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【 CASE REPORT 】

Acquired Thrombotic Thrombocytopenic Purpura Following BNT162b2 mRNA Coronavirus Disease Vaccination in a Japanese Patient

Kikuaki Yoshida[1], Ayaka Sakaki[1], Yoriko Matsuyama[1,2], Toshiki Mushino[1], Masanori Matsumoto[3], Takashi Sonoki[1] and Shinobu Tamura[1]

Abstract:
A 57-year-old man without underlying diseases presented with fatigue, loss of appetite, and jaundice 1 week after receiving the first dose of the BNT162b2 mRNA coronavirus disease 2019 (COVID-19) vaccine and showed hemolytic anemia with fragmented erythrocytes and severe thrombocytopenia 2 weeks after receiving the vaccine. An a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13) activity level of <10% and ADAMTS13 inhibitor positivity confirmed the diagnosis of acquired thrombotic thrombocytopenic purpura (TTP). Combination therapy with plasma exchange, corticosteroid, and rituximab improved the clinical outcome. We herein report the first Japanese case of TTP possibly associated with vaccination. Physicians should be alert for this rare but life-threatening hematological complication following COVID-19 vaccination.

Key words: acquired thrombotic thrombocytopenic purpura, COVID-19, BNT162b2 mRNA vaccine, plasma exchange

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Introduction

The development and widespread use of vaccines are important to prevent the spread of new infections of coronavirus 2019 (COVID-19), which began at the end of 2019. In Japan, three vaccines (BNT162b2, mRNA-1273, and ChAdOx1) were approved beginning in May 2021 (1). These vaccines were administered sequentially to healthcare workers, the elderly, and adult patients with underlying diseases. Myocarditis was observed following BNT162b2 mRNA vaccination in a few cases, but no serious adverse events or sequelae were reported (2, 3). Although rare, thromboembolic events with thrombocytopenia have been described after viral vector vaccination with ChAdOx1 in Europe (4-7). Although the benefits of vaccination still outweigh the risk of adverse events, the association of COVID-19 vaccination with thromboembolic events should not be overlooked and further evaluation is needed.

We herein report the first Japanese case of acquired thrombotic thrombocytopenic purpura (TTP) after BNT162b2 mRNA vaccination for COVID-19.

Case Report

A 57-year-old healthy man received his first dose of the BNT162b2 mRNA COVID-19 vaccine. One week later, the patient complained of fatigue, loss of appetite, and jaundice. He visited a primary care physician and received fluid replacement under suspicion of heat stroke. The symptoms gradually worsened, and he was referred to our hospital one week after his first visit. He had a history of acute hepatitis of unknown cause but had not taken any medication.

The Glasgow Coma Scale score for the patient upon admission was E3V5M6. His body temperature was 37.0℃, and other vital signs were normal. He tested negative for se-

[1]Department of Hematology/Oncology, Wakayama Medical University, Japan, [2]Department of General Internal Medicine, Hashimoto Municipal Hospital, Japan and [3]Department of Blood Transfusion Medicine, Nara Medical University, Japan
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Correspondence to Dr. Shinobu Tamura, stamura@wakayama-med.ac.jp

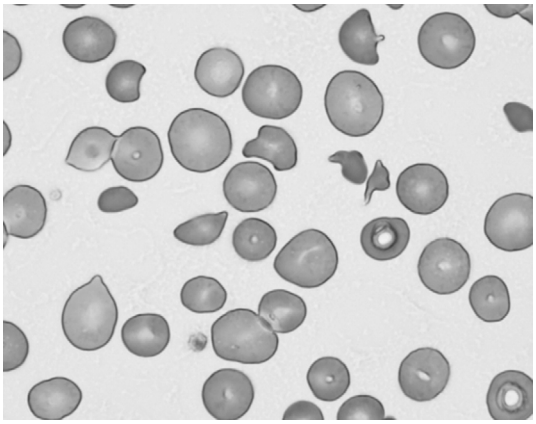

Figure 1. A peripheral blood smear examination on admission to our hospital showing fragmented erythrocytes.

