IJBC 2017; 9(3): 93-96

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir

CASE REPORT

Macrophage Activation Syndrome as the First Presentation of Juvenile Idiopathic Arthritis

Hassan Abolghasemi[1,2], Ehsan Shahverdi[3,4*], Reyhaneh Niknam[5], Fatemeh Beiraghdar[2], Shirin Afkhami Fard[6]

[1]Pediatric Congenital Hematologic Disorders Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Pediatrics, Baqiyatallah University of Medical Sciences, Tehran, Iran
[3]Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran
[4]Blood and Cancer Research Center, MAHAK Pediatric Cancer Treatment and Research Center, Tehran, Iran
[5]School of Medicine, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran
[6]Mashhad Azad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

Article History:
Received: 16.03.2017
Accepted: 10.07.2017

Keywords:
Macrophage activation syndrome
Juvenile idiopathic arthritis
Hemophagocytic macrophage
First presentation

**Corresponding author:*
Ehsan Shahverdi,
Iranian Blood Transfusion Organization (IBTO) Tower, Hemat Exp.way, Tehran, Iran
Tel: +98 21 8860 1606
Fax: +98 21 8821 2105
Email: shahverdi_ehsan@yahoo.com

ABSTRACT

Macrophage activation syndrome (MAS) is a rare feature of rheumatic disorders in children and adolescence and its presentation as the first symptom of rheumatic disorders is very infrequent.

A 9-year-old girl, in whom MAS developed, was admitted to our Hospital in Tehran, Iran. She suffered from high grade fever and rash followed by multiple joint swelling months afterwards. Bone marrow aspiration and biopsy showed normocellular marrow with a cellularity of 90%. Benign-looking macrophages were remarkably increased; many of them showed hemophagocytic features. According to the presentation of long-standing fever and observation of "hemophagocytic macrophage" in bone marrow, MAS was diagnosed for the patient. Additionally, due to recurrent joint swelling in following months, she was diagnosed to be affected by "Juvenile Idiopathic Arhtritis" complicated by MAS.

MAS is a rare complication of rheumatic disorders which should be considered as the first presentation of rheumatic disorders in children specifically in those presenting with high fever, hepatosplenomegaly, lymphadenopathy and severe cytopenia.

Please cite this article as: Abolghasemi H, Shahverdi E, Niknam R, Beiraghdar F, Afkhami Fard S. Macrophage Activation Syndrome as the First Presentation of Juvenile Idiopathic Arthritis. IJBC 2017; 9(3): 93-96.

Introduction

Macrophage activation syndrome (MAS) is a life-threatening complication of rheumatic disorders, particularly systemic Juvenile Idiopathic Arthritis (JIA).[1] It is associated with uncontrolled activation of T lymphocytes and macrophages.[2] This uncontrolled activation of immune system develops in a group of diseases including infectious, neoplastic and rheumatic disorders.[3] Patients may become acutely ill with non-remitting high fever, hepatomegaly, splenomegaly, lymphadenopathy, pancytopenia, liver disease, coagulopathies and neurologic symptoms.[4] Macrophage activation syndrome is a rare feature of rheumatic disorders in children and its presentation as the first symptom of rheumatic disorders is rarer. Clinicians usually use the Hemophagocytic lymphohistiocytosis (HLH) criteria for diagnosis of MAS in practice. HLH should be considered in differential diagnosis of every pediatric patient with fever, splenomegaly, lymphadenopathy and pancytopenia.[5] Herein, we describe a 9-year-old girl who was diagnosed with MAS as the first presentation of systemic JIA.

Case Presentation

A 9-year-old girl was admitted with high grade fever

(T>39°C) of one month duration and bicytopenia. Past medical history and family history was unremarkable. During her admission, she developed limb weakness with a predominance of upper limbs and skin rash on her left leg. The patient was constantly febrile with pallor and cervical lymphadenopathy. Later on, hepatosplenomegaly, maculopapular rash on left leg and multiple joint swelling and tenderness became evident as the main physical findings. The patient met the criteria of American College of Rheumatology for the classification of Juvenile Idiopathic Arthritis and the diagnosis was applied accordingly.[6]

Complete blood count showed white blood cell count 12,000/ L (neutrophil 78%; lymphocyte 17%; monocyte 4.7%), hemoglobin 8.4 g/dL, hematocrit 27.2%, and platelet count 84,000/ L. Liver function tests were increased with AST 80 IU/L (up to 40) and ALT 45 IU/L (up to 41), serum albumin 2.7 g/dL (normal: 3.8-5.4 g/dL), Alkaline Phosphatase 286 IU/L (up to 240) and LDH 1431 IU/L (207-414). Renal function tests were normal. Other laboratory results were as follows: sodium 130 mEq/L, total cholesterol 114 mg/dL, Triglyceride 136 mg/dL, and serum ferritin >3000 ng/mL (7-140). Erythrocyte sedimentation rate was 54 mm/hr and C-reactive protein was 72.2 mg/dL (up to 5). Coagulation tests and disseminated intravascular coagulation profiles showed prothrombin time 13.4 sec (normal control 12 sec), activated partial thromboplastin time 26 sec (normal control 25-35sec) and fibrinogen 668 mg/dL (180-530).

