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【 CASE REPORT 】

Relapse of Ulcerative Colitis with Immune Thrombocytopenia and Pyoderma Gangrenosum Subsequent to Receiving COVID-19 Vaccination

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Abstract:
This case illustrates the complex interactions of the immune responses after vaccination and highlights their potential connections to various autoimmune conditions. A 22-year-old man with quiescent ulcerative colitis (UC) presented with abdominal pain, rectal bleeding, and thrombocytopenia 7 days after receiving the third COVID-19 mRNA vaccination. Laboratory data confirmed the diagnosis of immune thrombocytopenia. High-dose intravenous immunoglobulin administration boosted the patient's platelet count. Simultaneously, colonoscopy revealed that his UC had relapsed. Although salazosulfapyridine briefly improved his symptoms, his stool frequency worsened one week later. The patient also developed pyoderma gangrenosum. Subsequent treatment with infliximab notably improved both pyoderma gangrenosum and UC.

Key words: inflammatory bowel disease, ulcerative colitis, pyoderma gangrenosum, immune thrombocytopenia, anti-TNF-α antibody

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Introduction

Adverse events following vaccination are often associated with immune reactions that are mediated by inflammatory cytokines. Previous reports have indicated that COVID-19 mRNA vaccination can lead to the new onset or recurrence of autoimmune diseases (1) as well as relapse of ulcerative colitis (UC); (2) the mechanisms underlying these adverse events are assumed to be linked to the activation of the Th1 pathway with increased concentrations of IFN-γ, IL-2, and IL-12p27 following COVID-19 vaccination (3). In addition, infiltration of neutrophils into tissues and an increase in serum TNF-α concentration have been shown to correlate with the occurrence of these adverse events (4, 5).

We herein report a case of UC in a patient who experienced relapse following COVID-19 mRNA vaccination. Furthermore, the patient developed immune thrombocytopenia (ITP) and pyoderma gangrenosum (PG), which had not manifested before vaccination.

Case Report

A 22-year-old man had been diagnosed with UC 1 year previously at a local hospital. He attained clinical remission following treatment with vedolizumab, which was administered every two months. He had a history of acute pancreatitis following administration of steroids and 5-aminosalicylic acid. However, after receiving a third dose of the COVID-19 mRNA vaccine (BNT162b2, Pfizer/BioNTech), he experienced abdominal pain and an increased frequency of bowel movements accompanied by rectal bleeding. Seven days later, he presented to our hospital with severe thrombocytopenia and was hospitalized.

His vital signs were as follows: blood pressure, 138/89 mmHg; heart rate, 115 beats per minute; body temperature, 36.6°C; and SpO_2, 98% (breathing ambient room air). A physical examination revealed no abnormal findings, includ-

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Table.

Hematology		AST	22 U/L	FBS	142 mEq/L
WBC	6,600 /μL	ALT	22 U/L	HbA1c	5.4 %
Neut	45.6 %	LDH	187 U/L		
Lym	36.4 %	ALP	68 U/L	**Coagulation**	
Hb	12.0 g/dL	γ-GT	27 U/L	PT	76 %
Ht	37.2 %	T-Bil	0.6 mg/dL	APTT	36.3 s
MCV	80.7 fL	CK	85 U/L	FDP	11.6 μg/dL
Plt	2,000 /μL	BUN	13.5 mg/dL		
IPF	31.2 %	Cre	0.82 mg/dL	**Immunology**	
ESR(1hr)	41 mm	eGFR	99.3 mL/min/1.73m^2	CRP	6.59 mg/dL
		Na	138 mEq/L	ANA	negative
Biochemistry		Cl	101 mEq/L	PA-IgG	518 ng/10^7 cells
TP	6.7 mg/dL	K	3.8 mEq/L	anti-helicobacter pylori antibody	<3 U/mL
Alb	3.4 mg/dL				

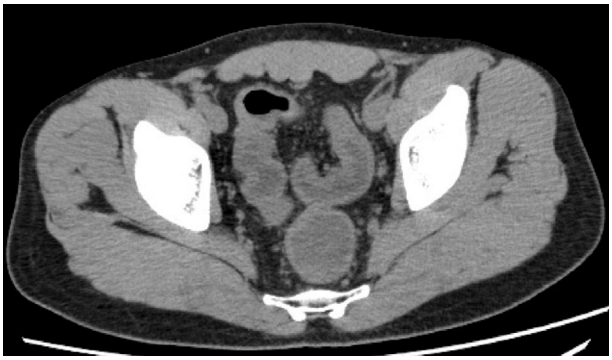

Figure 1. Abdominal CT showed intestinal edema from the descending colon to the rectum.

