Gallstones and Choledocolithiasis with Severe Cholestatic Jaundice in β-Thalasemia Intermedia Patient

Suharjo B Cahyono, Putut Bayupurnama**, Neneng Ratnasari**, Siti Nurdjanah***

* Department of Internal Medicine, Charitas Hospital, Palembang

** Division of Gastroentero-hepatology, Department of Internal Medicine, Faculty of Medicine, University of Gadjah Mada/Dr. Sardjito General Hospital, Jogjakarta

ABSTRACT

Geographically, β-thalassemia can be found in many countries including in Indonesia. Thalassemia intermedia referred to patients as being too haematologically severe to be called minor, but too mild to be called major. Patients with thalassemia intermedia usually present themselves to medical attention in later childhood or even adulthood and are sustainable without the need for regular transfusion therapy. Three main factors are responsible for the clinical sequele of thalassemia intermedia: chronic anemia, ineffective erythropoiesis, and iron overload.

There are many complications related to β-thalassemia intermedia such as gastroentero-hepatology diseases (splenomegaly, gallstones, choledocolithiasis, predispose patients to liver fibrosis and cirrhosis), vascular, endocrine and bone diseases. About 55-63% thalassemia intermedia patients suffer from gallstone with 68–85% of these patients undergo cholecystectomy, and 67-90% patients undergo splenectomy. Therefore, ultrasound examination is required to be performed regularly during illness and before patient underwent surgery or splenectomy to detect the presence of gall stones. In this case report a patient with gallstones and choledocholithiasis was reported. Severe cholestatic jaundice in β-thalassemia intermedia was diagnosed six months before hospitalization. The patient underwent open cholecystectomy and exploration common bile duct stones.

Keywords: *β-thalassemia intermedia, gallstones, choledocolithiasis, iron overload*

ABSTRAK

Secara geografis, talasemia-β dapat ditemukan di berbagai negara termasuk di Indonesia. Istilah talasemia intermedia merujuk pada pasien yang secara hematologi terlalu berat bila dikatakan talasemia minor, namun terlalu ringan untuk dianggap sebagai talasemia mayor. Pasien dengan talasemia intermedia biasanya mengalami problem klinis pada akhir masa kanak kanak atau bahkan pada usia dewasa dan mereka masih belum membutuhkan terapi transfusi secara teratur. Ada tiga faktor utama yang mendasari komplikasi pada talasemia, yaitu anemia kronik, eritropoiesis yang tidak efektif dan kelebihan mineral besi.

Beberapa komplikasi yang berhubungan dengan talasemia-β diantaranya adalah penyakit gastroentero-hepatologi (splenomegali, batu empedu, koledokolitiasis, risiko pasien mengalami fibrosis dan sirosis hati), penyakit vaskuler, endokrin dan tulang. Sekitar 55–63% talasemia intermedia menderita batu empedu dan 68 - 85% pasien tersebut menjalani tindakan kolesistektomi, dan 67–90% pasien menjalani splenektomi. Dengan demikian, pemeriksaan ultrasonografi perlu dilakukan secara berkala selama periode sakit dan saat sebelum pasien menjalani tindakan operasi atau splenektomi untuk mendeteksi adanya batu empedu. Pada kasus ini, dilaporkan pasien yang menderita batu empedu dan koledokolitiasis. Diagnosis talasemia intermedia dengan ikterik kolestasis berat dilaporkan enam bulan sebelum masuk rumah sakit. Pada pasien dilakukan tindakan kolesistektomi terbuka dan pemeriksaan batu empedu.

