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Thrombosis with thrombocytopenia syndrome associated with COVID-19 vaccines

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ABSTRACT

Background: Current vaccines for the Coronavirus Disease of 2019 (COVID-19) have demonstrated efficacy with low risk of adverse events. However, recent reports of thrombosis with thrombocytopenia syndrome (TTS) associated with adenovirus vector vaccines have raised concern.

Objective: This narrative review summarizes the current background, evaluation, and management of TTS for emergency clinicians.

Discussion: TTS, also known as vaccine-induced immune thrombotic thrombocytopenia, is a reaction associated with exposure to the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) and AD26.COV2-S (Johnson & Johnson) vaccine, which may result in thrombocytopenia and thrombotic events. There are several case series of patients diagnosed with TTS, but the overall incidence is rare. TTS is characterized by exposure to one of the aforementioned vaccines 4–30 days prior to presentation, followed by thrombosis, mild-to-severe thrombocytopenia, and a positive platelet factor-4 (PF4)-heparin enzyme-linked immunosorbent assay (ELISA). Thrombosis typically involves atypical locations, including cerebral venous thrombosis and splanchic vein thrombosis. Evaluation should include complete blood count, peripheral smear, D-dimer, fibrinogen, coagulation panel, renal and liver function, and electrolytes, as well as PF4-heparin ELISA if available. Consultation with hematology is recommended if suspected or confirmed. Treatment may include intravenous immunoglobulin and anticoagulation, while avoiding heparin-based agents and platelet transfusion.

Conclusions: With increasing vaccine distribution, it is essential for emergency clinicians to be aware of the evaluation and management of this condition.

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1. Introduction

In response to the Coronavirus Disease of 2019 (COVID-19) pandemic, multiple vaccines have been developed and distributed worldwide [1-3]. Initial trials reported rare cases of anaphylaxis and low rates of serious adverse effects [4]. More recent reports describe cases of thrombosis with thrombocytopenia syndrome (TTS), previously known as vaccine-induced immune thrombotic thrombocytopenia (VITT), associated with venous and arterial thromboembolism [5-12].

The two primary vaccines associated with TTS currently include the ChAdOx1 nCoV-19 (Oxford-AstraZeneca [AZ]; also known as Vaxzevria) and AD26.COV2-S (Johnson & Johnson [J&J]) vaccines [7-21]. The ChAdOx1 nCoV-19 and AD26.COV2-S vaccines consist of recombinant adenovirus vectors from a chimpanzee adenovirus or human adenovirus, respectively, which encode a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein [11,12,14]. On March 14, 2021, several European countries halted administration of the ChAdOx1 nCoV-19 vaccine due to potential safety concerns, including thrombocytopenia and thrombosis [7,11,15]. As of April 4, 2021, 169 cases of cerebral venous thrombosis (CVT) and 53 cases of splanchic vein thrombosis associated with TTS were found from approximately 34 million ChAdOx1 nCoV-19 vaccine administrations in the European Union [11,15]. On April 13, 2021, the United States Food and Drug Administration and the Centers for Disease Control and Prevention (CDC) recommended pausing administrations of the AD26.COV2-S vaccine due to concern of TTS [7,11,16-18]. There were 15 reported cases of thrombosis from over 6.8 million doses of the AD26.COV2-S vaccine administered at that time [11,16-18]. In the United Kingdom as of April 14, there were 77 cases of TTS associated with CVT and 91 cases of TTS associated with thrombosis in other veins with 32 deaths, from over 21.2 million doses administered of the ChAdOx1 nCoV-19 vaccine [7,11,15,19]. As of May 16, 2021, there have been no cases of TTS associated with the mRNA-based vaccines from Moderna or Pfizer-BioNTech [11,12,15,18]. Importantly, the CDC and European Medicines Agency state the overall benefits of the ChAdOx1 nCoV-19 and AD26.COV2-S vaccines outweigh
risks of side effects including TTS, with less than 1 case of TTS per 100,000–250,000 vaccinated adults [11,12,15,18]. On April 23, 2021, the Advisory Committee on Immunization Practices recommended continued use of the ChAdOx1 nCoV-19 and AD26.COV2-S vaccines for those aged ≥18 years [11-13,15-21].

