

[CASE REPORT]

Acquired Amegakaryocytic Thrombocytopenia in Adult-onset Still's Disease: Successful Combination Therapy with Tocilizumab and Cyclosporine

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Abstract:

Adult-onset Still's disease (AOSD) sometimes demonstrates hematologic disorder, whereas acquired amegakaryocytic thrombocytopenia (AAT) involvement is extremely rare. We herein report a 67-year-old woman with relapse of AOSD who concomitantly developed AAT. Thrombocytopenia along with high disease activity of AOSD was resistant to high-dose prednisolone, even in combination with methotrexate and tacrolimus. However, alternative treatment with cyclosporine after administering tocilizumab resulted in the improvement of thrombocytopenia, ultimately demonstrating that combination therapy based on suppressing the intractable disease activity of AOSD and subsequently adding a reliable immunosuppressant was required to achieve remission.

Key words: adult-onset Still's disease, acquired amegakaryocytic thrombocytopenia, thrombocytopenia, tocilizumab, cyclosporine, serum ferritin

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Introduction

Adult-onset Still's disease (AOSD) is a systemic autoimmune inflammatory disease manifesting as spikes of a fever, polyarthritis, evanescent rash, pharyngitis, lymphadenopathy, and hepatosplenomegaly. Some complications related to AOSD appear in the active phase of this disease. In particular, macrophage activation syndrome (MAS), disseminated intravascular coagulation (DIC), and thrombotic thrombocytopenic purpura (TTP) can be life-threatening complications (1, 2).

These hematologic abnormalities cause thrombocytopenia, which is demonstrated in approximately 15% of patients with acute AOSD (3) and can be a predictive factor of the prognosis (1, 4). Even though immune thrombocytopenia (ITP) is also a representative autoimmune disorder showing thrombocytopenia and frequently found in certain autoimmune diseases, such as systemic lupus erythematosus (SLE)

and antiphospholipid syndrome (5, 6), ITP is rarely involved in AOSD, with only one case report describing its involvement in a case of systemic idiopathic juvenile arthritis (7).

Acquired amegakaryocytic thrombocytopenia (AAT) is another rare hematologic disorder manifesting as severe thrombocytopenia with a marked reduction in or absence of megakaryocyte in the bone marrow tissue. The pathogenesis of AAT remains unclear, but immune-mediated interaction has been noted (8, 9).

We herein report a patient who developed refractory AAT along with the deterioration of AOSD in whom the co-administration of tocilizumab (TCZ) with cyclosporine (CsA) resulted in a favorable outcome.

Case Report

A 67-year-old woman who had a 13-year history of AOSD was admitted to our hospital following appetite loss, general fatigue, and diffuse cutaneous rash together with

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thrombocytopenia. She had initially experienced a spiked fever, evanescent rash, lymphadenopathy, splenomegaly, and polyarthritides with explicit laboratory findings, including an increased number of leukocytes ($13,760/\mu\text{L}$; normal, $3,300\text{--}8,600/\mu\text{L}$), neutrophils ($11,500/\mu\text{L}$; normal, $1,170\text{--}5,780/\mu\text{L}$), and platelets ($42.3 \times 10^4/\mu\text{L}$; normal, $15.8 \times 10^4\text{--}34.8 \times 10^4/\mu\text{L}$) as well as elevated serum levels of C-reactive protein (CRP) (9.78 mg/dL ; normal, $<0.10\text{ mg/dL}$) and ferritin ($3,894\text{ ng/mL}$; normal, $10\text{--}120\text{ ng/mL}$). These findings established the diagnosis of AOSD according to the criteria proposed by Yamaguchi et al. (10).

Tacrolimus (TAC) and methotrexate (MTX) were sequentially administered with an increase in the prednisolone (PSL) dose, since she had experienced disease recurrence several times. However, she had shown no relapsing events within the latest 6 years while maintaining her regular medication (TAC, 1 mg daily; MTX, 10 mg weekly; PSL 8 mg daily).

