CASE REPORT

Macrophage activation syndrome as initial manifestation of adult-onset Still’s disease

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Abstract
Macrophage Activation Syndrome (MAS) is an aggressive and potentially life threatening disease which can occur in rheumatologic diseases, more in systemic juvenile idiopathic arthritis and less in adult onset Still’s disease. We presented here a 22-yr-old female who was admitted with high fever for 3 weeks before admission. According to physical and laboratory results and after ruling out infections and malignancies, she was diagnosed with adult onset Still disease. Despite treatment initiation and improvement, she became dramatically ill one week later and jaundice was created. In physical and laboratory data, high fever, pancytopenia and impaired liver function tests and increased serum ferritin levels were found. Bone marrow aspiration and biopsy showed active hemophagocytosis. She was diagnosed with Macrophage Activation Syndrome associated with adult onset Still’s disease and managed with high-dose corticosteroids and cyclosporine. After this treatment she completely recovered.

Key words: Adult-onset Still’s Disease, Hemophagocytosis, Macrophage Activation Syndrome

INTRODUCTION
Still’s disease (SD) is a systemic inflammatory disorder of unknown etiology and is a subgroup of juvenile idiopathic arthritis known as systemic-onset juvenile idiopathic arthritis (sJIA). Adult-onset Still’s disease (AOSD) is the adult form of Still’s disease, and affects people older than 16(1, 2). Macrophage activation syndrome (MAS) is a serious complication that is thought to be caused by excessive activation and proliferation of T lymphocytes and macrophages (1). Macrophage activation syndrome belongs to the secondary or reactive hemophagocytic syndromes and it may be appropriate to classify macrophage activation syndrome as a secondary form of hemophagocytic lymphohistiocytosis (HLH) (3). The frequency of macrophage activation syndrome is reported to be about 12% in adult onset Still’s disease (4). It has an acute and dramatic process which can complicate conditions like systemic juvenile idiopathic arthritis (sJIA), adult-onset Still’s disease (AOSD), systemic lupus erythematosus, drug reactions, and viral infections (2, 5). Patients usually present with acute illness, no remission of high fever, hepatosplenomegal, lymphadenopathy, severe cytopenia, liver disease, and intravascular coagulation (1). Here, we present macrophage activation syndrome in a patient with adult onset Still’s disease who was treated successfully with corticosteroid and Cyclosporin A.

CASE REPORT
A 22-year-old female patient was referred to our rheumatology department of Imam-Reza Hospital, Mashhad, Iran with complaints of fever and diffused skin rash. The fever had begun 2 or 3 weeks before admission and was usually higher in late afternoon
and was accompanied by a skin rash. She did not have any photosensitivity, oral ulcers or Raynaud phenomenon. Her familial and medical history was clear and she denied any unusual habits. Physical examination revealed a temperature of 39 °C, sinus tachycardia and tachypnea. Laboratory data were as follows: hemoglobin (12.3 g/dl), leukocytes (22,000 per cubic millimeter with 86% neutrophils), platelets (219,000 per cubic millimeter), erythrocyte sedimentation rate (ESR) (110 mm/h), strongly positive C-reactive protein (CRP), creatinine (0.8 mg/dl). Liver function tests and urinalysis were normal. Ferritin level was 450 µg/l (N=20–200). There were no pathological findings on chest x-ray and high resolution computerized tomography (HRCT), echocardiography and abdominal and pelvic ultrasonography showed no abnormality. Serologies for Epstein–Barr virus (EBV), cytomegalovirus (CMV), hepatitis B virus (HBV), hepatitis C virus (HCV), Parvovirus, and rheumatoid factor and antinuclear antibody were negative and blood cultures were sterile. After repeating blood cultures, a single culture was positive for staphylococcus aureus. Therefore, she was transported to infectious disease ward and received broad spectrum antibiotics. Cultures became sterile. However, no clinical improvement happened. During this time, the patient developed a fever higher than 39 °C, and concomitantly, she was reported to have a macular salmon rash on her trunk. All of the antibiotics were discontinued and with regards to her condition, she was treated with prednisolone 0.5mg/kg per day. The day after the treatment, fever declined and she was reported to have an increasing well being. Acute phase parameters normalized. Despite this short course of improvement (less than a week), she became dramatically ill again, fever returned and blood pressure dropped; jaundice appeared and she developed intermittent dyspnea and hemoptysis. She also had altered mental status. On physical examination, she had a large hemotoma on her left leg and her temperature was 39.5 °C. Laboratory data were as follows: hemoglobin (7.4 g/dl), leukocytes (2200 per cubic millimeter (with 48% neutrophils), platelets (25,000 per cubic millimeter), creatinine (0.9 mg/dl). Erythrocyte sedimentation rate was 30 mm/hr and C-reactive protein was positive. ALT (298 U/l), AST (241 U/l), total bilirubin (5.5 mg/dl), ALP (765 IU/L (up to 125), lactate dehydrogenase (LDH) 1,574 IU/L (up to 500), albumin (2.7 g/dl), fibrinogen (210 mg/dl), ferritin (940 µg/l), D-dimer (1.32 mg/dl (N=0.3–0.8), prothrombin time (12 ns (98% activity), activated partial thromboplastin time (aPTT) (37 ns (N=35–45 ns), fibrin degradation product (4.6 g/mL (normal<5), antithrombin III (120%). Cholesterol and triglyceride were normal. Serologies for EBV, CMV, and varicella-zoster virus (VZV) were negative. No source of infection could be detected; cultures remained sterile, and there were no signs of microangiopathic anemia or even malaria. Chest radiography was also normal. Bone marrow aspiration and biopsy showed histiocytes with active hemophagocytosis (Fig1, 2). There were some macrophages actively phagocytizing platelets and red blood cell fragments (Fig1) and there were also macrophages with platelets and WBC fragments in cytoplasm (Fig 2). She was diagnosed with macrophage activation syndrome associated with adult onset Still’s disease and she was transferred to ICU. Intravenous methylprednisolone pulse (1 g/day for 3 days) and IVlg (2 gr/kg for 5 days) were administered followed by intravenous dexamethasone (8 mg 3 times a day). Supportive and palliative treatments (e.g. packed cell transfusions and GCSF) were added. But her signs and symptoms persisted and even she experienced a respiratory failure, due to an acute pulmonary edema secondary to systolic heart failure (Ejection fraction =30%). Then, cyclosporine (5mg/kg/d) was added to dexamethasone, which caused significant subjective and objective clinical improvement after a few days. Liver function test normalized, and blood cell counts recovered. One month later, she was discharged from hospital with prednisolone 60 mg/d and cyclosporine 5mg/kg/ per day and was followed by regular clinical visits and paraclinical evaluations. To date, 3 years after the initiation of the symptoms, the patient has no complaint, physical examination and all of the laboratory data are normal and over the past year, all of the medication has been stopped.