vere acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by a polymerase chain reaction test using a nasopharyngeal swab. The laboratory data obtained upon admission were indicative of severe thrombocytopenia, hemolytic anemia, and renal dysfunction (Table 1). We identified fragmented erythrocytes in the peripheral blood at 17.6% (Fig. 1). Non-contrast computed tomography (CT) revealed no evidence of infectious disease or malignancy, and brain CT revealed no signs of intracranial hemorrhaging. Blood culture tests were also negative after several days. The patient's ADAMTS13 activity and inhibitor levels were <0.5% and 1.9 Bethesda units (BU)/mL, respectively. Based on these findings, we made a diagnosis of acquired TTP. Antibody against the PF4-heparin complex was not found by a latex immunoturbidity assay in the serum sample. However, titers of 2 types of Immunoglobulin G (IgG) antibodies targeting the receptor-binding domain of SARS-CoV-2 spike protein were high [23.5 AU/mL (reference value <1.0 AU/mL, SARS-CoV-2 S-IgG assay, Lumipulse (Fujirebio, Tokyo, Japan)) and 153 U/mL (reference value <1.0 U/mL, anti-SARS-CoV-2 Spike Assay, Elecsys (Roche Diagnostics International, Rotkreuz, Switzerland))].

The patient was admitted to our hospital at night on a weekend. Soon after admission, 4 units of fresh-frozen plasma (FFP) were transfused; however, he developed anaphylactic shock and respiratory distress 1 h after the start of the transfusion. These adverse events improved shortly after an intramuscular injection of adrenaline.

On the second day of admission, the patient was transferred to the intensive-care unit (ICU) and initially treated with plasma exchange and 1 mg/kg/day intravenous prednisolone. FFP at 2 plasma volumes was used as a replacement solution. Fig. 2 shows the clinical course and changes in the platelet count, ADAMTS13 activity levels, and ADAMTS13 inhibitor levels after the start of plasma exchange. After the second day, no further anaphylaxis occurred in the patient. On the fifth day of admission, the platelet count had increased to within the normal range, and plasma exchange was completed. On the same day, the patient was discharged from the ICU and administered 375-mg/m^2 rituximab to prevent TTP exacerbation. However, on the ninth day of admission, his platelet count decreased markedly, so daily plasma exchange treatment was restarted. His ADAMTS13 activity levels decreased to 0.5%, and his ADAMTS13 inhibitor levels increased to 1.7 BU/mL. These findings indicated the occurrence of exacerbated TTP.

With the restart of the plasma exchange treatment, the platelet count and ADAMTS13 activity levels exhibited an upward trend. Treatment with plasma exchange was discontinued on the eighth day after restart. Subsequently, a second exacerbation did not occur. The patient received four weekly infusions of rituximab, and high-dose prednisolone was tapered gradually. The ADAMTS13 activity levels remained above 20% (Fig. 2). On the 34th day of admission, the patient was discharged in good condition.

Discussion

As of September 18, 2021, 11 cases of *de novo* acquired TTP have been reported following COVID-19 vaccination worldwide (8-16). Furthermore, three patients with TTP relapsed after receiving the BNT162b2 mRNA vaccine (14, 17). Table 2 summarizes the clinical characteristics of the 12 total cases of *de novo* acquired TTP, including the present case (8-16). Four patients from Belgium, Germany, and Israel had no underlying disease, and our patient also had no significant problems listed in the pre-vaccination medical questionnaire (8). Most of the cases were reported after the first dose, and the onset of symptoms occurred one to two weeks after vaccination. In all cases, plasma exchange and immunosuppressive therapy, such as the use of corticosteroids, were performed immediately, and the clinical outcome was generally good. Patients who present with clinical symptoms, such as shortness of breath, neurological symptoms, and petechial hemorrhaging after COVID-19 vaccination, should be encouraged to seek immediate medical attention. Furthermore, to make an early and accurate diagnosis in patients with clinical symptoms of thrombocytopenia after COVID-19 vaccination, clinicians should be alert for the possible occurrence of acquired TTP.

Although the pathogenesis of TTP associated with COVID-19 vaccines is unknown, several reports have associated the development with other vaccines, most frequently those against influenza virus (18-24). In the case of the influenza vaccine, the onset of TTP typically occurred 5-14 days after vaccination (18, 19, 22-24). In addition, the onset of TTP occurred 15 days after the administration of a 23-valent pneumococcal polysaccharide vaccine (21). The causal association between acquired TTP and vaccination is primarily supported by a time correlation and not through the identification of cross-reactive epitopes between antigens in these vaccines and ADAMTS13. These onset timings after COVID-19 vaccination are consistent with those after the administration of other vaccines (Table 2). Furthermore, the first dose of the COVID-19 vaccine induced high titers of anti-SARS-CoV-2-neutralizing IgG in three cases, including

