Clinical Case Report

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Kawasaki disease shock syndrome complicated with macrophage activation syndrome in a 5-month old boy

A case report

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Abstract

Rationale: Kawasaki disease (KD) is an acute febrile systemic vasculitis of unknown etiology and often occurs in children under 5 years old. During the acute phase, approximately 5% of children with KD develop hypotension and shock, a severe condition termed KD shock syndrome (KDSS). Macrophage activation syndrome (MAS), another life-threatening complication, has been reported to be associated with KD, although rarely. KDSS complicated with MAS is extremely rare. In this article, we present our experience in the diagnosis and treatment of KDSS complicated with MAS.

Patient concerns: A 5-month boy with fever for 5 days was diagnosed with KD. After 2 doses of intravenous immunoglobulin and regular antiinflammatory treatment at a local hospital, the fever did not subdue. He was admitted to our department on the 10th day of illness. The boy developed KDSS on the 11th day of illness. In the mean time, the boy had hepatosplenomegaly, and laboratory tests showed hypertriglyceridemia, hypofibrinogenemia, decreased blood red cells and platelets, increased ferritin and soluble sIL2Rα, and reduced natural killer cell activity.

Diagnosis: The patient had KDSS complicated with MAS.

Interventions: Emergency antishock therapy along with high-dose steroid with a longer tapering course was carried out. Following these treatments, fever subsided and other symptoms and signs relieved, but progressive coronary dilatation occurred, warfarin was thereby administered.

Outcomes: The patient was discharged 30 days after hospitalization. Echocardiography at the 2 month follow-up showed regression of coronary aneurysm.

Lessons: Laboratory testing is critical for the diagnosis of MAS and we recommend that 2009 HLH diagnostic criteria be used for the diagnosis of MAS in KD. Emergency treatment of shock and a longer course of high-dose steroid anti-inflammatory therapy are vital for the management of KDSS complicated with MAS.

Abbreviations: CRP = C-reactive protein, HLH = hemophagocytic lymphohistiocytosis, IVIG = intravenous immunoglobulin, KD = Kawasaki disease, KDSS = Kawasaki disease shock syndrome, LADA = left anterior descending artery, MAS = macrophage activation syndrome, RCA = right coronary artery, WBC = white blood cell.

Keywords: anti-inflammatory therapy, HLH diagnostic criteria, Kawasaki disease, Kawasaki disease shock syndrome, macrophage activation syndrome

1. Introduction

Kawasaki disease (KD) is an acute febrile systemic vasculitis of unknown etiology and often occurs in children under 5 years old.[1] During the acute phase, approximately 5% of children with KD develop hypotension and shock, a severe condition termed KD shock syndrome (KDSS).[2–4] Macrophage activation syndrome (MAS), also known as secondary hemophagocytic lymphohistiocytosis (HLH), is a life-threatening complication associated with autoimmune and/or inflammatory disorders including KD; it is caused by excessive and persistent activation of macrophages.[5] The incidence of MAS in pediatric patients with KD has been reported to range 1 to 2%.[6,7] While KDSS or MAS each alone arising in KD has been documented in the literature,[2–4,6–11] KDSS complicated with MAS has not been reported. In this article, we present the clinical and laboratory features, and the treatment outcomes of a KDSS case complicated with MAS.

2. Report of the case

This case report study was approved by the Medical Research Review Board of Children's Hospital, Capital Institute of Pediatrics, Beijing, China (approval number: KSSHERLL2018015). The board waived the requirement to obtain informed consent from the parents because this is a retrospective study.

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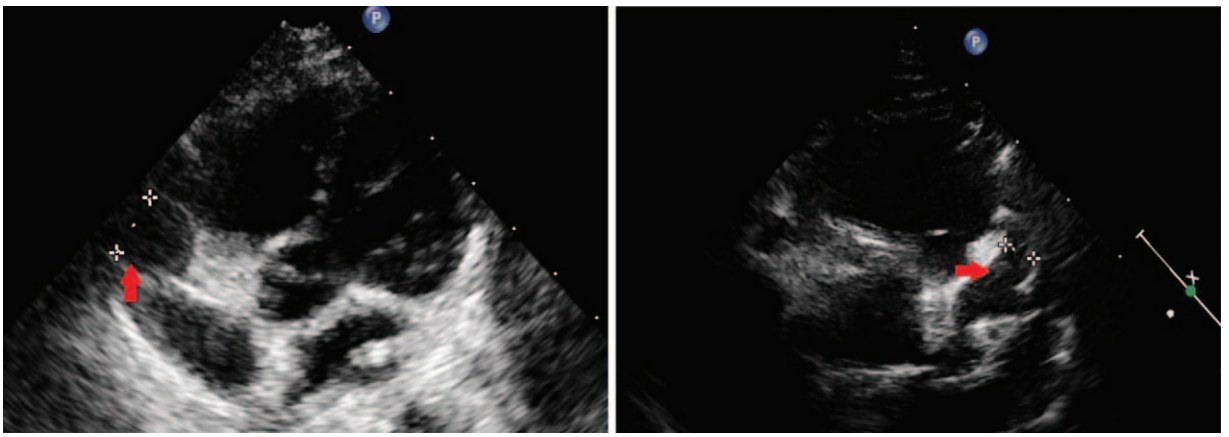

