Treatment with eltrombopag of severe immune thrombocytopenia and hemolytic anemia associated with COVID-19 pneumonia: a case report

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Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19). Whether SARS-CoV-2 can trigger an autoimmune reaction against platelets and red blood cells remains unclear. Herein, we report a case of COVID-19 pneumonia associated with severe immune thrombocytopenia and hemolytic anemia. An 83-year-old woman was admitted to the hospital because of both dyspnea and diffuse muco-cutaneous bleeding. Exams revealed hemolytic anemia (HA), severe immune thrombocytopenia (ITP), and bilateral pneumonia. Molecular testing confirmed a diagnosis of COVID-19 pneumonia. Thrombocytopenia did not respond to first-line treatment with immunoglobulin, corticosteroids, and platelet transfusions. Addition to therapy of the thrombopoietin receptor agonist, eltrombopag, resulted in full recovery. COVID-19 can be associated with ITP and HA. There are neither guidelines nor clinical experience on the treatment of COVID-19-associated ITP and our case, showing complete response to eltrombopag, may help clinicians in their practice during the COVID-19 pandemic.

Plain language summary

The case of an 83-year-old woman with COVID-19 pneumonia associated with two severe blood diseases that cause platelet and red cell destruction

Coronavirus disease 2019 (COVID-19) is caused by a virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We do not know exactly whether this virus can stimulate our immune system to react against platelets and red blood cells. Herein, we report a case of COVID-19 pneumonia associated with two severe blood diseases, immune thrombocytopenia, which causes platelet destruction, and hemolytic anemia, which causes red cell destruction. An 83-year-old woman was admitted to the hospital because of both difficulty in breathing and diffuse bleeding in mucosae and skin. Exams revealed hemolytic anemia, severe immune thrombocytopenia, and pneumonia in both lungs. Molecular testing confirmed a diagnosis of COVID-19 pneumonia. The first treatment with immunoglobulin, corticosteroids, and platelet transfusions was not enough to cure thrombocytopenia; the addition of eltrombopag which acts on the thrombopoietin receptor agonist resulted in full recovery. COVID-19 can be present together with immune thrombocytopenia and hemolytic anemia. As there are no guidelines on the treatment of immune thrombocytopenia in patients with COVID-19 and the clinical experience is limited, the complete response achieved with eltrombopag may help clinicians in their practice during the COVID-19 pandemic.

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Introduction

Recently, a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in Wuhan (China) and rapidly spread worldwide.[1,2] Pneumonia is the most frequent serious manifestation of SARS-CoV-2 infection and is characterized primarily by fever, dry cough, dyspnea, and bilateral infiltrates on chest imaging. Common laboratory findings include lymphocytopenia and increased lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, and D-dimer levels.[3,4] In patients with coronavirus disease 2019 (COVID-19), thrombocytopenia identifies severely ill patients who develop microangiopathy and disseminated intravascular coagulation, and is associated with an increased risk of in-hospital mortality.[5,6] Whether SARS-CoV-2 may also cause thrombocytopenia by eliciting an immune reaction against platelets remains unclear. Herein, we report a case of COVID-19 pneumonia associated with severe immune thrombocytopenia (ITP) and hemolytic anemia.

