Successful Treatment of Immune Thrombocytopenic Purpura with Intracranial Hemorrhaging and Duodenal Bleeding Following SARS-CoV-2 Vaccination

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Abstract:
Several vaccines have been developed for coronavirus disease 2019 - caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - in record time. A few cases of immune thrombocytopenic purpura (ITP) following SARS-CoV-2 vaccination have been reported. We herein report a 90-year-old man who received the Pfizer-BioNTech SARS-CoV-2 vaccine (BNT162b2) and developed severe thrombocytopenia with intracranial hemorrhaging and duodenal bleeding, consistent with vaccine-related ITP. He was successfully treated with intravenous immunoglobulin, prednisolone, and eltrombopag and discharged without cytopenia. Vaccine-related ITP should be suspected in patients presenting with abnormal bleeding or purpura after vaccination.

Key words: immune thrombocytopenic purpura, SARS-CoV-2 vaccine, bleeding

Introduction
The novel infectious pathogen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to the ongoing coronavirus disease 2019 (COVID-19) pandemic. Vaccination is a crucial step to overcoming this pandemic, and many vaccines have been developed in a rapid timeframe.

Vaccine-induced immune thrombotic thrombocytopenia (VITT) has been reported after SARS-CoV-2 vaccination, especially after the ChAdOx1 nCoV-19 vaccine (AstraZeneca) (1). However, a few cases of immune thrombocytopenic purpura (ITP) following the administration of the Pfizer-BioNTech, Moderna, and AstraZeneca SARS-CoV-2 vaccines have also been reported recently (2).

We herein report a case of severe thrombocytopenia due to ITP with intracranial hemorrhaging and duodenal bleeding after receiving the recent Pfizer-BioNTech SARS-CoV-2 vaccine.

Case Report
The patient was a 90-year-old previously healthy Japanese man with a history of hypertension, hyperlipidemia, and myocardial infarction who received the Pfizer-BioNTech SARS-CoV-2 vaccine (BNT162b2). He had no history of excessive bleeding or thrombocytopenia, and laboratory results 1 year earlier had shown a normal hemoglobin concentration of 15.3 g/dL, white blood cell count of 7.45×10^9/L, and platelet count of 224×10^9/L. He had no allergic history and had not taken any new medications. Seven days after the first vaccination, he developed gastric distress and purpura on the arms and legs. Nine days after the first vaccination, he was brought to the emergency department by ambulance due to impaired consciousness.

His vital signs on hospital admission were as follows: Glasgow Coma Scale (GCS) score, E3V2M5; heart rate, 115 beats/min; blood pressure, 119/50 mmHg; and body temperature, 36.0°C. A physical examination revealed pallor of palpebral conjunctiva and extensive purpuric rash affecting the arms and legs, without jaundice, swollen lymph nodes,
Figure 1. Results of a bone marrow examination on admission. A bone marrow examination revealed normocellular marrow with increased megakaryocytes without dysplasia on megakaryocytes (May-Giemsa stain ×10).

or splenomegaly. His stool was tarry. The results of laboratory tests are shown in Table. A complete blood count demonstrated severe thrombocytopenia and anemia. The platelet-associated immunoglobulin G level was elevated, but other autoantibodies were negative. Antibodies to complexes of platelet factor 4 (PF4) and heparin were not detected by the latex agglutination test. A bone marrow examination showed a normocellular marrow with increased megakaryocytes and no dysplastic megakaryocytes (Fig. 1). Ring sideroblasts were found in 52% of erythroblasts. A chromosome analysis revealed a normal karyotype. The patient was diagnosed with ITP.

Brain computed tomography (CT) revealed left small subcortical hemorrhaging, small subarachnoid hemorrhaging in the left occipital region, and acute subdural hematoma in the cerebral falx (Fig. 2). However, magnetic resonance imaging (MRI) revealed that there was no cerebral infarction and thrombosis, including cerebral venous sinus thrombosis. Conversely, abdominal contrast-enhanced CT revealed duodenal bleeding with no evidence of arterial or venous thrombosis (Fig. 3).

He was treated with 40 mg of prednisolone daily, 10 g of intravenous immunoglobulin for 5 days, and blood transfusion of concentrated platelets and red blood cells. He underwent upper gastrointestinal endoscopy to manage the duodenal bleeding, but endoscopic hemostasis was difficult to achieve. Surgical intervention for the brain hemorrhaging and subdural hematoma was also difficult because of thrombocytopenia.

