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【 CASE REPORT 】

Effective Treatment with Tocilizumab in a Rheumatoid Arthritis Patient Complicated with Human T-cell Leukemia Virus Type 1-associated Myelopathy

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Abstract:
A 61-year-old woman with human T-cell leukemia virus type 1 (HTLV-1)-associated myelopathy (HAM)/tropical spastic paraparesis (TSP) and interstitial pneumonia (IP) was admitted to our hospital. She complained of sicca symptoms, polyarthralgia, and swollen joints. She was diagnosed with rheumatoid arthritis (RA) and Sjögren's syndrome. Methotrexate and anti-tumor necrosis factor therapy were not utilized because of the inclusion of severe respiratory disorders among the complications and the neurological symptoms of HAM/TSP. Tocilizumab monotherapy improved the RA disease activity without exacerbating HAM/TSP. The present case suggests that tocilizumab might be a suitable treatment option in patients with RA and HAM/TSP.

Key words: antirheumatic therapy, biologic, human T-cell leukemia virus type 1, myelopathy, rheumatoid arthritis, tocilizumab

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Introduction

Human T-cell leukemia virus type 1 (HTLV-1) is the causative agent of adult T-cell leukemia (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) (1, 2); however, the pathogenesis of these HTLV-1-associated disorders remains unclear.

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by bone destruction and chronic inflammatory arthritis. The estimated global prevalence of RA ranges from 0.5% to 1.0% in the general population (3). A recent study reported that there were approximately 1 million HTLV-1 carriers in Japan (4), suggesting that the estimated number of HTLV-1-positive patients with RA in Japan might range from 5,000 to 10,000. Therefore, rheumatologists might encounter HTLV-1-positive RA patients in daily clinical practice in areas endemic for HTLV-1 infection in Japan (4). In the past two decades, standardized antirheumatic therapies based on methotrexate and biologics revolutionized the clinical outcomes of patients with RA (5). Interestingly, several reports have suggested that HTLV-1-positive patients with RA exhibit attenuated responses to anti-tumor necrosis factor (TNF) biologics (6, 7). Terada et al. reported a patient with RA whose HAM/TSP-associated neurological symptoms were exacerbated after the administration of both tocilizumab and abatacept (8). In addition, several studies have reported HTLV-1-positive patients with rheumatic disorders who developed ATL during immunosuppressive treatments including methotrexate and biologics. Therefore, it is possible that the efficacy and safety of antirheumatic therapies including methotrexate and biologics might differ between HTLV-1-positive and HTLV-1-negative patients with RA.

We herein report a patient with HAM/TSP who developed

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Table. Laboratory Data at the Admission of Our Hospital.

<CBC>		<Blood chemistry>		<Serology>	
WBC	6,500 /μL	TP	6.47 g/dL	CRP	2.79 mg/dL
Neut.	71.0 %	Alb	3.24 g/dL	IgG	1,505 mg/dL
Lymph.	9.0 %	BUN	18.2 mg/dL	KL-6	708 U/mL
Mono.	11.0 %	Cre	0.46 mg/dL	MMP-3	137.2 ng/mL
Eosino.	4.0 %	AST	18 IU/L	RF	8.1 IU/mL
Abnormal-Lymph.	4.0 %	ALT	12 IU/L	ACPA	<0.6 U/mL
RBC	465×10^4 /μL	LDH	230 IU/L	ANA	×320 (cytoplasmic and granular)
Hb	11.2 g/dL			anti-SS-A	<1.0 U/mL
Plt	28.2×10^4 /μL			anti-SS-B	<1.0 U/mL
				<ESR>	94 mm/h

