Coronavirus (COVID-19) Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)

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Continuing Education Activity

Coronavirus disease 2019 (COVID-19), the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to have significant morbidity and mortality across the world, with many nations enduring multiple outbreaks of this viral illness. Many vaccines (BNT162b2, mRNA-1273, Ad26.COV2.S, and ChAdOx1 nCoV-19) have been developed at an unprecedented speed using distinctive technologies to prevent COVID-19. This article will highlight the role of the interprofessional team in the management of patients with the rare syndrome of vaccine-induced immune thrombotic thrombocytopenia (VITT).

Objectives:

- Review the epidemiology of VITT.
- Describe the pathophysiology and pertinent clinical features of VITT.
- Review the treatment options in the management of VITT.
- Describe the importance of an interprofessional approach in managing patients affected with VITT that would lead to better patient care and improved outcomes.

Access free multiple choice questions on this topic.

Introduction

Coronavirus disease 2019 (COVID-19), the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to cause significant morbidity and mortality across the world, with many nations enduring multiple outbreaks of this viral illness. Besides the importance of infection control measures to prevent or decrease the transmission of SARS-CoV-2, the most crucial step to contain this global pandemic is by vaccinating individuals to prevent SARS-CoV-2 infection in communities across the world. Many vaccines have been developed at an unprecedented speed using distinctive technologies to prevent COVID-19. Vaccination triggers the immune system resulting in the production of neutralizing antibodies against SARS-CoV-2. Four vaccines, namely the BNT162b2, mRNA-1273, Ad26.COV2.S and ChAdOx1 nCoV-19 have been approved or granted emergency use authorization(EUA) to prevent COVID-19 in many nations worldwide, including the United States. One exception to this is the ChAdOx1 nCoV-19 vaccine, which has not yet received a EUA or approval from the U.S. Food and Drug Administration (FDA) for use in the U.S. The BNT162b2 and mRNA-1273 vaccines are both mRNA-based, while the Ad26.COV2. S and ChAdOx1 nCoV-19 vaccines incorporate replication-incompetent adenoviral vectors in them.

In late February 2021, a new clinical syndrome characterized by thrombosis at atypical sites combined with thrombocytopenia was observed in multiple patients' days after vaccination with the ChAdOx1 nCoV-19 vaccine.[1] In April 2021, similar clinical sequelae were reported in patients after vaccination with the Ad26.COV2. S vaccine.[2] Preceding the approval of these vaccines, the clinical constellation of this new syndrome was not observed in clinical trials of the ChAdOx1 nCoV-19 vaccine, and a single case was observed in the Ad26.COV2. S vaccine trial recipient.[3] Furthermore, the incidence of major adverse effects has remained exceptionally low following the vaccination of more than 400 million people worldwide.[4] This novel clinical syndrome demonstrated striking similarities to heparin-induced thrombocytopenia; however, in the absence of prior heparin exposure was named vaccine-induced immune thrombotic thrombocytopenia (VITT). It is also known as vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) in some European nations and Canada. Conversely, of more than 180 million doses of BNT162b2 or mRNA-1273 vaccines administered so far, this clinical syndrome has not been reported.

Per the American Society of Hematology, vaccine-induced immune thrombotic thrombocytopenia (VITT) is defined as a clinical syndrome characterized by all of the below described abnormal laboratory and radiologic abnormalities occurring in individuals 4 to 30 days after vaccination with Ad26.COV2. S or ChAdOx1 nCoV-19 vaccines.

- Development of thrombosis at uncommon sites includes cerebral venous sinus thrombosis (CSVT)/splanchnic venous thrombosis.
- Mild to severe thrombocytopenia. However, a normal platelet count does not exclude the possibility of this syndrome in its early stages.
- Positive antibodies against platelet factor 4(PF4) identified by enzyme-linked immunosorbent assay (ELISA) assay.

Although the extraordinary speed of vaccine development against COVID-19 and robust ongoing mass vaccination efforts worldwide, the incidence of this newly described vaccine-induced phenomenon is associated with vaccination with Ad26.COV2.S or ChAdOx1 nCoV-19 vaccines attempt to overturn the significant progress made so far in halting the spread of SARS-CoV-2.

This review article aims to describe the etiology, epidemiology, pathophysiology, clinical features, diagnosis, and management of COVID-19 vaccine-induced thrombotic immune thrombocytopenia based on the latest available published literature.

