THALASSEMA β MAJOR WITH EXTRAHEPATIC CHOLESTASIS AND CHOLELITHIASIS IN GIRL 11 YEARS 9 MONTHS

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Abstract

Cholestasis can be caused by functional impairment of hepatocytes in bile secretion and/or by obstruction at any level of the bile excretory pathway. In patients with thalassemia, chronic hemolysis occurs, which results in unconjugated bilirubin crystallizing and eventually forming stones. Furthermore, there can be a build up of bilirubin in the bile duct so that it clogs and interferes with the release of direct bilirubin, resulting in cholestasis. The novelty of this study is to examine the incidence of cases of Thalassemia Major with Cholestasis Extrhepatis and Cholelithiasis in 11 Years 9 Months Girls. The purpose of this study is to describe the incidence of cholestasis and cholelithiasis that occur due to the hemolysis process in thalassemia β major with the main complaints of abdominal pain and jaundice throughout the body. The patient was diagnosed based on laboratory findings, namely elevated transaminase enzymes, direct bilirubin, and multislice computerized tomography of the abdomen with contrast examination. The management of this patient was endoscopic retrograde cholangiopancreatography and ursodeoxylic acid, accompanied by thalassemia therapy. Conclusion of this research has a good prognosis because of the good response. Although cholestasis is rare in thalassemia in children, pediatricians should be aware of this and seek immediate treatment.

Keywords: Thalassemia; Cholestasis; Cholelithiasis.

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1. INTRODUCTION

Hemolytic anemia is the premature destruction of red blood cells, which can become chronic or life-threatening. Hemolytic anemia is defined as the destruction of red blood cells before their normal life span of 120 days. Thalassemia is a group of inherited autosomal recessive hematological disorders that cause hemolytic anemia due to decreased or absent globin chain synthesis (1)(2).

Thalassemia belongs to the group of eight major catastrophic diseases. Data from the Indonesian Thalassemia Foundation and the Association of Parents of People with Thalassemia Indonesia (YTI/POPTI) has shown that in Indonesia, the number of cases of this disease has continued to increase from 2011 to 2015. In 2015, the number of cases was known to have reached 7,029 cases (3).

Cholestasis can be caused by functional impairment of hepatocytes in bile secretion and/or by obstruction at any level of the bile excretory pathway. Cholestatic jaundice can be classified into intrahepatic or extrahepatic cholestasis, depending on the degree of obstruction to bile flow. Clinically, cholestasis causes retention of bile constituents in the blood (4).

Gallstones occur when substances in bile reach their solubility limit. As bile becomes concentrated in the gallbladder, it then becomes saturated with these substances, which in time precipitate into small crystals. In patients with high heme turnover, such as chronic hemolysis, unconjugated bilirubin will crystallize and eventually form stones (5). The degree of hemolysis also influences the development of cholelithiasis in thalassemia major. Elevated serum bilirubin levels as a result of chronic hemolysis may also be involved in gallstone formation as described above (5). The laparoscopic approach is the standard of care for cholelithiasis and cholecystitis. Common bile duct stones can be removed by preoperative or postoperative ERCP, or surgery by exploration of the common bile duct (6)(7).

In this report, we described a thalassemia β major with extrahepatic cholestasis and cholelithiasis in a girl aged 11 and years 9 months in terms of the clinical presentation, imaging findings, diagnosis, and treatment.

2. CASE PRESENTATION

An eleven-year-old and a nine-month-old girl suffered from abdominal pain, paleness, icterus, and vomiting for one day. On physical examination of patients with a history of being diagnosed with thalassemia β major and regularly undergoing treatment since the age of one year, it was found that there was pallor, jaundice, and facial coolness. There was an enlarged liver with an average size of the right lobe palpable liver of 8 cm below the xiphoid process and the left lobe of 5 cm below the costal arch with a flat surface, no tenderness, sharp edges, supple consistency, and Schuffner's spleen IV. The patient's skin color is gray. On anthropometric examination, H/A 47% with impression short stature. On laboratory examination, anemia was found with a hemoglobin level of 7 g/dl with a hypochromic microcytic erythrocyte
index, leukocytosis with a leukocyte level of 15,800/mm³ and a direct bilirubin level of 13.34 mg/dl, indirect bilirubin 4.63 mg/dl, total bilirubin 17.97 mg/dl, SGOT 137 U/L, SGPT 142 U/L, HbA2 4.6%, HbF>40%, ferritine 1025 ng/ml and transferrin saturation of 34.8%. On ultrasound examination (USG), the abdomen showed cholecystitis with multiple choledoliths and sludge in it and choledocoliths. The multi-slice computed tomography (MSCT) whole abdomen with contrast was found on the gallbladder, i.e., thickened walls with regular mucosa. Multiple stone densities (122 HU) were seen inside, with the largest size being +/- 1.4 cm x 0.8 cm. The liver looks enlarged, the surface is regular with sharp tips, the parenchymal density is within normal limits, and the intra and extrahepatic ducts are dilated. The impression of intrahepatic and extrahepatic cholestasis that causes choledoliths is accompanied by cholecystitis and hepatosplenomegaly (figure 1). On examination of magnetic resonance imaging (MRI), cholangiopancreatography found an enlarged liver with parenchymal intensity within normal limits. Dilated intra and extrahepatic biliary ducts were seen with a cut off at the distal common bile duct. No vascular dilatation was seen. The gallbladder was found to be within normal limits with thickened walls, the intensity of the surrounding fluid and multiple signal voids being seen in it (figure 2). The conclusion of this examination is hepatosplenomegaly, intra and extrahepaticcholestatic with cut off images on the common bile duct and causes suspected distal common bile duct stones and cholecystitis with choledoliths in it.

