Occurrence of adult-onset Still's disease after coronavirus disease 2019 BNT162B2 vaccination in a patient with ulcerative colitis

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CASE REPORT

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The authors report no conflict of interest.

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The study was approved by the Competent Authorities and Ethics Committees of National Defense Medical College (approval no. 4609). Written informed consent was obtained from all patients.

PATIENT CONSENT STATEMENT

Published with written consent of the patient.

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Not applicable

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Not applicable

KEY CLINICAL MESSAGE

This case indicates that severe acute respiratory syndrome coronavirus 2 vaccination can trigger a hyperinflammatory response classified as adult-onset Still's disease in a patient with ulcerative colitis, which is extremely rare.

SUMMARY

A woman in her 50s with a history of stable ulcerative colitis for 20 years, managed using salazosulfapyridine, presented with migratory rashes, spiking fever, edema, and joint pain that started one week after receiving the BNT162B2 mRNA vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Laboratory tests revealed extremely high serum ferritin levels. The patient was diagnosed with adult-onset Still's disease (AOSD) based on the relevant classification criteria after ruling out other diseases. Detection of high levels of interleukin-18, an inflammatory cytokine related to AOSD, supported the diagnosis. Non-steroidal anti-inflammatory drug monotherapy alone resulted in significant improvements of both the abovementioned symptoms and the elevated inflammatory marker levels. AOSD in a patient with ulcerative colitis is extremely rare. Only one case of AOSD with ulcerative colitis was reported before the coronavirus disease 2019 era. This case indicates that SARS-CoV-2 vaccination can trigger a hyperinflammatory response classified as AOSD in a patient with ulcerative colitis, which is extremely rare.

KEYWORDS

adult onset Still's disease, COVID-19 vaccine, SARS-CoV2, ulcerative colitis

INTRODUCTION

Adult-onset Still's disease is a systemic autoinflammatory illness characterized by recurrent spiking fever, fleeting salmon-pink skin rashes, and polyarthritis.[1] Although the etiology of adult-onset Still's disease remains elusive, dysregulation of immune cells, particularly macrophages and T cells, and the release of various proinflammatory cytokines such as interleukin (IL)-18 may play significant roles in its development.[2] Reportedly, vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could induce a hyperinflammatory state by triggering the production of spike proteins[3]; however, the correlation between SARS-CoV-2 vaccination and hyperinflammation remains to be elucidated. Moreover, the coexistence of adult-onset Still's disease with ulcerative colitis, an inflammatory intestinal disease involving the colon, is extremely rare. Only one case of adult-onset Still's disease with ulcerative colitis has been reported to date.[4] Herein, we report a case of a patient with stable ulcerative colitis who developed adult-onset Still's disease after receiving the first dose of a SARS-CoV-2 vaccine and was treated using nonsteroidal anti-inflammatory drugs (NSAIDs) alone.

CASE HISTORY/EXAMINATION

A woman in her 50s with a history of stable ulcerative colitis for over 20 years presented to our hospital with a complaint of migratory joint pain. One week before presentation, she experienced arthralgia in her elbow and right hip, accompanied by throat pain, skin rashes, and intermittent daily fever that started abruptly. She developed intermittent migratory rashes on her limbs following daily fever spikes (up to approximately 38), demonstrating a possible temporal relevance between the rashes and fever. Bilateral ankle pain and loss of appetite followed, leading her to seek medical care at a hospital, where acetaminophen (400 mg as needed) was prescribed. Although the joint pain in her elbows and hip disappeared, acetaminophen was not effective for relief of the ankle pain. Furthermore, she experienced bilateral wrist pain and visited another hospital for further pain relief. Celecoxib (100 mg two times/day) was prescribed and was partially effective for pain relief. She was subsequently referred to our hospital for further treatment.

The patient had no significant medical history other than ulcerative colitis, which was diagnosed in her 30s and managed using salazosulfapyridine (3000 mg per day). The patient showed no acute deterioration under this treatment, and her annual colonoscopy showed no flares in her intestines. Her family history was

insignificant and she had no allergies, travel history, history of insect exposure, or history of sexual activity that may explain the migratory rashes and arthralgia.

On her first visit, she presented with an afebrile status accompanied by tachycardia (105 beats per minute). Salmon-pink maculopapular rashes with abrasions were observed on her forearms, abdomen, and lower legs (Figure 1A). Her anterior neck lymph nodes showed painless lymphadenopathy (maximum diameter, 15 mm). She reported tenderness in multiple joints, including the wrists and ankles, and the pain was intensified with active joint movement.

DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS AND TREATMENT

Laboratory tests performed on admission revealed leukocytosis (16,700 cells/mm^3) with neutrophilia (14,863 cells/mm^3), a C-reactive protein level of 35.2 mg/dL, an erythrocyte sedimentation rate of 98 mm/h, and a ferritin level of 1651.5 ng/mL. Positron emission tomography-computerized tomography (PET-CT) indicated 18F-fluorodeoxyglucose uptake in the lymph nodes (neck, axillary, mediastinal, inguinal, and liver), spleen, and bone marrow. Axillary lymph node biopsy revealed reactive lymphoid follicular hyperplasia with no malignant changes.

The presence of granular cast and microscopic hematuria prompted admission for fear of acute kidney failure. An anti-streptolysin titer returned negative results. Twelve days after admission, the patient's ferritin levels increased to 2382.6 ng/mL and her IL-18 levels (131000 pg/mL) were extremely high.

Hepatitis B surface antigen, anti-human parvovirus B19 immunoglobin M, and interferon gamma assays for tuberculosis showed negative results. Autoimmune-related assessment, including antinuclear antibody, rheumatoid factor, anti-citrullinated peptide antibody, anti-ds DNA antibody, anti SS-A antibody, and anti-neutrophil cytoplasmic antibodies tests, showed normal results.

Ceftriaxone as an empiric antibiotic therapy was started immediately after admission because the nephrologists considered the risk of infection-related acute glomerular nephritis. However, we discontinued the antibiotics five days later after confirming negative blood culture results and rapid improvement in urine sediment with no pathognomonic casts, which is not compatible with the indications of acute kidney injury that requires kidney biopsy.

Diagnosis of adult-onset Still's disease requires a thorough clinical investigation to rule out other possible inflammatory diseases, including malignancies, infections, and other rheumatic diseases. Malignant lymphoma is a fatal condition that mimics adult-onset Still's disease. Biopsies of the patient's lymph nodes and skin showed no malignant cells, and her good response to NSAIDs was incompatible with the outcomes of malignant lymphoma. Results of a PET-CT scan did not suggest any solid malignant tumor. In addition, cancer screening, including a pap smear, ruled out cervical cancer.

Considering the patient's negative blood culture results and lack of apparent exposure, infectious diseases characterized by skin rashes and fever, including Lyme disease, syphilis, and acute hepatitis B, were ruled out. Autoimmune diseases associated with relevant antibodies, including systemic lupus erythematosus, anti-neutrophil cytoplasmic antibody-related vasculitis, and rheumatoid arthritis, were also ruled out by negative blood test results, which did not meet the classification criteria for each disease.

The patient's medical history, physical examination findings, and lab test results indicated that the diagnostic criteria for adult-onset Still's disease were met (Yamaguchi's criteria[5]; three of four major criteria [arthralgia/arthritis, typical rash, and leukocytosis] and four of five minor criteria [sore throat, lymphadenopathy, abnormal liver function test results, and negative rheumatoid factor and antinuclear antibody assays] were met). Furthermore, her serum IL-18 levels increased to 131,000 pg/mL, and her ferritin levels increased as her symptoms worsened, which strongly supported the diagnosis of adult-onset Still's disease. PET-CT findings showing high absorption in the bone marrow demonstrated a typical pattern for adult-onset Still's disease. Thus, new-onset Still's disease was considered the most likely diagnosis.

We initially considered restarting acetaminophen instead of NSAIDs to relieve the patient's joint pain, even

though NSAIDs are generally contraindicated for patients with ulcerative colitis because they may trigger a relapse.[6,7] We finally decided to continue the NSAID therapy considering that the severe arthralgia that was affecting her motor function was improving with the use of celecoxib.

We started the patient on loxoprofen and gradually increased its dose while continuing salazosulfapyridine and confirming the absence of hematochezia or abdominal pain, a sign of relapsing ulcerative colitis. If treatment failed, we planned to intensify the dose of steroid or tocilizumab treatment, which is reportedly effective for adult-onset Still's disease. The patient responded to the NSAID therapy with loxoprofen (180 mg daily [maximum dose]) and showed a gradual and significant improvement in the fever, rashes, and fatigue. She was subsequently discharged from our hospital within three weeks.

