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EDITORIAL

Thrombosis After Vaccination With Messenger RNA–1273: Is This Vaccine-Induced Thrombosis and Thrombocytopenia or Thrombosis With Thrombocytopenia Syndrome?

Vaccine-induced thrombosis and thrombocytopenia (VITT), also referred to as thrombosis with thrombocytopenia syndrome, is a rare and potentially life-threatening disorder described in previously healthy persons after receipt of 1 of 2 adenovirus-based SARS-CoV-2 vaccines (AstraZeneca [ChAdOx1] or Johnson & Johnson [Ad26.COV2.S]) (1). The syndrome is characterized by moderate to severe thrombocytopenia and thrombosis, generally occurring 5 to 30 days after vaccine administration. Thrombosis in atypical locations, particularly the cerebral venous sinuses and splanchnic veins, is a hallmark of the disorder (1).

Although the mechanism of VITT has only begun to be elucidated, it seems similar to but also distinct from heparin-induced thrombocytopenia (HIT) in certain respects. In both VITT and HIT, IgG antibodies bind to platelet factor 4 (PF4) on the surface of platelets, resulting in widespread platelet activation. Indeed, antibodies to complexes of PF4 and polyanion ("HIT antibodies") have been detected in most of the confirmed cases of VITT by enzyme-linked immunosorbent assays, typically at high titers (>1.0 optical density [OD] units) (1). However, unlike HIT, VITT occurs in the absence of antecedent heparin exposure, and VITT antibodies do not depend on the presence of heparin to bind PF4 and activate platelets.

The true incidence of VITT remains unknown, but it seems to be very rare. The highest reported incidence is 5 cases among about 130 000 Norwegian recipients of the ChAdOx1 vaccine (2). In comparison, the Centers for Disease Control and Prevention has confirmed 28 cases among more than 8 million recipients of the Ad26.COV2.S vaccine (3).

In their article, Sangli and colleagues describe catastrophic thrombosis after the second dose of the SARS-CoV-2 messenger RNA (mRNA)–1273 vaccine from Moderna (4). Until now, there have been no confirmed cases of VITT after either of the mRNA vaccines despite administration in the United States alone of more than 110 million doses of the mRNA-1273 vaccine and 135 million doses of the Pfizer–BioNTech mRNA vaccine (BNT162b2) (as of 7 May 2021) (3). This case meets the Brighton Collaboration case definition of VITT, with severe thrombocytopenia and thrombosis without prior heparin exposure (5). (Our correspondence with the authors confirmed there was no exposure to heparin products in the 100 days before presentation.) It also fulfills the additional diagnostic criteria outlined in recent guidance by the International Society on Thrombosis and Haemostasis with an elevated D-dimer level and high titer HIT antibodies as measured by enzyme-linked immunosorbent assay (6). We are in full agreement with the authors' decision to treat the described case as VITT and do not advocate delaying treatment in such cases. However, extra caution is needed before attributing the patient's presentation to the mRNA-1273 vaccine.

What else should be considered when evaluating a potential case of VITT? First, the frequency of elevated HIT antibodies in an asymptomatic population is low but not zero. Researchers detected weakly positive (0.5 to 1.0 OD units; reference range, <0.5 OD units) antibody titers against complexes of PF4 and polyanion in approximately 7% of healthy persons after receipt of either an adenoviral (ChAdOx1) or mRNA (BNT162b2) vaccine (7). None of the antibodies in these asymptomatic persons were platelet activating. Thus, weak positivity for HIT antibodies should not be the sole diagnostic criterion for VITT.

In the current case, the anti-PF4 and polyanion enzyme-linked immunosorbent assay titer was strongly positive at greater than 2.0 OD units. This laboratory result certainly increases the suspicion for VITT. Still, VITT is not the only entity associated with high-titer HIT antibodies, thrombosis, and thrombocytopenia without prior heparin exposure. Spontaneous HIT is a subtype of "autoimmune HIT" occurring without heparin exposure, which was first reported by Warkentin and Greinacher in 2008 (8). It is a rare condition, with only 33 cases described in the literature (8). Spontaneous HIT occurs most frequently after orthopedic surgery. It has also been reported in medical patients in association with infection (8). Sangli and colleagues confirmed that their patient did not have recent orthopedic surgery. They could not confirm whether the patient had any infections before admission, although his blood culture results were positive for methicillin-sensitive *Staphylococcus aureus* approximately 1 week after presentation (4). Had this infection been present on admission, it would be impossible to discern VITT from spontaneous HIT triggered by infection. Ongoing surveillance, as is being done by several regulatory and public health agencies, is needed to determine whether the mRNA-1273 vaccine is capable of inducing VITT.

