

## A Deterioration of Anemia in Hemoglobin E Disease caused by Cholestatic Hepatitis A

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### ABSTRACT

*Patients with hemoglobin E disease usually have mild hemolytic anemia and mild splenomegaly. Acute infection including acute inflammatory disease of the liver caused by hepatitis A viral, which attacks patients with previous hemolytic anemia, may result in deterioration of anemia.*

*A 17-year-old female patient was admitted with chief complaint of having jaundiced body and non-specific prodromal symptoms within one week prior to admission. Physical examination revealed jaundiced skin and sclera as well as tenderness in right upper quadrant of the abdomen. Laboratory tests revealed microcytic hypochromic anemia with hemoglobin (Hb) level of 6.3 g/dL, increased reticulocyte count and abnormal morphology of erythrocytes on blood smear. Hemoglobin electrophoresis indicated hemoglobin E disease and serologic tests suggested a positive anti-HAV immunoglobulin M (IgM) with increased level of liver enzymes and functions. Abdominal ultrasound showed hepatosplenomegaly without extra-hepatic cholestasis.*

*The working diagnosis was hepatitis A with intrahepatic cholestasis and hemoglobin E disease. The patient was treated with hepatoprotector and ursodeoxycholic acid. Anemia was not treated specifically. It was assumed that hemolytic anemia was worsened by acute infection of hepatitis A viral. The assumption had been proven to be right since there was improvement of anemia after the acute infection had recovered. Patients with hemoglobin E disease usually have mild anemia; however, in this case, the hemoglobin level decreased significantly due to the acute co-infection.*

**Keywords:** *hemoglobin E disease, anemia, acute infection, acute hepatitis A infection*

### ABSTRAK

*Pasien dengan hemoglobinopati E pada umumnya menderita anemia hemolitik ringan dan splenomegali. Infeksi akut seperti infeksi hepatitis virus A, yang mengenai pasien dengan riwayat anemia hemolitik sebelumnya dapat memperburuk derajat anemia.*

*Seorang perempuan berusia 17 tahun datang dengan keluhan utama badan tampak kuning disertai gejala awal non spesifik sejak satu minggu sebelum masuk rumah sakit. Pemeriksaan fisik menunjukkan sklera dan kulit tampak pucat disertai nyeri tekan pada kuadran kanan atas abdomen. Pemeriksaan laboratorium menunjukkan anemia mikrositik hipokrom dengan kadar hemoglobin (Hb) 6,3 g/dL, retikulositosis dan kelainan morfologi eritrosit pada sediaan apus darah tepi. Hasil elektroforesis Hb memberikan kesan hemoglobinopati E. Tes serologis menunjukkan IgM anti-HAV positif dengan peningkatan fungsi dan enzim hati. Kesan hepatosplenomegali tanpa kolestasis ekstrahepatik didapatkan pada hasil ultrasonografi abdomen.*

*Diagnosis kerja pasien ini adalah hepatitis A disertai kolestasis intrahepatik dan hemoglobinopati E. Pasien diterapi dengan hepatoprotektor dan asam ursodeoksikolat, namun anemia tidak diobati secara spesifik. Perburukan anemia hemolitik yang terjadi diduga terjadi karena adanya infeksi hepatitis virus A yang menyertai.*

*Dugaan ini semakin kuat seiring dengan perbaikan anemia yang terjadi setelah infeksi akut teratasi. Anemia hemolitik pada pasien hemoglobinopati E biasanya ringan, namun pada kasus ini penurunan signifikan kadar Hb terjadi karena adanya infeksi akut yang menyertai.*