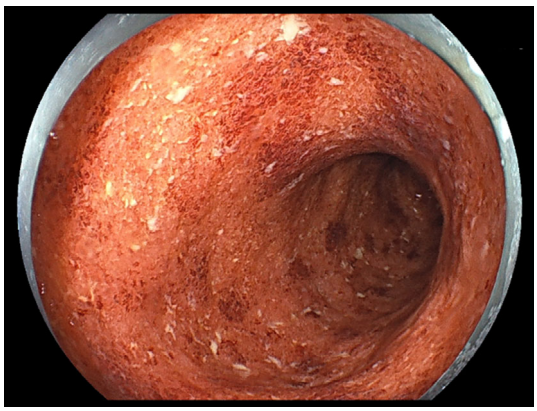

Figure 2. Endoscopic image of the sigmoid colon. There was friability, marked erythema, absence of a discernible vascular pattern, and erosions from the sigmoid colon to the rectum. The Mayo endoscopic subscore was 2 points.

ing skin rashes or subcutaneous bleeding.

Laboratory results, summarized in Table, demonstrated a severe decrease in platelet count (2.0×10^3/μL), a high level of C-reactive protein (6.59 mg/dL, normal range 0-0.14), a remarkably elevated level of platelet antigen-IgG (518 ng/10^7 cells, normal range 9-25), and no increase in anti-Helicobacter pylori antibody. A diagnosis of ITP was established, prompting the initiation of a 5-day course of high-dose intravenous immunoglobulin (IVIg) 500 mg/day on day 1. Following IVIg treatment, his platelet count increased to 22.8×10^4/μL. However, he continued to experience rectal bleeding, and his hemoglobin level dropped to 7.1 g/dL, necessitating four units of erythrocyte transfusion.

On day 5, computed tomography revealed intestinal edema extending from the descending colon to the rectum (Fig. 1), indicating UC relapse. Subsequent colonoscopy revealed friability, marked erythema, absence of a discernible vascular pattern, and erosions extending from the sigmoid colon to the rectum (Fig. 2), corresponding to a Mayo endoscopic sub-score of 2 points. Additional treatment for UC was initiated with oral salazosulfapyridine at a dose of 2,000 mg/day on day 5, mainly because over half of the patients with mesalamine intolerance tolerated mesalamine after switching to another formulation (6). Administration of salazosulfapyridine promptly alleviated rectal bleeding, and he was discharged from the hospital on day 9.

One week later, the patient revisited our hospital because of a fever and frequent bowel movements. Painful skin ulcers measuring approximately 1.5 cm appeared on his right breast along with a similar skin ulcer on his left buttock. Blood tests indicated a normal platelet count (31.6×10^3/μL), but elevated C-reactive protein (10.21 mg/dL) and decreased albumin (2.2 mg/dL) levels were noted. We suspected that his UC had worsened and that he had become intolerant of mesalamine. We stopped the administration of mesalamine and initiated treatment with 400 mg infliximab (an anti-TNFα antibody inhibitor). As demonstrated in the clinical course (Fig. 3), his symptoms improved promptly, and his C-reactive protein level decreased to 0.94 mg/dL within 7 days. A dermatologist diagnosed him with PG based on the skin ulcers [please check this carefully] and administered topical steroid treatment. Infliximab was administered again after two and six weeks. The PG also healed, and epithelialization was observed after six weeks (Fig. 4).

