Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9519-22
Intern Med 62: 449-452, 2023
http://internmed.jp

【 CASE REPORT 】

Psoas and Mediastinal Abscesses during Intravenous Tocilizumab Treatment in Multicentric Castleman Disease

Kazuto Togitani[1], Fumiya Ogasawara[1], Yu Arakawa[2], Natsuki Sugimura[3], Ryohei Miyazaki[4] and Kensuke Kojima[1]

Abstract:

Tocilizumab has been used to treat idiopathic multicentric Castleman disease (iMCD). As tocilizumab prevents interleukin-6 from exerting pro-inflammatory effects, there is some concern about a delayed diagnosis of severe infections during tocilizumab treatment. Although serious infections during tocilizumab therapy have been previously described in patients with rheumatoid arthritis, they have not been reported in iMCD. We herein report a case of disseminated *Staphylococcus aureus* infection after a superficial skin wound followed by psoas and mediastinal abscesses with pyogenic spondylodiscitis in an iMCD patient with diabetes. Physicians should be alert for the occurrence of disseminated *S. aureus* infection after even minor skin injury during tocilizumab therapy.

Key words: abscess, mediastinum, methicillin-susceptible *Staphylococcus aureus*, multicentric Castleman disease, psoas, tocilizumab

(Intern Med 62: 449-452, 2023)
(DOI: 10.2169/internalmedicine.9519-22)

Introduction

Castleman disease (CD) is a rare group of lymphoproliferative disorders subdivided by disease extent into unicentric CD and multicentric CD (MCD), and the latter is further etiologically divided into idiopathic MCD (iMCD), human herpes virus-8 (HHV8)-associated MCD (HHV8-MCD), and polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder and skin changes (POEMS)-associated MCD (POEMS-MCD) (1). iMCD is subclassified into iMCD-thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, organomegaly (iMCD-TAFRO), and iMCD-not otherwise specified (iMCD-NOS) (1). In Japan, iMCD accounts for the large majority of MCD cases (2, 3).

Since interleukin-6 (IL-6) plays a central role in the pathogenesis of iMCD (4), agents inhibiting interactions between IL-6 and its receptor have been used for its treatment (5, 6). The anti-IL-6 antibody siltuximab and the anti-IL-6 receptor antibody tocilizumab have been respectively approved in US and Japan. In Japan, tocilizumab has been approved for use in rheumatoid arthritis (RA), juvenile idiopathic arthritis, adult-onset Still's disease, cytokine release syndromes, and coronavirus disease 2019 (COVID-19), as well as in MCD. Anti-IL-6 therapy might mask signs and symptoms of infection through its anti-inflammatory effects, and indeed, serious infections have been reported in patients with RA during therapy (7). In contrast, infectious complications during anti-IL-6 therapy have only been sporadically described in MCD patients (8).

We herein report a case of disseminated *Staphylococcus aureus* infection leading to psoas and mediastinal abscesses with pyogenic spondylodiscitis after a superficial skin injury in a tocilizumab-treated iMCD patient with diabetes.

The simultaneous occurrence of psoas (9) and mediastinal abscesses (10) has not been reported, even in immunosuppressed patients. Our experience emphasizes that careful monitoring must be performed during tocilizumab treatment, as IL-6 receptor inhibition strongly suppresses acute-phase reactants, which might mask infection-related signs and

[1]Department of Hematology, Kochi Medical School, Kochi University, Japan, [2]Department of Respiratory Medicine and Allergology, Kochi Medical School, Kochi University, Japan, [3]Department of Orthopedic Surgery, Kochi Medical School, Kochi University, Japan and [4]Department of Thoracic Surgery, Kochi Medical School, Kochi University, Japan
Received: February 4, 2022; Accepted: May 9, 2022; Advance Publication by J-STAGE: June 21, 2022
Correspondence to Dr. Kazuto Togitani, togitani@kochi-u.ac.jp

