COVID-19 Presenting With a Challenging Combination of Thrombocytopenia and Thrombosis

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Abstract
Coronavirus disease 2019 (COVID-19) causes various hematological abnormalities, leading to several complications in the disease course. We report two COVID-19 cases presenting with a combination of thrombocytopenia and coagulopathy complications in late 2020. A 73-year-old male with a history of immune thrombocytopenic purpura (ITP) presented with acute ischemic stroke and acute thrombocytopenia in the setting of COVID-19. He was managed with steroids and intravenous immunoglobulin (IVIG) and had a subsequent acute ischemic stroke with microhemorrhages. Another 72-year-old female with a history of cryptogenic liver cirrhosis and chronic thrombocytopenia presenting with acute thrombocytopenia in the setting of COVID-19 was managed with steroids and IVIG. She had a coagulopathic complication of deep venous thrombosis (DVT) later in her disease course managed with inferior vena cava filter and low-dose enoxaparin, but she subsequently died with a bleeding complication of retroperitoneal hemorrhage. Despite the aggressive ongoing research, the treatment options for severe COVID-19 are limited to date and the mortality remains high. Both these cases are examples of challenging situations that the physicians are currently facing with COVID-19 pandemic.

Keywords: COVID-19; Thrombocytopenia; Coagulopathy; Thrombosis

Introduction
Coronavirus disease 2019 (COVID-19) presents with varying severity and several complications, frequently involving hemostatic system [1]. Various hematological abnormalities are reported in COVID-19 patients, some of which have prognostic significance. Guan et al [2] reported lymphopenia in 83.2% of their study patients, thrombocytopenia in 36.2% and leukopenia in 33.7%, and the level of these abnormalities was directly correlated with severity of COVID-19. Platelet changes were commonly reported leading to several complications in the disease course such as thrombocytopenia, systemic hypercoagulability and thromboembolic events [1]. Here we report two challenging cases where COVID-19 presented with thrombocytopenia and thrombosis together, complicating the course and management of this disease.

Cases Reports
Case 1

Investigations
A 73-year-old male with a past medical history of metastatic poorly differentiated lung adenocarcinoma status post two cycles of carboplatin + pembrolizumab, poorly controlled rheumatoid arthritis, chronic immune thrombocytopenic purpura (ITP), recent upper extremity deep venous thrombosis (DVT) and pulmonary embolism (PE) for which he was receiving anticoagulation therapy with apixaban, was admitted with acute change in mental status. His last dose of chemotherapy was more than a month before his initial presentation.

Diagnosis
His polymerase chain reaction (PCR) testing for COVID-19 was positive. Computed tomography (CT) scan of head without contrast showed chronic age-related microvascular changes without any acute intracranial pathology. Magnetic resonance imaging (MRI) of the brain with and without contrast showed left cerebral acute infarcts with microhemorrhages, punctate right occipital infarct, left parietal signal abnormalities
and punctate foci of enhancement. Initial lab testing revealed: white blood cell count of $5.03 \times 10^9$/L of which lymphocytes were 13%, D-dimer $> 20 \mu$g/mL, partial thromboplastin time (PTT) of 32.6 s, international normalized ratio (INR) of 1.2, platelet count of 60,000/mm$^3$. His baseline platelet count was around 75,000/mm$^3$. The etiology of his thrombocytopenia was presumed to be exacerbation of his chronic ITP in setting of COVID-19 infection. His platelet counts progressively trended down to below 40,000/mm$^3$.

**Treatment**

Apixaban was held and he was given 3 days of intravenous (IV) dexamethasone 4 mg every 6 h followed by 2 days of intravenous immunoglobulin (IVIG) 1 g/kg. Platelet count slightly improved but remained below 60,000/mm$^3$. His D-dimer was persistent at $> 20 \mu$g/mL; however, given his refractory thrombocytopenia, his anticoagulation was decided to be held. He was discharged home with oral prednisone 15 mg daily. He was re-admitted the very next day with blurred vision, and MRI of the brain showed interval evolution of previously seen infarct in the left cerebral hemisphere, large acute infarct in right temporal lobe with microhemorrhages.

