

Macrophage Activation Syndrome Associated with Hepatitis a Virus in a Child with Systemic Onset Juvenile Idiopathic Arthritis – A Case Report .

Mohammad Imnul Islam¹, Mohammed Mahbubul Islam², Manik Kumar Taliukder³, Shahana Rahman⁴

¹Associate Professor, Department of Paediatrics, ²Assistant Professor, department of Paediatrics, ³Assistant Professor, department of Paediatrics , ⁴Professor of Paediatrics, department of Paediatrics BSMMU.

Abstract:

Macrophage Activation Syndrome (MAS) is a rare but a grave complication of systemic onset juvenile idiopathic arthritis (SOJIA). It occurs as a result of immune dysfunction of macrophages and T lymphocyte. A twelve-year old boy diagnosed case of SOJIA presented with high grade fever, diffuse abdominal pain, vomiting and jaundice. He had high ALT, abnormal coagulation profile and Anti HAV IgM was positive. He had also high ferritin and triglyceride level which were very much suggestive for MAS. Infection especially Epstein Barr Virus, Herpes viruses and drugs are the common triggers for the development of MAS in association with SOJIA patients. MAS associated with hepatitis A virus are very rare. Only a few case reports are available in the literature. Considering its rarity and grave prognosis we are reporting a case of hepatitis A associated Macrophages Activation Syndrome in a systemic onset juvenile idiopathic arthritis.

Keywords: Macrophage Activation Syndrome, Hepatitis A infection, Systemic onset juvenile idiopathic arthritis.

[BSMMU J 2015 ; 8 (2) : 121-124]

Introduction:

Macrophage activation syndrome (MAS) is a clinical condition caused by the excessive activation and proliferation of lymphocytes and macrophages.¹ It is considered as a form of secondary hemophagocytic lymphohistiocytosis occurring in a patient with a rheumatic condition, predominantly systemic onset juvenile idiopathic arthritis (SOJIA)². Infections (especially herpes viruses) and drugs have been identified as the most common triggers for this association³. Few cases of Hepatitis A virus (HAV)-associated reactive lymphohistiocytosis and MAS have been reported in adults and in children from different countries^{4,5}. We are reporting a case of MAS associated with HAV infection in a child with systemic onset JIA from Bangladesh.

Case Report:

“H”, a 12-year-old boy came in the pediatric ward of Bangabandhu Sheikh Mujib Medical University

(BSMMU), Dhaka, Bangladesh in June 2014 with yellow coloration of eyes and skin for 14 days. He had high grade continued fever for same duration. He also had associated diffuse abdominal pain and vomiting. “H” was diagnosed as a case of SOJIA since his 3 years of age and was on regular treatment and follow up. He was declared as clinical remission on medication (CRM) in September 2013 with methotrexate, hydroxychloroquine and thalidomide. Prior to that, he had several episodes of relapse and remission during last 9 years. He had no history of bleeding manifestation, altered consciousness, urinary complaints and ingestion of any offending drugs.

On examination, the boy was moderately malnourished (weight for age Z score: -1.8). Vitals were stable except temperature, which was 103° F. He was deeply icteric, febrile but very much cooperative. Abdomen was diffusely tender and distended. There was tender hepatomegaly. Spleen was just palpable. Other systemic examinations including neurological examination were normal. Investigations showed normal blood count, moderately high ESR (45 mm in the 1st hour), high ALT (619 U/L), high serum bilirubin (7.1 mg/dl), high prothrombin time

Corresponding Author: Dr Mohammad Imnul Islam, Associate Professor Department of Paediatrics, BSMMU, Dhaka, Bangladesh. M- 01711393049. Email : imon27@gmail.com.

(INR: 1.66) and positive immunoglobulin M (IgM) anti-HAV antibody.

“H” was diagnosed as a case of ‘Systemic JIA with Acute Viral Hepatitis A infection’. All the medications including MTX, hydroxychloroquine and thalidomide were discontinued. He was treated with antibiotic (I/v ceftriaxone), lactulose and vitamin K1, H2 blockers and supportive measures for viral hepatitis. After admission and management, his physical wellbeing and appetite improved but fever and jaundice did not improve. Prothrombin time became normal (INR 1:1) Subsequently, on 2nd week of admission “H” became very toxic. Temperature was persistently more than 105^o F. He developed ankle edema and mild ascites, but neurological examinations were normal. There was further increase of hepatosplenomegaly.

