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CASE REPORT

Vaccine-induced immune thrombotic thrombocytopenia presenting with normal platelet count

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Abstract
Adenoviral-vector based vaccines for coronavirus disease 2019 (COVID-19) have been linked with a thrombotic syndrome, vaccine-induced thrombotic thrombocytopenia (VITT). A key clinical question is whether VITT can be reliably ruled out by the absence of thrombocytopenia. We report on three patients who presented to our institute with this syndrome. Noteworthy in our presentations are two patients who presented for medical assessment of thrombotic symptoms with a normal platelet count, one preceding and one following a period of thrombocytopenia. Prompt diagnosis of VITT is critical to prevent rapid patient decline. We provide herein a new diagnostic algorithm that we believe will help optimally capture case presentations of VITT. These cases broaden and refine our understanding of the disease process and highlight to practitioners that VITT cannot be adequately ruled out by thrombocytopenia alone.

KEYWORDS
COVID-19, diagnosis, thrombocytopenia, thrombosis, vaccines

1 | INTRODUCTION

Rapid development and distribution of safe, effective vaccines are critical for control of the coronavirus disease 2019 (COVID-19) pandemic. COVID-19 vaccine trials showed reassuring safety signals, and many received expedited approval.1,2 After widespread deployment, concerns emerged that the adenovirus-based vaccines ChAdOx1-nCov-19 and Ad26.COV2.S were associated with a syndrome of unusual thromboses, now known as vaccine-induced immune thrombotic thrombocytopenia (VITT).3-5 We report on three cases of VITT that highlight the clinical heterogeneity of this syndrome, in particular that thrombocytopenia alone cannot be used to rule out a diagnosis of VITT.
2 | METHODS

Written informed consent for publication was obtained from all patients. Institutional review board approval for this publication was not required. The authors vouch for the accuracy and completeness of the presented data.

The VITT testing pathway for the University of Alberta Hospital in Edmonton, Canada, includes two local assays for heparin-induced thrombocytopenia (HIT): an immunoturbidimetric rapid HIT assay (Instrumentation Laboratories, Bedford, MA) and an anti–platelet factor 4 (PF4) IgG antibody-based ELISA (Immucor GTI Diagnostics, Waukesha, WI, USA). Additional testing is then completed at the McMaster Platelet Immunology Laboratory in Hamilton, Canada, including confirmatory anti-PF4 antibody-based ELISA (IgG/IgM/IgA LIFECODES PF4 Enhanced assay; Immucor GTI Diagnostics) and a serotonin release assay (SRA) modified with PF4 enhancement. All patients in this report had VITT testing drawn when VITT was suspected and had positive anti-PF4 ELISA testing with confirmation of platelet-activating antibodies.

3 | CASE HISTORIES (Table S1)

3.1 | Patient 1

A woman in her 40s received her first dose of ChAdOx1-nCoV-19 vaccine on April 29, 2021 (day 0). On day 7, she presented to a community hospital with acute bifrontal headache, nausea, and transient aphasia, with a platelet count of 216 × 10^9/L and D-dimer 0.75 mg/L (fibrinogen-equivalent units [FEU]; normal range, <0.5 mg/L FEU). A diagnosis of migraine was made, and neuroimaging was not performed. On day 9, she returned to the community emergency department with worsening headache and diplopia, with a platelet count of 13 × 10^9/L and D-dimer >10.00 mg/L (FEU). Enhanced assay; Immucor GTI Diagnostics). Unenhanced computed tomography (CT) scan of the head suggested extensive cerebral venous sinus thrombosis (CVST). Following transfer to a tertiary center, a CT venogram confirmed CVST without intracranial hemorrhage. She was initiated on fondaparinux 10 mg daily and 2 days of intravenous immunoglobulin (IVIg) (1 g/kg, capped at 100 g for an actual body weight of 122 kg).

On day 10, her Glasgow Coma Scale score decreased, with signs of increased intracranial pressure and platelets 30 × 10^9/L. CT venogram revealed new subdural hematoma and progression of CVST. Subsequently, dexamethasone 40 mg daily for 4 days was initiated, followed by taper, and a third dose of IVIg at 50 g were given. Anticoagulation was switched to argatroban (activated partial thromboplastin time target, 70–80 seconds). The patient also underwent endovascular thrombus removal with partial extraction. Magnetic resonance imaging of the brain performed on day 13 showed bilateral arterial embolic events in watershed territory.

