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CASE STUDY

A case of corticosteroid-refractory adult-onset Still's disease successfully controlled with tocilizumab despite transient neutropenia and thrombocytopenia

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Abstract

We report a case of a 50-year-old woman with adult-onset Still's disease (AOSD). Even after receiving steroid pulse therapy and high-dose oral corticosteroid medication, the patient's serum ferritin level increased, while the number of neutrophils and platelets decreased. However, fever, erythema, sore throat, and arthralgia ceased. Therefore, we administered intravenous tocilizumab (TCZ). However, neutropenia, thrombocytopenia, and exacerbation of hyperferritinemia occurred after the first TCZ infusion. After the second TCZ infusion, the values returned to normal, and we discontinued prednisolone successfully without any flare-ups of AOSD. We reviewed case reports describing adverse events after TCZ administration in AOSD patients.

KEYWORDS
adult-onset Still's disease, hyperferritinemia, neutropenia, thrombocytopenia, tocilizumab

1 | INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare systemic febrile inflammatory disorder of unknown etiology characterized by four major symptoms: high spiking fever, arthralgia or arthritis, evanescent salmon-pink maculopapular rash, and hyperleukocytosis.[1] The pivotal role of macrophage activation leading to overproduction of Th1 cytokines, such as interleukin (IL)-1β, IL-6, IL-18, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, is well-established in AOSD.[2] Tocilizumab (TCZ) inhibits IL-6 signaling and has been shown to be effective for AOSD treatment.[3] In contrast, macrophage activation syndrome (MAS) has been reported as a serious adverse event of AOSD under TCZ treatment.[4–6] We describe a case of corticosteroid-refractory AOSD successfully controlled with TCZ despite transient neutropenia and thrombocytopenia after TCZ administration. To examine the difference between AOSD cases with TCZ-associated MAS or cytopenia, and those that did not develop MAS or cytopenia after TCZ administration, we reviewed previously reported cases.

2 | CASE REPORT

A 50-year-old Japanese woman was admitted to our department with fever, skin rash, sore throat, and polyarthralgia. Six days earlier, she had developed fever, generalized skin eruption, and pharyngalgia. Three days later, she additionally complained of arthralgia on the fingers and ankles. Prior to admission, her symptoms had not subsided with prescribed antihistamines and acetaminophen.

On admission, she had a fever of 38.5°C. Disseminated edematous erythematous macules, some of which were coalescing, were observed on the trunk and all four limbs (Figure 1A,B). The cutaneous exanthema was associated with the febrile episodes and disappeared during the afebrile periods. No purpura was observed.

