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CASE REPORT

Etanercept-refractory adult-onset Still's disease with thrombotic thrombocytopenic purpura successfully treated with tocilizumab

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Abstract We report the case of a 69-year-old Japanese woman who presented with thrombotic thrombocytopenic purpura (TTP) which had manifested soon after the onset of adult-onset Still's disease (AOSD). Her disease was multi-drug resistant. She had undergone treatment with high-dose glucocorticoids, two courses of steroid pulse therapy, and cyclosporine A. The patient initially had a favorable response to the administration of etanercept (an anti-tumor necrosis factor agent) and glucocorticoids. However, her disease became refractory to etanercept after 6 months. Therefore, we administered tocilizumab (a humanized monoclonal anti-IL-6 receptor antibody) which dramatically improved the patient's refractory AOSD with TTP. This is the first report of an effective treatment for AOSD with TTP using the biological agents. Our report strongly suggests that biological agents, especially a humanized monoclonal anti-IL-6 receptor antibody, may be a new option for a safe and effective treatment of multi-drug-resistant AOSD and TTP associated with AOSD.

Keywords Adult-onset Still's disease · Etanercept · Thrombotic thrombocytopenic purpura · Tocilizumab

Introduction

Adult-onset Still's disease (AOSD) is a multi-systemic inflammatory disease of unknown cause. It affects various organs and is characterized by a typical spiking fever, arthritis, rashes, and leukocytosis [1]. Cytokines (e.g., interleukin 1 (IL-1), IL-6, and IL-18), interferon γ, and tumor necrosis factor (TNF) may play a role in the pathogenesis of the disease [2]. Thrombotic thrombocytopenic purpura (TTP) is a multi-systemic disorder characterized by consumptive thrombocytopenia, microangiopathic hemolytic anemia, neurological abnormalities, renal dysfunction, and fever. The coexistence of AOSD and TTP is so rare that, to our knowledge, only 11 cases exist in the medical literature. There are no reports of the use of biological agents to treat patients affected by both AOSD and TTP. Here, we report an extremely rare case of a patient with multi-drug-resistant AOSD and TTP that was refractory to etanercept (an anti-TNF agent) whom we successfully treated with tocilizumab, a humanized monoclonal anti-IL-6 receptor antibody.

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Case report

A 69-year-old Japanese woman suffering from spike fever, polyarthralgia, sore throat, and an evanescent rash was admitted to her local hospital. She had no remarkable past medical history. Laboratory examination revealed a white blood count (WBC) of 15.6×10^9/L (91% neutrophil), hemoglobin 12.1 g/dL, platelet count 234×10^9/L, and erythrocyte sedimentation rate (ESR) of 65 mm/h. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were normal. The level of aspartate aminotransferase (AST) was 107 U/L (normal 13–33 U/L); alanine aminotransferase (ALT), 52 U/L (normal 6–27 U/L); and lactate dehydrogenase (LDH), 1,334 U/L (normal 119–229 U/L). The C-reactive protein level was 15.6 mg/dL and

serum ferritin, 13,232 mg/L (normal 5–80 mg/L). Urinalysis was normal. Chest radiography, electrocardiogram, and transthoracic echocardiogram were also normal. Transabdominal echography and abdominal computed tomography (CT) showed splenomegaly. Blood, urine, and stool cultures were negative. The results of acid-fast stained smears and culture ruled out a diagnosis of tuberculosis. Laboratory evaluations ruled out infections and systemic or malignant diseases. From these findings and based on the Yamaguchi criteria, the physicians at her local hospital diagnosed her with AOSD [3].

