Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.2891-23
Intern Med 63: 809-814, 2024
http://internmed.jp

【 CASE REPORT 】

An Elderly Patient Developed Ulcerative Colitis after SARS-CoV-2 mRNA Vaccination: A Case Report and Review of the Literature

Takahito Shimada[1,2], Jun Takada[2], Atsushi Baba[1], Masahide Iwashita[1], Takao Hayashi[1], Teruo Maeda[1] and Masahito Shimizu[2]

Abstract:
An 86-year-old man presented to our hospital with symptoms of diarrhea and bloody stool, which had manifested two weeks after receiving his third severe acute respiratory syndrome coronavirus 2 mRNA vaccination. Colonoscopy revealed diffuse, rough-surfaced mucosa extending from the ascending colon to the rectum. Despite attempting probiotic treatment, the patient's condition did not improve, leading to admission. Endoscopic findings at admission worsened. Based on endoscopic and histopathological findings, the patient was diagnosed with ulcerative colitis. Corticosteroids and 5-aminosalicylic acid were administered, and the clinical symptoms improved. Subsequently, the disease worsened during steroid tapering, and filgotinib was added, leading to steroid-free remission.

Key words: ulcerative colitis, SARS-CoV-2 mRNA vaccine, adverse event, inflammatory bowel disease, elderly patient

(Intern Med 63: 809-814, 2024)
(DOI: 10.2169/internalmedicine.2891-23)

Introduction

Since December 2019, the novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a worldwide pandemic (1, 2). SARS-CoV-2 mRNA vaccines are widely used to prevent disease onset and to reduce disease severity. However, there have been a few reports of adverse events caused by SARS-CoV-2 mRNA vaccines, such as pericarditis and myocarditis (3). There have also been a few case reports of ulcerative colitis (UC) or inflammatory bowel disease (IBD) that developed after SARS-CoV-2 mRNA vaccination (4-8). However, these patients are generally at an age when UC and IBD are more likely to develop, making it difficult to prove a causal relationship with vaccination.

We herein report an elderly patient with a rare case of new-onset UC after SARS-CoV-2 mRNA vaccination.

Case Report

An 86-year-old man presented with a chief complaint of diarrhea and bloody stool lasting for at least the past 2 weeks. These symptoms had manifested two weeks after the third SARS-CoV-2 mRNA-1273 vaccination. He had no appreciable medical history and only mild hypertension and hyperuricemia as comorbidities. He was taking febuxostat as a regular medication for hyperuricemia; however, there have been no changes in regular medications in the past few years and no use of occasional medications. He had undergone colonoscopy nine years prior, and no abnormal findings had been noted.

Colonoscopy at the first visit revealed diffuse rough-surfaced mucosa, redness, and unclear blood vessels extending from the ascending colon to the rectum (Fig. 1). Considering the recent disease onset, the patient was followed-up with probiotics. Ten days later, the patient was admitted

[1]Department of Internal Medicine, JA Gifu Koseiren Gifu/Seino Medical Center Nishimino Kosei Hospital, Japan and [2]Department of Gastroenterology, Gifu University Graduate School of Medicine, Japan
Received: September 8, 2023; Accepted: November 16, 2023; Advance Publication by J-STAGE: January 2, 2024
Correspondence to Dr. Jun Takada, takada.jun.h7@f.gifu-u.ac.jp