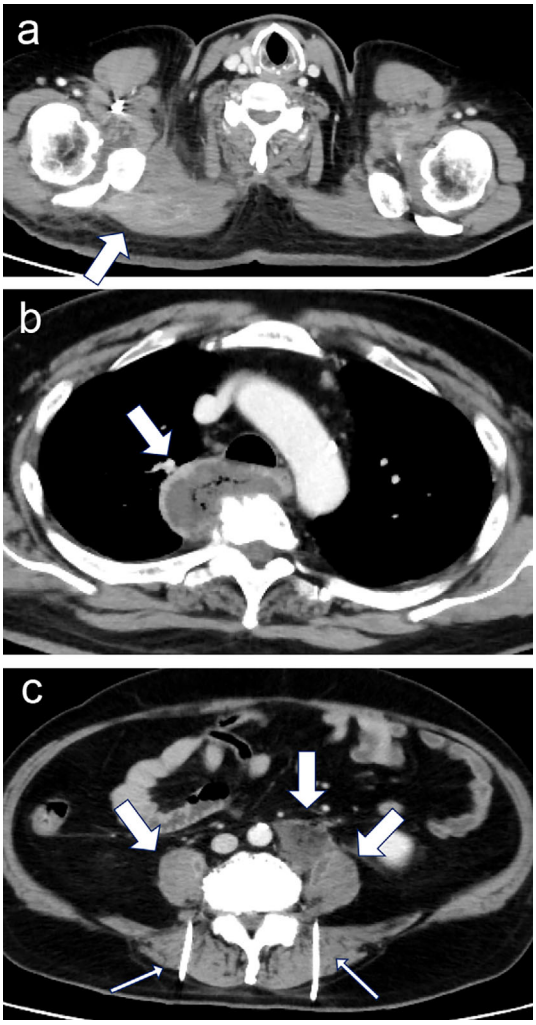

Figure 1. **Chest CT scan showing right trapezius muscle swelling (a) and a posterior mediastinal paravertebral abscess (b). Abdominal CT scan showed bilateral psoas muscle abscesses, a left retroperitoneal abscess, and bilateral psoas muscle drainage tubes that were inserted on day 6 (thin arrows) (c).**

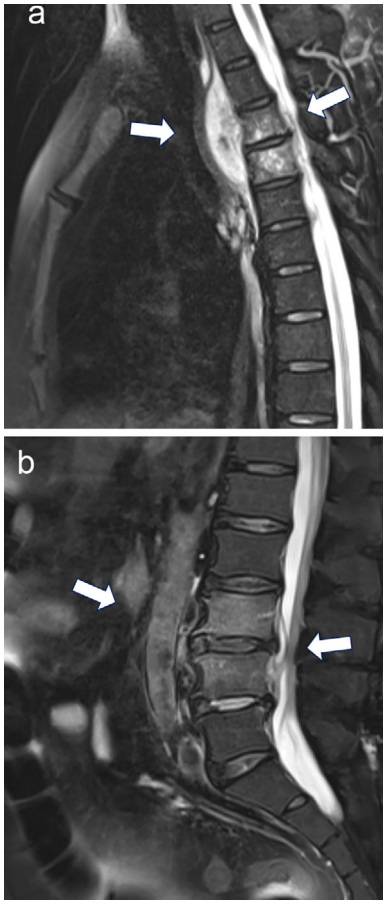

Figure 2. **T2-weighted sagittal MRI of the thoracic and lumbar spine showing spondylitis and peripheral abscesses at Th5-6 (a) and L3-4 (b) spinal levels.**

symptoms and hinder the timely diagnosis of infection.

Case Report

A 56-year-old man who had worked as an excavator operator and received bi-weekly intravenous tocilizumab (8 mg/kg) for iMCD was brought to the Emergency Ward by ambulance presenting with severe shoulder and back pain. He had a 10-year history of type 2 diabetes mellitus and a 4-year history of iMCD. He had complained of general malaise at the time of the iMCD diagnosis, and his laboratory data at that time had been as follows: C-reactive protein (CRP): 8.1 mg/dL, hemoglobin (Hb): 11.6 g/dL, and immunoglobulin G (IgG): 4,301 mg/dL. He had commenced tocilizumab treatment one year after being diagnosed with iMCD, which resulted in an improvement of his general fatigue and inflammatory biomarkers, including CRP, IgG, and Hb.

