Abstract

Macrophage Activation Syndrome (MAS) occurs as a severe life-threatening complication of several chronic rheumatic diseases. It is more frequent with systemic onset juvenile arthritis and adult onset Still's disease.1 It can be primary, infection related, malignancy associated or autoimmune.3 We report a case of Macrophage Activation Syndrome presenting as pyrexia of unknown origin (PUO) and pancytopenia in the absence of any known triggering factor.

Introduction

Pyrexia of unknown origin (PUO) is often a physician's nightmare. Macrophage activation syndrome is one of the rare causes of PUO. Macrophage activation syndrome is thought to be caused by excessive activation and proliferation of T lymphocytes and macrophages. It is characterised by pancytopenia, liver dysfunction, coagulopathy and neurological symptoms. Cytokines mediate most of the neurological symptoms.

Case Report

A 63-year-old male was referred to our internal medicine department after being treated in multiple hospitals as a case of pyrexia of unknown origin. He had a history of high grade fever, abdominal discomfort and headache of four week’s duration. On examination his blood pressure was 130/80 mmHg; pulse was 120 bpm. He had pallor and icterus. On gastrointestinal examination he had hepatomegaly. Other systemic examinations were found to be normal. Initial investigations showed pancytopenia with haemoglobin of 10.8 g/dl, Total Leucocyte Count of 2430 cells/cu mm, Differential Count – Neutrophils 58%, Lymphocytes 35%, Eosinophils 3%, Monocytes 6%, Platelet count of 10,000 cells/mm² and ESR of 7 mm in the 1st hour. Liver Function Tests were deranged with SGOT = 170 IU/L, SGPT = 187 IU/L, Alkaline Phosphatase = 432 U/L, S. Albumin = 2 gm/dl, Total Protein = 5 gm/dl and Sodium of 127 meq/L, Potassium 3.7 meq/L, chloride 97 meq/L. Thyroid function tests and urine examination were normal.

He was further investigated for infective etiology with blood culture, urine culture, Dengue IgM and NS1, MP QBC, Widal, HIV, HBsAg, HCV and Mantoux; all of which turned out to be negative. Serum PSA was normal. Chest X-ray PA view was suggestive of COPD and USG abdomen also revealed hepatomegaly. Meanwhile he was started on a broad-spectrum antibiotic, Piperacillin-Tazobactum. Despite the IV antibiotic, he continued to have high spikes of fever with body temperature reaching 104°F and ESR remained persistently low.

Bone marrow study was done in view of pancytopenia, which showed a normocellular marrow with haemophagocytosis. Low ESR and the marrow findings, provided a major clue to make a provisional diagnosis of MAS. With this, we further did work-up for MAS with RA factor, ANA and ANA profile turning out to be negative. His fasting lipid profile was done, and showed elevated triglycerides; Triglycerides = 297 mg/dl, HDL = 16 mg/dl, LDL = 83 mg/dl, S. Ferritin = 5600 ng/ml, Fibrinogen = 86 mg /dl, LDH of 512 and a prolonged aPTT.

These investigation were consistent with the final diagnosis of MAS secondary to an unknown trigger. Hence patient was started on high dose methylprednisolone, following which he showed dramatic improvement. At the time of discharge, he was afebrile and was discharged on tapering doses of steroids.

Discussion

MacrophageActivation Syndrome (MAS) occurs as a life-threatening complication of several chronic rheumatic diseases, particularly Systemic Juvenile Idiopathic Arthritis (SJIA). It has also been observed in juvenile systemic lupus erythematosus, Kawasaki’s disease, Adult onset Still’s disease, Poly Arteritis Nodosa, Mixed connective tissue disease, Pulmonary sarcoidosis, Systemic sclerosis, Dermatomyositis and Sjogren’s syndrome. MAS can be generally classified as primary and secondary MAS. Secondary MAS can be further classified into MAS associated with infections, immunological or internal malignancy. The infections triggering MAS mainly includes viruses like EBV, CMV, and HIV.

The clinical presentation of MAS is generally acute. Initially patient may present as a case of PUO, where there...
is a sudden onset of non-remitting high grade fever with hepatosplenomegaly and lymphadenopathy. CNS dysfunctions in the form of headache or seizure may occur. Pancreatitis, hypofibrinogenemia, elevated triglycerides, Serum Ferritin, Serum LDH and the liver enzymes, and low sodium levels are demonstrated on blood testing. Coagulation profile is often abnormal. This is associated with a precipitous fall in ESR reflecting the degree of hypofibrinogenemia. Bone marrow study shows evidence of haemophagocytosis. The patients may show a paradoxical improvement of the underlying inflammatory disease at the onset of MAS, with disappearance of signs and symptoms of arthritis.

The pathogenesis of MAS is often unclear. There may be severe impairment of cytotoxic function of NK cells and cytotoxic T-Lymphocytes. This leads to the loss of cytotoxic function of NK cells and cytotoxic activity via IFN-γ, TNF-α and IL-1B causes decrease in all cell lines leading to profound depression in all three blood cell lines. Increased IL-1B secreted by macrophages elevates ferritin level. TNF-α causes inhibition of lipoprotein lipase and thus leads to hypertriglyceridemia. Plasminogen activation by IL-1B, elevated IFN-γ and TNF-α causes disseminated intravascular coagulation which results in coagulopathy. Elevated IL-6 causes acute renal failure. IFN-γ causing cholestasis and engagement of cell death surface receptor Fas by Fas ligand (Fasl) causing apoptosis lead to liver dysfunction.

There are two stages for the diagnosis of MAS. The first stage includes the following

I. PUO, hepatosplenomegaly, cytopenia of at least two cell lines.
II. Normal or a fall in ESR, Hypofibrinogenemia (<250 mg/dl).  
III. Hypertriglyceridemia (>160 mg/dl), elevated serum ferritin (>10,000 ng/ml).  
IV. Elevated liver enzymes and serum LDH.
V. Bone marrow features of hemophagocytosis.

The second stage of diagnosis of MAS includes identifying if-

I. Primary cause or
II. Secondary cause
  a. Infections
  b. Immunological disorder
  c. Malignancy

In patients with MAS, bone marrow aspirate does not always show hemophagocytosis however, failure to demonstrate hemophagocytosis does not exclude the diagnosis of MAS.

The treatment of MAS is based on the parenteral administration of high doses of corticosteroids usually started with intravenous methylprednisolone pulse therapy (30 mg/kg) for three consecutive days followed by 2-3 mg/kg/day in four divided doses. Administration of high dose intravenous immunoglobulins, cyclophosphamide, plasma exchange and etoposide provide conflicting results. Cyclosporin A is found to be effective in severe or corticosteroid-resistant macrophage activation syndrome.

In our case, there was no demonstrable triggering factor. He responded very well to corticosteroids. He is on follow up.

Conclusion

PUO, especially in cases with underlying immunological diseases, should prompt a search for this rare entity called macrophage activation syndrome.

References