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【 CASE REPORT 】

Severe Immune Thrombocytopenia after COVID-19 Vaccination: Two Case Reports and a Literature Review

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Abstract:

We herein report two cases of coronavirus disease 2019 (COVID-19) vaccine-induced immune thrombocytopenia (ITP). A 69-year-old Japanese man developed severe thrombocytopenia after COVID-19 vaccination. He had oral bleeding and hemoptysis but no thrombotic symptoms. He improved rapidly with oral prednisolone therapy. A 34-year-old Japanese woman had generalized purpura after COVID-19 vaccination. Her platelet count improved rapidly after treatment with prednisolone and eltrombopag. The occurrence of two cases of ITP after COVID-19 vaccination at a single institution suggests that there could be more such undiagnosed cases, especially cases of mild secondary ITP.

Key words: immune thrombocytopenia, vaccination, COVID-19

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Introduction

There is an ongoing pandemic of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 infection. The first case occurred in Wuhan, China, in December 2019.

The United States Food and Drug Administration has issued emergency authorization for three COVID-19 vaccines. However, vaccine-related adverse events have been reported. Cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) after AstraZeneca ChAdOx1 COVID-19 vaccination have been reported (1-3), but there are few reports of immune thrombocytopenia (ITP) after COVID-19 vaccination (4-14). We herein report two cases of severe ITP after COVID-19 vaccination from our institution.

Case Reports

Case 1

A 69-year-old man with a history of well-controlled postoperative intestinal obstruction and hypopharyngeal cancer, for which he had undergone surgery with construction of a permanent tracheal fistula, received his first dose of the Pfizer-BioNTech COVID-19 vaccine. Three days after vaccination, he visited our hospital for a routine evaluation of his intestinal obstruction. Although he had no symptoms, a complete blood count obtained at that time showed a platelet count of 72×10^9/L. He received the second-dose of the vaccine three weeks after the first dose. Ten days after second-dose vaccination, he was referred to our hospital due to oral bleeding and hemoptysis.

He exhibited no signs or symptoms of thrombosis. He was on several medications, but no new drugs had been recently added. A physical examination revealed no abnormalities other than oral bleeding and severe purpura. He had a platelet count of 6×10^9/L, while blood cell (WBC) count of 6,700/μL, and hemoglobin level of 16.1 g/dL. The results of other laboratory tests are shown in Table 1. *Helicobacter pylori* antibody positivity and hepatitis B and C antibody negativity were noted. An examination of a peripheral blood smear revealed no fragmented red blood cells, platelet clumping, or blasts.

The patient received 1 mg/kg/day of oral prednisolone (PSL). Intravenous immunoglobulin (IVIG) and steroid pulse therapy were not administered because the patient did not consent to hospitalization. Three days after initiation of

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oral PSL therapy, his platelet count was 100×10^9/L. *H. pylori* eradication therapy was started. Oral PSL therapy was continued for 14 days, and the dose was subsequently tapered. He did not develop bleeding or thrombocytopenia. The patient's clinical course is shown in Figure a.

Table 1. Laboratory Test Results.

Parameter	Level	
	Case 1	Case 2
White blood cells (/μL)	6,700	7,900
Hemoglobin (g/dL)	16.1	13.9
Platelets (×10^9/L)	6	3
Aspartate aminotransferase (U/L)	31	16
Alanine aminotransferase (U/L)	26	12
Lactate dehydrogenase (U/L)	281	173
Blood urine nitrogen (mg/dL)	24.2	16.7
Creatinine (mg/dL)	1.26	0.69
Total bilirubin (mg/dL)	0.6	0.5
Total protein (g/dL)	7.6	7.7
Albumin (g/dL)	4.4	4,7
PT (s)	-	11.1
APTT (s)	-	32.0
Fibrinogen (mg/dL)	-	314
D-dimer (μg/mL)	-	0.0
HBs Ag (IU/mL)	0.00	0.00
HBs Ab (mIU/mL)	0.15	0.50
HBc Ab (S/CO)	0.14	0.06
HCV Ab (S/CO)	0.07	0.05
Helicobacter pylori Ab (U/mL)	15.7	<3.0

