Hemoglobin H Disease Complicated by Autoimmune Hemolytic Anemia: A Case Report

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Abstract: Hemoglobin H disease is a genetically transmitted disease and its main clinical manifestation is congenital microcytic hemolytic anemia. It has been rarelycomplicated by autoimmune hemolytic anemia (AIHA). Herein we report a case of 20-year old woman who firstly presents with severe hemolytic anemia without hepatosplenomegaly, Hb 3.3 g%, Hct 11.6 %, MCV 98.6 fL, MCH 27.8 pg, NRBC 32/100 WBC, reticulocyte 19.4%, direct and indirect Coombs' tests +2. She is diagnosed as severe hemolytic crisis due to AIHA and treated with corticosteroid and later danazol, cyclophosphamide and azathioprine, sequentially. She does not completely respond to therapy, her Hb levels fluctuate between 6.0 to 9.2 g%, mean 7.6±1.6 g%, MCV 77.8±3.0 fL, MCH 22.0±1.3 pg. Hbelectrophoresis showsHb A2AHBart and genotype study confirms the diagnosis of Hb H disease. At first, thalassemia is overlooked because the MCV and MCH levels appear normal until the hemoglobin concentration is partially raised following the treatment of AIHA and the MCV and MCH become obviously low. AIHA may be associated with thalassemia because the red blood cells in thalassemia always have bizarre shape, fragmentation, membrane deformation or alloantibody binding, leading to expose new antigens and promote an immune reaction, resulting in AIHA. In conclusion, if the patients with AIHA do not respond well to steroid or other immunosuppressants, thalassemia such as Hb H disease should be excluded particularly in case of new onset of the low MCV.

Key Words: Hemoglobin H Disease, Autoimmune Hemolytic Anemia

บทคัดย่อ: โรคฮีโมโกลบิน เอช ที่ซ้ำเติมด้วย Autoimmune Hemolytic Anemia: รายงานผู้ป่วย 1 ราย
สมชาย อินทรศิริพงษ์, พ.บ.*, วัชรินทร์ ยิ่งสิทธิ์สิริ, พ.บ.*, จุรี บุญดำรงสกุล, พ.บ.*
หน่วยโลหิตวิทยา กลุ่มงานอายุรกรรม โรงพยาบาลมหาราชนครราชสีมา จ.นครราชสีมา 30000
เวชสารโรงพยาบาลมหาราชนครราชสีมา 2558; 37: 155-60.

