Case Report

The Appearance of the Band of Hemoglobin H in a Patient of Hemoglobin H Disease and the Activity of Rheumatoid Arthritis: A Case Report

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Hemoglobin H disease is a genetic disorder characterized by the moderate degree of microcytic hemolytic anemia and diagnosed by the presence of the Hb H band on the hemoglobin electrophoresis. In this paper, we report a case of Hb H disease whose diagnosis is delayed because of active rheumatoid arthritis. She was a 64-year-old Thai patient who had been definitely diagnosed as having rheumatoid arthritis for 16 years. She was referred to a hematologist because of the long-term microcytic anemia. On the physical examination, she only had marked pallor without hepatosplenomegaly. The first blood test showed Hb 4.4 g%, Hct 13.2%, MCV 53.5 fL, MCH 17.8 pg, WBC 5,600/mm^3, platelet 121,000/mm^3, and reticulocyte 4.4%, while the Hb electrophoresis was Hb A_2A, Hb A_2 2.4%, Hb F 0.2%, and ferritin 1,470.8 ng/ml. When the activity of rheumatoid arthritis was well controlled with methotrexate, prednisolone, and sulfasalazine, the second blood test showed Hb 7.0 g%, Hct 21.3%, MCV 65.1 fL, and MCH 20.3 pg, while Hb electrophoresis was A_2A(H?), Hb A_2 6.1%, and Hb F 0.7%. Later the third blood test showed Hb 7.9 g%, Hct 23.0%, MCV 64.3 fL, and MCH 22.0 pg, while Hb electrophoresis was Hb A_2ABartH, Hb A_2 2.1%, and Hb F 1.6%. Finally, she was hematologically diagnosed as Hb H disease. Our patient showed that Hb H band in Hb H disease was absent when the Hb concentration was markedly low during active rheumatoid arthritis but the band became apparent when the Hb concentration was increased during the remission of rheumatoid arthritis.

Keywords: *Band of hemoglobin H, Hemoglobin H disease, Rheumatoid arthritis*

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Hemoglobin H (Hb H) consists of all four beta globin chains or the beta globin tetramer that is mainly found in Hb H disease, the hereditary hemolytic anemia. It results from the deletional lesion of the three-fourths of the alpha globin genes, leading to the severe deficiency of alpha globin chains and the formation of the tetramer of the excess beta globin chains.

On the hemoglobin electrophoresis by the high-performance liquid column chromatography (HPLC) method, Bio-Rad®, the Hb H is found as the fastest band. Hb H accounts for 0.8 to 40%[1] of the total Hb concentration that is 8.58±1.16 g[2] in adults with Hb H disease at the steady state. When the stress is exposed, the Hb level may abruptly decrease for 3 g% within one day from the hemolytic crisis.

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Some pathologies may affect the presence of the band of Hb H, for congenital such as the co-incidence of Hb and beta thalassemia or beta hemoglobinopathy, e.g., Hb AE Bart disease, the band of Hb H is absent[5]. Likewise, when Hb H disease patient is complicated by iron deficiency anemia, the band of Hb H is also missing[8]. In this case, the Hb H band was found absent during active rheumatoid arthritis.

Case Report

A 64-year-old Thai woman had been definitely diagnosed as having rheumatoid arthritis for 16 years and irregularly followed at the rheumatology clinic of the Maharat Nakhon Ratchasima Hospital. The frequently used drugs consisted of prednisolone 2 to 3 tablets, sulfasalazine and chloroquine. The last drug was switched to methotrexate 1 to 5 tablets a week after retinitis was detected. The last physical examination revealed persistence of the inflammation of both wrists, all metacarpo-phalangeal, and proximal inter-phalangeal joints.

Hematologists were consulted because of severe persistent anemia. She was found to have pallor, no hepatosplenomegaly, and no thalassemic facies.