At admission, a physical examination revealed a body temperature of 37.0°C , systemic erythematous eruption, and splenomegaly. Neither lymphadenopathy nor arthritis was shown. A laboratory examination showed normal finding for the renal function without any abnormalities on a urine test. The serum levels of total bilirubin, lactate dehydrogenase, and alkaline phosphatase were within the normal range, although slightly increased serum levels of aspartate transaminase (43 U/L ; normal, $13\text{--}30\text{ U/L}$) and alanine transaminase (51 U/L ; normal, $7\text{--}23\text{ U/L}$) were noted. The platelet count was $9.1 \times 10^4/\mu\text{L}$, whereas the leukocyte count was within the normal range ($7,960/\mu\text{L}$) without any abnormal finding on a peripheral blood smear. The hemoglobin levels were also within the normal range (11.6 g/dL ; normal, $11.6\text{--}14.8\text{ g/dL}$), and no crushed erythrocytes were noted. Increased serum levels of CRP and ferritin were shown (12.79 mg/dL and $1,159\text{ ng/mL}$, respectively). No positivity for rheumatoid factor or autoantibodies, including antinuclear antibody, anti-ds DNA antibody, anti-Sm antibody, anti-U1-RNP antibody, anti-SS-A/Ro antibody, anti-SS-B/La antibody, anti-phospholipid antibodies, and anti-neutrophil cytoplasmic antibodies specific for either myeloperoxidase or proteinase-3 were reported. Negative reactions to the platelet-associated IgG and heparin-induced thrombocytopenia platelet factor 4 antibody were also demonstrated. The serum levels of haptoglobin were within the normal range, and those of complement factors remained normal or high, as follows: C_3 (94.0 mg/dL ; normal, $86\text{--}160\text{ mg/dL}$), C_4 (19.8 mg/dL ; normal, $17\text{--}45\text{ mg/dL}$), and CH_{50} (60.1 U/mL ; normal, $30\text{--}53\text{ U/mL}$). Immune complex (C1q) was undetected in the serum. Normal plasma levels of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 activity were detected. Coagulation tests including prothrombin time, activated partial thromboplastin time, and fibrinogen had normal results. Serological tests for hepatitis C virus, human-immunodeficiency virus (HIV), parvovirus B19, and cytomegalovirus (CMV) were negative. The levels of procalcitonin and (1,3)- β -D-glucan were also

within the normal range. Even though she had previously been diagnosed as an inactive hepatitis B virus (HBV) carrier, the levels of HBV DNA and HBV surface antigen were undetectable.

A systemic survey with whole-body computed tomography revealed no findings suggestive of malignancy, infection, or other visceral abnormalities except for splenomegaly. Gastrointestinal endoscopy also revealed neither neoplastic nor ulcerative findings; in addition, the findings of *Helicobacter pylori* infection were negative.

Intravenous infusion of methylprednisolone (mPSL) (1 g daily for 3 consecutive days) was started, and the PSL dose was increased to 60 mg (1 mg/kg), resulting in the short-term improvement of thrombocytopenia and decreased serum levels of ferritin (Fig. 1). Subsequently, TAC was increased to 2 mg daily, ultimately adjusting the blood trough concentration to 7.6 ng/mL. However, diffuse skin eruption and general fatigue persisted; furthermore, the number of platelets had again decreased approximately three weeks after the mPSL administration. TAC and MTX were stopped due to concerns of adverse drug reactions; nevertheless, the deterioration of thrombocytopenia persisted, along with increases in the serum levels of ferritin.

A bone marrow biopsy was therefore performed when the platelet count reached $6.3 \times 10^4/\mu\text{L}$. The pathological findings demonstrated moderate hypocellular marrow and an apparent decrease in megakaryocytes despite the maintenance of myeloid, lymphoid, and erythroid cell differentiation without proven hemophagocytosis or dysplasia (Fig. 2). The number of megakaryocytes was 0-1 per 10 microscopic fields at high-power magnification. *In situ* hybridization to Epstein-Barr virus (EBV)-encoding RNA was negative in the bone marrow specimen. Accordingly, she was found to have thrombocytopenia ascribable to AAT along with the deterioration of AOSD.

