INTERNAL MEDICINE

□ CASE REPORT □

Etanercept-Induced Lupus Accompanied by Hemophagocytic Syndrome

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Abstract

Hemophagocytic syndrome (HPS) is a severe, potentially life-threatening disorder characterized by an excessive activation of macrophages, such as may occur in the setting of lupus. A 62-year-old Japanese woman treated with etanercept for rheumatoid arthritis developed persistent fever, cytopenia, coagulopathy, and hyperferritinemia. Simultaneously, lupus-like features including pleuritis, hypocomplementemia, and positive autoantibodies were observed. She was diagnosed with HPS related to etanercept-induced lupus, and underwent immunosuppressive therapy with successful recovery. To our knowledge, this is the first case of etanercept-induced lupus accompanied by HPS. This case suggests that HPS should be considered as a complication during TNF-α inhibitor therapy.

Key words: hemophagocytic syndrome, drug-induced lupus, TNF-α inhibitor, rheumatoid arthritis

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Introduction

Hemophagocytic syndrome (HPS) is rare and frequently life-threatening despite treatment. It may develop as a complication of several disorders including malignancies, infections, and autoimmune diseases. HPS is characterized by an overwhelming activation of macrophages, lymphocytes, and cytokine overproduction (1).

Since the advent and subsequent widespread use of tumor necrosis factor (TNF)-α inhibitors therapy for the treatment of systemic inflammatory disorders, such as rheumatoid arthritis (RA) and Crohn's disease, several cases of drug-induced lupus (DIL) and "lupus-like" syndromes associated with the use of TNF-α inhibitors have been reported (2). DIL can be defined as a syndrome of "lupus-like" signs, such as fever, arthralgias, rash, and serositis, temporally associated with the use of a drug implicated in induction of autoimmunity, which resolves after withdrawal of the offending drug (2).

Although cases of HPS in association with systemic lupus erythematosus (SLE) (3) and RA treated with TNF-α inhibitor (4, 5) have been reported recently, there have been no such published case reports on HPS with TNF-α inhibitor-induced lupus. To the best of our knowledge, we describe here the first reported case of etanercept-induced lupus accompanied by HPS.

Case Report

A 62-year-old Japanese woman with an 8-year-history of seropositive RA, treated with etanercept for 3 years, was referred to our hospital because of persistent high fever, pancytopenia, and disseminated intravascular coagulation (DIC).

At the initiation of etanercept treatment, laboratory data showed normal blood counts (leukocyte counts: 7,200/μL, hemoglobin level: 11.6 g/dL, platelet count: 250,000/μL), and serum complement levels were slightly elevated only in C3 (C3: 142 mg/dL, normal 44 to 102 mg/dL, C4: 33 mg/dL, normal 14 to 49 mg/dL, CH50: 45 U/mL, normal 31 to

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Table 1. Laboratory and Coagulation Data

