Macrophage Activation Syndrome Associated with Etanercept in a Child with Systemic Onset Juvenile Idiopathic Arthritis

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Systemic onset juvenile idiopathic arthritis or hemaphagocytic syndrome occurs in 10% to 41% of all subtypes of JIA and can be defined as the presence of arthritis in one or more joints associated with daily fever above 39°C for at least 15 days, together with the presence of at least one of the following manifestations: rheumatoid rash, generalized lymphadenopathy, pericarditis, pleuritis, hepatomegaly and/or splenomegaly [1].

Macrophage activation syndrome, a secondary hemophagocytic lymphohistiocytosis, is a potentially severe complication of SOJIA [1-4]. The clinical manifestations and laboratory alterations of MAS are persistent high fever, hepatosplenomegaly, lymphadenopathy, rash, encephalopathy, pancytopenia, increased liver enzymes, hypofibrinogenemia, and high levels of serum ferritin and triglycerides. The hallmark of this syndrome is activated macrophage phagocytosing hematopoietic elements in bone marrow aspirate [1].

Of note, MAS in SOJIA patients can be triggered by viral or bacterial infectious agents and medications, specially non-steroidal anti-inflammatory drugs, methotrexate, sulfasalazine, penicillamine [1,4], and rarely by anti-tumor necrosis factor-alpha agents [2,3].

During a 2 year period 200 rheumatic diseases patients received anti-TNFα agents in the infusion center of our University Hospital. Of the 24 children, only 1 (4.2%) had MAS associated with SOJIA after the introduction of etanercept treatment.

PATIENT DESCRIPTION

A 2.5 year old boy had high fever (> 39°C) daily for 12 weeks, evanescent erythematous rash, generalized lymph node enlargement, hepatosplenomegaly, pericarditis, pleuritis and chronic polyarthritis (shoulders, elbows, wrists, hips, knees and ankles). The diagnosis of SOJIA was determined according to the International League of Associations for Rheumatology classification criteria and he is being followed at the Pediatric Rheumatology Unit in our pediatric department.

He was treated with NSAIDs/indomethacin (2.7 mg/kg/day for 1 year), prednisone (1.5 mg/kg/day for 4 months) and methotrexate (1 mg/kg/week for 2 years). At age 4.5 years old, he had active disease with polyarthritis (elbows, wrists, hips, knees and ankles) and interstitial pneumonitis. At that time, cyclosporine A (5.0 mg/kg/day) and prednisone were given concomitantly with methotrexate and after 10 months he was in stable clinical remission. When he was 8 and 9 years old, prednisone and cyclosporine A were stopped, respectively, and treatment with methotrexate was continued. At age 10 years 7 months, his disease was systematically active with involvement of multiple joints and he was treated with the anti-TNFα agent etanercept (0.8 mg/kg/week, subcutaneously) together with naproxen (15 mg/kg/day) and methotrexate (1 mg/kg/week).

At age 10 years 11 months he was hospitalized with high fever (> 39°C), rash, arthritis of ankles, and pneumonia and was treated with ceftriaxone. At that point, methotrexate and etanercept were stopped. After 10 days hospitalization, he presented with neurological abnormalities (headache and lethargy), vomiting and purpura. He was moved to the pediatric intensive care unit of our university hospital. The laboratory tests showed low hemoglobin concentration (10.7 g/dl), low white blood cell count (3200/mm^3), low platelet count (44,000/mm^3), low fibrinogen (66 mg/dl), high prothrombin time (18.1 sec) and incoagulable activated partial tromboplastin time. Liver enzyme and bilirubin levels were elevated: aspartate aminotransferase 796 IU/L (normal

JIA = juvenile idiopathic arthritis
SOJIA = systemic onset juvenile idiopathic arthritis
MAS = macrophage activation syndrome

