Macrophage Activation Syndrome

MK Kumar*, MK Suresh**, D Dalus***

Abstract
Macrophage Activation Syndrome is a rare and potentially fatal disease, to be considered in patients with a SIRS like clinical presentation. Falling ESR and hyperferritinemia in the appropriate clinical setting can be the greatest clues. We report a case in which a female admitted with fever and rash, initially had systemic inflammatory response syndrome (SIRS) like clinical presentation, but eventually proved to be a rare case of fatal Macrophage Activation Syndrome. ©

INTRODUCTION
Hemophagocytic lymphohistiocytosis (HLH) or Macrophage Activation Syndrome is a rare and potentially fatal disorder of normal but overactive histiocytes. In Hemophagocytic lymphohistiocytosis there is an overwhelming activation of normal T cells andmacrophages which can cause clinical and hematological alterations. The clinical presentation is in many aspects similar to the so-called SIRS. And death is inevitable in the absence of treatment. In this case report, a female admitted with fever and rash, initially had SIRS like clinical presentation, but eventually proved to be a rare case of fatal Macrophage Activation Syndrome. This case is presented to enlighten the physicians regarding the clinical entity of Macrophage Activation Syndrome to be suspected when patients presented with fever unresponsive to antibiotics, general fatigue, falling ESR, pancytopenia of unknown origin and liver dysfunction with elevated ferritin.

CASE HISTORY
A 57 year old housewife was referred to our institution with the history of fever, rash and bodyache of 2 weeks duration. Since 2 months she has been having progressive dyspnoea and low grade fever. Investigations done in a local hospital were negative and she was put on bronchodilators with the diagnosis of allergic bronchitis. She improved with the medications. Two weeks back her symptoms worsened and she developed fever and rash. She then got admitted in another local institution where she took a course of antibiotics. There, her general condition deteriorated and she was referred.

On examination, she was conscious, febrile (39°C) and tachypnoeic. She was having generalised edema, conjunctival congestion, ecchymosis and icterus. She was not cyanosed and there was no demonstrable flap. Pulse was 112/mt and arterial pressure of 100 / 60 mm Hg. Patient had splenomegaly and free fluid. There were fine crepitations involving the left lung base. Heart sounds were normally heard and no murmur. There was no sign of meningeal irritation, no focal neurological deficit and normal fundus.

On investigating, urine examination showed protein trace and a few pus cells. Blood examination revealed Hb of 8.5 gm%; TC of 3500/cmm; DC of P 75 L 20 E 5, ESR of 8 mm/1 st hr (repeated ESR was 6 mm/1 st hr). We noticed that the ESR done 2 weeks back was 54 mm/ 1 hr. She was having progressive fall in the ESR with serial monitoring. She had thrombocytopenia, with platelet count 39,000/cmm. Peripheral smear report showed microcytic hypochromic anemia, anisopikilocytosis, and polychromatic cells, shift to left with toxic granules, decreased platelet count and no malarial parasite. ECG showed sinus tachycardia. Chest X ray revealed alveolar opacities involving left lower zone. ABG showed hypoxemia. Liver function tests revealed bilirubin 7.2 mg%, total protein4.3 mg%, albumin 2 mg %, SGOT / SGPT 324 / 156, SAP 204. Renal functions tests showed blood urea 60 mg% and creatinine 3 mg%. RBS was 116 mg%; there was hypocalcaemia with calcium of 7mg% and phosphate 3.8 mg%. Serial monitoring of INR showed 1.52, 1.75, and 2.5.

Anti Nuclear Antibody, Rhumatoid Factor, Viral markers for Human Immunodeficiency Virus, hepatitis A,B,C and E, serology for Weil’s and Dengue, Widal, Rapid Malarial Test, Mantoux test, sputum AFB were negative and VDRL was non-reactive. Serum TSH was1.3 mIU / L. ECHO showed no evidence of infective endocarditis and normal systolic function. Urine and
blood culture and sensitivity were sterile. Sonogram of abdomen revealed splenomegaly, ascites and right pleural effusion. Brucella Agglutination Test was negative. Serum ferritin was elevated [1250 ng /ml; (0 - 150 ng / ml)].

With the diagnosis of atypical pneumonia with multiple organ dysfunction she was shifted to the medical intensive care unit; where she was started on extended spectrum penicillins and cefazidime, blood products for coagulopathy. (She already received a course of antibiotics from the local hospital from which she was referred). With the course of time there was no clinical improvement; but there was a progressive fall in ESR. So a bone marrow study was done which showed increased number of histiocytes with hemophagocytosis.

The clinical scenario was very much suggestive of Hemophagocytic lymphohistiocytosis (macrophage activation syndrome secondary to atypical pneumonia) with fever, rash, splenomegaly, falling ESR, pancytopenia and hemophagocytosis. She was put on ventilatory support and given a course of intravenous immunoglobulin, in addition to the antibiotics, in a dose of 4 grams / day. In spite of our efforts she succumbed on the sixth post admission day.