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โรค Hemoglobin H เป็นโรคที่ถ่ายทอดได้ทางพันธุกรรม อาการที่สำคัญคือ ภาวะโลหิตจางจากการที่เม็ดเลือดแดงแตกง่าย และ มีขนาดเล็กตั้งแต่เกิดการมีโลหิตจางซ้ำเติมด้วย autoimmune hemolytic anemia (AIHA) แบบในผู้ป่วยรายนี้ยังพบได้น้อยผู้ป่วยเป็นหญิง อายุ 20 ปี มาพบแพทย์ครั้งแรกด้วย โลหิตจางอย่างรุนแรงจากภาวะเม็ดเลือดแตกง่าย แต่ตับม้ามไม่โต, Hb 3.3 g%, Hct 11.6 %, MCV 98.6 fL, MCH 27.8 pg, NRBC 32/100 WBC, reticulocyte 19.4%, direct and indirect Coombs' tests +2 จึงได้ให้การวินิจฉัยว่าเป็นภาวะเม็ดเลือดแดงแตกง่าย เข้าขั้นวิกฤตเนื่องจาก AIHA และให้การรักษาด้วย corticosteroid ต่อด้วย danazol, cyclophosphamide และ azathioprine เป็นลำดับ ผู้ป่วยตอบสนองต่อการรักษาไม่ดีเท่าที่ควรระดับ Hb แกว่งอยู่ระหว่าง 6.0 ถึง 9.2 g%, เฉลี่ย 7.6±1.6 g%, MCV 77.8±3.0 fL, MCH 22.0±1.3 pg ตรวจ Hbelectrophoresis พบ Hb A2AHBart และตรวจยีนส์ก็ยืนยันว่าผู้ป่วยเป็นโรค Hb H ตอนแรกธาลัสซีเมียถูกมองข้ามไปเพราะค่า MCV และ MCH อยู่ในเกณฑ์ปกติจนกระทั่งค่าความเข้มข้นของ Hb เพิ่มขึ้นมาบ้างหลังการรักษา AIHA แล้วค่า MCV และ MCH ที่ต่ำก็ปรากฏความจริง AIHA อาจจะมีความเกี่ยวข้องกับธาลัสซีเมียก็ได้ เพราะรูปร่างของเม็ดเลือดแดงในผู้ป่วยธาลัสซีเมียมักเป็นแบบแปลก ๆ ขาดเป็นชิ้นส่วน ผิวเซลล์ที่อาจจะเปลี่ยนแปลงหรือมี alloantibody มาเกาะทำให้เกิด antigens ใหม่ และก่อปฏิกิริยาภูมิต่อต้านได้ ในที่สุดก็อาจก่อให้เกิด AIHA ได้อาจจะพอสรุปได้ว่า ถ้าผู้ป่วย AIHA ตอบสนองต่อการรักษาด้วย steroid หรือ ยากดภูมิต้านทานอื่น ๆ ไม่ดีเท่าที่ควร อาจจะต้องนึกถึงธาลัสซีเมีย เช่น Hb H ด้วยโดยเฉพาะในรายที่ MCV ต่ำทีหลัง

คำสำคัญ: โรคฮีโมโกลบิน เอช, Autoimmune Hemolytic Anemia

Introduction

Hemoglobin H disease, one of the alpha thalas-semias of clinical significance,is a genetically transmitted disease. It is resulted from the combination of the alpha-thalassemia-1 and alpha-thalassemia-2 genes, leading to the severe degree of deficiency of alpha globin chains. The ratio of alpha to beta globin chains ranging from 0.2 to 0.7[1] and the excessive beta globin chains will combine themselves to form a tetramer, the so called Hb H (β4). Its main clinical manifestation is moderate hemolytic anemia, mean Hbconcentration is around 9-10 g%, with occasional hemolytic crisis when exposes to oxidative stress[2].

Autoimmune hemolytic anemia (AIHA) is an acquired hemolytic disease due to autoantibody directly against the antigen situated on the red blood cells surface. It may occur itself or develops following some groups of diseases:autoimmune group such as systemic lupus erythematosus or SLE, malignancies and rarely in beta-thalassemia[3,4]. For alpha thalassemia, one case of Hb H disease who presented with severe hemolytic crisis from AIHA as well asthe immune thrombocytopenia was mentioned[5]. Herein we report another case of Hb H disease that is complicated by AIHA.

Case Report

A 20-year old woman was referred to our department because ofthe severe anemia, fatigue for a few days after she recovered from a four-day fever. The hematocrit was 16%. Noobvious bleeding was observed. On the physical examination, she had severe anemia and mild jaundice, nohepatosplenomegaly, no bruise.

Blood tests: Hb 3.3 g%, Hct 11.6 %, MCV 98.6fL, MCH 27.8 pg, MCHC 28.2 g%, RDW 22.6 %, WBC 17,700/mm3, platelet 367,000/mm3, NRBC 32/100 WBC, hypochromia 1+, anisocytosis +1,

macrocytosis +1, poikilocytosis +1, schistocytosis+1, reticulocyte 19.4%

The direct Coombs' test +2and indirect Coombs' test +2,inclusion body-negative, G6PD-normal, ANA and anti-ds DNA-negative, VDRL, HBsAg, anti-HCV and anti-HIV all were negative, ESR 48/hr, ferritin 448.0ng/mL, LE cell-negative, creatinine 0.7 mg%, albumin 4.0 g%, globulin 5.3 g%, cholesterol 94 mg%, triglyceride 122 mg%, AST 62 U/L, ALT 30 U/L, alkaline phosphatase 150 U/L, urine hemosiderin-negative, total bilirubin 5.3 mg%, direct bilirubin 2.1 mg%

Urinalysis was normal.