**Kata kunci:** hemoglobinopati E, anemia, infeksi akut, hepatitis virus A

## INTRODUCTION

Hemoglobin E disease is a congenital hemolytic anemia disorder, which includes structural abnormality of the hemoglobin caused by a mutation of beta chain of hemoglobin.<sup>1,2</sup> To confirm the diagnosis, a blood test such as hemoglobin electrophoresis can be performed.<sup>3</sup> Usually, hemoglobin E disease is manifested by the symptoms of mild thalassemia, which appears as mild microcytic hypochromic anemia.<sup>2</sup> In several cases, anemia occurs more prominently, particularly when there is simultaneous acute co-infection.<sup>4</sup> Moreover, anemia in acute infections may occur due to several factors including previous medical condition. The severity of anemia depends on patient's medical condition. Patients who have previous underlying disease will have more severe anemia than patients who do not have previous illness.<sup>5</sup> Anemia also occurs as hematologic complication of hepatitis A viral infection. In patients with hemoglobin E disease and hepatitis A viral infection, the hemoglobin level will significantly decrease.<sup>6</sup> Hepatitis A virus commonly causes severe cholestasis syndrome with abnormal clinical, laboratory and histology findings.<sup>7</sup> The laboratory findings include increased alkali phosphatase and gamma glutamyltransferase serum level, increased bilirubin serum level, reduced prothrombin time and minimal increase of aminotransferase serum level. Clinical findings may include pruritus, malaise, xanthoma, steathorea, which usually can be found in patients with fat-soluble vitamin deficiency. Histological findings of bilirubin obstruction (bilirubinostasis), hepatocyte degeneration (cholestasis), small biliary duct destruction, pericholangitis, portal edema and biliary cirrhosis can also be found.<sup>8,9</sup> Cholestasis due to hepatitis A viral infection is almost certainly intrahepatic with pruritus as the main symptom.<sup>7</sup>

Hepatitis A with cholestasis is treated by total bed rest, diet and nutrition for liver disease in accordance with the clinical condition, as well as symptomatic and adjuvant therapy.<sup>6</sup> To relieve the cholestasis, ursodeoxycholic acid is used. Previous studies indicated that administration of ursodeoxycholic

acid regimen may cause significant reduction of liver enzymes and bilirubin serum level and improves the generalized pruritus symptom.<sup>7,10</sup>

Hemoglobin E disease belongs to minor thalassemia.<sup>3</sup> The management of hemoglobin E disease is similar to management of minor thalassemia itself.<sup>6</sup> Anemia that occurs in hemoglobin E disease is treated as in general cases.<sup>10</sup> But if the anemia is prominent, packed red cells (PRC) transfusion is frequently needed.<sup>5</sup> It is important to notice whether the recovery of acute infection is followed by improved hemoglobin level. If the anemia does not improve, further investigation to confirm the etiology of anemia should be carried out.<sup>3,11</sup>

## CASE ILLUSTRATION

A 17-year-old female patient was admitted with chief complaint of having jaundiced body since one day prior to the admission. She had one-week history of fever, headache, myalgia, loss of appetite, nausea and vomiting before the admission. She also reported dark urine since 3 days prior to admission. The patient lived in a dormitory with low hygiene standard, which was overcapacity for students housing and the dining room was located near the bathroom. Her physical examination revealed signs of anemia, as well as jaundice, mild splenomegaly, mild hepatomegaly and abdominal tenderness in the right upper quadrant. She also had poor nutritional state with body mass index of 18.1 kg/m<sup>2</sup>.

Laboratory results on admission showed a condition of hypochromic microcytic anemia with hemoglobin level 6.3 g/dL, hematocrit 26%, low mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin volume (MCHC) level, and high reticulocytes count (4.2%). The immunoserological findings demonstrated anti-HAV IgM level of 2.73 IU/mL with aspartate transaminase (AST) activity level of 791 U/L and alanine aminotransferase (ALT) level of 837 U/L, direct bilirubin level of 8.37 mg/dL, indirect bilirubin level of 4.57 mg/dL, total bilirubin level of 12.94 mg/dL, phosphatase alkali level of 260 U/L, and gamma glutamyltransferase activity level of 72 U/L.

The working diagnosis on admission was hepatitis A and hemolytic anemia. A significant decreased level of hemoglobin and splenomegaly had directed the diagnosis to thalassemia. The next laboratory results showed normal serum iron level, normal ferritin level and the total iron binding capacity (TIBC) was also normal. A blood smear indicated hypochromic microcytic anemia with existence of target cells, spherocytes, and teardrop cells. However, the hemoglobin electrophoresis suggested hemoglobin E disease. The abdominal ultrasound showed mild hepatosplenomegaly without dilatation of biliary tree (Figure 1). The patient was advised to have a total bed rest. She was given metoclopramide tablet 10 mg thrice daily orally to relieve nausea and vomiting. Ursodeoxycholic acid tablet 500 mg twice daily was administered to reduce the cholestatic symptoms. Hepatoprotector was given to improve the elevated liver enzymes. The anemia was only being observed without any specific medication.