Figure 1. The multi-slice computed tomography (MSCT) whole abdomen with contrast was found on the gallbladder, i.e., thickened walls with regular mucosa. Multiple stone densities were seen inside, with the largest size being +/- 1.4 cm x 0.8 cm.

Figure 2. Cholangiopancreatography Using magnetic resonance imaging (MRI): Red arrows indicate dilated intra and extra hepatic biliary ducts.
The definitive diagnosis was thalassemia major, accompanied by extrahepatic cholestasis, cholecystitis, elevated transaminase enzymes, hemochromatosis, and short stature. We were treated using endoscopy retrograde cholangiopancreatography (ERCP) for cholestasis with the result of jaundice obstruction due to common bile duct stones/sludge and distal narrowing of the common bile duct. Stricturectomy was performed and continued with the extraction of sludge out of CBD (figure 3), packed red cell (PRC) transfusion, deferasirox, folic acid, vitamin E for thalassemia major, and antibiotics for cholecystitis. After receiving therapy, the patient's condition improved with a decrease in direct bilirubin levels to 2.31 mg/dl, SGOT 19 U/L, SGPT 20 U/L, leukocytes 6600/mm³ and an increase in hemoglobin of 11.3 gr/dl. After 33 days of treatment, the patient was allowed to be an outpatient.

Discussion

A case of thalassemia β major with extrahepatic cholestasis and cholelithiasis in a girl aged 11 years and 9 months is reported. The patient complained of abdominal pain, the whole body being yellow and pale, and had history of being diagnosed with β thalassemia major. In our hospital, laboratory examination found anemia with microcytic hypochromic erythrocyte index, elevated HbF, increased ferritin, elevated direct bilirubin, and transaminase enzymes, and on magnetic resonance imaging revealed cholestasis, cholelithiasis, and cholecystitis.

Thalassemia is a genetic disorder that involves the formation of abnormal hemoglobin. A patient with thalassemianot only has lower levels of hemoglobin in his bloodstream but also does not have good quality hemoglobin. Thalassemia affects men and women equally and occurs in about 4.4 out of every 10,000 live births.(5). Thalassemia occurs due to changes in the globin gene on human chromosomes. A second consequence of impaired globin biosynthesis is the imbalanced synthesis of the respective chain subunits with the result of decreased or cessation of β-globin chain production, giving rise to the β thalassemia syndrome. (1). The hemoglobin tetramer is highly soluble and has reversible oxygen-carrying properties for oxygen transport and delivery under physiological conditions. In β thalassemia, there is accumulation and deposition of -globin chains due to continuous overproduction, and unpaired chain aggregates

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precipitate and form inclusion bodies, which causes oxidative membrane damage in red blood cells, resulting in apoptosis and destruction of underdeveloped erythroblasts in the bone marrow.(8).

Cholestasis is defined as stagnation, or at least a marked reduction, in bile secretion and flow. Cholestasis can be caused by functional impairment of hepatocytes in bile secretion and/or by obstruction at any level of the biliary excretory pathway, from the level of liver parenchyma cells on the basolateral (sinusoidal) membrane of the hepatocytes to the ampulla of Vater in the duodenum.(4). Cholelithiasis or gallstones are hardened deposits of digestive juices that can form in the gallbladder. These gallstones can develop further into complications such as cholecystitis, cholangitis, choledochohilitisiasis, gallstone pancreatitis, and rarely cholangiocarcinoma.(7). Cholestasis can occur in all age groups.(4). Most cases of cholelithiasis in children are associated with underlying factors, such as hemolytic disease, a history of treatment with total prenatal nutrition, Wilson's disease, and cystic fibrosis and the use of multiple medications. Hemolytic causes mostly appear in children aged one to five years.(8).