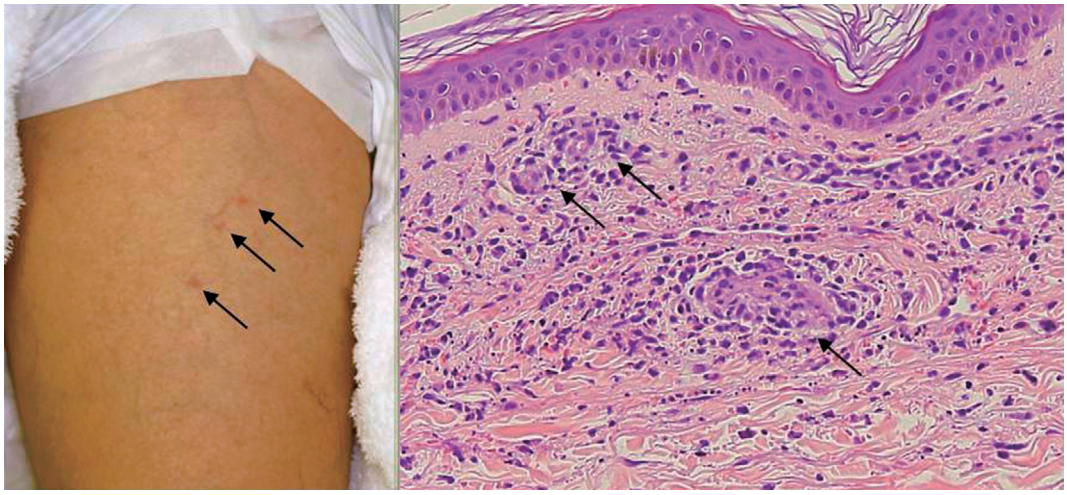
WBC (/μL)	3,090	IgG (mg/dL)	3,121
Neutrophil (%)	83	IgA (mg/dL)	434
Eosinophill (%)	2	IgM (mg/dL)	302
Lymphocyte (%)	10	C3 (mg/dL)	22
Hb (g/dL)	8.3	C4 (mg/dL)	3
Plt (/μL)	12,000	CH50 (U/mL)	8
BUN (mg/dL)	17	ANA	×1280
Cr (mg/dL)	0.59		homogeneous
Na (mEq/L)	126	dsDNA	14
K (mEq/L)	4.0	Anti-smith antibody	(-)
Cl (mEq/L)	96	RF (IU/mL)	720
AST (IU/L)	67	Ferritin (ng/mL)	5,340
ALT (IU/L)	24	CRP (mg/dL)	4.1
LDH (IU/L)	475	FDP (μg/mL)	90.3
TP (g/dL)	6.8	D-dimer (μg/mL)	46.9
Alb (g/dL)	2.0	Fbg (mg/dL)	206
T-Bil (mg/dL)	1.1	PT time (second)	11.5
ALP (IU/L)	174	PT-INR	0.89
γ-GTP (IU/L)	20	APTT (second)	35.4

49 U/mL). Anti-nuclear antibodies (ANA) were positive at a titer of 1 : 640. Nine months before admission, leukocytopenia (2,770/μL) slowly developed without clinical symptoms. Six months before admission, serum complement levels started to decrease (C3: 82 mg/dL, C4: 8 mg/dL, CH50: 32 U/mL) and low titers of anti-double strand (ds) DNA antibodies (16 IU/mL, normal <12 IU/mL), and high titer of anti-single strand (ss) DNA antibodies (50 AU/mL, normal < 25 AU/mL) were detected. Five months before admission, leukocytopenia between 2,000 and 3,000/μL persisted without obvious infection, despite reduction of the methotrexate dosage from 6 to 4 mg per week. One month before admission, there was sustained leukocytopenia without a decrease of hemoglobin or platelets (blood cell 2,750/μL, hemoglobin 11.8 g/dL, platelet count 152,000/μL). Serum complement levels and anti-DNA antibody were checked again to rule out DIL, and decreased complement levels (C3: 37 mg/dL, C4: 3 mg/dL, and CH50: 8 U/mL) and slightly elevated anti-dsDNA antibody (35 IU/mL) and anti-ssDNA antibody (115 AU/mL) were detected.

Three weeks before admission, she started to develop redness, swelling, and warmth on her left lower extremity with a high fever. Three days later, she was admitted to a local hospital with a diagnosis of cellulitis, and subsequently was started on 2 g per day of cephazolin intravenously. Six days later, blood culture yielded methicillin-sensitive *Staphylococcus aureus* (MSSA). Although the localized redness and swelling on her left lower extremity improved, she had persistent fever of over 39℃. Five days before transfer, the follow-up laboratory data showed pancytopenia with white blood cell count 2,000/μL, hemoglobin 8.5 g/dL, platelet count 84,000/μL, D-dimer 43 μg/mL (normal <1.0 μg/mL), and fibrin/fibrinogen degeneration product (FDP) 58 μg/mL (normal <5 μg/mL), suggestive of DIC. She was transferred to our hospital for further evaluation and treatment.

