Editor's key points

- Vaccine-induced thrombotic thrombocytopenia (VITT) reactions to adenovirus vector–based COVID-19 vaccines are considered adverse events of special interest.
- While Canada largely moved away from the use of these COVID-19 vaccines in 2021, other countries continue to rely on them as part of their pandemic responses. Thus, this case report adds to the global body of knowledge on adverse events related to adenovirus vector–based vaccines.
- Treatment of VITT remains a challenge, but a diagnostic algorithm published in Ontario provides helpful guidance relevant to primary care professionals.
- Early diagnosis and timely hospital treatment are critical elements of care for VITT. Patients should be provided with clear instructions on follow-up care regarding unresolved symptoms.

Points de repère du rédacteur

- La thrombocytopénie immunitaire prothrombotique induite par le vaccin (TIPIV) en réaction à des vaccins à vecteur viral à base d'adénovirus contre la COVID-19 est considérée comme un événement indésirable d'intérêt particulier.
- Même si le Canada a largement cessé d'utiliser ces vaccins contre la COVID-19 en 2021, d'autres pays continuent de s'y fier dans le cadre de leur réaction à la pandémie. C'est pourquoi ce rapport de cas vient s'ajouter au corpus mondial de connaissances sur les événements indésirables associés aux vaccins à vecteur viral à base d'adénovirus.
- Le traitement de la TIPIV demeure difficile, mais un algorithme diagnostique publié en Ontario offre des conseils utiles, appropriés aux professionnels des soins primaires.
- Le diagnostic rapide et un traitement en temps opportun à l'hôpital sont des éléments essentiels dans les soins pour une TIPIV. Il faut donner aux patients des instructions précises sur les soins de suivi concernant les symptômes toujours présents.

COVID-19 vaccine–induced thrombotic thrombocytopenia

Adverse event associated with adenovirus vector–based vaccines

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In response to the COVID-19 pandemic, scientists developed 69 COVID-19 vaccines in just 1 year, including the AstraZeneca and Johnson & Johnson adenovirus vector–based vaccines.[1,2] The AstraZeneca vaccine has been recognized globally as one of the most affordable, effective, and portable of the COVID-19 vaccines.[1,2] Real-world data have shown that even 1 dose of the vaccine is highly effective in preventing acute COVID-19 symptoms, hospitalization, and death.[2] The AstraZeneca vaccine was useful in Canada in early phases of COVID-19 vaccination efforts owing to its portability. However, adenovirus vector–based COVID-19 vaccines have now been linked to the rare and sometimes fatal vaccine-induced thrombotic thrombocytopenia (VITT), a syndrome similar to heparin-induced thrombotic thrombocytopenia. This new syndrome is associated with a low platelet count and the risk of dangerous cerebral, pulmonary, and abdominal thrombi.[3,4]

Vaccine-induced thrombotic thrombocytopenia may develop between 2 and 28 days after vaccination.[3,4] Timely identification of VITT is a critical element of care. The Ontario COVID-19 Science Advisory Table has published recommendations, including an algorithm, to help guide the identification of patients at risk of VITT.[5]

In March 2021 the National Advisory Committee on Immunization recommended the preferential use of messenger RNA COVID-19 vaccines in authorized age groups instead of adenovirus vector–based vaccines, in part owing to their higher efficacy[6] but also in response to reports of adverse events associated with the latter.[7] By the middle of May 2021, 28 suspected cases of VITT had been identified in Canada following the administration of more than 2 million doses of the AstraZeneca vaccine, and 4 VITT-related deaths had been reported in the country.[8] The Canadian government subsequently did not renew orders for adenovirus vector–based COVID-19 vaccines[9]; however, these vaccines continue to be used effectively in other countries, and this case report adds to the global body of knowledge on vaccine-related adverse events. Although some COVID-19 vaccines may increase the risk of thromboembolic disease,[10] COVID-19 infections carry a much higher risk of thromboembolism.[11]

Case

Mrs A., a 46-year-old civil servant, requested a same-day family physician telephone consultation. She complained of pain in her right lower leg lasting 3 days and described this pain as a burning sensation. She did not have any swelling, bruising, or rash in the lower leg. She also did not report any shortness of breath, chest pain, headache, or abdominal pain. She had no previous history of thromboembolic disease. The pain improved with ibuprofen and she believed her symptoms were the result of recent exercise. However, she mentioned that she had received the AstraZeneca vaccine 11 days prior to the consultation. After discussion, the family physician and Mrs A. decided on expectant management. Mrs A. was instructed to contact the clinic if she developed any new symptoms.

