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Macrophage Activation Syndrome as the First Impression of Kawasaki Disease; A Case Report

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Abstract

Introduction

Macrophage activation syndrome (MAS) is a rare and life-threatening complication of Kawasaki Disease (KD) that is usually diagnosed at the same time or after KD. We report a case of MAS as the initial manifestation of KD.

Case Report

A previously healthy 3-year old girl was admitted to the pediatric infectious diseases ward of Bahrami Children's Hospital, Tehran, Iran. She had a 3-day history of fever and lymphadenopathy which persisted despite antibiotic therapy. Patient's general condition gradually worsened and she developed loss of consciousness. After being diagnosed with MAS based on laboratory findings, she developed mucocutaneous manifestations of KD. She responded to methylprednisolone pulse therapy, intravenous immunoglobulin and dipyridamole. The follow-up at 2 weeks and 2 months showed no abnormal findings.

Conclusion

MAS may manifest even before the diagnosis of KD is made. Early recognition of MAS associated with KD and prompt treatment with corticosteroids can improve the outcome.

Key Words: Children, Iran, Macrophage Activation Syndrome, Kawasaki Disease.

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1- INTRODUCTION

Macrophage activation syndrome (MAS) is described as a rare and life-threatening complication of infections, malignancies, and autoimmune or auto-inflammatory conditions (1). It is characterized by an over-reaction of inflammatory pathways caused by a persistent activation of T lymphocytes and macrophages, leading to excessive cytokine secretion (2).

MAS manifests as non-resolving fever, organomegaly, impaired central nervous system function, pancytopenia, hyperferritinemia, increased lactate dehydrogenase, hypertriglyceridemia and decreased liver function (1). Systemic juvenile idiopathic arthritis (SJIA), and systemic lupus erythematous are among the most common pediatric rheumatologic conditions associated with MAS (3, 4).

Less frequently, MAS has been reported as a complication of Kawasaki disease (KD), presenting with persistent fever and resistance to intravenous immunoglobulin (IVIG) (5, 6). Most cases of KD-associated MAS are diagnosed at the same time or after the diagnosis of KD is made (7). In this article, we report a KD patient who presented with MAS.

2- CASE REPORTS

A previously healthy 3-year-old girl was admitted to the pediatric infectious diseases ward of Bahrami children's hospital, Tehran, Iran, with a 3-day history of fever and unilateral neck masses. On physical examination, she had high-grade fever (temperature, 39.2 ℃), and tender palpable lymph nodes on the left side of neck. There was no sign of abdominal organomegaly or arthritis and the rest of physical examination was non-significant. Blood tests showed white blood cell (WBC) count, 27300/mm3; hemoglobin, 10.3 g/dL; platelet count (PLT), 376,000/ml; total bilirubin, 1.07 mg/dL, direct bilirubin, 0.78 mg/dL; aspartate aminotransferase (AST), 21 IU/L; alanine aminotransferase (ALT), 30 IU/L; C-reactive protein (CRP), 76 mg/dL and erythrocyte sedimentation rate (ESR), 92 mm/hr. Ultrasonography of neck showed multiple reactive lymphadenopathy in the third zone of the left side of the neck suggestive of lymphadenitis. An infectious process was suggested and treatment with intravenous cloxacillin was initiated. On the 2nd day of admission, a generalized maculopapular skin rash developed; raising suspicions of drug reaction. Subsequently, cloxacillin was stopped and antibiotic regimen was changed to clindamycin and amikacin.

An antihistaminic agent was also prescribed. On the 3rd day of admission (6th day of fever), a 39.3 ℃ fever was still persistent, accompanied by gradual worsening of patient's general condition and decreasing level of consciousness. The patient had a mild tachycardia compatible with fever. Otherwise, she needed no hemodynamic support and had a normal blood pressure. Laboratory tests showed a decrease in all blood cell counts and an increase in CRP, liver transaminases, total bilirubin and direct bilirubin (**Table.1)**.