The blood tests showed Hb 4.4 g%, hematocrit (Hct) 13.2%, mean corpuscular volume (MCV) 53.5 fL, mean corpuscular hemoglobin (MCH) 17.8 pg, MCH concentration (MCHC) 37.3 g%, red cell distribution width (RDW) 30.6%, white blood cell (WBC) 5,600/mm^3, platelet 121,000/mm^3, reticulocyte 4.4%, first Hb electrophoresis using the HPLC, Bio-Rad®, Variant™ II: Hb A_2A, Hb A_2 2.4%, Hb F 0.2%, ferritin 1,470.8 ng/mL (normal 24 to 336), serum iron 54 mcg/dL (normal 35 to 165), and total iron-binding capacity (TIBC) 267 mcg/dL (normal 259 to 388). The diagnosis of anemia of chronic disease with thalassemia trait was proposed and treatments aimed for rheumatoid arthritis was recommended.

Aspartate transaminase (AST) 17 U/L, alanine transaminase (ALT) 9 U/L, alkaline phosphatase 123 U/L, albumin 3.5 g%, globulin 2.7 g%, cholesterol 168%, direct bilirubin 0.1%, total bilirubin 0.5%, creatinine 1.45 mg%, normal thyroid, and cortisol levels.

During the long course of treatment for rheumatoid arthritis, she had never been transfused.

Three months later, the blood tests were Hb 6.0 g%, Hct 19.0%, MCV 57.1 fL, MCH 18.1 pg, and RDW 33.6%, while the second Hb electrophoresis was Hb A_2A, Hb A_2 5.0%, and Hb F 0.4%.

Three months later, the third blood tests were Hb 7.0 g%, Hct 21.3%, MCV 65.1 fL, MCH 20.3 pg, and RDW 31.6%, while the third Hb electrophoresis was A_2A(H?), Hb A_2 6.1%, and Hb F 0.7%.

Finally, three months later, the fourth blood test were Hb 7.9 g%, Hct 23.0%, MCV 64.3 fL, MCH 22.0 pg, and RDW 31.3%, while the fourth Hb electrophoresis was Hb A_2ABartH, Hb A_2 2.1%, and Hb F 1.6%.

Polymerase chain reaction (PCR) for alpha thalassemia-1 genotypes was positive for the Southeast Asian deletion type, and for alpha thalassemia-2 genotypes 3.7 kb deletion, but this patient did not have the test.

The bone marrow study showed normal trilineage.

HIV antigen/antibody, hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and anti-nuclear antibody (ANA) were all negative.

The final diagnosis was Hb H disease of which the degree of anemia was aggravated by the anemia of chronic disease during active phase of rheumatoid arthritis. The main treatment was still aimed to control the activity of rheumatoid arthritis into remission with disease-modifying anti-rheumatic drugs (DMARDs). Blood was occasionally transfused when the severe anemia from either acute hemolytic crisis or the aggravation by active rheumatoid arthritis was encountered. Other treatments for Hb H disease included the genetic counseling and folic acid.

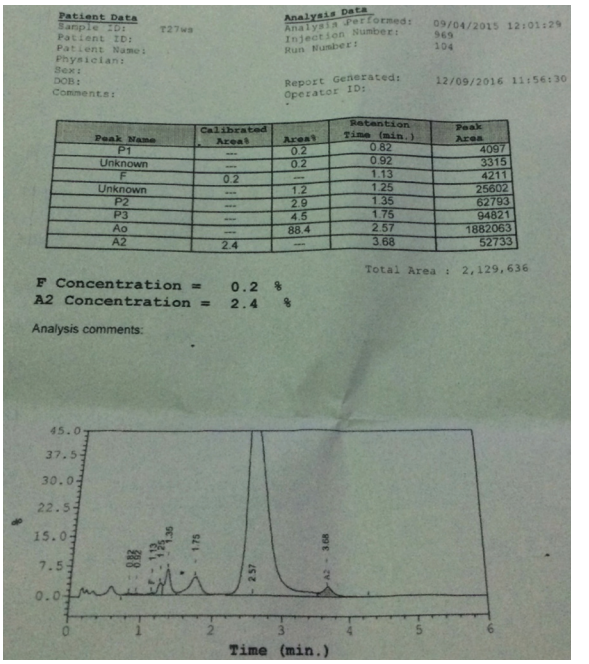

Fig. 1 Hb electrophoresis.