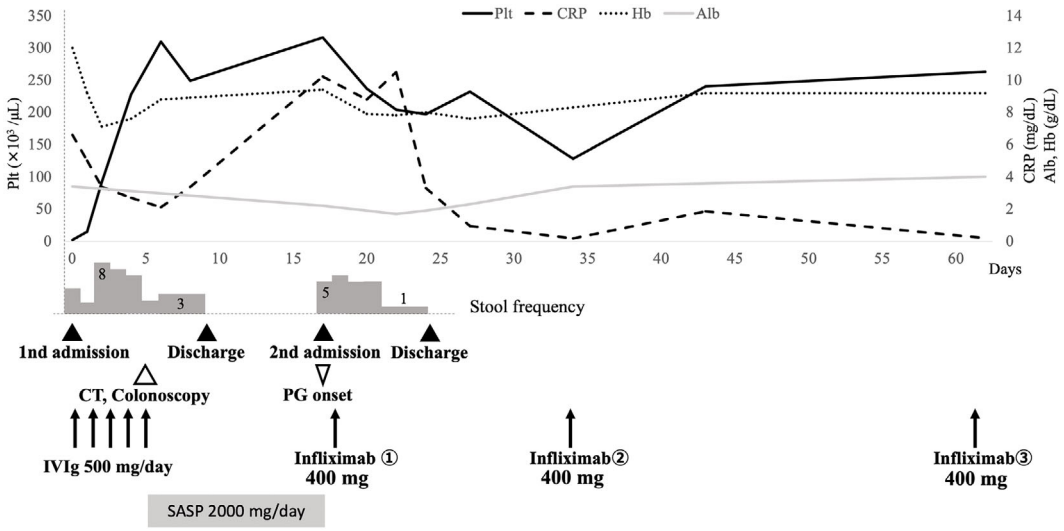

Figure 3. **Clinical course and changes in the platelet count, hemoglobin, albumin, and CRP level.**

