Title: COVID-19 vaccine (mRNA BNT162b2) and COVID-19 Infection-Induced Thrombotic Thrombocytopenic Purpura in Adolescents

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Abbreviations Table

TTP	thrombotic thrombocytopenic purpura
TCH	Texas Children's Hospital
SLE	systemic lupus erythematosus

TPE	therapeutic plasma exchange
ITP	immune thrombocytopenia
VITT	vaccine-induced immune thrombotic thrombocytopenia

Abstract

The mRNA COVID-19 vaccine and COVID-19 infection caused by the SARS-CoV-2 virus may be immunologic triggers for the development of thrombotic thrombocytopenic purpura (TTP). There is not yet literature that discusses TTP induced by COVID-19 vaccination or infection in pediatric or adolescent patients. We describe 4 adolescents presenting with TTP (both *de novo* and relapsed disease) following administration of the Pfizer COVID-19 vaccine or after COVID-19 infection. Our observations demonstrate that the Pfizer-BioNTech mRNA vaccine and COVID-19 infection can act as triggers for the development/relapse of both congenital and acquired TTP.

Introduction

The mRNA COVID-19 vaccine and COVID-19 infection caused by the SARS-CoV-2 virus may be immunologic triggers for the development of both acquired and congenital thrombotic thrombocytopenic purpura (TTP). We present a case series of adolescents presenting with TTP (including both *de novo* and relapsed disease) following administration of the Pfizer-BioNTech mRNA BNT162b2 anti-COVID-19 vaccine or after COVID-19 infection.

Results

Methods:

Patients were identified through presentation to the Texas Children's Hospital (TCH) Hematology Center for evaluation of TTP. Patient characteristics and clinical course data were collected from the electronic medical record and are shown in Table 1. This study was conducted with Baylor College of Medicine Institutional Review Board approval.

Case Descriptions:

Patient 1 is a 19-year-old Hispanic female previously diagnosed with acquired TTP at 14 years of age who developed fever, ecchymoses, and hemoglobinuria two days after receiving the initial dose of the Pfizer-BioNTech COVID-19 vaccine. Her physical exam was notable for bilateral sub-orbital and lower extremity petechiae and bruising at IV insertion sites. Her admission labs were significant for thrombocytopenia and signs of intravascular hemolysis (Table 2). ADAMTS13 activity at presentation resulted <5%, confirming a relapse of TTP. Of note, her prior disease course had been complicated by the development of systemic lupus erythematosus (SLE)-specific autoantibodies without evidence of organ dysfunction, and a prior TTP relapse at

age 18. Treatment included daily therapeutic plasma exchange (TPE) for four days, methylprednisolone one gram daily for three days followed by a taper, rituximab 375 mg/m^2 weekly for four doses, and caplacizumab 11 mg daily for 28 days.

Patient 2 is a 15-year-old Hispanic female who presented with fatigue, ecchymoses, and headache three days after the first dose of Pfizer-BioNTech COVID-19 vaccine. Laboratory evaluation revealed severe thrombocytopenia, anemia with reticulocytosis, and an ADAMTS13 activity <5% (Table 2). She received TPE for four days, methylprednisolone one gram daily for three days followed by a taper, and rituximab 375 mg/m^2 weekly for four doses. Her treatment course was complicated by a vesicular rash and neuropathy, presumably due to Herpes Zoster.

Patient 3 is 17-year-old Hispanic female with asthma and non-alcoholic fatty liver disease who presented with altered mental status and hematuria. Her admission labs were significant for thrombocytopenia and evidence of hemolysis, with ADAMTS13 activity <5% (Table 2). During hospitalization she developed left-sided hemiparesis, headache, hearing loss, and perioral numbness. Brain imaging was negative for stroke. She had no known clinical COVID-19 infection or exposure but had positive SARS-CoV-2 IgG antibodies (type not obtained) that resulted at an outside hospital prior to transfer. She had no evidence of other recent infections that may trigger an immune-mediated process. Her treatment course included TPE for five days, methylprednisolone three mg/kg/day for three days followed by a taper, rituximab 375 mg/m^2 weekly for four doses, and caplacizumab 11 mg daily for 30 days.

