

Acute hemolytic crisis in a patient with hemoglobin constant spring disease: a case report

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Abstract

Hemoglobin Constant Spring (CS) is an abnormal alpha hemoglobinopathy with 172 amino acids. For Hb CS disease, the patients mostly have mild anemia with normocytosis. So far it is very unusual for Hb CS disease to present with acute hemolytic crisis during febrile illness. This paper was aimed to present a case of acute hemolytic crisis during having pneumonia that was later proved to harbor Hb CS disease. A 59-year-old Thai woman presented with fever, dry cough and pallor for 3 days. The physical examination revealed body temperature 38.5 degree Celsius, frank anemia and jaundice. The blood tests showed: Hb 5.1 g%, WBC 18,540/mm³, platelet 193,000/mm³, MCV 82.3 fl, polychromasia 1+, AST 25 U/L, ALT 18 U/L, direct bilirubin 1.8 mg%, indirect bilirubin 13.5 mg%, sputum C/S yielded *H. parainfluenzae* and *K. pneumoniae*, negative direct anti-globulin tests. The chest film was compatible with pneumonia. She responded well to antibiotics and blood transfusion. Four months later, her blood tests showed: Hb 10.5 g%, MCV 82.3 fl, Hb analysis: A₂ACS, Hb CS 5.8%, Hb A₂ 1.4%, indirect bilirubin 4.8 mg%. The alpha-thalassemia-1 (SEA and Thai deletions) was not found. She was finally diagnosed as Hb CS disease that was complicated by acute hemolytic crisis during pneumonia. Although there is no proper explanation why few Hb CS disease patients behave like Hb H disease patients, *viz.*, having mild anemia at the steady state and sudden development of hemolytic crisis during fever, different genetic background of Hb CS is suspected to play role.

Introduction

Acute hemolytic crisis is characterized by the sudden drop of hemoglobin level with signs of red blood cell (RBC) destruction such as an increased indirect bilirubinemia and signs of compensated RBC production such as an increased polychromasia. The destruction is more rapid than the production [1]. It can complicate any chronic hemolytic anemia particularly Hb H disease if the patients expose to oxidation, for instance, the high fever from an infection [2].

Hemoglobin Constant Spring (Hb CS) is the abnormally elongated alpha globin chain variant derived from the point mutation of the termination codon, the substitution of TAA with CAA. So, 141 amino acid polypeptide of alpha globin chain was added with 31 amino acid residues. In the homozygous forms, the patients mostly have mild hemolytic anemia with normal MCV and mild splenomegaly in some cases [3], Hb 11.5 g%, MCV 87 fl, MCH 26.3 pg, reticulocyte 11.5% with marked basophilic stippling, no free haptoglobin. And the Hb analysis consisted of Hb CS 6.8%, Hb A₂ 1.4%, Hb Bart 1.5% and the rest was Hb A [4]. The acute hemolytic crisis has been the very rare complication in Hb CS disease even in the areas of high prevalence of Hb CS such as Thailand [5] or Malaysia [6], Hb can drop from 10.7 g% at the steady state to 5.0 g% during the crisis from viral infection [6]. Herein we report an additional case of acute severe hemolytic crisis in the patient who was later proved to harbor Hb CS disease.

Case report

A 59-year-old Thai woman was admitted because of fever with dry cough, pallor and jaundice for 3 days. She had no blood loss or dark urine. The physical examination revealed BT 38.5 degree Celsius, P 114/min, frank pallor and jaundice, no splenomegaly.

The blood tests included: Hb 5.1 g%, Hct 15.3%, WBC 18,540/mm³, N 86.4%, L 7.1%, platelet 193,000/mm³, MCV 82.3 fl, MCH 27.3

pg, MCHC 33.2 g%, RDW 15.9% , macrocyte 1+, polychromasia 1+, anisocytosis 1+, few microcyte, creatinine 0.84 mg%, eGFR 76.8 ml/min, albumin 3.9 g%, globulin 3.0 g%, AST 25 U/L, ALT 18 U/L, alkaline phosphatase 66 U/L, direct bilirubin 1.8 mg%, indirect bilirubin 13.5 mg%, hs troponin-I 104.9 (normal <20 ng/L), CK-MB 0.8 (normal <6.6 mg/ml), sputum C/S yielded numerous *H. parainfluenzae* and few *K. pneumoniae*, hemo C/S yielded no growth, influenza test-negative, negative direct and indirect anti-globulin tests, and normal coagulation tests.

