-ERCP pancreatitis. Laboratory evaluation on the 9th day of treatment revealed persistent mild anemia (hemoglobin 9.7 g/dL) requiring a red blood cell transfusion.

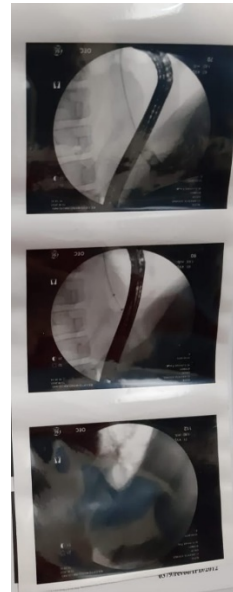


Figure 2. Endoscopic retrograde

On the 10th and 11th days of treatment, the pain further reduced to a VAS score of 1, with no fever, nausea, or vomiting. Hemodynamic parameters remained stable, and bowel function normalized. Oral fluid intake was gradually reintroduced and tolerated well.

By the 14th day of hospitalization, the patient's abdominal pain had significantly subsided. She was discharged on the 15th day with a prescription for ursodeoxycholic acid for continued gallstone dissolution, paracetamol for pain relief, and omeprazole) for gastric acid suppression.

One month later, the patient returned for follow-up. Examination revealed intermittent right upper quadrant pain (VAS 3-4) managed with analgesics, with no other significant symptoms. The patient was then scheduled for a definitive laparoscopic cholecystectomy. Pre-operative physical examination revealed a moderately ill but alert, with normal vital signs. Pre-operatively, the patient received a packed red blood cells transfusion due to severe anemia (Hb: 7.4) as well as frozen plasma transfusion and vitamin K due to prolonged APTT (1.9 times).

The patient underwent a successful laparoscopic cholecystectomy on the 3rd day of treatment. Post-cholecystectomy bile duct images are shown in **Figures 3**. Post-operatively, the patient experienced minimal pain, but developed diarrhea without blood or mucus, which resolved within 4 days. By the 7th day, her condition was stable, and she was discharged with follow-up instructions.

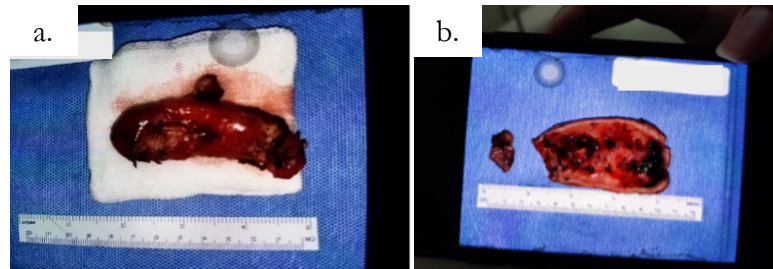


Figure 3. Post-cholecystectomy bile duct images. a. Intact bile duct; b. Incised bile duct

At a one-week follow-up appointment, the patient reported no new complaints. Examination revealed a well-healing surgical site, and she had resumed a normal diet. Surgical wound image is shown in **Figure 4**.



Figure 4. Post-cholecystectomy surgical wound

The patient's prognosis are *bonam* for *ad vitam*, *dubia ad bonam* for *ad functionam*, *bonam* for *ad sanationam*.

Discussion

Cholelithiasis, the presence of gallstones, is a well-known issue in adults, but uncommon in children.¹ It is more prevalent in females compared to males. This sex disparity is attributed to the influence of estrogen, which binds to receptors in the liver and upregulates cholesterol secretion into bile, promoting gallstone formation.³ In this case, although the patient, a 12-year-old girl, had not yet reached menarche, her gender placed her at a higher risk for developing gallstones.³

A summary of various causes and risk factors for cholelithiasis is presented in **Figure 5**.⁴ Children with thalassemia have a 10 – 20% higher risk of cholelithiasis compared to the general population, often remains asymptomatic for many years.² This was the

case for this patient, whose underlying beta-thalassemia major likely contributed to her condition.

