Aplastic crisis in hereditary spherocytosis associated with Kawasaki disease

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Title

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To the editor:

Hereditary spherocytosis (HS) is one of the most common congenital hemolytic anemia. Infections augment clinical and subclinical hemolysis in patients with HS. On the other hand, severe aplastic crisis occurs in

human parvovirus B19 (B19V) infection. No other specific causes of aplastic crisis have been recognized in HS patients. Here we report severe anemia in a HS patient during the course of acute phase Kawasaki disease (KD). The comparison of iron profiles and hepcidin levels in this patient between KD and B19V infection indicated that KD-associated severe anemia occurred as an episodic hypoplasia. This is the first report of KD-driven aplastic crisis in HS patients.

A five-year-old HS boy was admitted to our hospital because of high-grade fever lasting 6 days. He presented with prolonged jaundice at birth and received a diagnosis of non-severe HS because of spherocytosis without family history. This active boy showed 10-11.5 g/dL of hemoglobin concentrations, mild splenomegaly and jaundice (Figure 1 upper). Laboratory data on admission were as follows; hemoglobin: 7.4 g/dL, reticulocyte: 29×10^9/L, indirect bilirubin: 1.6 mg/dL, ferritin: 315.5 μg/dL, serum iron: 14 μg/dL, and C-reactive protein (CRP): 78.8 mg/L. On 9th febrile day, he received the diagnosis with KD due to fever, conjunctival injection, lip erythema, extremity changes, and slightly dilated coronary arteries. Intravenous immunoglobulin (IVIG 2 g/kg) and oral aspirin (30 mg/kg/day) led to a prompt defervescence on the next day. Coronary artery lesions regressed within one month. Hemoglobin concentration showed a nadir of 6.6 g/dL on day 11th of KD, and gradually improved without red cell transfusion.

Iron profiles monitored during the course of KD were compared with those in his aplastic crisis at age 6 years (Figure 1). Serum hepcidin-25 levels were measured by using liquid chromatography/mass spectrometry (Medical Care Proteomics Biotechnology, Ishikawa, Japan)[1]. The reference range of hepcidin-25 in healthy adult controls was 7.8±7.0 ng/mL[2]. The hepcidin level reached a maximum of 28.5 ng/mL on day 9th of KD and 162 ng/mL on day 3th of febrile aplastic crisis in B19V infection. The hepcidin levels peaked at the nadir of hemoglobin concentration and declined with improved symptoms. Hepcidin is the key iron-regulating peptide synthesized and released by hepatocytes[3, 4]. Iron overload and interleukin (IL)-6 induce hepcidin secretion, that suppresses iron metabolism and reduces hematopoiesis[4, 5]. Serum IL-6 levels are elevated in infection or non-infectious systemic inflammation. Previous reports showed that hemoglobin levels in KD patients were 1.9 g/dL and 1.3 g/dL lower than those in healthy controls and febrile controls, respectively[6, 7]. Considering the kinetics of reticulocyte counts and indirect bilirubin levels along with iron profiles, prolonged inflammation of KD appeared to trigger severe anemia in this patient. Inflammation control by IVIG effectively reduced the hepcidin level with prompt recovery of anemia. On the other hand, iron-burden by red cell transfusion without inflammation control led to the delayed reduction of circulating hepcidin in B19V-induced aplastic crisis. This first reported case of KD-driven aplastic crisis was less severe than B19V-induced aplastic crisis, but the pathophysiology shared hepcidin-mediated iron metabolism.

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Disclosure of potential conflict of interest

The authors declare that they have no relevant conflicts of interest.

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Figure legend

FIGURE 1

The clinical course during KD compared with AC. Trends of hemoglobin (g/dL), indirect bilirubin (mg/dL), reticulocyte ($\times 10^9$/L), serum iron (μg/dL), ferritin (ng/mL), hepcidin (ng/mL), and CRP (mg/L); serum level of hepcidin at day 15 was below the detection limit of 2.0 ng/mL, and the treatment; IVIG 2 g/kg and aspirin initial dose 30 mg/kg/day at day 9, decreased to 5 mg/kg/day from day 13. The data one year after KD and five months before AC were the same time point.