

Macrophage activation syndrome in an inadequately treated patient with systemic onset juvenile idiopathic arthritis

Juneja M¹, Jain R², Mishra D³

¹Professor, ²Senior Resident, ³Assistant Professor, Department of Pediatrics, Maulana Azad Medical College (University of Delhi), New Delhi, India.

Abstract

Macrophage activation syndrome is a rare and potentially life threatening complication of childhood rheumatic disorders. It is described most commonly with systemic onset juvenile idiopathic arthritis (soJIA). The major clinical manifestations are non-remitting fever, hepatosplenomegaly, lymphadenopathy, bleeding diathesis, altered mental status and rash and may mimic a flare of soJIA. The characteristic laboratory findings are leucopenia, thrombocytopenia and dramatic elevation of urinary β 2 microglobulin. Corticosteroids and cyclosporine are the drugs commonly used in its management. Early diagnosis and prompt treatment can be life saving. We report a case of 12 year old female child with inadequately treated systemic onset juvenile idiopathic arthritis who developed fatal macrophage activation syndrome. The diagnosis and management of macrophage activation syndrome are discussed.

Key words: Macrophage activation syndrome, systemic onset juvenile idiopathic arthritis, leucopenia, children.

Macrophage activation syndrome (MAS) is a clinical syndrome caused by excessive activation and proliferation of well-differentiated macrophages. MAS occur in heterogeneous group of conditions including infections, neoplasms, drug induced and rheumatic disorders. It is described most commonly with systemic onset juvenile idiopathic arthritis (soJIA)^{1,2}. Most of the previously reported patients with soJIA and MAS were under regular therapy for the arthritis. We herein describe a patient with inadequately treated soJIA who developed macrophage activation syndrome, thereby causing a diagnostic confusion between flare of soJIA and MAS.

Case report

A 12 yrs old female presented with a 10-day history of high grade continuous fever and cough along with progressive abdominal distension for 8 days, breathlessness for 2 days, and swelling over the feet for 1 day. She was symptomatic from last 4 years with swelling, pain and formation of deformity in multiple joints, and had been diagnosed as systemic onset juvenile idiopathic arthritis (soJIA) 1 year back and was being treated with naproxen. Patient had only partial relief of symptoms and was not taking the drug regularly or coming for regular review. The parents had stopped naproxen, 2 months back and were using some traditional (*ayurvedic*) drugs.

On examination at admission, patient was cooperative but resented handling. She had respiratory distress with respiratory rates of 39/min, intercostals retractions, severe pallor, bilateral small cervical lymph nodes and pedal edema. Bilateral ankle joints were swollen and tender. Joint deformities were present in bilateral knee, elbow, wrist and proximal and distal interphalangeal joints. Chest examination revealed right sided crepitations. Liver was 6 cm below costal margin in mid-clavicular line and spleen was 5 cm below costal margin. Haemoglobin was 5.4 gm/100ml, total leucocytes count was $8300 \times 10^9/L$ (polymorphs 61%, lymphocytes 35%, eosinophils 2% and monocytes 2%) and platelet count of $58,000 \times 10^9/L$. Blood urea was 85 mg/100ml and serum creatinine was 4.1 mg/100ml. Further investigations were requisitioned and a provisional diagnosis of flare of soJIA with pneumonia was entertained, and treatment started with intravenous fluids, injection Ceftriaxone and blood transfusion.

ESR was markedly raised (135 mm in 1st hour). Liver enzymes (Alanine aminotransferase 72 U/L, Aspartate aminotransferase 106 U/L, Alkaline phosphatase 1756 U/L) were raised. C-reactive protein and rheumatoid

Correspondence

Dr. Monica Juneja
C-77 South Extension -II New Delhi 110049
E-mail: drmonicajuneja@gmail.com

factor were positive. Serum ferritin was 1338 ng/ml. Chest radiograph showed right paracardiac pneumonia. Ultrasonography of the abdomen showed hepatosplenomegaly and renomegaly with increased renal cortical echogenicity with accentuated corticomedullary differentiation.