**Follow-up and outcomes**

Given his multiple comorbidities with poor prognosis, he was placed on home hospice care and expired within few days.

**Case 2**

**Investigations**

A 72-year-old female with aortic stenosis status post bioprosthetic valve and cryptogenic liver cirrhosis with chronic thrombocytopenia (bone marrow biopsy in past excluded leukemia, aplastic anemia or lymphoproliferative disorder) had an initial hospital admission for COVID-19-related pneumonia and was treated with dexamethasone and remdesivir. During this admission, she was noted to have a platelet count of 11,000/mm$^3$ without any signs and symptom of bleeding and D-dimer of 2.8 \mu g/mL. Her baseline platelet count was 40,000/mm$^3$. She received a dose of IVIG 0.5 g/kg with slight improvement in platelet count and was discharged home. She had a second hospital admission for fall within couple of days, during which her WBC count was 10.49 $\times 10^9$/L, lymphocytes were 5.2%, PTT was 25.5 s, INR was 1.4, platelet count was 24,000/mm$^3$ without any signs of bleeding. She was treated with 90 mg of prednisone daily and was discharged with a plan to taper prednisone by 10 mg every 3 days. Two days later, she had third hospital admission for worsening shortness of breath.

**Diagnosis**

CT ruled out PE and showed persistent bilateral lung infiltrates consistent with COVID pneumonia. Her platelet count during this admission was less than 25,000/mm$^3$. Duplex of lower extremity showed bilateral occlusive DVT in femoral and popliteal veins extending up to right common femoral vein.

**Treatment**

Interventional radiology-guided inferior vena cava filter was placed. There was no improvement in platelet count with high-dose steroid or IVIG. Her bone marrow biopsy showed hypercellular bone marrow with adequate mature granulopoiesis and megakaryopoiesis without increased blasts, myelodysplastic syndrome, or marrow involvement by lymphoma. She was treated with two doses of romiplostim 100 \mu g, 4 days apart, after which platelet count increased to $> 40,000/\mu$L and she was placed on anticoagulation therapy with subcutaneous enoxaparin 0.5 mg/kg two times daily.

**Follow-up and outcomes**

Four days later, she was readmitted with retroperitoneal bleed, hypoxemic respiratory failure, and hypotension with a platelet count of 334,000/\mu$L. She was placed on comfort care measures and expired.

**Discussion**

Thrombocytopenia or thrombosis are commonly seen in COVID-19 patients, and the combination of these complications is particularly challenging.

**Thrombocytopenia**

Thrombocytopenia is reported to be mild to moderate in most COVID-19 cases without causing significant bleeding complications [3, 4]. Thrombocytopenia and platelet-to-lymphocyte ratio were reported to have a prognostic role in COVID-19 [4-6]. On admission, thrombocytopenia was reported in 35.8% of patients who had a composite outcome of admission to intensive care unit (ICU), requiring mechanical ventilation or death in 14 days, and 52.6% in patients who died in 14 days [5]. The in-hospital mortality was also directly correlated with severity of thrombocytopenia [6].

The causes of thrombocytopenia are unclear, but several mechanisms were proposed as described in Table 1 [1, 3, 4, 7]. Management of thrombocytopenia is usually supportive and depends on the cause of thrombocytopenia. Critical causes such as thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia must be excluded first [8]. ITP is a diagnosis of exclusion. Steroids such as prednisolone at a dose of 1 mg/kg tapered after 2 weeks is standard first-line therapy [8]. IVIG is second-line therapy in ITP patients who fail to respond appropriately to steroids [8]. Platelet transfusion should be avoided in patients without significant hemorrhage due to
the risk of thrombosis in COVID-19 [8]. Thrombopoietin receptor agonists should also be avoided given the risk of thrombosis in COVID-19 patients [8]. Due to the risk of developing severe COVID-19, it is better to avoid immunosuppressant drugs [8].