PT: prothrombin time, APTT: activated partial thromboplastin time, HBs: hepatitis B surface, HBc: hepatitis B core, HCV: hepatitis C virus, Ag: antigen, Ab: antibody

Case 2

A 34-year-old woman with no significant medical history presented to our hospital with generalized purpura. She had received her second dose of the Moderna COVID-19 vaccine three weeks before the symptom onset. She had been using oral contraceptive pills for dysmenorrhea. She had severe purpura without any thrombotic symptoms, and all other physical examination findings were normal. She had a platelet count of 11×10^9/L.

Bone marrow aspiration cytology revealed normocellular marrow with no atypical cells or blast proliferation. Because her platelet count had been only slightly elevated and her symptoms improved in four days, we decided to follow her progress without treatment. However, at the 1-week follow-up visit, she complained of irregular vaginal bleeding and had a platelet count of 3×10^9/L, WBC count of 7,900/μL, and hemoglobin level of 13.9 g/dL. The results of other laboratory tests are shown in Table 1. Hepatitis B and C antibody negativity were noted.

She received 1 mg/kg/day of oral PSL. IVIG and steroid pulse therapy were not administered to avoid the side effects of steroid pulse therapy and due to the high cost of IVIG. The platelet count increased to 60×10^9/L 4 days after treatment. When the dose of PSL was tapered, the platelet count decreased to 40×10^9/L. Therefore, 12.5 mg/day of eltrombopag, a thrombopoietin receptor agonist, was started as second-line treatment, following which the platelet count increased to 125×10^9/L. The patient's clinical course is shown in Figure b.

Discussion

We encountered two cases of secondary ITP that might

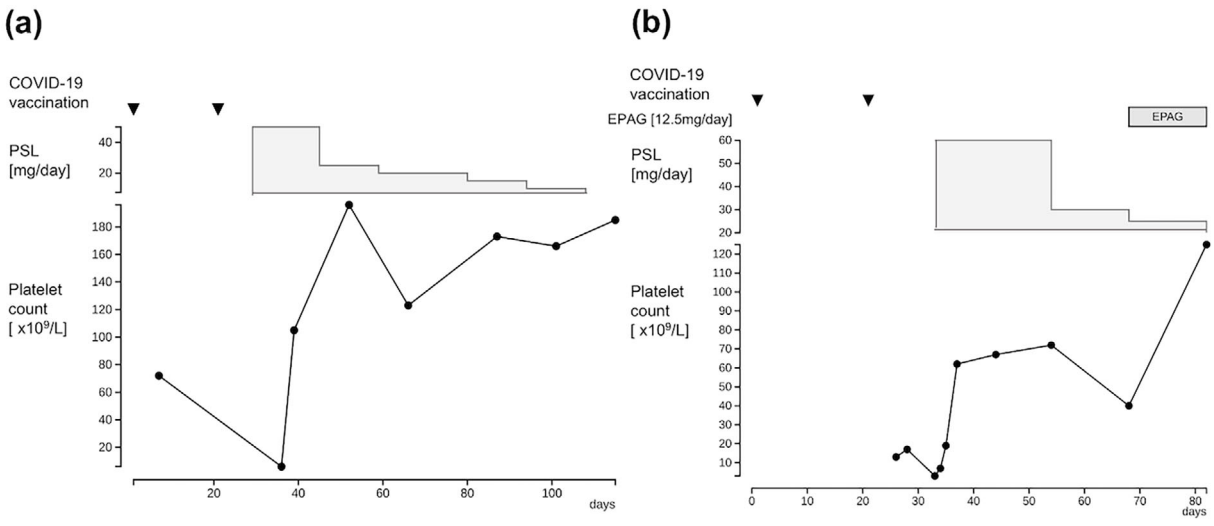

Figure. Clinical course of two patients with immune thrombocytopenia after COVID-19 vaccination. (a) Patient 1, (b) Patient 2. PSL (both patients) and EPAG (patient 2) were administered as treatment. The platelet count increased after PSL administration (black line). The time axis shows the number of days after first-dose vaccination. COVID-19: coronavirus disease 2019, EPAG: eltrombopag, PSL: prednisolone

Table 2. Background Information of Patients with ITP after COVID-19 Vaccination.

