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HEMATOLOGY: BRIEF REPORT

COVID-19 vaccine (mRNA BNT162b2) and COVID-19 infection-induced thrombotic thrombocytopenic purpura in adolescents

Luna Vorster[1] | Susan E. Kirk[2] | Eyal Muscal[3,4] | Jenny M. Despotovic[2] | Clay T. Cohen[2] | Sarah E. Sartain[2]

[1]Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas, USA

[2]Department of Pediatrics, Section of Hematology/Oncology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

[3]Department of Pediatrics, Section of Rheumatology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

[4]Department of Pediatrics, Section of Neurology/Developmental Neuroscience, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

Correspondence
Sarah E. Sartain, 6701 Fannin St., Suite 1580, Houston, TX 77030, USA.
Email: sartain@bcm.edu

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 three 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.

KEYWORDS
acquired TTP, COVID-19, TTP, vaccination

1 | 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.

2 | RESULTS

2.1 | Methods

Patients were identified through presentation to Texas Children's Hospital 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.

2.2 | Case descriptions

Patient 1 is a 19-year-old female previously diagnosed with acquired TTP at age 14 years who developed fever, ecchymoses, and hemoglobinuria 2 days after receiving the initial dose of the Pfizer-BioNTech COVID-19 vaccine. Her physical examination was notable for bilateral suborbital and lower extremity petechiae and bruising at IV insertion sites. 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 4

Abbreviations: ITP, immune thrombocytopenia; SLE, systemic lupus erythematosus; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura; VAERS, Vaccine Adverse Event Reporting System.

TABLE 1 Patient characteristics and summary of COVID-19 vaccination or infection-induced TTP course

Patient	Age (years)	Sex	Medical history	Vaccine status	Prior COVID infection	TTP symptoms	Treatment	Treatment side effects	Current clinical status
1	19	F	TTP	Pfizer-BioNTech mRNA vaccine dose 1	Not reported; SARS-CoV-2 PCR not detected at time of relapse	Bruising, hemoglobinuria	TPE x 4 days methylprednisolone, rituximab, caplacizumab	None to-date	In remission
2	15	F	Arrhythmia of unknown etiology, previously on metoprolol	Pfizer-BioNTech mRNA vaccine dose 1	Not reported; SARS-CoV-2 Anti-Spike IgM positive after vaccination	Fatigue, bruising	TPE x 4 days, methylprednisolone, rituximab, FFP infusion	Herpes zoster infection, weight gain	In remission
3	17	M	ASD/VSD repaired; precocious puberty treated with hormone suppression	Unvaccinated	3 weeks prior to presentation with symptomatic infection; COVID antibodies positive ~3 months after initial presentation	Initial hematuria; representation with jaundice, pallor, neurologic abnormalities; refractory	TPE x 5 days, rituximab, prednisone, cyclosporine, caplacizumab, FFP infusion	Hypertension during steroid course	Receiving Koate-DVI infusions biweekly

Abbreviations: ASD, atrial septal defect; FFP, fresh frozen plasma; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura; VSD, ventricular septal defect.

TABLE 2 Laboratory results on presentation of COVID-19 vaccination or infection-induced TTP

Labs on presentation	Patient 1	Patient 2	Patient 3
Hemoglobin (g/dl)	12.4	6.5	11.9
Platelet (cells/μl)	7000	33,000	352,000
Absolute reticulocyte (cells $\times 10^6/\mu$l)	0.103	0.286	0.082
Unconjugated bilirubin (mg/dl)	5.3	1.4	0.3
Lactate dehydrogenase (U/L)	836	354	465
C3 (mg/dl)	129	130	147
C4 (mg/dl)	30	Not obtained	21
ADAMTS13 activity (%)	<5	<5	<5, inhibitor 0.4 (ref range < 0.4) Novel homozygous variant in the *ADAMTS13* gene, NM_139025.4:c.1584+5G > A
Presence of schistocytes on peripheral smear	Yes	Yes	Unknown[a]