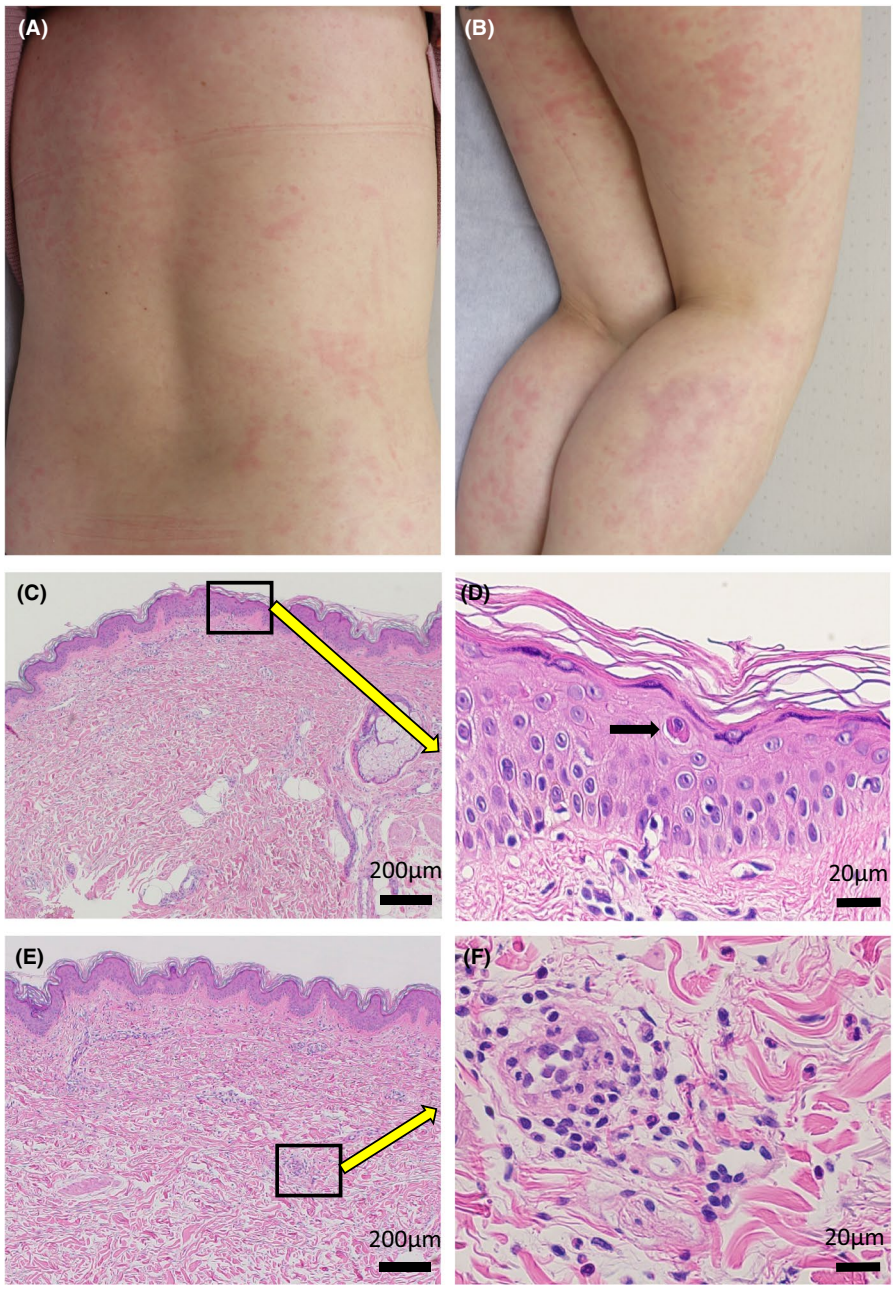

FIGURE 1 Clinical appearance and histopathological findings. Disseminated edematous erythematous macules, some of which were coalescing, were observed on the trunk (A) and lower limbs (B). A biopsy specimen taken from the abdominal skin exhibited dyskeratotic cells (black arrow) in the epidermis (C, D), and perivascular inflammatory infiltrate composed mainly of neutrophils and lymphocytes in the upper dermis (E, F)

The laboratory data were as follows: leukocytes 11,700/μL (neutrophils 10,354/μL), hemoglobin 14.2 g/dL, platelets 23.3 × 10^4/μL, aspartate aminotransferase 35 U/L, alanine aminotransferase 40 U/L, lactate dehydrogenase 223 U/L, blood urea nitrogen 11 mg/dL, creatinine 0.74 mg/dL, triglycerides 110 mg/dL, C-reactive protein (CRP) 11.7 mg/dL, ferritin 2141 ng/mL, and soluble interleukin-2 receptor (sIL-2R) 520 U/mL. Antinuclear antibodies and rheumatoid factor were negative. The results of serological tests for Epstein-Barr virus were compatible with past infection. Blood cultures were negative. Whole-body computed tomography revealed no signs of infection or malignancy. A biopsy specimen taken from the abdominal skin exhibited dyskeratotic cells in the epidermis (Figure 1C,D), and perivascular inflammatory infiltrate composed mainly of neutrophils and lymphocytes in the upper dermis (Figure 1E,F). These findings established the diagnosis of AOSD according to the criteria proposed by Yamaguchi et al.[1]

A daily dose of 30 mg oral prednisolone (PSL) was started, but the fever persisted (Figure 2). She was treated with methylprednisolone (mPSL) pulse therapy (1000 mg/day) intravenously for 3 days starting on day 8, followed by 60 mg/day of oral PSL. The fever, skin eruption, sore throat, and arthralgia ceased immediately. However, the serum CRP level did not progressively decrease. On day 22, the serum ferritin levels re-increased, and the neutrophil and platelet counts began to drop. Thereafter, oral PSL was substituted with 6 mg/day of oral betamethasone, and a second course of mPSL pulse therapy was performed for 3 days from day 27 to day 29. Although these intensified remedies led to the normalization of the CRP levels, the serum ferritin levels continued to rise, along with a drop in the number of neutrophils and platelets in the blood. This suggested a diagnosis of corticosteroid-refractory AOSD, and we administered TCZ (8 mg/kg) intravenously in addition to steroid therapy on day 30.