Serological tests for viral infections such as Epstein-Barr virus, cytomegalovirus and herpes simplex virus, Wright and Widal agglutination tests were all negative. There was no evidence of viral infections or hepatitis. A Blood culture positive for Acinetobacter was reported. Complement and immunoglobulin levels were as follow: C3 171 mg/dL, C4 23 mg/dL, CH-50 95 mg/dL, IgG 1866 mg/dL, IgA 253 mg/dL, IgM, 127 mg/dL. Antinuclear antibody (ANA) was negative.

Bone marrow aspiration and biopsy showed normocellular marrow with a cellularity of 90%. Granulocytic and megakaryocytic lineages were normal in maturation, but erythroid lineage was hypoplastic. Benign-looking macrophages were remarkably increased; many of them showed hemophagocytic features (figure 1). As a result, she was diagnosed as having MAS complicating JIA; in fact, MAS was the first presentation of the underlying rheumatologic disease in the patient.

Intravenous dexamethasone (4 mg/day) was administered followed by IVIG (10 g/day). However, his symptoms and clinical signs did not improve. Fever was sustained and abnormal laboratory findings such as pancytopenia and transaminitis was not corrected. Consequently, immunosuppressive therapy with methylprednisolone (2 mg/kg/day for three days which was switched to oral prednisolone) and cyclosporine (2.5 mg/kg/day) was started. On the two next days after treatment with cyclosporine, fever disappeared. After 5 days, cytopenia recovered to hemoglobin 10 g/dL, hematocrit 36.1%, and platelet count 110000/ L. Liver function tests also normalized with AST 12 IU/L, ALT 26 IU/L, and serum ferritin decreased to 1100 ng/mL.

The patient then was referred to the rheumatology department while she was receiving treatment with cyclosporine and prednisolone. Cyclosporine discontinued after one year. The patient is in remission for both conditions (JIA and MAS) on 5 mg prednisolone every other day.

Discussion

MAS and its association with JIA was first defined by Hadchouel et al. in 1985.[7] Stephan et al. proposed the term MAS in 1993.[8] Based on literature review; up to 2008, more than 100 MAS cases have been reported worldwide.[9] The mortality rate is reported to be about 8% to 22%.[10] Early recognition and immediate treatment play an important role in prognosis of this entity. However, because of the lack of the established formal and universally accepted criteria, diagnosis of MAS is often difficult and confusing. Clinicians usually use the HLH criteria for MAS in practice as mutually are heterogeneous diseases, despite the fact that both originate from histolytic disorder and are recognized as a subtype of HLH.[11]

