CASE REPORT

MACROPHAGE ACTIVATION SYNDROME ASSOCIATED WITH ADULT ONSET STILL'S DISEASE

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Macrophage activation syndrome (MAS) is a potentially lethal complication of chronic rheumatological conditions like ankylosing spondylitis, rheumatoid arthritis, and adult-onset Still's disease (AOSD). It is a multisystem inflammatory syndrome caused by immense cytokine release from activated lymphocytes and macrophages. We give an account of the incidence of a twenty years old Asian girl suffering from non-remitting fever and an evanescent rash for last ten weeks. Physical examination and laboratory work-up suggested high grade fever, pancytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia and impaired liver function. Bone marrow biopsy was also done. It showed active hemophagocytosis. She was diagnosed as a case of Macrophage Activation Syndrome associated with Adult Onset Still's disease. She was treated with high dose steroids and cyclosporine and recovered completely.

Keywords: Adult Onset Still's disease; Macrophage Activation Syndrome; hemophagocytosis; Bone Marrow Biopsy

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INTRODUCTION

Macrophage activation syndrome is classified among the group of hemophagocyticlymphohistiocytosis (HLH), which includes familial HLH and secondary HLH. Several causes precipitate secondary HLH, including infection, drugs, malignancy and rheumatic disorder.[1] Macrophage activation syndrome belongs to the secondary or reactive hemophagocytic syndromes and has been classified as a secondary form of secondary hemophagocyticlypmhohistiocytosis.[2] Studies have shown theproportion of macrophage activation syndrome in adult onset Still's disease is reported to be approximately 12%.[3]

It has an acute and dramatic process which can complicate other conditions like systemic juvenile idiopathic arthritis (sJIA), adult-onset Still's disease, systemic lupus erythematosus, drug reactions, and viral infections.[4,5] Excessive activation and proliferation of T-lymphocytes and macrophages are the main characteristics of MAS. Hypercytokinemia, including high levels of interleukin, interferon and tumour necrosis factor are also associated with MAS.[6,7]

This study aimed to report a successfully treated case of macrophage activation syndrome which is linked with adult onset Still's disease.

CASE REPORT

A twenty-one years old girl with a 10-week history of non-remitting high-grade fever presented to our department. The fever was usually higher in the evening, continuous with no response to antipyretics. Fever was accompanied with malaise and a diffuse (evanescent) maculopapular skin rash over her face and trunk. Her past medical history was unremarkable for rheumatic diseases, severe infections and immunodeficiency. There was no family history of rheumatic diseases either. She gave history of one episode of a tonic-clonic seizure, lasting for 2 to 3 minutes, along with loss of consciousness, tongue bite and up-rolling of eyes. She had been drowsy since admission. Before admission to our department, patient was being investigated and treated for endocarditis at another hospital where blood cultures, ECG and Echocardiography were done. She was on treatment with antipyretics, inj. gentamycin and inj. vancomycin.

Her clinical examination showed pyrexia of 102° F, blood pressure of 100/70 mmHg, heart rate of 115 beats per minute, respiratory rate of 24 breaths per minute and an oxygen saturation of 98% at ambient air. She had a widespread rash, more prominent on face and torso along with pale conjunctivae, bilateral pulmonary basal crackles and fluctuating level of sensorium. Abdomen was soft and non-tender. There was no synovitis and no pericardial frictions rub. We started instrumental and laboratory tests to rule out the presence of autoimmune, infectious, or neoplastic disease. Repeated blood and urine cultures were done. A thorough infection screen including Hepatitis B and C, T-spot for T.B, R.A factor, ANA, ANCA, Brucella IgG and IgM, ASO titre revealed negative results.