[a]Labs from initial encounter with Texas Children's Hematology; had already received treatment at prior hospital.

days, methylprednisolone 1 g daily for 3 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 female who presented with fatigue, ecchymoses, and headache 3 days after the first dose of Pfizer-BioNTech COVID-19 vaccine. Laboratory evaluation revealed severe thrombocytopenia, anemia with reticulocytosis, and ADAMTS13 activity <5% (Table 2). She received TPE for 4 days, methylprednisolone 1 g daily for 3 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 a 17-year-old male with a history of precocious puberty previously on hormonal treatment who presented to an outside institution with bruising 3 weeks after PCR-testing confirmed symp-

tomatic COVID-19 infection. He was initially treated with intravenous immunoglobulin for presumed immune thrombocytopenia (ITP). 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 5 days, prednisone 60 mg BID with prolonged taper, and rituximab 375 mg/m^2 weekly for 4 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 initiated due to poor response with prior immunosuppression. *ADAMTS13* gene sequencing was obtained.

He was referred to Texas Children's Hospital 3 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 revealed a novel homozygous variant in *ADAMTS13*, NM_139025.4:c.1584+5G > A, suspected to be pathogenic. Guided by experience in congenital TTP,[1,2] his immunosuppression was discontinued and plasma infusions were initiated. He was transitioned to Koate-DVI infusions twice weekly without further immunosuppression, as Koate may play a role in congenital TTP treatment.[1,2] Targeted *ADAMTS13* sequencing revealed each parent carries one copy of the variant.

3 | DISCUSSION

Our observations demonstrate that the Pfizer-BioNTech mRNA vaccine and COVID-19 infection can trigger 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 vaccine-induced immune thrombotic thrombocytopenia,[5,6] a postvaccination 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. The rapid onset of TTP in our cohort likely reflects the robust immunologic response induced by COVID-19 vaccination or infection. COVID-19 vaccine-induced TTP in adults has been reported to occur as early as 7 days after vaccination.[10] A similar disease time course has been described in adults after COVID-19 and influenza infections.[11,12] In the case of influenza-induced TTP, the authors propose that the infection triggers the anti-ADAMTS13 IgG inhibitor[12]; development of inhibitory antibodies after COVID-19 vaccination may be particularly robust in adolescents with predisposition to autoimmunity.

In addition to vaccine-triggered immune events, there are reports of a variety of immune phenomena documented after COVID-19 infection, particularly the development of autoimmune disease, such as Guillain-Barré syndrome or SLE.[13,14] TTP is often triggered by infection, and the occurrence of TTP after COVID-19 infection is in line with previously published data. Booth et al. describe 31 adults in the Oklahoma TTP registry who presented with TTP after bacterial, viral, or fungal infections. They suggest severity of infection may be more closely linked to TTP development than type of infection.[15]

In the case of inherited TTP, Galbusera and colleagues address a "two hit model," highlighting cases in which patients with *ADAMTS13* mutations manifest TTP after an infection or pregnancy.[16,17] Mouse models of ADAMTS13 deficiency suggest 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.[18] These studies imply that an immunologic event, such as an infection or vaccination, triggers inherited TTP. Patient 3 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.[19–21] Increased complement activation is also a potential 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 spike protein transcription.[22] 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 is extremely rare. Upon review of the US Vaccine Adverse Event Reporting System (VAERS), there have been between 50 and 100 reports of TTP, and five of those were in patients <21 years old.[23] Of note, the VAERS data may not be entirely accurate, as some cases may not have been reported and the search criteria may not have included all TTP cases. 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

The authors declare that there is no conflict of interest.

ORCID

Jenny M. Despotovic https://orcid.org/0000-0001-9569-3636
Clay T. Cohen https://orcid.org/0000-0001-6819-4049
Sarah E. Sartain https://orcid.org/0000-0003-2204-4568

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