Kawasaki Disease with Autoimmune Hemolytic Anemia

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Background: Association of autoimmune haemolytic anaemia has been seldom reported with Kawasaki disease. **Case characteristics**: A 7-month-old boy, presented with prolonged fever, erythematous rash, severe pallor and hepatosplenomegaly. **Observations**: Positive Direct Coombs test and coronary artery aneurysm on echocardiography. He was managed with steroids along with intravenous immunoglobulins and aspirin. **Outcome**: Early identification of the condition helped in the management. **Message**: Patients of autoimmune hemolytic anemia with unusual features such as prolonged fever, skin rash, and mixed antibody response in Coombs test should be evaluated for underlying Kawasaki disease as a possible etiology.

Keywords: *Autoimmunity, Coombs test, Coronary artery aneurysm.*

Autoimmune haemolytic anemia (AIHA) occurs in children either secondary to infections, autoimmune conditions and drugs, or may be primary [1]. Several hematological abnormalities have been described in Kawasaki disease. AIHA is a rare association, and most cases have occurred after infusion of intravenous immunoglobulins (IVIG) in Kawasaki disease [2]. Simultaneous occurrence of AIHA with Kawasaki disease has been very rarely observed [3-7].

CASE REPORT

A 7-month-old boy presented with fever for 1 month along with maculopapular rash all over the body with erythema of palms and soles at the onset of illness. He was noted to have anemia and was transfused thrice in the first one month of illness. Blood culture grew *Klebsiella pneumoniae* and he was started on antibiotics accordingly. As fever persisted and anemia progressed to cause cardiac decompensation, he was referred to our center. Difficulty in cross-matching of blood was noted at the blood bank of the referring hospital. At the time of admission to our center, he had fever, severe anemia, mild icterus, generalized lymphadenopathy and hepato-splenomegaly. In addition, he had erythema of palms and soles, and desquamation was noted on extremities. Hemoglobin was 3.6 g/dL, white blood cell count 41.7×10^9/L with 78% neutrophils, and platelet count was 407,000/μL; corrected reticulocyte count was 3.4%. Peripheral smear examination showed anisopoikilocytosis, polychromasia, neutrophilic leucocytosis with monocytosis and few atypical lymphocytes. C-Reactive protein was 94 mg/L; Direct Coombs Test (DCT) was positive (3+) and showed a mixed pattern: IgG 3+, IgM 3+, C3d 3+, IgA and C3c negative. Mycoplasma IgM was positive. Polymerase chain reaction (PCR) for cytomegalovirus (CMV) was 19362 copies/mL. PCR for Ebstein-Barr virus was negative. There was no evidence of pneumonia on chest *X*-ray. Bone marrow examination showed erythroid hyperplasia.

In view of the prolonged fever, erythematous rash and desquamation of extremities, he was investigated for underlying Kawasaki disease. 2D Echocardiography showed aneurysms of the main coronary arteries; left main coronary artery 4.6 mm (Normal range 1.23-2.4 mm; Z score 7.9); left anterior descending artery 3.97 mm (Normal range 1.06-1.76 mm; Z score 12.2); right coronary artery 3.87 mm (0.9-1.86 mm; Z score 8.5) along with mild mitral regurgitation and good biventricular function. A diagnosis of Kawasaki disease was made as per AHA guidelines [8,9]. He received IVIG at 2 g/kg as a single dose, along with aspirin (80 mg/kg/day). In view of AIHA, prednisolone was started at a dose of 2 mg/kg/day along with supportive transfusion therapy. Azithromycin was given for 5 days. Child became afebrile within 24 hours and hemoglobin remained stable after transfusion (***Fig.* 1**). He was discharged after 4 days

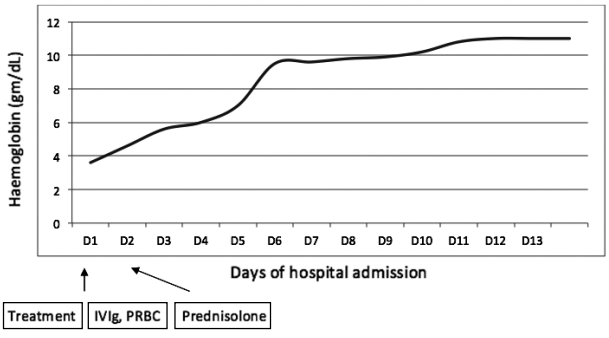

FIG. 1 *Trend of hemoglobin rise in a child with Kawasaki disease and autoimmune hemolytic anemia.*

of admission on aspirin and steroids. CMV PCR was repeated which was negative, and hence no definitive treatment for the same was given. Dose of steroids is at present being tapered slowly and aspirin is being continued at antiplatelet dose. Clinically there is regression of lymphadenopathy and hepatosplenomegaly. He is being kept under close follow up for monitoring the size of coronary aneurysms.

DISCUSSION

Hematological abnormalities known to occur with Kawasaki disease include neutrophilic leucocytosis, thrombocytosis and normocytic anemia. The association of AIHA with Kawasaki disease has been rarely observed. In the index case reported by Kawasaki, the patient had fall in hemoglobin and positive DCT at multiple occasions. However, since no other patient in the original series had similar findings, this was not reported in his landmark English publication [3].

Reticulocyte response was not as brisk as expected for the degree of hemolysis in our case. AIHA has been reported to have reticulocytopenia due to the autoimmune destruction of RBC precursors and increased apoptosis [1]. The pattern of antibodies as observed by monospecific DCT in our case was also unusual. Usually the antobody pattern observed in AIHA is IgG in warm antibody-mediated AIHA and paroxysmal cold hemoglobinuria, and IgM in cold agglutinin disease, with respective thermal amplitudes. A mixed pattern was observed in our case with 3+ positivity for IgG, IgM and C3d. Mixed type AIHA account for a minor percentage of the total AIHA cases in children, and is seen usually secondary to drugs and rheumatological conditions [1,4].

In most cases of AIHA with Kawasaki disease, it has been reported as a complication following IVIG infusion [2]. IVIG can produce hemolysis directly by isohemagglutinins or by stimulating B lymphocytes resulting in the production of RBC autoantibodies [6]. In our patient, onset of AIHA occurred prior to IVIG administration , ruling out this possibility. The reasons for AIHA in our patient includes any one or a combination of the underlying rheumatological condition (Kawasaki disease), and infections such as Mycoplasma, CMV or *Klebsiella* – all of which were detected at various time points. The resolution of hemolysis in our patient coincided with the resolution of Kawasaki disease. Clinical response and improvement was seen after starting steroids along with IVIG and aspirin.

We conclude that patients of AIHA with unusual features such as prolonged fever, skin rash, or mixed antibody response in DCT should be evaluated for underlying rheumatologic diseases such as Kawasaki disease. Early identification and management will help in reducing complications of both problems.

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