

Hemophagocytosis in the Acute Phase of Fatal Kawasaki Disease in a 4 Month-Old Girl

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Background: Kawasaki disease is a systemic vasculitis predominately affecting coronary arteries. Hemophagocytic lymphohistiocytosis can complicate the course of Kawasaki disease. Rare cases of secondary hemophagocytic lymphohistiocytosis occurring during the acute phase of Kawasaki disease have been reported.

Case Report: We report here a 4 month-old girl with diffuse coronary ectasia and secondary hemophago-

cytic lymphohistiocytosis occurring during the acute phase of incomplete Kawasaki disease.

Conclusion: Due to the large overlap in clinical symptoms, the presence of atypical findings for Kawasaki disease should suggest the possible diagnosis of hemophagocytic lymphohistiocytosis in these patients.

Keywords: Coronary artery dilatation, hemophagocytic lymphohistiocytosis, Kawasaki disease, macrophage activation syndrome

Kawasaki disease (KD) is a systemic vasculitis of unknown etiology predominately affecting medium-sized vessels such as the coronary arteries, which mainly involves infants and children (1). Hemophagocytic lymphohistiocytosis (HLH), is a systemic inflammatory disorder characterized by uncontrolled histiocytic proliferation, hemophagocytosis, macrophage activation, and up-regulation of inflammatory cytokines, which can complicate the course of KD (2-4). In most of the reported cases, HLH develop long after treatment or during the recurrent course of the disease (3-6). Herein we report a case with secondary HLH occurring during the acute phase of fatal KD in a 4 month-old girl.

CASE PRESENTATION

A previously healthy 4-month-old girl was admitted to a local hospital because of fever for 3 days and hospitalized for investigation and parenteral treatment. She was referred to our hospital because of prolonged fever and with a diagnosis of pneumonia at day 7 of febricity. Upon physical examination at admission, a fever of 39°C, hepatosplenomegaly and a 2/6 grading systolic ejection

murmur with normal chest auscultation findings were present. Her hemoglobin concentration was 9.6 gr/dL with a mean corpuscular volume of 77 fL, and her white blood cell (WBC) and platelet count were 25×10^3 and 919×10^3 , respectively. Liver and kidney function tests were normal, C-reactive protein (CRP) level was 127 mg/L (range 0-5mg/L) and erythrocyte sedimentation rate (ESR) was 70 mm/h (range 9-20) (Table 1). Chest x-ray demonstrated no infiltration. She was consulted to pediatric cardiology because of murmur and echocardiography demonstrated a large secundum type atrial septal defect and moderate pulmonary valve stenosis with normal coronary artery structure. The detailed history and physical examination for classical findings of Kawasaki disease revealed mild oropharyngeal findings without any conjunctivitis, skin rash, peripheral extremity findings and typical lymphadenopathy. She had hepatosplenomegaly on admission and tests for the investigation of possible diagnosis of HLH were performed. Ferritin level was 386 ng/mL, fibrinogen level was 544 mg/dL (range 238-498 mg/dL), and total triglyceride and cholesterol levels were in the normal range with a value of 121 and 104 mg/dL, respectively.

Fever continued and her clinical condition deteriorated in the following 3 days. The repeat blood tests demonstrated he-