Intravenous immunoglobulin infusion (IVIg) (0.4 g daily for 5 days) was added because the readministration of mPSL was insufficient for improving the thrombocytopenia and high serum levels of ferritin; however, a reduction in the platelet counts was still demonstrated along with an increase in the serum ferritin levels (Fig. 1). Therefore, TCZ was intravenously administered at 560 mg (8 mg/kg) every 4 weeks. The platelet count increased after the first infusion of TCZ, and decreased serum levels of ferritin were also obtained. The administration of CsA, whose trough blood concentration was adjusted to 150-200 ng/mL, was additionally required because the platelet count was revealed to have again decreased. Consequently, she achieved and has maintained clinical remission.

Discussion

Complication with a hematologic abnormality is often involved in the acute phase of AOSD (1, 4, 11). In the present patient, thrombocytopenia was concomitantly found when the deterioration of AOSD was demonstrated. Regarding the

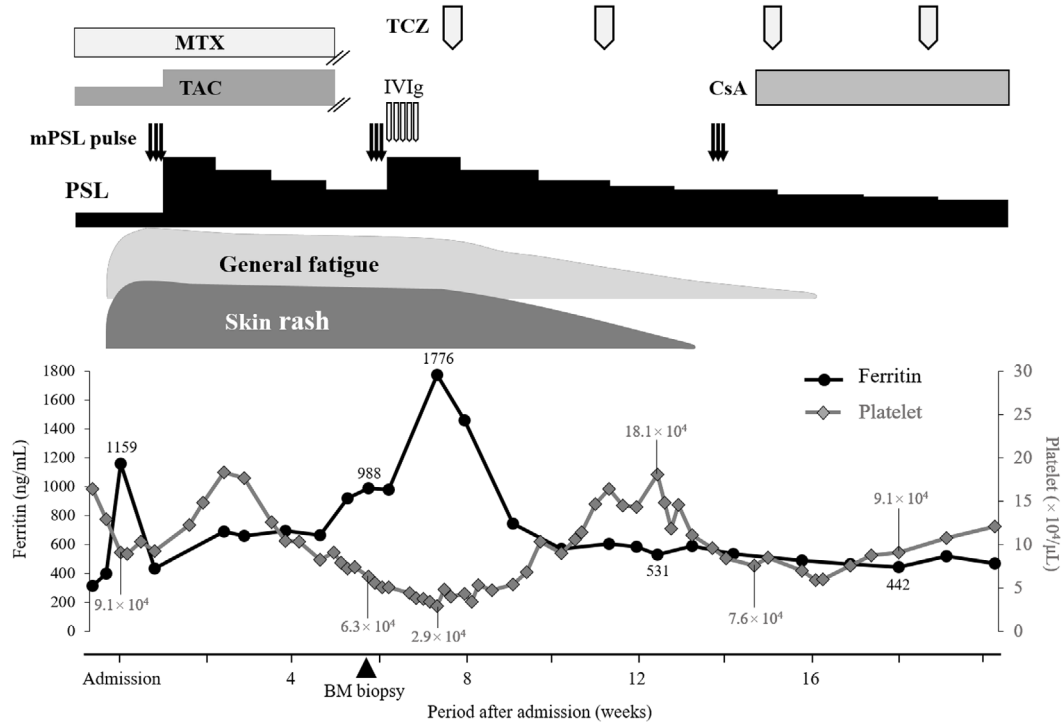


Figure 1. The clinical course of the patient. MTX: methotrexate, TAC: tacrolimus, mPSL pulse: intravenous infusion of methylprednisolone (1 g daily for 3 days), PSL: prednisolone, IVIg: intravenous immunoglobulin infusion (0.4 g daily for 5 days), CsA: cyclosporine, TCZ: tocilizumab [560 mg (8 mg/kg) every 4 weeks], BM: bone marrow

