Case Report

# The transiently high percentage of hemoglobin F during active hemolysis due to an autoimmune hemolytic anemia in a hemoglobin E trait

Somchai Insiripong and Likhasit Sanglutong

Department of Medicine, MaharatNakhonRatchasima Hospital

***Abstract:***

***Background:*** *Actually the percentage of hemoglobin F in an adult hemoglobin E trait is around 0.9 ± 0.7% whereas Hb E is 29.4 ± 2.3%.* ***Objective:*** *The study aimed to report an adult Hb E trait that had transiently high hemoglobin F during active hemolysis due an autoimmune hemolytic anemia (AIHA).* ***Case Presentation:*** *A 19-year-old Thai woman presented with acute fever, chills, and jaundice for 3 days. The physical examination revealed a body temperature of 38.5 °Celsis, PR 134/min, no goiter, marked pallor, mild jaundice and just palpable hepatosplenomegaly. The blood tests showed: Hb 3.6 g/dL, WBC 12 x10$^{9}$/L, platelet 331 x10$^{9}$/L, NRBC 11/100 WBC, MCV 133.0 fL, reticulocyte 5.0% and ferritin 91.2 ng/mL. Concerning Hb analysis by HPLC method: Hb E 28.7%, Hb F 8.7%, direct antiglobulin tests-positive, indirect bilirubin 1.7 mg/dL, ESR 119 mm/hour, ANA/ANF-positive, and coarse speckled nuclear titer > 1:1,280. Her diagnosis was acute hemolytic crisis due to an AIHA with underlying either Hb E heterozygosity or beta thalassemia / Hb E disease and treatment was corticosteroid. Six weeks later, her signs comprised Hb 13.0 g/dL, MCV 86.2 fL, Hb E 28.5%, Hb F 1.0%. The Hb E heterozygosity could be concluded. The percentage of Hb F in Hb E trait was found transiently high during the active hemolysis due to AIHA and became normal after the recovery of hemolysis.* ***Conclusion:*** *During active hemolysis, the Hb analysis in Hb E trait should be delayed. Otherwise it may lead to the misdiagnosis of beta thalassemia / Hb E disease.*

***Keywords :*** ● *Autoimmune hemolytic anemia* ● *Hemoglobin E trait* ● *Transiently high hemoglobin F*

***J Hematol Transfus Med. 2018;28:473-7.***

*Received 9 July 2018 Corrected 1 November 2018 Accepted 12 November 2018*

*Correspondence should be addressed to Somchai Insiripong, MD., MaharatNakhonRatchasima Hospital, NakhonRatchasima 30000*

*Email: chaikorat@gmail.com*

## รายงานผู้ป่วย

# ฮีโมโกลบิน เอฟ สูงชั่วคราวในระหว่างที่มีเม็ดโลหิตแดงแตกรุนแรงจากภูมิคุ้มกันต้านเม็ดเลือดแดงตนเองในผู้ที่เป็นพาหะฮีโมโกลบิน อี

สมชาย อินทรศิริพงษ์ และ ลิขสิทธิ์ แสงลู่ทอง
กลุ่มงานอายุรกรรม โรงพยาบาลมหาราชนครราชสีมา