One week before admission, the patient suffered abrasions on both knees. He had washed the wound with water and applied an over-the-counter disinfectant. The wounds hurt for two days during the process of wound healing. On admission, his body temperature was 38.9°C, blood pressure was 117/68 mmHg, and heart rate was 117 bpm. A physical examination revealed swelling and tenderness of the right trapezius and quadriceps muscles. The skin on both his knees showed pigmentation after wound healing. Although he did not adopt the iliopsoas limb position, he could not lift his lower limbs freely. There was no evidence of dental or oro-pharyngeal infections and no cervical cellulitis.

A laboratory evaluation showed leukocytosis [white blood cell count (WBC) 29,100/μL], elevation of CRP (3.46 mg/dL), hyperglycemia (blood glucose 343 mg/dL), hyperbilirubinemia (total bilirubin 2.0 mg/dL), and hemoglobin A1c (6.9%). Ten days before admission, his WBC, lymphocyte and neutrophil counts, and immunoglobulin levels were within the normal range. Computed tomography (CT) (Fig. 1) and magnetic resonance imaging (MRI) (Fig. 2) showed swelling of the right trapezius muscle and spondylodiscitis at L3-4 and Th5-6, along with an abscess in the right paravertebral space and bilateral iliopsoas muscles. Blood bacterial culture detected *S. aureus*. Transesophageal echocardiography showed no evidence of endocarditis. Brain abscesses were not detected by contrast-enhanced CT. The

diagnosis of psoas and mediastinal abscesses with pyogenic spondylodiscitis was thus confirmed.

Tocilizumab was stopped, and parenteral antimicrobial therapy with meropenem and vancomycin was commenced until an antimicrobial susceptibility test showed methicillin-susceptible *S. aureus* (MSSA). On the fourth hospital day, the antibiotic regimen was de-escalated to intravenous cefazoline. Although the right shoulder pain gradually decreased after starting antibiotic therapy, CT-guided percutaneous drainage of bilateral iliopsoas abscesses (on days 6 and 26) and surgical drainage of the mediastinal abscess (on day 17) were required for control of the abscesses. Although tocilizumab discontinuation did not lead to exacerbation of iMCD, the drug was re-started two months later. Furthermore, intravenous cefazoline was switched to oral cefalexin from day 60 onwards for an additional six weeks. He was discharged from the hospital on day 64 and has been continuing tocilizumab treatment for iMCD without recurrence of MSSA at eight months since the onset of infection.

Discussion

Severe infections following anti-IL-6-directed therapy have been reported in patients with RA (7, 9, 11-14), giant cell arteritis (GCA) (14), Takayasu arteritis (15), adult-onset Still's disease (16), and COVID-19 infection (17). However, they have not been reported in iMCD patients, except for a single case report in a patient on siltuximab (8). The lower incidence and younger onset of iMCD [0.1 per 100,000 patient-years (18), median age: 48.0 years (2)] than that of RA [1,000 per 100,000 patient-year (19), median age: 60.0 years (20)] seem to contribute to the rarity of reported severe infections during anti-IL-6 therapy in iMCD patients. Potential risk factors for serious infection in RA patients receiving tocilizumab include concurrent or medical history of respiratory disorders, prednisolone dose at baseline ≥5 mg/day, age ≥65 years old (21), disease duration ≥10 years (12, 20), exposure to more than three previous disease-modifying anti-rheumatic drugs, and concomitant therapy with proton-pump inhibitors (12); diabetes mellitus is not among the risk factors (12, 20, 21). Our patient did not have any of the above risk factors.

Post-marketing surveillance has indicated a higher incidence of infectious complications under tocilizumab treatment in iMCD patients than in RA patients [35.2% (135/384) versus 10.0% (792/7,901)] (2, 20-23). Sepsis is also reportedly more frequent in iMCD than RA [1.6% (6/384) versus 0.2% (15/7,901)] (2, 20-23). Therefore, it is possible that severe infections occur more frequently in iMCD patients than in RA patients receiving tocilizumab.

Despite the severe infection in our case, his CRP level was low (maximum value was 3.46 mg/dL) relative to the high WBC count (29,100/μL). It is possible that tocilizumab might strongly suppress the increase in CRP, which might delay the diagnosis of infection (12).