Coagulopathy

Thrombosis is one of the dreaded complications and a major cause of morbidity and mortality in COVID-19 [9]. COVID-19 with acute respiratory distress syndrome was associated with more thrombotic complications [7]. Klok et al reported 27% venous thromboembolism and 3.7% arterial thrombosis in COVID-19 ICU patients despite at least standard dose thromboprophylaxis [10]. PE was reported to be most common [10].

Various coagulation abnormalities are hallmark of COVID-19 coagulopathy. Elevated D-dimer and fibrinogen, prolonged prothrombin time and activated PTT, mild thrombocytopenia were commonly reported [1, 9, 10]. High D-dimer and fibrin degradation product (FDP) levels, prolonged prothrombin time and activated partial thromboplastin time were associated with higher mortality rate [11]. Elevated D-dimer levels can also be used to predict risk of thrombosis [12]. In very severe cases, a disseminated intravascular coagulopathy (DIC) like state was reported with extremely elevated D-dimer; however, fibrinogen level is often normal or elevated in COVID-19 unlike in classic DIC [1, 9].

Platelets, endothelium and inflammatory cells were involved in COVID-19-associated coagulopathy, of which platelets were reported to have a significant role. Following are the proposed mechanisms of COVID-19-associated coagulopathy as described in Table 2 [1, 13].

Thromboprophylaxis was showed to lower incidence of DVT in COVID-19 hospitalized patients [12]. Thromboprophylaxis with heparin was associated with lower mortality in COVID-19 with elevated D-dimer and increased risk for thrombosis [14]. Physical therapy and hydration in addition to thromboprophylaxis during hospitalization are important measures to prevent thrombosis. Low-molecular-weight heparin is first-line standard thromboprophylaxis; however appropriate dose recommendation is not certain to date [1, 7, 9, 15]. Thromboprophylaxis is recommended in all COVID-19 hospitalized patients unless contraindicated in situations such as active bleeding, platelet count < 25 × 10⁹/L or significantly low fibrinogen level [1]. Mechanical preventive measures can be used when anticoagulation is contraindicated [7]. Several trials are ongoing but currently there is no evidence supporting prophylactic use of antiplatelet agents to prevent COVID-19 thrombotic complications [1, 9]. Drugs such as argatroban seem to be promising agents theoretically in treating severe COVID-19 cases; however randomized trails are required to support evidence [16].

Therapeutic anticoagulation with either unfractionated or low-molecular-weight heparin is recommended to treat COVID-19 thrombosis [9, 15]. Oral anticoagulants should be used when anticoagulation is contraindicated [7].

| Proposed mechanisms of thrombocytopenia | References |
|----------------------------------------|------------|
| Direct inhibition of hematopoiesis through binding to angiotensin-converting enzyme-2 on hematopoietic tissues and organs | Xu et al [3], Zhang et al [4], Mei et al [7] |
| The inflammatory cytokine-mediated destruction of hematopoietic progenitor cells | Xu et al [3] |
| The inflammatory cytokine-mediated inhibition of hematopoiesis or megakaryocytepoiesis | Zhang et al [4], Mei et al [7] |
| Decreased production of thrombopoietin either by damaged liver cells or inflammation | Zhang et al [4] |
| Block release of platelets from megakaryocytes in capillary beds of consolidated lung | Xu et al [3], Zhang et al [4] |
| Damaged endothelium triggers platelet aggregation and microthrombi formation and thereby increasing platelet consumption | Xu et al [3], Zhang et al [4], Mei et al [7] |
| Viral-mediated platelet-leukocyte aggregation | Wool et al [1] |
| SARS-CoV-2-induced autoimmune destruction of platelets | Xu et al [3], Zhang et al [4], Mei et al [7] |
| Hyperactivated platelets swallowed by hepatic/splenic macrophage | Mei et al [7] |

