Macrophage Activation Syndrome Induced by Etanercept in a Patient with Systemic Sclerosis

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Macrophage activation syndrome is a form of secondary hemophagocytic lymphohistiocytosis associated with rheumatic diseases, neoplasia and/or infection [1]. More frequent in children, it has recently been described in an increasing number of adults. Although pathogenetically unclear, MAS is characterized by excessive activation and proliferation of T cells and macrophages leading to an overwhelming systemic inflammatory reaction with a disproportionate release of tumor necrosis factor, interleukin-6 and other cytokines. MAS is often misdiagnosed as sepsis or the exacerbation of an underlying disease [1]. It consists of acute-onset, persistent high fever, neuropsychiatric changes, splenomegaly, hepatomegaly, lymphadenomegaly, reduced number of red cells, white cells and platelets, abnormal liver function, and prolonged thrombin and prothrombin times.

Systemic sclerosis is a chronic rheumatic disease in which cytokines play an important pathogenic role. Biological agents are used today for the treatment of rheumatic disease in children and adults. Infliximab and etanercept for treating systemic sclerosis yield beneficial results and few adverse effects. In a study of 18 patients etanercept appeared to be efficacious in ameliorating active inflammatory joint disease, and it was safe and well tolerated. Health assessment questionnaire scores indicated an improvement following the treatment [2]. On the other hand, patients with juvenile idiopathic arthritis on anti-TNF therapy have an increased incidence of MAS [4]. There have been only two adverse reports on MAS in patients with scleroderma, both related to infliximab and described as a secondary effect of the possibly associated infection that triggered the syndrome. Etanercept or infliximab blocks TNF or TNF receptors and could theoretically aid in the treatment of MAS, but reports are conflicting, with both benefits and adverse reactions described. Etanercept has been used for the treatment of macrophage activation syndrome [3].

We present a patient with systemic sclerosis in whom MAS was precipitated by etanercept, since it was the only new variable prior to the onset of MAS that could explain the onset of the syndrome and there was no other triggering factor

PATIENT DESCRIPTION

A 70 year old woman with tight, shiny and brittle skin as well as hair loss on her forearms, hands, ankles and feet was admitted with complaints of diffuse arthralgias and synovitis in the proximal interphalangeal and metacarpo-phalangeal joints, Raynaud's phenomenon and shortness of breath. She was on symptomatic treatment for several months and underwent an open lung biopsy subsequent to X-ray findings of interstitial increased markings. She was referred for evaluation. A skin biopsy showed increased collagen and absence of fat. Antinuclear antibody was positive while other serologic tests (anti-Ro, anti-LA, anti-RNP, anti-SN, anti-SCL-70, anti-Jo1, anti-DNA) were negative. The diagnosis of systemic sclerosis was based on the history and clinical findings. The patient denied a history of hypertension, alopecia, kidney disease or other illnesses, but was intolerant to non-steroidal medications. Physical examination showed blood pressure of 110/70 mmHg, pulse 72/min, 22 breaths/min, and weight 51 kg. She had sclerodermatous changes on the dorsum of her hands and proximal fingers and mild sinovitis in the interphalangeal and metacarpo-phalangeal joints. Fine rales were heard in both bases with no other important changes. She did not have cardiomegaly and heart sounds were regular and rhythmic with no murmurs or gallop. No pedal edema was detected and the rest of the examination was normal. Echocardiogram revealed a pulmonary pressure of 18 mmHg and mild pericardial thickening. Because of her intolerance to non-steroidal anti-inflammatory medication, prednisone 7.5 mg daily was given for her arthritis.

On reevaluation 3 weeks after the biopsy, she was asymptomatic and doing well and the physical examination was unremarkable. She was scheduled to