Kata kunci: *talasemia-β intermedia, batu empedu, koledokolitiasis, kelebihan mineral besi*

INTRODUCTION

Approximately 7% of the world's population is affected by hemoglobin disorders, and between 300,000–500,000 infants are born each year with severe homozygous disease. Geographically, β-thalassemia can be found in the Mediterranean, Middle East, Africa, India, Myanmar, South East Asia including Southern China, Malaysia and Indonesia.[1,2] Normal human adult hemoglobin A (HbA) (which represents approximately 98% of circulating hemoglobin) consists of two pairs of globin chain, $\propto_2\beta_2$, of which synthesis is normally tightly coordinated to ensure equal production. The tetramer of $\propto_2\delta_2$ forms hemoglobin A_2, which normally comprises 1-2% of adult hemoglobin and the tetramer of $_2\gamma_2$ forms hemoglobin F (HbF), which is the major hemoglobin of fetal life but comprises < 1% of adult hemoglobin.[3]

β-thalassemia, one of the most common inherited hemoglobinopathy in the world, is due to autosomal mutations in the gene encoding β-globin which induce an absence or low-level synthesis of this protein in erythropoietics cells. The reduced β globin chain synthesis results in relative increase in the percentages of HbA_2 and HbF compared to HbA. In the presence of reduced β chain, the excess ∝ chain is unstable and precipitates, leading to damage of red blood cell membranes. Thalassemic patients suffer from anemia resulting from shortened erythrocyte survival due to hemolysis, and erythroid precursors premature death in bone marrow.[4,5]

This case report described clinical performance, complications and how to manage β-thalasemia intermedia patient with complication of gallstones and choledocolithiasis.

CASE REPORT

A 31 year old female was admitted to hospital with chief complaint of yellow eyes and skin, nausea, itching, tea-colored urine, no pale stools and mild epigastric pain for about four days before she was hospitalized. She said that she did not suffer from dyspnea, fever or spontaneous bleeding. Before episode of her disease she did not consume drugs, herbal remedies or alcohol and she said that she was healthy with no past history of diabetes mellitus, chronic hepatitis, hypertension, and gallstone disease.

Six months before hospitalization she was diagnosed with β-thalassemia intermedia and four bags of packed red cells were transfused. On physical examination there was no abnormal finding except for profound severe jaundice (yellow eyes and darken skin), liver enlargement (about 3 cm below the costae margin) and a palpable spleen (schuffner II). On the first day of admission, laboratory examination showed that hemoglobin 10.5 g/dL, leukocyte count 7,500 mm^3, platelet count 150,000/mm^3, increased level transaminase such as aspartate aminotransferase (AST) 95 U/L and alanine transaminase (ALT) 130 U/L, alkaline phosphatase (AP) 236 (35-105) U/L, increased gamma-glutamyl transpeptidase or γ-GT 187 U/L, increased total and direct bilirubin (58.6 mg/dL and 49.9 mg/dL). However, the results of protein, albumin, activated partial thromboplastin time (APTT) and prothrombin time (PT), fasting blood sugar and electrolyte were within normal limits. Fasting blood sugar and electrolyte were still normal.

Blood films suggested anemia, which may be caused by thalassemia or iron deficiency. But further laboratory examination confirmed the diagnosis of β-thalassemia due to the presence of high level of HbA_2 >13% and foetal hemoglobin (HbF) 33.5. Accompanied with normal total iron binding capacity (TIBC), ferum and iron binding capacity (IBC) with high level of ferritin. Viral hepatitis sero-markers were negative for anti HCV, HBsAg and Anti HAV.

According to those clinical data and ultrasonography (USG) results, the diagnosis of this patient was gallstones and suspected common bile duct (CBD) stones (Figure 1) with severe cholestatic jaundice in β-thalassemia patient. She was given isotonic infusion, oral ursodeoxycholic acid (Urdafalk 1,500 mg once daily) methylprednisolone 16 mg three times daily. On day 14th of hospitalization, after the challenge test with methylprednisolone, bilirubin level was decreased to 10.67 mg/dL.

