A Successful Venous Thromboprophylaxis in a Patient with Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT): a case report of the first reported case in Thailand

Archrob Khuhapinant  
Mahidol University Faculty of Medicine Siriraj Hospital

Tarinee Rungjirajittranon  
Mahidol University Faculty of Medicine Siriraj Hospital

Bundarika Suwanawiboon  
Mahidol University Faculty of Medicine Siriraj Hospital

Yingyong Chinthammitr  
Mahidol University Faculty of Medicine Siriraj Hospital

Theera Ruchutrakool (✉ truchutrakool@gmail.com)  
Mahidol University Faculty of Medicine Siriraj Hospital  https://orcid.org/0000-0001-5717-515X

Research Article

Keywords: COVID-19 vaccine, thrombocytopenia, thrombosis, vaccine-induced immune thrombotic thrombocytopenia

DOI: https://doi.org/10.21203/rs.3.rs-702766/v1

License: ☑️ This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License
Abstract

Background

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare but fatal complication of Coronavirus Disease 2019 vaccine. Many reports of VITT have mostly been in the Caucasian population. Here, we present first reported case from an oriental population.

Case presentation

A 26-year-old female who had severe headache and severe thrombocytopenia 8 days after administration of the ChAdOx1 nCoV-19 vaccine developed by AstraZeneca. Although no thrombosis was demonstrated by imaging studies, she had very highly elevated d-dimer level during hospitalization. Serology for antibody against platelet factor 4 was positive on several days with very high optical density readings. Furthermore, we found the antibody could induce spontaneous platelet aggregation without the presence of heparin. We decided to treat her with intravenous immunoglobulin, high-dose dexamethasone, and a prophylactic dose of apixaban. She improved rapidly and was discharged from the hospital 6 days after admission. Neither thrombocytopenia nor thrombosis was subsequently detected at three weeks follow-up.

Conclusions

Despite lower rate of thrombosis, VITT can present in Asian population. Early detection and prompt treatment of VITT can improve patients' clinical outcome. Thromboprophylaxis of non-heparin anticoagulants also results in prevention of clot formation.

Background

The Coronavirus Disease 2019 (COVID-19) pandemic has affected health issues and economic systems globally. Shortly after the first case series was reported from China in December 2019(1), the number of new cases increased exponentially. COVID-19 is a serious emerging pandemic infectious disease with high mortality rate of up to 2% in infected patients (2). Although the disease can be controlled by social distancing, mask wearing, and face shield wearing, immunization with a vaccine against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) should be the method of choice implemented to combat the COVID-19 pandemic. Four different types of vaccine are currently available (3), and vaccination was started in March of 2021 with most reports of adverse events following immunization reporting minor ones. However, several groups of people receiving the ChAdOx1 nCoV-19 vaccine, an engineered non-replicating viral vector vaccine using an adenovirus developed by AstraZeneca, developed a vaccine type-specific complication named vaccine-induced immune thrombotic thrombocytopenia (VITT). Patients usually developed thrombocytopenia and thrombosis (4–6) within 4–28 days after the first dose of vaccine (4–6). Most of the cases were young and previously healthy females (4–6). Up to 38–80% of reported cases had severe thrombosis in the venous sinus system of brain (4–6). The
mortality rate of VITT was high and was 18% (71 of 390) in the United Kingdom, the country with the highest number of reported cases in the world (7). Although the association between adenovirus viral vector vaccines and thrombocytopenia along with thrombosis is uncertain, it is believed certain components of the vaccine could induce platelet aggregation and cause thrombocytopenia, eventually leading to thrombosis (8). Moreover, it has been assumed the mechanism of VITT and autoimmune/spontaneous heparin-induced thrombocytopenia/thrombosis (HIT/T) are similar (9). Although reports of VITT have mostly been in the Caucasian population, there have been no reports from an oriental population receiving this type of vaccine. In Thailand, the vaccination program for COVID-19 was launched in May 2021, and mass vaccination with the ChAdOx1 nCoV-19 vaccine developed by AstraZeneca has been gradually rolled out to the Thai population since June 2021. Shortly after the start of this roll out, the first patient with VITT in Thailand presented to our institution.

