Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Correspondence

Coronavirus disease associated immune thrombocytopenia: Causation or correlation?

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Thrombocytopenia

Dear Editor,

The coronavirus disease (COVID-19) is a novel multisystemic viral disease and coagulopathy and immune dysregulation have been proposed as major factors for the rapid evolution of the disease to a severe stage.[1,2]

Here, we describe three cases of immune-mediated thrombocytopenia during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease. Literature data have reported five patients of COVID-19 with presentations ranging from asymptomatic to severe hemorrhagic complications.[3,4]

Patient 1 was a 69-year-old woman with a recent history of cerebral lymphoma, who was admitted for pulmonary embolism that occurred during the chemotherapy. During the hospitalization, she developed respiratory distress, and a nasopharyngeal swab tested positive for SARS-CoV-2. On admission, her platelet count was 130 $\times$ 10^9/L.

Her treatment included enoxaparin 4000 U BID, dexamethasone 16 mg daily, and ceftriaxone. After starting oxygen therapy her respiratory symptoms improved.

On day 7, her platelet count drastically dropped to 70 $\times$ 10^9/L without hemorrhagic manifestations. Since a pseudothrombocytopenia was ruled out, a careful diagnostic workup was performed to further characterize the thrombocytopenia and IgM anti-platelet autoantibodies (APA) were positive; anti-heparin/platelet factor 4 (anti-PF4), ANA, and extractable nuclear antigen antibodies tested negative.

Treatment with enoxaparin was continued and the patient gradually recovered from the SARS-CoV-2 infection. Upon discharge, the platelet count was 132 $\times$ 10^9/L.

Patient 2 was an 88-year-old man with a history of coronary artery disease and recent hip replacement. He was diagnosed with an asymptomatic SARS-CoV-2 infection during a diagnostic workup for a flare of congestive heart failure. On admission, his platelet count was at 99 $\times$ 10^9/L, and he presented no hemorrhagic manifestations. Investigating the etiology of thrombocytopenia, APA IgM autoantibodies and ANA were tested positive.

The ANA titer was 1:80 with a "speckled" pattern. Anti-PF4 antibodies were negative thus excluding HIT. Eight days after admission, the patient experienced respiratory failure and underwent a high-resolution chest computed tomography that revealed the presence of COVID-related interstitial pneumonia. The patient was admitted to the intensive care unit where he was treated with methylprednisolone 1 mg/kg/day and administered non-invasive ventilation. At discharge, his platelet count was 214 $\times$ 10^9/L.

Patient 3 was a 31-year-old man with a known exposure to SARS-CoV-2, admitted for high fever and dyspnea. His platelet count at admission was 114 $\times$ 10^9/L.

A nasopharyngeal swab confirmed the SARS-CoV-2 infection. He was treated with enoxaparin, hydroxychloroquine (HCQ), and ceftriaxone. The patient tested negative for hepatitis B, C and human immunodeficiency virus infections.

His platelet count further decreased to 80 $\times$ 10^9/L and enoxaparin treatment was discontinued. Anti-PF4 antibodies were negative, while IgM APA antibodies resulted

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Table 1 Clinical and laboratory features of COVID-19-associated thrombocytopenia.

	Age (years)	Clinical features	Platelet count at SARS-CoV-2 diagnosis	Autoantibodies	Steroid Treatment	Platelet count on discharge after SARS-CoV-2 recovery
Patient 1	69	respiratory distress without hemorrhagic complications	70×10^9/L	IgM APA	Dexamethasone 16 mg daily	132×10^9/L
Patient 2	88	respiratory failure due to COVID-related interstitial pneumonia, without hemorrhagic complications	99×10^9/L	IgM APA and ANA (speckled pattern)	methylprednisolone 1 mg/kg/day	214×10^9/L
Patient 3	31	respiratory distress due to interstitial pneumonia without hemorrhagic complications	80×10^9/L	IgM APA	prednisone 1 mg/kg/day	375×10^9/L

APA: anti-platelet autoantibodies.

positive. Because of the worsening of the interstitial pneumonia, the patient was treated with prednisone 1 mg/kg/day. He completely recovered from the SARS-CoV-2 infection, and his platelet counts normalized.

On discharge, the platelet count of the patient was 375×10^9/L. It is a consolidated fact that viral infections can induce immune thrombocytopenia through a mechanism of molecular mimicry.[5]

This phenomenon forms the foundation of our hypothesis that SARS-CoV-2 may play a role in the development of an immune reaction in infected patients. This hypothesis is highly plausible in addition to the several observations in our patients: the exclusion of all other probable causes of thrombocytopenia (i.e. sepsis, enoxaparin), the presence of APA autoantibodies, and the rapid and complete response to steroid therapy.

The role of autoimmunity in COVID-19 is currently poorly studied. In our experience, approximately 50% of the patients with COVID-19-related interstitial pneumonia have one or more autoantibodies (manuscript submitted).

In the three cases here described, only one patient tested positive for ANA with a speckled pattern.[4] From a speculative point of view, it is interesting that COVID-19 can induce an increased risk of both stroke through thromboembolism and hemorrhage through thrombocytopenia.[4,6]

In our series of COVID-19 infected patients, we observed a prevalence of antiphospholipid antibodies up to 20% (manuscript submitted). However, none of the three patients here described had those autoantibodies.

The complexity and heterogeneity of the presentations of COVID-19 justify the struggle in treating these patients and the extreme variability of the proposed protocols. It is important to consider that, in the clinical care for COVID-19 patients, tailored therapy and adaptation of clinical choices on a case-by-case basis may be more beneficial to the patients than standardized treatments (Table 1). The SARS-CoV-2 virus has exhibited extreme phenotypic heterogeneity, and there is still much to be discovered. Thus, we deduce that monitoring these patients over time may reveal the hidden mechanisms, thus suggesting a potential treatment.[5]

Authors' contributions

Study concept and design: S. Pascolini, L. Muratori and P. Muratori: Data collection: S. Pascolini A. Granito, L. Muratori, M. Lenzi and P. Muratori; Writing and critical revision of the draft: S. Pascolini, A. Granito, L. Muratori, M. Lenzi and P. Muratori.

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Patient consent for publication

Obtained.

Declaration of competing interest

The authors declare no potential conflicts of interest to disclose.

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