

# Acquired Thrombotic Thrombocytopenic Purpura After BNT162b2 COVID-19 Vaccine: Case Report and Literature Review

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**Abbreviations:** TTP, thrombotic thrombocytopenic purpura; aTTP, acquired thrombotic thrombocytopenic purpura; PE, plasma exchange; CBC, complete blood count; AIT, autoimmune thrombocytopenia; VITT, vaccine-induced immune thrombosis and thrombocytopenia; HUS, hemolytic uremic syndrome; ULWF, ultralarge von Willebrand factor multimers.

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## ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy that is deadly if not treated promptly. The treatment of choice in patients presenting with TTP is plasma exchanges. However, immunosuppressive therapy and caplacizumab have significantly improved outcomes in TTP. This microangiopathy is classically divided into 2 entities: hereditary and acquired TTP (aTTP), caused by an autoantibody against *ADAMTS 13*. We present a case study of a patient with TTP occurring after a second dose of the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine along with a review of the literature. A 55-year-old patient presented with gastrointestinal symptoms, anemia, and severe thrombocytopenia. The blood film revealed the presence of schistocytes. A diagnosis of aTTP was established because the patient had severe *ADAMTS 13* deficiency and autoantibodies against *ADAMTS 13* were positive. This episode occurred 10 days after the patient received the COVID-19 vaccine. The patient received plasma exchanges, prednisone, rituximab, and caplacizumab and achieved complete remission. Ten patients with aTTP induced by the COVID-19 vaccine have been reported in the literature. Most of these situations

occurred after the second dose of COVID-19 vaccine, and 7 patients were noted to have received the BNT162b2 vaccine. Caplacizumab was used in 6 patients, and complete remission was achieved in 8 patients.

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy presenting in one-third of patients as a clinical pentad. Typically, this pentad is composed of fever, renal failure, neurological symptoms, thrombocytopenia, and microangiopathic hemolytic anemia. The diagnosis is suspected based on broad clinical manifestations and thrombocytopenia and hemolytic anemia of mechanical origin indicated by the presence of schistocytes. The diagnosis of TTP is confirmed by a severe deficiency of *ADAMTS 13* activity (<10%).

In France, the incidence of TTP is 1.5 cases per million per year in adults,<sup>1</sup> with a high mortality if treated improperly. Although the treatment of choice for TTP is plasma exchange (PE), immunosuppressive therapy has significantly improved outcomes with a reduced length of hospitalization.<sup>2</sup>

This microangiopathy is classically divided into 2 entities: hereditary TTP (historically known as Upshaw-Schulman syndrome) caused by a genetic mutation of the *ADAMTS 13* gene and acquired TTP (aTTP), an autoimmune disease resulting from the development of an autoantibody directed against *ADAMTS 13*.

Studies have shown that aTTP can be caused by a variety of triggers including infections, pregnancy, malignancies, autoimmune diseases, and vaccines. Vaccine-induced thrombocytopenia has been reported in the literature, including rare cases of patients with vaccine-induced aTTP.<sup>3-5</sup> Vaccination against COVID-19 has played an important role in controlling the pandemic. However, some adverse events have been observed, including rare cases of patients with TTP. We report a case of a patient with TTP occurring after a second dose of the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine along with a review of the literature.

## Case Report

Our patient was a 55 year old Caucasian woman. She presented to the emergency department with fatigue, nausea, and diarrhea persisting for

the previous 3 days. The patient also reported headache, and dizziness. Her background medical history included hypothyroidism, appendectomy, and amygdalotomy. Physical examination showed no particular signs aside from petechiae. A complete blood count (CBC) revealed anemia and severe thrombocytopenia (TABLE 1). The patient had normal hemoglobin and platelet counts with no history of hemolysis before admission.

Further tests showed an increase in lactate dehydrogenase with significantly elevated total bilirubin and indirect bilirubin (TABLE 1). The patient's haptoglobin level was depleted. The blood film revealed the presence of schistocytes at 2%. This finding raised suspicion for TTP.

Renal and hepatic blood panels were normal (creatinine = 62 µmol/L, alanine aminotransferase = 42 IU/L, and aspartate aminotransferase = 19 IU/L). The patient's calculated PLASMIC score<sup>6</sup> was 7, predicting a high risk for TTP (TABLE 2). The French score was 2 (creatinin < 200 > µmol/l, Platelet < 30\*10<sup>9</sup>/l), also predicting a high risk for TTP.<sup>7</sup>

Cerebral MRI was performed and showed no signs of thrombosis. Laboratory investigation for other causes of microangiopathy was negative: The antinuclear antibody screen and shiga-toxin-producing *Escherichia coli* screening were negative, and the complement cascade evaluation was normal.

Lupus anticoagulant, anticardiolipin antibody, and anti-beta 2 glycoprotein I antibody assays were negative. The ADAMTS 13 activity confirmed the diagnosis of TTP with a severe deficiency (<5%). An anti-ADAMTS 13 antibodies screen was positive at 90 U/mL. Extensive anamnesis showed that the patient had received her second dose of BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine 10 days before the onset of symptoms. Hence, the diagnosis of aTTP induced by COVID-19 vaccine was established.