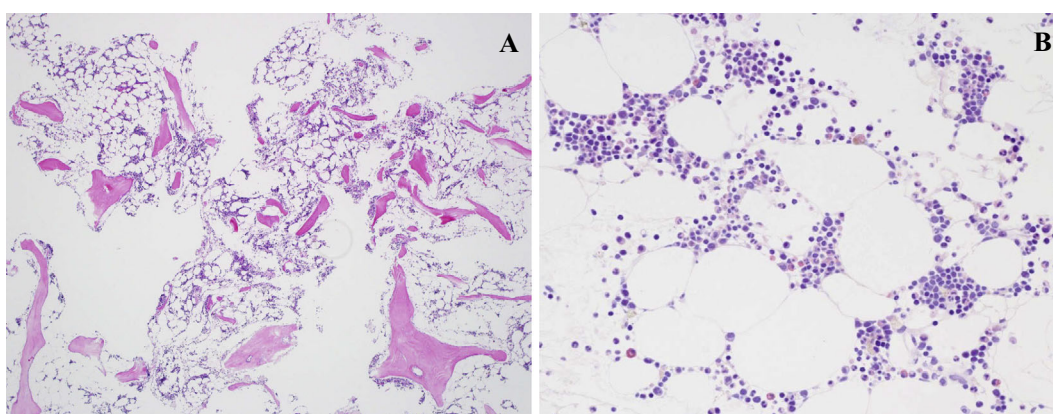


Figure 2. The pathological finding of the bone marrow biopsy, showing $\times 40$ and $\times 200$ magnification images (A and B, respectively). The bone marrow specimen showed moderate hypocellular finding and a remarkable decrease in megakaryocyte, whereas normal findings were noted for myeloid, lymphoid, and erythroid cells differentiation without dysplasia or obvious phagocytosis.

complications related to active AOSD, which play a major role in thrombocytopenia, MAS should be suspected and it is also implicated in the prognosis of AOSD patients (2, 12-14). DIC and TTP have been also shown to be life-threatening hematologic disorders that can occur in the active phase of the disease (1-3). However, our patient showed no evidence of DIC or TTP according to the laboratory findings, nor was MAS observed based on the relevant diagnostic criteria (14, 15).

AAT has been defined as an independent thrombocytopenic disease that is differentiated from other causal disor-

ders, such as ITP, aplastic anemia, and myelodysplastic syndrome, but its development can sometimes be induced by exposure to certain toxins and viruses, including HIV, CMV, EBV, and parvovirus B 19 (8, 9, 16). The present patient had no evidence of causal viral infections or toxic exposure, so the pathological findings of the bone marrow, in which a marked reduction in megakaryocytes was revealed despite the retention of other myeloid progenitor cells, had to be considered in order to exclude ITP and achieve a definitive diagnosis of AAT.

AAT has been reported to occur as a consequence of

some autoimmune diseases, including SLE, systemic sclerosis (SSc), and eosinophilic fasciitis (17-20). Regarding AOSD, only one case has been reported (21). Given the clinical findings of concomitant general fatigue, skin eruption, splenomegaly, and elevated serum levels of ferritin along with thrombocytopenia, the pathogenic mediators in acute AOSD might influence the development of AAT. Furthermore, thrombocytopenia is reportedly promoted along with increases in serum ferritin levels, which is strongly associated with the disease activity of AOSD (1, 4, 22), definitively demonstrating the correspondence between thrombocytopenia and the disease activity in AOSD.

While neither the peripheral destruction of platelets nor splenomegaly has been considered a prevalent characteristic of AAT (9, 23), the present patient showed splenomegaly associated with the disease activity of AOSD, suggesting that the peripheral destruction of platelets ascribable to splenomegaly might concomitantly exist together with AAT, although AAT is the underlying cause of thrombocytopenia.