Currently, MAS is widely recognized as a severe

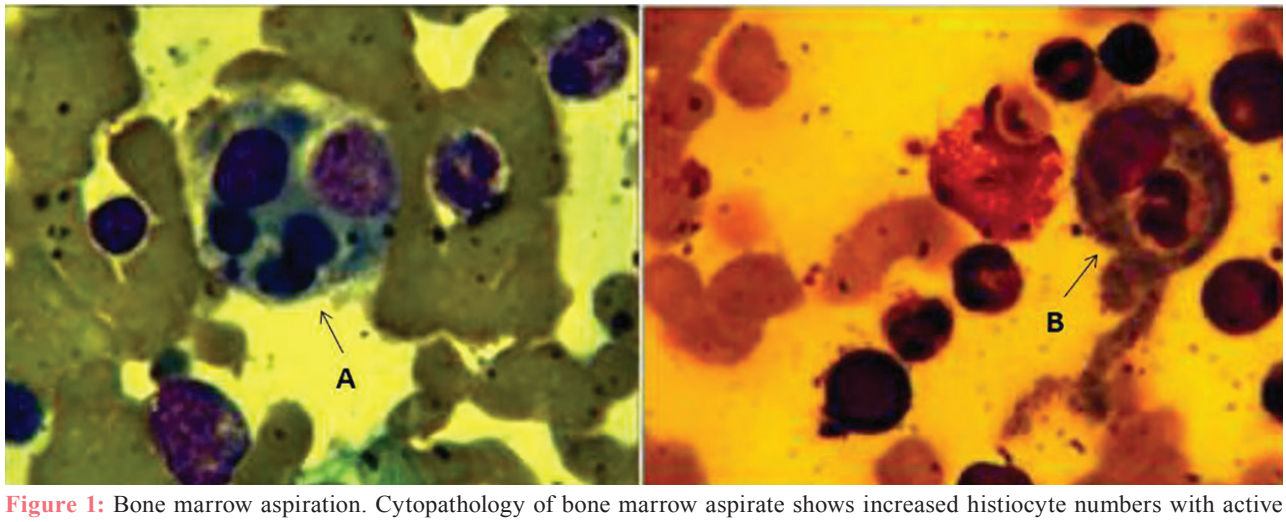

Figure 1: Bone marrow aspiration. Cytopathology of bone marrow aspirate shows increased histiocyte numbers with active hemophagocytosis (WrightGiemsa stain, ×400). **A**: A macrophage phagocytosing RBC. **B**: phagocytosis of neutrophil by macrophage.

and potentially fatal complication of JIA and has been commonly used to characterize the hemophagocytic syndrome that may develop in children with chronic rheumatic diseases specially systemic JIA.[7] MAS occurs during the clinical course of underlying Systemic JIA characterized by repetitive disease flares. Clinically, the pattern of fever and skin rash is not the same as JIA, although both entities share in common manifestations such as lymphadenopathy, hepatomegaly and splenomegaly.[1] Trigger factors may be drugs such as aspirin, nonsteroidal anti-inflammatory drugs, methotrexate and viral infections, specially Epstein-Barr virus and family of herpes viruses.[2] The diagnostic hallmark of MAS is hemophagocytosis in the bone marrow.[12] Our patient did not fulfill MAS criteria initially;[13] however, hemophagocytosis, which was found later in bone marrow aspirate was compatible with the diagnosis of MAS. The sensitivity and specificity of clinical and laboratory findings of MAS are defined.[14] The other variables that were in favor of MAS in our patient were serum ferritin ≥10,000 ng/mL, triglycerides ≥160 mg/dL, AST ≥40 IU/mL, ALT ≥40 IU/mL, gamma-glutamyl transferase ≥40 IU/mL and platelet count ≤150,000/L along with hepatomegaly and splenomegaly. Variables that did not prove sufficiently sensitive and specific included fever $\geq 38^0$ c, lymphadenopathy, neurological manifestations, arthritis, rash, WBC ≤4,000/ L, ESR ≤50 mm/hr, LDH ≥ 900 IU/mL, bilirubin ≥1.2 mg/dL, fibrinogen 668 mg/dL and serum sodium of ≤130 mEq/L.

Hyperferritinemia is also a notable marker of MAS development making early and aggressive immunosuppression possible.[15] In our case, clinical and laboratory features of MAS improved dramatically after the initiation of immunosuppressive treatments.

MAS is a fulminant complication generally presenting in an acute and dramatic way. A review of the cases reported in the literature showed that MAS usually occurs during JIA treatment, but in our case it occurred as the presenting manifestation of JIA.

Clinical manifestations of MAS is occult and hard to diagnose in absence of clinical suspicion. In a recent cohort study to differentiate MAS in JIA from familial HLH and virus-associated HLH, a notable number of patients diagnosed with MAS showed values for white blood cells (84%), neutrophils (77%), platelets (26%), and fibrinogen (71%), which were within or above the normal range.[16] The exact incidence of MAS in childhood systemic inflammatory disorders is not entirely clear.[17] Moradinejad et al.[18] reported an incidence of MAS to be 8.2% in Still's disease. Although it generally develops in the early phase of JIA, it has been known to occur up to 14 years after diagnosis.

Triggers like infections or medications may precede the onset of MAS[1]. In our case, blood culture was positive for acinetobacter that might have been acted as a trigger.

JIA complicated by MAS is associated with significant morbidity and mortality. High-dose corticosteroid is the initial treatment in MAS and cyclosporine is used for severe or corticosteroid-resistant cases[(4)]. Currently, a standard treatment protocol for MAS is still lacking. Our experience in this case confirmed the efficacy of cyclosporine therapy. Results point out that the appropriate cyclosporine serum level during the onset of MAS should be as high as 200 - 300 ng/ml. Also IVIG may play a crucial role in the treatment of recurrent MAS.