OUTCOME AND FOLLOW-UP

Figure 2 shows the clinical course of the case. NSAID therapy was significantly and continuously effective in relieving the patient's joint symptoms. She was discharged nine days after admission following significant improvement in her symptoms. We continued the usual recommended dose of NSAIDs (loxoprofen 60 mg three times/day), and no side effect or reactivation of ulcerative colitis, bloody diarrhea, or abdominal pain occurred. Follow-up endoscopy performed nine months later showed no abnormalities in the patient's large intestine.

Considering the significant improvements in arthralgia, edema, and fever, as well as the normalized inflammatory indicators within three months of NSAID monotherapy (loxoprofen 60 mg three times/day), administration of steroids or tocilizumab was deemed unnecessary. The rashes also disappeared within three months (Figure 1B). We gradually decreased the dose of loxoprofen considering the possible risk of recurrent ulcerative colitis, and finally discontinued the NSAID therapy within 12 months. All joint symptoms, fever, and rashes disappeared, and the patient's ferritin, C-reactive protein, and IL-18 levels normalized at the completion of follow-up in one year.

With regard to anti-SARS-CoV2 vaccination status, the patient commented as follows (The following perspective was translated by the author as English is not the patient's native language): "I was worried about the joint symptoms, as they interfered with my daily activities. However, pain killers relieved my joint pain gradually but significantly. The possible relationship between my disease and coronavirus disease 2019 vaccination is a bit worrisome, and I contemplated whether I should receive another shot. I will consider the consensus of the doctors and the prevalence of coronavirus disease 2019 when deciding."

DISCUSSION

Development of adult-onset Still's disease following mRNA SARS-CoV-2 vaccination suggests that the vaccine can cause a hyperinflammatory response. Multiple cases of new-onset adult-onset Still's disease following SARS-CoV-2 vaccination have been documented.[8-13] Flares of adult-onset Still's disease have also been reported, suggesting a possible correlation between the disease and SARS-CoV-2 vaccines.[14-17] The reported cases of new occurrence of adult-onset Still's disease after SARS-CoV-2 vaccination, including the present case, are summarized in Table 1.

TABLE 1 New-onset adult-onset Still's disease following the patient's first SARS-CoV-2 vaccination

Age (years) and sex (M/F)	SARS-CoV-2 vaccine (type and name)	Medical history	Onset (days/ weeks/ months after vaccination)	Serum ferritin (ng/mL)	Serum IL-18 (pg/m)	Medication	Reference

Age (years) and sex (M/F)	SARS-CoV-2 vaccine (type and name)	Medical history	Onset (days/ weeks/ months after vaccination)	Serum ferritin (ng/mL)	Serum IL-18 (pg/m)	Medication	Reference
22 M	mRNA BNT162B2	NS	13 days	54,921	NA	Methylprednisolone Dexamethasone Anakinra IVIG	8
36 M	Vector ChAdOx1 nCoV-19	NS	1 day	1482	NA	Methylprednisolone	8
36 F	mRNA BNT162B2	NS	10 days	4312	NA	Methylprednisolone Tocilizumab	9
53 M	Vector ChAdOx1 nCoV-19	NS	10 weeks	3140	NA	Prednisone	10
20 F	Vector ChAdOx1 nCoV-19	NS	10 days	11,491	NA	Naproxen	11
47 F	Vector ChAdOx1 nCoV-19	NS	3 weeks	404	NA	Methotrexate Tocilizumab	11
35 F	Vector ChAdOx1 nCoV-19	NS	3 months	>100,000	NA	Methylprednisolone	11
59 F	mRNA BNT162B2	NA	10 days	11,491 IL-18	[?]5000	Methylprednisolone Prednisolone Tocilizumab Cyclosporin	12
35 M	mRNA-1273	NA	24 days	1263	NA	Prednisolone	12
65 M	Vector ChAdOx1 nCoV-19	Psoriatic arthritis	1 day	1550	NA	Prednisone Anakinra	13
50 F	mRNA BNT162B2	UC	21 days	2383	131000	Loxoprofen	Our case

NS, not significant; NA, not available; IVIG, intravenous immunoglobulin; UC, ulcerative colitis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IL, interleukin; M, male; F, female

The ages of the patients in these cases ranged from 22 to 65 years, and they had few comorbidities. All patients had new-onset adult-onset Still's disease, which was treated using NSAIDs, steroids, tocilizumab,

anakinra, and intravenous immunoglobulin. All the patients recovered after treatment. Some hyperinflammatory responses after vaccination can be self-limiting; however, cases similar to those listed in Table 1, wherein the symptoms meet the classification criteria for adult-onset Still's disease and improve after treatment, should be carefully assessed without dismissing the symptoms as simple side effects of the SARS-CoV-2 vaccine. In addition, patients should be appropriately notified when a diagnosis is made.