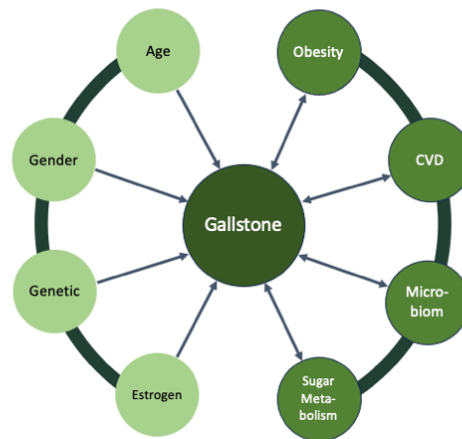


Figure 5. Influencing factors occurrence of cholelithiasis⁴

Cholelithiasis Pathogenesis in Thalassemia

Thalassemia is a genetic blood disorder affecting hemoglobin production. Iron overload and the underlying hemolytic process in beta-thalassemia, which this patient has, contribute to cholelithiasis development through several mechanisms.⁵ First, ineffective erythropoiesis and increased hemolysis in these patients lead to elevated bilirubin production, a potential precursor for gallstone formation.^{6, 7} Secondly, iron overload, a complication of chronic transfusion therapy in thalassemia, may contribute to gallbladder dysfunction and stone formation.⁸ Thirdly, studies have shown that bile in patients with thalassemia major exhibits altered properties compared to healthy individuals. It demonstrates increased motility but reduced contractility, leading to slower gallbladder emptying, higher residual bile volumes, and potentially promoting cholesterol precipitation and stone formation.⁹

Clinical Presentation and Differential Diagnosis

Approximately 60% of children with cholelithiasis experience symptoms, primarily due to blockage in the biliary system.^{10, 11} This blockage can cause right upper quadrant abdominal pain (biliary colic) and inflammation of the gallbladder (cholecystitis).¹¹ Common presenting features include pain in the right upper quadrant upon inspiration (Murphy's sign), nausea, vomiting, and sometimes fever, with these symptoms becoming more prevalent in teenagers compared to younger children.^{1, 6, 11, 12} Notably, the patient in this case presented with right upper quadrant pain radiating to the shoulder, nausea, vomiting, and weight loss, but without fever.

It's crucial to differentiate cholelithiasis from other conditions presenting with similar symptoms. Peptic ulcer disease typically causes epigastric pain on an empty stomach or after meals, and is diagnosed through endoscopy revealing ulcers in the stomach or

duodenum. Acute cholecystitis presents with right upper quadrant pain and tenderness, often with fever and elevated inflammatory markers in blood tests. Additionally, ultrasound reveals a thickened gallbladder wall. Cholangitis presents with Charcot's triad (fever, jaundice, and right upper quadrant pain), and is confirmed with MRCP and abdominal ultrasound to detect bile duct stones.¹

In this case, the absence of fever and leukocytosis in laboratory tests, coupled with the ultrasound findings of multiple gallstones, pointed towards cholelithiasis. A comprehensive history, physical examination, and imaging studies like ultrasound are essential for an accurate diagnosis.¹

Diagnostic Workup

While no single laboratory test definitively diagnoses cholelithiasis, several blood tests are crucial for determining the underlying cause and preventing complications. These tests may include: Complete blood count, liver function tests to evaluate for potential liver damage, lipid profile, reticulocyte count, hemoglobin electrophoresis, genetic tests (if a genetic predisposition to gallstones is suspected), serum amylase, and lipase levels to rule out co-existing pancreatitis.¹