TNFα = tumor necrosis factor-alpha
NSAID = non-steroidal anti-inflammatory drug

0–20 IU/L), alanine aminotransferase 165 IU/L (normal 6–20 IU/L), total bilirubin 1.68 mg/dl (normal 0.05–0.3 mg/dl), and direct bilirubin 0.87 mg/dl (normal 0.1–0.6 mg/dl). His erythrocyte sedimentation rate was 23 mm/hour, reactive C protein was 130 mg/L, urea 79 mg/dl and creatinine 1.5 mg/dl. Of note, his serum ferritin levels (18,446 ng/ml), D-dimer concentration (2400 ng/ml) and fasting triglycerides (216 mg/dl) were high. A bone marrow aspirate showed activated macrophage with erythrophagocytosis. All serological tests (hepatitis A, B and C virus, Epstein-Barr virus, cytomegalovirus and human immunodeficiency virus) were negative. Cultures of blood and urine were negative.

A diagnosis of MAS was reached based on clinical and laboratory findings and he was treated three times daily with intravenous methylprednisolone (30 mg/kg) and intravenous cyclosporine A (2.0 mg/kg/day) followed by prednisone (1.0 mg/kg/day) and oral cyclosporine A (5.0 mg/kg/day). His clinical manifestations ameliorated dramatically within 48 hours and laboratory tests showed marked improvement in one week. He remained stable without relapse of MAS and SOJIA during the 3 months follow-up.

COMMENT

This patient had a potentially life-threatening complication of SOJIA but exhibited an adequate response to intravenous methylprednisolone and cyclosporine A. Interestingly, MAS was reported in 7 of our 198 SOJIA patients (3.5%) [1]. Several clinical and laboratory manifestations of MAS may be similar to active SOJIA and sepsis [1,4]. However, various clinical and laboratory findings simultaneously observed in our patient – such as encephalopathy, pancytopenia, coagulation abnormalities, and high levels of liver enzymes and hypertriglycerides – are more suggestive of MAS. Moreover, the high level of ferritin and phagocytes of bone marrow-derived elements (hemophagocytic histiocytes) confirmed this diagnosis since they are hallmarks of this disease [4].

MAS following etanercept treatment was previously described in two SOJIA patients, one after four weekly doses and the other after 2 years of therapy [2,3]. Patients with MAS have a decreased natural killer function with a possible reduction of the capacity to eradicate infected cells and to eliminate antigen stimulation. This deficiency induces T cell activation and proliferation with hypercytokinemia (interferon-gamma and granulocyte macrophage colony-stimulating factor) and macrophage stimulation. The activation of these cells causes an increase in TNFα, interleukin-1 and 6 production with a severe systemic inflammatory reaction [4]. Alternatively, recent studies have suggested that macrophages may play an anti-inflammatory part in MAS, which may cause confusion as to how antigen-presenting cells contribute to the disease pathogenesis [5].

On the other hand, the mechanism whereby etanercept triggers MAS remains unclear. The possible association with viral and bacterial infections is supported by the report of Epstein-Barr virus infection in an MAS patient on etanercept treatment [3]. Likewise, we speculate that bacterial pneumonia was the possible trigger of MAS in the patient described here who was under biological therapy.

There is no standard treatment for MAS patients with rheumatic diseases, but it is recommended that all drugs, including anti-TNFα agents, be withdrawn [1], although two cases of resistant MAS were successfully treated with etanecept [5]. The mainstay of MAS treatment is, in fact, intravenous methylprednisolone and cyclosporine A [1,5]. The present report reinforces the importance of an early diagnosis and prompt introduction of aggressive treatment to achieve a favorable prognosis in MAS patients. The temporal association of anti-TNFα therapy and bacterial infection suggests that these two factors may play a pivotal role in the deregulation of macrophage-lymphocyte interactions of this syndrome.

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"Today you are You, that is truer than true
There is no one alive who is Youer than You"

Dr. Seuss (1904-1991), American cartoonist and writer of children's books, notably *Green Eggs and Ham*, *The Cat in the Hat*, and *One Fish Two Fish Red Fish Blue Fish*. Numerous adaptations of his work have been created, including eleven television specials, three feature films, and a Broadway musical