The platelet count started to increase and reached 48×10^9/L on the sixth day from the start of the treatment, and his consciousness gradually improved to a GCS score of E4V5M6. However, the platelet count gradually decreased to 15×10^9/L on the 14th day of the treatment. Therefore, 12.5 mg of eltrombopag daily was started on the 24th day. Blood transfusion of concentrated platelets was required for the prevention of additional serious bleeding. On the 67th day, his platelet count improved to 148×10^9/L with a hemoglobin

### Table. Laboratory Data on Admission.

| Peripheral blood | Blood chemistry | Bone marrow |
|------------------|-----------------|-------------|
| WBC 7.70×10^9/L  | AST 8 U/L       | NCC 12.6×10^4/μL |
| Seg 84.0 %       | ALT 5 U/L       | MgK 217/μL   |
| Lymph 7.0 %      | LDH 159 U/L     | M/E 2.2     |
| Mono 9.0 %       | T-bil 0.7 mg/dL | Erythroblast 28.2 % |
| RBC 1.750×10^12/L| BUN 51.3 mg/dL  | Myeloblast 0.5 % |
| Hb 5.3 g/dL      | Cre 0.77 mg/dL  | Promyelocyte 0.2 % |
| Ht 16.0 %        | Glucose 195 mg/dL| Myelocyte 18.4 % |
| MCV 91 fl        | Sodium 133 mEq/L| Metamyelocyte 15.4 % |
| MCH 30.3 Pg      | CK 66 U/L       | Stab cell 10.5 % |
| MCHC 33.1 %      | CRP 4.51 mg/dL  | Segmented cell 15.3 % |
| Reti 92×10^9/L   | WT1 <50 copy/μgRNA | Eosinophil 1.3 % |
| PLT 3×10^11/L    | ANA <40 times   | Basophil 0.1 % |
| IPF 7.7 %        | PAIgG 131.4 ng/10^7PLT | Monocyte 1.6 % |
| Blood coagulation| H. pylori IgG <10 U/mL | Lymphocyte 5.3 % |
| PT (INR) 1.13    | ADAMTS13 activity 35 % | Plasma cell 2.7 % |
| APTT 24.5 s      | ADAMTS13 inhibitor <0.5 BU/mL |
| Fib 287 mg/dL    | HIT IgG <1.00 U/mL |
| D-dimer 2.2 μg/mL|                |

WBC: white blood cells, Seg: segmented cell, Lymph: lymphocyte, Mono: monocyte, RBC: red blood cells, Hb: hemoglobin, Ht: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, Reti: reticulocyte, PLT: platelet, IPF: immature platelet fraction, PT (INR): prothrombin time (international normalized ratio), APTT: activated partial thromboplastin time, Fib: fibrinogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, Cre: creatinine, CK: creatine kinase, CRP: C-reactive protein, ANA: antinuclear antibody, PAIgG: platelet-associated IgG, ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, HIT: heparin-induced thrombocytopenia, NCC: nucleated cell count, MgK: megakaryocyte.
Figure 2. Brain computed tomography scan on admission. The scan revealed an acute subdural hematoma in the cerebral falx (A, arrowhead) and small subcortical hemorrhaging (B, arrowhead).

Figure 3. Abdominal contrast-enhanced computed tomography scan on admission. The scan revealed duodenal bleeding (arrowheads).

discussion

We described a case of rapid and severe thrombocytopenia with intracranial hemorrhaging and duodenal bleeding post-Pfizer-BioNTech SARS-CoV-2 vaccination. Various adverse effects after SARS-CoV-2 vaccination have been reported. The most commonly reported adverse events have been pain, tenderness, redness, and swelling at the injection site (3). Other common adverse events include non-serious systemic reactions, such as a fever, headache, myalgia, and arthralgia (3). Less-frequent adverse events are hypersensitivity to one or more vaccine components (4), and an even rarer adverse event is serious thrombosis with thrombocytopenia, termed VITT (4). Recently, a few cases of ITP have been reported. Post-SARS-CoV-2 vaccination ITP has been reported following the Pfizer-BioNTech (5-10), Moderna (5, 11-13), and AstraZeneca vaccines (8, 14, 15).

ITP is mediated by platelet antibodies that accelerate platelet destruction and inhibit their production (16). Most cases have been considered idiopathic, but cases have been described following various infections and vaccinations (17). It is known that ITP occurs after the measles-mumps-rubella (MMR) vaccinations as well as the measles and rubella infection (16). Given that ITP has been associated with the MMR vaccine and natural measles and rubella infection, it was considered biologically plausible to suspect an association with SARS-CoV-2 vaccines (2), since ITP has also been associated with SARS-CoV-2 infection as well (18). Several mechanisms have been ascribed to the pathogenesis, including molecular mimicry between the vaccine antigen and platelet proteins (17). Another explanation is inflammation and autoimmune processes as a response to SARS-CoV-2 vaccines, in which type I interferon has been created as well as other messenger ribonucleic acid vaccines (17).