Discussion

At the Hb concentration of 8.58±1.16 g% of the steady state[2], the Hb H, the fastest Hb band on the Hb electrophoresis using HPLC method, Bio-Rad®, accounts for only 7.9±5.5%, range 0.99 to 23.1%[2]. When the Hb H patient was complicated by the anemia of chronic disease due to the definitely diagnosed rheumatoid arthritis according to 2010 Rheumatoid Arthritis Classification Criteria[3], the Hb concentration was diminished to be 4.4 g%, the Hb H fraction was proportionally also decreased until its band on the Hb electrophoresis was hardly seen. However, when the inflammation from rheumatoid arthritis was in remission, the Hb concentration raised to 7.9 g%, closed to that of Hb H disease at the steady state, and the band of Hb H could be first detected. However, it could not be simply concluded the disappearance of the band of Hb H on the first Hb electrophoretic pattern depended on either the severely low Hb

concentration itself or the active phase of rheumatoid with accompanying anemia. Furthermore, the severe anemia may be contributed by chloroquine and/or sulfasalazine used in our case for easily inducing the remission of rheumatoid arthritis, because both are anecdotally in the drug list to be avoided in patients with Hb H disease due to the risk of hemolytic crisis.

In fact, 64% of patients with rheumatoid arthritis have anemia of which the degree varies according to the duration of the disease but reciprocal to the indices of the severity of the disease such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tumor necrosis factor-alpha (TNFalpha), interleukin-1-beta[7]. The anemia of chronic disease (ACD) is always characterized by the averaged Hb concentration of 10.4±2.2 g%[9] with normocytic, normochromic or less often microcytic red blood cell (RBC)[10]. In case of Hb level less than 9 g% and/or MCV less than 80 fL, it may not be solely attributed by ACD and other causes including iron deficiency anemia and thalassemia should be considered. Additionally, the iron deficiency anemia can be totally excluded if the serum ferritin more than 50 ng/mL[11]. Our case had ferritin >1,000 ng/mL, so thalassemia is searched for but it was missed three times because of too low level of total Hb and possibly the instability and easy precipitate of the Hb H itself[12]. Other reasons that can caused missing of Hb H such as active inflammation effect heat labile property of Hb H, but effect from DMARDs was less likely because it did not decrease white blood cells, which are the most commonly suppressed.

If the results of Hb electrophoresis of the first three times were believed, the diagnosis of Hb H disease would be missed. If the absence of Hb H band seems to depend on the activity of rheumatoid arthritis, the chronic inflammatory autoimmune disease that has the natural course as remission and relapse alternately, do other chronic inflammatory diseases such as systemic lupus erythematosus (SLE) might affect the Hb H band like this[15].

Our patient signifies that when the patient with severe anemia of microcytosis who has normal Hb electrophoresis and increased serum ferritin during active inflammatory disease is encountered, the Hb electrophoresis should be retested again after the remission of such disease or else the genotypes of alpha thalassemia-1 and alpha-thalassemia-2 should be studied[13] after the first normal Hb electrophoresis. Moreover, if the diagnosis of Hb H disease is established following the alpha thalassemia genotypes study, beta thalassemia study should also be considered, because it is one factor that cause the absence of Hb H band on the Hb electrophoresis[14].

What is already known on this topic?

The common causes of microcytic anemia in rheumatoid patients are anemia from blood loss from using NSAIDs and iron deficiency anemia. After anemia gone worse even though clinical of rheumatoid arthritis was in remission. Intensive work up for cause of anemia may reveal Hb A_2ABartH.

