



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

## BRIEF REPORT

# Acquired thrombotic thrombocytopenic purpura: A rare disease associated with BNT162b2 vaccine

Hannah Maayan<sup>1</sup> | Ilya Kirgner<sup>2,3</sup> | Odit Gutwein<sup>1</sup> | Katrin Herzog-Tzarfati<sup>1</sup> | Naomi Rahimi-Levene<sup>1,3,4</sup> | Maya Koren-Michowitz<sup>1,3</sup> | Dorit Blickstein<sup>1</sup> 

<sup>1</sup>Department of Hematology, Shamir Medical Center, Zerifin, Israel

<sup>2</sup>Blood Bank and Apheresis Unit, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

<sup>3</sup>Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

<sup>4</sup>Blood Bank, Shamir Medical Center, Zerifin, Israel

## Correspondence

Dorit Blickstein, Department of Hematology, Shamir Medical Center, Zerifin, Israel.  
Email: doritb@shamir.gov.il

## Abstract

**Background:** In December 2020 the Israeli Health Ministry began a mass vaccination campaign with the BNT162b2 vaccine. This was an important step in overcoming the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) pandemic. Autoimmune phenomenon have been described after receiving vaccinations.

**Patients/Methods:** Here we describe a case series of patients who developed acquired Thrombotic Thrombocytopenic Purpura, a rare autoimmune disease, within several days of receiving the BNT162b2 vaccine.

**Conclusions:** A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity should be evaluated in patients with history of aTTP before and after any vaccination, especially the SARS-CoV-2 vaccination, and immunosuppression treatment should be considered before vaccination in cases of low ADAMTS13 activity. Patients should be closely monitored after the vaccine for clinical situation and laboratory data. Post vaccination thrombocytopenia assessment should include immune thrombocytopenic purpura, vaccine-induced immune thrombotic thrombocytopenia and acquired thrombotic thrombocytopenic purpura.

## KEYWORDS

ADAMTS-13, acquired thrombotic thrombocytopenic purpura, autoimmunity, BNT162b2 vaccine, SARS-CoV-2

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), is a highly contagious illness that can cause severe morbidity and mortality especially in older adults and those with co-existing medical conditions.<sup>1</sup> It was declared a global pandemic in March 2020, and resulted in devastating medical, economic, and social consequences.<sup>1</sup> This challenge posed the need for a safe and effective vaccine against SARS-CoV-2.

In December 2020, results of the phase 2/3 part of the global trial evaluating the safety, immunogenicity, and efficacy of the BNT162b2 vaccine in adults 16 years and older were published.<sup>1</sup> BNT162b2 was shown to be 95% effective in preventing COVID-19 compared to placebo, with low incidence of serious adverse events.<sup>1</sup>

These data resulted in emergency approval of the BNT162b2 vaccine in several Western countries. Israel initiated a mass vaccination campaign in December 2020 and nearly five million people received the BNT162b2 vaccine.<sup>2</sup>

Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare, rapidly fatal disorder if not diagnosed and treated promptly.<sup>3</sup> aTTP is caused by development of auto-antibodies to the von Willebrand

Koren-Michowitz and Blickstein contributed equally to this work.

Manuscript handled by: David Lillicrap

Final decision: David Lillicrap, 1 June 2021

cleaving protein, A Disintegrin and Metalloproteinase with a Thrombospondin type 1 motif, member 13 (ADAMTS-13).<sup>3</sup> This causes development of von-Willebrand factor-platelet aggregates and microvascular thrombosis due to endothelial injury.<sup>3</sup>

Several cases of COVID-19-related aTTP were reported recently.<sup>4</sup> Here we present a case series of aTTP developing up to 28 days following the BNT162b2 vaccination. The study was approved by the local institutional review board committees.

## 2 | PATIENTS AND METHODS

Four patients from two academic medical centers were identified from mid-February to mid-March 2021. Presumed diagnosis of aTTP was made using the PLASMIC score<sup>5</sup> and prompt treatment was initiated. Diagnosis was confirmed in all cases showing low ADAMTS-13 activity and high antibody levels.