Etiology

Several cases of uncommon thrombotic events associated in combination with thrombocytopenia were observed in patients who were vaccinated with ChAdOx1 nCoV-19 vaccines.[5][6] Although a causal relationship has not been well defined, the increased reporting in the UK as well as in Europe of CVST and thrombocytopenia in individuals vaccinated with ChAdOx1 nCoV-19 compared to totally absent cases in individuals who were immunized with BNT162b2 or mRNA-1273 vaccines proved to be a strong indication that this syndrome was potentially associated with the ChAdOx1 nCoV-19 vaccine.[7]

Due to the rarity of this clinical syndrome among vaccinated individuals, there is currently no evidence suggesting that individuals with prior history of thrombosis or risk factors for developing thrombosis are at increased risk of developing VITT. It is also unclear at this time as to why this immune-mediated thrombosis manifests mainly in the cerebral vessels and splanchnic circulation.[8]

Epidemiology

The incidence of VITT is extremely low. The true causal relationship between this novel clinical entity and the vaccines has not been established yet but is considered plausible based on a statement issued by The World Health Organization(WHO) on 7 April 2021. As per the European Medicines Agency (EMA), the incidence of VITT after vaccination with ChAdOx1 nCoV-19 is estimated to be between 1 in 125,000 and 1 in 1 million. Notably, more than 80% of the patients in reported cases of VITT were females and aged between 20 to 55 years of age.

After a brief pause in the administration of the ChAdOx1 nCoV-19, the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) completed internal reviews and favored resuming vaccination with this vaccine, emphasizing that the benefits of the vaccine outweigh the risk of developing thrombosis. However, the causal relationship wasn't described by either agency. Recently, of the nearly 6.8 million doses of Ad26.COV2. S, a small number of female patients aged between the ages of 18 and 48 developed a similar clinical constellation of cerebral venous sinus thrombosis and thrombocytopenia that occurred 6 to 13 days after vaccination.[2][3] The CDC and the FDA have recommended a pause in vaccination with Ad26.COV2. S vaccine in the U.S. to allow for further review of this vaccine.

Pathophysiology

The pathogenesis of vaccine-induced thrombotic thrombocytopenia is not known at this time. However, given its clinical presentation and biochemical similarities to heparin-induced thrombocytopenia, which is a prothrombotic and potentially life-threatening condition, a similar immune-mediated response induced by these adenoviral vector vaccines has been postulated as immune complexes with a mixture of antibody specificities similar to HIT was noted in the serum of patients who developed this syndrome.[6][1]

Based on a report by the Society of Thrombosis and Haemostasis Research (GTH), it has been hypothesized that postvaccination antibodies are formed against platelet antigens as a part of the immune stimulation process. These antibodies trigger massive platelet activation against PF4, resulting in immune thrombotic thrombocytopenia.[8] Cross-reaction between the vaccine and platelets or PF4 has also been highlighted as a potential contributing factor in the pathogenesis of this syndrome especially knowing that adenovirus can bind to platelets resulting in platelet activation. Further clinical studies are needed to determine the pathophysiological mechanism of this new syndrome precisely.[6]

History and Physical

A detailed clinical history regarding the onset and duration of symptoms, vaccination history that includes exact timing, drug history, particularly recent exposure to heparin, should be obtained by treating providers.

Pertinent Clinical Features Concerning VITT

- New neurologic symptoms such as severe, recurrent, or persistent headaches, seizures, blurry or double vision, focal weakness, aphasia
- Severe abdominal pain or persistent nausea and vomiting
- Backache
- Shortness of breath
- Chest pain
- Leg pain and or swelling
- Petechiae or purpura

Evaluation

Laboratory Assessment in VITT

Based on the treatment guidelines by the British Society of Haematology (BSH), Society of Thrombosis and Haemostasis Research (GTH), and American Society of Hematology (ASH), patients suspected of VITT should undergo initial laboratory workup and imaging modalities as described below.