Abnormal-Lym: abnormal lymphocyte, Alb: albumin, ALT: alkaline phosphatase, ANA: antinuclear antibody, ACPA: anti-cyclic citrullinated peptide antibody, anti-SS-A: anti-Sjögren's syndrome A antibody, anti-SS-B: anti-Sjögren's syndrome B antibody, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CBC: Complete blood cell counts, Cre: creatinine, CRP: C-reactive protein, Eosino.: eosinophil, ESR: erythrosedimentation rate, Hb: hemoglobin, IgG: immunoglobulin G, KL-6: Krebs von den Lungen-6, LDH: lactate dehydrogenase, Lymph.: lymphocyte, MMP-3: matrix metalloproteinase 3, Mono.: monocyte, Neut.: neutrophil, Plt: platelets, RBC: red blood cell, RF: rheumatoid factor, TP: total protein, WBC: white blood cell

seronegative RA and had a concurrent diagnosis of Sjögren's syndrome (SS). She was initially administered oral prednisolone (PSL) at 45 mg per day for interstitial lung disease (ILD) and RA, and the dosage of PSL was reduced gradually. However, her arthralgia persisted, and treatment with tocilizumab successfully improved the RA disease activity score without exacerbating the HAM/TSP or inducing ATL development. Tocilizumab might be suitable as a therapeutic option for RA in patients with HAM/TSP. However, improvement of HAM/TSP-associated symptoms might be dependent on corticosteroid therapy rather than tocilizumab.

Case Report

A 61-year-old woman with a 3-month complaint of polyarthralgia was admitted to our hospital. She had previously been diagnosed with HAM/TSP, ILD, and HTLV-1-associated uveitis (HU) at 57, 57, and, 59 years old, respectively. She was being treated with methylprednisolone pulse therapy intermittently due to worsening of HAM/TSP-associated symptoms such as altered gait. The patient's mother had died of ATL.

At the time of admission, a physical examination revealed multiple swollen and tender joints bilaterally, mainly involving the metacarpophalangeal and proximal interphalangeal joints, wrists, and knees. The patient also complained of sicca symptoms, such as dry eyes and dry mouth. The patient was evaluated for her HAM/TSP status by a neurologist. The patient's Osame motor disability score was 6 at the time of admission, indicating that she needed bilateral support to walk (9). The levels of C-reactive protein and matrix metalloprotenase-3 were elevated at 2.79 mg/dL and 137 ng/mL, respectively (Table). She was negative for anti-citrullinated protein antibody (ACPA) and rheumatoid factor (RF). Although she was positive for anti-nuclear antibody (1:320, cytoplasmic and granular type), she was negative for both anti-SS-A and anti-SS-B antibodies. When she developed HAM at 2014, a blood test had shown her to be negative for anti-SS-A antibody.

Hand X-rays showed narrowing of the joint spaces and bone erosions in both wrists and the proximal interphalangeal joints which were indicating on-set of RA (Fig. 1A). Power Doppler (PD) ultrasonography (US) of the wrists revealed signs of PD, suggesting synovial tissue inflammation (Fig. 1C). Magnetic resonance imaging of the right hand also revealed bone erosions with synovitis (Fig. 1E, F). Based on these radiological findings, she was diagnosed with seronegative RA according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria (10). In addition, Schirmer's test revealed decreased tear secretion of <5 mm per 5 minutes. Fluorescein staining of the corneas showed dry eyes. The Gum test also revealed a decreased saliva secretion. Salivary gland scintigraphy showed a decreased uptake and washout in the bilateral submandibular glands and right parotid gland. The histopathological examination of the labial salivary glands showed mild lymphocytic infiltration around the salivary ducts (Fig. 2A). More than 2 lymphocytic foci per 4 mm^2 were observed in these specimens according to the focus score. Therefore, she was also diagnosed with SS based on the Japanese Ministry of Health criteria for the SS diagnosis that were revised in 1999 (11). These results suggested that the patient exhibited the clinical features of HTLV-1-seropositivity with SS (12).