MAS = macrophage activating syndrome

TNF = tumor necrosis factor

begin a combined regimen of methotrexate and etanercept, but because methotrexate was unavailable she was only given etanercept 25 mg subcutaneously and was maintained on 7.5 mg prednisone. Intense pruritus developed on her upper extremities that lasted for 8 hours on the day of the injection. Seventy-two hours later she was admitted to the emergency room following 48 hours of nausea, vomiting and abdominal pain; a few hours before admission she developed cough with hemoptysis and was increasingly lethargic. She was febrile, hypotensive, tachycardic and tachypneic (blood pressure 90/60, heart rate 120/min, respiratory rate 40); she had mild jugular venous distension, lymphadenomegaly, a systolic murmur, bilateral rales, tenderness over the right upper abdominal quadrant, and edema in the lower extremities. Laboratory tests showed white blood cells $14.9x10^3$, hemoglobin 5.49 g/dl, hematocrit 21.9, platelets 10^3x10^3, blood urea nitrogen 73 mg/dl, creatinine 7.2 mg/dl, aspartate aminotransferase 183 mg/dl, alanine aminotransferase 96 mg/dl, erythrocyte sedimentation rate 40 mm, low fibrin level, high level of fibrin degradation products, elevated triglycerides 290 mg/dl, and sodium 130 mg/dl. A chest X-ray showed a new bilateral interstitial pattern. A mixed respiratory and metabolic acidosis was observed and she was admitted to the intensive care unit with multiorgan failure as evidenced by renal, liver and respiratory failure. Bronchoscopy demonstrated pulmonary hemorrhage. All cultures and samples of blood, urine, stool, pharynx and bronchial aspirates, which were taken and done repeatedly, were negative for fungi, bacteria and parasites.A bone marrow aspirate revealed multiple macrophages phagocyting cell elements and ferritin. Serum ferritin was 852 ng/ml (normal 4–283 ng/ml, Abbot Axsym Systems, (Abbott Labs, IL, USA) and increased to > 1800 mg/ml on the following days. A diagnosis of MAS was made and the patient was started on cyclosporine and high dose methylprednisolone (30 mg/kg). She required invasive mechanical ventilation and hemodialysis. She also developed melena and a clotting disorder with a non-measurable prothrombin time. There was bleeding from the venipunture sites. Intravenous immunoglobulin was added, with no response. The patient died after 12 days. Limited autopsy with the consent of the family showed changes in the skin consistent with late-stage systemic sclerosis; changes in the liver compatible with erythrophagocytosis, with severe small-droplet steatosis, lipofuscinosis and marked intranuclear vacuolization; interstitial pneumonic changes in the lungs associated with systemic sclerosis, with no evidence of recent hemorrhage or infection; and initial signs of hypertensive cardiomyopathy.

COMMENT

The disease course in our patient, a 70 year old woman, began with shortness of breath, skin changes and arthalgias, with no definitive diagnosis. Symptomatic therapy was initiated. After several months of disease a lung biopsy was performed. Evaluation by a rheumatologist based on the clinical, skin and lung biopsy findings led to the diagnosis of systemic sclerosis. Owing to her intolerance of non-steroidal drugs she was started on 7.5 mg prednisone for the arthritis. Prednisone at a low dose has not been shown to be contraindicated in scleroderma patients or to induce systemic sclerotic renal crisis. Evaluation at the time showed that her condition was stable with amelioration of the joint symptoms and no clinical or laboratory changes. She received etanercept, a TNF antagonist reported to have a beneficial effect on patients with systemic sclerosis; however, within a few hours she developed a non-specific pruritus and MAS.

In a previous report describing MAS in a patient with systemic sclerosis who was receiving infliximab, the MAS was thought to be triggered by an Ebstein-Barr associated viral infection. MAS is triggered by viruses, bacteria, *Mycobacterium*, fungi and other parasites for which various medications are given. Our patient, however, had no evidence of infection in any of the repeated cultures – blood, sputum, urine and stool. Although etanercept has been used successfully in the treatment of MAS [3], it failed in our patient and was even thought to be responsible for the MAS. Etanercept has been associated with triggering MAS in patients with juvenile rheumatoid arthritis, and reports show an increased incidence of MAS in patients on etanercept therapy [4]. The clinical manifestations of MAS include fever, general malaise, fatigue, and mood and behavior changes, severe neurologic deficits, as well as hepatosplenomegaly with abnormal liver function test, low fibrinogen, high level of acute-phase reactants, reduced number of red cells, white cells and platelets, elevation of triglycerides and marked elevation of blood ferritin levels. Macrophages phagocyting blood elements are present in the liver, spleen and bone marrow, and hemorrhage occurs. Our patient had all these features. None of the signs or symptoms could have been interpreted as a systemic sclerotic renal crisis. Her liver findings were consistent with the diagnosis of MAS, since hemophagocytosis was present.

CONCLUSIONS

Macrophage activating syndrome is often underdiagnosed because clinicians are unfamiliar with the diagnosis, especially in adults. Physicians should be more alert to this entity; there is much to learn about this syndrome and the clinician must be able to identify cases that might behave as MAS and might respond only to therapy directed at their triggering factors, or that need additional therapy with methylprednisolone, cyclosporine or etoposide, which is also used in the treatment of

MAS. This diagnosis should also be considered in all patients with autoimmune disease, especially if there appears to be a reactivation of the underlying disease with signs of multiorgan system failure, with or without the presence of viral, fungal or bacterial disease, or when new medications are given. Much has to be learned about the relationship of these triggering factors and the onset of MAS.

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