

Macrophage Activation Syndrome: A Potentially Fatal Complication of Kawasaki Disease

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ABSTRACT

Kawasaki disease is an acute vasculitis of childhood. Macrophage activation syndrome is a rare life threatening complication. In this article, we report a five-year-six-month old girl patient with Kawasaki disease who developed irritability, hepatosplenomegaly, and pancytopenia after treatment with intravenous immunoglobulins. Patient's blood test and bone marrow aspiration results suggested macrophage activation syndrome. The patient responded to dexamethasone in a dose of 10 mg/m²/day.

Keywords: Immunoglobulin; Kawasaki disease; macrophage activation syndrome.

Macrophage activation syndrome (MAS) is a rare complication of childhood with rheumatic disease.¹ This syndrome has been reported in association with many rheumatic diseases, especially systemic juvenile rheumatoid arthritis.² MAS occurs secondary to many diseases, including infections, neoplasms, hematological conditions, and rheumatic disorders. It is characterized by persistent fever, pancytopenia, liver dysfunction, hepatosplenomegaly, hyperferritinemia, hypofibrinogenemia, elevated serum lactate dehydrogenase, and hypertriglyceridemia.^{1,3,4}

CASE REPORT

A five-year-six-month old girl was admitted with history of high fever for seven days. There was bilateral non-purulent conjunctivitis from the fourth day of fever along with erythema of tongue and lips. Blood count results on admission were: hemoglobin 9.6 g/dL, total leukocyte count 20,300/dL, platelet count 392,000/dL, erythrocyte sedimentation rate (ESR) 84 mm in

first hour, and C-reactive-protein 128 mg/L. Widal and Mantoux tests were negative. On examination, irritability, left cervical lymphadenopathy sized 2.5x2.5 cm, and hepatomegaly were detected. Investigations showed alanine aminotransferase of 369 U/L, serum albumin of 2.4 g/dL, and a sterile blood culture. Urine microscopy revealed 15 pus cells/high power field while culture was sterile. Echocardiography showed perivascular cuffing with lack of tapering in left anterior descending coronary artery. A diagnosis of Kawasaki disease (KD) was made and intravenous immunoglobulins (IVIg) were administered at 2 g/kg over 24 hours. We started IVIg on 11th day of fever as fever persisted with features of continuing inflammation.

After being afebrile for 24 hours, fever recurred. Patient became irritable, developed bleeding per rectum and increased size of liver and splenomegaly were noted. Repeat blood counts showed hemoglobin of 7 g/dL, total leukocyte count of 4,700/dL, platelet count of 88,000/dL, ESR of 04 mm in first hour, and C-reactive-protein of 256 mg/L. Alanine

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aminotransferase increased to 565 U/L, and bilirubin was 3.8 mg/dL (conjugated 2.9 mg/dL) International normalized ratio was 1.8 seconds and activated partial thromboplastin time was 65 seconds. Persistent fever, hepatosplenomegaly, deteriorating liver function and pancytopenia along with decreasing ESR raised the suspicion of MAS. Further blood investigations were: ferritin >2,000 ng/dL, fibrinogen 102 mg/dL, triglyceride 313 mg/dL, and lactate dehydrogenase 1,568 U/L. Bone marrow aspiration demonstrated phagocytosis of hematopoietic cells by well differentiated macrophages that was diagnostic of MAS.⁵

We started dexamethasone 10 mg/m²/day. Fever gradually subsided, blood count results normalized on day 18, and the child was discharged after 13 days on oral aspirin 5 mg/kg/day. We continued dexamethasone in a tapering dose for eight weeks. The patient is now clinically well and on regular follow-up.

DISCUSSION

Kawasaki disease is an acute multi system vasculitis of small and medium sized arteries. Patient usually responds to single dose of IVIg but our patient had a recurrence of fever despite intravenous administration of IVIg and she deteriorated rapidly after 24 hours. Refractory fever occurs in 10% of patients with KD despite treatment with IVIg where suggested treatment is intravenous pulse therapy with methylprednisolone or infliximab.⁶ Persistent fever following IVIg administration, low blood counts, and ESR and hepatosplenomegaly led us to investigate the presence of MAS.

Macrophage activation syndrome patients have profoundly depressed natural-killer cell function. Natural-killer cells and cytotoxic T-lymphocytes fail to kill infected cells and thus remove the source of antigenic stimulation leading to persistent antigen-driven activation and proliferation of T-cells associated with persistent production of cytokines that stimulate macrophages. Cytotoxic dysfunction leads to persistent expansion of T cells and macrophages, and escalating production of proinflammatory cytokines.⁷⁻⁹

There have been few reported cases of MAS in KD. Latino et al.¹⁰ reported that 1.9% of KD

patients had additional clinical findings of MAS, and 10 out of 12 patients with KD in their series met at least five of the eight criteria necessary for diagnosis of MAS. Treatment beyond the standard KD protocol (aspirin + IVIg) was necessary in all but one patient. Eight of these patients were also given multiple doses of IVIg. We administered dexamethasone therapy after single dose of IVIg with dramatic response.¹¹

Kawasaki disease patients are known to be at increased risk for coronary artery lesions. We demonstrated MAS as another possible complication associated with KD, which, although rarely, may complicate the course of KD. We showed that prompt treatment with dexamethasone may result in favorable outcome. We also presented a review of the literature that supports the inclusion of MAS as an infrequent complication of KD.⁵

Declaration of conflicting interests

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