Chest high-resolution computed tomography showed traction bronchiectasis in the lower lobes and polycystic changes (Fig. 2B). The percentage of lymphocytes in the bronchoalveolar lavage fluid (BALF) collected by bronchoscopy was elevated at 71.2%. The HTLV-1 proviral load (PVL) in the BALF was lower than that in the peripheral blood mononuclear cells (2.4 copies/100 mononuclear cells in BALF vs. 4.8 copies/100 peripheral blood mononuclear

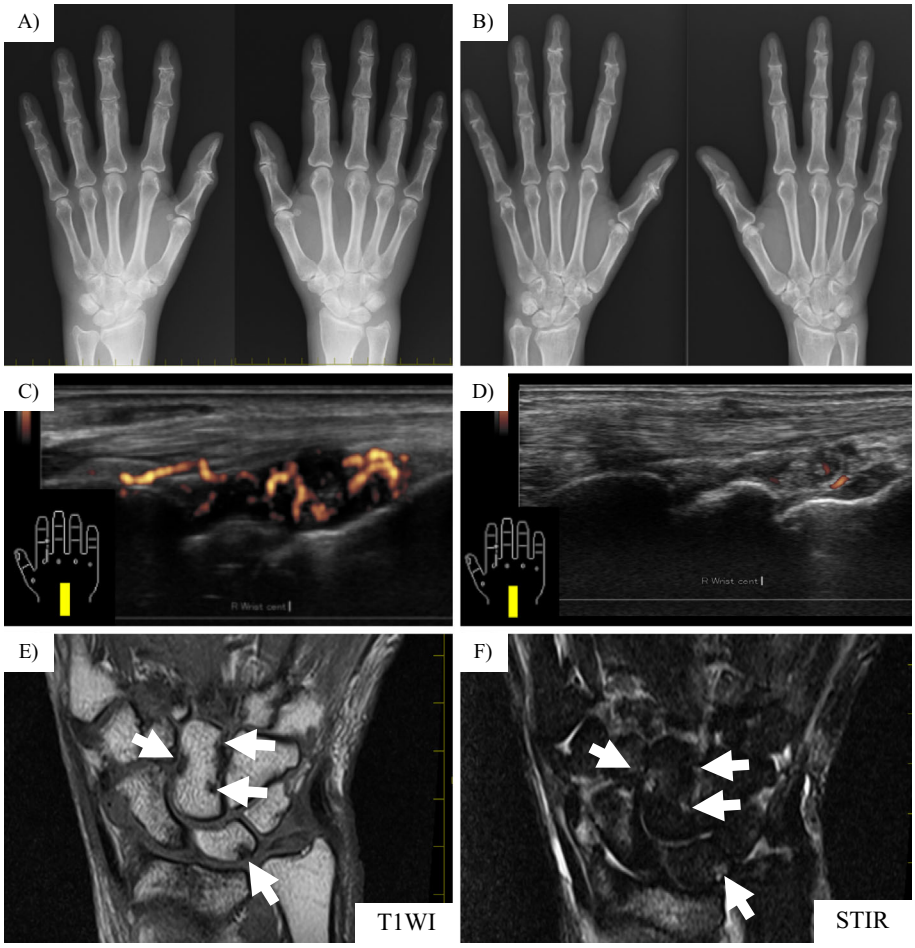


Figure 1. Radiological imaging studies of the patient. Hand X-rays at admission (A) and 1.5 year after the initiation of tocilizumab treatment (B). Hand X-rays showed narrowing of the joint spaces and bone erosions in both wrists and the proximal interphalangeal joints, indicating the onset of RA (A). There were no remarkable changes in the findings of hand X-rays between these two time points. Power Doppler ultrasonography (PDUS) of the right wrist at admission (C) and at 6 months after treatment with tocilizumab (D). PDUS of the right wrist shows hypertrophy of the synovial tissue with hypervascularity, consistent with the inflammation of synovial tissues (C). These findings improved after treatment with tocilizumab (D). Magnetic resonance imaging of the right hand (E, F). T1-weighted image (T1WI) shows some bone erosion (arrowheads) (E). Short T1 inversion recovery (STIR) imaging reveals high-intensity areas in the joint spaces (arrowheads) (F). These findings are consistent with active synovitis.

cells, respectively). Based on studies reporting that the HTLV-1 PVL in BALF was comparable to that in the peripheral blood of patients with HTLV-1-associated bronchioloalveolar disorder (13, 14), the ILD in the present patient was considered not to be associated with HTLV-1. In addition, SS and RA were considered more likely to be associated with the ILD presentation. Therefore, the patient was concomitantly diagnosed with RA and SS in addition to HAM/TSP, HU, and ILD.