Additional tests were ordered, showing serum ferritin, 1960 ng/ml; D-dimer, 2.81 mcg/ml; triglycerides, 327 mg/dl; troponin I, < 0.01 ng/ml and serum albumin, 2.8 g/dL. The patient was suspected of MAS because of persistent fever, CNS dysfunction and laboratory findings compatible to the 2016 consensus criteria for MAS (1). Meanwhile, bilateral non-exudative conjunctivitis, cracked red lips and strawberry tongue also appeared (**Figure.1**). Abdominal ultrasound revealed a mild splenomegaly. Echocardiography showed mild bilateral coronary dilation (left main coronary artery diameter 3.2 mm and right coronary artery diameter 2 mm), and a mild mitral regurgitation. No parameters of ventricular

dysfunction were recorded. Based on the latest statement of American Heart Association (AHA) regarding diagnosis and management of KD (8), the patient was suspected of MAS associated with KD. Kawasaki disease shock syndrome (KDSS) was considered as differential diagnosis but was ruled-out based on normal blood pressure and paraclinical findings. Treatment with 3 doses of methylprednisolone pulse therapy was initiated. As the patient was proved to be glucose-6-phosphate dehydrogenase (G6PD) deficient, high dose acetylsalicylic acid (ASA) was contraindicated and she received one dose of IVIG alongside anti-platelet therapy with dipyridamole. Three days after initiation of therapy, fever subsided and after one week of treatment, patient's general condition and laboratory values were also improved (**Table.1**). On the 10th day of admission, we started oral glucocorticoid with prednisolone. Laboratory and echocardiographic findings improved and the patient was discharged after 15 days of hospitalization. Prednisolone was tapered during a course of 6 weeks. The follow-up at 2 weeks and 2 months showed no abnormal findings.

Table-1: Comparison of laboratory data at the time of admission, diagnosis of MAS and one week after treatment.

Parameters	On admission	On MAS diagnosis	One week after treatment
WBC count, /mm3	27300	14,000	12600
Hb, gr/dl	10.3	7.1	10.7
PLT count, /mm3	376,000	169,000	287,000
ESR, mm/h	80	77	80
CRP. mg/dl	76	133	95
AST, IU/L	21	53	37
ALT, IU/L	30	63	49
Total bilirubin, mg/dl	1.07	2.6	-
Direct bilirubin, mg/dl	0.78	1.9	-
Ferritin, ng/ml	-	1960	918
Triglyceride, mg/ml	-	327	-
Troponin I, ng/ml	-	<0.01	-
D-dimer, mcg/ml	-	2.81	0.84

MAS: Macrophage activation syndrome; WBC: White blood cell; Hb: Hemoglobin; PLT: platelet count; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: Alanine aminotransferase.

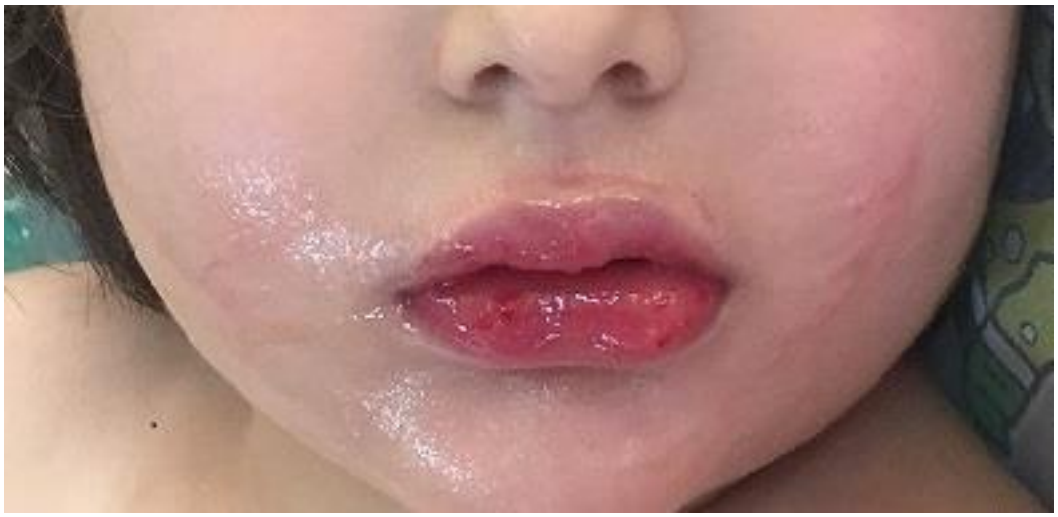

Fig.1: Red, cracked lips in a 3-year old girl with macrophage activation syndrome as the primary manifestation of Kawasaki Disease.