The patient underwent methylprednisolone (1 g/day) and cyclosporine A (CyA; 150 mg/day) treatment administered intravenously for 3 days, followed by prednisolone (PSL) at 60 mg/day (1 mg/kg) per os, but this did not control her symptoms. Ten days after finishing the steroid pulse therapy, she underwent a second steroid pulse (1 g/day) and CyA (150 mg/day) treatment for 3 days, followed by PSL at 40 mg/day per os and CyA at 100 mg/day. This did not fully control her disease. Ten days later, she developed severe oliguria, suddenly became confused and agitated, and had acute renal failure (urea nitrogen 113.9 mg/dL, creatinine 4.4 mg/dL), anemia (hemoglobin 8.1 g/dL), and thrombocytopenia (platelet count 92×10^9/L). These findings led us to the clinical diagnosis of TTP associated with AOSD. Her disease remained uncontrollable despite the administration of daily plasma exchange for 3 days. She was referred to our hospital for further treatment.

On admission, she was agitated and her Glasgow coma scale score was 7. She was in mild respiratory distress with a regular, respiratory rate of 20 breaths/per minute. Her temperature was 38.0°C; pulse, 100 beats/min; and blood pressure, 118/82 mmHg. Hematological findings were a WBC of 24.2×10^9/L (95% neutrophil), hemoglobin, 8.0 g/dl; platelet count, 48×10^9/L; and an ESR, 23 mm/h. The PT and APTT were normal. Biochemical values for the LDH level was 1267 U/L; urea nitrogen, 127 mg/dL; creatinine, 4.7 mg/dL; AST, 257 U/L; ALT 78, U/L; total bilirubin, 5.1 mg/dL; and direct bilirubin, 4.0 mg/dL. Electrolyte levels indicated hypocalcemia (Ca, 6.1 mg/dL) and hyperphosphatemia (P, 6.5 mg/dL). Her serum ferritin level was markedly elevated (37,000 mg/L). The Coombs test was negative and the serum haptoglobin level was decreased (13 mg/dL). The peripheral blood smear contained red cell fragmentation (2.65%). Urinalysis detected 11 to 30 red cells and six to ten leukocytes per high-power field and proteinuria (1.5 g/day). She had a normal brain CT at this point.

She received daily plasma exchange, hemodialysis, blood transfusion, and PSL at a dose of 40 mg/day. On the third hospital day, she had a tonic–clonic generalized seizure, after which she remained comatose. That same day, her respiratory distress worsened. Arterial blood gas tests revealed severe hypoxemia (PaO_2 of 42 mmHg) and hypercapnia ($PaCO_2$ of 61 mmHg). Chest CT displayed bilateral pleural effusion and diffuse alveolar densities. She required intubation and mechanical ventilation. We believed that AOSD produced these clinical features, so we treated her with etanercept (an anti-tumor necrosis factor agent) at a dosage of 50 mg/week. Within a month, her fever resolved; the levels of serum ferritin, ALT, and LDH decreased to 2,833 mg/L, 21 U/L, and 252 U/L, respectively; the platelet count rose to 131×10^9/L, her renal function returned to normal, and her respiratory condition improved.

We successfully extubated her on the 27th hospital day. We ceased plasma exchange after 16 sessions on the 29th hospital day. Along with the continuous administration of etanercept, we continued enteral PSL, gradually tapering it to 10 mg/day. Two months after presentation, the patient's TTP and AOSD were almost fully controlled, except for her consciousness disorder. On the 35th hospital day, brain magnetic resonance (MR) imaging using the techniques of diffusion-weighted imaging and fluid-attenuated inversion recovery revealed bilateral diffuse high-intensity areas in the cerebral white matter. Electroencephalography showed generalized slowing and voltage suppression. These findings did not indicate neurological features typical of TTP such as ischemic and hemorrhagic strokes and reversible posterior leukoencephalopathy syndrome [4]. However, we administered aspirin (100 mg/day) for her consciousness disorder in case of TTP-associated microangiopathic cerebral infarction.