Patient number	Age (years)/ sex	Complications and comorbidities	Dose	Days from vaccination to thrombocytopenia	Reference
1	53/male	Crohn's disease	Second	8	4
2	67/male	ITP, seizure disorder, atrial fibrillation	First	2	4
3	59/female	ITP, SLE	First	2	4
4	36/female	ITP	First	14	5
5	47/female	ITP, IDA hypothyroidism	First	18	6
6	39/female	Polycystic ovary syndrome	Second	3	7
7	22/male	None	First	3	8
8	27/male	None	First	10	9
9	63/male	DM, HT, dyslipidemia	First	14	9
10	39/female	Hashimoto's disease	Second	6	9
11	24/male	ITP, AIHA	Second	21	9
12	41/female	Multiple allergies	First	1	10
13	72/male	Autoimmune thyroiditis treated with radioiodine therapy	First	11	11
14	71/female	Latent hyperthyroidism, breast cancer, stroke	First	11	11
15	66/male	HT, mild thrombocytopenia	First	2	11
16	64/female	HT, chronic obstructive pulmonary disease, steatosis, hepatitis	First	15	11
17	60/male	HCV, cirrhosis, CKD, HT, congestive heart failure	First	1	12
18	82/female	HT, dementia	Second	4	13
19	56/female	None	Second	14	13
20	95/male	HT, DM, gastric ulcer, hyperlipidemia, bladder cancer	Second	2	14
21	69/male	Intestinal obstruction, hypopharyngeal cancer	Second	10	This study
22	34/female	None	Second	21	This study

COVID-19: coronavirus disease 2019, ITP: immune thrombocytopenia, SLE: systemic lupus erythematosus, IDA: iron deficiency anemia, DM diabetes mellitus, HT: hypertension, AIHA: autoimmune hemolytic anemia, HCV: hepatitis C virus, CKD: chronic kidney disease

have been adverse events associated with COVID-19 vaccination. ITP is a rare disease that is characterized by a platelet count of $<100\times10^9$/L. It is caused by immune-mediated destruction of platelets and inhibition of platelet production, which increases the risk of bleeding, although bleeding symptoms are not always present. The most common form of ITP is idiopathic. However, 20% of ITP cases have secondary causes, such as infection, medications, autoimmune disorders, and malignancy (4). There have been reports of ITP after vaccination with the hepatitis B virus, human papilloma virus, varicella zoster, pneumococcus, *Haemophilus influenzae*, polio, diphtheria-tetanus-acellular-pertussis, and measles-mumps rubella (MMR) vaccines (15). The risk of developing ITP after vaccination varies. Although the attributable risk is low (1 in 25,000 after MMR vaccination), the relative risk of ITP after MMR vaccination is high (16). A French study showed that 45.8% of drug-induced ITP cases were vaccine-induced (17). Vaccine-induced ITP should be considered during the differential diagnosis of thrombocytopenia in patients with a recent history of vaccination.

ITP can also occur after COVID-19 vaccination. There are reports of VITT after AstraZeneca ChAdOx1 COVID-19 vaccination (1-3); however, ITP after COVID-19 vaccination has rarely been reported (Table 2, 3), especially considering the number of people who have been vaccinated against COVID-19. A recent study reported that out of 20 million people who received COVID-19 vaccination in North America, 17 were newly diagnosed with secondary ITP, and the authors assumed that the incidence of ITP after vaccination is approximately the same as that of primary ITP (18). However, the fact that we encountered two such patients in a short period at a single institution and that most of the reported cases are of severe thrombocytopenia suggests that there are other asymptomatic cases of mild to moderate ITP after COVID-19 vaccination that have not been detected.