Case Presentation

A 26-year-old female presented with severe headache for 5 days. She had been previously healthy without comorbidities eight days earlier when she had been scheduled for the first dose of ChAdOx1 nCoV-19 vaccine (AstraZeneca) vaccination. She had no adverse event following immunization until three days later when she developed a severe headache. She did not report any fever, myalgia, blurred vision, nausea, or vomiting. Her headache was not improved by acetaminophen and mefenamic acid. One day prior to admission, she noticed multiple discrete reddish spots at both lower legs without bleeding gums or epistaxis. On examination, mildly pale conjunctiva and petechiae at both legs were noted while other examinations were unremarkable. The initial complete blood count showed a hemoglobin of 9.7 g/dL, mean corpuscular volume of 71.5 fL, white blood cell count of 3.66 x 10^9/L (neutrophil 75%, lymphocyte 18%, monocyte 4.7%, eosinophil 2% basophil 0.3%), and platelet count of 22 x 10^9/L. Prothrombin time was 11.9 seconds (normal range, 9.8–12.9 seconds), activated partial thromboplastin time was 25.8 seconds (normal range, 21.8–30.2 seconds), and fibrinogen was 173.8 mg/dL. D-dimer was 9452 ng/mL (normal d-dimer, < 500 ng/mL). NS-1 antigen, dengue IgM, and IgG serologic testing were negative. SARS-CoV2 RNA test was negative. Lupus anticoagulants, anticardiolipin IgM, IgG, as well as anti-β2 glycoprotein I IgM and IgG were negative. Magnetic resonance imaging, angiography, and venography of brain were normal without evidence of thrombosis. Computed tomography angiography of the pulmonary arteries showed no pulmonary embolism, and computed tomography of abdomen was unremarkable.

Due to the high degree of suspicious of VITT, we performed a test for antibody against platelet factor 4 (PF4) by enzyme-linked immunosorbent assay-based assay (Zymutest HIA IgG, HYPHEN BioMed, Neuville-sur-Oise, France), and the result was positive with an optical density (OD) of 2.10 (normal OD, < 0.4) (Fig. 1). After we added heparin at a concentration of 100 units/mL, the OD was lower at 0.09 (Fig. 1). We then demonstrated a functional test of antibody by a heparin-induced platelet aggregation (HIPA) test. Platelet rich plasma from healthy volunteer with blood group O was incubated with the patient's serum for one hour. Low doses (0.1 and 0.5 unit/mL) and a high dose (100 units/mL) of heparin and normal saline were added into the mixture mentioned above. Platelet aggregation was assessed by
light transmission (AggRAM Analyzer®, Helena Laboratories, Beaumont, Texas). Platelet aggregation of >25% was detected after adding the low concentrations of 0.1 and 0.5 unit/mL of heparin, but it was absent at 100 unit/mL (Table 1). Without adding heparin, spontaneous platelet aggregation was also detected.

| Heparin for final concentration, units/mL | Platelet aggregation, % |
|------------------------------------------|------------------------|
|                                          | D0  | D1  | D4  |
| 0.1                                      | 31.8| 18.7| 16.8|
| 0.5                                      | 46.0| 20.4| 15.3|
| 100                                      | 15.9| 19.2| 18.7|
| Saline                                   | 30.0| 16.0| 6.9 |

Table 1
Heparin-induce platelet aggregation results of the patient

After discussion with the patient, we promptly started treatment with 2 days of 1 g/kg of intravenous immunoglobulin (IVIG) infusion and dexamethasone 40 mg per day for severe thrombocytopenia, and we administered 2.5 mg of apixaban every 12 hours for thromboprophylaxis. We opted to monitor thrombus formation by d-dimer level because we did not find evidence of thrombosis by imaging studies, and d-dimer level gradually decreased during the hospital course after treatment (Fig. 2). After 6 days of IVIG and dexamethasone treatment, the platelet count had slowly increased to 97 x 10^9/L (Fig. 2). Her symptoms were improved, and she was discharged from the hospital by day 6. At three weeks follow-up, the number of platelet counts was 134 x 10^9/L (Fig. 2) and no clinical thrombosis was detected.

