Treatment of Severe Immune Thrombocytopenic Purpura Associated with COVID-19

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Patient: Female, 48-year-old
Final Diagnosis: COVID-19 infection • severe idiopathic thrombocytopenic purpura
Symptoms: Bruising • headache • hemoptysis • nausea
Medication: —
Clinical Procedure: —
Specialty: Hematology • Infectious Diseases

Objective: Rare coexistence of disease or pathology
Background: COVID-19 is associated with many hematological manifestations, including lymphopenia and thrombosis. There have been rare occasions in which thrombocytopenia has been reported as the sole clinical presentation of COVID-19.

Case Report: This is the case report of a 48-year-old Hispanic female patient with COVID-19 presenting as severe isolated thrombocytopenia. The patient presented to the Emergency Department with hemoptysis, spontaneous bruising, and excessive vaginal bleeding and also reported a recent flu-like illness. On examination, she was found to have bilateral subconjunctival hemorrhage, diffuse oral ulcers, epigastric abdominal tenderness, and ecchymosis on her chest, with scattered petechiae and palpable purpura on her lower limbs. Laboratory results were significant for a platelet count of 0×10^9 and an immature platelet fraction of 34.1%. Owing to clinical suspicion, the patient was tested for COVID-19, and her test result was positive. She was treated with intravenous immunoglobulin, prednisone, rituximab, vitamin C, and zinc. Upon achieving hemodynamic stability, she was discharged to follow up with a hematologist in the outpatient setting.

Conclusions: Hematological consequences of COVID-19 are becoming more prevalent. The mechanism behind this manifestation could be bone marrow failure, formation of platelet autoantibodies, or consumptive coagulopathy. These critical manifestations are necessary to manage, especially in severe forms like in our patient. Steroids and rituximab combination therapy have proven to be the most effective regimen.

Keywords: COVID-19 • Immunoglobulin G • Prednisolone • Rituximab • Thrombotic Thrombocytopenic Purpura, Acquired

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/932557
**Background**

It is well established that COVID-19 affects not only the respiratory system but also multiple body systems. The manifestations of the disease [1] have varied, including simple upper respiratory tract symptoms, headaches, myalgia, complicated lower respiratory tract involvement leading to development of acute respiratory distress syndrome and even requiring intubation, viral myocarditis, and gastrointestinal symptoms, including nausea, vomiting, and diarrhea. The hematopoietic system is also believed to be a common target for the SARS-CoV-2 virus, with lymphopenia and mild thrombocytopenia being the primary hematologic presentations. The degree of thrombocytopenia has also been seen to affect the overall severity of the disease [2], with an increased risk of in-hospital mortality [3]. We hereby describe a case of COVID-19 in a middle-aged woman with severe isolated thrombocytopenia being the reason for clinical presentation and admission.

**Case Report**

The patient was a 48-year-old Hispanic woman with a past medical history significant for hypertension and hyperlipidemia who presented to the Emergency Department with multiple symptoms, including hemoptysis, mouth ulcers, spontaneous bruising, nausea, vomiting, non-radiating epigastric abdominal pain, excessive vaginal bleeding, headaches, and fatigue. The patient reported having had a flu-like respiratory illness a week prior to presentation for which she was evaluated at urgent care and was given a course of amoxicillin and prednisone for possible bronchitis. After a few days of antibiotic and steroid therapy, her fever improved but her cough worsened, and she started to cough up blood-streaked phlegm, along with having generalized weakness, painful mouth ulcers, vaginal bleeding, and diffuse bruising in the upper anterior chest and predominantly lower extremities. The patient denied having any prior history of bleeding or similar illness, and her family history was negative for bleeding disorders.

