Case Report

Macrophage activation syndrome: A fatal complication of systemic-onset juvenile idiopathic arthritis – A case report

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ABSTRACT

Macrophage activation syndrome (MAS) is a life-threatening complication of systemic-onset juvenile idiopathic arthritis (sJIA) marked by the sudden onset of non-remitting high-grade fever, lymphadenopathy, hepatosplenomegaly, and profound depression in all three blood cell lines and elevated serum liver enzyme levels. Although MAS can occur in any systemic rheumatological disorder, it is most common in sJIA. In children with sJIA, the clinical picture may mimic sepsis or an exacerbation of the underlying disease. Early and aggressive immunosuppression is likely to benefit these patients. Hereby, we report a case of a 6-year-old male patient who presented with high-grade fever, joint pain, and rashes and was diagnosed as systemic-onset juvenile idiopathic arthritis with MAS.

Key words: Children, Macrophage activation syndrome, Systemic-onset juvenile idiopathic arthritis

Systemic-onset juvenile idiopathic arthritis (sJIA) is one of the most common pediatric chronic illnesses. The prevalence rate of the disease varies widely (3.5–5 cases/100,000). sJIA as a subtype includes about 10–15% of all juvenile idiopathic arthritis (JIA) [1]. sJIA is defined as arthritis affecting one or more joints usually in the juvenile age group (<16 years of age) with or preceded by fever of at least 2 weeks duration that is documented to be daily ("quotidian") for at least 3 days which may be associated with evanescent erythematous rash (salmon pink) or generalized lymph node enlargement or hepatosplenomegaly and serositis, with a total duration of illness of >6 weeks.

Macrophage activation syndrome (MAS) is a rare condition, reported to occur in the context of infectious, malignant, metabolic, and autoimmune diseases [2]. This potentially life-threatening complication has been found in approximately 7–13% of sJIA patients; although, subclinical MAS was found in bone marrow of more than 53% sJIA patients at the time of diagnosis [3]. However, diagnosis is often challenging as the disease can mimic infections and malignancies. We, hereby, report a case of a 6-year-old male patient who was diagnosed as sJIA with MAS. This case report highlights the association of MAS with sJIA and its clinical implications. Although this association is very rare, the pediatricians should be aware of the typical clinical presentation and laboratory investigations so as to timely diagnose and treat this complication.

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CASE REPORT

A 6-year-old male child presented with the complaints of pain and swelling over joints for the past 1 month, fever for 1 month, and rashes 1 month back after 3 days of joint swelling. The patient had high-grade fever more than 103°F for 1 month, almost continuous in nature and swelling of large joints knee, ankle, and shoulders, limiting the joint movements. There was a history of maculopapular rashes over trunk about 3 weeks ago, which lasted for about 5–6 days without any post-rash staining. There was no history of altered bowel or bladder habits, abdominal distension, bleeding from any site, or altered mentation. There was no history of delayed milestones, blood transfusions, diabetes, or thyroid disorder. No similar family history was present.

On examination, the child was conscious and well oriented. He was pale and febrile (103°F) with stable vitals. His weight was 14 kg (below −3 standard deviation [SD]), height was 102 cm (between −2 and −3 SD), and body mass index was 13.46 (between −1 and −2 SD of normal). His development was normal for the age. There were enlarged, non-tender, mobile lymph nodes present in the cervical region. On musculoskeletal examination, bilateral large joints including knee, ankle, and shoulder joints were tender and swollen but local temperature was not raised. Per abdomen examination revealed hepatosplenomegaly.

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Cardiovascular, respiratory, and central nervous system examinations were essentially normal.

On laboratory investigations, his hemoglobin (HB) was low (8 g/dl), total leukocyte count was 8500/mm^3 with 70% polymorphs, erythrocyte segmentation rate (ESR) was 50 mm, and platelet count was 250,000/mm^3. His C-reactive protein (CRP) was elevated (48.3 mg/l) and peripheral smear (PS) showed microcytic hypochromic anemia. Direct and indirect Coombs tests were negative and HB electrophoresis was normal. Other laboratory investigations including liver and renal function tests, serum electrolytes, lipid profile, coagulation profile, and arterial blood gas analysis were within normal limits. Various tests, done to rule out the infectious causes of fever, were normal including the rapid card test for malaria, Widal test, serology for Leptospira, Leishmania, and scrub typhus, urine routine and microscopy, blood and urine cultures, work-up for tuberculosis, HIV antibodies, HBs antigen, and anti-hepatitis C virus antibodies. His antinuclear antibodies (ANAs), rheumatoid factor (RF), and anti-dsDNA were negative and no LE cells were found in PS.