On admission she denied any constitutional symptoms other than fever, chills, and anorexia. There was no history of specific trauma to her left lower extremity. Her past medical history revealed bilateral total knee arthroplasty and left total hip arthroplasty. Her medications included 3 mg per day of oral prednisolone, 4 mg per week of methrotrexate, and 25 mg per week subcutaneous etanercept, which was discontinued one week before admission. There was no smoking or drinking habit. She was alert and oriented, and in mild distress. On examination, her temperature was 38.7℃, blood pressure 150/77 mmHg, pulse rate 125 beats per minute, respiratory rate 25 per minute, and SpO_2 93% on 2 liter nasal cannula. There was no jugular venous distension. Cardiac examination revealed tachycardia without murmur or gallop. Lungs were clear to auscultation. There was no organomegaly or palpable lymphoadenopathy. She had mild swelling, erythema, and tenderness on her left lower extremity. No rash or arthritis was noted. Neurological examination was normal. White blood cell count was 3,000/μL (neutrophils 83%, lymphocytes 10%), platelet count 12,000/μL, plasmin α2-plasmin-inhibitor complex 5.6 μg/mL (normal <0.8 μg/mL), thrombin-antithrombin complex 20.1 μg/L (normal <3 μg/L), fibrinogen (Fbg) 206 mg/dL (normal 183 to 381 mg/dL), D-dimer 46.9 μg/mL, and FDP 90.3 μg/mL. Mild liver dysfunction (aspartate aminotransferase 67 IU/L, alanine aminotransferase 24 IU/L) was noted, and the ferritin level was elevated (5,340 ng/mL). The results of the other laboratory tests on admission are listed in Table 1. Urinalysis showed no hematuria, proteinuria, or casts. Blood gas analysis, drawn while breathing ambient air, revealed pH 7.446, $PaCO_2$ 32.1 mmHg, PaO_2 74.6 mmHg, and HCO_3^- 21.7 mEq/L. All blood cultures were negative. Venous ultrasound showed no findings suggestive of deep vein thrombosis in the legs. The tentative diagnosis was uncontrolled cellulitis due to MSSA infection accompanied by DIC. Intravenous 4 g per day of cephazolin was continued with nafamostat mesilate 150 mg per day and a platelet transfusion.

On hospital day 2 respiratory failure developed rapidly. There were no rales or wheezes. The chest x-ray showed bilateral pleural effusion with normal cardiac silhouette. Echo-



A B

Figure 1. **A: Palpable non-branching macular rash appeared on the left thigh (arrows), B: Skin biopsy showing leukocytoclastic vasculitis.**

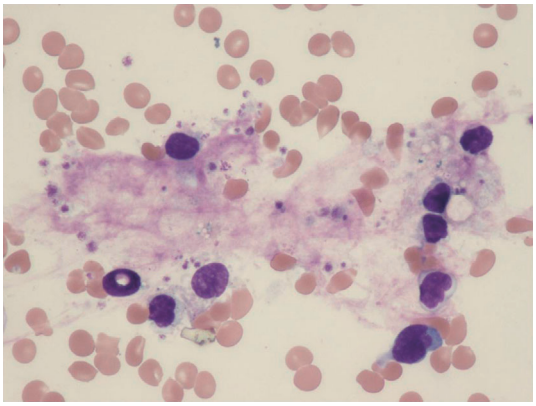


Figure 2. **Bone marrow aspirate. Cluster of macrophages engulfing cellular debris (May-Giemsa stain, ×400).**

cardiography revealed no left ventricular dysfunction, valvular dysfunction, or right ventricular load. We suspected acute respiratory distress syndrome due to sepsis. At this point, the white blood cell count dropped to 2,080/μL (neutrophils 73%, lymphocytes 22%) and hypofibrinogenemia (149 mg/dL) developed. Platelets were transfused for severe thrombocytopenia. She was intubated under general anesthesia, and started on 500 mg per day of methylprednisolone for three days. Her urinary output decreased to 20 mL/hr (0.3 mL/kg per hour), and continuous hemodiafiltration (CHDF) was initiated. No hematuria or proteinuria was observed and fractional excretion of Na was 0.2%, suggesting the cause of the acute kidney injury to be pre-renal. Cephazolin was discontinued, and 1 g per day of meropenem, 1,200 mg per day of linezolid, 3,000 U per day of dalteparin, 1,500 U per day of antithrombin III, and 300 mg (4.8 mg/kg) per day of sivelestat were started.