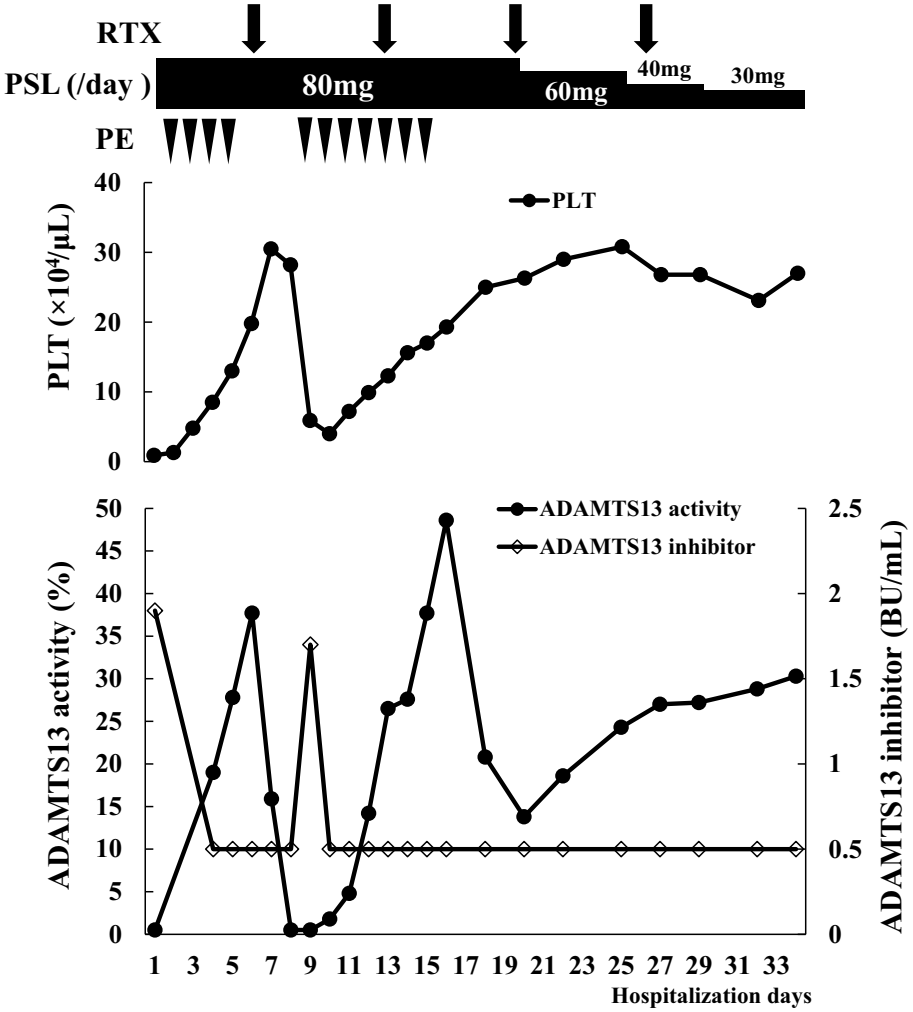

Figure 2. **Clinical course of our patient after admission to our hospital. BU: Bethesda units, PE: plasma exchange, PLT: platelet count, PSL: prednisolone, RTX: rituximab**