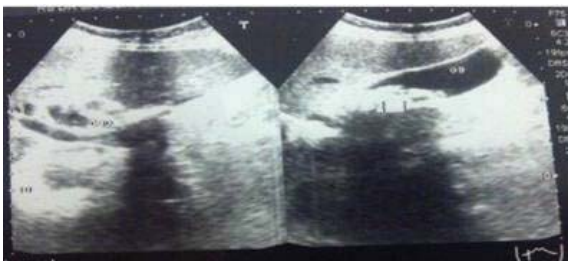

Figure 1. Common bile duct dilated on liver sonography (left) and multiple stones in gallbladder (right)

On day 17th of hospitalization, patient underwent endoscopic retrograde cholangio-pancreatography (ERCP) procedure (Figure 2). Before ERCP procedure patient was transfused with 300 cc of packed red cells. The ERCP showed dilation and multiple stones in common bile duct. ERCP and sphyncteretomy failed to evacuate CBD stone, because there were

multiple stones and the lumen of distal CBD to be smaller after confirmed by open surgery. Patient was then planned to undergo CBD open surgery and splenectomy. On day 20th of hospitalization, patient underwent open cholecystectomy and CBD exploration with anastomosis of the common bile duct to the duodenum (choledochu-duodenostomy) and splenectomy. During exploration, the surgeon found multiple black gallstones and common bile duct stones. Because the lumen of distal common bile ducts was smaller, the surgeon conducted anastomosis of the common bile duct to the duodenum. On the 30th day of hospitalization patient went home in a good condition and total bilirubin level was 2.5 mg/dL.

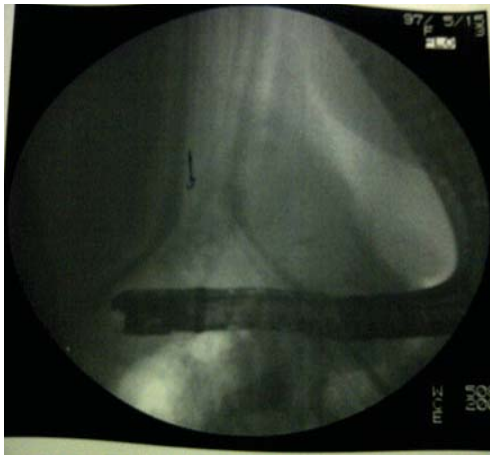

Figure 2. Endoscopic retrograde cholangio-pancreatography showed dilation and multiple stones in common bile duct

DISCUSSION

There are minor (asymptomatic or mild performance), intermedia and major β thalassemia. Thalassemia intermedia was first described by Rietti-Greppi-Micheli, who referred to patients as being "too haematologically severe called to be minor, but too mild to be called major". This criteria differs thalassemia major from intermedia at presentation.[6] Patients with thalassemia intermedia usually present themselves to medical attention in later childhood or even adulthood. They show mild to moderate anemia with hemoglobin level ranging between 7 and 10 mg/dL, which are sustainable without the need for regular transfusion therapy.[7] In this case, patient was diagnosed as thalassemia intermedia according to the clinical performance (age, moderate liver/spleen enlargement, Hb level, transfusion need) and laboratory results (HbA_2 > 13% and HbF = 33.5%).

Three main factors are responsible for the clinical sequele of thalassemia intermedia: chronic anemia, ineffective erythropoiesis (is the main cause of chronic anemia), and iron overload.[8] Clinical consequences of anemia are splenomegaly (resulting from entrapment of abnormal red cells in the spleen) and increased erythropoietin synthesis that stimulates erythroid marrow expansion. Bone marrow expansion also results in characteristic deformities of the skull and face, severe osteopenia, and increased iron absorption. There are several complications in thalassemia intermedia compared to major.[6] Iron overload has important clinical consequences in patients with thalassemia intermedia. In thalassemia major iron overload is primarily caused by transfusions, but in thalassemia intermedia iron overload is caused by combination of ineffective erythropoietin and decrease serum levels of hepcidin, which control the concentration of ferroportin on the intestinal epithelium, so that it is increased intestinal iron absorpsion.[7]