| Proposed mechanisms of coagulopathy | References |
|------------------------------------|------------|
| SARS-CoV-2 binds to ACE2 on host cell membrane by using its spike protein. Both SARS-CoV-2 and its spike protein can directly activate platelets leading to platelet aggregation and leukocyte-platelet aggregation subsequently leading to thrombus formation. | Zhang et al [13] |
| Immature platelets are elevated in COVID-19, which are functional and increase the risk of coagulopathy. | Wool et al [1] |
| COVID-19 triggers significant inflammatory reaction leading to endothelial damage and clot formation. | Wool et al [1] |

COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
be avoided due to possible interactions with antiviral agents [15]. Antiplatelet agents are used in acute treatment of arterial thrombotic complications [9].

Treatment options for severe COVID-19 cases are limited to date. More randomized controlled trials are required to better understand the pathophysiology of this disease and develop better treatment options.

**Learning points**

Various hematological abnormalities associated with various complications are reported in COVID-19. A combination of thrombocytopenia and thrombosis as seen in the above reported cases, is particularly challenging.

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**Conflict of Interest**

No conflict of interest to disclose.

**Informed Consent**

Verbal consents were given by the patients or their significant others in the case where patient is not available to consent.

**Author Contributions**

Sushmita Khadka wrote up the case presentations. Swapna Ravi wrote up the rest of the manuscript. All other authors helped with literature review and formatting the manuscript.

**Data Availability**

The authors declare that data supporting the findings of this study are available within the article.

**References**

1. Wool GD, Miller JL. The impact of COVID-19 disease on platelets and coagulation. Pathobiology. 2021;88(1):15-27.
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-1720.
3. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol. 2020;99(6):1205-1208.
4. Zhang Y, Zeng X, Jiao Y, Li Z, Liu Q, Ye J, Yang M. Mechanisms involved in the development of thrombocytopenia in patients with COVID-19. Thromb Res. 2020;193:110-115.
5. Maquet J, Lafaurie M, Sommet A, Mouls G. Thrombocytopenia is independently associated with poor outcome in patients hospitalized for COVID-19. Br J Haematol. 2020;190(5):e276-e279.
6. Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y, Shang Y. Thrombocytopenia and its association with mortality in patients with COVID-19. J Thromb Haemost. 2020;18(6):1469-1472.
7. Mei H, Luo L, Hu Y. Thrombocytopenia and thrombosis in hospitalized patients with COVID-19. J Hematol Oncol. 2020;13(1):161.
8. Pavord S, Thachil J, Hunt BJ, Murphy M, Lowe G, Laffian M, Makris M, et al. Practical guidance for the management of adults with immune thrombocytopenia during the COVID-19 pandemic. Br J Haematol. 2020;189(6):1038-1043.
9. Gu SX, Tyagi T, Jain K, Gu VW, Lee SH, Hwa JM, Kwan JM, et al. Thrombocytopenia and endotheliopathy: crucial contributors to COVID-19 thromboinflammation. Nat Rev Cardiol. 2021;18(3):194-209.
10. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145-147.
11. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847.
12. Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, Zhang C, et al. Deep vein thrombosis in hospitalized patients with COVID-19 in Wuhan, China: prevalence, risk factors, and outcome. Circulation. 2020;142(2):114-128.
13. Zhang S, Liu Y, Wang X, Yang L, Li H, Wang Y, Liu M, et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J Hematol Oncol. 2020;13(1):120.
14. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-1099.
15. Miesbach W, Makris M. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. Clin Appl Thromb Hemost. 2020;26:1076029620938149.
16. Aliter KF, Al-Horani RA. Thrombin inhibition by Argatroban: potential therapeutic benefits in COVID-19. Cardiovasc Drugs Ther. 2021;35(2):195-203.