The symptoms of adult-onset Still's disease in the reported cases generally started three weeks after vaccination. To our knowledge, the present case is the first reported case of a patient with ulcerative colitis who developed adult-onset Still's disease after SARS-CoV-2 vaccination and was treated using an NSAID alone. The distinguishing characteristics of the present case are the presence of ulcerative colitis as a comorbidity and the positive response to NSAID treatment even with extremely high levels of IL-18, which is suggested to be an inflammatory marker of adult-onset Still's disease[2]and is correlated to the severity of active adult-onset Still's disease.[18] Patients with adult-onset Still's disease show extremely high IL-18 levels compared with patients with other inflammatory diseases.[18] Sequential measurement of IL-18 level may be useful in guiding treatment as it can reflect disease activity in adult-onset Still's disease.[19] A clinical practice guideline suggests that IL-18 level in addition to ferritin and C-reactive protein levels can be used to evaluate the extent of inflammation in Still's disease.[20] The guideline also indicates that NSAIDs can be used in addition to the mainstay treatment comprising systemic steroids, which can be used to alleviate symptoms with mild adult-onset Still's disease.[20]

In the present case, the positive response to NSAID treatment in the presence of high IL-18 levels after SARS-CoV-2 vaccination supports the diagnosis of adult-onset Still's disease. The involvement of inflammatory cytokines, which can be induced by post-vaccination new-onset adult-onset Still's disease or adult-onset Still's disease flares, may imply that the common background etiology includes inflammasomes and hyperinflammation through macrophage activation and proinflammatory cytokines, such as IL-6, IL-18, and tumor necrosis factor.

Adult-onset Still's disease is a rare comorbidity in patients with ulcerative colitis. Only one case of Crohn's disease with adult-onset Still's disease has been reported.[4] Multifactorial factors that are likely relevant to the coexistence of adult-onset Still's disease and inflammatory bowel disease include intestinal microbiota, mucosal barrier, genetic susceptibility, and environmental factors; however, no definitive etiology has yet been clarified.[21] Although ulcerative colitis can present with extraintestinal symptoms involving the skin and joints that can be similar to the presentation of adult-onset Still's disease, the rarity of the coexistence of the two diseases suggests the independence of their pathologies. Nevertheless, the present case indicates that even though the coexistence of ulcerative colitis and adult-onset Still's disease is rare, SARS-CoV-2 vaccines may trigger a specific inflammatory process in patients with ulcerative colitis. The patient's hyperinflammatory status suppressed by salazosulfapyridine may have been substituted by an autoinflammatory condition triggered by SARS-CoV-2 vaccination.

In conclusion, this is the first report of the occurrence of adult-onset Still's disease in a patient with ulcerative colitis. The possibility of autoinflammatory conditions such as adult-onset Still's disease should be considered when evaluating or treating symptoms suspected to be side effects of SARS-CoV-2 vaccination, regardless of the comorbidities associated with such symptoms.

AUTHOR CONTRIBUTIONS

Takahiro Kobayashi : Conceptualization; data curation; project administration; writing-original draft. **Kenichi Hashimoto** : Project administration; supervision; writing-review and editing.**Yasuyoshi Kusanagi:** Supervision; writing-review and editing.**Yuji Tanaka:** Supervision; writing-review and editing.