Thrombocytopenia began improving after the second IVIg dose and normalized by day 15. Fibrinogen activity fell to 0.9 g/L on day 13 without other clinical or laboratory evidence of disseminated intravascular coagulation; argatroban interference with the Clauss fibrinogen assay was suspected, and values normalized following a further 1:2 dilution. On day 17, she was switched to therapeutic apixaban. Figure 1A summarizes her course. She has had a near full neurological recovery to date.

3.2 | Patient 2

A woman in her 60s received her first dose of the ChAdOx1-nCoV-19 vaccine on April 23, 2021 (day 0). From days 7 to 11, she developed nausea, emesis, exertional dyspnea, dry cough, and myalgias followed by headache. On day 17, she presented to a community hospital with right calf swelling and pain and abdominal tenderness. Investigations revealed a platelet count of 37 × 10^9/L, D-dimer >10.00 mg/L (FEU), and deep vein thrombosis (DVT) on Doppler ultrasound (US). Enhanced chest CT confirmed pulmonary embolism (PE) and abdominal US showed right portal vein thrombosis. Following a 2-day course of IVIg 1 g/kg daily, and ongoing apixaban, her platelet count normalized within 2 days. She has no other known complications to date.

3.3 | Patient 3

A man in his 60s received his first dose of ChAdOx1-nCoV-19 vaccine on March 16, 2021 (day 0). On day 1, he underwent a transrectal prostate biopsy, complicated by Escherichia coli bacteremia requiring admission on days 3 to 6 and days 23 to 26. Due to gross hematuria, he did not receive thromboprophylaxis on his first
admission but received low-molecular-weight heparin prophylaxis during his second admission. Thrombocytopenia developed on day 3 and persisted beyond day 26. On day 25, he developed left leg discomfort, progressing to exertional tachycardia and dry cough as an outpatient. These symptoms were not endorsed to the attending team. On day 51, he presented to an emergency department (ED) for
progressive symptoms, and left leg US and enhanced chest CT confirmed DVT and PE, with a normal platelet count (286 × 10^9/L). He was anticoagulated with a single-dose of tinzaparin and thereafter rivaroxaban. He did not receive IVIg or corticosteroids. He has since improved to near baseline. Concern for potential VITT was raised only after a referral was received at a tertiary care center. This patient’s clinical course is described in Figure 1B.

4 | DISCUSSION

VITT is a newly described disease process wherein an immune response to adenoviral vector-based vaccination against COVID-19 results in thrombocytopenia and thrombosis. Early recognition of the resemblance to autoimmune HIT, including the presence of anti-PF4 platelet-activating antibodies, has been integral to rapidly developing diagnostic and treatment algorithms. The full scope of VITT is not yet understood, and while similarities exist between VITT and autoimmune HIT, the extent to which these entities overlap is unknown. The cases we presented highlight novel features concerning the diagnosis of VITT, pertinently, that a normal platelet count on presentation cannot be used to safely rule out VITT.

This case series illustrates deviations from existing algorithms. To our knowledge, we report the first two cases of VITT where platelet count was normal at first presentation for thrombotic symptoms. Unfortunately, initial overreliance on the presence of thrombocytopenia at thrombotic presentation led to delayed recognition and neuroimaging for patient 1. Maintaining a strong index of suspicion may have resulted in prompt recognition and treatment before severe thrombocytopenia and progressive symptoms developed. Patient 3 was diagnosed with VITT on day 59, well beyond the expected window; however, his symptoms of DVT and PE started on day 25. His platelets had remarkably normalized at the time of his presentation, while severe thrombocytopenia and progressive symptoms developed. This case illustrates the importance of remaining vigilant for VITT, as patients may present for care in a delayed fashion.

CVST complicated by intracerebral hemorrhage is the most serious presentation of VITT and associated with excessive mortality. Emergent care is needed for those presenting with suggestive symptoms after receiving an adenoviral vector COVID-19 vaccine, with deleterious outcomes after a delayed diagnosis. Prior case series illustrate the potential for VITT-associated CVST to be aggressive and rapidly fatal. Case 1 demonstrates that even if these patients survive, they tend to have a more protracted course of recovery, with slower platelet rise and requirement of multiple lines of therapy (eg, additional doses of IVIg, steroid therapy, and in refractory cases possibly plasmapheresis). On the other end of the spectrum, cases presenting without CVST appear to have a better clinical course. However, it is important to note that patients with VITT-associated DVT may still have a more aggressive course than typical DVT. Both of our patients with DVT also presented with symptomatic PE, and one additionally had a portal vein thrombosis. All presentations suggestive of VITT should be taken seriously.