Her RA disease activity score including the 28-joint count (DAS28) was 7.9 at the time of admission, suggesting a high disease activity according to the EULAR response criteria (15). In addition, hand X-rays revealed rapid progressive bone erosion in both wrists. Therefore, it was deemed necessary to start anti-rheumatic therapies, such as methotrexate and biologics, as soon as possible in order to repress both the inflammation and bone destruction. However, treatment with methotrexate was challenging for this patient. A lung function test indicated that the % vital capacity was 73%. In RA patients with ILD, a reduction in the % vital capacity below 80% is a contraindication for methotrexate treatment according to the Japan College of Rheumatology (JCR) guideline for methotrexate (16). Therefore, treatment with methotrexate was avoided as the initial anti-rheumatic drug. In addition, demyelinating diseases were a potential severe adverse effect of anti-TNF biologics, so anti-TNF biologic treatment was not considered in the current patient. Several reports have indicated that chronic inflammation of HAM results in demyelination of the spinal cord (17-21). For these reasons, we considered treatment with methotrexate plus anti-TNF biologics impossible because of these complications.

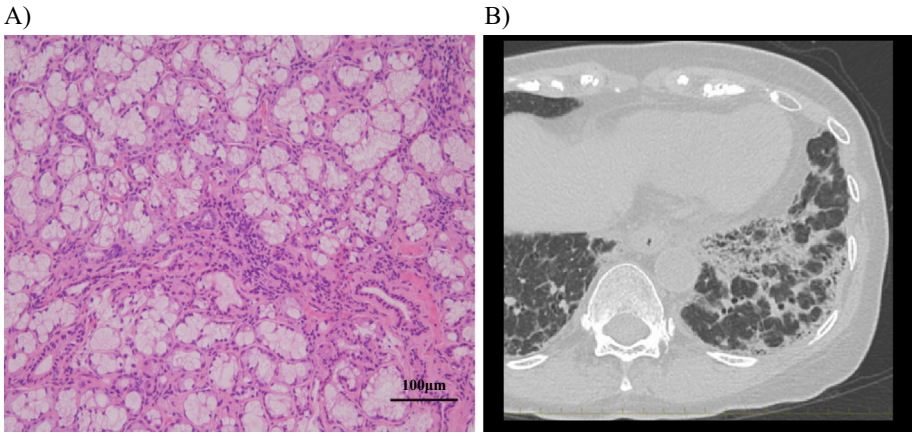
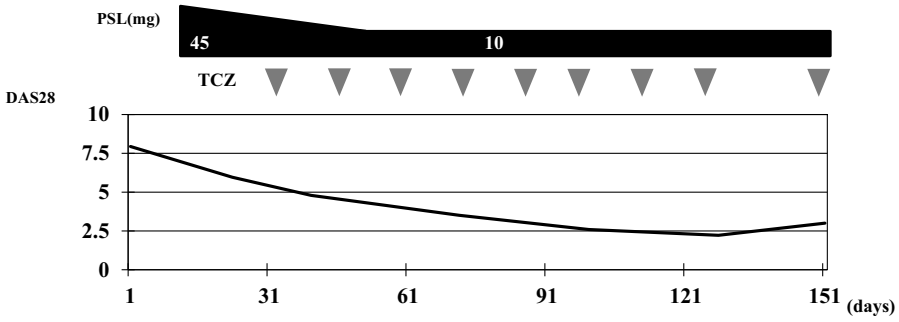


Figure 2. **Complications of the present case. (A) Histopathology of the biopsy specimen from a labial salivary gland (Hematoxylin and Eosin staining, 20× magnification). More than 2 lymphocytic foci per 4 mm^2 were observed in these specimens according to the focus score. No apparent fibrosis or atrophic changes are observed. (B) High-resolution computed tomography of the chest showing traction bronchiectasis in the lower lobes and polycystic changes.**