Because iron accumulation primarily occurs in hepatocytes, it can predispose patients to liver fibrosis and cirrhosis, and potentially, hepatocellular carcinoma.[7] Besides that, iron accumulation cause increased vascular diseases (leg ulcers, thromboembolism, pulmonary hypertension, cerebrovasculare and neural damage), endocrine diseases (diabetes mellitus, growth hormone deficiency, hypothyroidism, hypoparathyroidism and hypogonagism) and bone diseases.[9,10]

Hepatocellular carcinoma (HCC) frequently complicates hepatic cirrhosis secondary to viral infection or iron overload. Twenty-two cases of HCC were identified, the mean serum ferritin was 1,764 ± 1,448 ug/L and 80% had been infected by hepatitis C virus, whereas 19 of 22 patients were diagnosed after 1993, suggesting that this problem is becoming more frequent with the aging population of the thalassemia patients.[11] In this patient, clinically we found high level of ferritin, cholestatic jaundice, gallstones and choledocholithiasis as complication of the β thalassemia intermedia.

Cholestasis is an impairment of bile formation and or bile flow which may clinically present with fatigue, pruritus and, in its most overt form, jaundice. Besides bilirubinemia, the cut-off levels of AP and γ-GT to support diagnostic of cholestatic are 1.5 times of the upper limit of normal (ULN) for AP and > 3 times of ULN for γ-GT. Cholestasis may be acute or chronic. It is considered chronic if it last more than 6 months. The cause of cholestasis may be intrahepatic or extrahepatic. USG is usually the first step to differentiate between intrahepatic and extra hepatic, because this tool is rather sensitive and specific, non-invasive, portable and inexpensive.[12,13] This patient was confirmed suffer

from acute cholestasis because the symptoms appeared 4 days before hospitalization with extrahepatic cause (CBD dilated). Ursodeoxycholic acid (UDCA), nonspecific therapies that promote bile flow and short time oral corticosteroid were given to reduce the inflammation. The cause of severe cholestatic jaundice was not only obstructive CBD stones, but might be complicated with intrahepatal inflammation. It was verified with decreasing of bilirubin level (58.6 mg/dL to 10.63 mg/dL) after treated with steroid.

Gallstones are more commonly found in thalassemia intermedia than in thalassemia major because of ineffective erythropoiesis and peripheral haemolysis.[6] Gallstones typical of hemolitic anemia are so called black pigment stones. The colour of the stone is explained by its content of an insoluble black pigment that probably is a cross-linked network polymer bilirubinate. And about 40 to 80% of them are radiopaque.[14] About 55-63% thalassemia intermedia patients suffer from gallstone. Gallstones were more frequently found in patients with β-thalassemia intermedia and with less blood transfusion requirements. Eleven patients with cholelithiasis (44%) became symptomatic. Eight patients received operations on an elective or semi-elective basis. Another patient had incidental cholecystectomy during splenectomy.[15] In patients with β-thalassemia, ultrasound examination should be done to detect gallstones and especially before patient undergo splenectomy procedure.[7] A cholecystectomy may necessarily be performed, particularly if the patient is experiencing symptomatic gallstones. This should be undertaken to prevent cholecystitis, which can have serious consequences in the splenectomised patients.[7,16]

Up to 15% of patients with gallbladder stones exhibit concomitant stones in the CBD. The source of common bile duct stone are either migrate from gallbladder (secondary stone) or form primary within the bile ducts, but CBD stones are predominantly secondary stones.[17] There are several imaging modalities to detect stones in the common bile duct such as transabdominal USG, endoscopy ultrasonography (EUS), ERCP, intraoperative cholangiography, helical computed tomography cholangiography, magnetic resonance cholangio-pancreatography (MRCP).[18] Transabdominal USG is recommended as a preliminary investigation for CBD stone with sensitivity 22–65% and specificity 70–98%. In patients < 71 year old, common bile duct > 8 mm or evidence of stone in CBD has positive and negative predictive value: 77% and 98%, respectively. Intraoperative cholangiography and ERCP are generally considered to be the reference standard for diagnosis of CBD stone. However, EUS and MRCP are also recommended as being highly effective for confirming the presence of CBD stone.[19]