Mrs A. called back 72 hours later to report bruising on the dorsum of her right foot and tiny red spots over her lower leg. She described ongoing stiffness,

but no frank pain, in her lower right leg. She agreed to go for an assessment that evening at a community clinic. The evening examination revealed a 3-cm ecchymosis on her right foot and multiple nonblanchable red dots—petechiae—on both her lower legs. Both legs measured 25.5 cm in circumference at the calf and 10 cm above the medial malleolus, and there was no pain on dorsiflexion of the ankles. She had no headache, no chest pain, and no abdominal pain, and her leg stiffness was resolving. She was sent for outpatient bloodwork and was notified that this was likely an adverse effect related to the AstraZeneca vaccine and she would require close follow-up.

She saw her family physician 36 hours after the evening visit. The results of the bloodwork showed low platelet counts (35,000/µL; normal range 155,000/µL to 372,000/µL) with mild leukocytosis (12,600/µL; normal range 3200/µL to 9400/µL), mainly neutrophils. Her leg stiffness had resolved, but over the previous 24 hours she had developed new-onset left-sided chest pain that was worse on inspiration. The petechial rash had persisted. Her vital signs showed a tachycardia of 104 beats/min, blood pressure of 142/76 mm Hg, respiration rate of 16 breaths/min, temperature of 36.5°C, and oxygen saturation of 98%. Auscultation of her chest was clear. There was no headache or abdominal pain, but Mrs A. seemed anxious. She was sent to the emergency department (ED) for further assessment.

In the ED Mrs A. received an urgent computed tomography (CT) scan of her chest that documented a left lobar artery pulmonary embolus and secondary pulmonary hemorrhage, and her heparin-induced thrombotic thrombocytopenia enzyme-linked immunosorbent assay result was positive. She was started on the United Kingdom VITT protocol: intravenous immunoglobulin (1 dose), 1 mg/kg of prednisone, and argatroban[12]; she was transitioned to fondaparinux once her platelet count was above 100,000/µL. The CT venogram findings were negative for signs of cerebral venous sinus thrombosis. She was discharged with prescriptions for 50 mg of prednisone and 10 mg of oral apixaban twice daily for 1 week and then 5 mg of oral apixaban twice daily to complete 3 months of treatment. Hematology and primary care follow-up appointments were set for 1 week later, and Mrs A. was advised to seek urgent follow-up care for any headache or chest pain.

Discussion

This case illustrates the community evolution of a rare side effect of adenovirus vector–based COVID-19 vaccines. In summary, the patient received an AstraZeneca vaccine on day 0 and presented with a stiff lower limb on day 11, followed by a lower-extremity petechial rash on day 14 and pleural chest pain on day 16. Two community telephone consultations and 2 timely in-person consultations preceded the ED visit and hospital care. She was admitted to hospital with VITT syndrome and treated for a pulmonary embolism.

With an incidence of 1:60,000 in Canada, VITT represents a rare side effect of the adenovirus vector–based COVID-19 vaccines used here. Health Canada continues to collect reports of adverse events and recommends that patients with rare blood clots with unusual platelet counts do not receive a second dose of any version of these vaccines.[13] This case illustrates a diligent and timely community care approach with shared decision making. Vaccine-induced thrombotic thrombocytopenia is a newly recognized phenomenon in relation to the adenovirus vector–based vaccines, and knowledge regarding its recognition, investigation, and management is evolving. We have used the interim guidance put forward by the Ontario COVID-19 Science Advisory Table for the management of VITT in EDs and suggest its diagnostic algorithm (**Figure 1**)[5] would be helpful for primary care practitioners confronted with vaccine adverse event concerns.

Many family physicians shifted to providing care through virtual appointments during the COVID-19 pandemic. Telephone consultations have specific challenges—such as the lack of visual cues, which affects both the cognitive and affective nature of the patient narrative—and come with the inability to conduct a traditional physical examination. *Safety netting* is a recognized primary care strategy that may be used to reduce clinical risk in diagnostics in the face of limited data and uncertainty.[14] Safety netting involves ensuring patients with unresolved or worsening symptoms receive clear instructions on when and how to access follow-up care.[15]

Conclusion

Family physicians continue to provide care to patients presenting with a range of COVID-19 adverse effects. This case report illustrates some of the uncertainties encountered, the importance of safety netting, and the value of diagnostic guidance that could help front-line primary care providers. It is important to recognize that the use of telephone and virtual visits for primary care consultations, which expanded rapidly after the COVID-19 pandemic began, may affect the quality of data shared in doctor-patient interactions. Awareness of vaccine-related adverse effects, the use of video consultations, and the provision of clear instructions for follow-up care—safety netting—may improve community consultation outcomes.