In this patient it was necessary to suppress the disease activity of AOSD because thrombocytopenia had become exacerbated together with an increase in serum levels of ferritin, which is associated with the disease activity of AOSD. Relapse was induced despite the concomitant use of MTX and TAC, which have been found to exert therapeutic efficacy in cases of PSL-resistant AOSD (24-26). The trough blood concentration of TAC is usually maintained between 5 and 10 ng/mL, which are the ideal levels for achieving therapeutic efficacy without any adverse events (27-29); however, no favorable effect was obtained in the present patient despite adjusting the trough blood concentration to an appropriate level. Furthermore, although MTX and TAC administration was stopped because it has been suggested that the medications given prior to the onset of AAT should be withdrawn in order to ascertain whether or not they might be associated with the development of AAT (9), we ultimately realized that neither MTX nor TAC had influenced the occurrence of AAT.

The sustained symptoms related to active AOSD were successfully eliminated and serum ferritin levels reduced after administering TCZ, which is well-recognized as a potent biological agent conducive to a favorable outcome in multidrug-resistant AOSD (30, 31). The platelet count decreased along with increasing serum ferritin levels, suggesting that the disease activity in AOSD influenced the reduction in the platelet count. However, additional treatment was subsequently required in order to maintain the amelioration of AAT even after initiating TCZ.

Some immunosuppressive agents, such as corticosteroid, antithymocyte globulin, intravenous immunoglobulin, danazol, and cyclophosphamide, have been described as a useful empirical treatment for AAT; however, whether the therapeutic responses were invalid or transient in some patients has been a matter of concern (8, 9, 20). In contrast, CsA has predominantly demonstrated efficacy in patients with AAT related to several autoimmune disorders (8, 20, 21). In fact,

the additional administration of CsA contributed to the recovery from thrombocytopenia in the present patient. CsA is a calcineurin inhibitor (CNI) that suppresses the activation of T cells by inhibiting the intracellular activating signal via cyclophilin A. Therefore, abrogating the activation of T cells might ultimately be effective in repressing the development of AAT. TAC is also a CNI, and its intracellular signaling regulation is performed via the 12-kDa FK506-binding protein (32). Considering the clinical process in the present patient, suppressing disease activity in AOSD might be fundamentally required to induce the efficacy of CNIs as the optimal therapy for AAT, as TAC failed to show any therapeutic efficacy after AOSD became exacerbated. TAC eventually had to be withdrawn due to concerns about related adverse reactions in the acute phase. However, TAC may also be a useful agent for AAT when the regulation of AOSD activity can be simultaneously achieved.

Regarding the pathogenic mechanism of AAT, some *in vitro* investigations have shown immune-mediated interactions, notably the cell-mediated suppression of megakaryocyte colony formation (19, 33, 34). In addition, the depletion of T cells and macrophages has been shown to help improve the marrow megakaryocyte formation in AAT, suggesting that relevant immunocompetent cells might be implicated in the development of AAT. Indeed, both macrophages and effector T cells play crucial roles in the pathogenesis of AOSD (1, 14, 35), and the acceleration in an innate immune system affects the production of specific proinflammatory cytokines, such as interleukin (IL)-1 β , IL-6, and IL-18, which are also associated with the disease activity (36-38). In particular, IL-6 has a pleiotropic effect of inducing both innate and acquired immunities (39). The activation of macrophages was found to be regulated by treatment with TCZ (40). Therefore, the combination therapy of TCZ with CsA might be essential for broadly regulating the immune system disorders that tend to develop AAT concomitantly with AOSD deterioration.

Autoantibody against thrombopoietin receptor (c-Mpl) was identified as a causal mediator of AAT related to SLE and SSc (17, 18, 41), although the c-Mpl concentration was not evaluated in our case or in a previous report of AAT related to AOSD (21). Other humoral mediators affecting the suppression of marrow megakaryocyte might be involved, as suggested by previous reports (8, 9, 42). Despite such mediators not being examined, the present patient ultimately achieved remission thanks to combination therapy with TCZ and CsA; nevertheless, it may be necessary to clarify the overall pathogenic mechanism underlying the development of AAT related to AOSD in order to establish a definite diagnostic and advanced therapeutic strategy.

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

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