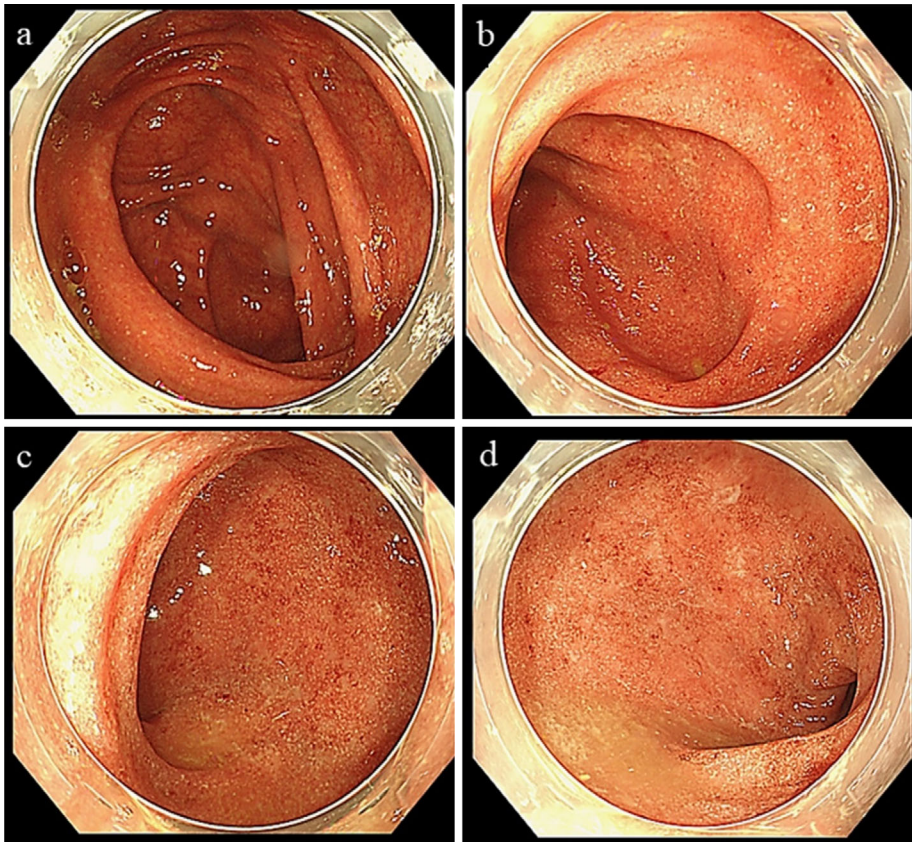

Figure 1. **Initial colonoscopy findings. Except for the cecum, there was continuous erythema and coarse mucosa from the rectum to the ascending colon, with indistinct vascular permeability: (a) cecum/ascending colon, (b) transverse colon, (c) sigmoid colon, and (d) rectum.**

Table 1. **The Laboratory Findings on Admission.**

Complete blood count		**Blood chemistry**			
White blood cell	2.34 ×10⁴/μL	Total protein	8.2 g/dL	Sodium	140 mEq/L
Neutrophil	88.9 %	Albumin	3.1 g/dL	Potassium	3.5 mEq/L
Eosinophil	0 %	Total bilirubin	1.2 mg/dL	Chloride	102 mEq/L
Red blood cell	4.13 ×10⁶/μL	Aspartate transaminase	30 IU/L	ESR 30	25 mm
Hemoglobin	13.7 g/dL	Alanine transaminase	24 IU/L	ESR 60	62 mm
Platelet	3.96 ×10⁵/μL	Alkaline phosphatase	84 IU/L	HBs antigen	Negative
		γ-GTP	27 IU/L	HBs antibody	Negative
		Amylase	78 IU/L	HBc antibody	Negative
		Creatine kinase	194 IU/L	HCV antibody	Negative
		Blood urea nitrogen	40.7 mg/dL	RPR	Negative
		Creatine	1.24 mg/dL	T-SPOT	Negative
		C-reactive protein	25.1 mg/dL	CMV antigen	Negative

ESR 30: Erythrocyte Sedimentation Rate per 30 minutes, ESR 60: Erythrocyte Sedimentation Rate per 60 minutes, HBs antigen: hepatitis B surface antigen, HBs antibody: hepatitis B surface antibody, HBc antibody: hepatitis B core antibody, HCV antibody: hepatitis C virus antibody, RPR: rapid plasma reagin, T-SPOT: T-SPOT. TB, CMV antigen: cytomegalovirus antigen

with worsening of symptoms. On admission, the laboratory findings were as follows: white blood cell (WBC) count 23,390/UL; hemoglobin (Hb) 13.7 g/dL; serum total protein (TP) 8.2 g/dL; serum albumin (Alb) 3.1 g/dL; blood urea nitrogen (BUN) 40.7 mg/dL; creatine (Cre) 1.24 mg/dL; and C-reactive protein (CRP) 25.1 mg/dL (Table 1). No pathogens were detected in stool cultures. Sigmoidoscopy performed at the time of admission revealed marked erythema and loss of vascular permeability from the rectum to the sigmoid colon, which was worse than that observed for the first time (Fig. 2). An initial colonoscopic biopsy showed a high degree of inflammatory cell infiltration, distortion, cryptitis, and goblet cell depletion (Fig. 3). Based on the endoscopic and pathological findings, the patient was diagnosed with elderly-onset UC (EOUC).