Figure 1. Coronary artery echocardiography. Echocardiographic examination was performed to measure coronary dilation. Shown in this figure is the echocardiograms obtained 1 day before discharge. Right coronary artery dilation is shown in the left-side image (RCA diameter measured at 9 mm as indicated by the red arrow) and the dilation of the left anterior descending artery is shown in right-side image (LADA diameter measured at 5.6 mm, as indicated by the red arrow). LADA = left anterior descending artery, RCA = right coronary artery.

A 5-month old boy with fever lasting for 5 days was admitted to a local hospital. Diagnosis of KD was made based on clinical findings, that is, rashes, conjunctivitis, strawberry tongue and extremity edema, and laboratory parameters, e.g., high white blood cell (WBC) counts and elevated C-reactive protein (CRP) levels. On the 6th day of illness, the patient was given a dose of intravenous immunoglobulin (IVIG, 1.5 g/kg). Additionally, aspirin (30 mg/kg) administration was initiated daily along with intermittent infusion of dexamethasone. The condition of the boy was not alleviated after treatment at the local hospital and he was transferred to our department on the 10th day of illness.

The diagnosis of KD was confirmed by us and key laboratory findings at our department were WBC: 54.23×10^9/L; CRP: 69 mg/L; procalcitonin: 0.66 ng/mL and albumin: 26 g/L (hypoalbuminemia). Echocardiography showed mild bilateral coronary dilation (LADA diameter 2.8 mm and RCA diameter 2.3 mm). The patient received a second dose of IVIG (2 g/kg) and methylprednisolone infusion was initiated (4 mg/kg/d, administered every 12 h), while aspirin was maintained at 30 mg/kg daily. Hypoalbuminemia was treated with human albumin infusion (1 g/kg). On the 11th day of illness, the patient developed KDSS with blood pressure of 65/35 mm Hg accompanied by oliguria, tachycardia and prolonged capillary refill time. In the meanwhile, hepatosplenomegaly was palpable, which was confirmed by ultrasound examination; low RBC and platelet counts were noted (RBC: 2.59×10^{12}/L and platelet: 67×10^9/L), prompting us to suspect that the child had MAS. Further laboratory testing was therefore performed, which showed serum ferritin at 283.11 ng/mL; fibrinogen at 1.67 g/L; triglyceride at 1.87mmol/L and HGB at 67 g/L. Other parameters included decreased natural killer (NK) cell activity (14.16%), elevated soluble CD25 (interleukin-2 receptor α, 19765 pg/mL) and proinflammatory cytokines (TNF-α, IL-6, IL-8 and IL-10). Aspartate transaminase and alanine transaminase were normal. Bone marrow examination was declined by the parents. The clinical and laboratory findings established the diagnosis of MAS following the HLH criteria for secondary HLH.[12,13] Emergency anti-shock therapy was applied, that is, fluid resuscitation, repeated intravenous human albumin infusion and dopamine administration. Methylprednisolone dosage was increased to 4.8 mg/kg/d for anti-inflammatory therapy and blood component (red cells only) transfusion was conducted. Two days later, fever subsided and the patient's condition was stabilized. He was afebrile for 4 days and methylprednisolone was reduced to 2.4 mg/kg/day on the 17th day of illness. A day after methylprednisolone reduction the patient had a recurrent fever with elevated CRP (50 mg/L). Methylprednisolone dosage was increased again to 4.8 mg/kg/d and tapered in 8 weeks (part of tapering was completed in our outpatient clinic). Progressive coronary dilation was observed during the entire period of hospitalization with the maximal diameter of 9 mm in RCA (Fig. 1) measured a day before the discharge. Antithrombotic prophylaxis was initiated with Warfarin. The patient was discharged 30 days after hospitalization. The follow-up at 2 months found no abnormalities by physical examination and regression of RCA aneurysm (7.3 mm) by echocardiography.

