Thrombocytopenia in the Time of COVID-19: A Case-Based Discussion of Immune Thrombocytopenia (ITP) versus Vaccine-Induced Thrombotic Thrombocytopenia (VITT)

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Abstract
The COVID-19 infection and associated treatments, including vaccination, can lead to a multitude of hematologic complications. Both vaccine-induced thrombotic thrombocytopenia (VITT) and immune thrombocytopenia (ITP) are possible causes of thrombocytopenia following an adenoviral vector vaccine. While ITP and VITT share many similarities, they have distinct differences and require specialized treatment. Therefore it is critically important to accurately distinguish between these two vaccine-induced disorders. We report a patient who presented with ITP approximately after 1 week of COVID-19 positive diagnosis and 3 weeks after the first dose of AstraZeneca vaccine.

Keywords: Immune thrombocytopenia (ITP); Vaccine Induced Thrombotic Thrombocytopenia (VITT); COVID-19

Résumé
L’infection à la COVID-19 et les traitements qui lui sont associés, dont la vaccination, peuvent entraîner une multitude de complications hématologiques. La thrombocytopenie thrombotique induite par le vaccin (TTIV) et la thrombocytopenie immunitaire (TI) sont deux causes de thrombocytopenie qui peuvent apparaître après avoir reçu un vaccin à vecteur adénoviral. Bien que la TI et la TTIV présentent de nombreuses similitudes, elles ont des différences marquées et exigent un traitement spécialisé. Il est donc d’une importance cruciale de les distinguer avec exactitude. Dans cet article, nous rapportons le cas d’un patient qui a présenté une TI environ une semaine après avoir reçu un diagnostic de la COVID-19 et trois semaines après avoir reçu une première dose du vaccin d’AstraZeneca.

Keywords: Immune thrombocytopenia (ITP); Vaccine Induced Thrombotic Thrombocytopenia (VITT); COVID-19
Thrombocytopenia Following an Adenoviral Vector COVID-19 Vaccine

Introduction

Primary immune thrombocytopenia (ITP) is an autoimmune disorder characterized by reduced platelet counts (<100 × 10⁹/L) and increased bleeding risk in the absence of other causes associated with thrombocytopenia.¹ Since its emergence, the COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), has affected over 21 million people worldwide. Acute respiratory distress syndrome (ARDS), cardiac complications, and thromboembolic events have contributed to the majority of COVID-19 mortality.² Among hematological complications, cases of ITP have been reported.³ Beginning in the late February 2021, a prothrombotic syndrome with thrombocytopenia, termed as vaccine-induced thrombotic thrombocytopenia (VITT), was observed in a small number of individuals who had received the ChAdOx1 CoV-19 vaccine (AstraZeneca, University of Oxford, and Serum Institute of India)⁴⁻⁷ as well as the Ad26.COVID2.S vaccine (Johnson & Johnson/Janssen),⁸,⁹ both adenoviral vector-based vaccines. Moreover, COVID-19 vaccination-induced ITP was described as well.¹⁰,¹¹ While ITP and VITT share many similarities, they have distinct differences and require specialized treatment. Hence, it is critically important to accurately distinguish between these two disorders.

We report a patient who presented with ITP approximately after 1 week of COVID-19 positive diagnosis and 3 weeks after having the first dose of the AstraZeneca vaccine.

Case Description

A 61-year-old female previously healthy, except for dyslipidemia, presented with a 1-day history of epistaxis, petechial rashes on the hands with bruising and blood blisters in the mouth and lips. She was taking atorvastatin and aspirin for primary prevention without any recent changes in her medication. On presentation, she also reported mild headache. This was 22 days after having the AstraZeneca COVID-19 vaccine and 7 days after the COVID-19 positive diagnosis; her COVID-19 symptoms were mild and did not require medical assessment. At the time of presentation at hospital, she denied having any calf tenderness or swelling, chest pain, dyspnea or pleuritic pain, abdominal pain, or gastrointestinal bleeding. In the emergency department, she was observed having excess bleeding from intravenous lines.