During recent decades endoscopy or laparoscopy has gained wide acceptance as an effective and less invasive alternative. Endoscopic sphincterotomy followed by laparoscopic cholecystectomy is the first choice to manage combined cholecysto-choledocholithiasis.[20] Because over 80% of gallstones are removed laparoscopically, laparoscopic CBD exploration is increasingly being performed. It is a difficult procedure; therefore it is only done by a selected group of laparoscopic surgeons.[17]

Although endoscopic and laparoscopic are the first choices for managing gallstones or CBD stones, open cholecystectomy and exploration of CBD still become a choice for several reasons. First, when there were concomitant problems or past surgeries, making a laparoscopic approach very difficult. Second, some patients undergo an open exploration because of conversion of a laparoscopic procedure, for example, caused by CBD injury. Third, a relative indication for open exploration is large or multiple stones or the need to perfom a transduodenal sphincteroplasty. Finally, open exploration is still considered the gold standard if the surgical team does not have the experience or feels uncomfortable with the laparoscopic approach, or qualified endoscopist is not available.[17] Morbidity and mortality of this procedure were low, with the percentage of retained stones was only 1-3%, and during long term follow up, revisional surgery was necessary in about 10% of the patients. In this case, patient underwent open exploration because there were combined surgical procedure (splenectomy) and there was no qualified endoscopist (ERCP).

The indication for splenectomy in β-thalassemia patients are poor growth and development, increased transfusion demand, hypersplenism and splenomegaly (when accompanied by symptoms such as severe left upper quadrant pain or possible splenic rupture).[21] Almost 67 to 90% thalassemia intermedia patients underwent splenectomy.[6] Many patients who undergo splenectomy appear to restore hemoglobin levels in short term by about 10-20 g/dL. Some of these patients demonstrate a marked improvement in growth and development. However, clinical observations have suggested that splenectomy in thalassemia contribute to an increased susceptibility to thrombosis and sepsis.[22] In this patient, splenectomy actually was not indicated because there was no severe splenomegaly or clinical

symptoms. Splenectomy was conducted while patient underwent open cholecystectomy and common bile duct explorasion, as a preventive action (because chance to undergo splenectomy is 67-90%).

There are number of options currently available for managing patients with thalassemia intermedia including splenectomy, transfusion therapy and iron chelating therapy. We still did not know whether our patient has iron overload associated liver injury or not. The principles methods of determining body iron levels are measurement of serum ferritin levels and assessment of liver iron concentration (LIC) from biopsy tissue. In this patient ferritin levels was increased that was caused by increased intestinal absorption and transfusion therapy. It was difficult to decide whether she need chelation therapy or not, because she did not underwent liver biopsy. Chelation therapy should be initiated when liver iron concentration exceeds 7 mg Fe per g dry weight.[22] Although the general performance of the patient after hospitalization was good, but in the future, complications related to iron overload and immune compromised, such as liver disease, common bile duct stones relapse, vascular, endocrine and bone disease might possibly happen. So, the patient should be monitored and evaluated regularly to prevent complications. Next, liver biopsy should be done to know whether there was iron overload or not.