In the present case, ITP was considered the most likely cause of thrombocytopenia. Although a latex agglutination test can be used to detect antibodies to complexes of PF4 and heparin in patients with heparin-induced thrombocytopenia, it has been widely accepted that rapid immunosorbent tests are not sensitive nor specific for a diagnosis of VITT (19). In addition, the detection of antibodies to PF4 - not complexes of PF4 and heparin - is required for the diagnosis of VITT (4). Although we did not examine antibodies to PF4 by ELISA, the present case did not meet the criteria for VITT due to the absence of thrombosis and low D-dimer concentration of 15.7 g/dL. He was discharged under treatment with 30 mg of prednisolone and 12.5 mg of eltrombopag daily (Fig. 4).

The patient provided his informed consent for the publication of this report.

Discussion

We described a case of rapid and severe thrombocytopenia with intracranial hemorrhaging and duodenal bleeding post-Pfizer-BioNTech SARS-CoV-2 vaccination.

Various adverse effects after SARS-CoV-2 vaccination have been reported. The most commonly reported adverse events have been pain, tenderness, redness, and swelling at the injection site (3). Other common adverse events include non-serious systemic reactions, such as a fever, headache, myalgia, and arthralgia (3). Less-frequent adverse events are hypersensitivity to one or more vaccine components (4), and an even rarer adverse event is serious thrombosis with thrombocytopenia, termed VITT (4). Recently, a few cases of ITP have been reported. Post-SARS-CoV-2 vaccination ITP has been reported following the Pfizer-BioNTech (5-10), Moderna (5, 11-13), and AstraZeneca vaccines (8, 14, 15).

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values. Ring sideroblasts, which are erythroblasts with iron-loaded mitochondria visualized by Prussian blue staining as a perinuclear ring of blue granules, appear exclusively under pathological conditions, including myelodysplastic syndromes (20). In our patient, ring sideroblasts were found in the aspirated bone marrow, but the hemoglobin concentration improved to the normal range during the clinical course. While the reason why ring sideroblasts were found is unclear, we consider the anemia observed on admission to have been caused by hemorrhaging.

The temporal relationship between vaccination and the onset of vaccine-related ITP has been reported. The onset of ITP after SARS-CoV-2 vaccination is reported to range from 1 to 23 days, with a median of 5.5 days after vaccination (2). In the present case, ITP was diagnosed 7 days after vaccination, which is consistent with previous reports. Therefore, clinicians should be vigilant regarding the possibility of vaccine-related ITP in patients presenting with abnormal bleeding or purpura in the early period (approximately one week) after vaccination.

In Japan, as of November 2, 2021, 52 cases of ITP have been reported as suspected adverse reactions to the Pfizer-BioNTech SARS-CoV-2 vaccine from medical institutions based on the Immunization Act published by the Ministry of Health, Labor and Welfare (21). Of these, four fatal events have been reported. Only one case has been reported in detail. In that previous case, platelet transfusion, dexamethasone, and additional intravenous immunoglobulin were ineffective, and he died of alveolar hemorrhaging (22).

SARS-CoV-2 vaccine-related ITP can be expected to respond to the same treatment as ITP. Many previous cases have been successfully treated with intravenous immunoglobulin and/or corticosteroids. There are also reports of slight resistance to corticosteroids and treatment with eltrombopag (11, 15).

Treatment of ITP consists of intravenous immunoglobulin, prednisolone, and eltrombopag, while treatment of VITT includes anticoagulation therapy in addition to intravenous immunoglobulin and high-dose glucocorticoids. SARS-CoV-2 vaccine-related ITP can be expected to respond to the same treatment as ITP, as previous cases have been successfully treated with intravenous immunoglobulin and/or corticosteroids (15). Blood coagulation tests and contrast-enhanced CT/MRI are useful for discriminating between ITP and VITT. Therefore, as shown in the present case, it may be crucial to initiate treatment for ITP promptly in cases with thrombocytopenia post-SARS-CoV-2 vaccination in the absence of thrombosis. In the present case, prompt intravenous immunoglobulin and adequate platelet transfusion prevented the spread of bleeding, which led to successful treatment.

While SARS-CoV-2 vaccination is an essential solution to the ongoing COVID-19 pandemic, vigilance against post-vaccination severe thrombocytopenia is required. ITP should be considered in patients who develop abnormal bleeding or purpuric rashes after vaccination, and clinicians should perform appropriate diagnostic tests and initiate prompt treatment. Further investigations are needed to reveal the association between the onset of ITP and SARS-CoV-2 vaccination.

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

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