We started PE right away, along with prednisone and rituximab at a dose of 375 mg/m<sup>2</sup>. However, because the patient's platelet numbers continued to drop, caplacizumab was introduced at day 5 in addition to the ongoing daily PE. Platelet numbers increased to finally normalize at

day 10. After 20 days of treatment, ADAMTS 13 levels were normal and the patient was subsequently discharged. Subcutaneous caplacizumab was continued at home to total 20 doses.

## Discussion

Since the launch of the COVID-19 vaccinations, vaccine adverse event reporting systems have been developed all over the world. Adverse events occurring after COVID-19 vaccination vary from simple events like headache, fever, and fatigue, which are described in the safety evaluation reports for COVID-19 vaccines,<sup>8,9</sup> to serious events like myocarditis and anaphylactic reactions.<sup>10</sup> Our patient presented with nausea and diarrhea 10 days after the second dose of a COVID-19 vaccine. The main laboratory finding in the initial workup was a severe symptomatic thrombocytopenia.

COVID-19 vaccine-related thrombocytopenia has been observed as an adverse event and described as various conditions, all of them involving autoimmunity.<sup>11</sup> Vaccine-triggered autoimmunity with vaccination has been known for decades, mainly involving epitope mimicry mechanisms.<sup>12</sup>

Thrombocytopenia induced by a COVID-19 vaccine can be caused by autoimmune thrombocytopenia (AIT),<sup>11</sup> which was the first diagnosis we considered in our patient. However, AIT is usually isolated in the CBC. In addition, the presence of schistocytes provided initial clues as to the diagnosis of TTP.

Another adverse event responsible for thrombocytopenia reported in the literature is vaccine-induced immune thrombosis and thrombocytopenia (VITT).<sup>13</sup> This condition has been observed more with the adenovirus-based coronavirus vaccines, and mostly after the first dose. Thrombocytopenia in VITT is caused by antibodies against platelet factor 4, in the absence of heparin. The severity of VITT is related to the occurrence of unusual-location thrombosis.

Although VITT and AIT are more frequently responsible for vaccine-induced thrombocytopenia, TTP has also been observed after COVID-19 vaccination. Most cases have been observed after BNT162b2 (Pfizer-BioNTech) COVID-19 vaccination,<sup>14-17</sup> but some were induced by ChAdOx1 nCov-19 (AstraZeneca)<sup>18,19</sup> (TABLE 3) and one case occurred after mRNA-1273 COVID-19 vaccine (Moderna) administration.<sup>20</sup>

Our patient received the second dose of the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine 10 days before the onset of symptoms. Her PLASMIC score predicted a high risk of severe ADAMTS 13 deficiency. Hence, aTTP induced by vaccination was the most likely diagnosis.

**TABLE 1. Complete Blood Count and Hemolysis Panel on Admission**

Biological Parameter (unit)	Value	Normal Range
Red blood cells (*10 <sup>12</sup> /L)	3.54	3.92–5.08
Hemoglobin (g/dL)	10.7	11.9–14.6
Hematocrit (%)	30.8	36.6–44.4
Mean corpuscular volume (fl)	87	82.2–98
Mean cell hemoglobin (pg)	30.2	27–32.3
Platelets (*10 <sup>9</sup> /L)	15	150–450
Neutrophils (*10 <sup>9</sup> /L)	5.67	2.1–8.89
Eosinophils (*10 <sup>9</sup> /L)	0	0.01–0.07
Basophils (*10 <sup>9</sup> /L)	0.02	0.01–0.07
Lymphocytes (*10 <sup>9</sup> /L)	1.05	1.26–3.35
Monocytes (*10 <sup>9</sup> /L)	0.61	0.25–0.84
Reticulocytes (*10 <sup>9</sup> /L)	100.9	20–120
Haptoglobin (g/L)	<0.02	0.4–2.8
Lactate dehydrogenase (IU/L)	645	120–246
Total bilirubin (µmol/L)	32	5–21
Direct bilirubin (µmol/L)	9	0–5
Schistocytes (%)	2	<1

The asterisks is to say that the number is multiplied bby 10<sup>9</sup>/L , for example it's as 5.67 \* 10<sup>9</sup>/L for neutrophils.

**TABLE 2. PLASMIC Score in Patient**

Items in PLASMIC Score	Score
Platelet count <30* 10 <sup>9</sup> /L	1
Hemolysis; reticulocyte count >2.5%, haptoglobin undetectable, or indirect bilirubin >2.0 mg/dL (34.2 µmol/L)	1 (haptoglobin undetectable)
Active cancer; treated for cancer within the past year	No: 1
History of solid-organ or stem-cell transplant	No: 1
MCV <9.0 × 10–14 L (<90 fl)	1
INR <1.5	1
Creatinine <2.0 mg/dL (176.8 µmol/L)	1
PLASMIC score	7

INR, international normalized ratio; MCV, mean corpuscular volume.