Vaccine-induced immune-related enteritis was suggested

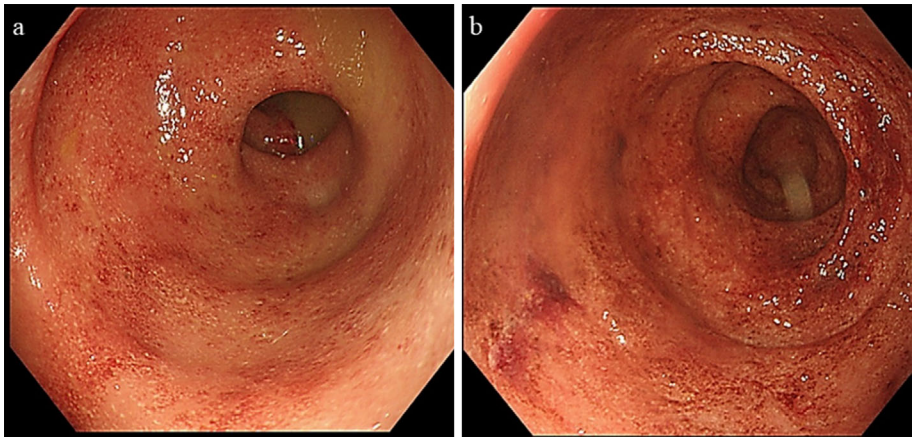

Figure 2. **Sigmoidoscopy findings on admission. Marked redness and loss of vascular translucency can be observed: (a) sigmoid colon and (b) rectum.**

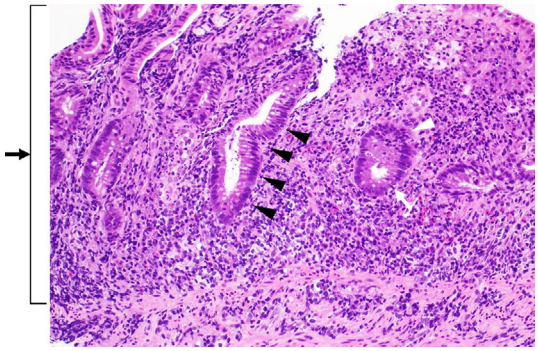

Figure 3. **Biopsy histopathology of initial colonoscopy showing a high degree of inflammatory cell infiltration (black arrow), distortion of crypts (black arrowheads), cryptitis (white arrow), and goblet cell depletion (white arrowhead).**

as a differential diagnosis but was ruled out because of the absence of epithelial cell apoptosis. Treatment with corticosteroids (prednisolone 60 mg/day for 1 week) and 5-aminosalicylic acid (5-ASA) was started. Both his symptoms and laboratory findings improved within a few days of treatment initiation, and the corticosteroid dose was gradually reduced. The patient was discharged from the hospital with a good response to treatment and showed improvement in both symptoms and endoscopic findings (Fig. 4, 5). However, the patient relapsed during corticosteroid tapering; therefore, filgotinib was added, and steroid-free remission was achieved.

Discussion

UC is a diffuse, nonspecific inflammatory disease that affects the colonic mucosa proximal to the rectum and often causes erosion and/or ulcers. Although the cause of UC has not been completely elucidated, it is believed to result from abnormal intestinal immunity and changes in the gut microbiota caused by environmental factors, such as diet and infection, particularly in genetically susceptible individuals (9). The proportion of EOUC cases is reportedly increasing, as is average age of onset (10); however, an onset over 85 years old is very rare.