**Figure 1.** The abdominal ultrasound showed mild hepatosplenomegaly without dilatation of biliary tree

On the third day of hospitalization, her gastrointestinal symptoms were improved. Laboratory results showed reduced direct bilirubin level of 5.48 mg/dL, indirect bilirubin level of 1.98 mg/dL, total bilirubin level of 7.46 mg/dL. The liver enzyme levels were also significantly reduced including aspartate transaminase (AST) activity level of 150 U/L and alanine aminotransferase (ALT) activity level of 203 U/L. After being hospitalized for a week, the patient was clinically improved and her laboratory results were getting better. The direct bilirubin was 0.79 mg/dL and total bilirubin was 1.48 mg/dL. The liver enzymes

level were AST of 23 U/L and ALT of 14 U/L. She was discharged from the hospital with final diagnosis of hepatitis A with cholestasis and hemoglobin E disease. After one month, there was improved hemoglobin level from a baseline level of 6.3 to 8.1 g/dL.

## DISCUSSION

The diagnosis of cholestatic hepatitis A was established based on clinical findings of acute viral hepatitis, including non-specific prodromal findings and gastrointestinal symptoms (malaise, anorexia, nausea and vomiting), flu-like syndromes (headache and myalgia), acute sudden onset symptoms, fever.

The prodromal symptoms ceased when the jaundice appeared, but other symptoms like anorexia, malaise, and fatigue persisted. The dark urine was followed by jaundiced skin.<sup>6,8,9</sup> Physical examination showed mild hepatosplenomegaly with abdominal tenderness in the right upper quadrant. Severe jaundice persisted before the complete recovery and it may be due to cholestasis.<sup>9</sup> However, the specific symptom for intrahepatic cholestasis such as pruritus was not found. The absence of pruritus may indicate that there was only mild increase of bilirubin level.<sup>8,9</sup> The positive immunoserological finding of anti-HAV IgM test has supported the diagnosis of acute hepatitis A. Increased serum level of direct, indirect, and total bilirubin as well as AST and ALT activity level less than 500U/L, elevated alkaline phosphatase of more than four folds have also supported the diagnosis of cholestatic type of hepatitis.<sup>9</sup> The abdominal ultrasound did not show any dilatation of biliary tree, which may indicate intrahepatic cholestasis.<sup>8,9</sup> However, identifying the etiology of hepatitis may help physicians to rule out the cholestatic type since the pathology of cholestasis due to hepatitis A viral infection must be intrahepatic type.<sup>6,8,9</sup>

The diagnosis of hemoglobin E disease was established based on clinical findings such as mild hepatomegaly, laboratory results that indicated hemolytic anemia (increased of reticulocytes count), blood smear test showed hypochromic microcytic anemia, target cells, spherocytes and the hemoglobin electrophoresis suggested hemoglobin E disease.<sup>2,3</sup> This case is special since usually patients with hemoglobin E disease have mild anemia with hemoglobin level about 10–13 g/dL, but in this case, her hemoglobin level was significantly reduced (6.3 g/dL).<sup>2,3,6</sup>

The cholestatic hepatitis A was treated according to the common standards.<sup>7</sup> The patient was hospitalized because of her severe gastrointestinal symptoms. To

reduce the cholestatic symptoms, the patient was given ursodeoxycholic acid since it has a good efficacy in improving bilirubin level in patients with cholestasis.<sup>7,10</sup> The patient was also given hepatoprotector as adjuvant therapy to improve her bilirubin and liver enzymes level. The combination of ursodeoxycholic acid and the hepatoprotector showed a better efficacy in improving bilirubin and liver enzymes level.<sup>6,7,10</sup>

The hemolytic anemia in this patient may not require any specific treatment. It is assumed that the deterioration of anemia in this patient was due to hepatitis A viral infection as the acute co-infection since the patient has suffered from hemoglobin E disease, the underlying disease.<sup>4,5</sup> The improvement of anemia, i.e. increased hemoglobin level from 6.3 g/dL to 8.1 g/dL after the hepatitis A infection has been recovered in one month observation has supported the hypotheses.<sup>5</sup>

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