Gallstones occur when substances in bile reach their solubility limit. As bile becomes concentrated in the gallbladder, it then becomes saturated with these substances, which in time precipitate into small crystals. These crystals, in turn, become trapped in the gallbladder mucus, producing gallbladder sludge. Over time, these crystals grow and form large stones. There are two types of gallstones, cholesterol and calcium bilirubinate. Cholesterol gallstones make up the majority of gallstones. The main component of these stones is cholesterol. Bilirubinate stones contain bilirubin. In patients with high heme turnover, such as chronic hemolysis, unconjugated bilirubin will crystallize and eventually form stones.(5).

The degree of hemolysis also influences the development of cholelithiasis in thalassemia major. Gallstone formation may also be exacerbated by elevated serum bilirubin levels as a result of chronic hemolysis. Based on the findings of this study, thalassemia major patients with cholelithiasis received an average blood volume (546±108.7 ml) more than patients without cholelithiasis (425.1±134.7 ml, P=0.007). In addition, the gallbladder of thalassemia major patients exhibited lower motility and contractility, longer emptying times, and higher residual and fasting volumes compared to healthy individuals. The abnormal mechanical properties of the gallbladder in thalassemia major patients may further contribute to the development of gallstones.(6). The etiopathogenesis of these patients is interrelated, starting with thalassemia major, which causes hyperbilirubinemia, which in turn causes the accumulation of bilirubin in the bile ducts so that it clogs and interferes with the release of direct bilirubin, resulting in cholestasis.
The clinical picture of thalassemia major is characterized by growth retardation, pallor, jaundice, weak muscle coordination, genu valgum, hepatosplenomegaly, leg ulcers, extramedullary hematopoiesis, and expanded erythropoiesis resulting in bone changes. Bone changes include long bone deformities and typical craniofacial changes such as Cooley facies, nasal bridge depression, mongoloid and maxillary hypertrophy(9).

The clinical manifestations of cholestasis can be acute, sudden, and rapid onset of jaundice, indicating acute pathology. The presence of pain, particularly epigastric pain or right upper quadrant pain prior to the onset of jaundice, may suggest choledocholithiasis or cholecystitis. Other clinical features observed in patients with chronic cholestasis include itching, fatigue, fat-soluble vitamin deficiency (A, D, E, and K), and xanthomas. The extent of jaundice can be used to assess the degree of hyperbilirubinemia. A jaundice examination should be performed on the conjunctiva, oral mucosa, and skin of the whole body(4). Patients with gallstone disease usually present with symptoms of biliary colic (intermittent episodes of constant, sharp, right upper quadrant abdominal pain often associated with nausea and vomiting), normal physical examination findings, and normal laboratory test results. Acute cholecystitis occurs when persistent stones escape from the cystic duct, causing the gallbladder to become distended and inflamed. Patients may also present with fever, pain in the right upper quadrant, and tenderness over the gallbladder (this is known as “Murphy's sign”)(7).

This patient with thalassemia major had symptoms of tissue anoxia and pallor due to anemia, jaundice, hepatosplenomegaly, cooley facies, and growth disorders, namely short stature and grayish skin. For clinical manifestations of cholestasis, the patient has jaundice, and for cholelithiasis, the patient complains of abdominal pain and fever, which indicat cholecystitis(10).

The diagnosis of thalassemia major is based on clinical manifestations and investigations. On routine blood examination, microcytic anemia, additional tests include serum ferritin, peripheral smear, and hemoglobin electrophoresis. Serum iron, total iron binding capacity, and transferrin are also required. Hemoglobin electrophoresis with thalassemia usually has reduced or absent HbA, increased HbA2 levels, and increased HbF(11).

Total direct bilirubin and serum fractionation should be checked to diagnose cholestasis. In cholestasis, direct hyperbilirubinemia accounts more than 50% of the total bilirubin. Serum alkaline phosphatase was also evaluated at 3 times the upper normal limit in cholestasis, whereas normal or mild elevations in transaminases (ALT/AST) were pure forms of cholestatic jaundice. Serum albumin is usually normal except in cirrhosis and chronic liver disease where, albumin is decreased. Abdominal ultrasound can help identify if there is dilation of the biliary ducts and help differentiate the cause of
hepatocellular cholestasis (where the ducts will be normal in size) versus biliary obstruction (where the ducts will be dilated). If a dilated biliary duct is encountered on the initial ultrasound, then magnetic resonance cholangiopancreatography can be used to assess the bile duct to identify stones, strictures vs malignancy. CT scan can also be helpful, but MRI has better sensitivity (12). In addition, tests such as endoscopy or magnetic retrograde cholangiopancreatography (ERCP/MRCP) are sometimes useful when treating patients with jaundice and dilated bile ducts or suspected cholangitis, but are usually obtained after ultrasound (13).

