Case Report

Influenza B Virus Triggering Macrophage Activation Syndrome in an Infant

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Abstract

Macrophage activation syndrome (MAS) is a potentially fatal complication caused by excessive activation and expansion of macrophages and T lymphocytes. It can be triggered by various infections and is characterized by the development of cytopenias, hyperferritinemia, liver dysfunction, and coagulopathy. We report a 10-month-old female infant with fever, convulsions, and hepatosplenomegaly. Laboratory data of bicytopenia, low erythrocyte sedimentation rate, and elevated liver enzymes suggested MAS. This was supported by the presence of hyperferritinemia with hypertriglyceridemia. MAS was triggered by influenza B virus. She responded to treatment with immunoglobulin and steroid.

Keywords: Bicytopenia, hyperferritinemia, hypertriglyceridemia, secondary hemophagocytic lymphohistiocytosis, thrombocytopenia

Introduction

Overactive histiocytes are responsible for a rare and potentially fatal disorder called macrophage activation syndrome (MAS). MAS may occur spontaneously, as a complication of active underlying disease, or may be triggered by an infection, a change in drug therapy or a toxic effect of a medication. We report on a case where MAS was triggered by influenza B virus, which has not been reported earlier to the best of our knowledge and emphasize that early recognition and aggressive management can reverse this complication.

Case Report

A 10-month-old female, first born out of nonconsanguinous parentage, of Asian origin presented with fever and cough of 6 days and two episodes of convulsions, loose stools and breathlessness of 2 days duration. On examination, infant had altered sensorium with heart rate: 110/min, respiratory rate: 64/min, blood pressure: 90 mmHg (systolic), capillary filling time: <3 s, bronchial breath sounds in bilateral mammary and left axillary area, liver span: 13 cm, spleen: Tip palpable, anterior fontanelle: At level, no skin or mucosal bleeds, and neurodeficits. Growth and development was appropriate for age. Provisional diagnosis of pneumonia with sepsis was considered. Preliminary laboratory investigations of anemia (hemoglobin 9 g/dl), lymphocytosis (P_{38} L_{60} E_2), thrombocytopenia (platelet 89,000cells/mm^3), peripheral smear: Microangiopathic hemolytic anemia, low erythrocyte sedimentation rate (ESR) (3 mm in 1st h) and elevated liver enzymes: Serum glutamic pyruvate transaminase (460U/L), serum glutamic oxaloacetic transaminase (2691 U/L), suggested hemophagocytosis. On further investigation of prolonged activated partial thromboplastin time (65.4), increased fibrin degradation products, hypertriglyceridemia (2.33 mmol/l), and hyperferritinemia (4652 ng/ml) confirmed MAS as per diagnostic criteria (2004).[1,2] Blood, urine cultures and workup for dengue, leptospira were negative. Intravenous methyl prednisolone (IVMP) was initiated at 30 mg/kg/day along with ceftriaxone, amikacin, and supportive therapy. There was clinical worsening with decreasing platelet count on day 2, hence intravenous immunoglobulin (IVIG) at 2 g/kg was added, and antibiotic changed to meropenem. She developed acute respiratory distress syndrome with shock on day 3 and was supported with mechanical ventilation and vasopressors. Anemia and thrombocytopenia were corrected with blood component therapy. IVMP was given for 5 days followed by

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oral prednisolone at 2 mg/kg/day. Throat swab virology (real time polymerase chain reaction) isolated influenza B virus. She was extubated after 6 days of ventilation. Feeds were gradually initiated, antibiotics were given for 10 days and she was discharged on prednisolone for 4 weeks. Cerebrospinal fluid analysis was not done due to thrombocytopenia. She is under follow-up for a year, gaining appropriate milestones and no major illness.

Discussion

Macrophage activation syndrome was first reported by Boone in 1976, and the term "MAS" was coined in 1993 by Stéphan *et al*.[3,4] MAS is a secondary or acquired form of hemophagocytic lymphohistiocytosis (HLH). Primary HLH is usually seen in rare autosomal-recessively inherited disorders due to several genetic defects involved in granule-mediated cytotoxicity, killing of infected cells, and termination of immunologic responses. Primary HLH is associated with mutations of the perforin gene (*PRF-1*, 10q21), other genetic abnormalities such as Chediak-Higashi syndrome, Griscelli syndrome, and X-linked lymphoproliferative syndrome.[5] MAS is seen in systemic onset juvenile idiopathic arthritis and other autoimmune/auto inflammatory conditions, malignancies, and viral infections.[6,7] Secondary HLH/MAS can be triggered by viral, bacterial, fungal infections, parasitic infestations or specific drug administrations.[8] The pathophysiology of MAS involves dysregulation of T-cytotoxic lymphocytes and natural killer cells, which fail to clear infected cells resulting in persistent antigen activation of T cells and excessive production of cytokines. The cytokine storm leads to abnormal production and activation of macrophages which results in an increased phagocytosis of blood elements. NK cells function is decreased in patients with secondary HLH/MAS.[5] HLH is similar in its clinical and laboratory characteristics with severe sepsis and related syndromes: Systemic inflammatory response syndrome (SIRS), multiorgan dysfunction syndrome (MODS), and MAS. There is a great difference in mortality rates, duration and regimen of treatments, and long-term outcome between patients treated for what is diagnosed as HLH and those treated for sepsis/SIRS/MODS/MAS.[9] Diagnosis of MAS can be difficult because there are no pathognomonic clinical findings. Diagnostic criteria were modified in 2004. MAS/secondary HLH diagnosis is established if 5 of 8 diagnostic clues are fulfilled: Two clinical criteria, fever and splenomegaly, and three laboratory diagnostic criteria, cytopenia (affecting ≥ 2 of 3 lineages in the peripheral blood with hemoglobin <9 g/L, platelets <100 × 10^9/dL and/or neutrophils <1 × 10^9/dL), hypertriglyceridemia (fasting triglycerides ≥2.0 mmol/L or ≥3 SD of the normal value for age), hypofibrinogenemia (fibrinogen ≤1.5 g/L or ≤3 SD) have to be combined with the evidence of hemophagocytosis in bone marrow, spleen or lymph nodes and no malignancy. Three new diagnostic clues have been considered: Absent or low natural killer cell activity, hyperferritinemia ≥500 g/L and increased sCD25 levels (≥2400 U/mL).[1,2] In MAS, the bone marrow aspirate does not always show hemophagocytosis in the initial stages. Repeat bone marrow aspirate may demonstrate hemophagocytosis.[8] Failure to demonstrate the histopathologic confirmation of MAS does not exclude the diagnosis.[10] Therapeutic protocol for MAS is not available: First line-treatment is usually by parenteral administration of high-dose corticosteroids (intravenous infusion of methylprednisolone at the dose of 30 mg/kg/day or 1 g/m^2 for 3–5 days). Mild forms respond to steroids alone in association with supportive medicaments. Steroid-resistant cases or the most severe forms of MAS require cyclosporine A.[5] IVIG helps in immunomodulation, and controlling hypercytokinemia.[5] Reactivation of MAS warrants serial monitoring of blood counts. As there was no recurrence, and child is thriving well, she was not investigated for primary HLH.

Conclusion

Macrophage activation syndrome/secondary HLH should be considered in a sick child with fever, splenomegaly, pancytopenia/bicytopenia, and low ESR (indicating low fibrinogen). Though rare, intensivists should be aware of this life-threatening entity.

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