COMMENTARY

Recognizing, managing and reporting vaccine-induced immune thrombotic thrombocytopenia

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In a related case report, Jones and colleagues describe a 63-year-old man who developed thromboses in his popliteal and pulmonary arteries.[1] The patient's thromboses were likely caused by vaccine-induced immune thrombotic thrombocytopenia (VITT), a rare complication of the ChAdOx1 nCoV-19 (Oxford–AstraZeneca) vaccine, which he had received 20 days previously.[1] We discuss some important lessons clinicians can learn from this case.

Thromboses secondary to VITT are often atypical and can be life-threatening. They have been reported to occur in a variety of vessels — both arteries and veins — including cerebral veins[2,3]. Vaccine-induced immune thrombotic thrombocytopenia and associated thromboses have been reported up to 30 days after receiving a dose of a SARS-CoV-2 vaccine that uses an adenoviral vector. The pathophysiology of VITT remains unclear, but something unique to the adenoviral vaccine constituents appears to stimulate the immune reaction responsible for VITT.[4,5]

The adenoviral vector vaccine that has been widely administered in Canada is ChAdOx1 nCoV-19 (Oxford-AstraZeneca); Alberta and Ontario halted its use on May 11, 2021, and other provinces have followed suit. The best, current global estimate of the incidence of VITT after receiving the first dose of the ChAdOx1 nCoV-19 vaccine is in the range of 1 in 26 000 to 1 in 127 000.[6] As clinicians become more aware of VITT, and diagnose and report it more frequently, the incidence may increase. Although VITT has been reported after the second dose of adenoviral vector vaccines, this seems less common.[6] The risk of VITT appears to be lower with the Johnson and Johnson vaccine,[6] and to our knowledge, no case of VITT has been described after receiving the widely administered mRNA vaccines.[6]

Vaccine-induced immune thrombotic thrombocytopenia can be an aggressive clinical syndrome, and based on reports thus far, 20%–50% of those affected die.[2–5] Given the serious clinical consequences of VITT, clinicians must maintain a high index of suspicion for VITT in patients presenting with symptoms suggestive of thrombosis in any vessel within 30 days of administration of an adenoviral vector SARS-CoV-2 vaccine, despite its low incidence. Early diagnosis is more likely if clinicians inquire about the type and timing of SARS-CoV-2 vaccination as part of standard history taking. Clinicians should seek expert consultation early and consider transfer to a centre that can provide critical care and specialized immunohematology care.

Important symptoms and signs of thrombosis associated with VITT include severe and persistent headache; blurred or double vision; unilateral weakness or change in sensation; chest, abdominal, leg or back pain; leg swelling; and shortness of breath. A complete blood cell count should be ordered for any patient for whom there is a suspicion of VITT.[6–9] Thrombocytopenia and thrombosis in a patient who received a viral vector vaccine within the previous 30 days markedly increases

KEY POINTS

- Vaccine-induced immune thrombotic thrombocytopenia (VITT) and associated thromboses have been reported up to 30 days after receiving a dose of a SARS-CoV-2 vaccine that uses an adenoviral vector, such as ChAdOx1 nCoV-19 (Oxford–AstraZeneca).
- Thromboses secondary to VITT are often atypical and may occur in both veins and arteries; based on reports thus far, 20%–50% of those affected by VITT die.
- Even though VITT is rare, clinicians must maintain a high index of suspicion for the clinical syndrome in patients presenting with symptoms suggestive of thrombosis who report having received an adenoviral vector vaccine.
- Clinicians should use the enzyme-linked immunosorbent assay for heparin-induced thrombocytopenia to screen for VITT; the diagnosis is confirmed using a modification of the functional platelet serotonin-release assay with added platelet factor 4, but treatment should start before diagnosis is confirmed, ideally with input from a hematologist.
- Report all cases of VITT to the appropriate regional health unit to ensure better understanding of the nature of the syndrome and of vaccine safety.

the probability of VITT. D-dimer and fibrinogen levels can help clinicians to assess for evidence of coagulation consumption.[9] Indeed, early VITT has been reported in patients with low platelets, high D-dimer or low fibrinogen levels alone, even without thrombosis.[10]

The screening test for VITT is an enzyme-linked immunosorbent assay (ELISA) for heparin-induced thrombocytopenia (HIT), which is positive in most patients with VITT.[5,9] The authors of the related case appropriately mention that other antibody assays (e.g., latex-enhanced immunoassays) used to identify HIT are usually negative in patients with VITT. Clinicians should make themselves aware of which assay is used in their hospital because many Canadian hospitals do not use the ELISA assay.[6,9] The diagnosis of VITT can be confirmed with a modification of the functional platelet serotonin-release assay with added platelet factor 4 (PF4), which is performed at the McMaster University Platelet Immunology Laboratory (Hamilton, Ont.). However, if a presumptive diagnosis of VITT has been made,[6] clinicians should promptly initiate appropriate treatment, preferably with guidance from a hematologist, without waiting for the results of confirmatory tests.

A current hypothesis proposes that VITT occurs because an antibody against PF4 triggers platelet activation, resulting in thrombosis and consumptive thrombocytopenia, similar to the mechanism seen in HIT, except without exposure to heparin. Given the novelty of VITT, treatment recommendations are based on those used for treating patients with HIT and on lessons learned from treating a small, but growing, number of patients with VITT. Treatment should address both the thrombosis and the patient's immune dysregulation. It is theoretically possible that heparin will exacerbate VITT because VITT antibodies may react with circulating PF4–heparin complexes.[1–8,10–12] Therefore, thrombosis should instead be managed with nonheparin anticoagulants, such as argatroban, fondaparinux or a direct oral anticoagulant. Management is made more challenging if the VITT-associated thrombosis is complicated by hemorrhage, particularly for patients with cerebral venous sinus thrombosis or stroke.[4,8,10]

Intravenous immunoglobulin has been used in the treatment of VITT based on previous experience of patients with severe HIT and thrombosis.[2–5,7,8,12] Intravenous immunoglobulin is believed to neutralize and block the pathogenic action of VITT antibodies, and in so doing, can raise the platelet count. Blood samples for HIT tests (ELISA and serotonin-release assays) should be drawn before intravenous immunoglobulin is administered.[9] Apheresis to remove circulating VITT antibodies may be warranted in patients who continue to deteriorate despite treatment.[2–5,7,8,12] Corticosteroids to dampen the aberrant immune response may also be considered.[4,7,8,12] Platelet transfusions should be avoided, given the risk of worsening the clinical syndrome by providing more antigen (i.e., PF4) to the circulating pathogenic antibodies, and should be considered only with expert hematology guidance.[2,3,5,7,8,12]

Given the uncertainty regarding the incidence, pathophysiology, clinical features and short- and long-term management of VITT, it is important that all cases of VITT in Canada be recognized and reported to the appropriate regional health unit (https://www.canada.ca/en/public-health/services/immunization/federal-provincial-territorial-contact-information-aefi-related-questions.html). Increased reporting will help us to better understand the nature of VITT, how best to treat it and to better characterize vaccine safety.

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