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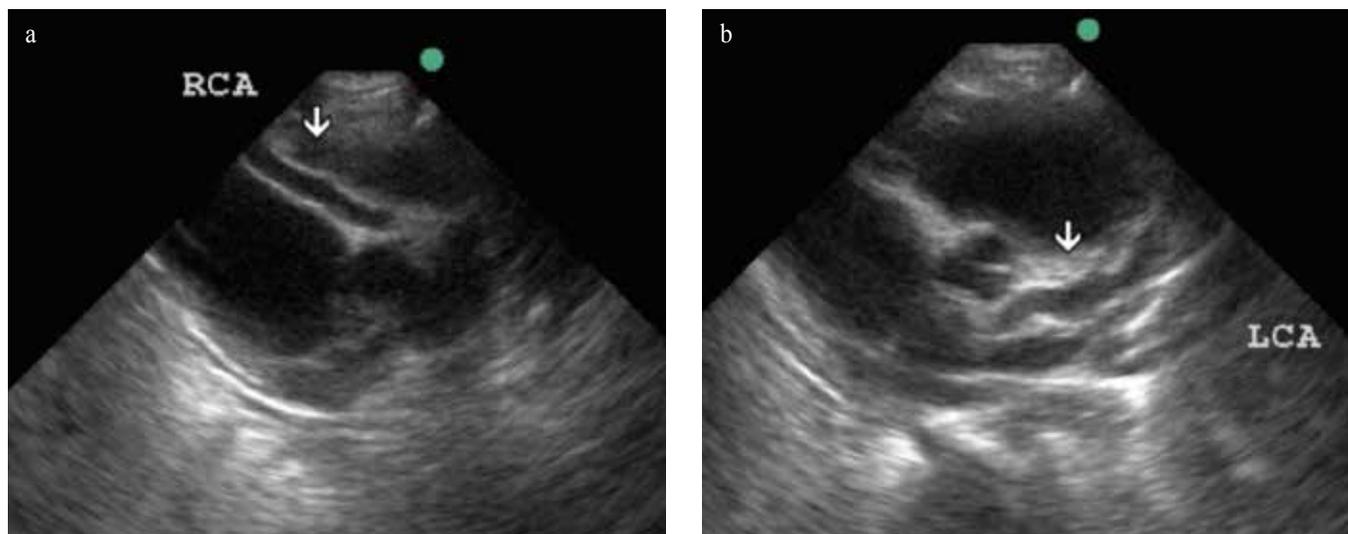


FIG. 1. a, b. Dilated right coronary artery with a diameter of 4.4 mm (a), dilated left coronary artery with an aneurysmal dilatation and a maximum diameter of 6.5 mm (b)

TABLE 1. Laboratory findings of the patient on admission (day 0) and 4th day of hospitalization

Test	Day 0	Day 4	Normal ranges
Hemoglobin (g/dL)	9.6	6.8	10.5-14
Hematocrit (%)	29.3	20.1	32-42
White blood cell ($\times 10^3$)	25	26	6-14
Platelet ($\times 10^3$)	919	92	150-400
C-reactive protein (mg/L)	127	158	0-5
Erythrocyte sedimentation rate (mm/h)	70	13	9-20
Fibrinogen (mg/dL)	544	199	238-498
Ferritin (ng/mL)	386	1320	7-140
Alanine aminotransferase (U/L)	8	28	13-45
Aspartate aminotransferase (U/L)	35	129	10-40
Lactate dehydrogenase (U/L)	484	436	180-430
Sodium (mmol/L)	134	131	139-146
Albumin/Globulin (g/dL)	3.2/2.5	2.3/3.8	
Triglyceride (mg/dL)	121	313	35-110

moglobin concentration of 6.8 gr/dL, WBC count of 26×10^3 , platelet count of 92×10^3 , CRP of 158 mg/L, and ESR of 13 mm/h (range 9.4-20.2), aspartate aminotransferase of 129 U/L and Na of 131 mmol/L, and albumin of 2.2 gr/dL (Table 1). Polymorphous skin rash developed during follow-up. A repeat echocardiogram was performed for KD and revealed diffuse coronary ectasia in both coronary arteries and fusiform dilatation with a maximum diameter of 6.7 mm and mild mitral regurgitation (Figure 1a, b). She was diagnosed as incomplete KD and intravenous immunoglobulin (Octagam: Octapharma AG; Lachen, Switzerland) with a dose of 2 g/kg and heparin (Nevparine, Mustafa Nevzat İlaç Sanayi; İstanbul, Turkey)

infusion was started on the 3rd day of admission. Her fever subsided after intravenous immunoglobulin transfusion. Creatinine kinase MB fraction and troponin levels were within the normal limit, whereas ferritin levels increased to 1320 ng/mL, fibrinogen levels decreased to 199 mg/dL and triglyceride levels increased to 313 mg/dL. An additional diagnosis of HLH secondary to KD was considered in the light of these findings and hepatosplenomegaly. She died on the 5th day of hospitalization shortly after realizing ST segment elevation attributed to possible myocardial infarction. The parents did not give permission for postmortem biopsy or bone marrow aspiration. Informed consent was obtained from the parents of the patient.