On presentation to the Emergency Department, the clinical examination was remarkable for an acutely sick-looking woman with normal vital signs and mild bradycardia, bilateral subconjunctival hemorrhage, diffuse oral ulcers and blisters, bilateral normal vesicular breath sounds, normal heart sounds, epigastric abdominal tenderness, ecchymosis on her chest with scattered petechiae, and palpable purpura on her lower limbs, without any tenderness of her extremities. A complete blood count study showed hemoglobin of 11.6 g/dL, WBC of 10.1×10³/uL, platelet count of 0×10⁹, and an immature platelet fraction of 34.1% (Table 1). A complete metabolic panel revealed electrolytes and liver function panel within the reference range and a creatinine level of 1.14 mg/dL (elevated from a baseline of 0.71 mg/dL from 6 months ago). A coagulation profile (Table 1) was also within the reference range, and a hemolysis study, including immature reticulocyte fraction, was low. A hepatitis panel was negative for hepatitis viruses. Inflammatory markers were noted to be elevated. A chest X-ray was unremarkable.

The patient was admitted for further evaluation and management. Owing to the patient’s respiratory symptoms and the diverse clinical presentation of the SARS-COV-2 virus, the decision was made to test for the virus, and a nasopharyngeal swab was obtained to perform the COVID test. She was empirically started on azithromycin, vitamin C, and zinc and placed in airborne, contact, and droplet isolation. She did not develop hypoxia and hence did not require escalation of oxygen supplementation or use of antiviral therapy. The hematologist was consulted for severe thrombocytopenia.

With a working diagnosis of severe idiopathic thrombocytopenic purpura (ITP), the hematologist recommended intravenous (i.v.) immunoglobulin twice and high-dose prednisone. The platelet count initially showed a mild increment to 5 from 0 but later started to trend downward. During this time, with no improvement in thrombocytopenia and continued scant hemoptysis, per the hematologist’s recommendation, the patient was started on rituximab 375 mg/m², once weekly for 4 doses, which were planned for the patient to complete as an outpatient. The trend of her platelet count is noted in Figure 1.

The nasopharyngeal swab sample was tested for SARS-CoV-2 with reverse transcriptase-polymerase chain reaction and was negative. A coagulation profile showed no evidence of thrombocytopenia, with the exception of a mild increment in platelet count. The patient improved clinically and was discharged on day 10 of hospital admission.

**Table 1. Lab results on day of presentation.**

|                      | Reference range & units | Day 1 of hospital admission |
|----------------------|-------------------------|----------------------------|
| WBC                  | 4.8-10.8×10³/uL         | 10.1                       |
| RBC                  | 4.2-5.4 M/uL            | 4.23                       |
| Hemoglobin           | 12-16 GM/dL             | 11.6                       |
| Hematocrit           | 37-47%                  | 34.6                       |
| MCV                  | 81-99 fl                | 81.8                       |
| MCH                  | 27-31 PG                | 27.4                       |
| MCHC                 | 33-37%                  | 33.5                       |
| Platelets            | 130-400×10³/uL          | 0                          |
| Immature platelet fraction | 1.1-7.1%             | 34.1                       |
| Protime              | 9.4-12.5 s              | 11.8                       |
| INR                  | 0.85-1.13               | 1.04                       |
| aPTT                 | 25.1-36.5 s             | 27.2                       |

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This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0). A complete metabolic panel revealed electrolytes and liver function panel within the reference range and a creatinine level of 1.14 mg/dL (elevated from a baseline of 0.71 mg/dL from 6 months ago). A coagulation profile was also within the reference range, and a hemolysis study, including immature reticulocyte fraction, was low. A hepatitis panel was negative for hepatitis viruses. Inflammatory markers were noted to be elevated. A chest X-ray was unremarkable. The patient was admitted for further evaluation and management. Owing to the patient’s respiratory symptoms and the diverse clinical presentation of the SARS-COV-2 virus, the decision was made to test for the virus, and a nasopharyngeal swab was obtained to perform the COVID test. She was empirically started on azithromycin, vitamin C, and zinc and placed in airborne, contact, and droplet isolation. She did not develop hypoxia and hence did not require escalation of oxygen supplementation or use of antiviral therapy. The hematologist was consulted for severe thrombocytopenia.
positive. The patient completed empiric treatment with azithromycin and was continued on supportive therapy. She did not develop hypoxia and hence did not meet the criteria for further antiviral treatment.