Case 1 was a 40-year-old healthy female of Filipino origin presenting 8 days after the second BNT162b2 vaccine complaining on somnolence, low-grade fever, and macroscopic hematuria. On presentation she was alert and oriented. Physical examination was remarkable for petechia and ecchymosis on the lower limbs.

Treatment included six sessions of plasma exchange (PEX), high-dose steroids, and caplacizumab. The patient is in complete remission (CR).<sup>6</sup>

Case 2 was a 28-year-old healthy male with morbid obesity (body mass index 50) presenting with an episode of dysarthria that lasted 15 minutes. Mild non-specific chest pain was noted several days prior to this episode. Physical exam including neurologic exam was normal, as was a computed tomography scan of the brain. He received the second dose of BNT162b2 vaccine 28 days prior to admission.

Treatment with five sessions of PEX, caplacizumab, high-dose steroids, and rituximab was initiated with rapid neurologic improvement and chest pain disappearance. The patient is in CR.<sup>6</sup>

Case 3 was a 31-year-old female with history of recurrent aTTP (2004–2015) last examined in January 2020, in excellent clinical and laboratory remission but 0% ADAMTS-13 activity and high antibodies titer (64 U/ml). Treatment with rituximab was offered but declined by the patient because of the pandemic. She presented with vaginal bleeding and purpura 13 days after receiving the first BNT162b2 vaccine.

Treatment with four sessions of PEX, steroids, rituximab, and caplacizumab was initiated, with clinical and laboratory improvement but ADAMTS-13 activity remained 0% with high antibodies titer (121 U/ml). Ten weeks after treatment ADAMTS-13 activity is 0%, ADAMTS-13 antibodies are low, and the patient continues caplacizumab.

Case 4 was a 30-year-old male with history of a single episode of aTTP in 2013, lost to follow-up. He presented with purpura on his limbs 8 days following the second dose of the BNT162b2 vaccine. Treatment with five sessions PEX, steroids, rituximab, and caplacizumab was initiated resulting in clinical and laboratory improvement

### Essentials

- Acute/relapsed acquired thrombotic thrombocytopenic purpura (aTTP) may be associated with BNT162b2 vaccine.
- Patients with aTTP should be evaluated for A Disintegrin and Metalloproteinase with a Thrombospondin type 1 motif, member 13 (ADAMTS-13) activity before and after vaccination.
- Immunosuppression should be considered before vaccination in cases of low ADAMTS-13 activity.
- One should consider the possibility of aTTP when evaluating post-vaccination thrombocytopenia.

at 1 week, and normal ADAMTS-13 activity and antibodies 5 weeks post PEX. The patient is in CR.<sup>6</sup>

ADAMTS-13 activity and antibody levels were determined by chromogenic ELISA (Technoclone). Serology for S and N antigens was done using the LIAISON® SARS-CoV-2 S1/S2 IgG (DiaSorin) and Elecsys Anti -Sars-cOv-2(Cobas, Roche Germany), respectively.

## 3 | RESULTS AND DISCUSSION

Patient demographic and laboratory data are summarized in Table 1. Mean age at presentation was 33 years, with first aTTP episode in two and relapse following long periods of remission in two cases. Patients presented at a mean of 14 days following BNT162b2 vaccination. All were negative for COVID-19 infection by PCR analysis, while serology was positive for the S antigen and negative for the N antigen in the two patients tested (one and two). All patients received PEX, corticosteroids, and caplacizumab, whereas rituximab was given to three.

Patients rapidly responded to treatment (defined as platelets >150 k/μl and lactic acid dehydrogenase <1.5xULN) with mean 4 days following presentation. At the time of this report, all patients are in clinical and laboratory response. Normalization of ADAMTS-13 activity was confirmed in three cases.