The seriousness of VITT, even if rare, should not be downplayed. Of the thrombotic events described in VITT, cerebral venous sinus thrombosis is of greatest concern given its propensity for hemorrhagic conversion and the difficulty of treating it with anticoagulation in the setting of thrombocytopenia. However, any potential risks of vaccination must be interpreted in the context of the overall morbidity and mortality of COVID-19 itself. Indeed, a recent analysis reported that even cerebral venous sinus thrombosis, a characteristic and highly feared manifestation of VITT, occurred much more frequently in patients hospitalized with COVID-19 (207.1 per million) than after vaccination with an adenovirus-based SARS-CoV-2 vaccine (0.9 to 3.6 per million) (9).

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Overall, it is difficult to establish a link between this fatal thrombotic event and the mRNA-1273 vaccine from 1 case report among the hundreds of millions of vaccine doses administered. Ongoing postlicensure surveillance is paramount. Clinicians should be vigilant for VITT in the appropriate context because prompt recognition and treatment are likely to improve outcomes.

In the 3 short months since VITT was initially described, several groups have developed guidance on diagnosis and treatment of this entity. Management generally involves avoidance of heparin, use of an alternative (nonheparin) anticoagulant, and intravenous immunoglobulin (10). Platelet transfusions should generally be avoided unless necessitated by serious bleeding or the need for emergent surgery. The remarkable speed with which clinicians and scientists have recognized this rare entity and developed evidence-based diagnosis and treatment guidelines should bolster public confidence in postlicensure vaccine safety monitoring. We remain confident in the safety of the SARS-CoV-2 vaccines and are encouraged by the willingness of the scientific community to report and act on suggestions of any vaccine-associated adverse events.

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References

1. **Cines DB, Bussel JB.** SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia [Editorial]. N Engl J Med. 2021;384:2254-2256. [PMID: 33861524] doi:10.1056/NEJMe2106315

2. **Schultz NH, Sørvoll IH, Michelsen AE, et al.** Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med. 2021;384:2124-2130. [PMID: 33835768] doi:10.1056/NEJMoa2104882

3. **Shimabukuro T.** Update: thrombosis with thrombocytopenia syndrome (TTS) following COVID-19 vaccination. Advisory Committee on Immunization Practices (ACIP); 2021. Accessed at www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/07-COVID-Shimabukuro-508.pdf on 17 June 2021.

4. **Sangli S, Virani A, Cheronis N, et al.** Thrombosis with thrombocytopenia after the messenger RNA–1273 vaccine. Ann Intern Med. 29 June 2021. [Epub ahead of print]. doi:10.7326/L21-0244

5. **Brighton Collaboration.** Interim case definition of thrombosis with thrombocytopenia syndrome (TTS). Accessed at https://brightoncollaboration.us/thrombosis-with-thrombocytopenia-syndrome-interim-case-definition on 14 June 2021.

6. **Nazy I, Sachs UJ, Arnold DM, et al.** Recommendations for the clinical and laboratory diagnosis of VITT against COVID-19: communication from the ISTH SSC Subcommittee on Platelet Immunology. J Thromb Haemost. 2021;19:1585-1588. [PMID: 34018298] doi:10.1111/jth.15341

7. **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. [PMID: 33988688] doi:10.1182/blood.2021012217

8. **Warkentin TE, Greinacher A.** Spontaneous HIT syndrome: knee replacement, infection, and parallels with vaccine-induced immune thrombotic thrombocytopenia. Thromb Res. 2021;204:40-51. [PMID: 34144250] doi:10.1016/j.thromres.2021.05.018

9. **Bikdeli B, Chatterjee S, Arora S, et al.** Cerebral venous sinus thrombosis in the US population, after adenovirus-based SARS-CoV-2 vaccination, and after COVID-19. J Am Coll Cardiol. 2021. [PMID: 34116145] doi:10.1016/j.jacc.2021.06.001

10. **International Society on Thrombosis and Haemostasis.** ISTH interim guidance for the diagnosis and treatment on vaccine-induced immune thrombotic thrombocytopenia. Accessed at https://cdn.ymaws.com/www.isth.org/resource/resmgr/ISTH_VITT_Guidance_2.pdf on 14 June 2021.

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