- **CBC with platelet count and peripheral blood smear**
    - Typical platelet nadir ranging from 9,000 to 107,000 have been reported.
- **Coagulation panel** (PT/INR and aPTT)
- **Fibrinogen**
    - Typically, low levels of fibrinogen have been noted in VITT.
- **D-dimer level**
    - Markedly elevated D-dimer levels were observed in the majority of cases.
- **Fibrinogen**
    - Typically, low levels of fibrinogen have been noted in VITT.
- **PF4-heparin ELISA**
    - GTH recommends this as the first test to be performed in their diagnostic algorithm.[8]
    - In most reported cases with no heparin exposure, the serum demonstrated vigorous reactivity on the PF4–heparin ELISA.
    - If negative, VITT can be ruled out as almost all reported VITT had positive PF4-heparin ELISA results.
    - If low positive, then patients should undergo the confirmatory PF4 platelet activation assay.
- **PF4 dependent platelet activation assay**
    - Serotonin release assay
    - P-selectin expression assay
    - Heparin-induced platelet activation (HIPA)

Pertinent Imaging Studies

- **Intracranial imaging** focused on evaluating for cerebral sinus venous thrombosis (CSVT) with either magnetic resonance imaging (MRI) venogram or computed tomography (CT) should be considered.
- **Transabdominal and Transthoracic imaging** focused on evaluating for splanchnic thrombosis and/or pulmonary emboli with computed tomography (CT) or magnetic resonance imaging (MRI) venogram should be considered.
- **Duplex Ultrasound** of the lower extremities should also be considered if clinically indicated for evaluation of deep vein thrombosis (DVT).

Treatment / Management

The American Society of Hematology treatment recommendations of VITT is similar to that severe HIT in patients presenting with thrombocytopenia, documented evidence or suspicion of thrombosis, positive or pending PF4-heparin ELISA. Based on the treatment guidelines from the British Society of Haematology (BSH), Society of Thrombosis and Haemostasis Research (GTH), and American Society of Hematology (ASH), the management of VITT is as follows:[8]

- Urgent administration of **high dose intravenous immunoglobulin (IVIG)** 1 gram/kg (ideal body weight) daily for two days
- Evaluation for HIT/VITT should be performed before administering IVIG to prevent false-negative test results due to potential interference of IVIG with ELISA and platelet activation assays.
- Given its close resemblance to HIT, the use of heparin may be harmful, and **non-heparin anticoagulants** should be considered such as:
- **Direct thrombin inhibitors**: Argatroban or bivalirudin

- **Direct oral anti-Xa inhibitors without heparin bridge**: Edoxaban, apixaban,dabigatran or rivaroxaban
- **Low molecular weight heparinoid devoid of heparin**: Danaparoid
- **Selective factor Xa inhibitor**: Fondaparinux

Other Treatment Recommendations

- Hematology specialist consultation must be sought as early as possible.
- IVIG and non-heparin-based anticoagulation should be initiated if there is a high suspicion for the diagnosis of VITT and PF4-ELISA results are pending.
- Platelet transfusions should be avoided and should be considered only if clinically indicated and at the advice of a hematologist.
- Fibrinogen must be corrected with fibrinogen concentrate or cryoprecipitate to maintain a fibrinogen level of >1.5 g/L.
- All forms of heparin that include heparin-based flushes must be avoided until VITT is ruled out.
- Patients should be transferred to a tertiary care center once the diagnosis of VITT is confirmed.
- Both the BSH and ASH recommend continuing systemic anticoagulation for a minimum of three months in patients with documented thrombosis.

Differential Diagnosis

- Heparin-induced thrombocytopenia (HIT)
- Thrombotic thrombocytopenic purpura (TTP)
- Hereditary thrombophilia
- Acquired thrombophilia
- Drug-induced (e.g., pentosan polysulfate, hypersulfated chondroitin sulfate)
- Thrombocytopenia reactive to an acute medical condition
- Immune thrombocytopenic purpura (ITP)
- Post vaccine ITP
- Antiphospholipid syndrome
- Atypical hemolytic uremic syndrome (HUS)
- Paroxysmal nocturnal hematuria (PNH)
- Malignant hematological disorders

Prognosis

Considering this newly described syndrome is evolving, the prognosis of vaccine-induced thrombotic thrombocytopenia is not known. This estimated mortality rate related to the use of ChAdOx1 nCoV-19 was calculated to be low at one death in a million.[9] However, considering thrombosis more commonly involves atypical sites such as cerebral veins, rapid identification of this syndrome is crucial to prevent long-term morbidity and mortality.