Patient 4 is a 17-year-old non-Hispanic male with a history of precocious puberty previously on hormonal treatment who presented to an outside institution with bruising three weeks after PCR-testing confirmed symptomatic COVID-19 infection. He was initially treated with intravenous immunoglobulin for presumed immune thrombocytopenia (ITP), though an ADAMTS13 panel was obtained at that time. One week later he presented to an outside hospital with jaundice, pallor, and altered mental status. His ADAMTS13 activity returned at <5% (Table 2), confirming a diagnosis of TTP. He received TPE for five days, prednisone 60 mg BID with prolonged taper, and rituximab 375 mg/m^2 weekly for four doses. He also received two 28-day courses of caplacizumab with improved platelet counts, but with recurrent thrombocytopenia and hemolytic anemia upon cessation. Cylcosporine 150 mg twice daily was also initiated due to poor response with prior immunosuppression. *ADAMTS13* gene sequencing was obtained.

He was referred to Texas Children's Hospital three months later for second opinion. At this time, SARS-CoV-2 Anti-Spike Protein IgG antibodies were positive, confirming prior infection. He received a fifth dose of rituximab 375 mg/m^2 while awaiting *ADAMTS13* gene sequencing, which eventually revealed a novel homozygous variant in *ADAMTS13*, NM_139025.4:c.1584+5G>A, suspected to be pathogenic. Guided by previous experience in congenital TTP,[1,2] his immunosuppression was discontinued and plasma infusions were initiated. He was then transitioned to Koate-DVI infusions twice weekly without further immunosuppression, as Koate may play a role in treatment of congenital TTP.[1,2] Targeted *ADAMTS13* sequencing revealed each parent carries one copy of the variant.

Discussion

Our observations demonstrate that the Pfizer-BioNTech mRNA vaccine and COVID-19 infection can act as triggers for the development/relapse of both congenital and acquired TTP. There have been episodes of *de novo* and relapsed TTP reported in adults after Pfizer-BioNTech mRNA immunization.[3,4] Oxford AstraZeneca and Janssen (Ad.26.COV2.S) COVID-19 (Johnson & Johnson) vaccines have been linked to the development of vaccine-induced immune thrombotic thrombocytopenia (VITT),[5,6] a post-vaccination immune hematologic disorder distinct from TTP. Furthermore, there have been multiple case reports of ITP observed after administration of both Pfizer-BioNTech mRNA and Moderna mRNA COVID-19 vaccines,[7–9] some of which have been severe with devastating complications. In addition to vaccine-triggered immune events, there are reports of immune phenomena documented after COVID-19 infection, particularly the development of autoimmune disease, such as Guillain-Barré syndrome or SLE.[10,11]

In the case of inherited TTP, Galbusera and colleagues address a "two hit model" in their perspective article examining the pathophysiology of inherited TTP. They highlight cases in which patients with *ADAMTS13* mutations manifest TTP after an infection or pregnancy.[12,13] Mouse models of ADAMTS13 deficiency have suggested that an environmental trigger may be needed in addition to a gene mutation to fully manifest TTP, with ADAMTS13 deficient mice developing TTP after the introduction of Shiga toxin.[14] These studies suggest that an immunologic trigger, such as an infection or vaccination, may act as a trigger for inherited TTP. Patient 4 further demonstrates the importance of performing genetic sequencing in suspected or confirmed patients with TTP who are not responding to standard TTP therapy or do not have a detectable inhibitor.

Proposed mechanisms for these immunologic phenomena include molecular mimicry, vaccine triggered activation of the innate and adaptive immune system, or trigger of previously dysregulated immune pathways, as may be the case in patient 1.[15–17] Increased complement activation is also being studied as a trigger for severe hematologic disease after exposure to the SARS-CoV-2 spike protein, either through active COVID-19 infection or vaccination with an mRNA vaccine that leads to transcription of the spike protein.[18] It is important to note that none of our patients had significantly low C3 or C4 levels (Table 2) at presentation, suggesting that in these cases, activation of the classical complement pathway may not be the underlying trigger.

This case series demonstrates the broad spectrum of clinical presentations that occur in the setting of COVID infection or vaccination-induced TTP. Importantly, despite our report of two cases of vaccine-induced TTP, the incidence of immune events after COVID-19 vaccination are extremely rare. As we show, COVID-19 infection itself can also trigger TTP, among many other severe and devastating consequences, and therefore, we continue to stress that the benefits of the vaccine outweigh the risks, especially with the development of new, more transmissible, and potentially virulent SARS-CoV-2 variants.

Conflict of Interest Statement: The authors declare no competing financial interests.

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