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Case Report

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Emerging Novel Etiology for Thrombotic Microangiopathies: COVID-19 Infection

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ABSTRACT

The novel and worldwide spread of coronavirus disease 2019 has important thrombotic complications, making it necessary to treat it with low-molecular-weight heparin. However, though it is very rare, it should be kept in mind that coronavirus disease 2019 infection might be complicated by thrombotic thrombocytopenic purpura, resulting in severe thrombocytopenia which makes heparin use contraindicated. The complications of thrombotic thrombocytopenic purpura have been elucidated after this pandemic infection. We report a case of acquired thrombotic thrombocytopenic purpura due to late hematological manifestation of coronavirus disease 2019 infection. A 47-year-old male patient who developed microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury (stage 3) with macroalbuminuria was diagnosed with thrombotic thrombocytopenic purpura based on very low plasma ADAMTS13 activity and borderline ADAMTS13 inhibitor level 4 weeks after coronavirus disease 2019 infection detected by positive nucleic acid amplification test (reverse-transc ription polymerase chain reaction). Coronavirus disease 2019 infection usually leads to thrombotic events, making it necessary to treat it with low-molecular-weight heparin. However, even though it is very rare, it should be kept in mind that coronavirus disease 2019 infection might be complicated by thrombotic thrombocytopenic purpura, resulting in severe thrombocytopenia, which makes heparin use contraindicated. This is the first case reporting the appearance of stage 3 acute kidney injury in thrombotic thrombocytopenic purpura due to coronavirus disease 2019 infection after a window period of 1 month and successful treatment with only steroids.

Keywords: Purpura, thrombotic thrombocytopenic, COVID-19, acute kidney injury

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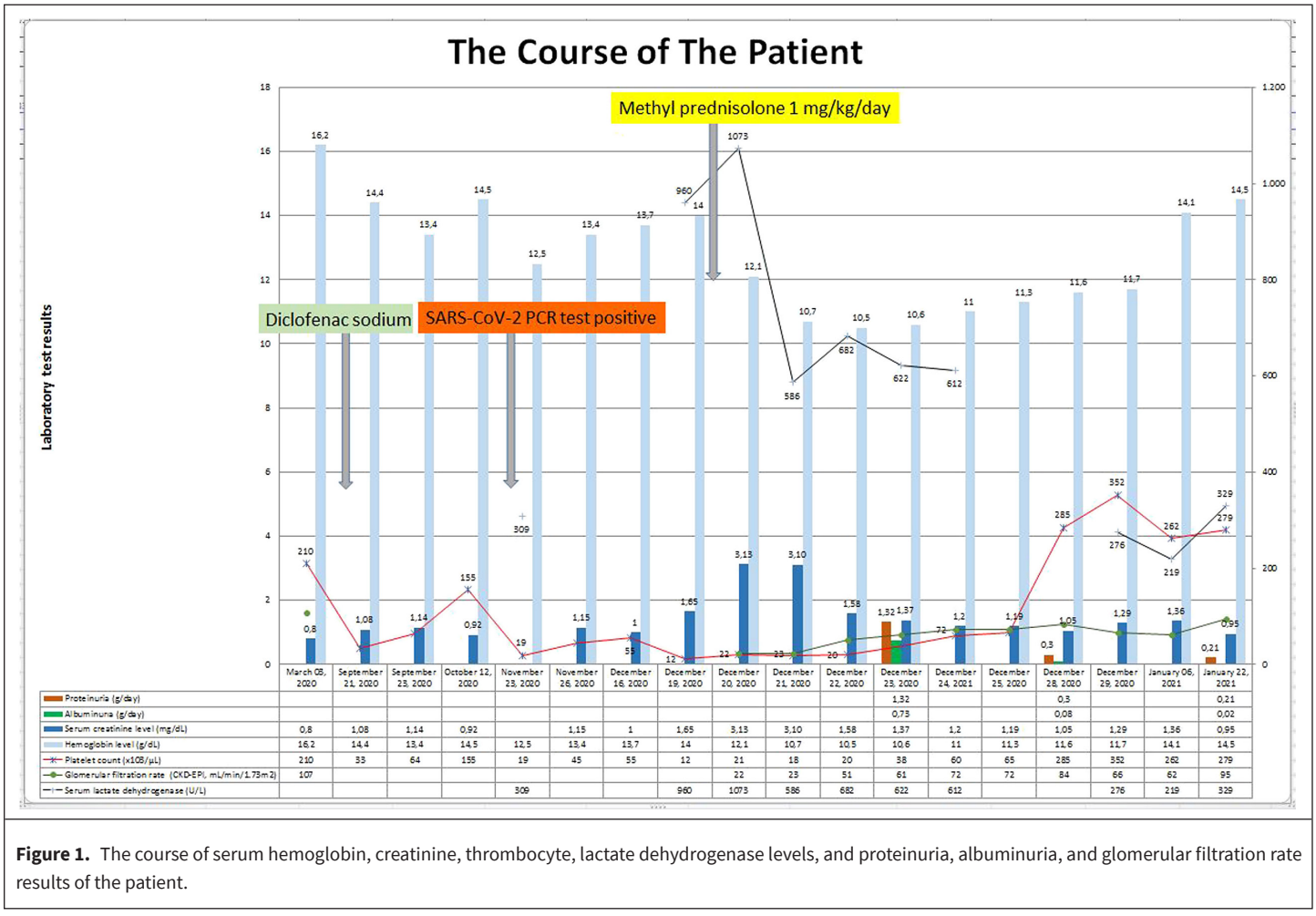
INTRODUCTION

When microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and acute kidney injury (AKI) are detected, thrombotic microangiopathy (TMA) is suspected.[1] Whenever TMA is clinically diagnosed, further evaluation for the presence of hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), and other causes such as malignities, sepsis, drugs, pregnancy, autoimmune diseases, and transplantation should be performed.[1] In addition to these entities, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) should also be investigated, as it has been reported to cause specific coagulopathy known as coronavirus disease 2019 (COVID-19)-associated coagulopathy (CAC).[2]

Herein, we present a case with MAHA, thrombocytopenia, and AKI diagnosed as acquired thrombotic thrombocytopenic purpura (TTP) in the month following the COVID-19 infection. This case is important as it presents the development of TTP in a patient with COVID-19 infection, which reminds us to follow up patients with respect to thrombocytopenia and bleeding complications in the COVID-19 pandemic, which mostly leads to thrombotic complications, making heparin necessary to administer. In addition, the present case also shows the emergence



	March 08, 2020	September 21, 2020	September 23, 2020	October 12, 2020	November 23, 2020	November 26, 2020	December 16, 2020	December 19, 2020	December 20, 2020	December 21, 2020	December 22, 2020	December 23, 2020	December 24, 2021	December 25, 2020	December 28, 2020	December 29, 2020	January 06, 2021	January 22, 2021
Proteinuria (g/day)												1,32			0,3			0,21
Albuminuria (g/day)												0,73			0,08			0,02
Serum creatinine level (mg/dL)	0,8	1,08	1,14	0,92		1,15	1	1,65	3,13	3,10	1,58	1,37	1,2	1,19	1,05	1,29	1,36	0,95
Hemoglobin level (g/dL)	16,2	14,4	13,4	14,5	12,5	13,4	13,7	14	12,1	10,7	10,5	10,6	11	11,3	11,6	11,7	14,1	14,5
Platelet count (x10^3/µL)	210	33	64	155	19	45	55	12	21	18	20	38	60	65	285	352	262	279
Glomerular filtration rate (CKD-EPI, mL/min/1.73m2)	107								22	23	51	61	72	72	84	66	62	95
Serum lactate dehydrogenase (U/L)					309			960	1073	586	682	622	612			276	219	329

Figure 1. The course of serum hemoglobin, creatinine, thrombocyte, lactate dehydrogenase levels, and proteinuria, albuminuria, and glomerular filtration rate results of the patient.

of TTP after a gap period of a month after COVID-19 infection and successful treatment of TTP with steroids only.