The prevalence of aTTP in Western countries is estimated as 2–6 cases per 10<sup>6</sup> per year.<sup>7</sup> This is roughly two to three cases per year in any Israeli hospital. We report on four cases of aTTP presenting within 4 weeks after BNT162b2 vaccination. This raised the suspicion of a shared precipitating event, and a presumptive association with the BNT162b2 vaccine.

aTTP is more prevalent in women,<sup>8</sup> with risk factors including pregnancy<sup>9</sup> and hormone-based treatments. Here, 50% of our small cohort were female and none of them were pregnant or on hormonal therapy.

The addition of caplacizumab to PEX and steroids resulted in rapid response<sup>6</sup> similar to that reported in the HERCULES study.<sup>10</sup>

TABLE 1 Demographic and laboratory parameters of aTTP patients

	1	2	3	4	Mean
Gender	Female	Male	Female	Male	
Age (y)	40	28	31	30	32
aTTP episode	First	First	Relapse	Relapse	
Vaccination dose	Second	Second	First	Second	
Days following vaccination (N)	8	28	13	8	14
Baseline laboratory					
Hemoglobin gr/dl (N:11.7–15.7)	9.9	9.1	7.7	10.8	9.4
Platelets K/ $\mu$ l (N:140–450)	12	38	15	11	19
Creatinine mg/dl (N:0.5–1.0)	0.92	1.5	1.2	1.44	1.26
LDH U/l (N: 240–480)	7129	3063	4000	1544	3169
Schistocytes %	6	6	10	6	7
Troponin ng/ml (N <0.03)	0.01	0.12	NA	NA	
PEX sessions (N)	6	5	4	5	5
Time to response <sup>a</sup> , days	3	4	3	5	4
ADAMTS-13 activity IU/ml (N: 0.4–1.3) (%)					
Baseline	0	0	0	0	0
At 5 weeks	0.52 (40)	0.77 (60)	0	0.6 (46)	0.47 (37)
ADAMTS-13 antibodies U/ml (N: 0–15)					
Baseline	51	113	64	21	62
At 5 weeks	1.9	8.9	10	10	7.7

Abbreviations: aTTP, acquired thrombotic thrombocytopenic purpura; ADAMTS-13, A Disintegrin and Metalloproteinase with a Thrombospondin type 1 motif, member 13; LDH, lactic acid dehydrogenase; NA, not applicable; PEX, plasma exchange.

<sup>a</sup>Defined as platelets >150 k/ $\mu$ l and LDH <1.5xULN.

Vaccine-associated autoimmunity is a well-known phenomenon attributed to either cross-reactivity between antigens or the adjuvant,<sup>11</sup> that is, systemic lupus erythematosus after the Human papilloma virus vaccine or Guillain Barre syndrome after the H1N1 vaccine.<sup>12</sup>

Moreover, case reports on aTTP following the H1N1 vaccine,<sup>13</sup> pneumococcal vaccine,<sup>14</sup> and others<sup>15</sup> were described.

Additional contributing factors to the possible association between the COVID-19 BNT162b2 vaccine and autoimmunity are the novel nucleic acid formulation and the accelerated development process imposed by the emergency pandemic situation.<sup>11</sup>

This report is to our knowledge the first observation of a cluster of aTTP patients associated with the BNT162b2 vaccine. Patients and physicians should be aware of aTTP occurrence or relapse following vaccination. It is recommended to test patients with history of aTTP for ADAMTS-13 activity before any vaccination and if low, vaccination should be delayed and immunosuppression (mainly steroids, as rituximab could jeopardize the immune response to vaccination) initiated.

In cases of relapsed aTTP, it is crucial to know the ADAMTS-13 level before vaccination in order to determine whether vaccination caused the development of new anti-ADAMTS-13 antibodies or was the second hit triggering the aTTP bout where ADAMTS-13 was already low.

Close clinical and laboratory monitoring, including ADAMTS-13 activity and platelet counts, is recommended for patients with previous aTTP following BNT162b2 vaccination. This will allow early recognition of ADAMTS-13 deficiency, prior to a clinical bout, and can result in treatment only with caplacizumab (with no or low-dose immunosuppression), until ADAMTS-13 recovery. Finally, as both immune thrombocytopenia and vaccine-induced immune thrombotic thrombocytopenia (VITT) were described after SARS-CoV-2 vaccination,<sup>16,17</sup> one should also consider the possibility of aTTP when evaluating post-vaccination thrombocytopenia.

