

# An Early Unexpected Immune Thrombotic Thrombocytopenic Purpura Relapse Associated with SARS-CoV-2 Infection: A Case Report and Literature Review

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## Keywords

SARS-CoV-2 · COVID-19 · Immune thrombotic thrombocytopenic purpura · Caplacizumab

## Abstract

SARS-CoV-2 has been reported as a possible triggering factor for the development of several autoimmune diseases and inflammatory dysregulation. Here, we present a case report of a woman with a history of systemic lupus erythematosus and antiphospholipid syndrome, presenting with concurrent COVID-19 infection and immune thrombotic thrombocytopenic purpura (TTP). The patient was treated with plasma exchange, steroids, and caplacizumab with initial good response to therapy. The course of both TTP and COVID-19 disease was mild. However, after ADAMTS-13 activity was normalized, the patient experienced an early unexpected TTP relapse manifested by intravascular hemolysis with stable platelet counts requiring further treatment. Only 3 cases of COVID-19 associated TTP were reported in the literature thus far. We summarize the literature and suggest that COVID-19 could act as a trigger for TTP, with good outcomes if recognized and treated early.

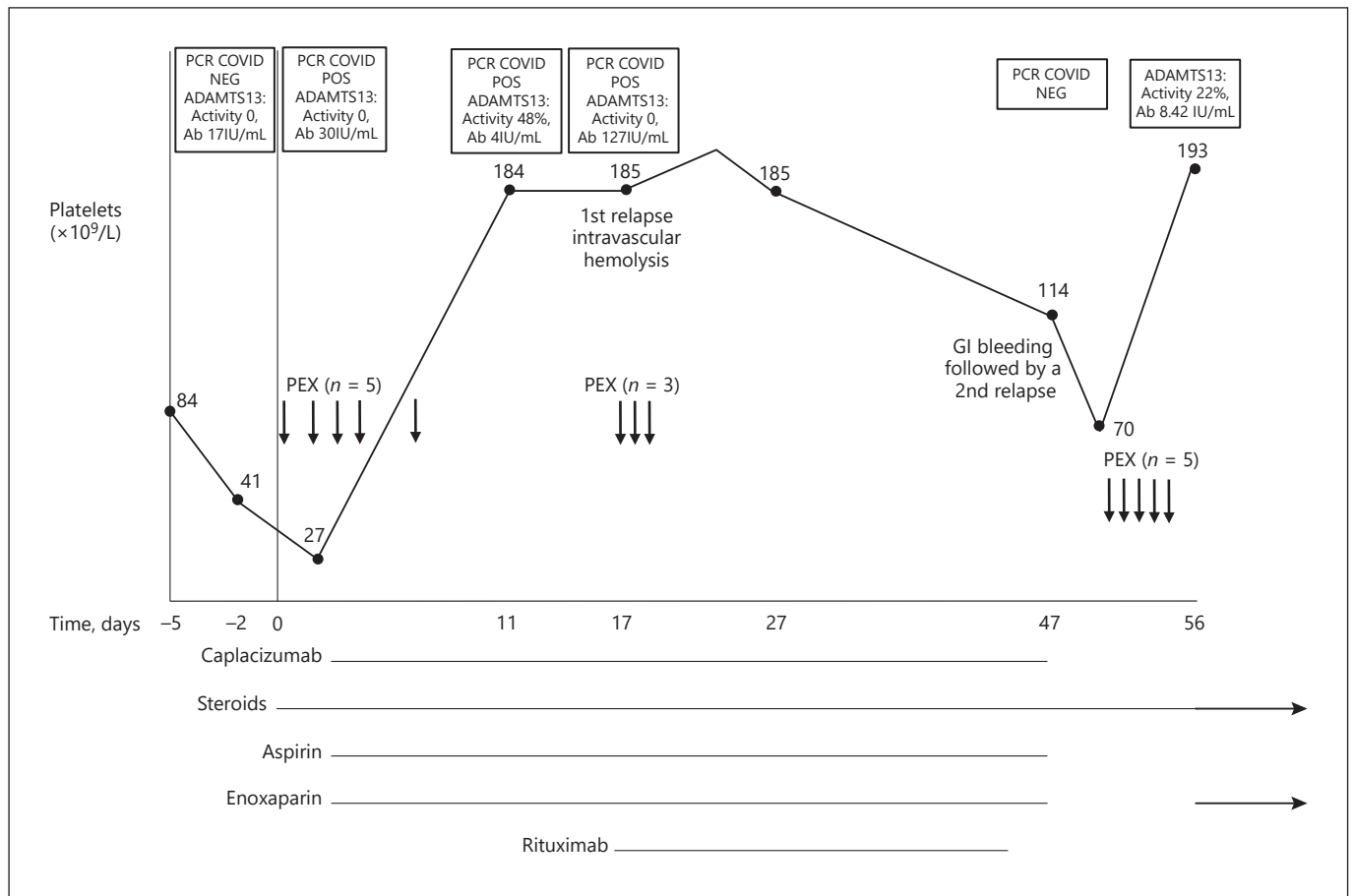
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## Introduction

