A Case Report: Systemic Lupus Erythematosus with Presenting of Macrophage Activation Syndrome

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Abstract

Macrophage activation syndrome (MAS) is a severe and rare fatal complication of systemic inflammatory diseases in childhood. MAS has been described in patients with several rheumatic diseases, including systemic onset juvenile idiopathic arthritis (SoJIA), systemic lupus erythematosus (SLE), and Kawasaki disease. Here, we describe a girl who presented clinical and laboratory features of MAS, and an initial manifestation of SLE.

Key words: Macrophage activation syndrome, systemic lupus erythematosus, therapy

Introduction

Macrophage activation syndrome (MAS) is characterized by pancytopenia, liver insufficiency, coagulopathy, and neurologic symptoms and is thought to be caused by the activation and uncontrolled proliferation of T lymphocytes and well-differentiated macrophages, leading to widespread hemophagocytosis and cytokine overproduction [1].

MAS is an acute, potentially fatal complication of rheumatic disorders in both adults and children. In adults, Fukaya et al. [2] reported the prevalence of MAS was 4.6% in SLE patients and 7.7% in Still disease patients.

Among pediatric rheumatic disorders, macrophage activation syndrome occurs much more frequently, particularly in systemic juvenile idiopathic arthritis (sJIA) [3–5]. However, this syndrome has been increasingly reported in patients...
with other pediatric inflammatory diseases, namely Kawasaki, juvenile dermatomyositis and periodic fever syndromes [6-10].

MAS associated with SLE is rare, with the incidence about 0.9 – 4.6 % [5]. Morales et al. [11] evaluated bone marrow specimens from 28 patients with SLE obtained during 30 episodes of cytopenia. They found that 22 specimens (73.3%) exhibited hemophagocytosis. Tsuji et al. [12] reported that 7 (9.6%) of 73 patients with SLE and liver dysfunction had hemophagocytic syndrome.

There are only a few reports of children with SLE who developed MAS as the first manifestation of their disease [13]. Bennett et al. [14] performed a retrospective cohort study by 121 children with MAS, and the reported frequency of SLE was 15%.

We report a girl who initially presented with MAS and eventually was diagnosed as having SLE.

### Case Report

An 11-years-old girl patient presented with pain of joints, weakness, epistaxis and fever for one month and after physical and laboratory examination, which revealed a thrombocyte concentration of 16000/mm3, she was accepted in our hospital for differential diagnosis. Her physical examination parameters were as follows: weight: 27 kg (10-25 percent); height: 137 cm (10-25 percent); temperature: 38.1 °C; heart rate: 110/min; blood pressure: 110/65 mmHg. The patient exhibited no rash, mucous membrane abnormalities, lymphadenopathy, or edema and arthritis but had pallor and weakness. Given these findings, we thought about differential diagnosis, focusing especially on systemic inflammatory diseases, systemic viral and bacterial infections, malignancy, systemic vasculitis or other rare diseases. The patient had pan-cytopenia (WBC: 3660/mm3, Hb: 10.6 g/dl, thrombocyte: 45000/mm3, respectively). Erythrocyte sedimentation rate

### Table 1. Patient’s laboratory tests.

<table>
<thead>
<tr>
<th>Tests</th>
<th>On admission</th>
<th>After PMP (7th day)</th>
<th>2 weeks After CyA treatment</th>
<th>Two mounts after first presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count (cells/mm3)</td>
<td>3660</td>
<td>7400</td>
<td>31600</td>
<td>12000</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>10.1</td>
<td>11.1</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Platelet count (cells/mm3)</td>
<td>45000</td>
<td>212000</td>
<td>446000</td>
<td>297000</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>20</td>
<td>4</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>242</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>1000</td>
<td>114</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>D-dimer (μg/L)</td>
<td>1155</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>Not done</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>243</td>
<td>80</td>
<td>-</td>
<td>149</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.5</td>
<td>0.6</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Autoantibodies, ANA, anti-dsDNA Ab, Coombs’ test</td>
<td>1/2560 homogenous pattern</td>
<td>1/640 homogenous pattern</td>
<td>1/160 homogenous pattern</td>
<td>1/160 homogeneous Pattern</td>
</tr>
<tr>
<td>Complement C3</td>
<td>Yes Low</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Complement C4</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

CA cyclosporine A, ESR erythrocyte sedimentation rate, CRP C-reactive protein, AST aspartate transaminase, ALT alanine transaminase, LDH lactate dehydrogenase, ANA antinuclear antibody.