In the present case, no pathogens were detected in the stool culture, there were no specific infectious findings on a biopsy, and no history of drug use was suspected as a cause. Therefore, infectious enteritis and drug-induced enteritis were ruled out. We identified EOUC as a definitive diagnosis based on endoscopic and histological findings. Histological findings appeared to be those of chronic IBD; however, in the present case, the initial endoscopy was performed two weeks after the symptom onset. A previous report showed that histopathological findings indicating chronic IBD-like changes were observed in specimens from approximately seven days after the onset of symptoms, and there was no significant difference in histopathological findings between acute-onset IBD and chronic IBD (11). Although the histological findings cannot rule out the possibility of unrecognized preexisting UC exacerbated soon after vaccination and new-onset UC unrelated to the vaccination, we consider the histopathological findings in the present case to not necessarily be indicative of a longstanding course but rather consistent with an acute course, based on the course and history of the disease.

COVID-19, a novel disease caused by SARS-CoV-2, led to the onset of a global pandemic in December 2019 (1, 2). Vaccination is considered an effective and safe means to control the spread of COVID-19 and reduce the risk of developing COVID-19 and its severity (12). Although SARS-CoV-2 vaccination has been effective in combating the virus, there have been reports of adverse events, such as myocarditis and pericarditis (3). There have also been a few case reports of UC or IBD that developed after SARS-CoV-2 mRNA vaccination (4-8, Table 2). In addition, these patients are at an age when they are more likely to develop UC and IBD, and it is difficult to prove a causal relationship with vaccination. The present patient was elderly at 86 years old, which is a very rare age for the onset of UC (10). Therefore, we considered this to be a case of vaccination-related EOUC. As with other reports, it is difficult to prove a causal

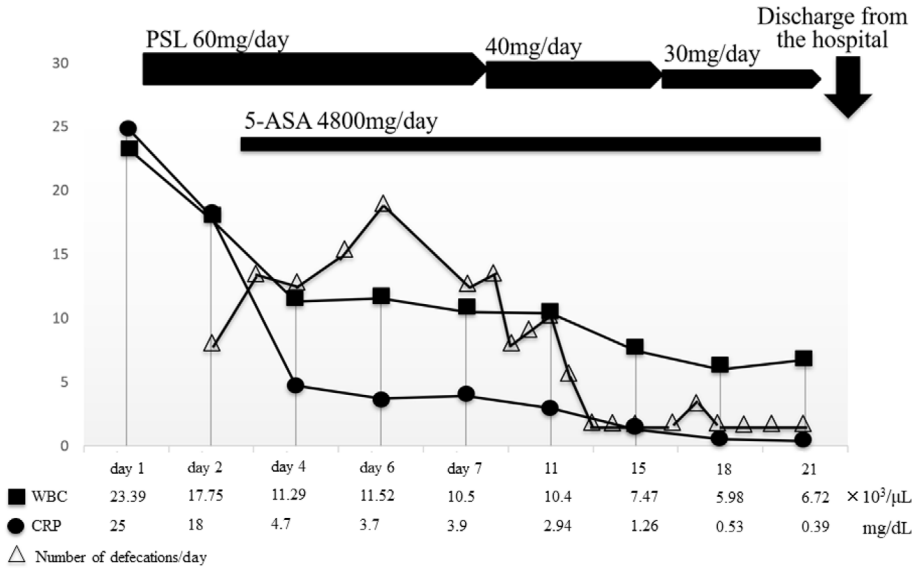

Figure 4. **Clinical course. Treatment with corticosteroids (prednisolone 60 mg per day for 1 week) and 5-ASA was started. Both symptoms and laboratory findings showed improvement within a few days after the start of treatment, and the corticosteroid dose was gradually reduced. The patient was discharged from the hospital with a good response to treatment. PSL: prednisolone, 5-ASA: 5-aminosalicylic acid, WBC: white blood cell, Hb: hemoglobin, CRP: C-reactive protein**