Case presentation

In April 2020, an 83-year-old Caucasian woman was admitted to the emergency room because of easy bruising, epistaxis, and gum bleeding. She also reported bloody urine and stools on one occasion. Laboratory exams performed on the day prior to admission revealed both thrombocytopenia (2000 mm³) and anemia (7.2 g/dl). The patient denied a personal or family history of bleeding and anemia and previous complete blood counts (CBCs) were normal. Her past medical history was unremarkable, and she did not take any medications except nebivolol for hypertension. However, 20 days prior to admission she developed fever, myalgia, and dyspnea, which were treated with azithromycin (5-day course). In April, there was a COVID-19 outbreak in Italy, but the patient denied close contact with confirmed or suspected cases of COVID-19. On examination, body temperature was 36.5°C. Oxygen saturation was 97% in room air, but then fell to 90%, and oxygen was administered through a nasal cannula (2 L/min). Diffuse ecchymosis on the skin and petechiae on the lips, oral cavity, and both lower limbs were observed. The rest of the physical examination was normal except for diminished breath sounds and rales at both lungs. Laboratory exams (Table 1) showed anemia, thrombocytopenia, leukocytosis, and lymphocytopenia. Levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), and fibrinogen were increased, while prothrombin time, partial thromboplastin time, and procalcitonin levels were in the normal range. No blasts, schistocytes, or platelet aggregates were found on repeated peripheral blood smears. A brain computed tomography (CT) scan revealed a left cortical microhemorrhage (5 mm). Moreover, chest CT showed bilateral consolidations and multiple patchy ground-glass opacities with peripheral distribution, suggesting COVID-19 pneumonia. However, molecular testing for SARS-CoV-2 was negative on two nasopharyngeal swabs (Diasorin assay). The patient was treated with two pools of platelets and a unit of packed red blood cells, intravenous prednisone (1 mg/kg), immunoglobulin (IVIG 400 mg/kg), antibiotics, and then transferred to our internal medicine ward. Reticulocytosis, haptoglobin consumption, and increased both LDH and indirect bilirubin suggested hemolytic anemia. The D-dimer value was elevated; however, normal antithrombin III activity, absence of both schistocytes and ADAMTS13 inhibitors, and normal ADAMTS13 activity made a diagnosis of thrombotic microangiopathy unlikely. Doppler ultrasound of both upper and lower extremities excluded venous thrombosis. Flow cytometry for CD55/CD59 including fluorescein-labeled proaerolysin (FLAER), triglycerides, ferritin, complement, anti-cardiolipin and anti-β2-glycoprotein I antibodies were normal/absent, making paroxysmal nocturnal hemoglobinuria (PNH), hemophagocytic syndrome, and antiphospholipid syndrome (APS) unlikely. The direct antiglobulin test (DAT-IgG and C3D) and testing for irregular antibodies were negative, while anti-platelet antibodies were present. Screening for viral infections (HIV, hepatitis B virus (HBV)/hepatitis C virus (HCV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), parvovirus-B19) and autoimmunity was negative except for subclinical hypothyroidism. A bone

marrow (BM) biopsy could not be performed because of the high bleeding risk, but peripheral blood cytometric immuno-phenotypic analysis was normal, although the absolute number of CD4+ T cells was reduced (369/mm^3, normal range: 493–1666). The patient continued treatment with IVIG (5 days), oral prednisone (1–1.5 mg/kg), and platelet transfusions. Hemoglobin levels increased progressively, while thrombocytopenia did not respond to treatment (Figure 1). Moreover, a follow-up brain CT scan performed on day 5 showed the development of a thin frontal subdural hematoma. Meanwhile, a further molecular test for SARS-CoV-2 on sputum (Seegene's Allplex 2019-nCoV assay) confirmed the diagnosis of COVID-19 and the patient was transferred to a COVID-19 ward and treated with COVID-19 standard therapy. In the COVID-19 ward the patient was treated with oxygen therapy and she did not undergo anti-viral treatment. On day 6, treatment with the oral thrombopoietin receptor agonist (TPO-RA) eltrombopag was initiated (starting dose: 25 mg/day, maximal dose: 75 mg/day). The patient did not report any side effects and liver function remained unchanged. In the following days, the platelet count progressively increased (Figure 1) and the subdural hematoma resolved spontaneously. On day 24 after admission, the platelet count was normal and two consecutive nasopharyngeal swabs for SARS-CoV-2 were negative. The patient was discharged from the hospital on tapering doses of eltrombopag (50 mg/day) and prednisone (25 mg/day). At the follow-up visit 15 days after hospital discharge, the patient was asymptomatic, and the platelet count was in the normal range.