Three independent case series of 39 patients were initially described in the New England Journal of Medicine associated with the ChAdOx1 nCoV-19 vaccine (Table 1) [7-10]. These patients had received the vaccine 5–24 days prior to presentation [7-10]. Over 80% of patients in the reports were female, with those <55 years also more commonly affected. Table 2 summarizes the TTS cases associated with both vaccines [7-10]. Patients were healthy or otherwise medically stable at the time of the vaccine, and few had prior thrombosis or risk factors for thrombosis. While these patients were overall healthy at the time of vaccination, mortality rates for TTS were approximately 40% [7-10]. Thus, TTS is an important complication that is critical for emergency physicians to consider.

2. Methods

The objective of this narrative review is to summarize the pathophysiology, evaluation, and management of TTS for emergency clinicians. To complete this narrative review, authors searched PubMed, Google Scholar, and Google for articles and resources using the keywords “thrombosis with thrombocytopenia syndrome” OR “vaccine-induced immune thrombotic thrombocytopenia” OR “thrombotic AND “thrombocytopenia” from database inception to May 16, 2021. The literature search was restricted to studies published in English. Authors reviewed all relevant resources and decided which resources to include for the review by consensus. A total of 45 resources were discovered on literature search, and 25 resources were selected for inclusion in this narrative review. Most resources included were case reports, case series, expert guidelines, or consensus statements, with the evidence quality limited by the lack of prospective data. As this is a narrative review, authors did not pool data.

3. Discussion

3.1. Pathophysiology

While the pathophysiology is not completely understood, the likely mechanism of TTS includes the formation of antibodies that act against platelet antigens. In turn, this triggers massive platelet activation, aggregation, and consumption, which reduces platelet count and results in thrombosis, similar to heparin-induced thrombocytopenia (HIT) [4,7,11,12,14,18]. HIT results from platelet activation and consumption against heparin-platelet complex, typically within 5–14 days of exposure to heparin [4,11,12,14,18,22]. TTS differs from HIT in that platelet activation, aggregation, and consumption is not dependent on exposure to heparin and less sensitive to inhibition with high-dose heparin [4,11,12,14]. TTS likely includes immune complexes with mixtures of antibody specificities resembling that of autoimmune HIT, which is not associated with heparin exposure [4,11,12,14]. In patients with TTS, thrombosis involves atypical locations, including CVT, as well as mesenteric vein thrombosis in the hepatic, portal, or splenic veins [7-12,18].

3.2. ED evaluation

TTS is characterized by exposure to the ChAdOx1 nCoV-19 or AD26.COV2-S vaccine 4–30 days prior to presentation, followed by arterial or venous thrombosis, mild-to-severe thrombocytopenia (<150 × 10⁹/L), and a positive platelet factor-4 (PF4)-heparin enzyme-linked immunosorbent assay (ELISA) [11,12,14,20,21]. Common post-vaccination symptoms include systemic symptoms such as fever, myalgias, fatigue, and headache, often in the first 24–48 h [11,12]. These do not suggest TTS, but rather a normal immune response. TTS should be suspected in those with severe, persistent (lasting over 3 days), or recurrent headache, abdominal pain, vomiting, dyspnea, chest pain, leg pain, or leg swelling which are present 4–30 days after receiving either the ChAdOx1 nCoV-19 or AD26.COV2-S vaccine [11,12,20,21]. As of April 2021, it is thought that patients with history of thrombosis or known thrombophilia do not have an increased risk of developing TTS after receiving the ChAdOx1 nCoV-19 or AD26.COV2-S vaccine [11,12,20,21].