On hospital day 3, a palpable non-branching macular rash appeared on the upper back and lower extremities (Fig. 1A). Skin biopsy showed diffuse polymorphonuclear leukocyte infiltration with nuclear dust at the walls of small vessels in the superficial dermis without thrombus formation, suggestive of leukocytoclastic vasculitis (Fig. 1B). The findings of hyperferritinemia, cytopenia, and DIC prompted us to investigate the possibility of HPS. Cytokine profile analysis included neopterin 122 nmol/L (normal <5 nmol/L), TNF-α 97 pg/mL (normal <15 pg/mL), interleukin (IL)-6 21 pg/mL (normal <5 pg/mL), and IL-18 1,860 pg/mL (normal <500 pg/mL). Additional laboratory tests showed elevated soluble IL-2R to 5,307 U/mL (normal 150 to 505 U/mL) with no data suggestive of Epstein-Barr virus (EBV) infection (anti EB nuclear antibody was positive with low titer: ×40) or cytomegalovirus infection. Bone marrow biopsy showed hypocellularity without any cells suggesting hematologic malignancy. The total nuclear cell count was 12,000/μL with 0.8% (normal <0.8 %) being hemophagocytic macrophages (Fig. 2). Although this proportion did not meet the criteria (3%) suggested by Tsuda (6), we presumptively diagnosed HPS on the basis of findings of pancytopenia, hyperferritinemia and the prominent increase of macrophage-tropic cytokines.

On hospital day 4, computed tomography of the chest and abdomen showed bilateral massive pleural effusion without obvious lung infiltrates, congestion, or lymphadenopathy. Thoracentesis yielded exudative pleural effusion with a normal glucose level, positive ANA at a titer of 1 : 1,280, and decreased complement level (C3: 8 mg/dL, C4: 1 mg/dL, and CH50: 6 U/mL), all compatible with serositis associated with SLE or RA (7, 8). We reviewed the laboratory data one month before the onset of cellulitis, which showed leukopenia, hypocomplementemia, positive ANA at a titer of 1 : 1,280, staining homogeneous pattern, and positive anti-dsDNA antibodies. Anti-histone antibodies were positive at 5.1 Units (normal <1.0 Unit). The patient was diagnosed with SLE, based on serositis, hematological abnormalities, positive ANA, and positive anti-dsDNA antibodies, and by ruling out alternative diagnoses.