***บทคัดย่อ***

***บทนำ*** *โดยทั่วไป ร้อยละของ ฮีโมโกลบิน เอฟ ในผู้ใหญ่ที่มี ฮีโมโกลบิน อี แฝง ประมาณ 0.9 ± 0.7 ขณะที่มี ฮีโมโกลบิน อี ประมาณ ร้อยละ 29.4 ± 2.3* ***วัตถุประสงค์*** *รายงานผู้ป่วยผู้ใหญ่ ที่เป็นพาหะฮีโมโกลบิน อี ที่มี ฮีโมโกลบิน เอฟ สูงชั่วคราว ในระหว่างที่มีภาวะวิกฤตเม็ดเลือดแดงแตกจากภูมิคุ้มกันต้านเม็ดเลือดแดงตนเอง* ***รายงานผู้ป่วย*** *หญิงไทย อายุ 19 ปี มาพบแพทย์ด้วย อาการไข้เฉียบพลัน หนาวสั่น และ ดีซ่านเป็นเวลา 3 วัน ตรวจร่างกายพบ อุณหภูมิ 38.5°ซ. ชีพจร 134 ครั้ง/นาที ไม่พบคอพอก แต่ซีดมาก มีดีซ่านเพียงเล็กน้อยคลำได้ตับและม้ามโตเล็กน้อย ตรวจเลือดพบ Hb 3.6 กรัม/ดล. WBC 12 x10$^{9}$/ลิตร corrected WBC 10.8 x10$^{9}$/ลิตร platelet 331 x10$^{9}$/ลิตร NRBC 11/100 WBC MCV 133.0 เฟมโตลิตร reticulocyte 5.0% ferritin 91.2 นาโนกรัม/มล Hb analysis โดยวิธี HPLC พบ Hb E 28.7% Hb F 8.7% direct antiglobulin tests ให้ผลบวก indirect bilirubin 1.7 มก/ดล. ESR 119 มม/ชม ANA/ANF ให้ผลบวก coarse speckled nuclear titer > 1:1,280 วินิจฉัยว่าเป็นภาวะวิกฤตเม็ดเลือดแดงแตกอย่างรุนแรงจากภูมิคุ้มกันต้านเม็ดเลือดแดงตนเองในผู้ที่อาจจะเป็นพาหะ ฮีโมโกลบิน อี หรือ เป็นโรคเบต้าธาลัส-ซีเมีย / ฮีโมโกลบิน อี ก็ได้และให้การรักษาด้วย corticosteroid 6 สัปดาห์ถัดมา Hb 13.0 กรัม/ดล. MCV 86.2 เฟมโตลิตร Hb E 28.5% Hb F 1.0% จึงสรุปการวินิจฉัยเป็นที่แน่นอนว่าเป็นพาหะ ฮีโมโกลบิน อี ฮีโมโกลบิน เอฟ สูง ในผู้ที่เป็นพาหะ ฮีโมโกลบิน อี เป็นการชั่วคราวเนื่องจากการมี ภาวะเม็ดเลือดแดงแตกจากภูมิคุ้มกันต่อต้านเม็ดเลือดแดงของตน และจะกลับเป็นปกติหลังจากหายจากเม็ดเลือดแดงแตกแล้ว* ***สรุป*** *ในระหว่างที่เม็ดเลือดแดงกำลังแตก การตรวจวิเคราะห์ฮีโมโกลบิน ในผู้ที่เป็นพาหะ ฮีโมโกลบิน อี จึงควรเลื่อนไปก่อน มิฉะนั้น อาจจะทำให้การวินิจฉัยพลาดว่าเป็นโรค เบต้าธาลัสซีเมีย / ฮีโมโกลบิน อี ได้*

***คำสำคัญ :*** ● *Autoimmune hemolytic anemia* ● *Hemoglobin E trait* ● *Transiently high hemoglobin F*
***วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2561;28:473-7.***

## Introduction

Hemoglobin E results from the combination of two normal alpha globin chains and two genetically abnormal beta globin chains of which the glutamic acid at the 26th position of the polypeptide chain is substituted by lysine. Hb E is highly prevalent in Thailand and the prevalence rate varies from 13.1% in the South to 45.5% in the Northeast[1]. Patients with homozygous Hb E usually present mild microcytic anemia, Hb11.4 ± 1.8 g/dL, MCV 70±4 fL, Hb F 1.8 ± 1.4% and Hb E 87.7 ± 5.9% whereas Hb E traits are almost all asymptomatic, Hb 12.8 ± 1.8 g/dL, MCV 84 ± 5 fL, Hb F 0.9 ± 0.7% and Hb E 29.4 ± 2.3%.[2]

When Hb E heterozygosity is co-transmitted with beta thalassemia heterozygosity, the patients usually present severe clinical symptoms e.g., Hb ranging from 3 to 11 g/dL[3], MCV 67 ± 6 fL, Hb E 58 ± 1.5% and Hb F 42 ± 1.5%[2]. In addition to beta thalassemia/Hb E disease, a high percentage of Hb F combined with Hb E on Hb electrophoresis can also be interpreted as the double heterozygosity of hereditary persistence of fetal hemoglobin and Hb E when the clinical presentation and hematological parameters appear quite normal[4]. Herein, we reported a case of transiently high percentage of Hb F combined with Hb E in Hb E trait during severe hemolytic crisis due to an autoimmune hemolytic anemia.