Table 1. **Laboratory Data of Patient with TTP on Admission to Our Hospital.**

Complete blood count (reference value)		**Blood chemistry (reference value)**			
White blood cell (3,300-8,600)	10,230 /μL	Total protein (6.6-8.1)	6.6 g/dL	Haptoglobin (19-170)	3 ng/mL
Neutrophil	70 %	Albumin (4.1-5.1)	4.1 g/dL	Cardiac troponin I (0-26.2)	620.0 pg/mL
Lymphocyte	22 %	Aspartate transaminase (13-30)	91 IU/L	Brain natriuretic peptide (<18.4)	49.8 pg/mL
Red blood cell (435-555)	175 ×10⁴/μL	Alanine transaminase (10-42)	48 IU/L	Ferritin (13-277)	780 ng/mL
Hemoglobin (13.7-16.8)	5.5 g/dL	Lactate dehydrogenase (124-222)	2,275 IU/L	Direct coombs	Negative
Hematocrit (40.7-50.1)	17.4 %	Total bilirubin (0.4-1.5)	4.3 mg/dL	ADAMTS13 activity (50-150)	<0.5 %
MCV (83.6-98.2)	99.4 fL	Direct bilirubin (0-0.2)	1.3 mg/dL	ADAMTS13 inhibitor (<0.5)	1.9 BU/mL
Reticulocytes	49.6 ×10⁴/μL	Creatinine (0.65-1.07)	1.57 mg/dL	Antinuclear antibody	×40
Platelet (15.8-34.8)	0.9 ×10⁴/μL	Blood urea nitrogen (8-20)	29.2 mg/dL	PR3-ANCA (<2.0)	<0.5 IU/mL
Fragmented erythrocytes	17.6 %	Alkaline phosphatase (38-113)	95 IU/L	MPO-ANCA (<2.0)	<0.5 IU/mL
Coagulation system (reference value)		γ-GTP (13-64)	18 IU/L	Immunoglobulin G (861-1747)	1,079 mg/dL
APTT (25.0-35.0)	25.0 s	Creatine kinase (59-248)	176 mg/dL	Immunoglobulin A (93-393)	225 mg/dL
Prothrombin time	12.3 s	Sodium (138-145)	135 mEq/L	Immunoglobulin M (33-183)	51 mg/dL
Prothrombin ratio (70-140)	96.1 %	Potassium (3.6-4.8)	3.5 mEq/L	PF4-heparin complex antibody	Negative
Fibrinogen (150-350)	353 mg/dL	Chloride (101-108)	100 mEq/L	SARS-CoV-2 antibody Spike (<1.0)	153 U/mL
FDP (0-5)	55.6 μg/mL	C-reactive protein (0.00-0.14)	1.17 mg/dL	SARS-CoV-2 antibody IgG Spike (<1.0)	23.5 AU/mL

ADAMTS13: a disintegrin-like and metalloproteinase with thrombospondin type 1 motif 13, APTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation products, γ-GTP: γ-glutamyl transpeptidase MCV: mean corpuscular volume, MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody, PF4-heparin complex antibody: platelet factor 4-heparin complex antibody, PR3-ANCA: proteinase 3-anti-neutrophil cytoplasmic antibody, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Table 2. **Review of the Literature On *de Novo* acquired Thrombotic Thrombocytopenic Purpura after Receiving COVID-19 Vaccination.**

Old Gender	Country	Symptoms	Underlying disease	Vaccine	Dose	Time after vaccination	ADAMTS13 activity	ADAMTS13 autoantibody	Treatment	Outcome	Ref
38 yr Female	Belgium	Bruises	No	BNT162b2	First	2 weeks	Undetectable	106 BU/mL	Plasma exchange, corticosteroids, rituximab, caplacizumab	Improved	(8)
37 yr Male	Kuwait	Dizziness, fatigue, headache	Secondary polycythemia	ChAdOx1	First	10 days	2.6%	Positive	Plasma exchange, corticosteroids, rituximab	Improved	(9)
62 yr Female	United States	Altered mental status	Hypertension, hyperlipidemia, hypothyroidism, gastroesophageal reflux disease	Ad26. COV2.S	First	37 days	<12%	Unknown	Plasma exchange, corticosteroids	Unknown	(10)
69 yr Male	United States	Shortness of breath, fatigue	Hypertension, chronic kidney disease, chronic hepatitis B, deep vein thrombosis, HIV	BNT162b2	Second	1 week	<2%	>90 U/mL	Plasma exchange, corticosteroids, rituximab	Improved	(11)
84 yr Female	Germany	Petechiae, partial hemiplegia, arterial hypertension	No	BNT162b2	First	16 days	1.6%	82.2 U/mL	Plasma exchange, corticosteroids, rituximab	Improved	(12)
83 yr Female	Italy	Severe anemia, macro-hematuria	Connective tissue disease, steroid-induced diabetes mellitus	BNT162b2	First	14 days	<10%	40 U/mL	Plasma exchange, corticosteroids, caplacizumab	Death (Probably by sudden cardiovascular event)	(13)
30 yr Female	Italy	Petechiae, headache, fatigue	β thalassemia	BNT162b2	First	8 days	<10%	77.6 U/mL	Plasma exchange, corticosteroids, caplacizumab	Improved	(13)
40 yr Female	Israel	Somnolence, low-grade fever, macro-hematuria	No	BNT162b2	Second	8 days	0%	51 U/mL	Plasma exchange, corticosteroids, caplacizumab	Improved	(14)
28 yr Male	Israel	Dysarthria, chest pain	No	BNT162b2	Second	28 days	0%	113 U/mL	Plasma exchange, corticosteroids, caplacizumab	Improved	(14)
14 yr Female	Canada	Fatigue, headache, confusion, bruising	Anxiety, iron deficiency, postprandial abdominal pain	BNT162b2	First	2 weeks	<1%	72 µ/mL	Plasma exchange, corticosteroids, rituximab, caplacizumab	Improved	(15)
80 yr Male	United States	Generalized weakness, malaise	Hypertension, type II diabetes mellitus, hyperlipidemia, gout, iron deficiency anemia	BNT162b2	Second	2 weeks	<2%	182 %	Plasma exchange, corticosteroids, rituximab	Improved	(16)
57 yr Male	Japan	Fatigue, appetite loss, jaundice	No	BNT162b2	First	1 week	<0.5%	1.9 BU/mL	Plasma exchange, corticosteroids, rituximab	Improved	Our Case