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Competing interests
None declared

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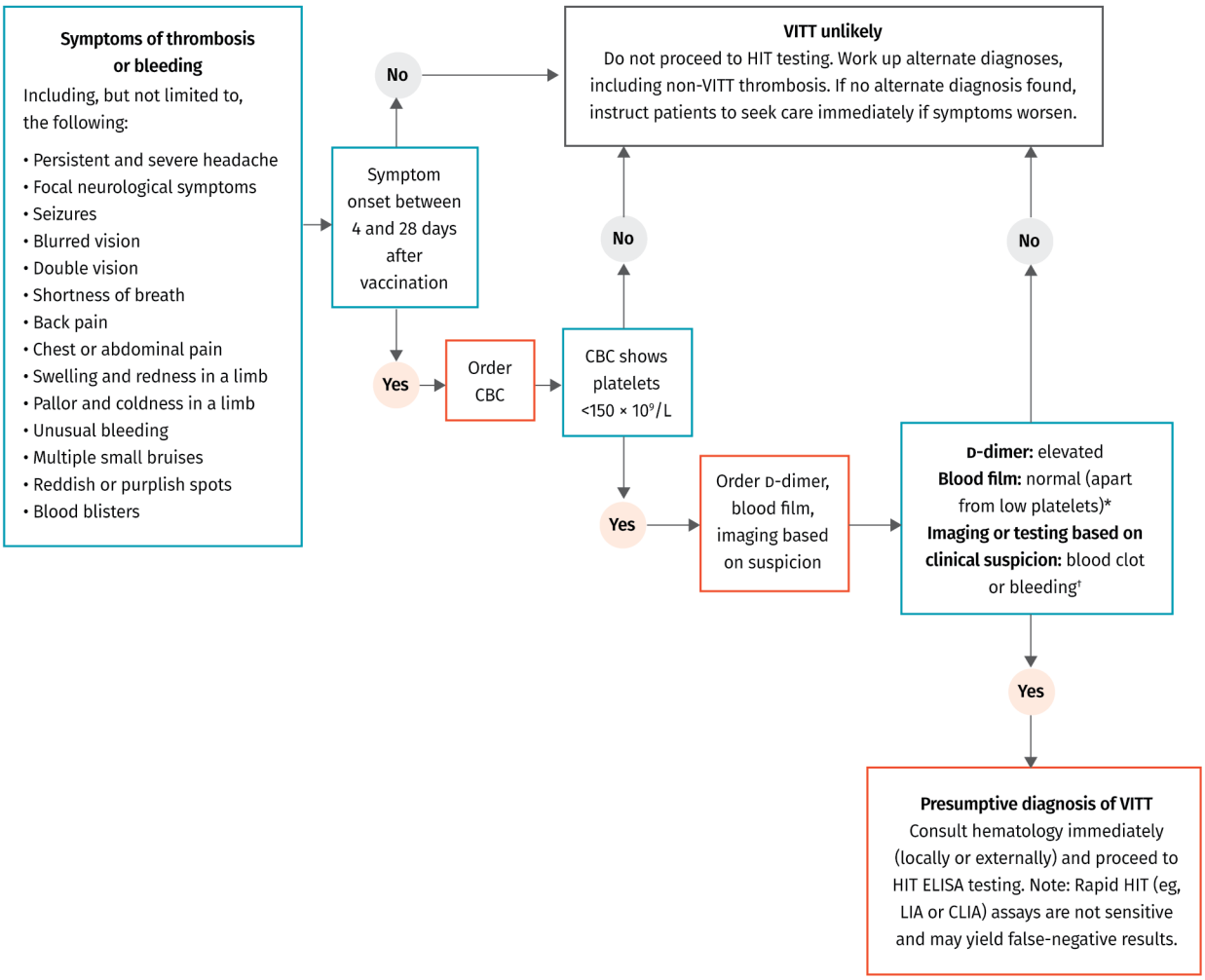
Figure 1. Decision-tree algorithm for diagnosing VITT



CBC—complete blood count, CLIA—chemiluminescent immunoassay, D-dimer—dimerized plasmin fragment D, ELISA—enzyme-linked immunosorbent assay, HIT—heparin-induced thrombocytopenia, LIA—latex immunoturbidometric assay, VITT—vaccine-induced thrombotic thrombocytopenia.

*Blood film to rule out platelet clumping as a cause of low platelet count.

†Not all cases of VITT initially present with a clot or bleeding. Patients with all of the features of presumptive VITT (low platelets, high D-dimer, presenting 4 to 28 days post-vaccination) but no blood clot or bleeding merit hematology consultation (locally or externally) to consider starting treatment until the results of confirmatory testing are available.

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