Four months later, symptoms of spike fever and skin rush and elevated levels of serum ferritin, ALT, and LDH had gradually resumed, despite increasing the PSL dosage to 20 mg/day and the constant administration of etanercept. Since her disease proved refractory to PSL and etanercept, we intravenously administered a 360 mg (8 mg/kg) dose of tocilizumab (a humanized monoclonal anti-IL-6 receptor antibody) in place of etanercept. Within a month after the administration of tocilizumab, her fever and skin rash gradually improved and the levels of serum ferritin, ALT, and LDH fell to normal. We tapered PSL to 10 mg/day within 2 months. The monthly administration of 360 mg of tocilizumab was safe and the patient had no infections. Her consciousness disorder and brain MR imaging findings did not improve significantly throughout her hospital stay. Nevertheless, no further fluctuations or flare-ups of AOSD and TTP occurred. We discharged her on the 307th hospital day (Fig. 1).

Discussion

Adult-onset Still's disease is a multi-systemic inflammatory disease of unknown cause that affects various organs and is characterized by a spiking fever, arthritis, rashes, and

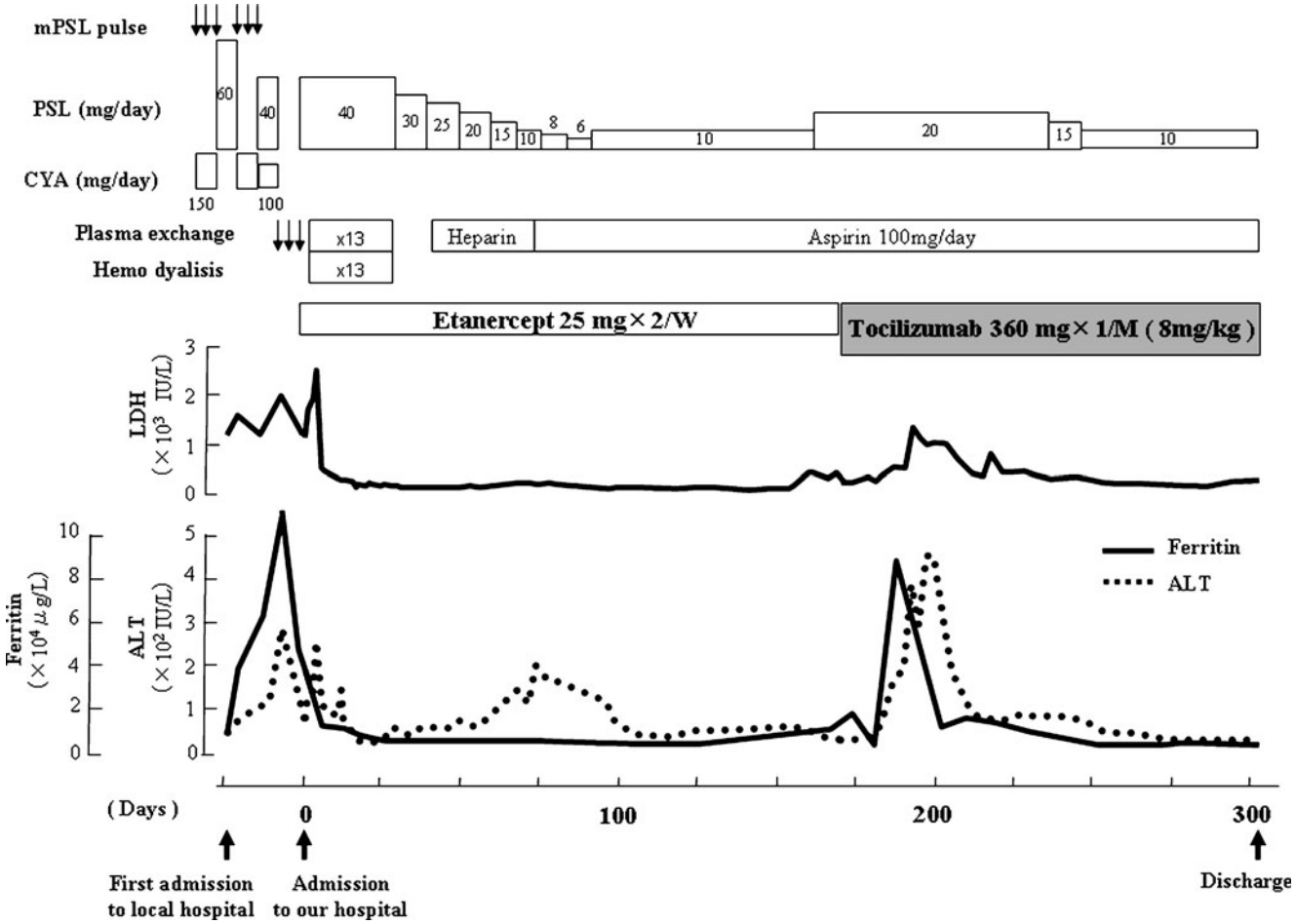

Fig. 1 Summary of the clinical course. Improvement on the levels of serum ferritin, ALT, and LDH by tocilizumab treatment in a patient with multi-drug-resistant and etanercept-refractory AOSD with TTP

leukocytosis [1]. Various cytokines (e.g., IL-1, IL-6, and IL-18), interferon γ, and TNF may have a role in the pathogenesis of AOSD [2]. Depending on the presentation and disease course, treatment approaches may include non-steroidal anti-inflammatory drugs, steroids, methotrexate, gold, azathioprine, leflunomide, cyclosporine, and biological agents (e.g., anti-TNF agents, anti-IL-1 receptor agents, or rituximab) [5]. Several publications have reported the use of anti-TNF agents—particularly infliximab and etanercept—in treating AOSD. However, anti-TNF agents seem ineffective in patients with refractory AOSD, and switching between anti-TNF agents for treatment can also be ineffective [5]. It is not clear why the use of anti-TNF agents or why switching between them is ineffective, but recent studies suggest that the degree of functional drug levels and clinical responses is correlated with the presence of antibodies against anti-TNF agents [6].