Discussion and conclusions

Our patient had COVID-19 pneumonia associated with immune thrombocytopenia (ITP) and hemolytic anemia. The timing of symptom onset indicates that SARS-CoV-2 infection preceded hematological abnormalities, suggesting a link between COVID-19 and the development of anemia and thrombocytopenia. SARS-CoV-2 infection might have triggered an autoimmune response against platelets and red blood cell antigens through molecular mimicry, as described for other viruses.[7] This is consistent with previous reports of COVID-19-associated ITP.[8–10] Besides acting as a direct inducer of autoimmunity, SARS-CoV-2 infection might have favored the

Table 1. Laboratory exams.

Variable	Reference range	Patient value
Hemoglobin (g/dl)	12.0–16.0	6.8
Reticulocytes (%)	0.5–2	7.7
White blood count (per mm^3)	4000–10,000	17,770
Lymphocytes (per mm^3)	1000–4000	440
Platelet count (per mm^3)	140,000–450,000	0
Reticulated platelets (%)	<10	0
Creatinine (mg/dl)	0.55–1.01	0.42
Triglycerides (mg/dl)	50–175	132
Indirect bilirubin (mg/dl)	0.2–0.8	0.9
Alanine aminotransferase (U/L)	5–35	7
Aspartate aminotransferase (U/L)	8–30	16
Creatine kinase (U/L)	25–140	49
Lactate dehydrogenase (U/L)	250–450	936
Prothrombin time, INR	0.8–1.2	1.17
APTT ratio	0.8–1.18	0.84
Fibrinogen (mg/dl)	200–400	431
Anti-thrombin III (%)	80–120	123
D-dimer (ng/ml)	<830	7124
Haptoglobin (mg/dl)	40–200	<10
Ferritin (ng/ml)	15–150	408
Procalcitonin (ng/ml)	<0.5	0.17
C-reactive protein (mg/L)	<5	27.3
Thyroid-stimulating hormone (μU/ml)	0.270–4.200	8.230
FT4 (pg/ml)	9.3–17.0	11.7
TPO antibodies (U/ml)	<34	74
Complement C3 (mg/dl)	72–150	81
Complement C4 (mg/dl)	9–31	16

APTT, activated partial thromboplastin time; FT4, free thyroxine; INR, international normalized ratio; TPO, thrombopoietin.

development of an autoimmune response by altering T-cell-mediated immune tolerance.[11] In keeping with this hypothesis, patients with COVID-19 have reduced Treg cells that are
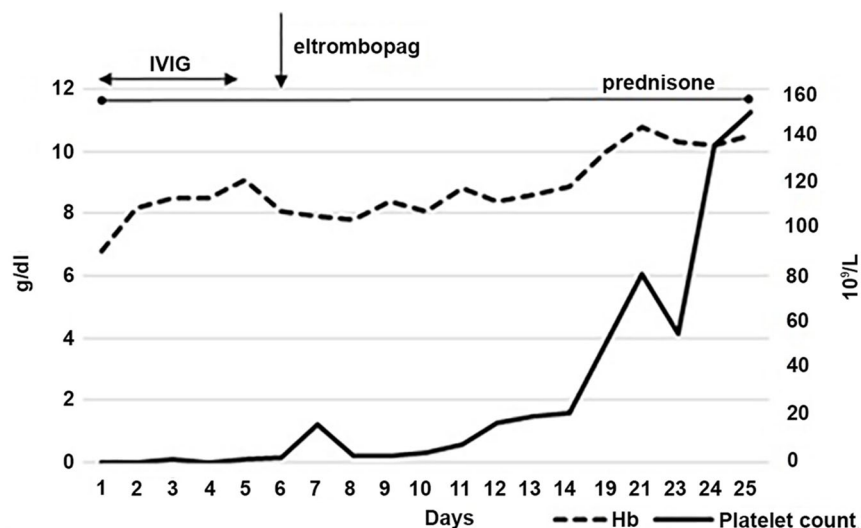
Figure 1. Time course of both hemoglobin levels and platelet count during hospitalization.

