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LETTER TO THE EDITOR

A case of thrombotic thrombocytopenic purpura associated with COVID-19

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Abstract
Acquired thrombotic thrombocytopenic purpura (TTP) is an autoimmune disease that can be triggered by different events, including viral infections. It presents as thrombotic microangiopathy and can lead to severe complications that often require management in the intensive care unit (ICU). We report a patient who presented with acquired TTP following COVID-19 infection. A 44-year-old woman presented to the emergency department with severe anemia, acute kidney injury and respiratory failure due to COVID-19. Clinical and laboratory findings were suggestive for thrombotic microangiopathy. On day 8 laboratory tests confirmed the diagnosis of acquired TTP. The patient needed 14 plasma exchanges, treatment with steroids, rituximab and caplacizumab and 18 days of mechanical ventilation. She completely recovered and was discharged home on day 51. Acquired TTP can be triggered by different events leading to immune stimulation. COVID-19 has been associated with different inflammatory and auto-immune diseases. Considering the temporal sequence and the lack of other possible causes, we suggest that COVID-19 infection could have been the triggering factor in the development of TTP. Since other similar cases have already been described, possible association between COVID and TTP deserves further investigation.

Keywords Thrombocytes · COVID-19 · Thrombotic thrombocytopenic purpura · Rituximab · Immunology and infectious diseases · Hemostasis and platelets

The recent COVID-19 pandemic was associated with numerous clinical conditions and unexpected scenarios, including hematologic and auto-immune syndromes. We describe the case of a patient presenting with severe COVID-19 pneumonia that developed TTP.

A 44-year-old woman with obesity and a history of previous deep vein thrombosis presented to the emergency department with a 2-day history of general weakness, dizziness and abdominal discomfort. History was negative for COVID-19 exposure. On physical examination she was alert without overt neurological dysfunction, she presented clinical signs of respiratory distress and diffuse abdominal discomfort without signs of peritoneal inflammation. Blood pressure was 90/60 mmHg, pulse rate 120 bpm and body temperature 37.2 °C.

Laboratory tests showed mild leucocytosis (12,590/μL) with normal formula, severe anemia (hemoglobin 6.0 g/dL) and normal platelet count (122,000/μL), creatinine 2.0 mg/dL and urea 119 mg/dL (BUN 55.5 mg/dL) with normal sodium and potassium. Arterial blood gas indicated acute hypoxic respiratory failure. Computerized tomography (CT) scan revealed bilateral interstitial pneumonia involving 25% of lung parenchyma, highly suggestive for COVID-19. A pharyngeal swab for SARS-CoV2 was positive. Blood and sputum cultures were negative and no other respiratory viruses were detected.

Treatment with oxygen, antibiotics, antivirals, hydration and blood transfusions was started. On the second day, the patient became confused and restless without focal neurologic deficit, blood pressure was 110/70 mmHg and saturation 94% while breathing 35% oxygen; blood tests showed persistent anemia despite blood transfusions and severe thrombocytopenia (platelet count 7000/μL), increase in

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creatinine level (2.3 mg/dL), lactate dehydrogenase (LDH) 2961 U/L, D-dimer >9000 ng/mL, normal prothrombine time (PT) and activated partial thromboplastin time (aPTT), fibrinogen 513 mg/dL. An arterial blood gas demonstrated worsening oxygenation with normal lactate level. The patient was admitted to the ICU, where she was intubated and mechanical ventilation was initiated. CT scan of the brain was negative.

On day 4, given the persistence of severe thrombocytopenia (11,000/μL) despite platelet transfusion, a blood smear was performed that revealed abundant schistocytes, while direct Coombs test was negative and haptoglobin level was low (<10 mg/dL). Unconjugated bilirubin was 2.0 mg/dL, Fibrinogen 470 mg/dL, PT and aPTT were normal, creatinine 1.7 mg/dL and urea 108 mg/dL. Following hematologic consultation, treatment with daily plasma exchange was started with replacement of one plasma volume. Upon suspension of the sedatives on day 6, the patient was arousable, but presented a left hemiparesis. Contrast CT scan of the brain was negative and the patient progressively recovered. On day 8, tests for depressed (<5%) ADAMTS13 activity and positive (57 U/mL) anti-ADAMTS13 antibodies confirmed the diagnosis of acquired TTP and methylprednisolone (1 mg/kg) was started.

On day 12, after 7 plasma exchanges and 5 days of methylprednisolone therapy, renal function had normalized, but platelet count was still 15,000/μL, hemoglobin 6.7 g/dL, LDH 609 U/L, with normal PT and aPTT and D-dimer 2500 ng/mL, fibrinogen 450 mg/dL; schistocytes were still present. On day 13 rituximab (375 mg/m^2 body surface area) was administered immediately after plasma exchange. Considering the ongoing COVID-19 infection and the risk for immunosuppression with repeated doses of rituximab, we decided to start caplacizumab to enhance response and prevent relapse. Starting from day 14, caplacizumab (10 mg daily) was administered and continued for 4 weeks.

Starting from day 16, we observed a rapid rise in platelet count, that reached 100,000/μL by day 18. Plasma exchange was continued on a daily basis until day 18, for a total of 14 plasma exchanges performed without related complications. On day 48, laboratory findings demonstrated a rise in ADAMTS13 activity (63%) and a reduction in anti-ADAMTS13 antibodies (12 U/mL), platelet count and hemoglobin level were within normal range and stable.

The patient did not suffer any hemorrhagic complication throughout the course of hospital stay. Renal replacement therapy was not needed. Respiratory failure improved slowly allowing for gradual weaning from mechanical ventilation. On day 20 she was transferred out of the ICU and after one more month she was discharged home without any residual neurological symptoms.

Acquired TTP is an autoimmune disease caused by the formation of antibodies against the metalloproteinase ADAMTS13 (A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13). Reduction in ADAMTS13 activity leads to the accumulation of Von Willebrand factor multimers followed by increase in platelets aggregability and thrombotic microangiopathy. Clinical manifestations typically include thrombocytopenia, mechanical hemolysis and anemia, renal failure, neurologic impairment and fever. Acquired TTP can be triggered by bacterial and viral infections, pancreatitis or immune stimulation such as vaccination [1].

The pathophysiology of anti-ADAMTS13 antibodies production following viral infection is still not completely understood. However, viral infections are well described triggers of TTP cases [2], and SARS-CoV2 have been described in correlation with different autoimmune and inflammatory diseases in both children and adults [3]. Finally, two cases of TTP were recently reported in patients diagnosed with COVID-19 [4, 5]. In both cases, thrombotic microangiopathy presented six days after initial symptoms of viral infection and COVID pneumonia was mild. In our case, the shorter time interval (three days) between symptoms onset and the manifestation of thrombotic microangiopathy might be due to a more severe form of viral infection and inflammatory response, as suggested by the severity of pneumonia, that eventually needed intubation and mechanical ventilation.

This is the third reported case of TTP associated with COVID-19. In all described cases, the temporal sequence and the lack of other possible causes may suggest a possible role for viral infection in the pathogenesis of TTP. However, data should be interpreted with caution, since definitive proof of the triggering role of SARS-CoV2 infection is still lacking.

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Compliance with ethical standards

Conflict of interest disclosure All the authors declared that they have no conflict of interest to disclose.

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