What this study adds?

The doctor taking care of rheumatoid patients with the problem of chronic anemia should be aware of other cause of anemia such as Hb H, in case of cannot find the cause of anemia.

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Potential conflicts of interest

None.

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การปรากฏของแถบฮีโมโกลบิน เอช ในผู้ป่วยโรคฮีโมโกลบิน เอช กับอาการกำเริบของโรคข้ออักเสบรูมาตอยด์: รายงานผู้ป่วย 1 ราย

ขวัญฤทัย ศรีพวาทกุล, สมชาย อินทรศิริพงษ์

โรคฮีโมโกลบิน เอช เป็นความผิดปกติที่ถ่ายทอดได้ทางพันธุกรรม มีลักษณะที่สำคัญ คือ อาการซีดปานกลาง เป็นแบบเม็ดเลือดแดงขนาดเล็ก และวินิจฉัยได้ด้วยการตรวจแยกชนิดของฮีโมโกลบินแล้วพบแถบของฮีโมโกลบิน เอช แต่ในรายงานนี้เป็นการศึกษาผู้ป่วยโรคฮีโมโกลบิน เอช ที่การวินิจฉัยทำได้ล่าช้าเนื่องจากการกำเริบของโรคข้ออักเสบรูมาตอยด์ โดยผู้ป่วยเป็นหญิงไทย อายุ 64 ปี ได้รับการวินิจฉัยเป็นที่แน่นอนแล้วว่าเป็น ข้ออักเสบรูมาตอยด์ มาเป็นเวลานาน 16 ปี ถูกส่งพบโลหิตแพทย์เพราะภาวะโลหิตจาง ประเภทเม็ดเลือดแดงเล็กมานานแล้ว ตรวจร่างกายพบเพียง อาการซีดมากอย่างเดียว โดยไม่พบตับม้ามโต ตรวจเลือดครั้งแรก Hb 4.4 กรัม%, Hct 13.2%, MCV 53.5 เฟมโตลิตร, MCH 17.8 พิโครกรัม, WBC 5,600/มม.^{3}, platelet 121,000/มม.^{3}, reticulocyte 4.4%, ตรวจแยกชนิดของฮีโมโกลบิน พบ Hb A_2A, Hb A_2 2.4%, Hb F 0.2%, ferritin 1,470.8 นก./มล. เมื่อรักษาจนอาการข้ออักเสบรูมาตอยด์ค่อยสงบขึ้นด้วยยาหลายขนานได้แก่ methotrexate, prednisolone, sulfasalazine ตรวจเลือดครั้งที่ 2 พบว่า Hb 7.0 กรัม%, Hct 21.3%, MCV 65.1 เฟมโตลิตร, MCH 20.3 พิโครกรัม, ตรวจแยกชนิดของฮีโมโกลบิน พบ Hb A_2A(H?), Hb A_2 6.1%, Hb F 0.7% ต่อมาตรวจเลือดครั้งที่ 3 พบ Hb 7.9 กรัม%, Hct 23.0%, MCV 64.3 เฟมโตลิตร, MCH 22.0 พิโครกรัม, ตรวจแยกชนิดของฮีโมโกลบิน พบ Hb A_2ABartH, Hb A_2 2.1%, Hb F 1.6% ให้การวินิจฉัยทางโลหิตท้ายที่สุดว่าเป็น โรคฮีโมโกลบิน เอช ผู้ป่วยรายนี้ได้แสดงให้เห็นว่าแถบของ ฮีโมโกลบิน เอช ในผู้ป่วยโรคฮีโมโกลบิน เอช หายไป เมื่อผู้ป่วยมีโลหิตจางมากในระหว่างการกำเริบของโรคข้ออักเสบรูมาตอยด์ แต่แถบจะกลับมาปรากฏเมื่ออาการโลหิตจางดีขึ้นในระหว่างที่โรคข้ออักเสบรูมาตอยด์อยู่ในความสงบ