His fundus and slit lamp examination were also normal. Ultrasonography (USG) of the abdomen showed hepatosplenomegaly while echocardiography was normal. Lymph node biopsy showed diffuse follicular hyperplasia suggestive of a chronic inflammatory state. Radiological investigations included X-ray of chest, hands, and knees which were normal. USG of knee joint showed the surface irregularity of the medial part of the epiphysis of the left lower end of femur. On the basis of clinical presentation (fever, polyarthritis and rash, hepatosplenomegaly, and lymphadenopathy) and investigation findings showing high ESR and CRP values, with negative ANA and RF assays, a diagnosis of sJIA was made and naproxen was started. His anti-SS-A/Ro antibodies, anti-SS-B/La antibodies, and HLA-B27 were also negative.

In the next 7 days, fever was persisting and his HB fell down to 5 g/dl; for which, he received three packed red blood cell transfusions. His liver function tests were deranged with serum glutamic-oxaloacetic transaminase of 314 IU/L, serum glutamic-pyruvic transaminase of 221 IU/L, and serum bilirubin of 1.5 mg/dl (direct 0.9 mg/dl). His CRP increased further (78.3 mg/l) with leukopenia (3800/mm^3) and thrombocytopenia (110,000/mm^3). Urine examination showed the presence of albumin (2+) while serum triglycerides were elevated. The patient also had an episode of seizures, but no clinical signs of meningitis were present. Cerebrospinal fluid examination showed 10 cells (mononuclear), protein 57 mg/dl, and sugar 33 mg/dl. Seizures were controlled with intravenous antiepileptics (phenytoin).

In view of the persistence of high-grade fever, seizures, leukopenia, thrombocytopenia, and deranged liver functions, a possible association of MAS with sJIA was suspected and serum ferritin was done which was highly elevated (14,551 ng/ml). The presence elevated serum ferritin levels along with thrombocytopenia, elevated AST, and triglyceride levels satisfied the 2016 criteria for classification of MAS in sJIA; hence, the diagnosis was confirmed. The patient was treated with intravenous methylprednisolone at a dose of 30 mg/kg/day (five pulses). Methotrexate was started after a short course of prednisolone (2 mg/kg/day); however, the patient did not improve. His fever, leukopenia, and thrombocytopenia persisted and he succumbed after 26 days of admission.

DISCUSSION

JIA is a form of an autoimmune chronic arthritis which usually starts before the age of 16 years and often persists for more than 6 weeks. As per the "International League of Associations for Rheumatology" classification, it has seven different subtypes and sJIA is one of these subtypes. MAS is an important and potentially lethal complication of sJIA which was described way back in 1996. Association with MAS has also been reported in systemic lupus erythematosus, Kawasaki disease, and other vasculitides in addition to sJIA [4].

The characteristic findings of MAS are long duration of fever, enlarged spleen, and liver with elevated liver enzymes with abnormal coagulation tests, decrease in the platelet counts and ESR, hypofibrinogenemia, hyperferritinemia, and hypertriglyceridemia. The index case has all these features; however, the repeat bone marrow aspiration could not be done as patient's general condition was not good and parents did not give consent for the same. On bone marrow examination, the presence of characteristic hemophagocytosis infiltrations helps to make the diagnosis of MAS. Apart from bone marrow, these hemophagocytic changes can also be seen in other organs such as lymph node, spleen, and liver [5]. It is caused by excessive activation and proliferation of T-lymphocytes and macrophages.

The exact etiology of this syndrome remains unclear; however, it is characterized by an excessive immune response with no control mechanism. Nowadays, MAS in sJIA is considered to be an acquired or secondary hemophagocytic lymphohistiocytic disorder. Although MAS in systemic rheumatic diseases bears clinical and biological similarities to other hemophagocytic conditions, it is unique in some distinct ways: MAS occurs with varying degrees of severity, ranging from the moribund child having persistent high-grade fever, icterus, and significant organomegaly, along with pancytopenia, coagulopathy, hepatic, and renal derangement to a unwell child having persistent fever without significant organomegaly, and only a mildly depressed blood cell lines along with no or mild coagulopathy.

