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Case Report

# THROMBOTIC THROMBOCYTOPENIC PURPURA AFTER VACCINATION AGAINST COVID-19 – A CASE REPORT

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**ABSTRACT**

Thrombotic thrombocytopenic purpura (TTP) is a rare but fatal thrombotic microangiopathy. Circulating AntiADAMTS13 antibodies produced in response to various triggering events, such as vaccinations, autoimmune disorders, malignancy, and administration of several drugs lead to acquired TTP (aTTP). This case concerns a 26-year-old male with aTTP after receiving the second dose of the Covishield vaccine (Oxford-AstraZeneca COVID-19 vaccine, code-named AZD1222). He presented with bruises, petechia, fatigue, dyspnea, and arthralgia post-vaccination. Laboratory reports showed thrombocytopenia, hemolytic anemia, a significant ADAMTS13 deficiency, and a high level of autoantibody titer against ADAMTS13. We treated the patient with plasma exchange therapy and prednisolone, and after the treatment, he recovered.

**Keywords:** Thrombotic thrombocytopenic purpura, COVID-19, Vaccination, Covishield, Plasma exchange therapy.

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## INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare but fatal thrombotic microangiopathic disorder, characterized by thrombocytopenia, hemolytic anemia, and ischemic organ damage of various degrees, affecting the brain, heart, and kidneys in particular [1]. Deficiency of the ADAMTS13 (Von Willebrand Factor [VWF] multimeric strings cleaving protease) is underlying pathophysiology [2,3]. Homozygous or compound heterozygous mutation in the ADAMTS13 gene is a cause of congenital TTP (Upshaw-Schulman syndrome), while circulating anti-ADAMTS13 antibodies lead to acquired TTP (aTTP). AntiADAMTS13 antibodies are produced in response to various triggering events, such as vaccinations, autoimmune disorders, malignancy, administration of several drugs, stress, pregnancy, and viral infections [4]. As a result, excessive levels of ultra-large VWF strings stay uncleaved, which binds to platelets and forms microthrombi, resulting in TTP clinical manifestations [5]. If left untreated, aTTP has a mortality rate of up to 90%. With the introduction of plasma exchange therapy and immunosuppressive agents, the survival rate has improved from <10% to 80–90% [6]. However, the patients who survive an acute episode are at risk of relapse and long-term morbidity. TTP shares clinical symptoms with several conditions, such as hemolytic uremic syndrome and other thrombotic microangiopathies, so diagnosis is challenging. The reference procedures for determining ADAMTS13 activity are complicated, and the results are rarely available in an emergency setting; as a result, initial treatment should be started based on the clinical presentation. Here, we present the case report of aTTP associated with the vaccination against COVID-19.

## CASE REPORT

A 26-year-old male patient presented to our hospital with petechia, bruises, arthralgia, dyspnea, fatigue, and fever for the past 4 days. He had already received both doses of vaccine with Covishield (Oxford-AstraZeneca COVID-19 vaccine, code-named AZD1222, using as a vector the modified chimpanzee adenovirus ChAdOx1) against SARS-CoV-2, 2 months and 10 days earlier before the presentation to our hospital. The first bruise was noticed over the left foot, 3 days after the second dose of the vaccination. There was no history of weight loss, vision disturbance, night sweat, cough, chest pain, and change in urinary or bowel habits. His personal history, family history, medical history, and medication history were all insignificant. On general examination, the patient was febrile with a body temperature of 102F; his oxygen saturation was 97% on room air, and no neurological abnormalities were noted.

We did blood sampling, and laboratory results showed thrombocytopenia with platelet counts of$52 \times 10^9$/L, and hemolytic anemia (hemoglobin level of 8 g/dl, 18% reticulocytes, 38% hematocrit, and <20 mg/dl of haptoglobin). Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were prolonged with the values of 39 s and 42 s, respectively. Other findings were elevated serum total bilirubin (1.6 mg/dl), raised serum lactate dehydrogenase level (480 U/L), and elevated D-dimer value (970 ng/ml). The fibrinogen level was raised to 482 mg/dl. The serum creatinine level was normal (0.9 mg/dl)(Table 1).

In further diagnostic workup, antibodies (IgG) against platelet factor-4 were not detected, ruling out vaccine-induced immune thrombotic thrombocytopenia (VIIT), which is associated with vaccination against COVID-19. Coombs's test was also negative. Shiga toxin in the stool came back negative, ruling out hemolytic uremic syndrome. Diagnosis of heparin-induced thrombocytopenia (HIT) also came negative. The patient was also subjected to real-time reverse transcription-polymerase chain reaction (RT-PCR) testing to diagnose COVID-19 infection, which came back negative. Based on the clinical findings and laboratory reports, a presumptive diagnosis of aTTP was made.