BU: Bethesda units, HIV: human immunodeficiency virus, yr: year-old, ref: reference

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our case. In addition, a marked decrease in ADAMTS13 activity levels and increased titer of the ADAMTS13 inhibitor were observed (8, 12). These findings suggest that the *de novo* acquired TTP in our patient, who had no underlying diseases, was associated with COVID-19 vaccination.

In April 2021, the US Food and Drug Administration and Centers for Disease Control and Prevention proposed the discontinuation of the administration of the Ad26.COV2.S viral vector vaccine because of the occurrence of thrombosis with thrombocytopenia syndrome (TTS) after vaccination, also termed vaccine-induced thrombotic thrombocytopenia (4-7). After ChAdOx1 viral vector vaccination, some cases of TTS were also reported (4-7). The diagnostic criteria for TTS include: 1) COVID-19 vaccination within 42 days, 2) any venous or arterial thrombosis (often cerebral or abdominal), 3) thrombocytopenia, and 4) the presence of antibody against the PF4-heparin complex (25). Post-vaccination TTP and TTS have similar clinical presentations but differ significantly in their treatments. Therefore, a differential diagnosis between these syndromes is very important. In our case, clinical findings, such as a headache and abdominal pain, were indicative of thrombosis but were not observed after vaccination, so the possibility of TTS was low. An enzyme-linked immunosorbent assay (ELISA) is the best diagnostic method for detecting anti-PF4/heparin antibodies in patients with TTS (26). However, we were unable to measure anti-PF4 antibodies by an ELISA, as it could not be performed on a commercial basis. However, even if we had performed an ELISA, our case would have shown a negative result.

The World Health Organization has recommended that patients who develop TTS following the first dose of COVID-19 vaccine not receive a second dose of the same vaccine (27). Furthermore, whether or not these patients should receive a second dose of another type of vaccine remains unclear. Both TTS and TTP may be driven by a vaccine-induced immune reaction. Overall, these findings suggest that patients with post-vaccination TTP should not be administered a second dose of the same vaccine.

Recently, a large prospective cohort study reported no causal association between the first dose of the BNT162b2 mRNA COVID-19 vaccine and adverse events, such as thrombocytopenia, thrombosis, or bleeding (28). However, the ChAdOx1 viral vector vaccine was associated with a slightly increased risk of immune thrombocytopenic purpura, suggesting an increased risk of arterial thromboembolic and bleeding events (28). These observations suggest that the immune response to the COVID-19 vaccine may have contributed to the development of these events. That cohort study was conducted in a limited area of the United Kingdom. When both mRNA and viral vector vaccination become widespread in Japan, the number of reported events may increase. Acquired TTP following vaccination is a rare adverse event but may be overshadowed by these thrombocytopenia and bleeding events.

In conclusion, this report suggests that the first case of acquired TTP in Japan may have been associated with the first dose of the BNT162b2 mRNA COVID-19 vaccine. However, some limitations exist concerning this interpretation of the association between the development of TTP and the administration of COVID-19 vaccines. First, only a few cases of TTP after COVID-19 vaccination have been reported despite the mass vaccination of millions of individuals worldwide. Second, the COVID-19 vaccination may have exacerbated preexisting TTP, although no clinical data were available before vaccination. Third, the mechanism by which vaccines trigger the development of new antibodies for ADAMTS13 remains unknown. Further biological studies are needed to verify when and how inhibitors (antibodies) against ADAMTS13 are produced during the immune response to vaccines, such as that for COVID-19.

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

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