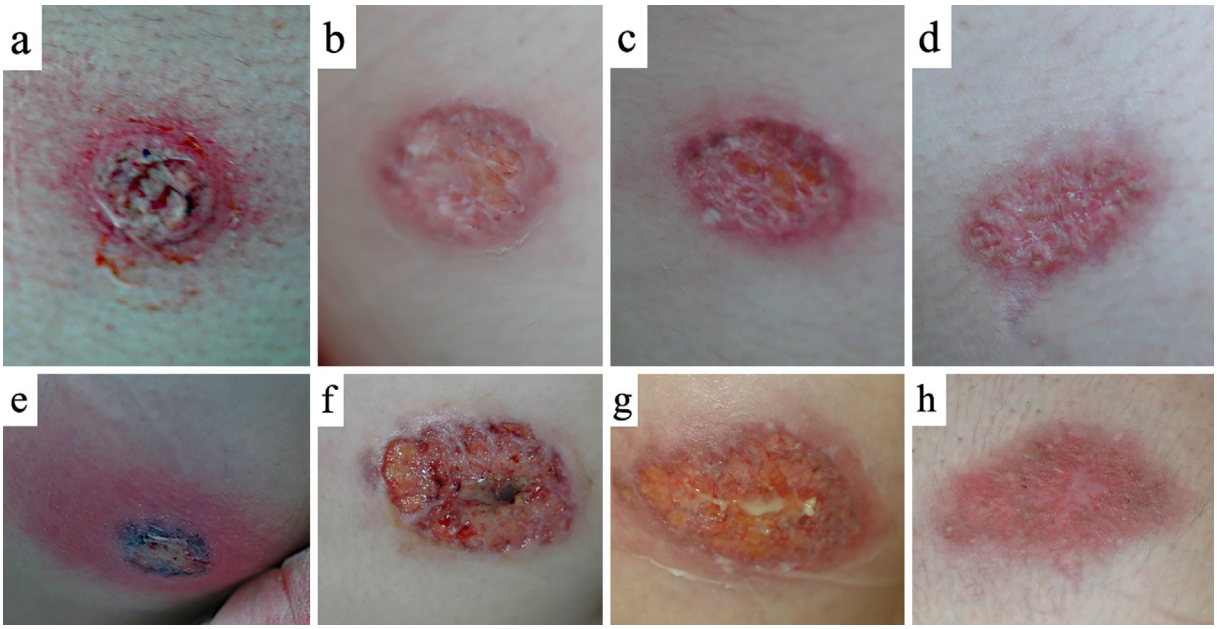

Figure 4. **Clinical course of pyoderma gangrenosum. abcd: right breast, efgh: left buttock. ae: On day 2 of admission (please check this carefully). There are painful skin ulcers about 15 mm in diameter. bf: Three days after Infliximab initiation. cg: One week after Infliximab initiation. dh: Six weeks after Infliximab initiation. The skin ulcers gradually healed and epithelialized with treatment of Infliximab and topical steroids.**

Discussion

In the present case, it was speculated that the COVID-19 vaccination caused a shift in the cytokine profile of UC from the acquired immune system to the Th1 and innate immune systems. This shift may have resulted in systemic TNF-α overproduction and an increase in neutrophils, subsequently leading to UC recurrence. While the natural course of UC typically involves an initial phase characterized by Th 1 and innate immune system predominance, followed by a shift to Th2 predominance (7), the present case suggests the re-emergence of Th1 dominance after vaccination. However, the risk factors for the recurrence of UC after COVID-19 vaccination are still unknown because of the limited number of cases reported to date (8).

PG is a rare neutrophilic dermatosis characterized by inflammatory ulcers on the skin. In Japan, 50.3% of patients with PG have underlying disease (9). Interestingly, 23.5% of patients with PG were found to have accompanying UC (9). However, the incidence of PG among inflammatory bowel diseases is rare, accounting for 0.75% of cases (10). The pathogenesis is suggested to involve TNF-α production, which is led by strong infiltration of CD3-positive T cells

and macrophages at the ulcer edge, as well as infiltration and activation of neutrophils mediated by inflammatory cytokines (11, 12). Systemic therapies for PG typically involve steroids and cyclosporine as first-line options, with anti-TNF-α agents being recommended as second-line options (13).

Recently, anti-TNFα antibody inhibitors, specifically infliximab and adalimumab, have been considered first-line treatments for UC with PG (14). In the present patient, the induction of steroids was challenging because of his history of pancreatitis, possibly caused by steroids. Therefore, we opted for infliximab induction, which resulted in rapid therapeutic effects for both PG and UC. This can be attributed to the mechanisms by which vaccination induces the production of inflammatory cytokines, such as TNF-α, and activates the Th1 pathway. Therefore, the use of anti-TNFα antibody inhibitors was effective not only for PG but also for UC in this patient.

Inflammatory bowel diseases are known to be associated with extraintestinal complications, such as arthritis, aphthous stomatitis, uveitis, primary biliary cholangitis, and primary sclerosing cholangitis. ITP is a rare extraintestinal complication (15). In most patients with UC accompanied by ITP, UC is typically present before ITP development. Previous reports have indicated that ITP is resolved by treatments targeting UC (16, 17). The proposed mechanism involves antigenic mimicry between the surface antigens of intestinal bacteria and platelet antigens, which leads to the production of antiplatelet antibodies. This may be due to intestinal mucosal damage in UC (18).

New-onset ITP following COVID-19 mRNA vaccination has been previously reported (19-21). The mechanism might involve molecular mimicry between the platelet surface antigen and viral proteins (22). However, whether or not general vaccine administration, including the COVID-19 mRNA vaccine, is associated with the occurrence of ITP in adults has not been established (23). In the present patient, relapse of UC led to an increase in surface antigens of intestinal bacteria, potentially contributing to the development of ITP.

PG has not typically been associated with the clinical activity of IBD (24), although UC was active in 81% of patients with PG in a previous report (25). In the present case, PG appeared later than ITP with UC relapse. This difference may be related to the different mechanisms underlying the development of these diseases.

In conclusion, we encountered a case of recurrent UC with ITP and PG development following COVID-19 vaccination. The recurrence of UC and the onset of PG were linked to changes in the cytokine profile associated with the administration of the vaccine, and a relapse of UC led to an increase in the surface antigens of intestinal bacteria that may have led to the development of ITP.

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

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