## Case Presentation

A 19-year-old Thai woman was admitted at the medical ward because of acute fever, chills, marked pallor and mild jaundice for three days. She did not have any blood loss. The physical examination revealed a body temperature of 38.5°Celsius., BP 131/70 mmHg, PR 134/min and she presented mild restlessness, marked pallor, mild jaundice and just palpable liver and spleen, with an oxygen saturation of 100%.

The blood tests included: Hb 3.6 g/dL, Hct 9.7%, WBC 12 x$10^9$/L, corrected WBC 10.8 x$10^9$/L, platelet count 331 x$10^9$/L, NRBC 11/100 WBC, MCV 133.0 fL, MCH 49.2 pg, MCHC 37.0 g/dL, RDW 20.4%, reticulocyte 5.0%, N 65%, L 24.0%, and ferritin 91.2 ng/mL. One day after admis-sion, the blood test was repeated, revealing Hb 3.0 g/dL and Hct 8.0%. The hemoglobin analysis using high performance liquid chromatography (HPLC) (Bio-Rad®) showed: Hb E 28.7%, Hb F 8.7%, and the direct and indirect antiglobulin tests were positive.

Other blood tests included: FBS 89 mg/dL, BUN 9.1 mg/dL, creatinine 0.98 mg/dL, cholesterol 122 mg/dL, direct bilirubin 0.6 mg/dL, indirect bilirubin1.7 mg/dL, AST 41 U/L, ALT 9 U/L, alkaline phosphatase 81 U/L, albumin 3.7 g/dL and globulin 3.9 g/dL.

Test for O. tsutsugamushi, HBsAg, anti-HCV, while leptospira antibodies IgG and IgM were all negative, while ESR 119 mm/hour, ANA/ANF-positive, coarse speckled nuclear titer > 1:1,280, and negative anti-dsDNA.

Additionally, the chest film study was unremarkable.

She was initially diagnosed as having acute hemolytic crisis due to autoimmune hemolytic anemia (AIHA) with underlying either Hb E heterozygosity or beta thalas-semia/Hb E disease. She was treated with intravenous dexamethasone and later oral prednisolone. Other treat-ments included oxygen therapy, acetaminophen and folic acid, and she responded, well to therapy.

Six weeks later, the blood tests were repeated: Hb 13.0 g/dL, Hct 39.5%, WBC 20.2 x$10^9$/L, platelet 393 x$10^9$/L, MCV 86.2 fL, MCH 28.4 pg, MCHC 33.0 g/dL, RDW 14.1%, N 83.8%, L 13.6%, ferritin 167.6 ng/mL, and negative direct antiglobulin test. The Hb analysis using the same method showed: Hb E 28.5% and Hb F 1.0%. Although the genotypes for beta thalassemia were not studied, a definite diagnosis of Hb E heterozygosity and complete remission from AIHA were finally concluded.

## Discussion

Our case tested positive using the direct antiglobulin test during acute severe hemolytic crisis. Therefore, the diagnosis of AIHA could be concluded and imme-diately treated with parenteral. She responded well to therapy. In general, 70-85% of the patients AIHA will respond well to corticosteroid that is considered, the first line of therapy.[6]

During an active hemolytic crisis due to AIHA, the percentage of Hb F was markedly increased (8.7%) while the Hb level strikingly dropped (3.6 g/dL), as compared with Hb F 0.9 ± 0.7% and Hb concentration of 12.8 ± 1.8 g/dL of Hb E traits at a steady state.[2] When AIHA was in complete remission, the Hb F and Hb level normalized, 1.0% and 13.0 g/dL, respectively. In fact, the mean proportion of F-cells in normal individnals is 2.7 ± 1.4%, ranging form 0.5% to 7.0%. Moreover, some inherited disorders such as the hereditary persistence of fetal hemoglobin[7], and several acquired conditions such as acute anemia, acute expansion in erythropoietic activity[8], acute hemolysis and bone marrow regeneration[9] can transiently produce more proportions of Hb F-cells. The greater the perturbation of the erythropoiesis, the higher degree of Hb F elevation[8] becomes and this is associated with an increased percentage of Hb F in the hemolysate[10]. This may explain why the percentage of Hb F was markedly increased in our patient during hemolytic crisis.

The percentage of Hb F among patients with beta tha-lassemia / Hb E disease is generally 42 ± 1.5%[2] but in some extreme cases, can be lowered to 3.4 ± 1.5% (range 1.8 to 4.8%)[11]. With Hb F 8.7% during severe hemolysis in our case the differential diagnoses could be either hemoglobin E trait with abnormally high Hb F or beta thalassemia / Hb E disease with extremely low Hb F. After Hb analysis was repeated, Hb E trait could be definitely concluded even without studying for the beta thalassemia genotype.