Coronavirus 2 (SARS-CoV-2) can cause autoimmune and/or auto-inflammatory dysregulation. Autoimmune thrombotic thrombocytopenic purpura (TTP) as a complication of SARS-CoV-2 infection has been reported in 3 cases thus far [1–3]. We report a woman with COVID-19 infection and acquired TTP who relapsed early during the acute infection.

## Case Presentation

A 62-year-old woman was transferred to our hospital for plasma exchange. She presented to another hospital due to acute epigastric abdominal pain 7 days earlier. She had a history of systemic lupus erythematosus (SLE), antiphospholipid syndrome (APLS), CVA, hyperlipidemia trigeminal neuralgia, and hypothyroidism. She was treated with low-dose prednisone, hydroxychloroquine, eltroxin, pregabalin, rosuvastatin, carbamazepine, ramipril, and clopidogrel. On admission, she had normal vital signs and mild epigastric tenderness. Hemoglobin (Hgb) was 11.7 g/dL, the platelet count was  $84 \times 10^9/L$ , and the total leukocyte count was  $12 \times 10^9/L$ . The Cr level was 0.43 mg/dL, and there was a slight elevation in liver en-



**Fig. 1.** Association between coronavirus 2 (SARS-CoV-2) PCR positivity, platelet count, ADAMTS13 activity, ADAMTS13 antibody titer, treatment institution, and relapse is shown above. COVID = SARS-CoV-2. ADAMTS13 activity reference range: 40–130%; ADAMTS13 inhibitor reference range: 0–15.00 IU/mL. Day 0 = admission to our hospital and initiation of plasma exchange.

zymes. Lactate dehydrogenase (LDH) was not measured. Abdominal X-ray and ultrasonography was normal. Past platelet counts were in the range of  $100\text{--}140 \times 10^9/L$ . The presumed diagnosis was peptic ulcer disease, and she was discharged.

Two days prior to the patient's referral to our hospital, she presented again with worsening right lower quadrant and flank abdominal pain. Vital signs were normal. The abdomen was soft and slightly tender, with 2 ecchymoses measuring 4 cm in the RLQ. Neurological examination was normal. Abdominal computed tomography showed a mild enlargement of the right kidney with perinephric fat infiltration and a mild dilatation of the right ureter and collecting ducts. HgB was 9.5 g/dL, platelets  $41 \times 10^9/L$ , and leukocyte count  $5.7 \times 10^9/L$ . Cr was 0.99 mg/dL, LDH was 937 U/L (normal range up to 450 U/L), haptoglobin

was  $<10$  mg/dL, PT and aPTT were normal, and fibrinogen was high 667 mg/dL. D-dimers were elevated to 4,536 ng/mL (normal up to 500 ng/mL). Peripheral blood smear showed schistocytes (online suppl. Fig. 1; see [www.karger.com/doi/10.1159/0005514283](http://www.karger.com/doi/10.1159/0005514283) for all online suppl. material). Immune TTP (iTTP) was suspected. There was no evidence for DIC as coagulation tests were normal and there were no thrombotic complications, making catastrophic aPLS unlikely. A nasopharyngeal swab for SARS-CoV-2 RNA in the nasopharynx was negative. ADAMTS-13 activity was measured and was nondetectable (0%) by a chromogenic ELISA (Technoclone, Vienna Austria) with borderline anti-ADAMTS-13 antibody levels of 171 U/mL (normal up to 151 U/mL). She received 2 units of fresh frozen plasma and was transferred to initiate emergent plasma exchange treatments.

**Table 1.** iTTP associated with COVID-19 infection: comparison of cases described in the literature and our case

Reference	Gender/age, years	TTP diagnosis time relative to SARS-CoV-2 infection	SARS-CoV-2 swab	COVID 19 disease severity	TTP treatment	TTP course
Our case	Female/62	Concomitant	Positive	Mild	PEX ( $n = 5$ , 1st relapse $n = 3$ , 2nd relapse $n = 5$ ), steroids, caplacizumab, and rituximab	Two relapses
Hindilerden et al. [1]	Female/74	Concomitant	Positive	Mild	PEX ( $n = 11$ ) Steroids	Lethargy – resolved
Albiol et al. [2]	Female/57	Concomitant	Negative (referred to as false negative, followed by positive serology)	Mild	Steroids, intravenous immunoglobulin PEX ( $n = 7$ )	Uneventful
Capecchi et al. [3]	Female/55	Relapsed TTP following recovery from SARS CoV-2	Negative (positive serology suggesting a recent infection)	Mild Severe post-COVID pulmonary complications	Plasma infusion PEX ( $n = 14$ ) Steroids caplacizumab	Severe neurological symptoms, multi-organ failure, DIC Intracranial hemorrhage

iTTP, immune thrombotic thrombocytopenic purpura.

