Original Research Paper

Volume - 13 | Issue - 07 | July - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Internal Medicine

TWO CASE REPORTS ON MACROPHAGE ACTIVATION SYNDROME IN NEWLY DIAGNOSED SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

Dr. C. Arshad Akeel* MD(Gen Med), FRCP (Glasg), FRCP (Ireland),FRCP (Edin), FACP (USA), ABTM (USA), FCCP (USA), FICA(USA), Senior Consultant, Department of Internal Medicine, Apollo Hospitals, Greams Road, Chennai *Corresponding Author

Dr. Sri Lasya Karjala DNB General Medicine Resident, Apollo Hospitals, Greams Road, Chennai.

ABSTRACT Macrophage activation syndrome(MAS) is a life-threatening immunological disorder. It has varied clinical, biological and histological characteristics. It is often difficult to differentiate from sepsis or disseminated intravascular coagulation(DIC). Here, we present a recently diagnosed case of systemic lupus erythematosus(SLE) who developed macrophage activation syndrome and another case of a patient, whose initial presentation of SLE, was with macrophage activation syndrome. Both the patients were young females who had chronic fever and later developed acute worsening of their clinical condition. They were treated with supportive care, steroids and immunosuppressants. One of the patients had a good recovery and the other patient was lost to follow up. The authors would like to emphasize on the association of this disorder with rheumatological diseases like SLE and on the need for the early recognition and treatment of this disorder, to decrease the mortality.

KEYWORDS : Hemophagic Lymphohistiocytosis, Macrophage activation syndrome, Systemic lupus erythematosus, Secondary HLH, A Case Report

INTRODUCTION:

Macrophage activation syndrome(MAS) is a subset of secondary hemophagocytic lymphocytosis(sHLH). It is an acute severe, often lethal immunological condition. Primary HLH is idiopathic and secondary is usually due to rheumatological conditions, infections or drugs.[1] Usually, patients present with high grade fever, hepatosplenomegaly, lymphadenopathy, hemorrhagic manifestations. The clinical picture may be very similar to sepsis or disseminated intravascular coagulation(DIC).[2] Early diagnosis and treatment are the key to reducing mortality. Currently, diagnosis can be arrived at, by using the scoring systems(H-Score) and treatment is mainly with steroids and supportive care.

Case Report:

Case 1:

This 17 year old asian female presented to the hospital with complaints of intermittent fever, rash and pain in the small joints of hands for 6 months. She had multiple lymphadenopathy on examination. She had anemia. Her blood and urine cultures did not reveal any growth.

A left inguinal lymph node biopsy was done and histopathological examination of the sample was inconclusive. It showed no evidence of infection. A trans-thoracic echocardiogram was done and it was normal. A computed tomography(CT) of the chest was done and it showed atelectasis, lymphadenopathy and fibrotic strands in both lungs. A bronchial wash was done and it was negative for infection. Her antinuclear antibody was 2+ positive. AntidsDNA, AntiCCP, RA factor and extended nuclear antigens were all negative. Her complement levels were normal. She was diagnosed with systemic lupus erythematosus and started on steroids, hydroxychloroquine and sulfasalazine. She was symptomatically better and she was discharged.

Next day, the patient developed new onset high grade fever spikes, recurrent vomiting, myalgia and transient rash all over the body predominantly over bilateral upper limbs. On examination, she had fever, tachycardia and hypotension. Her investigations revealed a sudden drop in hemoglobin and lymphocytosis. Her ferritin and triglyceride levels were elevated. She was given one unit of packed red cell transfusion. She was advised to undergo endoscopy but the patient and her family were not willing. A bone marrow examination was done and it showed hemophagocytosis (see figure 1).

She was diagnosed to have secondary hemophagocytic-lymphohistiocytosis as per H-score (see table1) and she was started on high dose steroids, mycophenolate mofetil, hydroxychloroquine under broad spectrum antibiotic cover. With supportive measures, the patient showed good improvement.