KL-6 (U/mL)	708	671	492
OMDS	6	6	6
HTLV-1 PVL (copies/100 PBMCs)	4.8	6.93	5.24

Figure 3. **The clinical course of the patient. Administration of tocilizumab (TCZ) improved the disease activity score including the 28-joint count (DAS28) without the exacerbation of human adult T-cell leukemia virus type 1 (HTLV-1) -associated myelopathy. The KL-6 level was also decreased after treatment with TCZ and prednisolone (PSL). However, this therapeutic regimen did not improve the Osame's motor disability score (OMDS). In addition, the HTLV-1 proviral load (PVL) did not change markedly during antirheumatic therapy in the present case. PBMCs: peripheral blood mononuclear cells**

We therefore started the patient on oral PSL at 45 mg per day for ILD and RA. The dosage of PSL was reduced gradually by 5 mg per week. Two weeks later, the patient was initiated on subcutaneous tocilizumab 162 mg every 2 weeks without methotrexate. Her DAS28 improved to 2.59 at 2 months after the initiation of tocilizumab (Fig. 3). The Krebs von den Lungen (KL)-6 level was reduced to 492 IU/mL from 708 IU/ml after the initiation of PSL treatment, and her chest radiographic findings had improved slightly. The neurological symptoms due to HAM/TSP and the ophthalmological symptoms due to HU did not worsen during the tocilizumab treatment.

The level of neopterin in cerebrospinal fluid (CSF) is well known to be a biomarker that reflects the disease activity of HAM/TSP, and neopterin in the CSF had been useful for evaluating the worsening of HAM/TSP-associated symptoms the present patient's historical clinical course. The neopterin value in the CSF was within the normal limit (<5.0 pmol/mL) at 4 months after the initiation of tocilizumab treatment.

Power Doppler ultrasonography (PDUS) of the wrist showed the disappearance of PD signals at six months after treatment with tocilizumab (Fig. 1D). Hand X-rays showed no progression of bone destruction at 1.5 years after tocilizumab treatment (Fig. 1B). During the relatively short-term clinical observation period of two years, tocilizumab did not

appear to influence the condition of HAM/TSP in the current patient. The PSL dose was maintained at 10 mg/day because reducing the dose below 10 mg/day resulted in the exacerbation of her HAM/TSP-associated symptoms, such as an altered gait. In addition, there were no clinical symptoms or laboratory findings suggesting the development of ATL.

Discussion

In the current patient with HAM/TSP who developed seronegative RA, radiological studies, such as PDUS and magnetic resonance imaging, were useful for the diagnosis of RA because the patient was negative for both ACPA and RF. Radiological evaluations were previously reported to be useful for the diagnosis of not only early RA but also seronegative RA (22-25). In addition, to detect bone erosion in early RA, magnetic resonance imaging is useful compared to plain radiography. However, the 2010 ACR/EULAR classification criteria for RA recommend the exclusion of other causes of arthritis, including SS (10). The present patient was diagnosed with SS based on the typical findings reported in HTLV-1-seropositive patients with SS (11). Arthritis due to SS generally presents without joint swelling or bone destruction; therefore, the cause of arthritis in our patient was considered to be seronegative RA rather than SS.

In the 1990s, HTLV-1-associated arthropathy (HAAP) was reported. The clinical features of HAAP have been reported to be mono- or oligo-arthropathy without bone destruction (26). The joint lesions of HAAP are predominantly large joints, such as the shoulders, wrists, and knees. These clinical features of HAAP differ from those of HTLV-1-positive RA. The current patient showed polyarthritis with joint space narrowing and erosive lesions. Patients with HAM/TSP who develop arthralgia should be evaluated not only for RA but also other causes of arthropathy, such as SS and HAAP. Even in cases that are seronegative for both ACPA and RF, it is important to investigate bone destruction and synovitis by radiological imaging studies for the diagnosis of early-stage RA in daily practice.

