BLOOD RESEARCH
Volume 56 · Number 4 · December 2021
https://doi.org/10.5045/br.2021.2021140

Perspective

Subclinical thrombotic thrombocytopenic purpura after vaccination with ChAdOx1 nCoV-19

Hee Ryeong Jang, M.D.,
Kyu-Hyoung Lim, M.D., Ph.D.

Department of Internal Medicine, Kangwon National University Hospital, Kangwon National University School of Medicine, Gangwon, Korea

Received on August 5, 2021; Accepted on September 10, 2021

*Hee Ryeong Jang and Kyu-Hyoung Lim contributed equally to this work.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The COVID-19 pandemic has increased hospitalization due to pneumonia with multi-organ diseases, resulting in high mortality and morbidity worldwide [1]. To manage the COVID-19 pandemic, the development and approval speed of anti-SARS-CoV-2 vaccines are unprecedented. As vaccination progresses, various vaccination-related adverse events have been observed, including unexpected cases of fatal thrombosis and thrombocytopenia, after the initial dose of the adenoviral vector nCoV-19 vaccine [2, 3]. These adverse events have been named vaccine-induced thrombotic thrombocytopenia (VITT). Its clinical features are similar to those of autoimmune heparin-induced thrombocytopenia with thrombocytopenia, thrombosis, and coagulation abnormalities. Thrombotic thrombocytopenia is thought to occur due to the production of autoantibodies against platelet factor 4 (PF4), which activates platelets, and the pathophysiology of such rare post-vaccination symptoms is considered another type of spontaneous heparin-induced thrombocytopenia [2, 3]. A diagnosis of this rare and unexpected adverse event requires PF4 immunoassay and evaluation of hematological parameters such as complete blood cell count, peripheral blood smear, fibrinogen level, and D-dimer level [2]. Diagnosis of VITT must fulfill the following 4 criteria: a history of COVID-19 vaccination, presence of venous or arterial thrombosis, thrombocytopenia (platelet count $<150{,}000/\mu L$), and positive PF4 enzyme-linked immunosorbent assay (ELISA) results. Herein, we have presented a subclinical case with severe thrombocytopenia and positive PF4-heparin ELISA results, except thrombotic events after vaccination with ChAdOx1 nCov-19.

Case presentation

A 39-year-old woman with a history of immune thrombocytopenic purpura (ITP) visited the outpatient clinic with a 3-day history of petechiae after vaccination with ChAdOx1 nCov-19. The patient was diagnosed with ITP in her teens. She underwent splenectomy at the age of 15 years. Subsequently, her platelet count remained stable; however, steroids were administered before and after childbirth. Eltrombopag, an orally administered small-molecule nonpeptide thrombopoietin receptor agonist, was administered from February to August 2017. This was the last treatment for ITP. Since 2018, the patient's platelet count has been stable on regular outpatient examinations (Fig. 1), although she had intermittent transient thrombocytopenia due to viral infection in the past.

The patient did not have fever or symptoms such as headache, abdominal pain, dyspnea, or limb edema at the

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

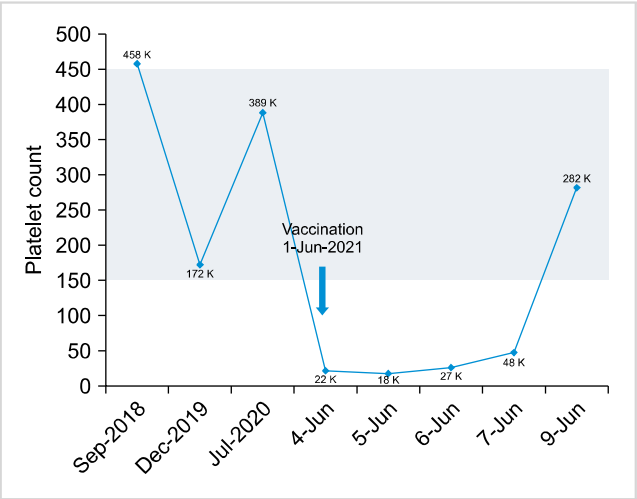

Fig. 1. Changes in the platelet count before and after ChAdOx1 nCov-19 vaccine.
Blue squared area: normal reference range of platelet count.