Since vertebral blood vessels give rise to upper and lower branches, it is likely that the lesions in the adjacent vertebral bodies in our patient were due to hematogenous dissemination of the infection (Fig. 2), and the pyogenic spondylodiscitis was due to tracking of the abscess into the surrounding soft tissues, causing psoas and mediastinal abscesses. Psoas abscesses have almost always been reported as developing secondary to pyogenic spondylitis (24). In contrast, posterior mediastinal abscesses are reported following thoracic surgery, esophageal perforation, and dental, pharyngeal, or cervical infections (25). Since our patient had neither decayed teeth nor other oral issues, his mediastinal abscess was not likely to be due to descending necrotizing mediastinitis.

Blood culture detected MSSA as the causative bacterial agent of spondylodiscitis in our case. *S. aureus* is the predominant pathogen for psoas abscesses and spondylodiscitis, accounting for half of non-tuberculous cases (range 20-84%) (24, 25). Distant foci of infection, such as the genitourinary tract (17%), skin and soft tissue (11%), intravascular devices (5%), gastrointestinal tract (5%), respiratory tract (2%), and oral cavity (2%) have been reported as possible causes of spondylodiscitis (26). In the present case, the abrasions on the patient's knees one week before the symptom onset were considered the gateway for MSSA infection. In addition, the most common risk factor for pyogenic spondylitis is reportedly diabetes mellitus (26).

In Japan, tocilizumab is recommended at higher dose in MCD than in RA (8 mg bi-weekly vs. 8 mg/kg monthly, respectively). Although it has been suggested that the tocilizumab dose can be reduced in cases where serum IL-6 concentrations gradually decrease during therapy (3), the tocilizumab dose in our patient was fixed at 8 mg bi-weekly until the onset of infection, as the IL-6 levels were not measured due to insurance-related limitations. Although long-term exposure to tocilizumab has not been reported as being associated with an increased risk of infectious complications (20-23, 27), reduction of tocilizumab exposure based on IL-6 levels or disease severity might be an option for minimizing the risk of infectious complications.

Conclusion

To our knowledge, this case report is the first to describe psoas and mediastinal abscesses secondary to MSSA-induced pyogenic spondylodiscitis during treatment with tocilizumab (8 mg/kg bi-weekly) for iMCD in a diabetic patient. This case report might suggest the need for caution following even minor injuries in patients with iMCD and diabetes mellitus under tocilizumab therapy, including possible tocilizumab dose adjustment.

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

Author's disclosure of potential Conflicts of Interest (COI).
Kensuke Kojima: Honoraria, Janssen Pharmaceutical, AstraZeneca and AbbVie; Research funding, Eisai, Daiichi-Sankyo,

Kyowa-Kirin, Otsuka Pharmaceutical and Asahi Kasei.