Standardized therapeutic strategies for RA have been established in the past two decades. Clinical remission of RA is a realistic goal of daily clinical practice according to the Treat to Target recommendations (27). In the present case, several complications, such as ILD and chronic neurological symptoms of HAM/TSP, had to be considered when deciding to administer disease modifying anti-rheumatic drugs. The Japanese College of Rheumatology recommends that methotrexate not be administered to patients with RA who have severe respiratory disorders (16). Pulmonary disorders, such as chronic obstructive pulmonary disease and ILD, are reported as risk factors for respiratory infections and methotrexate-associated ILD (28-30). In the current patient, the lung function test indicated a poor % vital capacity, which is considered a contraindication for methotrexate treatment. Anti-TNF biologic therapies have also been reported as risk factors for the emergence and worsening of demyelinating neuropathies in patients with RA (31, 32). HAM has been reported to be a demyelinating disease due to chronic inflammation in the spinal cord (19-21). Therefore, we considered avoiding administrating anti-TNF therapies to the current patient. In addition, the effect of anti-TNF agent monotherapy has been reported to be inferior to that of combination therapy with methotrexate. Therefore, neither methotrexate nor anti-TNF biologics were administered in the present patient. However, tocilizumab monotherapy improved the RA disease activity without the exacerbation of HAM/TSP or HU.

A previous study reported that the C-reactive protein levels were higher in HTLV-1-positive patients with RA than in HTLV-1-negative patients with RA (6). In addition, HTLV-1-positive RA patients showed an inadequate response against TNF inhibitors compared with HTLV-1-negative RA patients (7). The HTLV-1 Tax protein has been reported to promote the production of not only interleukin (IL)-6 but also soluble IL-6 receptor from the HTLV-1-infected cells (33, 34). Therefore, it is possible that HTLV-1-infection may be involved in worsening inflammatory responses of RA.

We speculate that tocilizumab is an effective treatment in HTLV-1-positive patients with RA. However, Terada et al. described a patient with HAM/TSP and RA whose symptoms associated with HAM/TSP and HU were exacerbated after the initiation of tocilizumab treatment (8). In the present case, tocilizumab treatment improved the RA without exacerbating the HAM/TSP. In addition, the neurological manifestations of HAM/TSP worsened after the corticosteroid dose was reduced to less than 10 mg/day, indicating that tocilizumab treatment was not effective against HAM/TSP. On comparing the clinical features between the present case and Terada's case, we found no remarkable differences between them. The role of IL-6 in the pathogenesis of HAM/TSP also remains unclear. Therefore, in the future, a clinical study registering a large number of RA patients complicated with HAM will be necessary to clarify the safe and efficient application of biologics, including IL-6 receptor inhibitors.

A high HTLV-1 PVL was reported to be a risk factor for HTLV-1-associated disorders, such as ATL and HAM/TSP (35, 36). Whether or not immunosuppressive agents influence the HTLV-1 PVL level and the development of ATL and HAM/TSP remains unclear. Umekita et al. showed that the HTLV-1 PVL levels in HTLV-1-positive patients with RA did not change markedly during antirheumatic treatment including methotrexate or biologics (37). In the present case, tocilizumab treatment did not appear to be effective in changing the HTLV-1 PVL during the relatively short observation period. However, several case reports have described the development of ATL in HTLV-1-positive patients with rheumatic disorders who were treated with methotrexate and biologics (38-40). Therefore, long-term follow-up will be necessary in the present patient to determine whether HAM/TSP exacerbation or ATL development might occur during tocilizumab treatment.

In conclusion, tocilizumab monotherapy improved the RA disease activity without exacerbating HAM/TSP or HU. Whether or not antirheumatic biologics are safe and efficient in patients with RA accompanied by HTLV-1-associated disorders, such as HAM/TSP and HU, remains unclear. Further studies including a large number of HTLV-1-positive patients with RA are necessary to resolve these clinical questions.

Written informed consent for the publication of this report was obtained from the patient.

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

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