

Enteric fever with macrophage activation syndrome

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ABSTRACT

Macrophage activation syndrome is a rare and potentially life threatening condition occur in association with infections, malignancies, autoimmune diseases and drugs. We report a rare case of enteric fever with macrophage activation syndrome. A 15 years old female presented with high grade fever, abdominal pain, nausea and vomiting, loose stool and malaise. Investigation revealed persistent thrombocytopenia, raised liver enzymes, dearranged renal function, typhi dot IgM positive, blood culture show salmonella typhi growth. In bone marrow aspiration was show hemophagocytosis. Macrophage activation syndrome is associated with a high mortality and fatal outcome if undiagnosed and untreated.

INTRODUCTION

Enteric fever is commonly encountered in Indian subcontinent, with different complications and outcomes. However, enteric fever complicated by macrophage activation syndrome (MAS) is very rarely reported.¹ It is potentially fatal disorder of normal but overactive macrophage, in which severe systemic inflammatory reaction characterised by over activation and proliferation of T cells and macrophages, with multiple organ involvement and multiorgan dysfunction. MAS belongs to a group of histiocytic disorders collectively known as hemophagocytic lymphohistiocytosis (HLH). A high index of suspicion is needed when patients presented with fever unresponsive to antibiotics, general fatigue, pancytopenia of unknown origin, abnormal liver function and elevated ferritin. We report a case of a previously healthy young female with enteric fever and MAS.

CASE HISTORY

A 15 years previously healthy female was admitted with complaints of fever since 5 days which was high grade with chills, intermittent associated with pain in upper abdomen, non radiating, dull aching, non colicky, off and on since 3 days with loose stools, semi-formed consistency, non-bloody, 5-6 episodes/day since 3 days, associated with nausea and vomiting, non-bloody, non-projectile, non-bilious which contain food particles in it 3-4 episodes/day for 2 days associated with generalised weakness since 2 days.

General examination revealed Icterus, mild dehydration, high grade fever, Pulse rate-90/min, BP- 100/60mmHg on right arm sitting position, Respiratory Rate- 20/min. Systemic examination revealed Soft, tender hepatomegaly, liver 4 cm below costal margin, splenomegaly. Heart sounds were normally heard and no murmur. There was no sign of meningeal irritation, no focal neurological deficit and normal fundus. Chest examination was normal.

At the time of admission investigation reveal, Blood examination revealed Haemoglobin of 10.1 gm/dl, TLC- 2700/cumm, DLC of N/L/M-87/11/2, PCV-19.25%, Platelet count-1,50,000/cumm, MCV-82.3 fl, ESR-44 mm/1st hour, Serum bilirubin (total)-5.11mg/dl, Serum bilirubin (direct)-4.11. SGOT-69 IU/L, SGPT-50 IU/L, serum alkaline phosphatase -298 IU/L, Gamma GT-151 IU/L, BUN-22 mg/dl, Serum creatinine-2.41 mg/dl, urine examination show mild proteinuria with pus cells 20-25 WBC/hpf, X-ray chest was normal, Typhidot IgM was positive, Dengue NS1 antigen was negative, Dengue serology was negative, malarial serology was negative, Blood culture show growth of salmonella typhi, urine culture was sterile, USG abdomen- hepatomegaly with splenomegaly, initially treatment started with injection ceftriaxone, injection ciprofloxacin, intravenous antipyretics, for diarrhea probiotic sachet and racecadotril is given, patient had persistent fever for which further investigation is sent anti HCV antibody non reactive, HbSAg was non reactive, anti HEV was negative, anti HAV was negative, Leptospira IgM and IgG was negative, Serum CRP was 2.72, G6PD Screening normal, patient developed rashes and itching all over body with breathing

difficulty for which antiallergic and nebulisation with salbutamol and ipratropium bromide is given she show decreasing trend of haemoglobin, platelet count and total leukocyte count along with increasing trend of SGOT, SGPT and bilirubin(total and direct) . Peripheral smear of blood show pancytopenia and repeat investigation show decreasing total leukocyte count, platelet count and haemoglobin inspite of treatment. Relevant reference sent to gastroenterologist for dearranged Liver function test and haematologist in view of pancytopenia and patient is further investigated. Serum ferritin level was >2000. Serum triglyceride was 205.8 mg/dl, fibrinogen level was 210.7 mg/dl, Patient received one unit of platelet apheresis in view of severe thrombocytopenia (platelet count -15,000/cumm) but platelet count was still 17,000/cumm. Patient was suspected as hemophagocytic syndrome and further investigated. Bone marrow aspiration and biopsy is done by haematologist which show numerous well differentiated macrophages actively phagocytosing hematopoietic cells. For which injection dexamethasone is given and patient was improved, her platelet count was 45,000/cumm, Hb was 8.9 gm/dl on next day and increased further and fever subsided.