These patients are more likely to benefit when an aggressive immunosuppression is started at an early stage. The index was in moderately severe category; therefore, high dose of corticosteroid was started but the patient did not respond and further deteriorated and finally died. The course of MAS varies widely and is often unpredictable, which ranges from a single episode of mild disease to a chronic and relapsing severe polyarthritis along with extra-articular symptoms leading to a high morbidity and mortality [6]. As the presenting features of MAS often mimic the flare-up of the underlying disease, making a diagnosis is often challenging and diagnosis is usually delayed.

Therefore, a high index of clinical suspicion is very important which along with supportive laboratory and bone marrow findings can help making a diagnosis of MAS. An increasing thrombocytopenia is characteristic while changes in hemoglobin or leukocyte counts are more variable. On the other hand, elevation in transaminase levels and coagulation abnormalities may not be present at onset of MAS. Multisystem involvement is a poor prognostic factor [7].

An early diagnosis and institution of an appropriate treatment is crucial to decrease the very high mortality of this disease. High-dose corticosteroid treatment is the suggested initial treatment of choice in MAS [8]; however, some patients seem to be corticosteroid resistant [9] as seen in our case. Studies have shown an increased tumor necrosis factor (TNF)-α level, both in sJIA and in patients with MAS in systemic rheumatic diseases suggesting a beneficial role of anti-TNF therapy in the treatment of MAS [10,11].

CONCLUSION

MAS is a rare and potentially fulminant complication of childhood rheumatic disease, primarily systemic-onset juvenile rheumatoid arthritis. Although it is difficult to differentiate MAS from a disease flare, it is crucial to ensure optimal outcome, as delay in specific therapy may prove deleterious.

REFERENCES

1. Schneider R, Laxer RM. Systemic onset juvenile rheumatoid arthritis. Baillieres Clin Rheumatol 1998;12:245-71.
2. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Annu Rev Med 2012;63:233-46.
3. Behrens EM, Beukelman T, Paessler M, Cron RQ. Occult macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis. J Rheumatol 2007;34:1133-8.
4. Pringe A, Trail L, Ruperto N, Buoncompagni A, Loy A, Breda L, *et al*. Macrophage activation syndrome in juvenile systemic lupus erythematosus: An under-recognized complication? Lupus 2007;16:587-92.
5. Minoia F, Davì S, Horne A, Demirkaya E, Bovis F, Li C, *et al*. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: A multinational, multicenter study of 362 patients. Arthritis Rheumatol 2014;66:3160-9.
6. Boom V, Anton J, Lahdenne P, Quartier P, Ravelli A, Wulffraat NM, *et al*. Evidence-based diagnosis and treatment of macrophage activation syndrome in systemic juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2015;13:55.
7. Sawhney S, Woo P, Murray KJ. Macrophage activation syndrome: A potentially fatal complication of rheumatic disorders. Arch Dis Child 2001;85:421-6.
8. Hadchouel M, Prieur AM, Griscelli C. Acute hemorrhagic, hepatic, and neurologic manifestations in juvenile rheumatoid arthritis: Possible relationship to drugs or infection. J Pediatr 1985;106:561-6.
9. Favara BE, Feller AC, Paulli M, Jaffe ES, Weiss LM, Arico M, *et al*. Contemporary classification of histiocytic disorders. The WHO committee on histiocytic/reticulum cell proliferations. Reclassification working group of the histiocyte society. Med Pediatr Oncol 1997;29:157-66.
10. de Benedetti F, Pignatti P, Massa M, Sartirana P, Ravelli A, Cassani G, *et al*. Soluble tumour necrosis factor receptor levels reflect coagulation abnormalities in systemic juvenile chronic arthritis. Br J Rheumatol 1997;36:581-8.
11. Prahalad S, Bove KE, Dickens D, Lovell DJ, Grom AA. Etanercept in the treatment of macrophage activation syndrome. J Rheumatol 2001;28:2120-4.

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