The chest film showed pulmonary infiltration at bilateral lower lobes, mild cardiomegaly. Impression: pneumonia and cardiomegaly. And the computerized tomography of the upper abdomen showed slight hepatomegaly, the gall bladder was operated due to symptomatic multiple gall stones when she was 55 years of age.

Six months before this admission: Hb 9.5 g%, Hct 29.1%, MCV 85.1 fl, MCH 27.8 pg, MCHC 32.6 g%, RDW 16.2%, few anisocytosis, few poikilocytosis, Hb analysis by the high-performance liquid chromatography method: A₂ACS, Hb A₂ 1.3%, Hb F 2.0%

She was diagnosed as pneumonia and acute severe hemolytic crisis and treated with cefotaxime, azithromycin and oseltamivir. Five units of packed RBC were transfused to her. The fever gradually subsided and she could be discharged on the 3rd day of admission.

Four months later, the blood was tested again, Hb 10.5 g%, Hct 35.4%, WBC 8,660/mm³, MCV 82.3 fl, MCH 27.3 pg, RDW 15.9%

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and Hb analysis by the capillary zone electrophoresis (CZE) method: A₂ACS, Hb CS 5.8%, Hb A₂ 1.4%, Hb F 1.8%, the PCR for alpha thalassemia-1 was negative for SEA and Thai deletions, AST 24 U/L, ALT 12 U/L, total bilirubin 5.1 mg% indirect bilirubin 4.8 mg%, and normal G-6-PD enzyme.

Her final diagnosis was Hb CS disease that experienced acute severe hemolytic crisis during having fever due to pneumonia.

Discussion

The diagnosis of Hb CS disease in our case was concluded based on the finding of 5.8% of Hb CS on Hb analysis using the CZE method during the steady state because the percentage of Hb CS ranged 4.7-5.3% in Hb CS disease and 0.4-0.7% in Hb CS traits [6].

From mild anemia, our case develops acute severe anemia from hemolytic crisis during fever that looks closely similar to Hb H disease patients when exposed to fever [2]. Furthermore, Hb CS disease patients were found [7-9] mimicking Hb H disease with [10] or without Hb CS trait [11] as an unusual cause of a hydrops fetalis in utero.

Hb CS disease may be complicated by an autoimmune hemolytic anemia leading to the sudden drop of Hb level until the Hb CS could be absent on Hb analysis [12] but the direct antiglobulin test was negative in our case. Other common causes of acute hemolytic crisis including G-6-PD deficiency and hereditary spherocytosis [13] could be excluded by the laboratory and morphology [14], respectively.

During hemolytic crisis, Hb level of a Hb CS disease patient could drop to 5.0 g% from 10.7 g% at the steady state [6]. Likewise, Hb was 5.1 g% in our case during crisis and blood transfusion was in need and later it was maintained at 9.5-10.8 g% without transfusion at the steady state.

There was no appropriate explanation why the minority of Hb CS disease patients has an unusual and potentially severe presentation as if they harbored Hb H disease. In China, 9 patients with Hb CS disease were found to have different manifestations, 4 had no symptom, 2 had mild anemia and splenomegaly and 3 had jaundice but all of them had similarly hypochromia, aniso-poikilocytosis and target cells in the smear [15]. The study in Thailand found haplotypic heterogeneity of Hb CS among different ethnic background in Southeast Asia, and the differences of Hb concentration and the MCV depend on the different genetic combination between Hb CS and other thalassemias and/or hemoglobinopathies [16].

Conclusion

A 59-year-old Thai woman with Hb Constant Spring disease developed acute severe hemolytic crisis during having pneumonia. Hb CS disease in our case seems to run the clinical course as if it were Hb H disease.

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