Repeat investigations showed low hemoglobin (6.6 gm/dl) and low ESR (10 mm in 1st hour). Total count was also low (3960/cmm) with low platelet count (126000/cmm). This time his serum bilirubin was 16.5 mg/dl (direct bilirubin was 12mg/dl), SGPT was 1681 U/L and alkaline phosphatase was 2200 U/L. Prothrombin time - INR was found as 1.95 and APTT was also prolonged. Serum albumin of “H” was markedly reduced (19 gm/dl). Urine and blood culture results were negative. ICT for malaria was also negative.

As the general condition of the boy including fever, appetite, edema and general wellbeing was gradually deteriorating, investigations were done to exclude MAS. Serum ferritin level was very high (11037µgm/lit), triglyceride level was also high (316mg/dl) and FDP was high-400µgm/dl (normal <10 µgm/dl). Bone marrow study did not find any evidence of haemophagocytosis.

From clinical presentation and investigations, we diagnosed “H” as a case of Hepatitis A associated with Macrophage Activation Syndrome (MAS) in a systemic onset JIA patients. He was managed by intra-venous injection of methylprednisolone for 3 consecutive days (30 mg/kg/day) followed by oral steroid (2mg/kg/day) in divided doses and higher antibiotics (Meropenem and Vancomycin). “H” was also given supportive manage-

ment of Hepatitis A including lactulose, H-2 blocker and ursodeoxycholic acid. Fever resolved immediately. But he was still icteric, very weak and ALT was quite high. Dose of prednisolone was gradually tapered off after normalization of blood count and serum ferritin level at 2 weeks. “H” was discharged after proper counseling after 30 days of hospital stay with advice of follow up. Clinical and biochemical disturbances improved very slowly over a period of next 2 months and finally normalized. Now the boy is on regular follow up and getting treatment with oral steroid (tapering dose), H 2 blocker, calcium plus vitamin D and vitamin B-complex.

Discussion:

A previously healthy young boy who was a known case of systemic onset JIA (On Remission) developed acute hepatitis induced by HAV, characterized by hepatomegaly, jaundice, vomiting and high continued fever. Subsequent development of edema, ascities, and persistence of fever, further enlargement of liver and spleen and sudden onset of relative cytopenias alerted us to the possibility of MAS. Hypertriglyceridemia, hypoalbuminemia, high level of fibrin degradation product (FDP) and very high level of serum ferritin supported the diagnosis. It has been suggested that measurement of ferritin levels over time may assist in the diagnosis of MAS and represent a useful indicator of disease activity, treatment response, and prognosis⁶.

Patient improved after administration of high dose intravenous methyl prednisolone therapy. So far known, this was the first reported cases of hepatitis A-associated MAS occurring in young boy with a diagnosis of systemic onset JIA in Bangladesh.

MAS is a severe and potentially fatal complication of systemic onset JIA. Excessive activation of macrophage and T cells leading to an overwhelming inflammatory reaction manifested as fever, hepatosplenomegaly, lymphadenopathy, severe cytopenias, serious liver disease and coagulopathy are characteristic features of MAS. Neurological symptoms can complicate and sometimes dominate the clinical course.⁷ The laboratory findings including cytopenias particularly thrombocytopenia,

elevated liver enzymes, hypertriglyceridemia, hyperferritinemia and hypofibrinogenemia are the essential criteria for diagnosing MAS. Numerous, well differentiated macrophages phagocytosing hematopoietic elements, the pathognomic features of MAS are often found in bone marrow^{7,8}.

Our patient "H" had cytopenias including gross thrombocytopenia, elevated liver enzyme (ALT), hypertriglyceridemia, hyperferritinemia and very high level of FDP. We did not find hemophagocytic macrophages in the bone marrow in our patient. Though marrow finding is pathognomic for MAS, it might not be constantly detectable at the onset and might be lacking in 40% cases⁹.

Many reports suggested that hamophagocytic macrophages may accumulate in tissues like liver, lymph node or lungs other than bone marrow. In some reports additional biopsies were performed due to initial failure to detect hamophagocytes in the bone marrow.⁸ In our case, additional tissue biopsy was not possible due to lack of cooperation from parental side. For formulation of the diagnosis, preliminary diagnostic guidelines for MAS in SJIA proposed by Ravelli, et al were followed here¹⁰.

A triggering event such as infection or modification of drug therapy can be identified in about half of MAS episodes. It can be precipitated by virtually any infectious agent: viral, bacterial, fungal and even parasitic. Viral illness, particularly EBV and other member of herpes family are mostly reported¹¹.

