Immune thrombocytopenia, severe hematological consequence in a patient with COVID-19: A case report

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Abstract. Since the first appearance of coronavirus disease 2019 (COVID-19), multiple studies have focused on this novel coronavirus. Within a few months, the clinical and paraclinical manifestations and the mechanisms by which these changes are induced were elaborated. Clinically, the virus mainly causes the common cold, but can also result in severe or fatal pneumonia/acute respiratory syndrome. Regarding the biological changes, similar to any other virus, it can lead to a reduced lymphocyte count. The second most common change is represented by a reduced thrombocyte count. Furthermore, most patients have blood clotting abnormalities, inflammatory syndrome, raised D-dimer and lactate dehydrogenase levels. Detection of immune thrombocytopenia in asymptomatic patients who tested positive for COVID-19 justifies the need to perform differential diagnosis and testing for COVID-19. Typically, patients with severe forms of COVID-19 develop mild thrombocytopenia, while severe thrombocytopenia is rarely reported. The aim of this case report was to present the situation in which one asymptomatic patient who tested positive for COVID-19 developed severe immune thrombocytopenia.

Introduction

The first reported case with the novel coronavirus was in December 2019 and originated in China. Since then, the novel coronavirus, officially named coronavirus disease 2019 (COVID-19), has spread worldwide (1-5). The coronavirus responsible for the current pandemic causes severe acute respiratory syndrome (SARS) and thus the virus is termed 'severe acute respiratory syndrome coronavirus-2' (SARS-CoV2). Most patients with COVID-19 develop a mild or moderate form of the disease, while others may not present symptoms at all. Common signs and symptoms can include nonproductive cough, fever or shivers, tiredness, muscle aches, headache, sore throat, shortness of breath and loss of taste or smell. Patients who are older or have multiple risk factors or comorbidities have an increased risk of developing severe illness. Moreover, some patients can develop acute respiratory distress syndrome, pneumonia, cardiovascular complications, acute kidney injury and hematological changes (1,5,6).

Hematological changes include lymphopenia and thrombocytopenia with normal white blood cell count or leukopenia and blood clotting abnormalities include prolonged activated partial thromboplastin time with normal prothrombin time (PT). In addition, most patients have elevated D-dimer levels (6-8).

Thrombocytopenia is a medical condition characterized by a low platelet count (<100,000/mm^3). Clinical manifestations are related to the small number of thrombocytes and range from the absence of symptoms to mild/moderate muco-cutaneous bleeding (purpura, petechiae, nosebleeds or bleeding gums) and sometimes to a life-threatening intracranial hemorrhage. Immune thrombocytopenia is the result of our own immune system that focuses its attack on self-antigens and destroys platelets. It is characterized by isolated thrombocytopenia and can even be a primary ailment or it can be triggered by several infectious diseases. Viruses such as human immunodeficiency virus, hepatitis C virus, Epstein-Barr virus or cytomegalovirus are the commonly involved pathogens followed by bacteria and fungi. Since the beginning of the COVID-19 pandemic, several cases of patients hospitalized with SARS-CoV-2 infection and thrombocytopenia have been reported. Even if the mechanisms by which the coronavirus causes thrombocytopenia remain unclear, several are described due to the severe proinflammatory state and cytokine storm (8-12).

Case report

In the present study, we report the case of a 60-year-old-woman who was referred to the emergency department complaining of recurrent episodes of spontaneous nosebleed and bleeding gums, symptomatology that started three days before the presentation, and tiredness that started one week prior. The

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patient had a personal history of type 2 diabetes treated with oral anti-diabetic medication (1,000 mg metformin taken twice a day) and did not report any allergies. On arrival, the patient was afebrile (T=36.2˚C) and the general condition was good. Auscultation of the heart and blood pressure (BP) were normal (heart rate=75 beats/min, BP=110/70 mmHg); auscultation of the lungs was normal with respiratory rate=16 breaths/min and oxygen saturation 98% in room air.

Complete blood count revealed normal white blood cell count, lymphopenia, normochromic normocytic anemia and severe thrombocytopenia. The initial blood tests carried out in the emergency room showed increased inflammatory markers (raised erythrocyte sedimentation rate, C-reactive protein and high ferritin levels), low activated partial thromboplastin time (APTT), hyperglycemia and high lactate dehydrogenase levels. Reverse transcriptase-polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 was positive.

Due to the extremely low platelet number and the SARS-CoV-2 infection, immune thrombocytopenia associated with the coronavirus disease was suspected. Given the increased risk of bleeding, the patient was admitted to the hematology department for further investigations.

Upon admission, the patient seemed well, still afebrile and the vital signs were detached. She had no family history of autoimmune hematologic diseases and took no medications aside from the anti-diabetic treatment. Skin examination revealed petechiae concentrated on her upper and lower extremities and on her abdomen, and an oral examination showed multiple wet purpuras over the lower lip, buccal mucosa and tongue. There was no palpable lymphadenopathy, and cardiac, pulmonary, abdominal, renal and neurologic examinations were normal, without any organomegaly or any other signs of bleeding. Of note, the patient did not experience fever or shivers, dry cough, fatigue, difficulty breathing or other symptoms associated with the coronavirus disease.

Laboratory tests confirmed the lymphopenia, normochromic normocytic anemia, severe thrombocytopenia (on admission platelet count was 0/mm^3 with reference range: 150,000-30,000/mm^3), raised inflammatory markers, low APTT with normal prothrombin time and international normalized ratio. Electrolytes, liver function tests, renal panel, iron levels, vitamin B12, uric acid level, total protein and serum protein electrophoresis were normal. D-dimer levels were elevated.