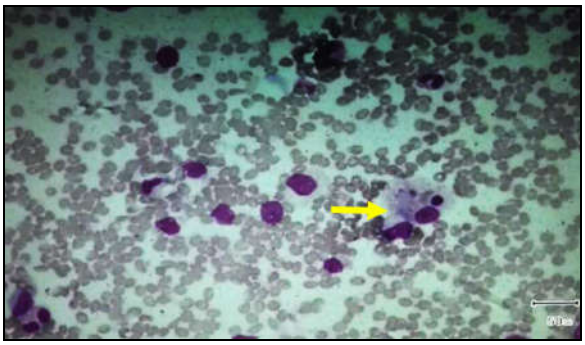

Figure-1: Hemophagocytic macrophage containing red blood cells, platelet and cell debris

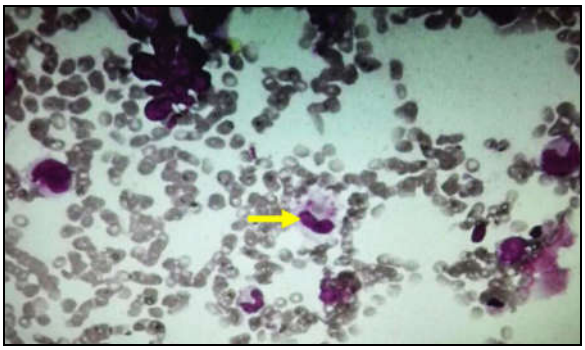

Figure-2: Hemophagocytic macrophage containing red blood cell, platelet and cell debris

Table-1: Laboratory data

Laboratory Results	Before diagnosis	At the time of diagnosis of MAS	After treatment for MAS	Reference range
Hb	8.5g/dl	9.4 g/dl	10.2 g/dl	12.0–16.0 g/dl
TLC	4.8/uL	3300/uL	66,00/uL	4000–11,000/uL
Platelets	162,000/uL	91,000/uL	277,000/uL	150–450/uL
Ferritin	-----	>200,000 ng/ml	172 ng/ml	10–120 ng/ml
Triglycerides	-----	357 mg/dl	278 mg/dl	30–200 mg/dl
Fibrinogen	-----	214 mg/dl	250 mg/dl	200–400 mg/dl
ALT	-----	106 U/L	32 U/L	5–40 U/L
AST	-----	580U/L	27 U/L	5–40 U/L
GGT	-----	162/L	41U/L	5–50 U/L
LDH	-----	4026 U/L	102U/L	250 U/L
ESR	-----	42 mm/1st hour	25 mm/1st hour	10-20mm/1st hour
CRP	-----	47.6 mg/L	2.6 mg/L	<5 mg/L
Albumin	-----	2.9 g/dl	3.6 g/dl	3.5–5.0 g/dl
Serum Calcium	8.3 g/dl	7.3 g/dl	8.1 g/dl	8.5–10.5 g/dl
Serum Sodium	136 mmol/L	124 mmol/L	140 mmol/L	135–145 mmol/L

The levels of blood urea, nitrogen, serum creatinine and total bilirubin were within normal range. On urinalysis, pus cells 12–15/HPF, RBCs 8-10/HPF and proteins +++ were found. Repeated urine culture showed Extensively Drug Resistant *Escherichia coli* >100,000 CFU/ml. The patient was subsequently started on nitrofurantoin 100 mg per oral 6 hourly according to antibiotic sensitivity report.

Two collections of negative blood cultures and no evidence of vegetations on echocardiography ruled out endocarditis. Patient was advised transthoracic oesophageal echocardiography. Bone Marrow aspiration revealed increased number of macrophages and hemophagocytosis. A diagnosis of Still's disease was made on the basis of these findings. According to EULAR/ACR 2016 criteria[8], the classification of MAS is based on following features:

Ferritin level greater than 684 ng/ml
And any two of the following:
Platelet count ≤180×10^9/litter
Aspartate aminotransferase level greater than 48 units/litter
Triglycerides more than 156 mg/dl
Fibrinogen ≤360 mg/dl

In the beginning, patient was given intravenous methylprednisolone 30mg twice every day for a period of four days along with oral hydrocholoroquine. After 4 days, hydrocholoroquine was stopped, and 100 mg cyclosporine twice daily was started while continuing methylprednisolone. Injectable steroids were substituted with oral prednisolone later along with one packed cell blood transfusion. Her condition became stable on this therapy. Intravenous immunoglobulins could not be given because the patient could not manage to pay for them. On the day of discharge, her Hb was 10.2 g/dl, platelets 277, 000/uL, TLC 6600/uL. Patient was discharged from the hospital and is now under follow-up at the outpatient clinic.