CASE PRESENTATION

A 47-year-old male patient who developed MAHA, thrombocytopenia, and AKI (stage 3) with macroalbuminuria 4 weeks after COVID-19 infection detected by positive nucleic acid amplification test (reverse-transcription polymerase chain reaction) was presented. The patient was admitted to our emergency room with nausea and vomiting. His physical examination revealed diffuse petechiae and arterial hypertension (150/110 mmHg). His medical history was insignificant except for 2 episodes of thrombocytopenia triggered by infection 10 years ago and non-steroidal anti-inflammatory drugs 2 months prior to September 21, 2020. After these episodes, the patient was well until he had myalgia due to COVID-19 infection (November 23, 2020) and received oral favipiravir as outpatient treatment 1 month ago. The past and current medical information of the patient is illustrated (Figure 1). Biochemical tests detected thrombocytopenia (12 000/µL) and acute kidney failure [estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD–EPI-cre-based); 22 mL/min/1.73 m^2] (Figure 1). Microangiopathic hemolytic anemia, defined as schistocytes, was detected in more than 5% of peripheral blood smears. His hemoglobin level decreased from 14 g/dL to 10.5 g/dL in 3 days without external or internal bleeding (Figure 1).

Evaluation of bone marrow aspiration and biopsy revealed normal cellularity and maturation of granulocytes, erythrocytes, and megakaryocytes. Reticulocyte count was 1%, haptoglobin level was 42 mg/dL (normal, 14-258), indirect bilirubin level was 2.49 mg/dL (normal, 0.3-1), serum lactate dehydrogenase level was 1073 U/L (normal, <248), international

MAIN POINTS

- Coronavirus disease 2019 (COVID-19) infection usually leads to thrombotic events (40%), making it necessary to treat it with low-molecular-weight heparin. However, even though it is very rare, it should be kept in mind that COVID-19 infection might be complicated by thrombotic thrombocytopenic purpura (TTP), resulting in severe thrombocytopenia, which makes heparin use contraindicated.
- This is the first case reporting the appearance of stage 3 acute kidney injury in TTP due to COVID-19 infection after a window period of 1 month and treated with only steroids successfully.

normalized ratio was 0.96 (normal, 0.85-1.15), fibrinogen level was 336 mg/dL (normal, 180-350), and complement 3 (C3) and complement 4 (C4) levels were 1.17 g/dL and 0.36 g/dL (normal range, 0.9-1.8; and 0.1-0.4, respectively). Antinuclear antibody was detected as positive at 1/100 titration by immunofluorescence assay. Blood cultures, direct Coombs test, and anti-double-stranded deoxyribonucleic acid antibody, anti-neutrophil cytoplasmic antibodies, and anti-extractable nuclear antigen antibodies were negative. Disseminated intravascular coagulation was discarded based on normal fibrinogen levels. The PLASMIC score was calculated as 6 points, indicating high probability of TTP.[3] Plasma ADAMTS13 activity, ADAMTS13 inhibitor, and ADAMTS13 antigen were found as 0.31% (severe deficiency, <10%), 14.66 U/mL (negative, <12 U/mL; borderline, 12-15; positive, >15), and 0.113 IU/mL (normal, 0.19-0.81), respectively, by enzyme-linked immunosorbent assay method. Genetic analysis did not identify any mutations in ADAMTS13 protein-coding domains. The patient was diagnosed with immune TTP based on the findings of very low plasma ADAMTS13 activity, borderline ADAMTS13 inhibitor level, severely decreased ADAMTS13 antigen, and absence of mutations in ADAMTS13 protein-coding domains.[3] At admission, before the test results were obtained, methylprednisolone (1 mg/kg/day per oral), amlodipine (5 mg/day), and parenteral fluids were administered to the patient. On the fourth day of treatment, serum creatinine level decreased from 3.13 mg/dL to 1.2 mg/dL, and on the eighth day, the platelet count increased from 12 000/μL to 285 000/μL. When the test results were obtained, TTP due to hematological manifestation of COVID-19 infection was diagnosed. However, the patient already recovered completely. Therefore, plasma exchange therapy was not performed. One month after the discharge, he was admitted to outpatient department with normal findings.