The symptoms including respiratory failure were gradu-

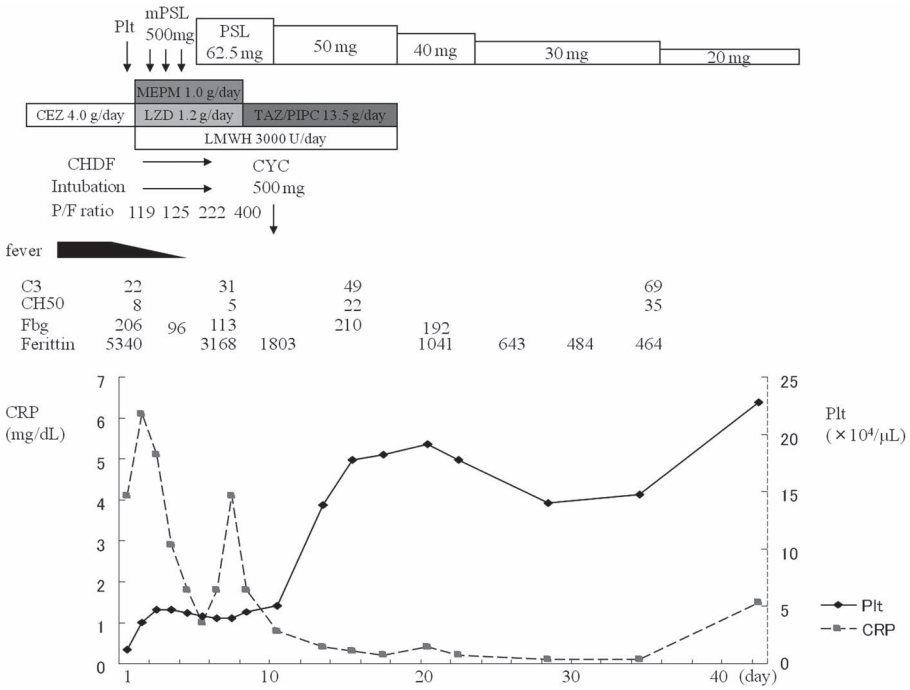


Figure 3. **Clinical course. Abbreviations: Plt: platelets, mPSL: methylprednisolone, PSL: prednisolone, CEZ: cephazolin, MEPM: meropenem, LZD: linezolid, TAZ/PIPC: tazobactam/piperacillin, LMWH: low molecular weight heparin, CHDF: continuous hemodiafiltration, P/F ratio: PaO_2/FiO_2, CYC: cyclophosphamide, Fbg: Fibrinogen, CRP: C-reactive protein**

ally improved with intravenous 500 mg per day of methylprednisolone for three consecutive days, followed by 62.5 mg per day oral prednisolone (1 mg per kg per day). Five days after initiating CHDF, her urinary output increased to 40 mL/hr and CHDF was terminated. On hospital day 7, follow-up cytokine profile analysis showed still elevated serum cytokine levels, suggesting the presence of uncontrolled HPS. We administered 500 mg per day of cyclophosphamide, with marked improvement of the clinical symptoms, such as respiratory failure, leukocytoclastic vasculitis, pancytopenia, and decrease of serum ferritin levels thereafter (Fig. 3).

Discussion

Here, we describe an RA patient who gradually developed etanercept-induced autoimmunity. This subsequently progressed to an active ”lupus-like” syndrome accompanied by HPS, triggered by Staphylococcal skin infection.

In this case, drug-induced autoimmunity gradually appeared without any obvious trigger during etanercept treatment, based on slightly decreased leukocyte counts and serum complement levels, and elevated titer of anti-DNA antibody before the onset of Staphylococcal skin infection. This infection was considered to be the trigger for the onset of active lupus, fulfilling four of the American College of Rheumatology criteria for SLE, based on serositis, leukocytopenia, thrombocytopenia, positive ANA and anti-dsDNA. It is difficult to determine whether the “lupus-like” symptoms were associated with RA, etanercept use, or neither. Shakoor et al stated that identification of DIL in RA patients is challenging because of an overlap of the clinical features (9). In most case reports, drugs are implicated as the etiology when the timing of the onset and remission of “lupus-like” symptoms are closely related to the period of TNF-α inhibitor therapy (2, 9-11). Although the data of immunological tests before treatment with etanercept are limited, the resolution of “lupus-like” symptoms with normalized leukocyte counts, anti-dsDNA antibodies, and complement levels after discontinuation of the etanercept treatment suggests an association between etanercept therapy and “lupus-like” symptoms in this case (Fig. 3).

HPS was first reported in 1939 by Scott and Robb-Smith (12). It is a macrophage-related histiocytic disorder characterized by an excessive activation of well-differentiated macrophages, resulting in high fever, cytopenias, liver dysfunction, coagulopathy, and hyperferritinemia. The disorder is divided into primary and secondary forms. Primary, or familial, HPS is a group of genetic diseases, frequently affecting children under the age of 2 years. Secondary, or reactive, HPS may develop as a severe complication of several disorders including malignancies and infections (1, 13). In 1995 and 1997, Kumakura et al reported cases of reactive HPS which were associated with autoimmune diseases (14, 15), and proposed a new disease entity, autoimmune-associated hemophagocytic syndrome (AAHS) (16), which has become widely accepted. Once a diagnosis of HPS is suspected, an underlying disease and a possible trigger should be sought.

Diagnostic guidelines of HPS were proposed by the Histi-

ocyte Society in 1991 and updated in 2004 (17). To facilitate the diagnosis of HPS, in 2009 the Histiocyte Society developed comprehensive diagnostic guidelines including both clinical and laboratory findings (18). Importantly, neither the 2004 nor 2009 criteria indicate hemophagocytosis as an absolute finding required for the diagnosis. If hemophagocytosis is absent in an initial biopsy specimen, a subsequent biopsy should be contemplated (1). Some authors have insisted that hemophagocytosis is not essential for the diagnosis of HPS nor should it be overestimated in the absence of any signs of massive histiocytic activation (19).