Over the next 24 hours, patient continued to be ill with fever and respiratory distress persisting and worsening of the mental status with severe irritability. In view of presence of hepatosplenomegaly, pancytopenia and worsening of mental status possibility of macrophage activation syndrome (MAS) was considered and bone marrow aspiration was performed. Cultures obtained were sterile and steroids were started. Patient had further worsening of sensorium and died on the same day. Bone marrow aspiration revealed macrophages phagocytosing hematopoietic elements. The final diagnosis was soJIA with MAS with pneumonia with possible renal amyloidosis.

Discussion

MAS has been described in association with soJIA with various triggering events like bacterial and viral illness (Ebstein-Barr Virus and hepatitis A infection are most commonly associated) and drugs like non-steroidal anti-inflammatory drugs, gold salts, sulfasalazine, methotrexate and even etanercept^{1,3-8}.

MAS bear close resemblance to a histiocytic disorder, secondary hemophagocytic lymphohistiocytosis. Precise underlying mechanisms have not been defined. Studies have described overproduction of cytokines originating from activated T lymphocytes and macrophage, dysfunction of natural killer cells and reduced expression of perforin (the protein that controls the cytotoxic activity of natural killer cells and T lymphocytes) in patients with MAS^{9,10}.

Clinically macrophage activation syndrome has a dramatic onset and may mimic a flare of soJIA. It can occur as a initial manifestation of soJIA^{1,2}. The major clinical manifestations of MAS are non-remitting fever, hepatosplenomegaly, lymphadenopathy, bleeding diathesis, altered mental status and rash^{1,2}. Large pericardial effusion is also described in one case report¹¹. The common causes of death in these patients are acute respiratory distress syndrome and central nervous system involvement². A flare of soJIA can present with arthritis, quotidian fever, hepatosplenomegaly, lymphadenopathy, evanescent rash and serositis. The common laboratory findings are leucocytosis, thrombocytosis, elevated ESR and hyperfibrinogenemia. We missed the diagnosis of MAS initially because arthritis was present, there were no mental changes, ESR was elevated and patient was inadequately treated, mimicking the flare of disease.

The characteristic laboratory findings in patient with MAS are leucopenia, thrombocytopenia and dramatic elevation of urinary β_2 microglobulin; with deranged coagulation profile with hypofibrinogenemia, deranged liver function tests, low ESR and anemia being commonly present^{1,2}. Hyperferritinemia and elevation of serum lactate dehydrogenase are also present in many cases². Derangement of renal function tests can occur during course of disease and has been implicated as a poor prognostic marker in one study¹. Other less common findings include hypertriglyceridemia, hypoalbuminemia and hyponatremia². Studies have documented elevation of serum β_2 microglobulin, soluble interleukin-2 receptor and soluble CD163 in patients with MAS and are promising diagnostic markers^{2,12}. The pathologic finding on bone marrow aspiration is the presence of well-differentiated macrophages actively phagocytosing hematopoietic elements.

MAS has aggressive clinical course and, early recognition and treatment is imperative. Death rates of 11-22 % are reported^{1,2}. Corticosteroids and cyclosporine are most commonly used drugs. Cyclosporine has been reported to produce prompt response when used in severe cases and in those who fail to respond to steroids^{2,13}. Cyclosporine may be chosen as a first line therapy or added to first line steroid treatment². Other treatment options include plasma exchanges, intravenous immunoglobulins and etoposide¹¹. Recently, Etanercept has been found to be useful in therapy resistant cases^{14,15}.

Conclusions

Macrophage activation syndrome can occur in heterogeneous group on conditions but it is most commonly described with soJIA. MAS may be a presenting manifestation of soJIA or can occur during the course of disease and may mimic a flare of soJIA. The clinical findings of non-remitting fever, hepatosplenomegaly and altered mentation along with laboratory findings of leucopenia and thrombocytopenia should alert the physician of this condition. Early recognition and prompt treatment of this life threatening condition with corticosteroids or cyclosporine is vital.

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