Upon admission to our hospital, the patient was in a good general condition. LDH was 1329 U/L, and platelet count was  $32 \times 10^9/L$ . Daily single volume plasma exchange was commenced along with intravenous hydrocortisone (100 mg  $\times$  3 per day) and folic acid supplementation. ADAMTS-13 activity and inhibitor were re-tested and were reported to be 0.07 (normal range: 0.40–1.3 IU/mL) and 30 IU/mL (normal range 0–15 IU/mL), respectively, which reconfirmed the diagnosis of acquired autoimmune TTP. Indirect and direct Coombs tests were negative. A second nasopharyngeal swab test for the detection of SARS-CoV-2 RNA was positive, and she was transferred to the COVID-19 ward. She had a mild cough and low-grade fever, with moderate interstitial infiltrates compatible with COVID-19 pneumonia (online suppl. Fig. 2). After the first plasma exchange, the abdominal pain resolved. By the third day of plasma exchange therapy, the patient's platelet count increased to  $91 \times 10^9/L$ , while the HgB level was 7.2 g/dL and LDH was 666 U/L. She was transfused with 1 leukoreduced RBC unit. Aspirin and enoxaparin dosed at 1 mg/kg once daily were administered daily. Treatment with caplacizumab was started before the fourth plasma exchange treatment. After 5 plasma exchanges, platelets increased to  $184 \times 10^9/L$ , and plasma exchange was discontinued. Repeat ADAMTS-13 test was normal, with an activity of 0.48 IU/mL and inhibitor of 4.1 IU/mL. The patient was discharged home 11 days after

admission to our hospital. During her hospital stay, she was clinically stable with no worsening respiratory symptoms. Upon discharge, she was still positive for SARS-CoV-2. At home, she continued treatment with prednisone 1 mg/kg once daily, aspirin, enoxaparin, folic acid, and daily caplacizumab. Six days later, she was rehospitalized with an HgB drop to 7.5 g/dL and weakness. The platelet count was  $185 \times 10^9/L$ , LDH increased to 865 U/L, Cr was 0.46 mg/dL, D-dimers 1,225 ng/mL, the direct Coombs test was positive, the indirect Coombs was positive, and anti-Jk<sup>a</sup> antibody was detected in serum and RBC eluate. We first assumed the patient had developed hemolysis of the single blood unit she had received; however, ADAMTS-13 activity was again undetected with a higher inhibitor of 127 IU/mL, suggesting relapsed TTP. She was treated with 3 additional plasma exchange courses, steroids, and caplacizumab. Rituximab 375 mg/m<sup>2</sup> was added once weekly for 4 cycles. HgB and LDH remained stable for 21 days after the first dose of rituximab, when the first negative test for COVID-19 received. Three weeks after discharge, she was hospitalized again with severe anemia and melena. HgB was 3.8 g/dL, while the platelet count was  $114 \times 10^9/L$ . LDH was within normal limits. Caplacizumab, LMWH, and aspirin were withheld. Endoscopic evaluation could not find the source of bleeding. After stopping caplacizumab, the platelet count decreased to  $70 \times 10^9/L$ , ADAMTS-13 activity was undetected, and she

was diagnosed with a second TTP relapse. Plasma exchange was resumed for 5 more cycles, until the platelet count was above  $150 \times 10^9/L$  for 2 days. Due to gastrointestinal bleeding, she only received LMWH (with no antiplatelet or caplacizumab). After plasma exchange, platelet count, HgB levels, and ADAMTS-13 were normalized. Fig. 1 summarizes the clinical course, treatment, and PCR positivity.

## Discussion

To the best of our knowledge, only 2 cases of TTP in an acutely infected COVID-19 patient have been reported thus far, although nasopharyngeal swab for the detection of SARS-CoV-2 RNA was positive in only one of them (1,2). Another case of relapsed TTP was reported in a woman after following a recovery from COVID-19 infection. She was tested to be seropositive for SARS-CoV-2 IgG with a negative nasopharyngeal swab [3] (Table 1).

