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CASE REPORT

Successful use of etanercept in the treatment of acute lupus hemophagocytic syndrome

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Abstract Hemophagocytic syndrome has been reported to be associated with systemic lupus erythematosus. A 25-year-old woman with systemic lupus erythematosus developed hemophagocytic syndrome that was refractory to the combination therapy with high-dose corticosteroid, cyclosporine, and high-dose intravenous immunoglobulin, and successfully treated with the tumor necrosis factor inhibitor, etanercept. This case report provided the first observation that etanercept may be useful for the treatment of hemophagocytic syndrome associated with systemic lupus erythematosus refractory to conventional therapy.

Keywords Etanercept · Hemophagocytic syndrome · Systemic lupus erythematosus · Tumor necrosis factor inhibitors

Introduction

Hemophagocytic syndrome (HPS) is a clinicopathologic entity characterized by increased proliferation and activation of benign macrophages with hemophagocytosis throughout the reticuloendothelial system [1]. HPS may develop as a rare but potentially fatal complication of several disorders including malignancies, infections, and autoimmune disorders. Although the pathogenic mechanisms still remain unknown, the excess of interferon-gamma (INF-γ) and tumor necrosis factor-alpha (TNF-α) produced by highly activated type 1 helper T cells and macrophages/histiocytes are suggested to have important roles in the pathogenesis of HPS [2, 3]. HPS has been reported in patients with various connective tissue diseases, such as systemic juvenile idiopathic arthritis, adult-onset Still's disease, scleroderma, dermatomyositis, and systemic lupus erythematosus (SLE) [4]. HPS developed in active SLE patients without evidences of other underlying cause of HPS, such as infections or malignancies, has been called "acute lupus hemophagocytic syndrome (ALHS)".

The first-line therapy for the treatment of HPS associated with autoimmune diseases includes high-dose corticosteroids and immunosuppressives, such as cyclophosphamide and cyclosporine [5]. High-dose intravenous immunoglobulin [6] and anticancer drugs have been used in the refractory cases. Here we report a case of ALHS that was refractory to the combination therapy with high-dose corticosteroids, cyclosporine, and high-dose intravenous immunoglobulin and that was successfully treated with TNF-α inhibitor, etanercept.

Case report

A 25-year-old woman was admitted to our hospital because of continuous fever lasting for 4 weeks and thrombocytopenia. She had no family history of HPS and had been well until 6 months before admission, when she began to have polyarthralgia. Physical examinations at first visit showed

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symmetrical polyarthritis without skin rashes and photosensitivity. Laboratory testing showed positive results of rheumatoid factor and high titers of antinuclear antibodies and anti-DNA antibodies. Kidney function and urinalysis were normal. These finding suggested that the patient had rheumatoid arthritis or arthritis with systemic lupus erythematosus and she was treated with low-dose prednisolone with minimal response. Subsequently, weekly low-dose methotrexate was added. Two months before admission, she developed bilateral non-infectious pleuritis. Antibodies against cyclic citrullinated peptide were negative. Magnetic resonance imaging of affected hand showed active arthritis without erosions and bone edema. The diagnosis of SLE was established by nonerosive polyarthritis, bilateral noninfectious pleuritis, and serological findings. She was treated with 30 mg/day of prednisolone. Pleural effusions and arthritis disappeared, but low-grade fever continued.

