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Macrophage Activation Syndrome in Kawasaki Disease

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Background: Kawasaki disease is an acute febrile vasculitis of childhood. Macrophage activation syndrome is a rare life threatening complication. **Case characteristics:** 4-year-old boy with Kawasaki Disease treated with intravenous immunoglobulins. **Observation:** He developed encephalopathy, hepatosplenomegaly and pancytopenia. Blood investigations and bone marrow aspiration suggested macrophage activation syndrome. **Outcome:** Good response to pulse methylprednisolone (30 mg/kg/d) for 5 days. **Message:** Macrophage activation syndrome may complicate Kawasaki disease.

Keywords: *Lymphoproliferative disorders, Mucocutaneous lymph node syndrome.*

Macrophage activation syndrome (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 [1,2].

CASE REPORT

A 4-year-old boy was admitted with history of high fever for 14 days. He had a history of diffuse maculopapular truncal rash which started on day-4 of fever and persisted for 4 days. There was bilateral non-purulent conjunctivitis from the 3rd to 6th day of fever along with erythema of tongue and lips. Blood counts done elsewhere on day-12 were: hemoglobin 9.6 g/dL, total leukocyte count 18.8 × 10^9/L, platelet count 886 × 10^9/L, Erythrocyte sedimentation rate (ESR) 70 mm in 1st hour, and C-reactive-protein (CRP) 86 mg/L. Widal and Mantoux tests were negative. On examination, he was irritable, and had pedal edema, orange brown chromonychia, right cervical lymphadenopathy and hepatosplenomegaly. Investigations showed serum sodium of 130 mmol/L, Alanine aminotransferase (ALT) of 263 U/L, serum albumin of 2.8 g/dL, and a sterile blood culture. Urine microscopy revealed 10-12 pus cells/ high power field; culture was sterile. Echocardiography showed perivascular brightness with lack of tapering in left anterior descending artery and an aneurysm measuring 5 mm. Aneurysm (4.6 mm) was also present in left main coronary artery. A diagnosis of Kawasaki disease (KD) was made and intravenous immunoglobulins (IVIg) were administered at 2 g/kg over 24 hours.

After being afebrile for 48 hours, fever recurred on day-17. He became drowsy, developed gum bleeding and further increase in size of liver and spleen. Repeat blood counts showed hemoglobin 6.8 g/dL, total leukocyte count 4.6 × 10^9/L, platelet count 16 × 10^9/L, ESR 12 mm in 1st hour and CRP 256 mg/L. ALT increased to 468 U/L, International normalized ratio was 1.8 and activated partial thromboplastin time was 68 seconds. Persistent fever, encephalopathy, hepatosplenomegaly, deteriorating liver function and pancytopenia along with

falling ESR raised the suspicion of MAS. Further blood investigations were: ferritin 15716 ng/dL, fibrinogen 96 mg/dL, triglyceride 463 mg/dL and lactate dehydrogenase 1775 U/L. Bone marrow aspiration documented phagocytosis of hematopoietic cells by well differentiated macrophages that was diagnostic of MAS.

Intravenous pulse methylprednisolone was given at 30 mg/kg/d for 5 days. Fever gradually subsided, blood counts normalized (on day-24), and the child was discharged after 13 days on oral aspirin 5 mg/kg/d. The patient is now clinically well and on regular follow-up. Echocardiography after 6 weeks showed regression of aneurysms.

DISCUSSION

Kawasaki disease is an acute multi system vasculitis of the small and medium-sized arteries with a predilection for coronaries. Our patient had all the clinical features of KD [3-5]. Our patient had a recurrence of fever despite intravenous administration of IVIg, and he deteriorated rapidly after 48 hours. Refractory fever occurs in 10% of patients with KD despite treatment with IVIg; the suggested treatment is intravenous pulse therapy with methylprednisolone or infliximab [6]. Persistent fever following IVIg administration, falling blood counts and ESR, hepatosplenomegaly, and alteration of mental status prompted us to investigate him for MAS.

MAS patients have profoundly depressed natural-killer (NK) cell function. NK 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 [10-12]. Latino, *et al.* [11] reported that 10 out of the 12 patients with KD in their series met at least 5 of the 8 criteria necessary for diagnosis of MAS. Treatment beyond the standard KD protocol (aspirin + IVIg) was necessary in all but 1 patient. Eight of these patients were also given multiple doses of IVIg. We administered methylprednisolone pulse therapy after single dose of IVIg with dramatic response.

We conclude that MAS may rarely complicate the course of KD; prompt treatment with pulse methylprednisolone may result in favourable outcome .

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