outpatient visit after vaccination. The patient had no history of anticoagulant use, including heparin use. Severe thrombocytopenia was observed (platelet count, 22,000/μL) at the initial examination on the day of admission. However, the international normalized ratio (INR), activated partial thromboplastin time (aPTT) and fibrinogen and D-dimer levels were within the normal ranges. In addition, PF4-heparin ELISA was commissioned by the Korea Disease Control and Prevention Agency to identify VITT in a clinical situation of severe thrombocytopenia after vaccination. After hospitalization, she complained of a mild headache. Magnetic resonance imaging showed no bleeding, thrombosis, or other abnormal findings. On the 2nd day of hospitalization, her platelet count decreased slightly to 18,000/μL, while other laboratory parameters such as aPTT, INR, and D-dimer level were normal. Due to the risk of bleeding and thrombosis, she was recommended complete bed rest and was closely observed. On the 3rd day of hospitalization, her platelet count showed spontaneous recovery without transfusion or drug administration, such as intravenous immunoglobulin or prednisolone. She wanted to be discharged. Thus, we followed up the patient in the outpatient clinic. On the 9th day after vaccination, the patient visited the outpatient clinic without any specific symptoms. Her platelet count returned to normal (282,000/μL). The PF4-heparin ELISA performed during hospitalization showed a weakly positive result with an optical density (OD) value of 0.81. The patient was counseled about avoiding the use of heparin in the future and cross-vaccination at the time of the 2nd dose of vaccination. The patient decided to continue the outpatient follow-up in the future.

Brief reviews

VITT is an unexpected adverse effect of adenoviral vector-based vaccination. Its exact incidence is unknown; however, it seems to be very rare. One study estimated the incidence of VITT as 1 in 26,000 individuals vaccinated with ChAdOx1 nCov-19 [4]. Only 1 case of VITT has been officially reported in South Korea. Based on the previously reported VITT cases, female sex and younger age (age, 30–55 yr) are considered risk factors for VITT. Previous studies have reported that VITT commonly occurs in females and younger individuals (age, 30–55 yr) within 10 days after vaccination [2, 3]. Nine of 11 patients and 4 of 5 patients with VITT were females in a German and Norwegian report, respectively [2, 3]. In another case series report from the United Kingdom, 61% (14/23) individuals with VITT were females [5]. In addition, thrombotic events occur in unusual sites such as the cerebral vein, internal jugular vein, and splanchnic vein [2, 3]. Similar to previous reports, in our case, a young female patient showed severe thrombocytopenia and PF4-heparin ELISA positivity within 10 days after vaccination, except thrombotic events. Moreover, unlike other cases, spontaneously recovery was observed in our case.

Previously reported VITT cases has high OD values (range, 2.02–3.8) on PF4-heparin ELISA. However, a weakly positive OD value (OD=0.81) was observed in our patient [2, 3]. PF4-dependent platelet activation was observed in the serum of patients with VITT [3]. There is a relationship between the titer of anti-PF4 antibodies and thrombotic events. Thiele *et al.* [6] reported a frequency of 8.0% positivity against PF4-polyanion among 138 vaccinated individuals with low OD values (range, 0.5–0.99). In addition, samples that showed low OD values did not show induced platelet activation in the presence of PF4. Moreover, none of the patients developed thrombosis. There are differences in the levels of immunoglobulin G antibodies against PF4-polyanion complexes between thrombotic cases and non-thrombotic cases [2, 3, 6]. In our case, a low OD (0.81) was observed without a thrombotic event.

VITT does not appear to occur more frequently in patients with ITP or is not associated with a specific type of COVID-19 vaccine. One study of COVID-19 vaccines in patients with ITP reported that 46 (88%) of 52 patients had no worsening of ITP symptoms within 14 days and that only 6 (12%) of 52 patients had severe exacerbation of thrombocytopenia with new petechiae, hemorrhage, and ecchymosis without arterial or venous thrombosis. However, VITT could not be confirmed because these 6 patients did not undergo the PF4 antibody test. Regarding the vaccine administered, messenger ribonucleic acid-based vaccines and adenoviral vector-based vaccines were administered to 5 patients and 1 patient, respectively [7]. Four patients had spontaneous remission, and only 2 patients were undergoing active treatment. Therefore, the safety of the 2nd vaccination in these patients needs to be carefully evaluated.

In conclusion, VITT is a very rare but serious adverse event after COVID-19 vaccination. It is necessary to interpret the relevant test results precisely to reduce the vaccination-related risk and protect people against SARS-COV-2.

Weak reactivity (OD range, 0.5–0.99) on PF4- heparin ELISA-positive results needs to be interpreted carefully in a clinical context. Further studies on the appropriate OD range of PF4-heparin ELISA associated with VITT are needed.

Authors' Disclosure of Potential Conflict of Interest

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 2020;324:782-93.
2. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med 2021;384:2092-101.
3. Schultz NH, Sørvoll IH, Michelsen AE, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384:2124-30.
4. Pottegård A, Lund LC, Karlstad Ø, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ 2021;373:n1114.
5. Scully M, Singh D, Lown R, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384:2202-11.
6. Thiele T, Ulm L, Holtfreter S, et al. Frequency of positive anti-PF4/polyanion antibody tests after COVID-19 vaccination with ChAdOx1 nCoV-19 and BNT162b2. Blood 2021;138:299-303.
7. Kuter DJ. Exacerbation of immune thrombocytopenia following COVID-19 vaccination. Br J Haematol 2021;195:365-70.