Laboratory investigations at admission were notable for severe thrombocytopenia (platelet count: 0 × 10⁹/L with normal hemoglobin and leukocyte count; fibrinogen of 5.18 g/L [normal range: 1.50–4.20 g/L]; D-dimer of 0.6 mg/fibrinogen equivalent units [normal value: <0.5 mg/fibrinogen equivalent units], and an international normalized ratio (INR) of 1 [normal range: 0.9–1.1]) with a normal blood film morphology and negative blood cultures (Figure 1). Other possible causes of thrombocytopenia, including antiphospholipid syndrome, thrombotic microangiopathy, hepatitis

Figure 1. Patient’s platelet count at presentation until discharge relative to time of administration of vaccine and the COVID-19 diagnosis.
B virus, hepatitis C virus, and human immunodeficiency virus (HIV), were excluded. A computed tomography (CT) of the head did not reveal any intracranial abnormalities, and her headache resolved completely. Abdominal ultrasound demonstrated no evidence of splanchnic vein thrombosis or splenomegaly. Of note, based on available published research at that time, the clinical presentation felt to be a low probability for VITT. As such, a heparin induced thrombocytopenia (HIT) ELISA assay was not sent.

A presumptive diagnosis of ITP was made. It remained unclear whether ITP was idiopathic or secondary to one or both vaccination and the COVID-19 infection. The patient was successfully treated with a combination of dexamethasone 40 mg daily for 4 days and 2 doses of intravenous immune globulin (IVIG) 1-g/kg body weight (on day 0 and 1). Her platelet counts normalized (Figure 1) with complete remission in her bleeding symptoms. Patient was checked for regular hematology follow-up following discharge. She continued in remission for over 12 months from presentation with a normal platelet count. The patient was offered subsequent messenger RNA (mRNA) COVID-19 vaccination; however, after reviewing the risks and benefits, she ultimately decided against it.

Discussion

Immune thrombocytopenia is an autoimmune disorder that involves autoimmune destruction of platelets of the body, resulting in thrombocytopenia. There is a wide clinical spectrum ranging from no or mild bleeding to life-threatening hemorrhage in severe cases. VITT is an immune-mediated process through platelet-activating antibodies against platelet factor 4 (PF4). It refers to a constellation of thrombocytopenia and thrombosis, with a predilection for cerebral venous and splanchnic circulation as well as pulmonary embolism.12 According to published case reports, this newly described syndrome is associated with markedly elevated D-dimer in almost all patients and low fibrinogen in more than 50% of patients.4–6

Vaccine-induced immune thrombotic thrombocytopenia has been reported following administration of adenoviral vector vaccines, namely the ChAdOx1 CoV-19 vaccine (AstraZeneca, University of Oxford, and Serum Institute of India)4–6 as well as the Ad26.COV2.S vaccine (Johnson & Johnson/Janssen).8,9 Recognizing VITT and identifying it from other causes of thrombocytopenia is particularly relevant at the present time as the Canadian government recently obtained thousands of doses of the Ad26.COV2.S vaccine following requests from several provinces, including Alberta Saskatchewan, British Columbia, and Ontario.13–15 The objective is to provide vaccines to patients who either have contraindications to mRNA vaccines, or to unvaccinated individuals who prefer adenoviral vector over mRNA vaccines. Moreover, globally, VITT has been a pertinent issue. The COVID-19 Vaccines Global Access (COVAX) is a global initiative with the goal of ensuring equitable access to the COVID-19 vaccines worldwide and facilitating donations of the COVID-19 vaccines to low-income countries. Adenoviral vector vaccines remains a key product distributed by COVAX, with 40 million doses of the ChAdOx1 CoV-19 vaccine sourced from the Serum Institute of India and allocated to various countries in November 2021. The United Kingdom has also committed to donating millions of doses of both ChAdOx1 CoV-19 and Ad26.COV2.S vaccines in 2022.16,17