3. Discussion

KDSS or MAS associated with KD is uncommon but can be life threatening, requiring prompt and proper management.[2–4,6–11] We treated a patient who had KDSS that was further complicated with MAS; we felt that early diagnosis of the complications especially MAS is essential to the effective treatment of these complications. Currently, there are 2 diagnostic criteria for MAS, namely, 2009 HLH diagnostic criteria[13] and 2016 classification criteria for MAS complicating systemic juvenile idiopathic arthritis (JIA).[14] Of the 2016 MAS criteria, confirmed diagnosis or suspicion of systemic JIA is a prerequisite. Therefore, the 2016 MAS criteria, in our opinion, are not suitable for diagnosis of MAS in KD. According to 2009 HLH diagnostic criteria, 5 of following 8 clinical and laboratory findings must be fulfilled for the diagnosis of MAS: fever; splenomegaly; bicytopenia; hypertriglyceridemia and/or hypofibrinogenemia; hemophagocytosis; low/absent NK-cell-activity; hyperferritinemia; and high soluble interleukin-2-receptor levels.[12,13] Following these criteria, the patient under our care had MAS. Of note, if 2 lines of blood cell counts fall below the normal range, other specific tests such as NK activity and soluble interleukin-2-receptor measurements, relevant to MAS diagnosis,[12,13] is highly recommended.

We detected prominent laboratory parameters, ominous inflammatory markers in particular, in the patient, which aligns

well with those reported in KD patients with either KDSS or MAS.[2–4,6–11] Patients with KDSS have been shown to have a higher risk of coronary complications,[2–4] and we observed the development of coronary aneurysm in the case. Coronary abnormalities are also seen in patients with MAS associated with KD;[6,10,11] however, it is found that MAS does not significantly affect the incidence of coronary abnormalities.[6] The impact of MAS, if any, on KDSS-induced coronary pathologies remains unresolved.

MAS is characterized by multisystem inflammation. Therefore, in addition to the standard KD treatment protocol that includes IVIG and administration of aspirin, potent anti-inflammatory therapy is needed for the management of KD associated with MAS. In this study, after the use of high dosages of methylprednisolone for 7 days, the condition of the patient improved. However, when the methylprednisolone dosage was reduced in half, fever and inflammation recurred, which contrasts with other reports showing that KD patients with MAS recovered after administration of methylprednisolone for 5 to 7 days.[8,11] The recurrence, as we saw, might be a result caused by the coexisting KDSS. Our data therefore suggest KDSS complicated with MAS requires a longer course of anti-inflammatory therapy. IVIG resistance occurs more commonly in KD patients complicated with KDSS or MAS than in those without the complications.[2,6] The boy in this study encountered IVIG resistance and a second IVIG was administered, in agreement with previously published findings.[2,6]

4. Conclusion

KDSS and MAS can be present simultaneously during acute KD; the impact of KDSS complicated with MAS on KD remains to be elucidated. Laboratory testing is critical for the diagnosis of MAS and we recommend that 2009 HLH diagnostic criteria be used for the diagnosis of MAS in KD. Emergency treatment of shock and a longer course of high-dose steroid anti-inflammatory therapy are vital for the management of KDSS complicated with MAS.

Author contributions

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Writing – review & editing: Lin Shi.

References

[1] McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135:e927–99.
[2] Kanegaye JT, Wilder MS, Molkara D, et al. Recognition of a Kawasaki disease shock syndrome. Pediatrics 2009;123:e783–9.
[3] Dominguez SR, Friedman K, Seewald R, et al. Kawasaki disease in a pediatric intensive care unit: a case-control study. Pediatrics 2008;122: e786–90.
[4] Gámez-González LB, Murata C, Muñoz-Ramírez M, et al. Clinical manifestations associated with Kawasaki disease shock syndrome in Mexican children. Eur J Pediatr 2013;172:337–42.
[5] Weaver LK, Behrens EM. Hyperinflammation, rather than hemophagocytosis, is the common link between macrophage activation syndrome and hemophagocytic lymphohistiocytosis. Curr Opin Rheumatol 2014;26:562–9.
[6] Wang W, Gong F, Zhu W, et al. Macrophage activation syndrome in Kawasaki disease: more common than we thought? Semin Arthritis Rheum 2015;44:405–10.
[7] Latino GA, Manlhiot C, Yeung RS, et al. Macrophage activation syndrome in the acute phase of Kawasaki disease. J Pediatr Hematol Oncol 2010;32:527–31.
[8] Muise A, Tallett SE, Silverman ED. Are children with Kawasaki disease and prolonged fever at risk for macrophage activation syndrome? Pediatrics 2003;112(6 pt 1):e495–496.
[9] Kim HK, Kim HG, Cho SJ, et al. Clinical characteristics of hemophagocytic lymphohistiocytosis related to Kawasaki disease. Pediatr Hematol Oncol 2011;28:230–6.
[10] Doğan V, Karaaslan E, Özer S, et al. Hemophagocytosis in the acute phase of fatal Kawasaki disease in a 4 month-old girl. Balkan Med J 2016;33:470–2.
[11] Mukherjee D, Pal P, Kundu R, et al. Macrophage activation syndrome in Kawasaki disease. Indian Pediatr 2014;51:148–9.
[12] Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–31.
[13] Filipovich AH. Hemophagocytic lymphohistiocytosis (HLH) and related disorders. Hematology Am Soc Hematol Educ Program 2009;2009: 127–31.
[14] Ravelli A, Minoia F, Davì S, et al. 2016 Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European league against rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016; 75:481–9.