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(ESR), serum amyloid A, C- reactive protein and urinary protein were not elevated, whereas ferritin, lactate dehydrogenase, transaminase, and fasting triglyceride were raised. In addition, she had elevated gamma globulin levels (Table 1). A thorough infection screen of repeated blood and urine cultures was negative for all viruses, including Herpes Simplex, Herpes Zoster, EBV, cytomegalovirus, Hepatitis B and C, HIV, Coxsackie and Parvovirus B19 viruses. The autoimmune profiles revealed positive antinuclear antibodies (1:2560 homogenous pattern), positive anti-dsDNA antibody (402 IU/ml), positive direct Coombs’ test (3+), and decreased levels of complement (C3:41.5 mg/dl, C4: 5.98 mg/dl, respectively). Anti-cardiolipin Ab, anti-β2 glycoprotein I Ab, and lupus anticoagulant were all negative.

Given that a bone marrow aspiration revealed hypocellular marrow with mild to moderate dyserythropoiesis, high histiocytes, and significant hemophagocytosis, a diagnosis of MAS associated with SLE was made.

Treatment with intravenous pulse methylprednisolone (three times, 30mg/kg/every other day, max 1g) was started. After pulse treatment, the patient was put on oral prednisolone 1mg/kg/day and cyclosporin A (CsA) (3 mg/kg/day). In addition to this treatment, the patient was given advice on a healthy lifestyle to cope with SLE (sun protection, adequate diet and physical exercise). Her steroid intake was tapered down in view of low disease activity of SLE was maintained.

After the treatment, pancytopenia returned to near normal. On the 15th day, bone marrow aspiration was repeated, and it was normal. Her ferritin level returned to normal 114 microg/L after first presentation. Up to the submission of the manuscript, she had no further complaints and no hematologic problems.

Discussion

Macrophage activation syndrome is a systemic reaction and serious complication in rheumatic diseases in childhood, considered by some authors as an acquired (secondary) form of hemophagocytic lymphohistiocytosis (HLH) [15,16]. It is caused by excessive activation and proliferation of T lymphocytes and macrophages. The etiology of this syndrome is not fully understood, but it is known that this disease is characterized by an excessive immune response with no control mechanism. In particular, a report of marked elevations of soluble cytokines in some children with MAS suggests that uncontrolled proliferation of cytotoxic T lymphocytes (CD8+) may underlie this disease [17].

The recognition that MAS is clinically similar to HLH has led many clinicians to use the diagnostic guidelines for HLH in the diagnosis of macrophage activation syndrome [10]. The criteria for MAS complicating systemic juvenile idiopathic arthritis (SJIA) were established by Ravelli A et al. [11]. Laboratory criteria include decreased platelet counts, elevated levels of aspartate amino-transferase, decreased white blood cell counts, and hypofibrinogenemia. Clinical criteria include hepatomegaly, hemorrhagic manifestations, and central nervous system dysfunction. The diagnosis of MAS requires the presence of at least 2 laboratory criteria or the presence of at least 1 laboratory criterion and 1 clinical criterion. The demonstration of macrophage hemophagocytosis in the bone marrow aspirate is required only in doubtful cases.

In this patient, in the absence of an identifiable infection the diagnosis of MAS secondary to acute SLE was established based on laboratory, clinical and bone marrow findings.

We eliminated SoJIA because there were no hepatosplenomegaly, arthritis and fever with rash. In spite of the pain in minor joints and prominent weakness, retinal vasculitis and uveitis were not observed on her eye examination for rheumatic diseases. Further testing showed positive antinuclear antibodies, positive anti-dsDNA, positive Coombs’ test, and decreased level of complement with regard to ACR criteria for SLE without proteinuria.

SLE-associated MAS might be underdiagnosed. Cytopenias are common and may have various origins in SLE. In a review of 38 MAS associated SLE patients, thrombocytopenia was a better indicator of MAS than leucopenia and anemia [13], while we observed the same findings in this patient. Parodi et al. [13] mentioned that the strongest indicator to separate MAS from active SLE was hyperferritinemia. Her ferritin level was found very high on admission and it decreased during the follow-up.

We obtained bone marrow aspirate for differential diagnosis for malignant disease, especially leukemia. We eliminated leukemia but the bone marrow aspiration showed mild to
moderate dyserythropoiesis, high histiyoitis, and significant hemophagocytosis.

MAS-associated SLE patients were reported to have cardiac involvement [20]. Our patient had no cardiac pathology.

The initial management of patients with MAS is usually with administration of high doses of corticosteroids [1]. Cyclosporine has been found to be dramatically effective in severe or corticosteroid-resistant instances of macrophage activation syndrome in children with autoimmune diseases [13]. We obtained a favorable outcome with high dose steroid and cyclosporine therapy in our patient.

In conclusion, MAS could be an initial presentation of SLE in children. If a patient presents these criteria we must consider MAS and perform bone marrow aspiration.

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References