At the initial presentation, the patient had MCV more than 100 fL during hemolytic crisis (133.0 fL), so her anemia could be classified as macrocytic anemia. Later her MCV normalized (86.2 fL) after she completely recovered from the crisis. The cause of this macrocytosis was supposed to be due to reticulocytosis (5.0 %)[12]. Her macrocytosis could mask the existence of Hb E heterozygosity in this patient, so the hemoglobin analysis should not have been ignored. This is true even in cases of macrocytosis during active hemolysis in areas where thalassemia prevalence of and/or hemoglobinopathy is strik-ingly high in Thailand[13,14]. However the Hb analysis will be reliable when performed after the hemolysis is completely under the control.

## Conclusion

A 19-year-old female Hb E trait was found to have a transiently high Hb F level (8.7%) with microcytosis (MCV 133.0 fL) during severe hemolysis due to autoimmune hemolytic anemia (Hb 3.0 g/dL). Later, Hb F normalized and macrocytosis disappeared after the AIHA was well controlled (HbF 1.0%, MCV 86.2 fL). Therefore the Hb analysis in Hb E trait should be delayed until the active hemolysis is well controlled.

## References


1. *Tienthavorn V, Pattanapongsthorn J, Charoensak S, Sae-Tung R, Charoenkwan P,Sanguansermsri T. Prevalence of thalassemia carriers in Thailand. Thai J Hematol Transf Med. 2006;16:307-12.*
2. *Vichinsky E. Hemoglobin E syndromes. ASH Education Book. 2007;2007:79-83.*
3. *Fucharoen S, Weatherall DJ. The hemoglobin E thalassemias. Cold Spring Harb Perspect. 2012;2:a011734.Doi:10.1101/ cshperspect. a011734*
4. *Fucharoen S, Fucharoen G, Sanchaisuriya K, Surapot S. Molecular characterization of thalassemia intermedia associated with HPFH-6/beta-thalassemia and HPFH-6/Hb E in Thai patients. Acta Haematol. 2002;108:157-61.*
5. *Bass GF, Tuscano ET, Tuscano JM. Diagnosis and classification of autoimmune hemolytic anemia. Autoimmun Rev. 2014;13:560-4.*
6. *Park SH. Diagnosis and treatment of autoimmune hemolytic anemia: classic approach and recent advances. Blood Res. 2016; 51:69-71. doi:10.5045/br.2016.51.2.69*
7. *Prakobkaew N, Fucharoen S, Fucharoen G, Siriratmanawong N. Phenotypic expression of Hb F in common high Hb F determinants in Thailand: roles of alpha-thalassemia, 5' delta-globin BCL11A binding region and 3' beta-globin enhancer. Eur J Haematol. 2014;92:73-9.*
8. *Stamatoyannopoulos G, Veith R, Galanello R, Papayannopoulou T. Hb F production in stressed erythropoiesis: observations and kinetic models. Ann NY Acad Sci. 1985;445:188-97.*
9. *Steinberg MH, Thein SL. Fetal hemoglobin (hemoglobin F) in health and disease. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on November 25, 2013.)*

10. *Wood WG, Stamatoyannopoulos G, Lim G, Nute PE. F-cells in the adult: normal values and levels in individuals with hereditary and acquired elevations of Hb F. Blood. 1975;46:671-82.*
11. *Wong P, Charoenporn P, Jermnim N, Sanguansermsri T. Beta-thalassemia / hemoglobin E with low hemoglobin F: report of 5 cases. Thai J Hematol Transf Med. 2006;16:323-6.*
12. *Kaferle J, Strzoda CE. Evaluation of macrocytosis. Am Fam Physicians. 2009;79:203-8.*
13. *Fucharoen S, Winichagoon P. Haemoglobinopathies in Southeast Asia. Indian J Med Res. 2011;134:498-506.*
14. *Srivorakun H, Singha K, Fucharoen G, Sanchaisuriya K, Fucharoen S. A large cohort of hemoglobin variants in Thailand: molecular epidemiological study and diagnostic consideration. PLoSOne. 2014;9(9): e108365.Doi:10.1371/journal.pone.0108365*