The present patient fulfilled both the 2004 and 2009 diagnostic criteria proposed by the Histiocyte Society, based on fever, bicytopenia, hypofibrinogenemia, hyperferritinemia, elevated sIL-2R, liver dysfunction, and hyponatremia, despite which, it was challenging to differentiate HPS from active flare of lupus since some clinical features may overlap (20). Recently, Parodi et al published a paper on this point (21). They reported that among laboratory features, hyperferritinemia is the most sensitive and specific finding for the diagnosis of HPS in juvenile SLE. Hence, the extremely high level of ferritinemia in the present case would support the presence of HPS. Furthermore, we observed prominently increased levels of macrophage-tropic proinflammatory proteins (neopterin, TNF-α and IL-6) relative to the levels of usual lupus patients (22). Shimizu et al reported that cytokine production including neopterin, IL-6 and IL-18 was enhanced in juvenile idiopathic arthritis-associated HPS and that such a cytokine profile may be a hallmark of HPS in juvenile idiopathic arthritis (23). Collectively, these findings would support the involvement of HPS in the present case. In addition, numerous papers have shown that drug-induced lupus does not usually require additional immunosuppressive therapy, and rarely progresses to an active state (24). Considering this point, it was difficult to attribute all severe complications to DIL alone in this case. We tentatively diagnosed HPS, and started intravenous pulse methylprednisolone followed by intravenous cyclophosphamide because any delay in the treatment of HPS often leads to a fatal outcome. Rouphael et al stated that an incomplete satisfaction of all HPS criteria should not preclude the initiation of therapy since it can be life-saving and some of the clinical criteria occur late in the course of the disease (1). The possibility of reactive HPS to other than staphylococcal skin infection was extensively investigated (1, 25). But no lymphoma or other infections including EBV-related conditions were detected in the present case.

The precise pathogenesis of HPS remains unknown. It is speculated that the culprit in this syndrome is a dysregulation of macrophage-lymphocyte interactions with subsequent increases in the levels of both T-cell-derived and macrophage-derived cytokines, particularly TNF-α, IL-1, IL-6, interferon gamma, resulting in a massive systemic inflammatory reaction, which may underlie this syndrome (23, 26). Furthermore, it is reported that not only cytokines but also autoantibodies and immune complexes might contribute to the development of HPS associated with autoimmune diseases (3, 16).

TNF-α inhibitor-induced lupus is known to differ significantly from non-TNF-α inhibitor-induced lupus. More than 50% of TNF-α inhibitor-induced lupus patients have dsDNA antibody and hypocomplementemia in contrast to other drug-induced lupus in which they are mostly normal (2). In the present case, dsDNA antibody was detected and complement levels were very low during the disease flare. In addition, cytokine profile analysis showed elevated cytokine levels. Thus, we speculate that these mechanisms may underlie the pathogenesis of HPS in TNF-α inhibitor-induced lupus (3, 16, 27).

Although bacteria-associated hemophagocytic syndrome has been reported in the literature, it is very rare (25). Aouba et al reported a case of HPS in an RA patient treated with TNF-α inhibitor, and implied that the immunosuppression thereby induced might be responsible for the *Escherichia coli* infection leading to massive cytokine production and finally HPS (4). They postulated that the cause of reactive HPS during infection consists of the infection itself as a trigger and an underlying immune defect as a predisposing factor (4). In the present case, we assume that the immune defect and autoimmunity induced by etanercept existed as a predisposing factor for infection, triggering HPS and active "lupus-like" syndrome.

In conclusion, we described here the first reported case of etanercept-induced lupus accompanied by HPS that responded well to intravenous methylprednisolone as well as intravenous cyclophosphamide. When unexplained persistent fever, cytopenia, coagulopathy, and hyperferritinemia appear during TNF-α inhibitor therapy, physicians should be aware that HPS can be a complication, for which diagnostic tests and treatment should be promptly implemented.

The authors state that they have no Conflict of Interest (COI).

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