The basis of the diagnosis of this patient with thalassemia major is based on clinical features supported by laboratory examinations in the presence of anemia with hypochromic microcytic erythrocyte index, increased ferritin levels, increased indirect bilirubin and hemoglobin electrophoresis with increased HbF and decreased HbA. For cholestasis based on clinical manifestations and an increase in direct bilirubin of more than 50% of total bilirubin and an increase in the transaminase enzyme. The diagnosis of cholestasis is based on clinical manifestations and supporting examinations, namely abdominal ultrasound, abdominal MRI and ERCP.

Treatment of thalassemia major requires periodic and lifelong blood transfusions to maintain hemoglobin levels higher than 9.5 g/dl and maintain normal growth. Transfusion-dependent patients are iron-overloaded and therefore require treatment with iron chelators starting between the ages of five and eight. Iron chelation therapy is generally started after the patient has received 10 to 20 transfusions or has a serum ferritin level of >1000 ng/mL and one of the most effective iron therapies is deferasirox (Press, 2016). As a result of increased erythropoiesis, daily oral supplementation with 1 mg of folic acid is recommended in thalassemia major and intermedia (11).

Management of cholestatic jaundice largely depends on the underlying etiology and the type of cholestasis. Usually, the treatment for obstructive cholestasis is biliary decompression. The management of hepatocellular cholestasis includes symptomatic treatment of the associated symptoms, while specific treatment for the underlying disease process should be initiated. In bile duct stones, endoscopic sphincterotomy with or without a stent can relieve the obstruction. Similarly, in benign bile duct strictures, dilation of the stricture and placement of a stent can relieve the obstruction (4). Medical treatment with ursodeoxycholic acid is an option. Common bile duct stones can be removed by preoperative or postoperative ERCP, or surgery by exploration of the common bile duct (5)(7).

This patient was given treatment for thalassemia major, namely oxygenation for anemia and tissue anoxia, continuous transfusion, adequate nutrition for nutritional needs, and given chelation, namely exjade and patients with vitamin E and folic acid for
antioxidants. Ursodeoxylic acid was given for cholestasis, for cholelithiasis and cholecystitis, antibiotics were given and cholecystectomy was treated.

The prognosis before 2000 was very poor for patients with thalassemia major. In the United Kingdom, approximately 50% of patients with thalassemia major die before the age of 35 years. Since 2000, the prognosis has changed dramatically; more than 80% of patients live over 40 years in the UK. This is due to the emergence of non-invasive methods to measure iron before clinical symptoms appear, new chelators, and increased safety measures at the time of blood transfusion\textsuperscript{12}. The outcome and prognosis of post cholecystectomy syndrome vary depending on the patient and the conditions at hand\textsuperscript{(14)}, including the procedures that may be performed. One study showed that 75\% of patients showed good pain relief at long-term follow-up. Follow-up care should be emphasized by the physician to ensure proper postoperative management. Post-cholecystectomy syndrome is the term used to describe the persistence of biliary colic or right upper quadrant abdominal pain with various gastrointestinal symptoms similar to those of patients with cholecystitis prior to cholecystectomy. As the name suggests, this syndrome may represent a continuation of symptoms caused by disturbed gallbladder pathology or the development of new symptoms. Symptoms include intolerance to fatty foods, nausea, vomiting, heartburn, flatulence, indigestion, diarrhea, jaundice, and intermittent episodes of abdominal pain. Post-cholecystectomy syndrome can appear early, usually in the postoperative period, but can also manifest months to years after surgery\textsuperscript{13}. The prognosis in this patient is dubia because the patient has hemochromatosis, which is iron overload in tissues with ferritin levels >1200 ng/dl which can be fatal, and there are possible complications from post cholecystectomy, so the patient must routinely undergo outpatient treatment.

3. CONCLUSION

A case of a girl aged 11 years and 9 months with thalassemia \(\beta\) major with extrahepatic cholestasis and cholelithiasis. She has received ERCP, ursodeoxycholic acid, a PRC transfusion, and iron chelation. The patient’s prognosis is dubia due to possible complications from post-cholecystectomy

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