DISCUSSION

The diagnosis of KD is based on the clinical features of fever for at least 5 days together with at least 4 or 5 other features including rash, bilateral conjunctival injection, changes in peripheral extremities, lymphadenopathy and oropharyngeal changes (1). Our patient had only fever lacking the other features upon physical examination and a detailed history at admission to our hospital on the 7th day of febricity. Later, during the follow-up, maculopapular skin rash was detected. The diagnosis of incomplete KD could be made after repeat echocardiogram demonstrating diffuse ectasia and saccular aneurysm of the coronary arteries. Our patient had fever, minimal oropharyngeal changes and skin rash in terms of classical KD findings. As we know that the incomplete form is found in 30-56% of the KD patients under 1 year of age, the presence of thrombocytosis at admission could be a warning sign for the diagnosis of KD (7,8).

Our patient had hepatosplenomegaly and anemia at admission and later developed hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, hyponatremia and hypoalbuminemia, normal erythrocyte sedimentation rate with deepening anemia and decreasing platelet levels from 919×10^3 to 92×10^3 within 3 days of hospitalization. We were unable to measure the cytokine levels or natural killer cell activity in our center and perform postmortem investigations because of the absence of parental consent. However, according to the diagnostic criteria for HLH proposed in 2009, our patient meets the criteria for the diagnosis of HLH (2).

Hemophagocytic lymphohistiocytosis is another cause of prolonged fever in children which has a large overlap of clinical symptoms with KD; also, the co-existence of these two entities has been reported (3-5,9,10). The mechanism by which HLH develops in these patients is unknown. Hypercytokinemia, as a result of abnormal immune-regulation, has been proposed to contribute to the pathogenesis of both diseases (2,4).

In most of the published cases of HLH associated with KD, KD had a prolonged or recurrent course. Kang et al. found that the median interval between the first episode of KD and the onset of HLH was 13.3 days (4). Rare cases of secondary HLH occurring during the acute phase of KD have been reported (9,10). Our patient had some features of HLH at admission, with a normal coronary artery structure detected by echocardiography. The second echocardiographic examination demonstrated coronary anomaly, suggesting that our patient had the coexistence of HLH and KD, either HLH secondary to KD, or both as a result of an as yet unknown common triggering mechanism.

In the literature, the age of patients with HLH secondary to KD ranges between 7 weeks to adolescence. Although KD is rare after the age of 5, a significant number of reported cases of HLH associated with KD cases are in children over 5 years-old (3,5,6). In most of these cases, HLH developed after a latent period after KD. Our patient was 4 months-old and HLH occurred in the acute phase of the disease. A similar presentation was reported by Titze et al. (9) and Chen et al. (10) in 7 week-old and 18 month-old patients, respectively. These findings may suggest older age as a predisposing factor for HLH and the younger ages for earlier onset HLH in KD patients.

Our patient died suddenly due to possible myocardial infarction on the 12th day of febricity. Laboratory parameters indicative for severe HLH were lacking in our patient, so we did not attribute the cause of death to HLH. The two previously reported similar cases with HLH developing in the acute phase of KD also died because of myocardial infarction (9,10). On the other hand, HLH associated with KD occurring long after treatment or during recurrent course KD had a better prognosis, suggesting that the co-existence of these two entities give rise to poor prognosis.

In conclusion, due to the large overlap in clinical symptoms, both KD and HLH should be considered in children with overlapping symptoms. The presence of atypical findings for KD such as hepatosplenomegaly, hyperferritinemia, hypertriglyceridemia or prolonged fever should prompt the suspicion of a

possible diagnosis of HLH in these patients. Repeated echocardiograms for the suspected diagnosis of KD may be helpful in atypical presentations.

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from the parents of the patient who participated in this study.

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