crucial in maintaining immune tolerance[12] and our patient showed both lymphocytopenia and diminished CD4+ T cells. Individuals with a known autoimmune disease are more prone to develop ITP, indicating that dysregulation of immune homeostasis may contribute to disease onset,[11] and our patient had subclinical Hashimoto's disease that is associated with ITP and confers resistance to standard therapy.[7] Reduced platelet production by the BM also plays an important role in ITP pathogenesis, providing a rationale for the therapeutic use of TPO-RA. Autoantibodies against platelets attacking mega-karyocytes (MKs), cytokines altering MK maturation/survival, and reduced production/response to TPO are believed to be involved.[11] Our patient had a low reticulated platelet count despite severe peripheral thrombocytopenia. Together with the response to eltrombopag, this suggests an impaired BM platelet production. In contrast, the count of reticulocytes was elevated, indicating a MK-specific phenomenon. It is tempting to speculate that in our patient COVID-19-induced cytokine storm might have hampered MK maturation/survival, thereby contributing to thrombocytopenia. In experimental animals the lung is a site of platelet biogenesis and a reservoir for MK progenitors,[13] raising the hypothesis that COVID-19 may also affect platelet synthesis by damaging the lung. In patients with COVID-19, endothelial damage and coagulation abnormalities can lead to micro-thrombus formation and

possibly platelet consumption.[5] However, it is unlikely that this mechanism played a major role in our patient, as coagulation parameters were normal except D-dimer levels, schistocytes were absent, common causes of thrombotic microangiopathy were excluded, and venous thrombosis was absent. The combination of ITP and autoimmune hemolytic anemia is characteristic of the Evans syndrome (ES). ES is a rare condition of profound dysregulation of the immune system that is often associated with other hematological, autoimmune, or lymphoproliferative disorders.[14] Our patient had no associated immune disorders except Hashimoto's disease and the prompt response to treatment of hemolytic anemia makes a secondary form of ES more likely. However, the patient requires a long-term follow-up for the early recognition of these associated disorders. According to the current guideline, our patient was treated with IVIG, corticosteroids, and platelet transfusions. Given the lack of response, eltrombopag was then added to therapy, as rituximab was not considered a treatment option, because of concomitant SARS-CoV-2 infection. A BM biopsy is usually performed prior to TPO-RA treatment to exclude secondary ITP due to hematological disorders, particularly in patients with cytopenia affecting two hematopoietic lines. However, in our patient BM biopsy was not performed because of the high bleeding risk and the life-threatening conditions of the patient suggested the prompt use of a TPO-RA. Eltrombopag

was effective in raising the platelet count, although a longer follow-up is required to determine whether treatment will result in complete remission.

We must consider, however, that the patient was treated with azithromycin and we cannot exclude the possibility of drug-induced thrombocytopenia and anemia. However, azithromycin rarely causes immune-mediated anemia and thrombocytopenia. Moreover, drug discontinuation usually leads to a rapid recovery, while in our patient hemolytic anemia and ITP developed after removal of the offending drug.[15,16] Second, DAT was negative, likely because of delayed testing (after 2 days of treatment in the emergency room with blood transfusions and corticosteroids); therefore, we could not confirm the diagnosis of autoimmune hemolytic anemia, although a false negative DAT was likely given the exclusion of an alternative diagnosis of hemolytic anemia. Unlike previous reports of COVID-19-ITP association, a key strength here is the exclusion of other potential causes of thrombocytopenia, including thrombotic microangiopathy, coagulopathy, PNH, hemophagocytic syndrome, and APS. In addition, we provide evidence that COVID-19-associated ITP non-responsive to standard therapy may be successfully treated with eltrombopag. In the absence of guidelines and clinical experience, our case report may help clinicians in their practice. In conclusion, a diagnosis of ITP should be considered in patients with both COVID-19 and thrombocytopenia. Moreover, TPO-RAs may represent a useful therapeutic tool in patients with severe ITP.

Author contributions
GG, EB, EC and SeC were in charge of the patient care; GG, EC, SeC, SiC, and MS wrote the manuscript; MA and FP performed laboratory measurements; FB and MD revised the manuscript.

Conflict of interest statement
The authors declare that there is no conflict of interest.

Ethics statement
Written informed consent was obtained from the patient for publication of this case report. Ethics approval is not required for case reports or case series deemed not to constitute research at our institution.

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