Case 2

This 22 year old asian female presented with intermittent low grade fever, non bilious vomiting, weight loss and loss of appetite for five months. She also had abdominal pain, amenorrhea, cough with hemoptysis for 5 months and developed bilateral lower limb swelling over 1 month. She was previously evaluated elsewhere with CT chest and it showed bilateral nodular lesions in lower lobes. She was found to have lymphadenopathy and fine needle aspiration cytology of the cervical lymph nodes revealed reactive lymphadenitis. She was admitted to our hospital for further management and care.

She was pale, dehydrated and icteric. Her baseline parameters showed metabolic acidosis, severe hyponatremia, pancytopenia and deranged liver function tests. A CT abdomen was done and it showed bulky pancreas with peripancreatic fluid collection. During hospital stay, she became hypothermic, hypotensive, hypoxic and had a sudden drop in GCS. She was intubated and autoimmune workup was done. ANA was 4+ positive. Anti dsDNA, Anti SSA (Ro) and AntiRo52 were positive. Her C3 and C4 levels were low. Her ferritin, triglycerides were elevated. Bone marrow examination could not be done as the patient was not willing. She was diagnosed with secondary HLH as per H-score (see table1).

She was started on intravenous steroid therapy. The patient developed anuria and required continuous renal replacement therapy. She had a drop in hemoglobin and developed coagulopathy. She was given multiple units of packed red cells and fresh frozen plasma transfusions. Her condition continued to remain critical and the family wanted to continue further care in a local hospital. She was discharged against medical advice and she was lost to follow up.

Table1: Comparison of H-score in Case 1 and Case 2 sHLH-Secondary Hemophagocytic-lymphohistiocytosis

Parameters	Number of points (criteria for scoring)	Case 1	Case 2
Known underlying immunosuppression	0 (no) or 18 (yes)	0	0
Temperature (°C)	Temperature (°C) 0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)	33	33
Organomegaly	Organomegaly 0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)	38	23
No. of cytopenias	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)	0	34
Ferritin (ng/mL)	0 (<2,000), 35 (2,000–6,000), or 50 (>6,000)	50	50
Triglyceride (mmoles/liter)	0 (<1.5), 44 (1.5–4), or 64 (>4)	64	64

Fibrinogen (g/L)	0 (>2.5) or 30 (≤2.5)	0	0
Serum glutamic oxaloacetic transaminase (IU/L)	0 (<30) or 19 (≥30)	19	19
Hemophagocytosis features on bone marrow aspirate	0 (no) or 35 (yes)	35	0
Total H-score		239	239
Probability of sHLH		98-99%	98-99%

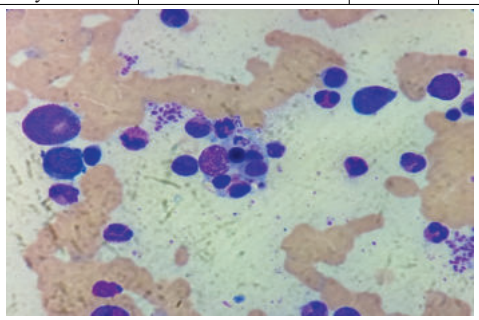

Image1: Leishman's stain of bone marrow aspirate depicting hemophagocytosis in case 1 patient

DISCUSSION

Macrophage activation syndrome is an acute, often lethal, severe inflammatory disorder. It can be primary (idiopathic) or secondary. Primary HLH is usually inherited and secondary is due to rheumatic diseases, infections, malignancies or drugs. Rheumatic diseases which are known to be associated with secondary HLH are systemic juvenile idiopathic arthritis, systemic lupus erythematosus, kawasaki disease and juvenile dermatomyositis. Drugs like non-steroidal inflammatory drugs, sulfasalazine, gold, methotrexate, adalimumab, etoposide and tocilizumab can trigger sHLH.[3] Infections that can precipitate HLH are brucellosis, rickettsial disease, Q fever, Epstein Barr virus, avian influenza subtype H5N1, visceral leishmaniasis and Histoplasmosis.[1] In our patients, the cause was identified as systemic lupus erythematosus. In SLE, the prevalence of MAS was between 0.9 to 4.6% and nearly 9.4% in patients with hepatic dysfunction.[2]