Patients who present outside of the expected time frame for VITT still require scrutiny. Case 3 best highlights this, although this case was not straightforward. The patient presented to an ED with DVT and PE over 50 days from his vaccine dose with a normal platelet count. In retrospect, these symptoms began on day 25 during a period of thrombocytopenia. While consumption and marrow suppression likely contributed to the initial onset of thrombocytopenia, the persistence despite multiple lines of broad-spectrum antibiotics beyond day 26 suggest an alternative mechanism of thrombocytopenia. Both the onset of platelet decline and platelet nadir are not in keeping with drug-induced thrombocytopenia. The pattern of testing is consistent with VITT, with negative immunoturbidimetric HIT assay, positive ELISA, and SRA confirming platelet-activating anti-PF4 antibodies. A recent study demonstrated anti-PF4 antibodies following ChAdOx-nCoV-19 are not uncommon, but these antibodies were nonactivating. The platelet-activating nature of patient 3’s antibodies suggest they are not bystanders and are directly involved in disease pathobiology. Speaking against classical HIT is the negative immunoturbidimetric assay, platelet decline preceding heparin exposure, and lack of platelet decline or worsening thrombosis following exposure to the single dose of the inciting low-molecular-weight heparin (LMWH) on presentation to the ED, still within 30 days of receipt of original doses of LMWH (Figure 1B). This case highlights that receipt of an adenoviral vector vaccine should increase the pretest probability of thrombosis during assessment for patients presenting with thrombotic symptoms and/or thrombocytopenia.

It is important to identify these “late presenters” as the subsequent clinical course may differ from those with other thromboses. Extrapolating from what we know about HIT, antibodies may persist for many weeks after vaccine exposure. In the short term, this is relevant for any patient who may be considering a second dose of a viral vector vaccine. Second, it is unknown what the risk of relapse thrombocytopenia and recurrent thrombosis following VITT may be, and close follow-up of patients with known antibodies is important. While HIT does not appear to be associated with long-term antibody production or an anamnestic response, we do not yet have long enough follow-up for patients with VITT to know if the pattern is the same.

Validated DVT and PE diagnostic algorithms established the sequence of testing based on pretest probability. A high pretest probability should always lead to diagnostic imaging. In addition, if the pretest probability is high and initial testing negative, serial testing and follow-up is recommended. In many suggested VITT algorithms, normal platelet count precludes VITT. Our cases highlight that, at the present time, VITT should not be excluded solely on the platelet count. The existing algorithms do not yet have branching pathways on how to follow patients with suspected VITT who do not meet the criteria of thrombocytopenia and thrombosis at symptom presentation. This may lead to missed diagnoses and significant consequences. On the other hand, an algorithm is necessary to prevent overtreating patients with nonspecific presentations. We suggest an updated diagnostic algorithm that is optimized to enhance detection of VITT cases (Figure 2).
We presented three different cases of VITT ranging from patients with a rapid response to treatment and excellent recovery, to patients with long and complicated clinical courses. VITT is a heterogeneous disease. Diagnosis requires a high index of suspicion, prompt investigation, and initiation of VITT specific treatment. In patients with a high clinical suspicion of the disease, close follow-up, serial laboratory monitoring, and potentially specialized VITT testing are important even if initial laboratory testing is normal or the presentation is late or the clinical course mild. Many questions around this newly discovered disease remain unanswered. Clinicians should continue to report their cases so we can refine our diagnostic and treatment algorithms for VITT.

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AUTHOR CONTRIBUTIONS
DP wrote the first draft of this manuscript and constructed initial figures and supplementary table. ET participated in laboratory analysis and troubleshooting in these cases. All authors made significant intellectual contributions to this article, including revisions to the manuscripts, direct input into the algorithm design, and overall direction of the manuscript messaging on important clinical pearls delivered by these cases.
RELATIONSHIP DISCLOSURE
The authors declare no conflicts of interest or funding sources that interfere with unbiased assessment of these cases.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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