DISCUSSION

After the report of a syndrome characterized by hemorrhage and neurologic, hepatic, hematologic, and metabolic manifestations by Hadchouel et al in 1985 and Stephan et al in 1993, activation syndrome was recognized to belong to secondary hemophagocytic syndrome (HS) (6). Hemophagocytic syndrome is an uncommon disorder characterized by inappropriate systemic proliferation of benign histiocytes throughout the reticuloendothelial system and hemophagocytosis (5). It can occur as primary hemophagocytic lymphohistiocytosis (HLH), but more commonly secondary (so called reactive Hemophagocytic syndrome (RHS)) to a variety of infections, neoplasms, drugs, autoimmune diseases, or various immunodeficiencies (5). Although macrophage activation syndrome commonly exists in juvenile idiopathic arthritis, it can also occur in other rheumatologic disorders such
as adult onset Still’s disease, Behcet disease, systemic lupus erythematus, dermatomyositis, Kawasaki disease, ankylosing spondylitis and sarcoidosis (3). The possible triggers consist of:

1. Drugs such as aspirin, other nonsteroidal anti-inflammatory drugs, sulfasalazine, gold salts or even etanercept
2. Viral (especially epstein bar virus, and herpes virus family) or bacterial infections.

However, it can also occur without any initiating event (6, 7).

Pathogenesis of macrophage activation syndrome is thought to be caused by deregulation of T lymphocytes and uncontrolled release of inflammatory cytokines (cytokine storm). There is also abnormal activation of macrophages and natural killer (NK) cell dysfunction caused by the mentioned cytokine storm which results in phagocytosis of hematopoietic elements. It was also reported that the number of NK cells decreased (3). Cytokines secreted by activated T cells and macrophages that are elevated during macrophage activation syndrome include: interferon- gamma, IL-12 and IL-18, which correlate with disease activity and pro-inflammatory cytokines IL-1β, IL-6 and tumor necrosis factor alpha (8).

In our patient, the diagnosis of adult-onset Still’s disease was made according to Yamagushi criteria (9). Our case had 3 out of four major criteria of Yamagushi criteria including a temperature of > 39°C for > 1 wk, leukocytosis>10000/mm³ with > 80% PMNs and typical rash. After the initial treatment of AOSD and secondary clinical deterioration, hemophagocytic syndrome was proposed. But an important differential diagnosis of this picture is reactivation of adult-onset Still’s disease itself.

