pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2021;17(4):570-572 / https://doi.org/10.3988/jcn.2021.17.4.570

Vaccine-Induced Immune Thrombotic Thrombocytopenia: First Case Report in South Korea

Min Kyung Kim[a]
Seongsoo Jang[b]
Sang-Hoon Na[c]
Soo-Mee Bang[d]
Ji Hyun Kim[a]

[a]Department of Neurology, Korea University Guro Hospital, Seoul, Korea
[b]Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[c]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[d]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

Dear Editor,

The coronavirus disease 2019 (COVID-19) pandemic is an ongoing global crisis. Among 11 vaccines recently introduced worldwide, vaccines using adenoviral vectors such as ChAdOx1 nCov-19 (AstraZeneca) and Ad26.COV2.S (Janssen) have been reported to rarely cause vaccine-induced immune thrombotic thrombocytopenia (VITT).[1] As at June 2021, approximately 7.9 million people had received the AstraZeneca vaccination in South Korea, and we have identified the first case of VITT presenting with cerebral venous sinus thrombosis.[2]

A previously healthy, 33-year-old male patient presented with recurrent successive generalized tonic–clonic seizures with prolonged confusion. Four days before admission he experienced worsening exploding headache confined to the left frontotemporal area, accompanied by nausea, vomiting, and general weakness. He had received the AstraZeneca vaccination 15 days prior to the headache onset. On arrival, he showed stuporous mentality, impaired awareness, and neck stiffness with no lateralizing neurological deficits. Emergent CT disclosed a small amount of intracranial hemorrhage in the left frontal lobe and high density lesions in the superior sagittal sinus. Subsequent diffusion-weighted imaging also showed dark signal lesions in the corresponding areas on a gradient recalled echo sequence (Fig. 1A). Cerebral venous thrombosis of the superior sagittal sinus was suggested, which was subsequently confirmed by CT venography (Fig. 1B). Laboratory tests revealed mild thrombocytopenia (platelet count, 75,000/mm^3) and markedly elevated D-dimer (>20 mg/L fibrinogen equivalent unit [FEU], reference range <0.5 mg/L FEU). The laboratory results for coagulopathy including fibrinogen, protein C activity, protein S activity, antithrombin III, antiphospholipid antibody IgM/IgG, anti-cardiolipin antibody IgM/IgG, anti-platelet antibody, and platelet-associated antibody were all negative or within normal ranges. Intravenous antiepileptic drugs (levetiracetam 1,500 mg and lacosamide 400 mg) and 20% mannitol (200 mL) were immediately administered to prevent recurrent generalized seizures and reduce the raised intracranial pressure. Anticoagulation treatment with oral edoxaban (60 mg/day) was also commenced under the impression of probable VITT, in compliance with the VITT guideline (http://ncov.mohw.go.kr/upload/ncov/file/202104/1618802689481_20210419122449.pdf). The screening test for antibodies against the platelet factor 4 (PF4)–heparin complex using a chemiluminescent immunoassay was negative but strongly positive when using an enzyme-linked immunosorbent assay (3.1 optical-density units, normal range <0.4 optical-density units).

The patient regained consciousness the next day and no further seizures occurred. An electroencephalogram showed regional sharp-waves in the left frontal area on a normal background. Thrombocytopenia and elevated D-dimer gradually improved to normal over the following 2 weeks (Fig. 1D). Repeat CT venography on hospital day 14 showed reductions in the hematoma size and perilesional edema as well as a marked resolution of venous thrombosis (Fig. 1C). He remained on an oral anticoagulant and was discharged to home on hospital day 19 without any neurological sequelae.

Received June 22, 2021
Revised July 28, 2021
Accepted July 28, 2021

Correspondence
Ji Hyun Kim, MD, PhD
Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine, 148 Gurodong-ro, Guro-gu, Seoul 08308, Korea
Tel +82-2-2626-3171
Fax +82-2-2626-1256
E-mail jhkim.merrf@gmail.com