In order to complete COVID-19 investigations, chest radiography and computed tomography (CT) were performed. Chest radiography showed bilateral lung infiltrates and the CT scan showed peripheral ground-glass opacities coexisting with consolidation and interlobular septal thickening involving all of the lung segments. Neither pleural/pericardial effusion nor mediastinal lymphadenopathy were reported. The CT scan description was highly suggestive of severe COVID-19 pneumonia.

Prior to the diagnosis of immune thrombocytopenia, other causes were considered. Therefore, viral markers for hepatitis B, C, human immunodeficiency virus and cytomegalovirus were within normal limits. Tumor markers such as carcinoembryonic antigen (CEA), cancer 19.9, cancer 125, α-fetoprotein were negative, abdominal ultrasound showed no changes and immunological profile regarding antinuclear antibody (ANA) and anti-dsDNA antibodies were negative. Atypical hemolytic uremia syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, sepsis or drug-induced thrombocytopenia were excluded.

The patient received antibiotic therapy with ceftriaxone, vitaminotherapy and proton-pump inhibitors. Antipyretics, oxygen therapy, and antihemorrhagic agents were not required and prophylactic anticoagulation was not indicated. Given the patient's severe form of COVID-19 pneumonia (the patient had no symptoms of the COVID-19 infection, and the disease had been documented by the CT scan and RT-PCR) associated with the severe thrombocytopenia, systemic corticosteroid therapy was initiated with dexamethasone once daily and a platelet transfusion was administered. After 48 h, due to the patient's unresponsiveness to steroids (thrombocytes <1,000/mm^3), and in order to immediately raise the platelet count, the patient required intravenous immunoglobulin (ivIg).

On day 8, the petechiae along with the purpuric lesions regressed and the patient stopped complaining of recurrent episodes of spontaneous nosebleeds and bleeding gums. The platelet count had increased to 65,000/mm^3 and the patient still tested positive for SARS-CoV-2; therefore we continued with systemic dexamethasone up to 10 days. However, owing to her personal history of type 2 diabetes along with the corticosteroid therapy, she developed uncontrolled hyperglycemia as a side effect, requiring the initiation of insulin therapy.

After two weeks of treatment, on her hospital discharge, the patient was afebrile, the clinical signs and symptoms disappeared, the platelet count increased to 154,000/mm^3 and all the other blood tests had normalized. RT-PCR testing for SARS-CoV-2 was negative.

Discussion

A recent review has shown that thrombocytopenia is associated with COVID-19 in 5-41.7% of the patients (10). Most of them develop mild thrombocytopenia (100-150x10^3/mm^3) and studies have revealed that patients experiencing severe forms of the disease had a lower platelet count than patients experiencing mild or moderate forms of the disease. Several studies have shown that thrombocytopenia can be independently associated with poor outcomes, and that patients who succumbed had a much lower platelet count than those who survived. However, severe thrombocytopenia has been rarely seen in patients hospitalized for COVID-19 and most cases were found to be immune thrombocytopenia, as in our case (10-13).

The particularity of our case lies in the fact that, although the patient tested positive for SARS-CoV-2 infection, she had no symptoms at all. Yet, the patient was diagnosed with coronavirus disease because of the hemorrhagic manifestations induced by the severe thrombocytopenia. The patient from the current case reported no symptoms or complications compared to literature describing more severe COVID-19 symptomatology in adults with immune thrombocytopenia associated with the coronavirus disease. At present, few patients with immune thrombocytopenia have tested positive for COVID-19 who did not present with any specific symptoms (14-17).

The most interesting aspect was the discrepancy between clinical status with an uninfluenced general condition and

paraclinical investigations that have highlighted severe COVID-19 pneumonia associated with severe thrombocytopenia (on admission platelet count was 0/mm^3). In addition, although thrombocytopenia is associated with poor outcome, the patient in the present case responded to therapy and has fully recovered (18).

Although there is no official status, as a result of the collected data, a practical guide for the management of adults with immune thrombocytopenia and COVID-19 has been developed. According to that, first-line therapy in these patients is corticosteroid therapy, whose dose and duration should be kept to a minimum (19-21). As a recent systematic review has shown, only 22% of patients were treated with corticosteroids alone, 29% with intravenous immunoglobulin alone and 24,5% received a combination of the two therapies mentioned (22). Intravenous immunoglobulin is either a second-line therapy in case of corticosteroid failure or used in order to immediately raise the platelet count and to control or prevent bleeding (20,22). As mentioned before, the patient received from the beginning dexamethasone which was associated with intravenous immunoglobulin on day 3 because of the lack of increment in platelet count. In addition, as we feared the risk of fatal bleeding, one platelet transfusion was administered (20,22). During this time period, other potential causes of immune thrombocytopenia were excluded.

Clinical and paraclinical remission with corticotherapy and intravenous immunoglobulin strengthened the diagnosis. The prognosis was good, leading to a complete recovery.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

OVB, and DP acquired, analyzed and interpreted all the patient data and had a major contribution in writing the manuscript. DP, OVB, MC and CR contributed to the conception and design of the current manuscript. All authors acquired, analyzed and interpreted the literature references. DP drafted the manuscript and OVB, MC and CR revised it critically for important intellectual content. OVB and DP confirm the authenticity of all the raw data. All authors have read and approved the final version to be published.

Ethics approval and consent to participate

Ethics approval was not needed as the manuscript is a case report. Informed signed consent to participate was obtained from the patient.

Patient consent for publication

As personal data were published, informed signed consent for publication was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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