Complications

- Thrombotic complications:[1][10]
    - Cerebral venous sinus thrombosis
    - Splanchnic vein thrombosis
    - Pulmonary embolism
    - Deep vein thrombosis
    - Arterial thrombosis
    - Ophthalmic vein thrombosis
- Intraparenchymal brain hemorrhage
- Ischemic stroke
- Disseminated intravascular coagulation (DIC)

Deterrence and Patient Education

- In most individuals, the risk of contracting COVID-19 and the risk of COVID-19 associated thrombosis and associated mortality is far greater than the risk of developing VITT.[11][9]
- The overall benefits of vaccination for prevention against COVID-19 must be reiterated.
- Adult individuals should be encouraged to speak to their clinician to discuss the risks and benefits before receiving the vaccination.
- Prior to vaccination, individuals should be educated about the clinical symptoms associated with this syndrome and should be advised to seek urgent medical treatment.

Enhancing Healthcare Team Outcomes

- Vaccination for prevention against COVID-19 is crucial in containing the spread of SARS-CoV-2 and controlling this pandemic.
- Given the concern of VITT in individuals vaccinated with the adenoviral vector vaccines(Ad26.COV2.S and ChAdOx1 nCoV-19) healthcare providers that include emergency medicine physicians, primary care physicians should maintain a high index of suspicion in patients presenting with symptoms on laboratory abnormalities suggestive of VITT as early recognition and management of this syndrome can prevent catastrophic complications.
- The recognition and management of VITT require an interprofessional team approach that includes hematology specialist physicians, nurses, laboratory staff, and pharmacists.
- Pharmacists should assist the physicians with different non-heparin anticoagulation formulations that are available in the formulary. Nurses taking care of patients should be aware of the syndrome's close resemblance with heparin-induced thrombocytopenia.
- They should receive education regarding avoiding heparin flushes and detailed instructions about weight-based administration of IVIG.
- There should be close communication between the ordering physician, the pharmacist, the nurse, and healthcare providers to keep themselves updated with the latest literature regarding this evolving new syndrome.
- Such a holistic approach would lead to early identification of this rare potential life-threatening syndrome, early treatment, which would significantly impact the morbidity and mortality associated with this syndrome.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

References

1. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med. 2021 Jun 03;384(22):2092-2101. [PMC free article: PMC8095372] [PubMed: 33835769]
2. Muir KL, Kallam A, Koepsell SA, Gundabolu K. Thrombotic Thrombocytopenia after Ad26.COV2.S Vaccination. N Engl J Med. 2021 May 20;384(20):1964-1965. [PMC free article: PMC8063883] [PubMed: 33852795]
3. Sadoff J, Davis K, Douoguih M. Thrombotic Thrombocytopenia after Ad26.COV2.S Vaccination - Response from the Manufacturer. N Engl J Med. 2021 May 20;384(20):1965-1966. [PMC free article: PMC8117965] [PubMed: 33861522]
4. Cines DB, Bussel JB. SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia. N Engl J Med. 2021 Jun 10;384(23):2254-2256. [PMC free article: PMC8063912] [PubMed: 33861524]
5. Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, Goldblatt D, Kotoucek P, Thomas W, Lester W. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021 Jun 10;384(23):2202-2211. [PMC free article: PMC8112532] [PubMed: 33861525]
6. Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, Wiedmann M, Aamodt AH, Skattør TH, Tjønnfjord GE, Holme PA. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021 Jun 03;384(22):2124-2130. [PMC free article: PMC8112568] [PubMed: 33835768]
7. Hunter PR. Thrombosis after covid-19 vaccination. BMJ. 2021 Apr 14;373:n958. [PubMed: 33853865]
8. Oldenburg J, Klamroth R, Langer F, Albisetti M, von Auer C, Ay C, Korte W, Scharf RE, Pötzsch B, Greinacher A. Diagnosis and Management of Vaccine-Related Thrombosis following AstraZeneca COVID-19 Vaccination: Guidance Statement from the GTH. Hamostaseologie. 2021 Jun;41(3):184-189. [PubMed: 33822348]
9. Mahase E. AstraZeneca vaccine: Blood clots are "extremely rare" and benefits outweigh risks, regulators conclude. BMJ. 2021 Apr 08;373:n931. [PubMed: 33832929]

10. Bayas A, Menacher M, Christ M, Behrens L, Rank A, Naumann M. Bilateral superior ophthalmic vein thrombosis, ischaemic stroke, and immune thrombocytopenia after ChAdOx1 nCoV-19 vaccination. Lancet. 2021 May 01;397(10285):e11. [PMC free article: PMC8046413] [PubMed: 33864750]
11. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. EClinicalMedicine. 2020 Dec;29:100639. [PMC free article: PMC7679115] [PubMed: 33251499]

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