On admission, the patient's temperature was 39.5°C and no evidence of arthritis or lymphadenopathy was observed. Laboratory data upon admission were as follows: WBC 3,800 μl^{-1} (neutrophils 57.0%, lymphocytes 38.0%, monocytes 5.0%, eosinophils 0%, basophils 0%), hemoglobin 9.1 g/dl, platelet count 74×10^3 μl^{-1}, fibrinogen 325 mg/dl, FDP 63.6 μg/dl, D-dimer 63.4 μg/dl, blood urea nitrogen 10.3 mg/dl, creatinine 0.7 mg/dl, lactate dehydrogenase 507 U/l, normal transaminases, C-reactive protein 6.1 mg/dl, ferritin 5,560 ng/ml. The test for antinuclear antibodies was positive (×320, homogeneous), and the serum level of anti-DNA antibodies was 42.5 IU/ml (normal range <10). Direct and indirect Coombs tests were negative. Serum complement levels were normal. The urinalysis showed no abnormalities. Thoracoabdominal computed tomography showed no abnormalities other than mild splenomegaly. Treatment with prednisolone (50 mg/day) combined with cyclosporine (200 mg/day) and intravenous bolus methylprednisolone (500 mg for consecutive 3 days) did not improve her febrile state and progressive pancytopenia. A bone marrow aspiration revealed normal hematopoiesis, no malignant cell invasion, but hemophagocytosis with activated histiocytes (Fig. 1). Repeated tests for infectious agents such as blood cultures; hepatitis B surface antigen; antibodies to hepatitis C virus, human immunodeficiency virus, and human T cell leukemia virus; and cytomegalovirus pp65 antigens were all negative. Serological responses of Epstein-Barr virus (EBV) were consistent with post-infectious state. The EBV genome load in the peripheral blood mononuclear cells was slightly increased (8.3×10^1 copies/10^6 cells [normal range $<2.0\times10^1$]), but was substantially smaller than those seen in patients with chronic active EB virus infection or EBV-related malignant lymphoma. She was then diagnosed as having ALHS. From the 52nd hospital day, high-dose intravenous immunoglobulin (20 g/day for consecutive 5 days) was administered, however, no improvement was observed. The patient refused the use of anti-cancer drugs such as vincristine or etoposide. Because of refractory HPS, she was given etanercept (25 mg, twice a week) from the 65th hospital day after obtaining written informed consent. Sustained fever, pancytopenia, and hyperferritinemia lasted 3 weeks after starting etanercept, but thereafter alleviated. The dose of prednisolone could be tapered. On the 92nd hospital day, WBC was 4,000 μl^{-1},

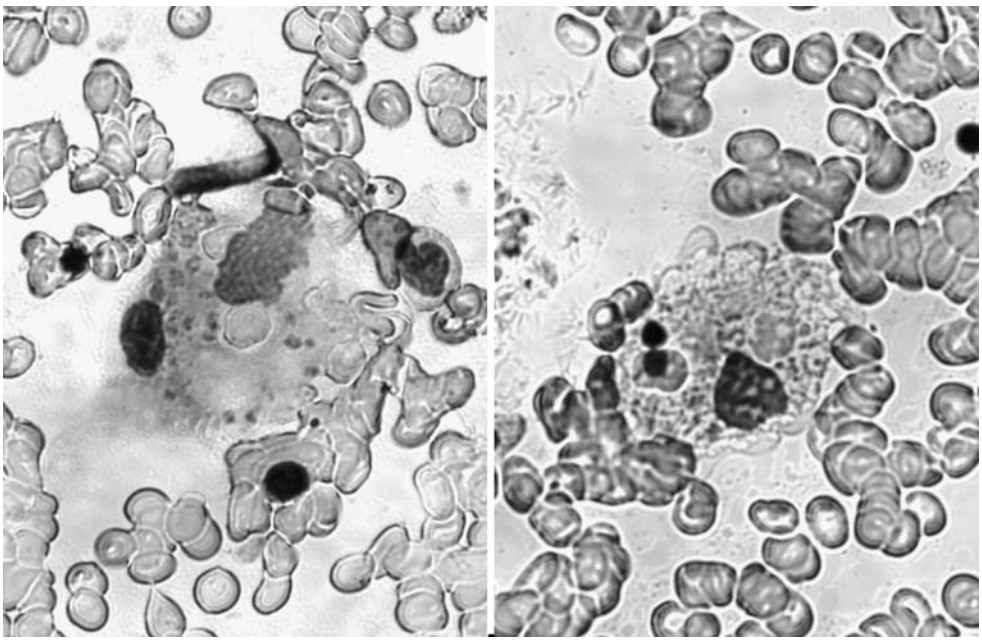

Fig. 1 A bone marrow smear shows activated histiocyte phagocytosing hematopoietic cells (May-Giemsa stain, ×400)

hemoglobin 11.2 g/dl, platelet count 110×10^3 μl^{-1}, and ferritin 149 ng/ml. The patient remains disease free for 6 months under combination treatment with low-dose corticosteroid, cyclosporine, and etanercept, without adverse events (Fig. 2).

Discussion

In this report we describe a patient with ALHS who was refractory to high-dose corticosteroids, cyclosporine, and high-dose immunoglobulin, but was successfully treated with additional administration of the TNF-α inhibitor etanercept.