We calculated the PLASMIC-score for estimating suspected ADAMTS13 deficiency, and the value was 5, indicative of intermediate risk. The patient was admitted to our hospital, ADAMTS testing was sent, and therapy with plasma exchange therapy (PEX) was started, suspecting aTTP. ADAMTS testing revealed, 3.6% activity of ADAMTS (normal range: 50–100%), and very low level of ADAMTS-antigen (0.09 IU/ml; normal level: 0.35–1.2 IU/ml). Antibodies against ADAMTS13 were detected in the ELISA at 53 units/ml (positive >16 units/ml), confirming the diagnosis of aTTP. During his 8-day hospital stay, the patient received four PEX using fresh frozen plasma. The therapy was complemented by intravenous prednisolone 1 mg/kg (70 mg) daily for 4 consecutive days. After the second PEX, the symptoms resolved, and by the fourth PEX, the platelet count was increased to $127 \times 10^9$/L, with no evidence of hemolysis, ADAMTS activity was increased to 37%, and ADAMTS antigen level was raised to 0.38 IU/ml. The patient was discharged on the 9$^{th}$ day with no clinical symptoms, except fatigue (Table 1).

**Table 1 : Overview of the laboratory results of the patient**

| Laboratory test (Unit) | Reference Range | Day 1 (Day of admission) | Day 2* | Day 3* | Day 5* | Day 8* | Day 18 |
|---|---|---|---|---|---|---|---|
| **CBC** | | | | | | | |
| Total WBC Count (cells /cmm) | 4,000–10,000 | 5200 | 5100 | 5600 | 5800 | 5400 | 5500 |
| Total RBC Count (million cells /cmm) | 4.5–5.5 | 4.7 | 4.8 | 5.0 | 4.8 | 4.9 | 4.9 |
| Hemoglobin (g/dl) | 13.5–17.2 | 8 | 7.8 | 8.8 | 10.2 | 11.6 | 13.7 |
| Hematocrit (%) | 42–52 | 38 | 36 | 39 | 40 | 42 | 42.2 |
| MCV* (fL) | 83–101 | 86 | 87 | 90 | 87 | 89 | 89 |
| MCHC* (g/dl) | 31.5–34 | 31.8 | 31.5 | 32.2 | 33 | 33.8 | 33 |
| Platelets (×10E$^9$ /L) | 150–400 | 52 | 58 | 80 | 87 | 127 | 196 |
| Reticulocytes (%) | 0.5–1.5 | 18 | 14 | 10 | 7 | 3 | 2 |
| **Hemostasis tests** | | | | | | | |
| PT* (s) | 9.4–12.5 | 39 | 41 | 30 | 21 | 14 | 12.2 |
| aPTT* (s) | 25–37 | 42 | 39 | 32 | 29 | 26 | 32 |
| INR* (ratio) | 0.8–1.2 | 5.2 | 5.6 | 3.7 | 2.3 | 1.4 | 1.0 |
| D-dimer (ng/ml) | <500 | 970 | 985 | 830 | 650 | 480 | 300 |
| Fibrinogen (mg/dl) | 200–400 | 482 | 426 | 398 | 360 | 278 | 246 |
| **Direct Coombs test** | | Negative | | | | | |
| **Test for VIIT** | | | | | | | |
| Anti-PF4* antibody | ≤0.399 | Negative | | | | | |
| **Haptoglobin level** (mg/dl) | 41–165 | <20 | 22 | 34 | 38 | 44 | 72 |
| **Creatinine level** (mg/dl) | 0.7–1.2 | 0.9 | 0.82 | 0.78 | 0.74 | 0.75 | 0.76 |
| **LDH*** (U/L) | 135–225 | 480 | 495 | 400 | 298 | 254 | 180 |
| **Total bilirubin** (mg/dl) | 0.0–1.2 | 1.6 | 1.6 | 1.4 | 1.3 | 1.2 | 1.2 |
| **Test for SARS-CoV-2** | | | | | | | |
| RT-PCR (Nasopharyngeal swab specimen) | | Negative | | | | | |

*Laboratory reports were done on the same day after a session of Plasma exchange therapy. MCV: Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, PF: 4-Platelet factor-4, LDH: Lactate dehydrogenase

The patient was called for follow-up after 10 days, and at the time of follow-up, the patient was recovered totally with no clinical symptoms. Laboratory reports, 10 days after the discharge of the patient, revealed normal findings with elevated platelet counts of 196 × $10^9$/L, a hemoglobin level of 13.7 g/dl, 2% reticulocytes, 72 mg/dl of haptoglobin, PT, and aPTT value of 12.2 s, and 32 s, respectively, fibrinogen level of 246 mg/dl, and D-dimer level of 300 ng/ml. No relapse of the condition was seen in this patient (Table 1).