#### ACKNOWLEDGMENTS

The authors thank their colleagues at the Shamir Medical Center and Tel Aviv Sourasky Medical Center for collaboration on the care of the patients.

#### CONFLICTS OF INTEREST

The authors declare no competing financial interests.

#### AUTHOR CONTRIBUTIONS

H. Maayan contributed to the data acquisition and interpretation and wrote the manuscript. I. Kirgner provided data on patients. I. Kirgner, O. Gutwein, K Herzog-Tzarfati, and N. Rahimi-Levene provided input on the manuscript and approved the final version. M.

Koren-Michowitz initiated and designed the study, interpreted the data, and provided input on the manuscript. D. Blickstein initiated and designed the study, contributed to the data acquisition and interpretation, and wrote the manuscript.

#### ORCID

Dorit Blickstein  <https://orcid.org/0000-0001-5693-1996>

#### REFERENCES

- Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med.* 2020;383(27):2603-2615.
- Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med.* 2021;384:1412-1423.
- Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol.* 2012;158(3):323-335.
- Albiol N, Awol R, Martino R. Autoimmune thrombotic thrombocytopenic purpura (TTP) associated with COVID-19. *Ann Hematol.* 2020;99(7):1673-1674.
- Li A, Khalighi PR, Wu Q, Garcia DA. External validation of the PLASMIC score: a clinical prediction tool for thrombotic thrombocytopenic purpura diagnosis and treatment. *J Thromb Haemost.* 2018;16(1):164-169.
- Cuker A, Cataland SR, Coppo P, et al. Redefining outcomes in immune TTP: an international working group consensus report. *Blood.* 2021;137(14):1855-1861.
- Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. *Blood Adv.* 2017;1(10):590-600.
- Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. *Blood.* 2017;129(21):2836-2846.
- Scully M, Thomas M, Underwood M, et al. Thrombotic thrombocytopenic purpura and pregnancy: presentation, management, and subsequent pregnancy outcomes. *Blood.* 2014;124(2):211-219.
- Knoebl P, Cataland S, Peyvandi F, et al. Efficacy and safety of open-label caplacizumab in patients with exacerbations of acquired thrombotic thrombocytopenic purpura in the HERCULES study. *J Thromb Haemost.* 2020;18(2):479-484.
- Talotta R. Do COVID-19 RNA-based vaccines put at risk of immune-mediated diseases? In reply to "potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases". *Clin Immunol.* 2021;224: 108665.
- Segal Y, Shoenfeld Y. Vaccine-induced autoimmunity: the role of molecular mimicry and immune cross reactivity reaction. *Cell Mol Immunol.* 2018;15(6):586-594.
- Dias PJ, Gopal S. Refractory thrombotic thrombocytopenic purpura following influenza vaccination. *Anaesthesia.* 2009;64(4):444-446.
- Kojima Y, Ohashi H, Nakamura T, et al. Acute thrombotic thrombocytopenic purpura after pneumococcal vaccination. *Blood Coagul Fibrinolysis.* 2014;25(5):512-514.
- Kadikoylu G, Yavasoglu I, Bolaman Z. Rabies vaccine-associated thrombotic thrombocytopenic purpura. *Transfus Med.* 2014;24(6):428-429.
- Lee EJ, Cines DB, Gernsheimer T, et al. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. *Am J Hematol.* 2021;96:534-537.
- Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *N Engl J Med.* 2021;384(22):2092-2101.

**How to cite this article:** Maayan H, Kirgner I, Gutwein O, et al. Acquired thrombotic thrombocytopenic purpura: A rare disease associated with BNT162b2 vaccine. *J Thromb Haemost.* 2021;19:2314–2317. <https://doi.org/10.1111/jth.15420>