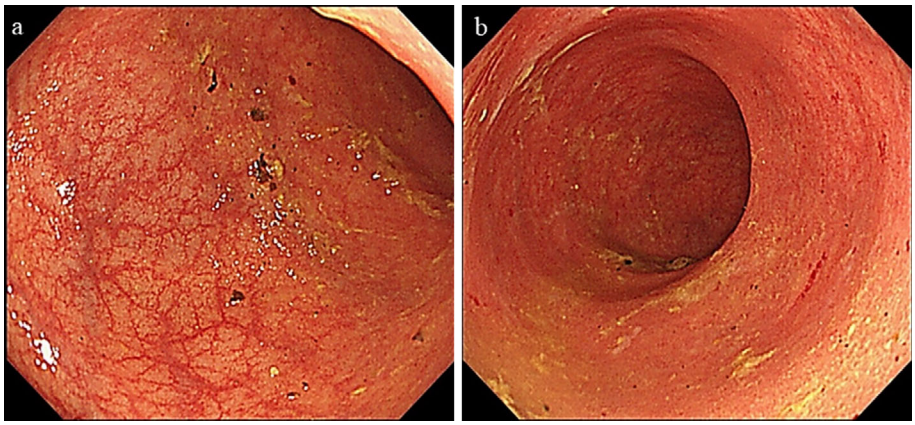

Figure 5. **Pre-discharge (day 21) sigmoidoscopy findings: (a) in the sigmoid colon, transparency improved, and endoscopic findings are within the normal range. (b) In the rectum some rough mucosa remained, and transparency was a little unclear, but improvement was seen.**

relationship between vaccination and the onset of UC; however, since the disease is rare in the very elderly, we believe it is more likely that vaccination triggered the disease.

Not only the SARS-CoV-2 mRNA vaccine but other vaccines have also been reported to be associated with the development of autoimmune diseases, such as narcolepsy, Guillain-Barré syndrome, multiple sclerosis, demyelinating neuropathy, systemic lupus erythematosus, postural orthostatic tachycardia syndrome, and others (13). This is because the vaccine can induce a cross-reactive immune response not only to viral components, but also to human tissue components that share common parts (molecular mimicry), leading to the development of autoimmune diseases (13). It has been reported that the SARS-CoV2 spike protein may interact with various human tissue antigens (14). Given the systemic symptoms observed in severe cases of COVID-19, it is speculated that post-vaccination adverse events may be associated with the spike protein found in both SARS-CoV-2 and its vaccines (15).

It has been reported that SARS-CoV-2 mRNA vaccination may worsen IBD; however, the rate of worsening is only 2.1% (16). This rate is similar to that previously reported in studies regarding the effect of influenza, pneumococcal, and shingles vaccination on the IBD course (16), and has been reported to have no impact on the relapse or exacerbation of IBD (16, 17). Regarding the development of UC with vaccines other than the SARS-CoV-2 vaccine, there are reports that show no association between vaccination and the devel-

Table 2. Cases of Inflammatory Bowel Disease Developed after SARS-CoV-2 MRNA Vaccination.

Case	Age	Gender	Onset	Type of vaccine	Diagnosis	treatment
1 (4)	64	Female	1 days after first dose	BNT162b2	Right-sided ulcerative colitis or intestinal Behçet disease	Steroid → 5-ASA
2 (5)	64	Female	1 day after third dose	BNT162b2	Severe enteritis resembling ulcerative colitis	Steroid → IFX (treatment for cytomegalovirus enteritis during the course of the disease)
3 (6)	49	Male	2 days after second dose	BNT162b2	Ulcerative colitis	Steroid+5-ASA
4 (7)	66	Female	Within 1 week after first dose → imploved → worsened after second dose	mRNA-1273	Ulcerative colitis	Steroid → IFX → tortal colorectal resection surgery
5 (8)	23	Male	8 days after second dose	MVC-COV1901	Vaccine-related ulcerative colitis and inflammatory bowel disease arthropathy	Details unknown
Present case	86	Male	2 weeks after third dose	mRNA-1273	Vaccination-related elderly onset ulcerative colitis	Steroid+5-ASA → filgotinib+5-ASA

5-ASA: 5-aminosalicylic acid, IFX: infliximab

opment of IBD (18).