**TABLE 3. Case Reports of TTP After COVID-19 Vaccination**

Author, Country	Vaccine	Vaccination Dose	Delay After Vaccine	Relapse/First Episode of TTP	Age (y)	Clinical Presentation	Treatment	Outcome
Chamarti et al, USA <sup>22</sup>	BNT162b2 (Pfizer-BioNTech)	Second	2 wks	First	80	Weakness, malaise	PE, prednisone, rituximab	Remission
Waqar et al, USA, Pakistan <sup>23</sup>	BNT162b2 (Pfizer-BioNTech)	Second	1 wk	First	69	Severe fatigue, shortness of breath	PE, prednisone, rituximab	Remission
Kirpalani et al, Canada <sup>21</sup>	BNT162b2 (Pfizer-BioNTech)	Second	2 wks	First	14	Fatigue, confusion, headache, bruising	PE, rituximab, caplacizumab	Remission
Karabulut et al, USA <sup>20</sup>	mARN-1273 (Moderna)	First	5 d	Relapse	48	Weakness and slurred speech	PE, rituximab, caplacizumab	Remission
Wang et al, Taiwan <sup>16</sup>	ChAdOx1 nCov-19 (AstraZeneca)	Not mentioned	30 d	Not mentioned	75	Bleeding (tongue)	PE	Not mentioned
Lee et al, UK, Malaysia <sup>19</sup>	ChAdOx1 nCov-19 (AstraZeneca)	First	12 d	First	50	Dysphasia and acute numbness	PE, prednisone, rituximab, aspirin, fondaparinux	Remission
Maayan et al, Israel <sup>17</sup>	BNT162b2 (Pfizer-BioNTech), case series	Second	8 d	First	49	Somnolence, low-grade fever, macroscopic hematuria	PE, steroids, caplacizumab	Remission
		Second	28 d	First	29	Dysarthria	PE, steroids, rituximab, caplacizumab	Remission
		First	13 d	Relapse	31	Purpura, vaginal bleeding	PE, steroids, caplacizumab	Patient still on caplacizumab
		Second	8 d	Relapse	30	Purpura	PE, steroids, rituximab, caplacizumab	Remission
Current patient	BNT162b2 (Pfizer-BioNTech)	Second	10 d	First	55	Nausea, diarrhea, headache	PE, prednisone, rituximab, caplacizumab	Remission

PE, plasma exchange; TTP, thrombotic thrombocytopenic purpura.

Hemolytic uremic syndrome (HUS) was also considered in the differential diagnosis because the patient had a thrombotic microangiopathy and gastrointestinal symptoms. However, the absence of renal impairment was more in favor of a TTP diagnosis. Yet we ruled out probable causes of typical or atypical HUS because the patient had normal complement exploration and negative shiga-toxin-producing *E. coli* screening. The diagnosis of aTTP was confirmed along with a severe *ADAMTS 13* deficiency. The delay between symptom onset and COVID-19 vaccination was consistent with the literature (TABLE 3). All reported cases have been observed in adults except for 1 case observed in an adolescent.<sup>21</sup>

The patient's *ADAMTS 13* levels at admission were severely deficient. In fact, in the absence of *ADAMTS 13* (ie, TTP), uncleaved ultralarge von Willebrand factor multimers (ULVWF) are accumulated. They interact with platelets through the GpIb/IX/V complex, inducing the formation of microthrombi. Those microthrombi are responsible for the clinical manifestations and the formation of schistocytes.<sup>24</sup> A severe *ADAMTS 13* deficiency is necessary for the development of TTP but not sufficient. The development of TTP is abruptly precipitated by the activation of the alternative complement pathway by ULVWF. Complement activation has also been described as a pejorative prognosis factor.<sup>25</sup> Our patient's favorable outcome after immunosuppressive therapy can be explained by her normal C3, C4, and CH50 levels.

For decades, PE has been the cornerstone of TTP treatment. However, recent advancements in aTTP pathophysiology understanding have led to the inclusion of rituximab as a front-line treatment along with PE. More recently, caplacizumab, an antibody targeting

domain A1 of von Willebrand factor was introduced. Caplacizumab showed satisfactory results, especially in patients with refractory TTP. Our patient received PE, prednisone, rituximab, and caplacizumab according to the HERCULES protocol.<sup>26</sup> The platelet count normalized after 10 days of treatment, and the patient is currently in complete remission.

Most patients with aTTP have been observed after receiving the second dose of a COVID-19 vaccine (TABLE 3). However, patients with relapse seem to be more frequently observed after receiving the first dose. Hence, the question is whether a patient should receive the COVID-19 booster. Because COVID-19 infection has also been observed as an aTTP trigger, the benefit-risk balance of vaccination should be carefully considered in such patients.

## Conclusion

This case report highlights the challenge of thrombocytopenia's etiology diagnosis after COVID-19 vaccination. Although VITT has been previously well described, aTTP related to COVID-19 may be less known and much is yet to be understood in the disease triggers, management, and prognosis. Caplacizumab seems to be an important therapy to consider and possibly include in front-line treatment in further studies.

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