Letter to the Editor

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The unique landscape of coronavirus disease 2019 coagulopathy and imminent bleedings at unusual sites: Pathophysiology matters

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Dear Editor,

We read with great interest the article by Presicce et al.[1] entitled "Wunderlich syndrome, an unexpected urological complication in a patient with coronavirus disease 2019 (COVID-19): A case report." The authors aimed to shed light on the pathophysiology, differential diagnosis, and management of a rare urological bleeding complication in the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Although the findings of the present case study were also discussed in a well-written article by Singh et al.,[2] we believe that several issues need to be highlighted and further clarified in this underrecognized field.

First, both Presicce et al.[1] and Singh et al.[2] supported the pathophysiological correlation between major bleeding events at unusual sites and COVID-19 illness severity with data on anticoagulation treatment, either prophylactic or therapeutic. More specifically, Presicce et al.[1] described the clinical course and outcome of a patient who received enoxaparin at a prophylactic dose before the development of a large retroperitoneal hematoma due to the spontaneous rupture of a renal artery branch. At this point, we suggest that a therapeutic anticoagulant approach or, ideally, an anti-factor Xa-guided administration of low-molecular-weight heparin (LMWH) should be adopted, given that the patient was obese and presented with markedly elevated D-dimer levels.[3]

On the other hand, Singh et al.[2] reported four severe cases of COVID-19-associated pneumonia complicated by major bleeding events at unusual locations while the patients received therapeutic anticoagulation. It is now clear that once COVID-19 is associated with a unique scenario of high thrombotic risk, anticoagulation is imperative in everyday clinical practice. However, the dose and duration of treatment with LMWH remain debatable, as significant adjustments may be required depending on the distinct characteristics of the affected patient as well as various other factors related to the patient admission laboratory and clinical findings.[4]

Second, none of the patients had any history of bleeding diathesis, trauma, thrombocytopenia, overt disseminated intravascular coagulation, or substantial hypofibrinogenemia in the complete blood workup at the time of bleeding. Thus, from a pathophysiological point of view, none of the patients were at high risk of bleeding, given that (1) COVID-19-associated thrombocytopenia was absent, and (2) COVID-19-associated coagulopathy was directed toward a hypercoagulable state instead of a hyperfibrinolytic profile. Indeed, high levels of D-dimers reflect the substantial release of plasminogen activators from the injured endothelium rather than a hyperfibrinolytic environment, in which severe hypofibrinogenemia may result in an increased risk of major bleeding.[5,6]

In addition, in a recent meta-analysis that included 41 studies on 17,601 patients, the authors identified that elevated levels of D-dimer and fibrinogen were the most robust hemostatic laboratory variables associated with disease severity and the persistent risk of thromboembolism.[7] Presicce et al.[1] reported a case of mild thrombocytopenia. It is well-known that mild or moderate thrombocytopenia in COVID-19 patients represents a strong marker of disease severity and is an important player in thromboinflammation, rather than an indicator of impending bleeding.[7]

Furthermore, Ciceri et al.[8] supported the hypothesis of functional implications of SARS-CoV-2-associated systemic inflammatory endotheliopathy in the pathogenesis of microvascular thrombosis and multiple bleeding foci in the distal microcirculation as a consequence of aberrant platelet recruitment.[9] In the same context, functional tests could have been used by Presicce et al.[1] to more accurately evaluate possible qualitative platelet disorders, considering that dysfunctional platelets contribute partially to a bleeding event.[10]

Based on the above, we also propose that the main underlying pathophysiological mechanisms involved in renal bleeding in this patient are either systemic coagulopathy induced by severe SARS-CoV-2 infection or the indirect consequences of antithrombotic therapy. Similarly, Coppola et al.[11] raised the important question of whether the underlying cause of spontaneous major abdominal bleeding in non-critically ill patients at low risk of bleeding is the synergistic effect of different predisposing factors. In particular, Coppola et al.[10] pointed out the fundamental role of significantly increased intra-abdominal pressure as a result of supporting continuous positive-airway pressure ventilation and bouts of severe coughing during the course of COVID-19 infection, mainly in those with bilateral interstitial pneumonia.