DISCUSSION

Whenever MAHA and thrombocytopenia were noticed, primary TMA syndromes (TTP, Shiga toxin-mediated HUS, drug-induced TMA, and complement-mediated TMA) and other systemic diseases (systemic lupus erythematosus, pregnancy-related preeclampsia, malignancies, infections, hypertension, and complications of stem cell and solid organ transplantations) should be questioned. Reduced levels of plasma ADAMTS13 activity (<10%) is the gold standard for discriminating other causes of TMA from TTP.[3]

Thrombotic thrombocytopenic purpura is a rare thrombopathy, leading to thrombocytopenia, MAHA, and organ ischemia resulting from lack of ADAMTS13 (the von Willebrand factor-cleaving protease) which inhibit adhesion of von Willebrand factor multimers to platelets and microthrombosis.[3] The severe deficiency of ADAMTS13 cases as in our patient is mostly due to immune-mediated mechanisms, whereas in a small number of cases, it resulted from genetic mutations which should be suspected when undetectable plasma ADAMTS13 activity without ADAMTS13 inhibitor is present. Then, biallelic pathogenic variants of *ADAMTS13* gene should be searched. The presence of ADAMTS13 inhibitor in these settings (TMA with severe deficiency of plasma ADAMTS13 activity) confirms the diagnosis of immune-mediated TTP.[3] Our patient had severe deficiency of plasma ADAMTS13 activity together with ADAMTS13 inhibitor. Hence, immune TTP was diagnosed. The incidence of TTP was reported to be nearly 3 patients/1 000 000 adults/year.[3] However, sporadic cases of TTP seem to be on the rise after the 2019 novel coronavirus pandemic. The first case of acquired TTP that occurred immediately after COVID-19 infection was reported by Albiol et al.[4] Afterward, 11 cases of TTP induced by simultaneous COVID-19 infection were published in the literature.[5-12] Occurrence of TTP after COVID-19 infection was reported with a time lag of 10 days in only one case.[13] Rest of the cases of TTP complications were reported after receiving mRNA-based anti-COVID-19 vaccination with approximately a time lag of 2 weeks.[14] Our case is the only one reporting TTP as a longer (1 month)-term complication after COVID-19 infection. Treatments for these patients included a combination of plasma exchange (PEx), intravenous immunoglobulin, dexamethasone or methylprednisolone (corticosteroids), rituximab, fresh frozen plasma, and caplacizumab which is a novel humanized nanobody (fragment of monoclonal antibody) against von Willebrand factor blocking the interaction with platelets.[15] The gold standard therapy for TTP is PEx. If nonresponse to PEx is observed, then other treatment options are usually recommended. However, caplacizumab is recommended as an initial form of therapy, if the patient is presented with severe and critical disease such as neurologic and cardiac manifestations, in addition to refractory cases to PEx, glucocorticoids, and rituximab.[15] In the present case, immune thrombocytopenia was initially thought to be a preliminary diagnosis, and methylprednisolone was started before the ADAMTS13 test results were revealed. Once, acquired TTP was diagnosed, the patient had already fully recovered without the need for PEx. Even though decreased plasma ADAMTS13 activity was reported among patients diagnosed with pneumonia due to SARS-CoV-2 infections with the need of mechanical ventilation, our patient had not needed ventilation support during SARS-CoV-2 infection and still developed immune TTP.[16]

The main hematological pathology observed in COVID-19 infection has been reported as microthrombi in alveoli and systemic vasculatures due to dysregulation of the coagulation cascade and disseminated intravascular coagulation.[17] Interestingly, Gavriilaki et al[18] found that missense mutations in genes leading to TMA such as *ADAMTS13*, *C3*, and *CFH* were independently associated with severe COVID-19 infections needing intensive care unit hospitalizations. In addition, a new hematological complication, immune TTP, has emerged. Our patient is the thirteenth case reporting TTP induced by COVID-19 infection and the first case reporting the development of TTP in the gap period of 1 month after COVID-19 infection and successful treatment with methylprednisolone only.

CONCLUSION

Coronavirus disease 2019 usually leads to thrombotic events (40%), making it necessary to treat them with low-molecular-weight heparin. However, even though it is very rare, it should be kept in mind that COVID-19 infection might be complicated by TTP, resulting in severe thrombocytopenia, which makes heparin use contraindicated and leads to bleeding complications. We would like to emphasize the importance of searching for kidney disease and thrombocytopenia in patients with COVID-19, especially before the administration of heparin, to prevent thrombotic complications of this pandemic. The present case shows even the emergence of TTP after a gap period of a month after COVID-19 infection and successful treatment of TTP with steroids only as the patient has recovered completely.

Informed Consent: Written informed consent for publication of this case report was obtained from the patient.

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