3- DISCUSSION

KD is an acute febrile systemic medium vessel vasculitis with an unknown etiology, mostly affecting children less than 5 years of age (8). It is characterized by fever for at least 5 days, accompanied by four out of five of the following manifestations: bilateral non-exudative conjunctivitis, oral mucosal changes, polymorphous rash, extremity changes, and cervical lymphadenopathy (9). MAS is an uncommon but life-threatening complication of KD, occurring in 1-2% of patients (5-7, 10). In most cases, MAS manifests as an exacerbation of KD despite standard treatment with ASA and IVIG (5-7). Less commonly, MAS may manifest before the diagnosis of KD is made (7). If not diagnosed and managed on time, MAS can lead to severe systemic complications and multi-organ failure in KD patients (1, 11). However, early diagnosis and treatment might be a challenge to physicians due to the overlap between the clinical and paraclinical manifestations of KD and MAS and the fact that there is no specific criteria for diagnosis of MAS in patients with KD (7). The diagnosis becomes more challenging when MAS occurs as a presenting manifestation of KD, as in our report. In our patient, typical mucocutaneous manifestations of KD (including bilateral non-exudative conjunctivitis, cracked red lips and strawberry tongue) appeared after the diagnosis of MAS was made. She primarily presented with a 3-day fever and lymphadenopathy and was later diagnosed with MAS as she showed non-remitting fever, lymphadenopathy, states of consciousness, hyperferritinemia, hypertriglyceridemia, hypoalbuminemia, elevated transaminases, increased D-dimers and decreasing blood cell counts. Similar findings have been reported by different studies of patients with KD and MAS (5-7, 10). KD complicated with MAS should also be differentiated from KDSS, a severe condition which occurs in 5-7% of KD patients (12, 13). Kanegaye et al. defined KDSS as hypotension and shock unrelated to IVIG administration during the acute phase of KD (13). It is found to be associated with lower PLT count and hemoglobin, higher CRP, positive D-dimer results, hypoalbuminemia and more-severe echocardiographic manifestations of ventricular dysfunction and coronary artery abnormalities (13, 14).

A very recent report described a pediatric patient with KD who did not respond to IVIG treatment and eventually developed hypotension and shock, accompanied by hypofibrinogenemia, hyperferritinemia, hypertriglyceridemia, bicytopenia, decreased natural killer cell activity and elevated soluble interleukin-2 receptor levels, leading to diagnosis of KDSS complicated with MAS (15). In our case, some of the laboratory findings in our case were similar to those in KDSS; however, the patient was normotensive and there was no need for fluid resuscitation or administration of vasoactive agents. She also had hyperferritinemia and hypertriglyceridemia which are not reported as characteristic parameters of KDSS patients (12-14).

Moreover, our patient's echocardiography showed mild coronary dilation and mitral regurgitation without ventricular dysfunction and cardiac troponin I, a marker of myocardial damage, was within the normal range. Although coronary involvement is seen in KD patients with MAS, it is found that MAS does not significantly induce coronary abnormalities (5, 16, 17). However, since persistent fever in KD patients is a risk factor for coronary artery pathologies and prolonged fever is a feature of MAS, the association between the two is considerable (18, 19). Among pediatric rheumatologic conditions, MAS occurs most commonly in SJIA (1-4).

On 2016, the following consensus diagnostic criteria was developed for MAS associated with SJIA: hyperferritinemia and any two of the following: decreased PLT count, increased AST level, low level of fibrinogen or hypertriglyceridemia (1). Since the laboratory findings of our patient corresponded to this criteria and considering that both KD (particularly incomplete KD), and SJIA might show similar manifestaions such as fever, rash, leukocytosis and increased CRP (20), SJIA was considered as a possible diagnosis. However, our patient did not have any sign of arthritis and the clinical manifestations were compatible with the AHA criteria of complete KD so the possibility was ruled out. The patient responded to treatment and her general condition and laboratory values were improved (Table.1).

4- CONCLUSION

Diagnosis of MAS in KD patients might be challenging as its manifestations might overlap with those of KD. We emphasize that MAS may manifest even before the diagnosis of KD is made. Early recognition of MAS associated with KD and prompt treatment with corticosteroids can improve the outcome.

5- CONFLICT OF INTEREST: None.

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