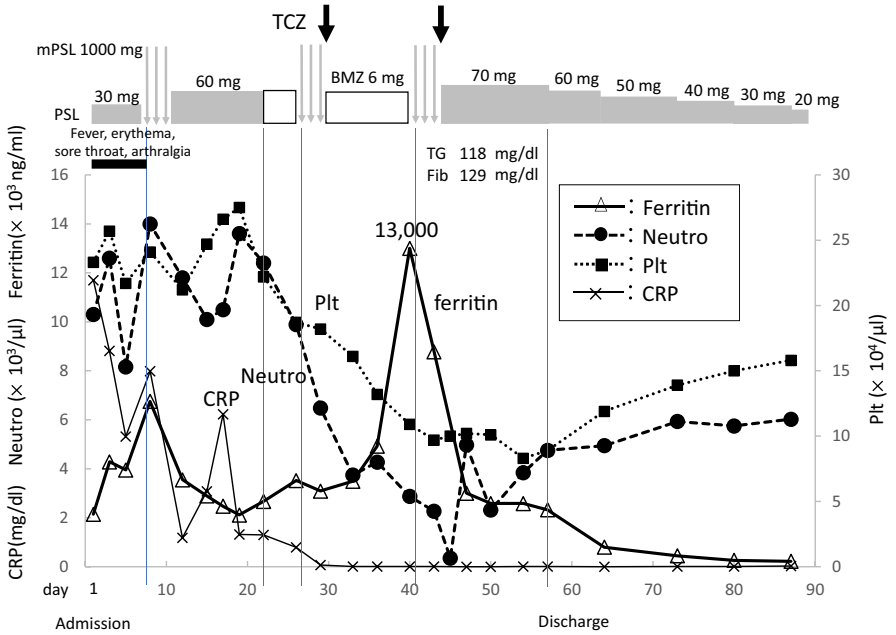

FIGURE 2 Clinical course after admission. Nonresponsive disease despite initial steroid therapy. Emergence of neutropenia and thrombocytopenia with exacerbation of hyperferritinemia after the first administration of tocilizumab. Normalization of neutrophil and platelet counts and serum ferritin levels after the second administration of tocilizumab. BMZ, betamethasone; CRP, C-reactive protein; Fib, fibrinogen; mPSL, methylprednisolone; Neutro, neutrophil count; Plt, platelet count; PSL, prednisolone; TCZ, tocilizumab; TG, triglyceride

Nevertheless, thrombocytopenia occurred on day 36, and serum ferritin levels continued to increase, reaching 13,000 ng/mL on day 40. For the following 3 days, a third course of mPSL pulse therapy was administered, resulting in a rapid reduction in serum ferritin level. However, the thrombocytopenia was not resolved, and neutropenia occurred on approximately day 44. On day 44, she received a second dose of TCZ. After that, the serum ferritin level steadily decreased, and the neutrophil and platelet counts returned to normal. During the immunosuppressive treatment, the number of cytomegalovirus (CMV) antigen-positive cells in the blood did not exceed one cell per slide, and the serum beta-D-glucan concentration was within the normal range. Therefore, we ruled out CMV and *Pneumocystis jirovecii* infections. We discontinued PSL successfully within 6 months without any flare-ups of AOSD.

3 | DISCUSSION

This report indicates that corticosteroid-refractory AOSD can be successfully controlled by adding TCZ. However, in our patient, neutropenia and thrombocytopenia transiently occurred in phase with exacerbation of hyperferritinemia after starting TCZ, from which a question arises as to whether TCZ is safe in the active phase of AOSD.

In our patient, the TCZ administration might have triggered the prestage of MAS. MAS can complicate AOSD[7] and is characterized by an overwhelming inflammatory reaction due to an uncontrolled and dysfunctional immune response involving the continual activation and expansion of T lymphocytes and macrophages, which results in massive hypersecretion of proinflammatory cytokines.[8] The recognition that MAS represents a secondary or reactive form of hemophagocytic lymphohistiocytosis (HLH) has led some experts to recommend the use of the HLH-2004 diagnostic guidelines.[9] Those guidelines have eight criteria: fever, splenomegaly, cytopenias affecting at least two of three lineages in the peripheral blood, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in the bone marrow, spleen, or lymph nodes, low or absent NK-cell activity, hyperferritinemia, and high levels of sIL-2R. The diagnosis of HLH can be established if five of the eight criteria are fulfilled. In our patient, three criteria (i.e., cytopenias, hypofibrinogenemia, and hyperferritinemia) were met after starting TCZ, which might have been a sign of the prestage of MAS triggered by TCZ, although it did not lead to a diagnosis of MAS.

Previous case studies showed that MAS,[4–6] cytopenia,[10] or neither MAS nor cytopenia[11,12] emerged after administration of TCZ to treat AOSD (Table 1). The mechanism of TCZ-associated MAS or cytopenia in AOSD patients has not been elucidated. Some researchers have suggested that the inhibition of a single cytokine pathway by an anticytokine agent such as TCZ may induce MAS as the consequence of an unfavorable imbalance in the cytokine network involved in AOSD.[6,13,14] Several serum cytokines, such as IL-1β, IL-6, IL-18, TNF-α, and IFN-γ, are involved in AOSD[2] and may trigger MAS.[15] IL-18 acts upstream of IL-6 in the inflammatory cytokine cascade.[16] TCZ monotherapy is considered to be unable to fully inhibit the inflammatory cytokine downstream of IL-18.[13] A group of those researchers also implied that to prevent cytokine imbalance caused by an anticytokine agent, nonselective immunosuppressive therapy, including glucocorticoids, methotrexate, and cyclosporin A, may be necessary to be used around the administration time of an anticytokine agent.[6,14] However, Table 1 showed that in the cases with TCZ-associated MAS[4–6] or cytopenia,[10] the serum level of CRP at the start time of TCZ was lower, which meant that the nonselective immunosuppressive therapy prior to TCZ therapy suppressed systemic inflammation more effectively, than in the cases that did not develop MAS or cytopenia after TCZ administration.[11,12] Thus,