Differentiating between ITP and VITT is critical due to significant differences in their pathophysiology and management. In our patient, given that she presented with severe thrombocytopenia 22 days after vaccination, the question of possible VITT was elicited, which has been described to occur within 30 days of receiving the COVID-19 vaccination.18 However, we felt her presentation was more in keeping with ITP, rather than VITT, for the following reasons: First, her primary complaint at presentation was mucocutaneous bleeding, which is typical in ITP; however, in published case series, it is not a common VITT feature. Of the reported more than 40 patients in case series, only one patient presented with significant bruising, and no other reported mucocutaneous bleeding such as epistaxis or wet purpura.4–6,17 Otherwise, all other reports concerning bleeding in VITT have been secondary to thrombotic complications. This included gastrointestinal bleeding secondary to splanchnic vein thrombosis, adrenal hemorrhage, and intracranial hemorrhage with concomitant cerebral venous sinus thrombosis.

Second, our patient on examination revealed no physical features or history of venous or arterial thrombosis. She reported a mild headache, for which brain was conducted. She also reported contrast allergy; hence, we were unable to perform CT venography. However, CT brain revealed no evidence of hemorrhage or infarction. Furthermore, she had no other clinical manifestations of cerebral venous sinus thrombosis (CVST), and her headache quickly resolved; therefore, diagnosis of CVST was excluded. Except for only one patient in the UK case series
who had no thrombotic events (diagnosis in this patient was made based on thrombocytopenia, high D-dimer, and positive PF4 immunoglobulin G [IgG] assay), nearly all other VITT patients had reported significant thrombotic events. Thus, the absence of thrombotic features favoured ITP over VITT.

Finally, in our patient, the D-dimer was marginally elevated, just by 1.2 times the upper limit of normal. In almost all the reported VITT patients, D-dimer was markedly elevated. In the UK series, for 21 patients with available D-dimer values, all patients had values greater than nine times the upper limit of normal. According to the VITT guidance statement published by the International Society of Thrombosis and Hemostasis (ISTH), D-dimer levels more than four times the threshold of VTE exclusion are highly suggestive of VITT. Our patient had normal INR and fibrinogen values. Although more variability has been observed concerning these values in the published data, fibrinogen was stated to be low in 57% of UK cases.

The diagnosis of VITT is considered confirmed by a positive PF4 ELISA in the appropriate clinical context of thrombosis, thrombocytopenia, and elevated D-dimer within 30 days of post-COVID-19 vaccines. Presence of thrombocytopenia without thrombosis, normal or near-normal D-dimer value, and normal fibrinogen led us to classify our patient as having low clinical probability for VITT. At the time this patient presented at hospital, optimal diagnostic pathways for VITT were not established. Extrapolating from HIT in which ELISA is not recommended for patients with low clinical probability because of risk of false positives, after careful discussion we decided against recommending HIT ELISA.

Regarding management, although the two entities share some similarities, namely use of immunomodulatory therapies, including IVIG, the most important divergent feature in management is initiation of anticoagulation. Based on the current comprehension, the pathophysiological basis of VITT is production of autoantibodies to PF4 provoked by adenoviral vector vaccines. PF4-antibody immune complexes bind to FcγIIa receptors found on platelets, which subsequently activate platelets, resulting in thrombophilia (prothrombotic state). Thus, speedy diagnosis of the disease and initiation of non-heparin anticoagulation is a mainstay of treatment. In contrast, ITP patients are at risk of bleeding, and initiation of anticoagulation in a severely thrombocytopenic ITP patient would be expected to further increase this risk and may result in adverse bleeding consequences.