Another study reported a sudden decrease in the platelet count in 12% of patients with chronic ITP who experienced new bleeding symptoms 2-5 days after COVID-19 vaccina-

Table 3. Clinical Information of Patients with ITP after COVID-19 Vaccination.

Patient number	Lowest platelet count after vaccination, $\times 10^9$/L	Treatment	Outcome	Reference
1	2	Dexamethasone, IVIG	Improved	4
2	2	Dexamethasone, IVIG	Improved	4
3	2.7	Dexamethasone	Improved	4
4	3	Dexamethasone, IVIG	Not available	5
5	1	Dexamethasone, IVIG	Improved	6
6	1	Methylprednisolone, IVIG	Improved	7
7	2	Dexamethasone, IVIG	Improved	8
8	1	IVIG, prednisone, dexamethasone	Improved	9
9	2	Prednisone	Improved	9
10	1	IVIG, prednisone, eltrombopag, romiplostim	Improved	9
11	2	IVIG, prednisone	Improved	9
12	39	Methylprednisolone, IVIG, dexamethasone	Improved	10
13	<5	Glucocorticoid, IVIG	Improved	11
14	<5	Glucocorticoid, IVIG, TPO-RA	Improved	11
15	<5	Glucocorticoid	Improved	11
16	6	Glucocorticoid	Improved	11
17	84	None	Improved	12
18	1	Platelet transfusion	Improved	13
19	3	IVIG, dexamethasone	Improved	13
20	1	Prednisolone, IVIG, platelet transfusion	Improved	14
21	6	Prednisolone	Improved	This study
22	3	Prednisolone, eltrombopag	Improved	This study

COVID-19: coronavirus disease 2019, ITP: immune thrombocytopenia, IVIG: intravenous immunoglobulin, TPO-RA: thrombopoietin receptor agonist

tion (19). Although most patients experienced ITP or thrombocytopenia 1-3 days after first-dose COVID-19 vaccination, other patients developed thrombocytopenia 10-21 days after first- or second-dose vaccination (Table 2). In case 1, the patient had thrombocytopenia three days after first-dose vaccination. He might have had anti-platelet antibodies before COVID-19 vaccination.

Almost all patients in previously reported cases of ITP after COVID-19 vaccination were treated with glucocorticoids (Table 3). Some patients received additional treatment with IVIG and/or a thrombopoietin receptor agonist (Table 3). In the case reported by Mantadakis et al., full recovery was achieved with IVIG in a patient with ITP after influenza vaccination (20). In another report, children with ITP after MMR vaccination were treated with IVIG (78/107; 73%) and glucocorticoids (21/107; 20%) (21). Most patients with ITP after vaccination in a previous study were successfully treated with IVIG and glucocorticoids (22). However, there are also reports of patients with COVID-19 vaccine-related ITP who improved with no treatment or platelet transfusion alone (Table 3). The possibility of spontaneous recovery should be considered in case 1, as the patient showed marked improvement in platelet levels in the first three days of treatment. The incidence of ITP after COVID-19 vaccination should be investigated, and patients in whom spontaneous recovery can be expected should be identified through follow-up. Although the rate of spontaneous recovery in patients with ITP after COVID-19 vaccination is unclear, it is necessary to treat patients with severe COVID-19 vaccine-related ITP with glucocorticoids and/or IVIG.

In conclusion, ITP can occur after COVID-19 vaccination. We estimate that the number of patients with mild to moderate ITP after COVID-19 vaccination has been underestimated, as cases involving asymptomatic patients are likely to remain undiagnosed. Early identification of patients with a bleeding tendency is necessary, and platelet counts should be measured after COVID-19 vaccination in these patients.

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

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