TABLE 1 Reports of adult-onset Still's disease cases with tocilizumab-associated macrophage activation syndrome or cytopenia, or those that did not develop macrophage activation syndrome or cytopenia after tocilizumab administration

Reference	Age/ Gender	Disease duration of AOSD	Therapy before TCZ (mg/day)	Therapy other than corticosteroids before TCZ	CRP (mg/dL) at the start time of TCZ	Ferritin (ng/mL) at the start time of TCZ	Start time of TCZ	Adverse events after TCZ	Onset of MAS or cytopenia
AOSD cases with TCZ-associated MAS									
Kobayashi et al[4]	57/F	3 weeks/ Initial flare	PSL (80–60[a])		3	—	35th day	MAS. CMVI, CD sepsis	After 1st TCZ (32 days)
Tsuchida et al[5]	19/F	>6 months/ Relapse	BMZ (1.5–3), PSL (40[a])	CyA (100–>100[a]), MTX (15[a,b])	4.91	—	—	MAS	After 1st TCZ (within a day)
Naniwa et al[6]	76/F	28 months/ Relapse	Pulse, DEX (13.2–9.9), PSL (60–20–60–40[a])	CyA (100–200–100[a])	0.27	1670	37th day	MAS	After1st TCZ (14 days)
AOSD cases with TCZ-associated cytopenia									
Yasaka et al[10]	44/F	—/Initial flare	PSL (>80–80[a])		2.53	2849	48th day	TCP	After 2nd TCZ
	59/M	—/Initial flare	PSL (100[a])		0.58	2582	5th month	TCP	After 2nd TCZ
	41/F	—/Relapse	PSL (90–120–90[a])	CyA, MTX	3.87	2602	2nd month	TCP, IAI	After 2nd TCZ
	46/M	—/Initial flare	PSL (70–40[a])		0.17	134	41th day	TCP	After1st TCZ
	73/F	—/Relapse	PSL (60[a])		1.1	8949	3rd month	TCP	After 2nd TCZ
	41/F	—/Initial flare	PSL (60[a])		0.57	275	21th day	TCP	After 2nd TCZ
Our patient	50/F	6 days/ Initial flare	Pulse (twice), PSL (30–60), BMZ (6[a])		0.07	3090	30th day	TCP, NP	After1st TCZ (6/14 days)
AOSD cases that did not develop MAS or cytopenia after TCZ administration[c]									
Vandemergel et al[11]	28/F	—/Initial flare	mPSL (0.5/ kg–6–32[a])		10.5	1060	>11th month	None	—
Kawaguchi et al[12]	29/M	1 month/ Initial flare	Pulse (twice), PSL (60[a])	CyA (100–150[a])	10	22,000	22th day	Oral candidiasis	—

Note: Reports of adult-onset Still's disease cases with tocilizumab-associated macrophage activation syndrome or cytopenia, or those that did not develop macrophage activation syndrome or cytopenia after tocilizumab administration.

Abbreviations: —, no data; AOSD, adult-onset Still's disease; BMZ, betamethasone; CD, *Clostridium difficile*; CMVI, cytomegalovirus infection; CRP, C-reactive protein; CyA, cyclosporine A; DEX, dexamethasone; IAI, intra-abdominal infection; MAS, macrophage activation syndrome; mPSL, methylprednisolone; MTX, methotrexate; NP, neutropenia; PSL, prednisolone; Pulse, steroid pulse therapy; TCP, thrombocytopenia; TCZ, tocilizumab.

[a]Dosage at the start time of tocilizumab.; [b]mg/week.; [c]Case report which described the presence or absence of adverse events after tocilizumab administration;

the inadequacy of nonselective immunosuppressive therapy cannot predict the development of TCZ-associated MAS or cytopenia.

Our study suggests that corticosteroid-refractory AOSD can be successfully controlled by administering TCZ. The reason for the transient neutropenia and thrombocytopenia transiently occurring in phase with hyperferritinemia after starting TCZ remains unclear. Future studies are required to investigate this issue.

CONFLICT OF INTEREST

The authors declares no conflict of interest.

DECLARATION SECTION

Approval of the research protocol: This study did not involve human participants assigned to an intervention or comparison group.

Informed consent: The authors obtained the informed consent of the patient.

Registry and the Registration No.: N/A.

Animal Studies: N/A.

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