Anakinra directly inhibits IL-1, demonstrating that IL-1 may have a causative role in AOSD. The direct blockade of the IL-6 receptor may also implicate IL-6 in the pathogenesis of AOSD. Fitzgerald et al. propose that a cytokine cascade may play a role in AOSD. They believe that TNF-α induces the production of IL-1, which stimulates the production of IL-6 [7]. Tocilizumab directly inhibits IL-6 (the downstream cytokine). Therefore, the monthly administration of tocilizumab may be more convenient than the daily administration of anakinra for clinical use. There are few reports concerning the efficacy of tocilizumab in treating AOSD. However, some reports have recently revealed that tocilizumab is effective in patients with treatment-resistant AOSD [8, 9].

TTP is a rare multi-system disorder characterized by consumptive thrombocytopenia, microangiopathic hemolytic anemia, neurological abnormalities, renal dysfunction, and fever. Endothelial damage may initiate a cascade of events in TTP, resulting in thrombotic microangiopathy [10]. Endothelial injury and activation triggers can be bacterial and viral infections, cytokines, neoplasms, transplantation, pregnancy, drugs (mainly chemotherapy), and anti-endothelial antibodies. Decreased activity of von Willebrand factor-cleaving protease (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS-

13)) also plays a prominent role in the pathogenesis of TTP [11]. In the presence of ADAMTS-13 inhibitors (e.g., antibodies against ADAMTS-13), intravascular platelet thrombi develop and present the clinical feature of TTP [12]. Common outcomes of untreated TTP are irreversible renal failure and death [10]. Plasma exchange therapy reverses the platelet consumption that is responsible for thrombus formation and other characteristic TTP symptoms. Plasma exchange is administered daily until the platelet count normalizes and hemolysis largely ceases, as evidenced by a normal serum LDH concentration [13].