## DISCUSSION

aTTP should be suspected in an individual having the symptoms of thrombosis, or thrombocytopenia (bruises, petechia, fever, fatigue, dyspnea, and headache) after vaccination against COVID-19. Blood sampling and initial laboratory workup with CBC, and coagulation tests (PT, aPTT, fibrinogen, and D-dimer) should be done in such a patient. Here, signs of thrombotic microangiopathy (low platelet count, coombs-negative hemolysis, elevation of reticulocytes, and high level of D-dimer) are suggestive of TTP, and diagnosis is confirmed by assessing the ADAMTS13 activity. Very low levels of ADAMTS-antigen and high titer of AntiADAMTS13 antibody (>16 units/ml) confirm the diagnosis.

In our patient, based on the clinical manifestations and laboratory reports, we made the diagnosis of aTTP, which was then confirmed by testing of ADAMTS activity. RT-PCR testing was also done in our patient to exclude COVID-19 infection, since it is necessary to test for COVID-19 infection to rule out the possibility of a hypercoagulable state or other systemic infection, because excess pro-coagulant factors may develop in an individual infected with COVID-19 infection, resulting in thrombosis and concomitant thrombocytopenia [7].

aTTP has been reported after vaccinations, in some cases, mainly against viral pathogens such as influenza or H1N1 [8,9]. In May 2021, the European Journal of Hematology published a case report of a 37-year-old male who developed aTTP 2 weeks after receiving the first dose of vaccine with Vaxzevria (AstraZeneca-Oxford COVID-19 vaccine) [10]. One other case of aTTP in a 62-year-old patient was also reported, 37 days after receiving the Ad26.COV2.S COVID-19 vaccine from Janssen Biotech [11]. Two cases of aTTP have been reported following vaccination with Comirnaty (BNT162b2 antiCOVID19 vaccine, Pfizer-BioNTech), where symptoms in one patient began at about 2 weeks after the first dose and became more severe 1 week after the second dose [12], while other patient experienced dyspnea and fatigue 1 week after the second dose [13].

Frick *et al*. reported an episode of TTP 24 h after typhoid immunization in 1960, implying that vaccination may be a triggering factor [14]. With TTP after influenza vaccination, the time duration between vaccination and TTP onset was between 5 and 14 days, and it was 15 days after vaccination with rabies vaccine and pneumococcal polysaccharide vaccine [15], while it was 3 days after the second dose in our case. The authors speculated that polysaccharide antigens in the pneumococcal vaccine or adjuvants may have contributed to the creation of the inhibitor against ADAMTS13 by cross-reactivity [15].

The pathophysiology behind vaccination-associated aTTP is not clear. Vaccination may lead to the development of autoimmune disorders such as TTP and immune thrombocytopenic purpura by activating the person's immunity by mediating an immunological response [14]. Few cases have been reported earlier, giving rise to new terminology of VIIT which is a rare occurrence [16]. Possible vaccine antigens against the ADAMTS13 gene, which generates a powerful immune response, have been discovered in studies [16], resulting in the release of more VWF from the endothelium that remains uncleaved and binds to platelet, forming microthrombi that results in TTP clinical manifestations. Anti-platelet factor-4 antibodies are observed in VIIT, similar to heparin complexes observed in HIT, suggesting a similar immunological mechanism [17]. However, because SARS-CoV-2 (COVID-19) is a novel disease, and there is limited information available on the adverse effects of the vaccination, more studies are needed to confirm any links between microangiopathic, thrombocytopenic thrombotic diseases, and the administration of COVID-19 vaccinations.

## CONCLUSION

aTTP following the vaccination against SARS-CoV-2 is rare but potentially fatal. ADAMTS13 activity and AntiADAMTS13 antibody titer should be assessed to confirm the diagnosis of aTTP, if indications of thrombotic microangiopathy (low platelet count, coombs-negative hemolysis, and elevated reticulocytes), and typical clinical manifestations such as bruises,

petechia, fever, fatigue, and dyspnea are found following vaccination against COVID-19. TTP is treated with plasma exchange therapy and corticosteroids, while splenectomy is only required in refractory disease.

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**AUTHORS' CONTRIBUTIONS**

All the authors have contributed equally to the data collection, its interpretation, and preparation of the manuscript.

**CONFLICTS OF INTEREST**

The authors have no conflicts of interest.

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**PATIENT'S CONSENT**

For the publication of this case report, written informed consent was obtained from the patient.

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