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Macrophage activation syndrome in Kawasaki Disease: More common than we thought?

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ABSTRACT

Objectives: To analyze the clinical characteristics, treatment, and outcomes of Kawasaki Disease (KD) patients associated with macrophage activation syndrome (MAS) and to compare two diagnostic standards (the HLH 2009 and Ravelli's criteria).
Methods: All of the studied patients with Kawasaki Disease (KD) were treated at The Children's Hospital, Zhejiang University School of Medicine, during 2007–2010. Clinical and laboratory findings were analyzed.
Results: In 719 KD patients, eight patients (1.11%, 81.3 ± 49.4 months, all male) were diagnosed by Ravelli's criteria, but only three (0.42%) patients were diagnosed by the HLH 2009 criteria. Aspartate aminotransferase increased significantly in all cases. Alanine aminotransferase, lactate dehydrogenase, and serum ferritin increased significantly in seven cases. Cytopenia and hypertriglyceridemia (> 1.5 mmol/L) were found in six and five cases, respectively. Hypofibrinogenemia (< 1.5 g/L) was found in two cases. Three cases showed evidence of hemophagocytosis, but only one case met the HLH 2009 criteria. Ectasia of the coronary arteries occurred in two cases. Seven patients were non-responsive to IVIG. One case died after the combined application of DXM, VP16, and CSA.
Conclusions: MAS may be a frequently under-recognized complication of KD, because the understanding of complications and diagnostic criteria are still in progress. The HLH 2009 criteria have low sensitivity and specificity for the diagnosis of MAS complicating KD. When hepatosplenomegaly is present in KD patients with abnormal laboratory findings, such as cytopenia, liver dysfunction, hyperferritinemia, elevated serum LDH, hypofibrinogenemia, and hypertriglyceridemia, the presence of MAS should be considered.

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Macrophage activation syndrome (MAS) is a phenomenon characterized by cytopenia, organ dysfunction, and coagulopathy associated with an inappropriate activation of macrophages. It mainly manifests as the exacerbation of primary illness, such as prolonged fever, rash, and hepatosplenomegaly, and hallmark features include liver dysfunction, elevated serum lactate dehydrogenase (LDH), hypofibrinogenemia, hyperferritinemia, hypertriglyceridemia, and pancytopenia [1]. The central role of macrophage activation in a hemophagocytic syndrome associated with pediatric rheumatic diseases was reported in 1985 [2].

The current classification of MAS is still imprecise. The widely used criteria for the diagnosis of MAS are the hemophagocytic lymphohistiocytosis (HLH) criteria, such as the HLH 2009 criteria [3]. However, the HLH criteria are inappropriate for diagnosis of secondary forms of MAS, since they were developed for familial forms that are homozygous-deficient in cytolytic pathway proteins. In order to address this concern and increase the accuracy of MAS diagnosis, Ravelli et al. [1] proposed a set of four laboratory criteria and three clinical criteria for the diagnosis of MAS complicating systemic juvenile idiopathic arthritis (sJIA); however, this protocol is not validated. However, new criteria are under development for MAS among sJIA patients [4].

Kawasaki Disease (KD), or mucocutaneous lymph node syndrome, is a disease of unknown etiology that most frequently affects children under 5 years of age. It is an acute, self-limited vasculitis, complicated by the formation of coronary artery aneurysms. The diagnosis is based on clinical presentation [5]. MAS is a relatively frequent complication of rheumatic diseases, and there have been several cases reported among children with KD [6].

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Table 1
The proposed HLH diagnostic criteria, 2009

Symptoms	Cases							
	1	2	3	4	5	6	7	8
1. Molecular diagnosis of HLH or XLP	No	No	No	No	No	No	No	No
2. Or at least three of four								
a. Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
b. Splenomegaly	No	No	No	No	No	No	Yes	No
c. Cytopenias (minimum of two cell lines reduced)	No	No	No	Yes	No	Yes	No	Yes
d. Hepatitis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
3. And at least one of four:								
a. Hemophagocytosis	No	Yes	No	No	–	No	Yes	Yes
b. ↑ Ferritin	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–
c. ↑ sIL2Rα (age-based)	–	–	–	–	–	–	–	–
d. Absent or much decreased NK function	–	–	–	–	–	–	–	–
4. Other results supportive of HLH diagnosis								
a. Hypertriglyceridemia	No	No	No	Yes	No	Yes	Yes	No
b. Hypofibrinogenemia	No	No	Yes	No	No	Yes	No	No
c. Hyponatremia	No	Yes	No	Yes	No	No	Yes	No
Diagnosed by these criteria	No	No	No	Yes	No	Yes	Yes	No

Since a few severe KD cases have some clinical and laboratory features of MAS, MAS is thought to complicate KD in some patients. However, there have been few reports on MAS in children with KD, because there is no consensus on how to establish MAS in KD. As KD is a disease of immune dysregulation, which is similar to sJIA, the HLH 2009 criteria and Ravelli's criteria can also be utilized for the diagnosis of MAS complicating KD.

Patients and methods

Definitions

All of the KD patients fulfilled the diagnostic criteria established by the MCLS research committee of Japan (2002) [5]. Two sets of criteria [the HLH 2009 criteria (Table 1) [3] and criteria proposed by Ravelli et al. for the diagnosis of MAS complicating sJIA (Table 2) [1]] were utilized to make the diagnosis of MAS complicated with KD.

Study population

The clinical data of 719 patients diagnosed with KD at The Children's Hospital, Zhejiang University School of Medicine, Hangzhou, China, from January 2008 to February 2011 were analyzed. Their medical records were reviewed retrospectively. The study was approved by the ethical committee of The Children's Hospital, Zhejiang University School of Medicine, and was based on the institution's guidelines for human studies. Patients with a co-diagnosis of KD and MAS were identified from the KD cases. Demographics, clinical signs, laboratory values, treatment, and coronary artery outcomes of the patients with a co-diagnosis of KD and MAS were extracted from the medical records. Laboratory values selected were those closest in time to when the diagnosis of MAS was established.

Outcome measures

Clinical and laboratory findings were analyzed according to the frequency of occurrence and duration of the illness. Fever was defined as a temperature of 38°C or higher. Hepatosplenomegaly and lymphadenopathy were determined according to physical examination records. Relevant laboratory data were extracted as described above and analyzed.

Statistical analysis

Descriptive statistical data analysis was performed with Microsoft Excel on Microsoft Windows Professional.

Table 2
Preliminary diagnostic guidelines for macrophage activation system complicating sJIA

Symptoms	Cases							
	1	2	3	4	5	6	7	8
Laboratory criteria								
1. Decreased platelet count ($\leq 262 \times 10^9$ per L)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
2. Elevated levels of aspartate aminotransferase (> 59 U/L)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Decreased white blood cell count ($\leq 4.0 \times 10^9$ per L)	No	No	No	No	No	Yes	No	Yes
4. Hypofibrinogenemia (≤ 2.5 g/L)	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Clinical criteria								
1. Central nervous system dysfunction	No	No	No	No	Yes	No	No	No
2. Hemorrhages (purpura, easy bruising, and mucosal bleeding)	Yes	Yes	No	Yes	No	Yes	No	Yes
3. Hepatomegaly (≥ 3 cm below the costal arch)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Histopathological criterion								
Evidence of macrophage hemophagocytosis in the bone marrow aspirate	No	Yes	No	No	–	No	Yes	Yes
Diagnostic rule								
The diagnosis of MAS requires the presence of any two or more laboratory criteria, or of any two or three or more clinical or laboratory criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

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