The initial recommended evaluation for TTS includes complete blood count (CBC), peripheral smear, D-dimer, fibrinogen, coagulation panel, and PF4-heparin ELISA (if available) (Table 3) [11,12,18,20,21]. Non-ELISA tests are not recommended [11,12]. Thus far in reported cases, almost all patients have demonstrated high levels of PF4-heparin ELISA levels, with a low platelet count (median platelet count

### Table 1

| Consideration | Schultz et al. | Scully et al. | Greinacher et al. |
|---------------|----------------|--------------|------------------|
| Design        | Cases in Norway after vaccine | Cases in the UK after vaccine | Cases in Germany and Austria after vaccine |
| Population    | 5 patients (4 female); age range 32–54 years; 3/5 on hormone treatment | 23 patients (14 female); age range 21–77 years (16 patients younger than 50 years) | 11 patients (9 female); age range 22–49 years |
| Presentation  | Onset 7–10 days after vaccine; CVT in 5 and multiple sites in 1; platelets 10–70 × 10⁹/L; all with antibodies to PF4; no heparin exposure | Onset 6–24 days after vaccine; CVT in 13, PE in 4, DVT and adrenal hemorrhage in 1, ischemic stroke in 2, portal vein thrombosis in 2; platelets 11–113 × 10⁹/L; 23 with antibodies to PF4 | Onset 5–16 days after vaccine; CVT in 9, splenic vein thrombosis in 3, PE in 3, other thromboses in 4; platelets 8–107 × 10⁹/L; all with antibodies to PF4; no heparin exposure |
| Outcome       | 3 deaths, 2 full recoveries | 7 deaths; 16 alive | 6 deaths; 4 recovering; 1 unknown |

CVT, cerebral venous thrombosis; DVT, deep venous thrombosis; PE, pulmonary embolism; PF4, platelet factor-4.

### Table 2

Comparison of TTS with ChAdOx1 nCoV-19 vaccine and AD26.COV2-S vaccine [11].

| Characteristic | ChAdOx1 nCoV-19 vaccine cases | AD26.COV2-S vaccine cases |
|---------------|-------------------------------|---------------------------|
| Total cases   | 246 CVT; 150 other locations | 12 CVT; 11 other locations |
| Age           | 21–77 years                   | 18–59 years               |
| Gender        | 2.5:1                         | 15:0                      |
| Symptoms      | Headache, backache, abdominal pain, visual disturbance, leg/arm weakness | Headache, lethargy, back pain, abdominal pain, neurologic symptoms |
| Thrombosis    | Cerebral veins, splanchic veins, DVT/PE, arterial thrombosis | Cerebral veins, splanchic veins |
| Platelet nadir | Positive                      | Positive                  |
| Platelet factor | Positive                     | Positive                  |
| 4-heparin assay | Positive                     | Positive                  |

CVT, cerebral venous thrombosis; DVT, deep venous thrombosis; PE, pulmonary embolism.

### Table 3

Published case series of TTS with the ChAdOx1 nCoV-19 vaccine [7-10].

| Study          | Cases in Norway after vaccine | Cases in the UK after vaccine | Cases in Germany and Austria after vaccine |
|---------------|-------------------------------|-----------------------------|---------------------------------------------|
| Schultz et al. | 5 patients (4 female); age range 32–54 years; 3/5 on hormone treatment | 23 patients (14 female); age range 21–77 years (16 patients younger than 50 years) | 11 patients (9 female); age range 22–49 years |
| Scully et al.  | Onset 7–10 days after vaccine; CVT in 5 and multiple sites in 1; platelets 10–70 × 10⁹/L; all with antibodies to PF4; no heparin exposure | Onset 6–24 days after vaccine; CVT in 13, PE in 4, DVT and adrenal hemorrhage in 1, ischemic stroke in 2, portal vein thrombosis in 2; platelets 11–113 × 10⁹/L; 23 with antibodies to PF4 | Onset 5–16 days after vaccine; CVT in 9, splenic vein thrombosis in 3, PE in 3, other thromboses in 4; platelets 8–107 × 10⁹/L; all with antibodies to PF4; no heparin exposure |
| Greinacher et al. | Onset 7–10 days after vaccine; CVT in 5 and multiple sites in 1; platelets 10–70 × 10⁹/L; all with antibodies to PF4; no heparin exposure | Onset 6–24 days after vaccine; CVT in 13, PE in 4, DVT and adrenal hemorrhage in 1, ischemic stroke in 2, portal vein thrombosis in 2; platelets 11–113 × 10⁹/L; 23 with antibodies to PF4 | Onset 5–16 days after vaccine; CVT in 9, splenic vein thrombosis in 3, PE in 3, other thromboses in 4; platelets 8–107 × 10⁹/L; all with antibodies to PF4; no heparin exposure |
20–30 × 10^9/L [7–12,18,21]. Fibrinogen levels are typically decreased while D-dimer levels are elevated [11,12]. Red blood cell fragmentation and hemolysis have occurred in at least one case, though these findings are rare in TTS [12,23]. The PF4-heparin ELISA may not return while the patient is in the ED. Thus, TTS should be presumed in patients with exposure to one of the aforementioned vaccines who have a concerning history and examination, thrombocytopenia, and an elevated D-dimer or low fibrinogen, rather than waiting for the results of PF4-heparin ELISA [11,12,20,21].