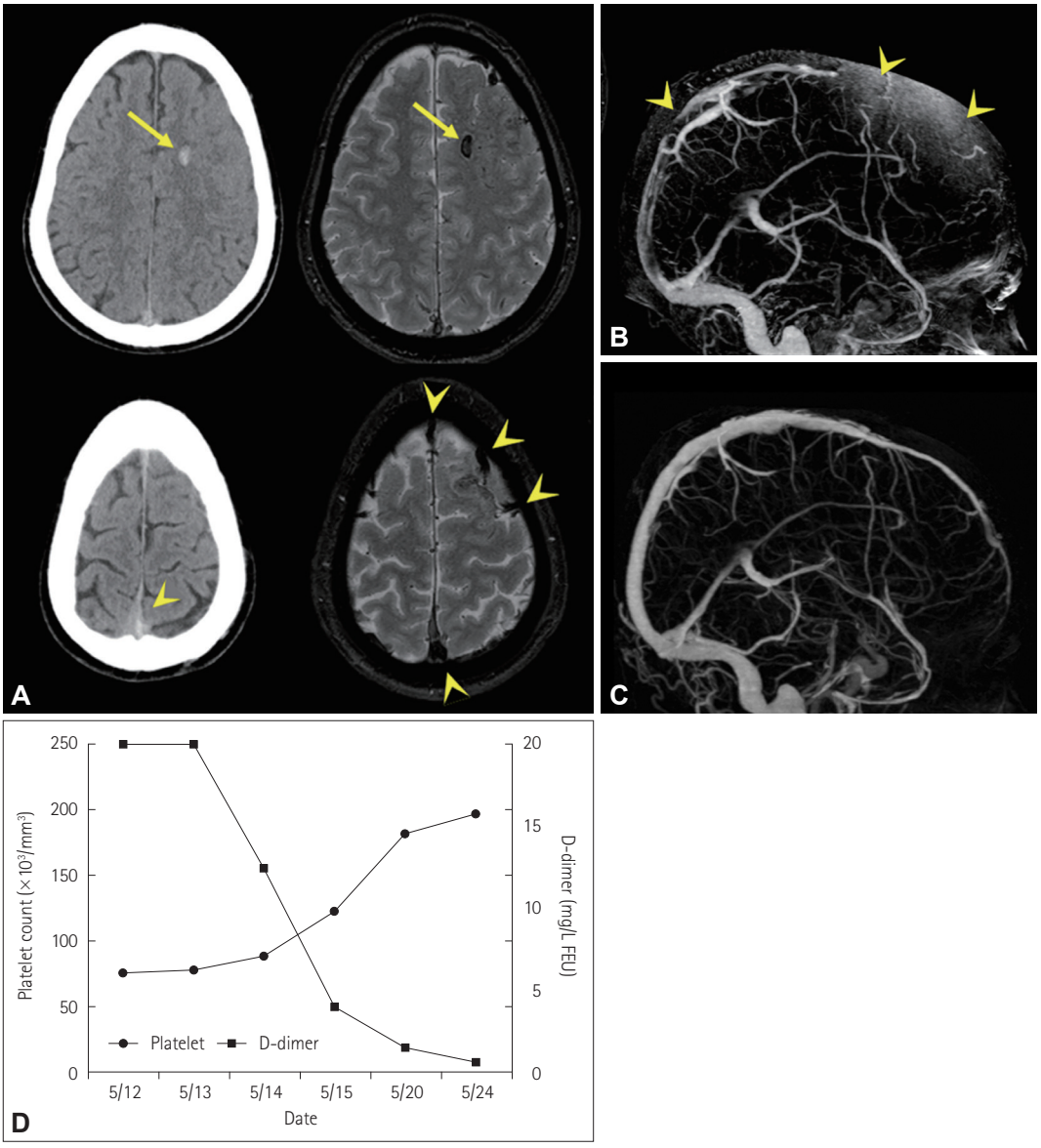

Fig. 1. A: CT (left panel) and gradient recalled echo (right panel) images showing a focal intracranial hemorrhage in the left frontal lobe (arrows), and hyperattenuating and hypointense lesions due to venous thrombosis in the superior sagittal sinus and cortical veins (arrowheads). B and C: Massive cerebral venous thrombosis (arrowheads) in the superior sagittal sinus and cortical veins was evident on initial CT venography (B), which had resolved on repeat venography (C). D: Dual-axis graph showing a gradual increase in the platelet count (circles) and a reduction in the D-dimer level (square) over 2 weeks. FEU, fibrinogen equivalent unit.