In the course of her hospitalization, the patient was noted to have chest pain and intermittent melena. She underwent a complete workup for acute coronary syndrome and pulmonary embolism, which was unremarkable. The patient’s chest pain was believed to be musculoskeletal in nature and was treated with pain medication and supportive care. The patient was also evaluated by a gastroenterologist for the mild melena, and the recommendation was to observe conservatively without need for endoscopic evaluation.

The patient’s overall hospital stay was uncomplicated, and she was able to be discharged in a stable condition with a plan to follow up with the Hematology Department as outpatient for the completion of the rituximab. Over the following 4 weeks, the patient continued to receive weekly rituximab, and her platelet numbers continued to improve significantly, as shown in Figure 2. She also continued oral prednisone, which was tapered over the following 5 months. She continued to tolerate the treatment well, with improvement in bruising and no further episodes of bleeding. Per an oncology consultation, the plan was to begin thrombopoietin mimetic in the event of a relapse.

**Discussion**

The novel SARS-COV-2 virus presents as an infectious disease causing an inflammatory response, thereby affecting multiple organ systems. Interestingly, the presentation, clinical manifestation, and severity of the disease continues to vary from one patient to another. The respiratory clinical manifestations have been noted to range from flu-like symptoms to full-blown acute respiratory distress syndrome.

From the hematologic perspective, SARS-COV-2 infection poses a higher risk of disseminated intravascular coagulation by causing coagulation abnormalities (prolonged PT and aPTT), an increase in fibrin degradation products, and severe thrombocytopenia [4]. This COVID-19-associated coagulopathy necessitates management similar to that of coagulopathy in any critically ill patient [5], with a focus on thromboembolic prophylaxis [6]. Most patients present with decreased platelet levels but seldom to the point where they experience bleeding [7], as was the case with our patient.

The mechanisms of a low platelet count associated with COVID-19 were proposed in a recent study. They can be divided into 3 main categories. First, the virus causes a decrease in platelet production by attacking the bone marrow and destroying progenitor cells through the activation of the cytokine storm. Second, platelet destruction can be increased by the formation of autoantibodies and immune complexes. According to Xu et al [7], “antibodies produced during viral infection may specifically bind to antigens on platelets through molecular mimicry, resulting in increased platelet destruction.” Third, there is increased platelet consumption secondary to endothelial injury in the lung, which leads to the formation of microthrombi. In a recent meta-analysis by Lippi et al including 9 studies [2], in which they evaluated the severity of disease based on the degree of thrombocytopenia, it was shown that the platelet count was significantly lower in patients with more severe COVID-19 disease, which could lead to increased mortality.
The presence of isolated thrombocytopenia in patients with COVID-19, even though it is not well studied owing to its rare occurrences, encourages us to be more vigilant in its assessment in clinical practice, thereby decreasing mortality in these patients. More severe outcomes, including intracerebral bleeding and death secondary to thrombocytopenia in patients with COVID-19, have also been reported [8].

In the present case, the patient had severe symptomatic thrombocytopenia but only a mild to moderate presentation of COVID-19. As per guidelines published by the American Society of Hematology [9], there are various treatment modalities for ITP with non-life-threatening bleeding, and based on the platelet count on presentation, treatment starts with observation and then progresses to corticosteroids, i.e. immunoglobulin, anti-D immunoglobulin, and rituximab. Combination therapy with dexamethasone and rituximab has been seen to be more effective [10]. Splenectomy or the use of thrombopoietin receptor agonists would be the next step in patients who remain unresponsive to therapy.

Our case report adds to the limited data regarding severe isolated thrombocytopenia and its management in patients with a mild to moderate disease presentation. The combination of systemic steroids with monoclonal antibodies like rituximab should be the mainstay of treatment for patients who develop ITP during an active SARS-CoV-2 infection. Although we know more today than we did at the start of the pandemic, there is still a lot to learn.

Conclusions

Our patient had a delayed response to intravenous immunoglobulins but responded positively to continued steroids and monoclonal antibodies. This case emphasizes that the most appropriate treatment course for patients presenting with immune thrombocytopenic purpura in the setting of SARS-CoV-2 infection is combination therapy with dexamethasone and rituximab, as shown by the rapid response in our patient with the initiation of dual therapy.

Department and Institution Where Work Was Done

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Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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