According to the classification criteria for the diagnosis of HLH shown in table 1(10) the standard definition requires the presence of at least five of nine clinical criteria, our case had 4 laboratory criteria and one clinical criteria.

Clinical and laboratory features of our patient were more consistent with macrophage activation syndrome rather than a simple recurrence of adult-onset Still’s disease plus the evidence of hemophagocytosis on bone marrow aspiration. However, the diagnosis of macrophage activation syndrome is often a challenge as it may mimic a flare of the underlying disease.

Cytopenias is one of the important diagnostic criteria for MAS that is observed in at least two of three lineages (4) as seen in our patient. Our patient developed icterus as the first sign of macrophage activation syndrome. She also possessed abnormal liver function tests. This condition might be secondary to macrophage activation syndrome (4).

The neurologic findings in our patient might have been associated with macrophage activation syndrome, too. It is known that there might be signs of cerebral involvement during the course of macrophage activation syndrome (7).

So, in this case, macrophage activation syndrome was our definite diagnosis and treatment was initiated. Corticosteroid alone has been successfully administered for treatment of macrophage activation syndrome or adult onset Still’s disease. However, some patients seem to be resistant to steroids (4), as seen in our case. Although various immunosuppressants have been used, there is no established treatment for adult-onset Still’s disease accompanied by macrophage activation syndrome.

For refractory cases or for cases in which the goal is reduction of corticosteroid dose, disease-modifying antirheumatic drugs (DMARDs) can be used. It was recommended to add DMARDs early in the course of the disease, especially in patients with prolonged febrile, polycyclic, or chronic articular disease patterns. Cyclosporin A seems to be effective therapy for corticosteroid-resistant macrophage activation syndrome (4). Therefore, we started Cyclosporin A in addition to corticosteroid because our patient was resistant to corticosteroid alone.

Inhibitors of tumor necrosis factor α (TNF- α) have proven their efficacy in the treatment of rheumatoid arthritis (RA), and are currently under investigation in adult-onset Still’s disease and macrophage activation syndrome, but these reports on adult-onset Still’s disease include few cases with macrophage activation syndrome (4).

According to biologic treatments, Maeshima et al introduced a case with adult-onset Still’s disease and macrophage activation syndrome that went into full remission after treatment with etanercept. The effect of etanercept was apparently enhanced by combining it with a sufficient dose of methotrexate (4).

In a similar case report described with Kobayashi et al, complete suppression of adult-onset Still’s disease activity by high-dose steroid therapy and cyclosporin A was achieved, and the treatment was followed by tocilizumab and rapid reduction of the therapeutic steroid dose. They suggested that the efficacy of tocilizumab for the active phase of adult-onset Still’s disease is unclear (11).

**CONCLUSION**

The presented case report shows that macrophage activation syndrome can happen in the context of adult-onset Still’s disease as a severe complication. When high fever develops in a patient along with pancytopenia, and multiorgan dysfunction with adult-onset Still’s disease, macrophage activation syndrome should be considered. With regards to
classification criteria for hemophagocytic lymphohistiocytosis (10), our case had 5 of nine criteria. We could not evaluate the natural killer cell function and measure the level of CD25 (soluble IL-2 receptor alpha). The use of new IL-1 and IL-6 blocking agents is likely to become the main treatment for adult-onset Still’s disease and, perhaps, change the long term outcome of this disease.

REFERENCES

Table 1. Diagnostic criteria for HLH*

<table>
<thead>
<tr>
<th>Diagnostic criteria for HLH</th>
<th>Present criteria in our case</th>
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<tbody>
<tr>
<td>Fever</td>
<td>quotidian fever over several weeks</td>
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<tr>
<td>Splenomegaly</td>
<td>No</td>
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<tr>
<td>Cytopenia</td>
<td>Yes</td>
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<td>Hypertriglyceridemia or</td>
<td>No</td>
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<td>Hemophagocytosis</td>
<td>Yes</td>
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<td>Hepatitis</td>
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<tr>
<td>Low or absent natural killer cell activity</td>
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<td>Serum ferritin &gt; 500 µg/l</td>
<td>940 µg/l</td>
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<tr>
<td>Soluble CD25 &gt; 2500 U/ml (sIL-2 receptor) &gt; 7200 U/ml</td>
<td>Not determined</td>
</tr>
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*according to HLH-2004 criteria (Henter JI et al.) (10).

Figure 1. A macrophage with platelets and RBC fragments in cytoplasm (Giemsa, 40×10, 100×10).

Figure 2. A macrophage with platelets and WBC fragments in cytoplasm (Giemsa, 40×10, 100×10).