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

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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 (COVID-19) vaccine and showed hemolytic anemia with fragmented erythrocytes and severe thrombocytopenia 2 weeks after receiving the vaccine. An 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

Introduction
The development and widespread use of vaccines are important to prevent the spread of new infections of coronavirus (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.

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 E3 V5M6. His body temperature was 37.0°C, and other vital signs were normal. He tested negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by a polymerase chain reaction test using a nasopharyn-
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 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 Inc., Tokyo, Japan]] and 153 U/mL [reference value <1.0 U/mL, anti-SARS-CoV-2 Spike Assay, Elecsys [Roche Diagnostics International Ltd., 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. Figure 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/m² 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 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 con-
Adverse event but may be overshadowed by these thrombo-
cytopenia and bleeding events. However, some limitations exist concerning the development of TTP and Fibrinogen (150-350) 353 mg/dL Chloride (101-108) 100 mEq/L SARS-COV-2 antibody Spike (<1.0) 153 U/mL 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: proteinase3-anti-neutrophil cytoplasmic antibody; SARS-COV-2: severe acute respiratory syndrome coronavirus 2.
Table 2. Review of the Literature On New-Onset Thrombotic Thrombocytopenic Purpura after Receiving COVID-19 Vaccination.

| Country   | Underlying Disease | Vaccine | Time after Vaccination | Activity | Treatment | Outcome | Ref |
|-----------|--------------------|---------|------------------------|----------|-----------|---------|-----|
| Belgium   | Thrombotic Thrombocytopenic Purpura | ChAdOx1 | First | 2 weeks | Undetectable | Improved | (8) |
| United Kingdom | Hypertension, hyperlipidemia, | COVID-19 | First | 10 days | Positive | Unknown | (9) |
| United States | Hypersplenism, hypercoagulable state | BNT162b2 | Second | 1 day | Undetectable | Improved | (10) |
| Germany   | Secondary polychromatophilia | BNT162b2 | First | 2 days | 100 BU/mL Plasma exchange, corticosteroids, rituximab | Improved | (11) |
| Italy     | Petechiae, Partial thrombocytopenia, acute kidney injury, macro-thrombocytopenia | No | First | 1 day | <10% | Improved | (12) |
| Italy     | Severe anemia, metabolic syndrome, decompensated diabetes mellitus | BNT162b2 | First | 14 days | <10% | Improved | (13) |
| United States | Hypertension, chronic kidney disease, chronic hepatitis B, deep vein thrombosis, HIV | BNT162b2 | First | 8 days | <0.6% | Improved | (14) |
| Belgium   | Fatigue,.setLayout(116,120,139,131) | No | First | 2 days | 82.3 BU/mL | Improved | (15) |
| United States | Hypertension, hyperlipidemia, | BNT162b2 | First | 16 days | <0% | Improved | (16) |
| United States | Hypersplenism, hypercoagulable state | BNT162b2 | Second | 2 weeks | 1 week | Improved | (17) |
| United States | Fatigue, | BNT162b2 | Second | 8 days | <1% | Improved | (18) |
| United States | Dyspnea, chest pain | No | First | 1 day | 72 U/mL | Improved | (19) |
| Canada    | Fatigue, headache, confusion, breathing difficulty, postpartum abdomen pain | BNT162b2 | Second | 2 weeks | <2% | Improved | (20) |
| United States | Hypertension, hyperlipidemia, | BNT162b2 | Second | 2 days | <0.5% | Improved | (21) |
| Japan     | Fatigue, angioedema, loss of function | BNT162b2 | First | 1 week | Improved | Improved | (22) |
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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