She was diagnosed as severe hemolytic crisis due to autoimmune hemolytic anemia (AIHA) and promptly treated with intravenous dexamethasone and later switched to oral prednisolone 60 mg a day. Her Hb concentration could not be raised to thenormal range within a few months therefore other immunosuppressive agents such as danazol, cyclophosphamide, azathioprine were sequentially tried. Her Hb levels werefluctuated between 6.0 to 9.2 g%, mean 7.6$\pm$1.6 g%, Hct 26.9$\pm$5.3 %, MCV 77.8$\pm$3.0 fL, MCH 22.0$\pm$1.3 pg. The Hb electrophores is was performed and showed HbA2® AHBart usingthe HPLC method (Biorad, VARIANT II). Alpha thalassemia-1 (SEA deletion type) and alpha thalassemia-2 (3.7 kb) were positive on genotype study. The diagnosis of AIHA with the underlying Hb H disease, deletional type, was definitely concluded.

Discussion

AIHA has been reported as a rare complication of thalassemia that more commonly affects beta thalassemiathan alpha-thalassemia. Singer et al found a high frequency (25%) of autoantibodies in thalassemia patients, mostly IgG warm antibodies, of which 18% had a significant hemolysis. It may be associated with alloimmunization, exposure to nonleukoreduced blood, and the absence of the spleen. Changes in the RBCs due to the cell fragmentation, membrane deformationor alloantibody binding, lead to expose new antigens and promote an immune reaction.The absence of an efficient filtering system for removal of damaged RBCs enhances the process[6].

Thalassemia is suspected in this case based on many clues; 1) her Hb level cannot be normalized in spite of full dosage ofcorticosteroid and other immunosuppressants, 2) the MCV and MCH are repeatedly shown lower than the normal ranges and 3) Thailand is an endemic area of thalassemias, hemoglobinopathies and their combinations[7]. Furthermore, the ratio between the hematocrit to hemoglobin even during active hemolysis is 11.6/3.3, 3.5 which is consistent with the characteristic of Hb H or related diseases[8]. These lead to the investigations for thalassemias until the final diagnosis of Hb H disease can be established.

The MCV in microcytic hemolytic anemia can be masked during the active hemolysis due to the markedly increased reticulocytes which usually have the larger size than the mature RBCs. For our case, not only MCV but also MCH are masked until thalassemia is overlooked at the first presentation and they become lower than the normal ranges after the severity of anemia is improved. In fact the MCV and MCH inHb H disease patients usually are 61.0$\pm$4.0 fL and 19.0$\pm$1.0 pg, respectively[9]. The chromosome 16 harbors not only the genes controlling alpha globin chain synthesisbut also the genes of severe combined

immune deficiency, especially the centromericend[10]. Likewise, the genes for beta globin chain synthesis situated at 11p15.5 resides of the chromosome 11 appearin close proximity to eight genes with profound roles in immune regulation. Beta-thalassemia accompanied by the autoimmune disease may be the result of haplotypal associations between the close proximity genes[11]. Furthermore, about 14.5 % of multi-transfused patients of thalassemia major show positivity of ANA at titer of 1:80 or above as compared with 1.9 % of control group[12].Nonetheless, the further studies are necessary to see the true association between the autoimmune diseases and various thalassemias.

Conclusion

A case of autoimmune hemolytic anemia with an underlying Hb H disease is reported. Firstly her Hb H disease is overlooked because the low MCV and low MCH, the important characteristics of thalassemia, are masked by the markedly increased reticulocytes during active hemolysis. Until thehemolytic process subsides, the low MCV and low MCH become apparent leading to the suspicion of thalassemia.

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