The association of microangiopathic hemolytic anemia with thrombocytopenia and renal failure in our patient led us to the clinical diagnosis of TTP associated with AOSD. TTP associated with AOSD is extremely rare. To our knowledge, this case is the 12th report in the medical literature [12]. The etiology of the coexistence of these disorders is unknown. However, the activity of cytokines, interferon γ, and TNF in AOSD may precipitate endothelial injury and activation and thrombotic microangiopathy, resulting in TTP. In our patient, ADAMTS-13 activity was unexpectedly normal at 58.6%, and we did not detect ADAMTS-13 inhibitors on admission. However, this result may be underestimated since the patient had already undergone three plasma exchange sessions just before admission to our hospital. Therefore, the presence of ADAMTS-13 deficiency or ADAMTS-13 inhibitors may have existed and played an important pathogenic role in this case. Therapeutic options for TTP include plasmapheresis, plasma infusion, the administration of corticosteroids, hemodialysis, aspirin, vincristine, intravenously administered immunoglobulins, cyclophosphamide and other immunosuppressive agents, and splenectomy [12]. However, the prognostic outcome of TTP associated with AOSD remains poor. Two of the 11 patients with TTP associated with AOSD had a fatal outcome [14, 15].

Several biological agents show efficacy in treating AOSD. However, there are no previous reports of using biological agents to treat patients with TTP and AOSD. Here, we report an extremely rare case of a patient with multi-drug-resistant and etanercept-refractory AOSD with TTP, which was accompanied by irreversible central nervous system involvement. Tocilizumab successfully resolved her symptoms. In summary, our report suggests that tocilizumab may be a new option for a safe and effective treatment of multi-drug-resistant AOSD and TTP associated with AOSD.

Disclosures None.

References

1. Efthimiou P, Paik PK, Bielory L (2006) Diagnosis and management of adult onset Still's disease. Ann Rheum Dis 65:564–572
2. Saiki O, Uda H, Nishimoto N et al (2004) Adult Still's disease reflects a Th2 rather than a Th1 cytokine profile. Clin Immunol 112:120–125
3. Yamaguchi M, Ohta A, Tsunematsu T et al (1992) Preliminary criteria for classification of adult Still's disease. J Rheumatol 19:424–431
4. Bakshi R, Shaikh ZA, Bates VE et al (1999) Thrombotic thrombocytopenic purpura: brain CT and MRI findings in 12 patients. Neurology 52:1285–1288
5. Fautrel B, Sibilia J, Mariette X et al (2005) Tumour necrosis factor alpha blocking agents in refractory adult Still's disease: an observational study of 20 cases. Ann Rheum Dis 64:262–266
6. Radstake TR, Svenson M, Eijsbouts AM et al (2009) Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. Ann Rheum Dis 68:1739–1745
7. Fitzgerald AA, Leclercq SA, Yan A et al (2005) Rapid responses to anakinra in patients with refractory adult-onset Still's disease. Arthritis Rheum 52:1794–1803
8. Matsumoto K, Nagashima T, Takatori S et al (2009) Glucocorticoid and cyclosporine refractory adult onset Still's disease successfully treated with tocilizumab. Clin Rheumatol 28:485–487
9. De Bandt M, Saint-Marcoux B (2009) Tocilizumab for multi-refractory adult-onset Still's disease. Ann Rheum Dis 68:153–154
10. Ruggenenti P, Noris M, Remuzzi G (2001) Thrombotic microangiopathy, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura. Kidney Int 60:831–846
11. Furlan M, Robles R, Galbusera M et al (1998) Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med 339:1578–1584
12. Sayarlioglu M, Sayarlioglu H, Ozkaya M et al (2008) Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome and adult onset Still's disease: case report and review of the literature. Mod Rheumatol 18:403–406
13. George JN (2006) Clinical practice. Thrombotic thrombocytopenic purpura. N Engl J Med 354:1927–1935
14. Masson C, Myhal D, Menard H et al (1986) Purpura thrombotique thrombopenique fatal chez une patiente atteinte dune maladie de Still de I'adulte. Rev Rhum Mal Osteoartric 53:389–391
15. Domingues RB, da Gama AM, Caser EB et al (2003) Disseminated cerebral thrombotic microangiopathy in a patient with adult Still's disease. Arq Neuropsiquiatr 61:259–261