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INTRODUCTION

Since the beginning of the COVID-19 disease pandemic, unprecedented efforts have made possible the rapid development of effective vaccines against SARS-CoV-2. Because they are globally distributed, these novel vaccines are continuously monitored for rare adverse events that could be related to their administration.

Thrombotic thrombocytopenic purpura (TTP) is a rare life-threatening disease characterized by microangiopathic hemolytic anemia, thrombocytopenia, and platelet-rich microthrombi causing organ damage. Most frequently, it is acquired because of autoantibody against the von Willebrand factor-cleaving metalloprotease ADAMTS13 (immune TTP). TTP is a hematologic emergency, with 90% mortality if untreated.1 Prompt treatment with plasma exchange, corticosteroid, and more recently inhibition of platelet-von Willebrand factor aggregation with the nanobody caplacizumab, can greatly improve outcomes.2,3 Although most cases of immune TTP are idiopathic, associations have been made with specific stimuli like pregnancy, malignancies, viral infection, and vaccination.

We report a case of severe de novo immune TTP in a young female following a first dose of Pfizer-BioNTech COVID-19 vaccine. This case also highlights the ability of caplacizumab to quickly halt disseminated thrombus formation in refractory TTP.

CASE PRESENTATION

A 22-year-old Caucasian female presented to the emergency room with hematuria of 3 days duration and repeated vomiting with some hematemesis. She denied any fever, neurological symptoms, gastrointestinal bleeding, or recent diarrhea.
Her medical records showed that she had had a miscarriage 3 months before. There was no personal or family history of autoimmune or hematological disorder. The patient had received her first dose of the Pfizer Bio-NTEch mRNA COVID-19 vaccine 3 weeks before presentation.

Upon admission, the patient was afebrile with normal vital signs. She appeared in no distress and was neurologically intact. The physical examination was unremarkable except for diffuse petechiae and mild abdominal tenderness.

Laboratory examination showed a white blood cell count of 10.9 × 10^9/L (71% neutrophils), hemoglobin of 11.7 g/dl (mean cell volume of 88 fl), platelet count of 9 × 10^9/L, and a reticulocyte count of 118 × 10^9/L (3%). Blood chemistry revealed increased total bilirubin (2.8 mg/dl, mostly indirect) and lactate dehydrogenase (919 IU/L) with undetectable haptoglobin. Schistocytes, microspherocytes, and polychromasia were observed on the peripheral blood smear. The creatinine level was slightly higher than baseline. Coagulation test and troponin were within normal range. Beta-hCG and direct antiglobulin test were negative. She tested negative for human immunodeficiency virus, hepatitis B and C, and Epstein-Barr Virus. Antiphospholipid antibody and antinuclear antibody were not detected. A COVID test by reverse transcriptase-polymerase chain reaction was negative.

With a PLASMIC score of 7, TTP was highly suspected. Blood samples for ADAMTS13 activity and inhibitor levels were collected and daily plasma exchange with fresh frozen plasma (1.5 total plasma volume for first session and 1 total plasma volume for subsequent sessions) was started immediately, along with prednisone (1 mg/kg/day) and folic acid. The ADAMTS13 activity was 0% (by Fluorescence Resonance Energy Transfer; normal: 56–133%) with an antibody titer of 16 (by enzyme-linked immunosorbent assay; normal: indetectable), confirming the diagnosis of immune TTP.

After an initial response, the patient became refractory with decreasing platelet count on day 6. Treatment was intensified with twice daily plasma exchange (1 total plasma volume), high-dose methylprednisolone (1000 mg IV), and rituximab (375 mg/m²). On day 7, she became increasingly unintelligible and difficult to rouse with new increase of troponin level (372 ng/L; normal <14 ng/L). Electrocardiogram and computed tomography of the head were normal. Laboratory values showed acute exacerbation of the microangiopathy (platelet 20 × 10^9/L and LDH 3600 IU/L). Caplacizumab was emergently obtained and administered while the now stuporous patient was receiving her second daily plasma exchange. Her clinical status immediately improved, followed by normalization of her platelet count on day 10. After a total of 15 sessions, plasma exchange was stopped on day 12 and the patient was discharged on prednisone and subcutaneous caplacizumab. On day 17, ADAMTS13 activity was still at 2% with autoantibody titer at 2. The patient completed 4 weekly doses of rituximab as an outpatient and began a slow steroid taper. Caplacizumab was discontinued on day 39, when ADAMTS13 activity had increased to 95% with no antibodies detected (Figure 1). The patient is still in remission with ADAMTS13 activity >150% now 5 months after presentation. She has declined the second COVID vaccine dose and her case has been reported to public health authorities.

### Essentials
- Immune thrombotic thrombocytopenic purpura (iTTP) is infrequently associated with vaccination.
- We report a case of severe refractory iTTP after administration of COVID-19 vaccine.
- Urgent administration of caplacizumab was able to quickly reverse organ dysfunction.
- Awareness of the potential association between iTTP and COVID-19 vaccination is prudent.

### 3 | DISCUSSION

COVID-19 is a unique global health challenge, and a mass vaccination program is the most promising way to get the pandemic under control. Many studies have demonstrated that vaccines are effective in preventing hospitalizations and deaths from SARS-CoV-2. Because vaccines are given to healthy people as a preventive measure, regulating their safety is of highest importance.

In June 2021, Israeli researchers noted a sudden increased in TTP cases with the introduction of the Pfizer coronavirus vaccine. Since then, a few cases of de novo or relapsed TTP after one or two doses of Pfizer vaccine have also been reported. Vaccines are known to be potential immunological trigger for autoimmunity and cases of immune TTP following vaccination have been reported before the covid pandemic. The precise mechanism is not proven but could be related to exposure to antigens with molecular mimicry to ADAMTS13. It is of interest that COVID-19 infection itself has been reported as a cause of immune TTP in the literature. Alternatively, vaccination or acute infection may act as a trigger for an acute TTP episode in a patient with underlying ADAMTS13 deficiency (“two-hit hypothesis”).

The temporal relationship suggest that the Pfizer-BioNTech mRNA vaccine might be the main trigger for the development of immune TTP in this patient. Despite prompt treatment, she had a refractory, almost fatal, course that was successfully salvaged by caplacizumab. Now in remission, she still is at a significant risk of relapse and long-term sequelae. We suggest that TTP be in the differential diagnosis of thrombocytopenia after COVID-19 vaccine. We agree with public health authorities that individual and public benefits of global vaccination greatly outweigh this rare adverse event.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### AUTHOR CONTRIBUTIONS

E. Laverdure: review of the literature and manuscript writing. C. Sperlich and S. Fox: critical revision of the manuscript. All authors provided direct patient care.
**FIGURE 1**  Platelet count, LDH level, ADAMTS13 enzyme activity and ADAMTS13 antibody level over the course of therapy. The patient had an exacerbation on day 6 with a prompt response to caplacizumab.

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