Conclusion

Macrophage activation syndrome is a rare complication of rheumatic disorders in children and should be considered in patients presenting with non-remitting high fever, hepatosplenomegaly, lymphadenopathy, severe cytopenia and liver disease. Interestingly, MAS and HLH both could be considered as differential diagnosis for lymphadenopathy, splenomegaly, and cytopenia; however, MAS can be observed as the first symptom of JIA in children and adolescence. In uncertain cases, a bone marrow aspiration for identification of haemophagocytosis is suggested.

Conflict of Interest: None declared.

References

1. Sawhney S, Woo P, Murray K. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. Arch Dis Child. 2001; 85(5):421-6. PubMed PMID: 11668110. PubMed Central PMCID: PMC1718981.
2. Ravelli A. Macrophage activation syndrome. Curr Opin Rheumatol. 2002;14(5):548-52. PubMed PMID: 12192253
3. Grom AA, Passo M. Macrophage activation syndrome in systemic juvenile rheumatoid arthritis. J Pediatr. 1996; 129(5):630-2. PubMed PMID: 8917224.
4. Ravelli A, De Benedetti F, Viola S, Martini A. Macrophage activation syndrome in systemic juvenile rheumatoid arthritis successfully treated with cyclosporine. J Pediatr. 1996; 128(2):275-8. PubMed PMID: 8636829.
5. Abolghasemi H, Shahverdi E, Dolatimehr F, Oghli R. Autoimmune lymphoproliferative syndrome misdiagnosed as hemophagocytic lymphohistiocytosis; a case report. IJBC. 2015; 7(4):198-200.
6. Brewer EJ Jr, Bass J, Baum J, Cassidy JT, Fink C, Jacobs J, et al. Current proposed revision of JRA Criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Section of The Arthritis Foundation. Arthritis Rheum. 1977; 20(2 Suppl):195-9. PubMed PMID: 318120.
7. 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(4):561-6. PubMed PMID: 3981309.
8. Stéphan JL, Zeller J, Hubert P, Herbelin C, Dayer JM, Prieur AM. Macrophage activation syndrome and rheumatic disease in childhood: a report of four new cases. Clin Exp Rheumatol. 1993; 11(4):451-6. PubMed PMID: 8403593.
9. Tristano AG. Macrophage activation syndrome: a

frequent but under-diagnosed complication associated with rheumatic diseases. Med Sci Monit. 2008; 14(3):RA27-36. PubMed PMID: 18301366.
10. Behrens EM, Beukelman T, Paessler M, Cron RQ. Occult macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis. J Rheumatol. 2007; 34(5):1133-8. PubMed PMID: 17343315.
11. Janka GE, Schneider EM. Modern management of children with haemophagocytic lymphohistiocytosis. Br J Haematol. 2004; 124(1):4-14. PubMed PMID: 14675403.
12. You CR, Kim HR, Yoon CH, Lee SH, Park SH, Kim HY. Macrophage activation syndrome in juvenile rheumatoid arthritis successfully treated with cyclosporine A: a case report. J Korean Med Sci. 2006;21(6):1124-7.
13. Ravelli A, Magni-Manzoni S, Pistorio A, Besana C, Foti T, Ruperto N, et al. Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Pediatr. 2005; 146(5):598-604. doi: 10.1016/j.jpeds.2004.12.016. PubMed PMID: 15870661.
14. Ravelli A, Magni-Manzoni S, Foti T, Besana C, Felici E, Trail L, et al. Macrophage activation syndrome in juvenile idiopathic arthritis: towards the development of diagnostic guidelines. Arthritis Rheum. 2001;44(Suppl):166.
15. Kim JD, Na DJ, Kang JH, Lee KS, Sung KY. A case of systemic-onset juvenile rheumatoid arthritis with multiple complications. J Korean Pediatr Soc. 1988;31(7):948-52.
16. Lehmberg K, Pink I, Eulenburg C, Beutel K, Maul-Pavicic A, Janka G. Differentiating macrophage activation syndrome in systemic juvenile idiopathic arthritis from other forms of hemophagocytic lymphohistiocytosis. J Pediatr. 2013; 162(6):1245-51. doi: 10.1016/j.jpeds.2012.11.081. PubMed PMID: 23333131.
17. Ravelli A, Caria MC, Buratti S, Malattia C, Temporini F, Martini A. Methotrexate as a possible trigger of macrophage activation syndrome in systemic juvenile idiopathic arthritis. J Rheumatol. 2001; 28(4):865-7. PubMed PMID: 11327264.
18. Moradinejad M, Ziaee V. The incidence of macrophage activation syndrome in children with rheumatic disorders. Minerva pediatrica. 2011;63(6):459-66. PubMed PMID: 22075800.