Discussion

Since the first three independent reports of case series were published in April 2021, the number of cases worldwide reported in the literature of patients with VITT associated with vaccination with the ChAdOx1 nCoV-19 vaccine developed by AstraZeneca is currently large and is becoming larger (4–6). The Ad26.COV2.S vaccine developed by Johnson and Johnson with similar adenovirus viral vector technology, was also reported to induce thrombocytopenia and thrombosis in the United States’ population (10). The ChAdOx1 nCoV-19 vaccine is a WHO-approved vaccine against SAR-CoV-2 and is widely used in Thailand. After the mass vaccination campaign in Thailand was launched in May 2021, approximately two million doses of the ChAdOx1 nCoV-19 vaccine have been administered to date. Thus, the incidence rate of VITT in the Thai population is approximately one in two million vaccinations, which is much lower than those reported in Caucasian populations (11). There are several possible explanations for the lower incidence of VITT in Thai population. First, Asian ethnicity is widely recognized to be associated with fewer thrombotic events than Caucasian ethnicity (12). This could be due to a lower rate
of inherited thrombophilia, such as prothrombin G20210A mutation or factor V Leiden in Asian ethnicity (13), and Asian people requiring lower doses of warfarin treatment might imply an antithrombotic tendency (14). Second, many reported cases of VITT had concomitant risks for thrombosis, such as antiphospholipid syndrome or oral contraceptive pill usage, which was not found in our patient.

Most of the patients with VITT presented with an unusual site of thrombosis, such as the cerebral venous sinus or the splanchnic vein with concomitant severe thrombocytopenia (4–6, 10). The onset of VITT was usually 4–28 days after vaccination (4–6, 10). Although the pathogenesis of VITT is uncertain, there have been many laboratory findings supporting the hypothesis that the mechanism of thrombocytopenia and thrombosis is similar to that of autoimmune HIT/T in that the anti-PF4 antibody may be induced by polyanions including lipid A in bacterial surfaces nucleic acids instead of heparin (9). For VITT, some components of the vaccine, for example, the adenovirus DNA, spike protein, and/or neoantigen induced by the vaccine, have been proposed to be key components that could induce PF4 release and anti-PF4 antibody production (15).

To the best of our knowledge, our patient is the first reported case of VITT in an Asian population, and she had severe thrombocytopenia 8 days after ChAdOx1 nCoV-19 vaccine administration. Pathologic anti-PF4 antibody was demonstrated by high OD and subsequently confirmed by functional HIPA test. Although most VITT cases developed thrombosis demonstrated either by clinical features or imaging studies, our patient did not have thrombosis after extensive investigations for occult clots. This might have been due to the high degree of suspicion and the early detection of VITT because some patients with VITT who come to hospital early may not have clinical thrombosis despite having a high level of d-dimer level detected (16). Although a rare side effect of immunoglobulin is thrombosis, IVIG is still an essential treatment to slow the progression of this disease (17). Immediate treatment with IVIG can decelerate the progression of the immune reaction and accelerate the recovery of the platelet count (18). Many guidelines also recommend starting treatment with IVIG in every case that is suspected of VITT without delay (19–21). With lessons learnt from our patient, we strongly support the use of anticoagulants other than heparin to prevent the clot formation. Furthermore, d-dimer level can be used to monitor thrombosis progression. Prophylactic anticoagulant for a duration of 3 months is recommended in patients with VITT (21).

Conclusions

In conclusion, our case report highlights that VITT can occur in Asian populations. Prompt treatment with IVIG, dexamethasone, and prophylactic anticoagulants can improve the patient’s outcome. More research data, especially about risk factors and the pathogenesis of the syndrome, are needed to encourage patients to get vaccinated confidently.