Imaging should be based on the patient’s presentation and physical examination. Patients with abdominal symptoms should receive computed tomography (CT) with intravenous (IV) contrast, while those with concern for cerebral venous thrombosis should undergo CT venography or magnetic resonance venography [11,12].

3.3. ED management

As this is a newly described condition, current treatment recommendations are based on similar conditions including autoimmune HIT [11,12,20,21]. Consultation with hematology is recommended if TTS is suspected [11,12,20,21]. Current recommendations state treatment should be initiated pending PF4-heparin ELISA if the patient demonstrates signs or symptoms of thrombosis and has one of the following: positive imaging, thrombocytopenia, or both [12]. Treatment includes intravenous immunoglobulin (IVIG), anticoagulation, and avoidance of heparin and platelet transfusion [11,12,20,21,24,25]. Prior to administration of IVIG, confirmatory testing should be obtained, as IVIG may cause false-negative test results [12,14]. IVIG should be given 1–2 g per kilogram daily for 2 days [11,12,20,21,24,25]. There is currently no consensus on treatment with corticosteroids, though several societies recommend they can be considered in those with platelet counts <50 × 10^9/L or if IVIG will be delayed [12,19,21]. Fibrinogen should be corrected to >1.5 g/L with fibrinogen concentrate or cryoprecipitate [11,12,19,21]. Once platelet levels are >30 × 10^9/L and fibrinogen >1.5 g/L, non-heparin anticoagulation should be started. First-line agents include argatroban or bivalirudin, provided activated partial thromboplastin clotting time (aPTT) is normal [11,12,19,21]. Apixaban or rivaroxaban may be considered [11,12,21]. The American Society of Hematology states fondaparinux or danaparoid may also be used [12]. Treatment duration for provoked venous thromboembolism (VTE) is 3 months. Patients on oral anticoagulant medications for conditions such as atrial fibrillation or previously diagnosed VTE should continue their medication during and after the vaccination [11,12]. Heparin may be used to treat VTE if the PF4-heparin ELISA and disseminated intravascular coagulation (DIC) testing are negative and the platelet count is normal. Antiplatelet agents are not recommended [11,12,20,21]. Due to the potential severity of TTS, patients with suspected or confirmed TTS should be admitted to the hospital for monitoring and further therapy [11,12,20,21]. Based on the available data, danger of COVID-19, vaccine efficacy, and rarity of TTS, continued use of these vaccines is recommended, especially in locations with limited vaccine availability [18].

4. Conclusions

With the emerging information regarding TTS and increasing vaccination rates in the population, it is crucial that emergency clinicians rapidly recognize this entity for prompt initiation of assessment and management. TTS is a rare condition associated with exposure to the ChAdOx1 nCoV-19 and AD26.COV2-S vaccines. Several case series describe patients with TTS, though the overall incidence is rare. TTS is characterized by exposure 4–30 days prior to presentation, followed by thrombosis, mild-to-severe thrombocytopenia, and a positive PF4-heparin ELISA. The most common areas affected include the cerebral and splanchic veins. Targeted testing in the ED can suggest the disease, such as CBC, peripheral smear, D-dimer, fibrinogen, coagulation panel, PF4-heparin ELISA; imaging based on assessment of positive imaging, thrombocytopenia, or both [11,12].

Conflicts of interest

There are no conflicts of interest for any author.

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