After discharge from the hospital, she has been following regularly in Rheumatology outpatient department. Initially, she was followed every two weeks and now being followed every two months.

Clinically, she is doing well. She is afebrile, joint pains are no more there. She is on cyclosporine, slowly tapering and currently on 100 mg twice daily dose. Steroids were tapered over a period of two months. Latest follow up lab work showed WBC count 7800/uL, platelet count 454000/uL, haemoglobin 12.8g/dL, ESR 23mm/1st hour, CRP 2

mg/L, Blood urea nitrogen 3.8 mg/dl, creatinine 0.4 mg/dl, serum ferritin 67ng/ml. Liver function tests, urine examination normal.

DISCUSSION

We have described a patient with clinical and laboratory features of Macrophage Activation Syndrome (MAS). Accurately diagnosing this disease is a challenge. We founded our diagnosis on the latest diagnostic criteria for MAS.[8]

To date, the pathogenesis of MAS is relatively unknown. It is considered an intensive systemic inflammatory reaction, resulting from a massive dysregulation of macrophage–lymphocyte interactions. These interactions provoke an increase in the levels of several cytokines, particularly TNF-α, M-CSF receptors, interleukin- (IL-) 1, IL-6, and interferon gamma- (IFN-)γ.[9]

Several therapeutic options are available but the foundation of treatment is steroids. An intravenous methylprednisolone pulse therapy (e.g., 30 mg/kg for a period of three consecutive days) followed by 2–3 mg/kg per day is the most common schedule.[10] In a setting of MAS associated with Still's disease, successful treatment with intravenous immunoglobulin, methotrexate, cyclosporine or a cyclophosphamide has been reported in anecdotal case series with or without the use of steroids.[11,12] In our case, intravenous immunoglobulins could not be used due to patients' inability to afford them. A lot of evidences enlighten the noticeable role of IL-1 as a driver of sJIA as well as Still's disease.[13,14] On the other hand, some reports suggested it as a trigger for MAS.[15] We treated our patient with cyclosporine due to non-availability IL1RA in Pakistan.

The Haematology department provided us with the bone marrow aspiration pictures showing many well differentiated macrophages actively engulfing hematopoietic cells including erythroblasts and platelets.

We encountered several technical hitches while diagnosing this patient. One of the hurdles was non-availability of biologics and some other workups like virology screening, viral cultures and frequent levels of cyclosporine which would have made our task easier in infective screening of the patient and in monitoring of the cyclosporine levels during treatment. Inability to pay for intravenous immunoglobulins and plasmapheresis which was our first choice of treatment was also one of the limitations in diagnosis. With multidisciplinary approach and readily available facilities, the diagnosis of MAS associated with Adult Onset Stills's Disease was made magnificently.

Macrophage activation syndrome associated with AOSD is a serious complication with high mortality (more than 50%), if not timely diagnosed and treated. So high index of suspicion should be there if patient is showing no response to treatment or any blood cell line is dropping and patient is fulfilling the other criteria of Macrophage Activation Syndrome. Early recognitions and treatment can save many lives in patients with AOSD.

To the best of our knowledge, till this time no case of Macrophage Activation Syndrome associated with AOSD from Pakistan has been reported.

Our report clarified that Macrophage Activation Syndrome can occur within a few days of overt manifestations of the primary disease. The patient rapidly developed symptoms of Macrophage Activation Syndrome. Moreover, our report illustrates that MAS might be a predictor for rheumatic diseases. Eventually, our patient made a successful clinical remission from MAS features.

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