**DISCUSSION**

Hemophagocytic lymphohistiocytosis (HLH) or Macrophage Activation Syndrome (MAS) is a rare and potentially fatal disease of normal but overactive histiocytes. It is of two types - Primary HLH and Secondary HLH (acquired HLH) which occurs after strong immunologic activation - systemic infection (virus, bacteria, and protozoa), autoimmune disorders, or underlying malignancy.

In Hemophagocytic lymphohistiocytosis there is overwhelming activation of normal T cells and macrophages which can cause clinical and hematological alterations. The clinical presentation is in many aspects similar to the so-called systemic inflammation response syndrome (SIRS). And death is inevitable in the absence of treatment.

The clinical entity has to be suspected when patients present with fever unresponsive to antibiotics, general fatigue, falling ESR, pancytopenia of unknown origin and liver dysfunction with elevated ferritin. The diagnostic criteria proposed by Histiocyte Society for inclusion in the International Registry for Hemophagocytic lymphohistiocytosis is as follows.

1. **Fever** - Seven or more days of a temperature as high as 38.5°C (101.3°F).
2. **Splenomegaly**.
3. **Cytopenia** - Counts below the specified range in at least 2 of the following cell lineages:
   - Absolute neutrophils less than 1000/mL;
   - Platelets less than 100,000/mL;
   - Hemoglobin less than 9.0 g/dL
4. **Hypofibrinogenemia or hypertriglyceridemia**.
5. **Hemophagocytosis**.
6. **Rash**

At least five of them have to be there to have a definite diagnosis. For confirmation tissue diagnosis is needed. Hemophagocytosis must be demonstrated in the bone marrow, spleen, or lymph nodes.

Macrophage Activation Syndrome has to be considered in patients with a SIRS like clinical presentation. Hyperferritinemia >10000 µg/l seems to be a good marker for defining patients with or at risk of developing MAS (and should be completed with a morphological assessment of hemophagocytosis) as well as an indicator for emergency administration of IVIG. But low ferritin does not rule out the condition as it may possibly reflect ferritin measurements some time after the peak of macrophage activation. This may be the reason for the relatively less elevated ferritin in our patient.

In the absence of prospective controlled trials, corticosteroids, cyclosporin A, and etoposide are administered with varied success. Recent case reports
show promising results with an anti-TNF-α approach and plasmapheresis.

This case is presented to enlighten physicians regarding the clinical entity of Macrophage Activation Syndrome to be suspected when patients presented with fever unresponsive to antibiotics, general fatigue, falling ESR, pancytopenia of unknown origin and liver dysfunction with elevated ferritin.

REFERENCES

Book Review

Fundamental Issues in Bio-medical Ethics with Real Life Examples for Better Understanding

AP Jain, Manish A Jain, Jitendra Ingole
Sewagram, Mahatma Gandhi Institute of Medical Sciences
Indian Price: Rs. 100/-

Ethical codes form the founding principles of medical profession. They embody the values of the time in which they have been formulated and the culture from which they emerge. They provide an ethical structure to govern the practice of the physicians and their relationship with the patients and society.

Biomedical ethics is a complex conglomerate of admirable attributes which a physician should try to possess in plenty. Medical profession has got admiration and adoration from the patients and the public. It is unfortunate, in the recent years the profession has witnessed a steady erosion of the ethics. It is failing to satisfy expectation of the patient and the society. The complexity of the medical profession and the demands by the public in the recent years has necessitated the renewal of the physician’s dedication to the patient’s interests and the intrinsic virtues necessary for the medical profession.

In this background, biomedical ethics has found a place in the undergraduate medical curriculum. Prof. Ajeet Jain and colleagues have highlighted in the book, the dilemmas encountered by the clinicians during their practice. The book contains 27 chapters. The introductory chapter deals with the approach to be made for ethical problem. Other chapters include topics such as doctor-patient relationship, confidentiality, professionalism etc. The language is simple and the authors have discussed various ethical problems by giving real life case scenario.

The authors have discussed the situations like breaking bad news, termination of life-sustaining treatment, truth telling and withholding the information, and end of life issues. The appendix carries the Geneva Convention code of medical ethics and the Hippocratic Oath. The authors have done a fine job of drawing the attention of medical profession towards the biomedical ethics. It answers many common situations that are encountered every day in clinical practice with examples.

The topics discussed in the book are relevant and useful to medical profession.

The Medical Professionalism Project jointly sponsored by the American Board of Internal Medicine (ABIM) and American College of Physicians (ACP) and European Federation of Internal Medicine in a collaborative effort has designed to raise the concept of professionalism within the consciousness of Internal Medicine and has brought out a charter in 2002 on medical professionalism dealing with the fundamental principles and professional responsibility to both patients and society to be followed by the physician.

The present book extends the theme admirably and the book is very useful to all clinicians. It covers a wealth of information that is not covered by standard text books. The book is recommended to all students, clinicians and research workers. The authors deserve congratulation for bringing out such a valuable book.

Dr. PS Shankar, M.D. FAMS, DSc
Emeritus Professor of Medicine and Medical Director
M. R. Medical College and Attached Teaching Hospitals
M.R. Medical College, Gulbarga, Karnataka