References

1. Dispenzieri A, Fajgenbaum DC. Overview of Castleman disease. Blood **135**: 1353-1364, 2020.
2. Murakami M, Johkoh T, Hayashi S, et al. Clinicopathologic characteristics of 342 patients with multicentric Castleman disease in Japan. Mod Rheumatol **30**: 843-851, 2020.
3. Kawabata H, Kadowaki N, Nishikori M, et al. Clinical features and treatment of multicentric Castleman's disease: a retrospective study of 21 Japanese patients at a single institute. J Clin Exp Hematop **53**: 69-77, 2013.
4. Nishimoto N. Interleukin-6 as a therapeutic target in candidate inflammatory diseases. Clin Pharmacol Ther **87**: 483-487, 2010.
5. van Rhee F, Voorhees P, Dispenzieri A, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood **132**: 2115-2124, 2018.
6. Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood **129**: 1646-1657, 2017.
7. Morel J, Constantin A, Baron G, et al. Risk factors of serious infections in patients with rheumatoid arthritis treated with tocilizumab in the French Registry REGATE. Rheumatology (Oxford) **56**: 1746-1754, 2017.
8. Cohen PR, Nikanjam M, Kato S, Goodman AM, Kurzrock R. Afebrile pneumonia in a patient with multicentric Castleman disease on siltuximab: infection without fever on anti-interleukin-6 therapy. Cureus **12**: e8967, 2020.
9. Vajdić ID, Štimac G, Pezelj I, Mustapić M, Grazio S. Psoas abscess during treatment with intravenous tocilizumab in a patient with rheumatoid arthritis: a case-based review. Rheumatol Int **41**: 819-825, 2021.
10. Motono N, Tanaka M, Machida Y, et al. A case of empyema and a posterior mediastinal abscess after an iliopsoas abscess secondary to Crohn's disease. Int J Colorectal Dis **31**: 709-710, 2016.
11. Nguyen MTT, Pødenphant J, Ravn P. Three cases of severely disseminated *Staphylococcus aureus* infection in patients treated with tocilizumab. BMJ Case Rep **2013**: bcr2012007413, 2013.
12. Lang VR, Englbrecht M, Rech M, et al. Risk of infections in rheumatoid arthritis patients treated with tocilizumab. Rheumatology (Oxford) **51**: 852-857, 2012.
13. Tsujimoto T, Takahata M, Kokabu T, Matsuhashi M, Iwasaki N. Pyogenic spondylodiscitis following anti-interleukin-6 therapy in a patient with rheumatoid arthritis (implication of hematogenous infection risk in degenerative intervertebral discs): a case report and review of the literature. J Orthop Sci **21**: 694-697, 2016.
14. Berman M, Ben-Ami R, Berliner S, et al. The effect of tocilizumab on inflammatory markers in patients hospitalized with serious infections. Case series and review of literature. Life (Basel) **11**: 258, 2021.
15. de Kruif MD, van Gorp EC, Bel EH, Gerlag DM, Kunst PW. Streptococcal lung abscesses from a dental focus following tocilizumab: a case report. Clin Exp Rheumatol **30**: 951-953, 2012.
16. Zhou S, Qiao J, Bai J, Wu Y, Fang H. Biological therapy of traditional therapy-resistant adult-onset Still's disease: an evidence-based review. Ther Clin Risk Manag **14**: 167-171, 2018.
17. Sampogna G, Tessitore N, Bianconi T, et al. Spinal cord dysfunction after COVID-19 infection. Spinal Cord Ser Cases **6**: 92, 2020.
18. Yoshizaki K. A reference guide for management of Castleman disease [Article in Japanese]. Rinsho Ketsueki (Jpn J Clin Hematol) **58**: 97-107, 2017.
19. Yamanaka H, Sugiyama N, Inoue E, Taniguchi A, Momohara S. Estimates of the prevalence of and current treatment practices for rheumatoid arthritis in Japan using reimbursement data from health insurance societies and the IORRA cohort (I). Mod Rheumatol **24**: 33-40, 2014.
20. Koike T, Harigai M, Inokuma S, et al. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. J Rheumatol **41**: 15-23, 2014.
21. Koike T, Harigai M, Inokuma S, et al. Postmarketing surveillance of tocilizumab for rheumatoid arthritis in Japan: interim analysis of 3881 patients. Ann Rheum Dis **70**: 2148-2151, 2011.
22. Actemra proper use guide for rheumatoid arthritis and juvenile idiopathic arthritis with polyarticular activity. (in Japanese) [Internet]. [cited 2022 Apr 5]. Available from: https://chugai-pharm.jp/content/dam/chugai/product/act/div/guide-ra/doc/act_guide_ra.pdf
23. Actemra proper use guide for Castleman's disease. (in Japanese) [Internet]. [cited 2022 Apr 5]. Available from: https://chugai-pharm.jp/content/dam/chugai/product/act/div/guide-cd/doc/act_guide_cd.pdf
24. Sato T, Kudo D, Kushimoto S. Epidemiological features and outcomes of patients with psoas abscess: a retrospective cohort study. Ann Med Surg **62**: 114-118, 2021.
25. Mylona E, Samarkos M, Kakalou E, Skoutelis A. Pyogenic vertebral osteomyelitis: a systematic review of clinical characteristics. Semin Arthritis Rheum **39**: 10-17, 2009.
26. Gouliouris T, Aliyu SH, Brown NM. Spondylodiscitis: update on diagnosis and management. J Antimicrob Chemother **65** Suppl 3: iii11-iii24, 2010.
27. Nishimoto N, Ito K, Takagi N. Safety and efficacy profiles of tocilizumab monotherapy in Japanese patients with rheumatoid arthritis: meta-analysis of six initial trials and five long-term extensions. Mod Rheumatol **20**: 222-232, 2010.