SLE patients with HPS should be investigated for the potentially concomitant underlying cause of HPS, including infection, malignancies, and drugs. With regard to differential diagnoses of underlying causes of HPS, we should mention some aspects of this case. First, a slight increased amount of EBV-DNA in peripheral blood mononuclear cells observed in this patient was about the same as the levels often seen in patients with SLE [7] and rheumatoid arthritis [8] without clinical EBV infections and was substantially smaller than those seen in patients with chronic active EB virus infection or EBV-related malignant lymphoma. Second, prior methotrexate use might be a possible trigger of HPS in this patient. Ravelli et al. reported on 6-year-old girl with systemic juvenile idiopathic arthritis who developed macrophage activation syndrome with intense and generalized pruritus 24 h after the first methotrexate dosing and improved within a week after withdrawal of methotrexate and additional administration of cyclosporine [9]. Our patient developed HPS after a 4-month course of methotrexate therapy and had no improvement in the clinical findings regarding HPS after withdrawal of methotrexate and administration of cyclosporine. Thus, we think the causal association of methotrexate and HPS in this patient is uncertain. Taking into consideration these factors mentioned above, we diagnosed the patient with ALHS.

HPS was characterized by abnormally activated histiocytes with hemophagocytosis. The abnormal increase of proinflammatory cytokines, such as INF-γ, TNF-α, interleukin (IL)-1, IL-2, IL-6, IL-12 and IL-18 are thought to play an important role in the pathogenesis of HPS. Although it is not clear which cytokines are more deeply involved, excellent clinical response to etanercept in our patient suggested that TNF-α has a major role among them in HPS associated with SLE. Henzan et al. reported on an SLE patient with refractory hemophagocytic lymphohistiocytosis without evidence of infection and malignancy was successfully treated with infliximab [10]. TNF-α inhibitors had been successfully used for the treatment of refractory HPS associated with systemic juvenile idiopathic arthritis [11] and adult-onset Still's disease [12]. These observations along with the clinical course of this report indicated that TNF-α plays a major role in the pathogenesis of HPS associated with autoimmune diseases.

It has been reported that anti-DNA antibodies [13] and drug-induced lupus [14] may appear during therapy with anti-TNF-α inhibitors. We used etanercept in this patient by consideration of the previous report that showed that anti-DNA antibodies were more frequently observed in patients treated with infliximab than those with etanercept [15]. Although we observed neither an increase of anti-DNA antibodies nor drug-induced lupus in this patient, careful follow-up is required.

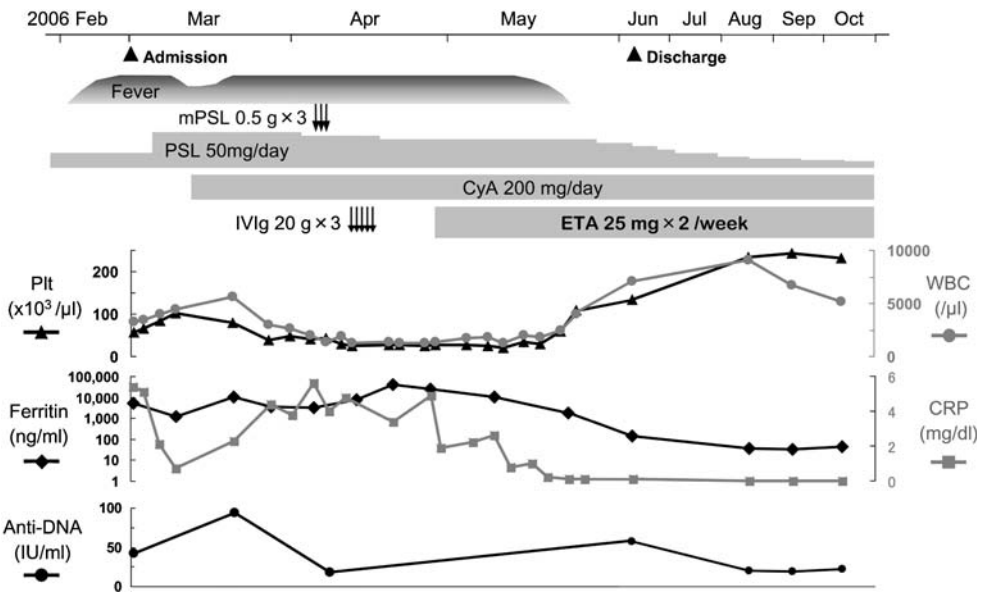

Fig. 2 Clinical course. Abbreviations: *CRP* C-reactive protein; *CyA* cyclosporine; *ETA* etanercept; *IVIg* intravenous immunoglobulin; *mPSL* methylprednisolone; *Plt* platelet count; *PSL* prednisolone; *WBC* white blood cell count

In conclusion, this case report provides the first observation that ALHS refractory to conventional therapy was successfully treated with additional administration of TNF-α inhibitor, etanercept. The concomitant use of these TNF-α inhibitors with corticosteroids and cyclosporine deserves further study in refractory ALHS or HPS associated with other autoimmune disorders.

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