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REFERENCES

1. Efthimiou P, Paik PK, Bielory L. Diagnosis and management of adult onset Still's disease. *Ann Rheum Dis.* 2006;65(5):564-572. doi:10.1136/ard.2005.042143
2. Inoue N, Shimizu M, Tsunoda S, Kawano M, Matsumura M, Yachie A. Cytokine profile in adult-onset Still's disease: a comparison with systemic juvenile idiopathic arthritis. *Clin Immunol.*2016;169:8-13. doi:10.1016/j.clim.2016.05.010
3. Baicus C, Delcea C, Pinte L, Dan GA. Hyper-inflammation after COVID-19 mRNA vaccination: at the crossroads of multisystem inflammatory disease and adult-onset Still's disease. Does terminology matter?*Rom J Intern Med.* 2022;60(1):3-5. doi:10.2478/rjim-2021-0035
4. Choi YJ, Yoo WH. Occurrence of ulcerative colitis in a patient with adult-onset Still's disease: Coincidence or correlated. *Arch Rheumatol.* 2017;32(3):253-256. doi:10.5606/ArchRheumatol.2017.6182
5. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. *J Rheumatol.*1992;19(3):424-430.
6. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative colitis in adults. *Am J Gastroenterol.* 2019;114(3):384-413. doi:10.14309/ajg.0000000000000152
7. Takeuchi K, Smale S, Premchand P, et al. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2006;4(2):196-202. doi:10.1016/s1542-3565(05)00980-8
8. Leone F, Cerasuolo P, Bosello S, et al. Adult-onset Still's disease following COVID-19 vaccination. *Lancet Rheumatol.*2021;3(10):e678-e680. doi:10.1016/S2665-9913(21)00218-6
9. Park SY, Lee KH. Adult-onset Still's disease after BNT162b2 mRNA COVID-19 vaccine. *J Korean Med Sci.* 2021;36(50):e344. doi:10.3346/jkms.2021.36.e344
10. Sweeney A, Tracey G, Garnham K. Adult-onset Still disease post-adenovirus vector COVID-19 vaccine. *Intern Med J.*2021;51(12):2144-2145. doi:10.1111/imj.15563
11. Padiyar S, Kamath N, Mathew J, et al. New-onset adult-onset Still's disease-like syndrome after ChAdOx1 nCoV-19 vaccination- a case series with review of literature. *Clin Rheumatol.*2022;41(5):1569-1575. doi:10.1007/s10067-022-06065-7
12. Matsuda M, Funakubo Asanuma Y, Yokota K, et al. New-onset adult-onset Still's disease following COVID-19 vaccination: Three case reports and a literature review. *Intern Med.* 2023;62(2):299-305. doi:10.2169/internalmedicine.0590-22
13. Bindoli S, Giollo A, Galozzi P, Doria A, Sfriso P. Hyperinflammation after anti-SARS-CoV-2 mRNA/DNA vaccines successfully treated with anakinra: Case series and literature review. *Exp Biol Med (Maywood).* 2022;247(4):338-344. doi:10.1177/15353702211070290
14. Magliulo D, Narayan S, Ue F, Boulougoura A, Badlissi F. Adult-onset Still's disease after mRNA COVID-19 vaccine. *Lancet Rheumatol.*2021;3(10):e680-e682. doi:10.1016/S2665-9913(21)00219-8
15. Sharabi A, Shiber S, Molad Y. Adult-onset Still's disease following mRNA COVID-19 vaccination. *Clin Immunol.* 2021;233:108878. doi:10.1016/j.clim.2021.108878
16. Ibáñez Vodnizza SE, Morales Murillo L, de la Rivera Vergara M, Martinez RS. Reactivation of adult-onset Still's disease after use of the COVID-19 ChAdOx1-S vaccine. *BMJ Case Rep.*2022;15(8):e249290. doi:10.1136/bcr-2022-249290
17. Kim JW, Jung JY, Suh CH, Kim HA. Flare of adult-onset Still's disease following mRNA COVID-19 vaccination: a case report and review of literature. *Clin Rheumatol.* 2022;41(5):1583-1589. doi:10.1007/s10067-022-06106-1
18. Girard C, Rech J, Brown M, et al. Elevated serum levels of free interleukin-18 in adult-onset Still's disease. *Rheumatology (Oxford).* 2016;55(12):2237-2247. doi:10.1093/rheumatology/kew300
19. Horiuchi Y, Hashimoto K, Horikoshi H, et al. Fulminant elderly adult-onset Still disease effectively treated with tocilizumab and methotrexate: A case report. *Medicine (Baltimore).*2022;101(28):e29354. doi:10.1097/MD.0000000000029354

20. Mimura T, Kondo Y, Ohta A, et al. Evidence-based clinical practice guideline for adult Still's disease. *Mod Rheumatol.*2018;28(5):736-757. doi:10.1080/14397595.2018.1465633
21. Lobatón T, Vermeire S, Van Assche G, Rutgeerts P. Review article: anti-adhesion therapies for inflammatory bowel disease. *Aliment Pharmacol Ther.* 2014;39(6):579-594. doi:10.1111/apt.12639

FIGURE CAPTIONS

FIGURE 1 (A) Salmon pink rashes with scratch dermatitis on the lower left leg. (B) Skin at three months following treatment.

FIGURE 2 Clinical course of the case, including data on the patient's body temperature, laboratory data, and treatment. CTRX, ceftriaxone; BT, body temperature; CRP, C-reactive protein; IL, interleukin.