Hepatitis A is a highly prevalent disease in developing countries¹². Hepatitis A-induced hemophagocytic syndrome in children with systemic JIA is previously reported from other countries⁵. It was also reported in previously healthy adults¹³.

MAS appears to occur with varying degree of severity. It ranges from moribund child with persistent high grade fever with significant organomegaly, icterus and suggestive laboratory parameters to the unwell child with persistent fever, no significant organomegaly, a relative drop in blood cell line and mild if any coagulopathy⁸. The presentation and course in our patient showed typical

features for MAS associated with HAV infection. Impending hepatic failure, observed in this case, has been reported in patients with very severe forms of MAS⁵.

MAS is a life threatening condition. So prompt administration of aggressive treatment is necessary; which is likely to achieve reversal of coagulation abnormalities and cytopenias. Injection methyl prednisolone pulse therapy for three consecutive days followed by high dose oral steroid is the main stay of the treatment. After normalization of hematological and coagulation abnormalities, steroids should be tapered off slowly⁷. Parental administration of cyclosporine A has been shown to be effective in patients with steroid resistant MAS¹¹.

MAS carry a grave prognosis, with mortality rates varying between 20% and 30%.³ Our patient received current standard therapy for MAS, leading to complete remission of MAS. HAV may have triggered severe MAS in this case, which is a potentially lethal complication of systemic onset JIA.

MAS is not a common problem in our daily practice. But it is essential to recognize early and start intensive therapy; otherwise it can cause very high mortality. So, a very high index of suspicion is important in a systemic JIA patient, who develops any infection or suddenly deteriorates. Necessary investigations also need to be done if MAS is suspected; as without laboratory results, diagnosis cannot be made with certainty.

References :

01. Ravelli A. Macrophage activation syndrome. *Curr Opin Rheumatol* 2002; 14:548-52.
02. Athreya BH. Is macrophage activation syndrome a new entity? [editorial]. *Clin Exp Rheumatol* 2002; 20:121-3.
03. Stéphan JL, Koné-Paut I, Galanbrun C, Mouy R, Bader-Meunier B, Pricur AM. Reactive haemophagocytic syndrome in children with inflammatory disorders. A retrospective study of 24 patients. *Rheumatology Oxford* 2001; 40:1285-92.
04. McPeake JR, Hirst WJ, Brind AM, Williams R. Hepatitis A causing a second episode of virus-associated haemophagocytic lymphohistiocytosis in a patient with Still's disease. *J Med Virol* 1993; 39:173-5.
05. Russo AGR, Rosenzweig SD, Katsicas MM. Hepatitis A associated with Macrophage Activation Syndrome (MAS) in a Systemic onset JIA patients: report of 2 cases. *J Rheumatol* 2008;

- 35:166-68.
06. Davi S, Ravelli A, Ruperto N, Martini A, Novelli A, Cron RQ et al. Toward the development of new diagnostic criteria for Macrophage activation syndrome. *Ann Paediatr Rheum* 2012; 1:1-7
 07. Grom AA. Macrophage Activation Syndrome. In Cassidy JT, Petty RE, Laxer RM, Lindsley CB editors. *Textbook of pediatric rheumatology*. 6th ed. Philadelphia: Elsevier Saunders, 2011; 674-81.
 08. Sawhney S, Woo P, Murry KJ. Macrophage Activation Syndrome: a potentially fatal complication of rheumatic disorder. *Arch Dis Child* 2001; 85: 421-26.
 09. Stabile A, Bertoni B, Ansuini V, Torraca ILa, Salli A, Rigante D. The clinical spectrum and treatment options of Macrophage Activation Syndrome in the paediatric age. *European Review for Medical and Pharmacological Sciences* 2006; 10: 53-59.
 10. 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; 146:598-604.
 11. Ciocca M. Clinical course and consequences of hepatitis A infection. *Vaccine* 2000; 18 Suppl 1:S71-S74.
 12. Onaga M, Hayashi K, Nishimagi T, Nagata k, Uto H, Kubuki Y et al. A case of acute hepatitis A with marked hemophagocytosis in bone marrow. *Hepato Res* 2000; 17: 205-11.
 13. Prieur A-M, Stéphan JL. Macrophage activation syndrome in children with joint diseases. *Rev Rheum Eng Ed* 1994; 61:385-388.
 14. Ravelli A, De Benedetti F, Viola S, Martini A. Macrophage activation syndrome in Systemic juvenile rheumatoid arthritis successfully treated with cyclosporine. *J Pediatr* 1996; 128:275-278.