Another key difference in the management of these two disorders is safety of platelet transfusion. In VITT, platelet transfusion may worsen the clinical condition, probably because of provision of more PF4, which can form immune complexes with the culprit antibody and result in further activation of platelets. In the largest case series to date from the United Kingdom, platelet transfusion was observed to be associated with progression of thrombosis. In a case series consisting of five VITT patients from Norway, 75% mortality rate was reported of the four patients who received platelet transfusion. Thus, interim guidance from ISTH among other groups has suggested avoidance of platelet transfusion in VITT patients. In contrast, platelet transfusion is considered safe in ITP patients. Although platelet transfusion may not be effective at raising platelet count, it can be used in severe or life-threatening bleeds with some reported success in hemostasis, generally in combination with other therapies.

**Conclusion**

In summary, both VITT and ITP are possible causes of thrombocytopenia following an adenoviral vector vaccine (Table 1). Presently, distinguishing between the two syndromes is particularly relevant, as Canadian government has recently distributed thousands of doses of the Ad26. COV2.S vaccine to different provinces and, moreover, adenoviral vector vaccines have been used globally. Both VITT and ITP are potentially life-threatening disorders, which require prompt recognition and treatment. Differentiating between the two is important, as anticoagulation is a cornerstone of treatment in the former but potentially dangerous in the latter. Additionally, platelet transfusion must be avoided in VITT, although could be administered safely in severe bleeding in ITP. As this is a pressing matter for clinicians working in locales where adenoviral vaccines are being administered, we wanted to share our experience and rationale in diagnosing our patient who presented with severe thrombocytopenia post-vaccine with ITP, rather than VITT. Absence of thrombotic manifestations, predominance of mucocutaneous bleeding, and near-normal D-dimer level, all ascertained on the first day of presentation, pointed toward ITP. We successfully restored her platelet count and bleeding with standard ITP treatment and did not give anticoagulation. The above-mentioned features could be used by clinicians as indications to reach proper diagnosis.
Table 1. Differences between ITP and VITT

<table>
<thead>
<tr>
<th></th>
<th>ITP</th>
<th>VITT</th>
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</thead>
<tbody>
<tr>
<td>Pathophysiology</td>
<td>The pathophysiology of ITP is multifactorial and includes: production of autoantibodies directed against glycoproteins on the platelet surface membrane resulting in peripheral platelet destruction and/or decreased production, T-cell-mediated platelet destruction, and platelet desialylation.(^2)</td>
<td>Production of autoantibodies to PF4. PF4-antibody immune complexes bind to FcγIIa receptors on platelet surface, which subsequently activates platelets and results in thrombophilia (prothrombotic state).</td>
</tr>
<tr>
<td>Primary clinical</td>
<td>Bleeding</td>
<td>Thrombosis +/- bleeding</td>
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<tr>
<td>presentation</td>
<td></td>
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<tr>
<td>Causes</td>
<td>Primary or secondary (medications, systemic diseases, systemic lupus erythematosus [SLE], vaccinations, chronic lymphocytic leukemia [CLL], viral infection; hepatitis B/C, helicobacter pylori or COVID-19 infection)</td>
<td>Provoked by adenovirus vector COVID-19 vaccines, including the AstraZeneca/COVISHIELD and Johnson &amp; Johnson/Janssen COVID-19 vaccines.</td>
</tr>
<tr>
<td>Blood works:</td>
<td></td>
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<tr>
<td>Platelet count</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Blood film</td>
<td>Isolated thrombocytopenia +/- enlarged platelets</td>
<td>Isolated thrombocytopenia</td>
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<tr>
<td>D-dimer</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Normal</td>
<td>Low in 50% of patients</td>
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<tr>
<td>HIT ELISA</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Management:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVIG(^*)</td>
<td>First line of treatment</td>
<td>First line of treatment</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>First line of treatment</td>
<td>Safe to use if indicated</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>Safe to use if indicated</td>
<td>May worsen the clinical condition</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Contraindicated</td>
<td>First line of treatment (non-heparin)</td>
</tr>
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Note: “Not all patients require IVIG for treatment of ITP. Potential indications include requirement to rapidly increase platelet count (in case of life-threatening bleeding) or intolerance to corticosteroids.

Disclosures

The authors have no funding resources and no commercial or non-commercial affiliations that may be perceived as a conflict of interest.

References