In the present case, it is possible that an abnormal immune response occurred after vaccination. However, it is challenging to determine whether to administer the fourth or a subsequent dose of the vaccine, as some reports indicate that vaccination does not affect the course of IBD (16, 17), while another report showed that vaccine-induced UC worsened with vaccination (7, Table 2). There are limited reports of UC or IBD related to vaccination, making it challenging to diagnose and establish a causal link with the vaccine. This also makes it difficult to distinguish it from UC. Further observations and data accumulation are required.

In conclusion, we reported an elderly patient who developed UC after SARS-CoV-2 mRNA vaccination. We also reviewed the available literature.

This research was conducted in accordance with the Declaration of Helsinki.

We obtained consent for publication in print from the patient.

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

References

1. Morens DM, Daszak P, Taubenberger JK. Escaping Pandora's box - another novel coronavirus. N Engl J Med **382**: 1293-1295, 2020.
2. Du M, Cai G, Chen F, Christiani CC, Zhang Z, Wang M. Multiomics evaluation of gastrointestinal and other clinical characteristics of COVID-19. Gastroenterology **158**: 2298-2301.e7, 2020.
3. Wong H-L, Hu M, Zhou CK, et al. Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases. Lancet **399**: 2191-2199, 2022.
4. Shimodaira Y, Watanabe K, Takahashi S, Koizumi S, Iijima K. Inflammatory bowel disease triggered by BNT162b2 mRNA vaccination for SARS-CoV-2. Inflamm Bowel Dis **28**: e75, 2022.
5. Takahashi Y, Shimodaira Y, Yoshida T, et al. A case of severe inflammatory bowel disease triggered by vaccination with SARS-CoV-2 mRNA. Nihon Shokakibyo Gakkai Zasshi (J Jpn Soc Gastroenterol) **120**: 325-329, 2023 (in Japanese, Abstract in English).
6. Cagatay AK, Suleyman S, Gupse A, Kamil O. Acute severe ulcerative colitis after mRNA coronavirus disease 2019 vaccination: can mRNA vaccines unmask inflammatory bowel diseases? ACG Case Rep J **9**: e00806, 2022.
7. Kothadia S, Ward C, Akerman P. New diagnosis of severe ulcerative colitis immediately following mRNA-1273 SARS-CoV2 vaccination. Am J Gastroenterol **116**: S1027, 2021.
8. Kuo HL, Lin TY, Leong PY. Case report of new-onset ulcerative colitis after MVC-COVI1901 vaccine injection for SARS-CoV-2. Int J Rheum Dis **26**: 1594-1598, 2023.
9. Nakase H, Uchino M, Shinzaki S, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease 2020. J Gastroenterol **56**: 489-526, 2021.
10. Takahashi H, Matsui T, Hisabe T, et al. Second peak in the distribution of age at onset of ulcerative colitis in relation to smoking cessation. J Gastroenterol Hepatol **29**: 1603-1608, 2014.
11. Surawicz CM, Haggitt RC, Husseman M, Mcfarland LV. Mucosal biopsy diagnosis of colitis: acute self-limited colitis and idiopathic inflammatory bowel disease. Gastroenterology **107**: 755-763, 1994.
12. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med **383**: 2603-2615, 2020.
13. Segal Y, Shoenfeld Y. Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. Cell Mol Immunol **15**: 586-594, 2018.
14. Vojdani A, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin Immunol **217**: 108480, 2020.
15. Trougakos IP, Terpos E, Alexopoulos H, et al. Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis. Trends Mol Med **28**: 542-554, 2022.
16. Weaver KN, Zhang X, Dai X, et al. Impact of SARS-CoV-2 vaccination on inflammatory bowel disease activity and development of vaccine-related adverse events: results from PREVENT-COVID. Inflamm Bowel Dis **28**: 1497-1505, 2022.

17. Lev-Tzion R, Focht G, Lujan R, et al. COVID-19 vaccine is effective in inflammatory bowel disease patients and is not associated with disease exacerbation. Clin Gastroenterol Hepatol **20**: e1263-e 1282, 2022.

18. Guillaume PC, Luc D, Corinne GR, Antoine C, Jean-Frédéric C, Laurent PB. Vaccination and risk for developing inflammatory bowel disease: a meta-analysis of case-control and cohort studies. Clin Gastroenterol Hepatol **13**: 1405-1415, 2015.