List Of Abbreviations
Declarations

Ethics approval and consent to participate

In Thailand, a care report does not require ethics approval. The patient has given her written permission to publish her personal data.

Consent for publication

Written informed consent was obtained from the patient for publication of the report and accompanying images. A copy of that consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

There was no source of funding for this study.

Authors’ contributions

AK collected and provided all patient data and imaging. TR1 and TR2 drafted the manuscript. TR2 made critical revisions to the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors are grateful to Ms.Suthirak Sitaposa, Ms.Tussnem Binhama, and Mrs.Yupa Nakkinkun for their laboratory technical support. We would like to thank Mr. Anthony Tan for editing the manuscript for English language.

Author details

Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.
References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.

2. Coronavirus (COVID-19) Mortality Rate. https://www.worldometers.info/coronavirus/coronavirus-death-rate/. Accessed 20 June 2021.

3. Forni G, Mantovani A, Forni G, Mantovani A, Moretta L, Rappuoli R, et al. COVID-19 vaccines: where we stand and challenges ahead. Cell Death & Differentiation. 2021;28(2):626-39.

4. Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021;384(23):2202-11.

5. Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021;384(22):2124-30.

6. 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(22):2092-101.

7. Coronavirus Vaccine-Weekly Summary of Yellow Card Reporting. https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting#yellow-card-reports. Accessed 20 June 2021.

8. Greinacher A, Selleng K, Wesche J, et al. Towards understanding ChAdox1 nCOv-19 vaccine-induced immune thrombotic thrombocytopenia (VITT). Preprint version. doi: 10.21203/rs.3.rs-440461/v1

9. Warkentin TE, Greinacher A. Spontaneous HIT syndrome: Knee replacement, infection, and parallels with vaccine-induced immune thrombocytopenia. Thromb Res. 2021;204:40-51.

10. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021. JAMA. 2021.

11. Chan BT, Bobos P, Oduyato A, et al. Meta-analysis of risk of vaccine-induced immune thrombotic thrombocytopenia following ChAdOx1-S recombinant vaccine. Preprint version. doi: 10.1101/2021.05.04.21256613

12. White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. Thromb Res. 2009;123 Suppl 4:S11-7.

13. Klatsky AL, Baer D. What protects Asians from venous thromboembolism? Am J Med. 2004;116(7):493-5.

14. Klatsky AL, Armstrong MA, Poggi J. Risk of pulmonary embolism and/or deep venous thrombosis in Asian-Americans. Am J Cardiol. 2000;85(11):1334-7.

15. Arepally GM, Ortel TL. Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT): What We Know and Don't Know. Blood. 2021. Epub ahead of print. doi: 10.1182/blood.2021012152.

16. Thaler J, Ay C, Gleixner KV, Hauswirth AW, Cacioppo F, Grafeneder J, et al. Successful treatment of vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). J Thromb Haemost. 2021. Epub
17. Rungjirajittranon T, Owattanapanich W. A serious thrombotic event in a patient with immune thrombocytopenia requiring intravenous immunoglobulin: a case report. J Med Case Rep. 2019;13(1):25.

18. Bourguignon A, Arnold DM, Warkentin TE, Smith JW, Pannu T, Shrum JM, et al. Adjunct Immune Globulin for Vaccine-Induced Thrombotic Thrombocytopenia. N Engl J Med. 2021. Epub ahead of print. doi: 10.1056/NEJMoa2107051.

19. 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. Epub ahead of print. doi: 10.1055/a-1469-7481.

20. American Society of Hematology. Vaccine-induced Immune Thrombotic Thrombocytopenia: Frequently Asked Questions. https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia. Accessed 20 June 2021.

21. Guidance from the Expert Haematology Panel (EHP) on Covid-19 Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT) version 1.7. https://b-s-h.org.uk/media/19590/guidance-version-17-on-mngmt-of-vitt-20210420.pdf. Accessed 20 June 2021.

Figures
Figure 1

Summary of platelet factor 4 antibody results of the patient
Figure 2

Timeline of platelet count and d-dimer level of patient