REFERENCES

1. Wirawan R, Setiawan S, Gatot D. Peripheral blood and hemoglobin electrophoresis pattern in beta thalassemia major patients receiving repeated blood transfusion. Med J Indones 2004;13;8-16.
2. Taher AT. Epidemiology and disease patophysiology: thalassemia [cited 2013 Aug 28]. Available from: URL: http//:www.ironcurriculum.esh.org/Activity/1817/abstract_1817.pdf
3. Damon LE, Andreadis C, Linker CA. Blood disorders. In: Maxine A, Papadakis, Stephen J McPhee, eds. Current Medical Diagnosis & Treatment. New York: McGraw Hill 2013.p.494–96.
4. Ribeil JA, Arlet JB, Dussiot M, Ivan CM, Courtois G, Oliver H. Ineffective erythropoiesis in β- thalassemia. Sci World J [serial online] 2013 [cited 2013 Sept 1]. Available from URL: http://dx.doi.org/10.1155/2013/394295
5. Olivieri NF. The β thalassemias. N Engl J Med 1999;341:99–109.
6. Taher AT, Musallam KM, Cappellini MD. Thalassemia intermedia: an update. Mediterr J Hematol Infect Dis 2009;1:e2009004.
7. Musallam KM, Taher AT, Eliezer AR. Beta-thalassemia intermedia: a clinical perspective. Cold Spring Harb Perspect Med 2012;2:a013482.
8. Taher AT, Musallam KM, Karimi M, El-Beshlawy A, Belhoul K, Daar S, et al. Overview on practice in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: the OPTIMAL CARE study. Blood 2010;115:1886-92.
9. Cappellini MD, Musallam KM, Taher A. Thalassemia intermedia [cited 2013 Sept 2]. Available from: URL: http://www.esh.org/files/doc/IRON2009_CAP.12(286-309).pdf.
10. Musallam KM, Cappellini MD, Wood JC, Motta I, Graziadei G, Tamim H, et al. Elevated liver iron consentration is a marker of increased morbidity and mortality in patients with β-thalassemia intermedia. Haematologica 2011;96:1065–612.
11. Borgna–Pignatti C, Vergine G, Lombardo T, Cappellini MD, Cianciulli P, Maggio A, et al. Hepatocellular carcinoma in the thalassemia syndromes. Brit J Haematol 2004;124:114-7.
12. Beuers U, Boberg K, Chapman RW, Oliver C, Pietro I, David EJ, et al. EASL clinical practice guidelines: management of cholestatic liver disease. J Hepatol 2009;51:237–67.
13. Heathcote EJ. Diagnosis and management of cholestatic liver disease. Clin Gastroenterol Hepatol 2007;5:776-82.
14. Lukens JN. The thalassemias and related disorders: quantitative disorders of hemoglobin synthesis. In: Richard Lee, John F, John L, Frixos P, John PG, George MR, eds. Wintrobe's Clinical Hematology. 10th ed. Philadelphia: Williams and Wilkins 1999.p.1109–30.
15. Goldfarb A, Grisaru D, Gimmon Z, Okon E, Lebensart P, Rachmilewitz EA. High incidence of cholelithiasis in older patients with homozygous beta thalassemia. Acta Haematol 1990;83:120–2.
16. Panigrahi I, Marwaha RK. Common queries in thalassemia care. Indian Pediatr 2008;43:513–8.
17. Verbesey JE, Birkett DH. Common bile duct exploration for choledocholithiasis. Surg Clin North Am 2008;88:1315–28.
18. Almadi MA, Barkun JS, Barkun AN. Management of suspected stones in the common bile duct. Can Med Assoc J 2012;15:884-92.
19. William EJ, Green J, Beckingham I, Park R, Martin D, Lombard M. Guidelines on the management of common bile duct stones (CBDS). Gut 2008;57:1004-21.
20. Boerma D, Schwartz MP. Management of common bile-duct stones and associated gallbladder stones surgical aspects. Best Pract Res Clin Gastroentrol 2006;20:1103-16.
21. Abi Saad GS, Musallam KM, Taher AT. The surgeon and the patient with beta-thalassemia intermedia. British J Surg 2011;98:751-60.
22. Taher AT, Musallam KM, Cappellini MD, David JW. Optimal management of beta thalassemia intermedia. British J Haematol 2011;152:512-23.

Correspondence:
Suharjo B Cahyono
Department of Internal Medicine
Charitas Hospital
Jl. Jend. Sudirman 1054 Palembang Indonesia
Phone: +62-274-553119 Facsimile: +62-274553120
E-mail: jbsb.cahyono@yahoo.com