We present a woman with a history of SLE and APLS, admitted with concurrent COVID-19 infection and acquired TTP. TTP has been described in association with SLE and APLS [4, 5]. Considering the rarity and complexity of this case, we have yet to decipher whether COVID-19 was the triggering factor for TTP or whether these were 2 diseases occurring simultaneously. Our patient suffered from abdominal pain 1 week before diagnosis of TTP, while the platelet count was  $84 \times 10^9/L$ . Since the patient had a mild chronic thrombocytopenia, TTP was not suspected upon her ER visit. Five days later, when diagnosis of TTP was confirmed, the first nasopharyngeal swab for SARS-CoV-2 was negative. Since the SARS-CoV-2 test performed approximately 24 h later in our hospital was positive, it is plausible that the first swab test was falsely negative, a common pitfall in the diagnosis of an early-stage COVID-19 infection. Therefore, the possibility of a COVID-19-triggered TTP is plausible, and iTTP could be a presenting manifestation for SARS-CoV-2 infection even before PCR positivity. Furthermore, it was demonstrated that normal ADAMTS13 activity in clinical remission are associated with a low risk of TTP relapse [6]. The fact that TTP recurred very early in our patient after ADAMTS-13 inhibitor normalized was surprising and supports the hypothesis that there was a continued trigger for the disease, such as COVID-19 infection.

COVID-19-associated coagulopathy leading to a prothrombotic state was shown to be associated with elevat-

ed von Willebrand factor (VWF) antigen and activity [7]. In a previous study, ADAMTS-13 levels were significantly reduced in all COVID-19 patients [8]. ADAMTS-13 plasma levels less than 30% were significantly associated with a higher mortality [9]. In our case, no clinical thrombotic complications have occurred, despite unmeasurable ADAMTS13 activity and the presence of antiphospholipid antibodies. However, the patient was treated early with enoxaparin aspirin and caplacizumab.

Clopidogrel-associated TTP was first identified in 1999 and is one of the most common drugs associated with TTP according to the FDA safety databases [10, 11]. Clopidogrel-associated TTP onset usually occurs within 2 weeks of drug initiation, and only in a minority of cases, ADAMTS-13 activity is reduced [10]. Therefore, clopidogrel as the triggering factor for TTP in this patient is unlikely. Still, the patient was advised to discontinue clopidogrel and switch to aspirin.

Caplacizumab is a humanized anti-VWF antibody which inhibits interaction between VWF large multimers and platelets [12]. Capecchi M et al. reported a case of a woman with relapsed TTP associated with a recent COVID-19 infection [3]. This woman had a life-threatening presentation of TTP with altered consciousness and multi-organ failure. Treatment with caplacizumab started early, with a platelet count rising within 6 h after the first injection. Our patient did not develop neurological symptoms and eventually had a mild course of TTP, although she relapsed early. Since caplacizumab is not immunosuppressive, it is not predicted to have an impact on COVID-19 disease. We decided to prescribe caplacizumab in order to try and avoid rituximab administration during acute SARS-CoV-2 infection as advised by guidelines [13] and also in order to reduce the number of plasma exchange treatments in view of the complexity of treatment at the COVID-19 department. Presuming that SARS-CoV-2 infection was a triggering factor to TTP, we also assumed it was safer to discharge the patient home while still positive for SARS-CoV-2 with the combination of steroids and caplacizumab. Indeed when she relapsed, thrombocytopenia did not develop probably because of caplacizumab treatment.

The fact that our patient had O+ blood type is consistent with the literature stating that for these patients, it take a shorter time to recover as measured by a fewer number of plasma exchanges needed for platelet recovery, in comparison to non-O blood group patients [14]. A delayed hemolytic transfusion reaction results in RBC hemolysis 1–28 days following blood transfusion. Delayed hemolytic transfusion reaction incidence is

~1:20,000 [15]. In our patient, anti-Jk<sup>a</sup> was seen. Multiple factors affect RBC alloimmunization including discrepancies of RBC antigens between the donor and recipient, HLA haplotypes, autoimmune diseases, and the presence of inflammation [16]. It is plausible that the both the inflammatory state caused by COVID-19 and autoimmunity contributed to the development of anti-Jk<sup>a</sup> following a single RBC transfusion, despite the fact that the Jk<sup>a</sup> antigen is not highly immunogenic.

In conclusion, SARS-CoV-2 infection may trigger the development of autoimmune TTP. Patients may have a favorable course if diagnosed and treated early. Early relapse may occur, despite initial response to therapy.

## Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

## Conflict of Interest Statement

The authors declare no conflict of interest.

## Author Contributions

All authors were involved in patient treatment. G.S. and M.K.C. wrote the manuscript. L.S., Y.S. V.Y., and A.G.G. have critically reviewed the manuscript.

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