Incident VITT has rarely been reported in people who have received vaccinations for COVID-19, with 348 VITT cases among 14.3 million recipients of the AstraZeneca vaccine in the UK and 32 cases among 10.2 million recipients of the Janssen vaccine in the USA reported to date.[3,4] The AstraZeneca vaccine is offered to people aged ≥30 years in South Korea, consistent with the European guideline based on the risk–benefit assessment of vaccine-induced serious complications and the prevention of COVID-19 infection. As at June 2021, there were 10 suspected cases of VITT out of 7.9 million recipients in South Korea; however, the presence of antibodies against the PF4–heparin complex was not confirmed by the enzyme-linked immunosorbent assay in all of the cases.[2]

The Greifswald Working Group has recently provided crucial insight into the pathogenetic mechanism that underlies VITT.[5] Similar to heparin-induced thrombocytopenia (HIT), the vaccination using the AstraZeneca and Janssen vaccines is likely to induce the formation of antibodies against platelet antigens through an inflammatory reaction and immune stimulation, culminating in massive platelet aggregation via the Fc receptor.[5] Since the mechanism of VITT closely resembles the specific immunological response of HIT, the guideline advises

avoiding the use of heparin and low-molecular-weight heparin preparations in cases of suspected VITT. The use of warfarin should also be avoided in cases of VITT, because it can paradoxically worsen the thrombosis and cause venous limb gangrene and skin necrosis in HIT. Meanwhile, non-heparin anticoagulants such as oral Xa inhibitors (e.g., rivaroxaban, apixaban, and edoxaban), direct thrombin inhibitors (e.g., argatroban), and fondaparinux are instead recommended for pharmacological thromboprophylaxis. Moreover, high-dose intravenous IgG (1 g/kg for 2 days) should be administered when the platelet count decreases to <50,000/mm^3 or to <100,000/mm^3 with evidence of major bleeding. It is particularly important that platelet transfusion is avoided since it can cause or exacerbate thrombotic conditions.[6]

Herein we have reported the first case of VITT in whom clinical and radiological abnormalities of cerebral venous thrombosis were completely reversed by administering an oral anticoagulant. Awareness that COVID-19 vaccines using adenoviral vectors rarely cause VITT would recognize this catastrophic condition and prompt the clinician to commence appropriate treatment and prevent unintentional grave outcomes.

Ethics Statement

The patient gave written informed consent for his information and CT/MR images to be published as a case report in a journal.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article (and its supplementary information files).

ORCID iDs

Min Kyung Kim	https://orcid.org/0000-0003-0694-9906
Seongsoo Jang	https://orcid.org/0000-0002-0045-1747
Sang-Hoon Na	https://orcid.org/0000-0002-1289-7965
Soo-Mee Bang	https://orcid.org/0000-0002-0938-3007
Ji Hyun Kim	https://orcid.org/0000-0003-3411-5714

Author Contributions

Conceptualization: Soo-Mee Bang, Ji Hyun Kim. Data curation: Min Kyung Kim, Sang-Hoon Na, Ji Hyun Kim. Formal analysis: Seongsoo Jang, Soo-Mee Bang. Supervision: Ji Hyun Kim. Writing—original draft: Min Kyung Kim, Soo-Mee Bang. Writing—review & editing: Ji Hyun Kim.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

None

REFERENCES

1. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *N Engl J Med* 2021;384:2092-2101.
2. Korea Disease Control and Prevention Agency. Updates on COVID-19 incidence and vaccination in Republic of Korea (as of 00:00, 2021 Jun 9) [Internet]. Cheongju: Korea Disease Control and Prevention Agency; 2021 Jun 9 [updated 2021 Jun 11; cited 2021 Jun 9]. Available from: http://kdca.go.kr/board/board.es?mid=a20501010000&bid=0015&list_no=713602&cg_code=&act=view&nPage=1.
3. Medicines and Healthcare products Regulatory Agency. Research and analysis: coronavirus vaccine - weekly summary of Yellow Card reporting [Internet]. London: Medicines and Healthcare products Regulatory Agency; 2021 [updated 2021 Sep 2; cited 2021 Feb 5]. Available from: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting.
4. Centers for Disease Control and Prevention. Selected adverse events reported after COVID-19 vaccination [Internet]. Atlanta, GA: Centers for Disease Control and Prevention; 2021 [updated 2021 Sep 2; cited 2021 May 27]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html.
5. Oldenburg J, Klamroth R, Langer F, Albisetti M, von Auer C, Ay C, et al. Diagnosis and management of vaccine-related thrombosis following AstraZeneca COVID-19 vaccination: guidance statement from the GTH. *Hamostaseologie* 2021;41:184-189.
6. Ahmed I, Majeed A, Powell R. Heparin induced thrombocytopenia: diagnosis and management update. *Postgrad Med J* 2007;83:575-582.