The pathophysiology of HLH has been commonly hypothesized as a defect in lymphocyte cytolytic function. Primary HLH is associated with defects in genes PRF1 and UNC13D. Predominantly IL-6 mediated pro-inflammatory cytokine environment is known to cause diminished natural killer cell cytolytic function, thereby prolonging the cell to cell interaction. This further amplifies the pro-inflammatory cytokine cascade resulting in hemophagocytosis.[4]

Clinical and laboratory features of MAS include sustained fever, pancytopenia, liver dysfunction, fibrinolytic consumptive coagulopathy and hyperferritinemia. Hemophagocytosis with CD163+ staining may be present in bone marrow, liver and spleen. But it is neither sensitive nor specific for HLH. Soluble interleukin 2 receptor alpha chain(sCD25) and soluble CD163(sCD163) have higher sensitivity and specificity for detection of MAS, but these tests are available only in selected sites.[4] Most of the patients are usually diagnosed based on HLH-2004 criteria.

The disease has a mortality of 5-35% in patients with SLE and mortality can increase up to 50% in adults.[3] It needs early treatment with supportive care and high dose intravenous corticosteroids. Cyclosporine and intravenous immunoglobulin can be added, if there is no initial response. Anakinra is documented to be rapidly effective in its treatment. Hematologists recommend treatment with etoposide, but it can cause organ toxicity and bone marrow suppression. Anti-thymocyte globulin can be tried in refractory cases.[5]

In conclusion, macrophage activation syndrome is a life-threatening clinical condition which requires early diagnosis to prevent death. Clinicians should be vigilant about this syndrome, especially in patients with rheumatic diseases. It has clinical similarity with DIC, but certain criteria like H score can help in the diagnosis. It needs early treatment with steroids along with supportive care.

Declaration:
Funding- None

Conflict Of Interest- None

Ethical Approval- Not required

REFERENCES:

1. Cascio A, Pernice LM, Barberi G, Delfino D, Biondo C, Beninati C, Mancuso G, Rodriguez-Morales AJ, Iaria C. Secondary hemophagocytic lymphohistiocytosis in zoonoses. A systematic review. Eur Rev Med Pharmacol Sci. 2012 Oct;16(10):1324-37. PMID: 23104648.
2. Lerkvaleekul B, Vilaiyuk S. Macrophage activation syndrome: early diagnosis is key. Open Access Rheumatol. 2018 Aug 31;10:117-128. doi: 10.2147/OARRR.S151013. PMID: 30214327; PMCID: PMC6124446.
3. Bojan A, Parvu A, Zsoldos IA, Torok T, Farcas AD. Macrophage activation syndrome: A diagnostic challenge (Review). Exp Ther Med. 2021 Aug;22(2):904. doi: 10.3892/etm.2021.10336. Epub 2021 Jun 24. PMID: 34257717; PMCID: PMC 8243343.
4. Crayne CB, Albeituni S, Nichols KE, Cron RQ. The Immunology of Macrophage Activation Syndrome. Front Immunol. 2019 Feb 1;10:119. doi: 10.3389/fimmu. 2019.00119. PMID: 30774631; PMCID: PMC6367262.
5. Ravelli A, Davì S, Minoia F, Martini A, Cron RQ. Macrophage Activation Syndrome. Hematol Oncol Clin North Am. 2015 Oct;29(5):927-41. doi: 10.1016/ j.hoc.2015.06.010. Epub 2015 Aug 25. PMID: 26461152.