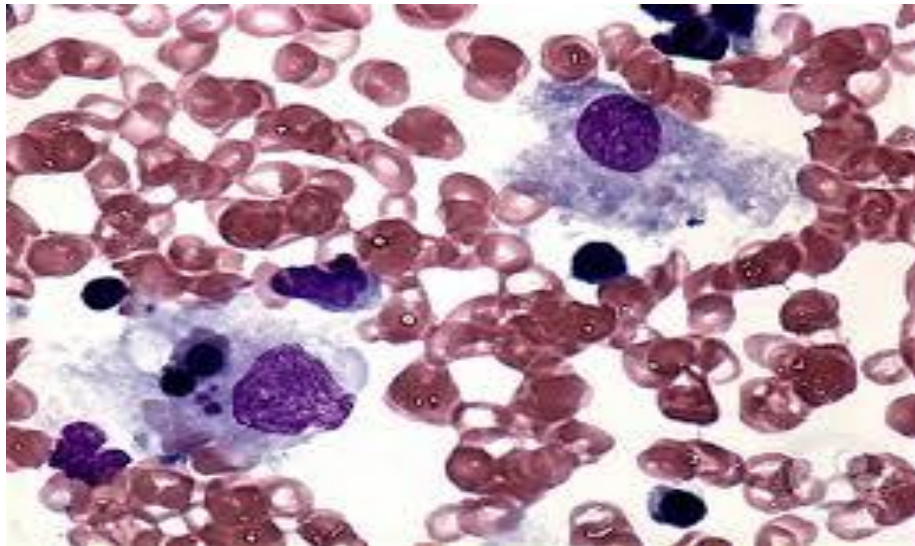


Figure1. Macrophage showing hemophagocytosis in bone marrow aspirate

Day	Hb (gm/dl)	TLC	Platelet count (/cumm)	Blood urea nitrogen (mg/dl)	Serum creatinine (mg/dl)	Serum bilirubin (total) (mg/dl)	Serum bilirubin (Direct) (mg/dl)	SGO T (IU/L)	SGPT (IU/L)	ESR (mm/1 st hr)
Day 1	10.1	2700	1,50,000	25	2.41	5.11	4.11	69	50.8	44
Day 2	9.0		1,06,000	34	2.14	5.67	4.65			
Day 3	8.9		84,000	26	1.23	6.10	4.28			
Day 4	8.7	1300	74,000	12	0.80	7.36	4.54	119.6	99.6	50
Day 6	7.9	1100	65000			6.10	4.27	126.8	89.6	45
Day 8	7.6	2000	17,000			2.22	1.11	80.7	92.4	
Day 9	7.9	3100	15,000							85
Day 10	8.9	2500	45,000		0.45	1.91	1.32			80
Day 11	8.5	3800	79,000			1.75	1.25			
Day 12	9.1	5900	2,87,000			1.61	1.30			65

DISCUSSION

Macrophage activation syndrome was first described by Hadchouel et al. In 1985 in 7 patients of rheumatic arthritis, six of whom had systemic onset juvenile idiopathic arthritis (So-JIA).² The term “macrophage activation syndrome” was eventually introduced in 1993 by Stephan et al.

It is a rare and potentially fatal disease of normal but overactive histiocytes. MAS belongs to a group of histiocytic disorders collectively known as hemophagocytic lymphohistiocytosis (HLH). It is of two types - Primary HLH or familial mainly seen in younger age group and Secondary HLH or reactive, which occurs after strong immunologic activation - systemic infection (virus, bacteria, and protozoa), autoimmune disorders, or underlying malignancy.³ The hallmark of this syndrome is severe impairment of cytotoxic activity of natural killer (NK) cells and T lymphocytes which is mediated through release of cytolytic granules containing perforins.³

There are no laid down criteria for the diagnosis of MAS. Diagnosis of HLH be based upon the following criteria, which were used in the HLH-2004 trial:

Five of the following eight findings:⁴

- Fever $\geq 38.5^{\circ}\text{C}$
- Splenomegaly
- Peripheral blood cytopenia, with at least two of the following: hemoglobin < 9 g/dL (for infants < 4 weeks, hemoglobin < 10 g/dL); platelets $< 100,000/\text{microL}$; absolute neutrophil count $< 1000/\text{microL}$
- Hypertriglyceridemia (fasting triglycerides > 265 mg/dL) and/or hypofibrinogenemia (fibrinogen < 150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent NK cell activity
- Ferritin > 500 ng/mL
- Elevated soluble CD25 (soluble IL-2 receptor alpha) two standard deviations above age-adjusted laboratory-specific norms

Evidence of hemophagocytosis may not be present in early stages however its absence does not rule out MAS. Measurement of serum ferritin levels can be a useful indicator of diagnosis and severity of illness.

Contrary to what is reported in the literature ESR was elevated

MAS should be tackled as a medical emergency and should be treated in an ICU setup. Treatment includes appropriate antibiotics and chemotherapeutic agents, corticosteroids, and immunosuppressives such as cyclosporin, cyclophosphamide, and IV immunoglobulin.^{5,6} Two types of agents are used i) to interrupt the function of activated macrophages and histiocytes. These are etoposide, steroid, and high dose IV immunoglobulin ii) to interrupt the function of activated lymphocytes (T cells) - These are steroids, cyclosporin, and antithymocyte globulin. Since TNF- α levels are elevated in MAS anti TNF- α agents have been used to achieve quick symptomatic relief. A commonly followed protocol consists of corticosteroids and etoposide with or without cyclosporin A. In MAS corticosteroid treatment (high dose oral or methyl prednisolone pulses) is usually effective. Cyclosporin A, as also other therapeutic measures for secondary HLH, have been used. Indications for these would be uncontrolled fever, progressive pancytopenia, DIC, and impending organ failure. Patients with HIV associated HLH, have been treated successfully with highly active anti-retroviral therapy.⁷

CONCLUSION

This case report is presented to emphasise that high index of suspicion is needed to make a diagnosis of MAS. In patient with enteric fever, pancytopenia and raised hepatic enzymes not responding to therapy should arouse suspicion of MAS. Serum ferritin level, serum LDH and urgent bone marrow examination must be done to confirm the diagnosis. Treatment should be aggressive as the mortality and fatal outcome is high.

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