Ultrasound is the imaging modality for diagnosing cholelithiasis, offering high accuracy with a sensitivity of 84% and specificity of 99%. It can detect gallstones as hyperechoic structures within the gallbladder lumen, often accompanied by distal acoustic shadowing. Biliary sludge, a precursor to gallstone formation, can also appear hyperechoic on ultrasound but lacks the acoustic shadow.¹ In cases where ultrasound findings are inconclusive, MRCP offers a detailed visualization of the biliary and pancreatic tree. ERCP serves a dual purpose, providing both diagnostic and therapeutic capabilities in situations of bile duct obstruction.^{1, 13} If ERCP is unavailable, intraoperative cholangiography can be performed during surgery, followed by cholecystectomy, the definitive treatment for cholelithiasis.¹³

Management Strategies

Management of cholelithiasis can be broadly categorized into approaches for symptomatic and asymptomatic stones.⁶ Patients experiencing recurrent abdominal pain are typically recommended for prompt surgical intervention (cholecystectomy) to prevent complications.¹³ In this case, the patient initially responded to pain medication, but due to increasing pain frequency, cholecystectomy became necessary. Currently, laparoscopic cholecystectomy remains the gold standard for treating symptomatic cholelithiasis, offering advantages like shorter hospital stays, reduced postoperative pain, and faster recovery compared to traditional open surgery.¹⁴

Ursodeoxycholic acid (UDCA) therapy is an option for patients with asymptomatic cholesterol gallstones in adults.¹ By inhibiting cholesterol absorption in the intestine, UDCA can decrease cholesterol saturation by 40-60%.^{14, 15} However, the role of UDCA in treating pediatric cholelithiasis is less established due to limitations like the need for long-term use, high recurrence rates, and potential side effects such as diarrhea and liver dysfunction.¹ In this case, the patient's history of frequent fatty food consumption prompted a trial of UDCA therapy, suggesting a possibility of cholesterol gallstones.

Complications

While asymptomatic in some cases, gallstones can lead to complications in up to 50% of patients within five years of diagnosis.¹ These complications include cholecystitis, choledocholithiasis, and acute pancreatitis. The reported incidence rates for these complications are approximately 27.7%, 10.6%, and 23.4%, respectively.¹⁴

It's important to note that pancreatitis can also occur as a post-ERCP complication (PEP). This can happen due to mechanical obstruction, such as edema or trauma to the papilla from excessive instrument manipulation during the procedure, or hydrostatic injury caused by contrast agents or irrigation fluids leading to local inflammation. PEP typically presents with abdominal pain and a significant elevation in pancreatic enzymes (amylase or lipase levels exceeding three times the upper limit of normal), which is what found in this patient.¹⁶

Some patients (10 – 40%) experience post-cholecystectomy syndrome (PCS), causing ongoing upper right abdominal pain due to alterations in bile flow patterns. The exact cause of PCS remains unclear, although it is thought to be linked to either organic or functional disorders of the digestive system.¹⁷

The prognosis for this patient is generally favorable (prognosis *ad vitam*) as it is uncomplicated cholelithiasis and does not pose a life threat.⁶ However, the prognosis regarding overall function (prognosis *ad functionam*) can be guarded (*dubia ad bonam*) due to the potential development of post cholecystectomy syndrome (PCS).¹⁷ Fortunately, the prognosis for complete recovery (prognosis *ad sanationam*) is excellent, with a very low recurrence rate of less than 1% following cholecystectomy.⁶

Conclusion

This case report describes a 12-year-old girl with beta-thalassemia major who presented with recurrent right upper quadrant abdominal pain. Ultrasound confirmed cholelithiasis, and MRCP revealed choledocholithiasis with common bile duct dilatation. ERCP facilitated gallstone removal, and the patient subsequently underwent a successful laparoscopic cholecystectomy.

This case highlights the increased risk of cholelithiasis in children with beta-thalassemia major. Early identification and intervention are crucial to prevent complications. The prognosis for patients with uncomplicated cholelithiasis treated with cholecystectomy is excellent, with a very low recurrence rate.

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Conflict of Interest

None declared.

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