Third, it is noteworthy that the vast majority of patients reported with major abdominal bleeding events were characterized by an increased rate of similar comorbidities such as cardiovascular disease, diabetes mellitus, obesity, and hypertension, which are well-known conditions with established atherosclerotic alterations.[2,11] This observation may explain the proneness of stiff abdominal vessels, such as atherosclerotic epigastric arteries, to rupture when abnormal force distribution is deployed during muscle contraction or an excessive increase in intra-abdominal pressure. Furthermore,

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the advanced age of affected patients may be another predisposing factor for abdominal bleeding, because the progressive weakening of the abdominal wall during aging is translated into the loss of vessel-supporting scaffold.

Given that there are limited data about spontaneous bleeding events in patients affected by COVID-19, the pathoetiology of bleeding remains enigmatic and constitutes another hemostatic paradox of SARS-CoV-2 infection. Disseminated intravascular coagulation, COVID-19-associated thrombocytopenia, and reduced fibrinogen levels during severe illness have been associated with major bleeding episodes, including gastrointestinal bleeding, pulmonary hemorrhage, spontaneous kidney hematoma, internal bleeding, and intracranial hemorrhage.[12]

Critically ill patients of advanced age and those with preexisting comorbidities upon anticoagulation with LMWH for the prevention or treatment of venous thromboembolism seem to be more susceptible to a major bleeding episode.

Surprisingly, in a nationwide self-controlled case series and matched cohort study conducted by Katsoularis et al.,[13] the researchers confirmed that COVID-19 was an independent risk factor for bleeding 2 months after COVID-19 infection especially in those with comorbidities or severe illnesses and during the first pandemic wave compared with the second and third waves. Thus, bleeding events may occur early in the course of COVID-19 infection and up to 60 days after hospitalization, provided that patients are on anticoagulation with LMWH.

In support of the above, we report 2 cases of spontaneous major bleeding events in patients with end-stage kidney disease undergoing hemodialysis. The first patient was a 76-year-old woman who was affected by COVID-19-associated bilateral interstitial pneumonia and developed a spontaneous major bleeding episode in the rectus sheath muscle 5 days after discharge from the hospital. Her underlying comorbidities included arterial hypertension, severe peripheral arterial disease, coronary artery disease, chronic obstructive pulmonary disease, and undifferentiated connective tissue disease under immunosuppressant therapy with prednisone and hydroxychloroquine.

Initially, the patient was supported with high-flow nasal cannula oxygen and treated with dexamethasone, ceftriaxone, azithromycin, clopidogrel, and prophylactic dose of enoxaparin. The patient was discharged after 21 days of hospitalization, and the postdischarge course remained uneventful with the same prophylactic dose of enoxaparin. However, 5 days after discharge, she complained of severe abdominal pain accompanied by a palpable infraumbilical abdominal mass and clinical signs of hemorrhagic shock. A massive ecchymosis extending from the left lower anterior abdominal wall to the external abdominal oblique muscles was also observed at the time of readmission (Fig. 1A).

Routine laboratory tests revealed severe anemia, whereas the platelet count and coagulation parameters, including fibrinogen levels and anti-factor Xa activity, were within normal values. Abdominopelvic computed tomography scan revealed an exceptionally large rectus sheath hematoma (RSH) outspreading unilaterally from the left-sided internal and external oblique muscles to the left transversus abdominis muscle and subcutaneous fat tissue (Fig. 1B). Conservative treatment with bed rest, analgesics, discontinuation of LMWH, and red blood cell transfusions were effective, and RSH resolved after 7 days of hospitalization.

The second patient was a 68-year-old man who was also affected by severe COVID-19-associated pneumonia that suddenly developed during hospitalization due to a spontaneous major bleeding event in the retroperitoneal space. His medical history included end-stage kidney disease that was maintained with hemodialysis due to autosomal dominant polycystic kidney disease, resistant hypertension,

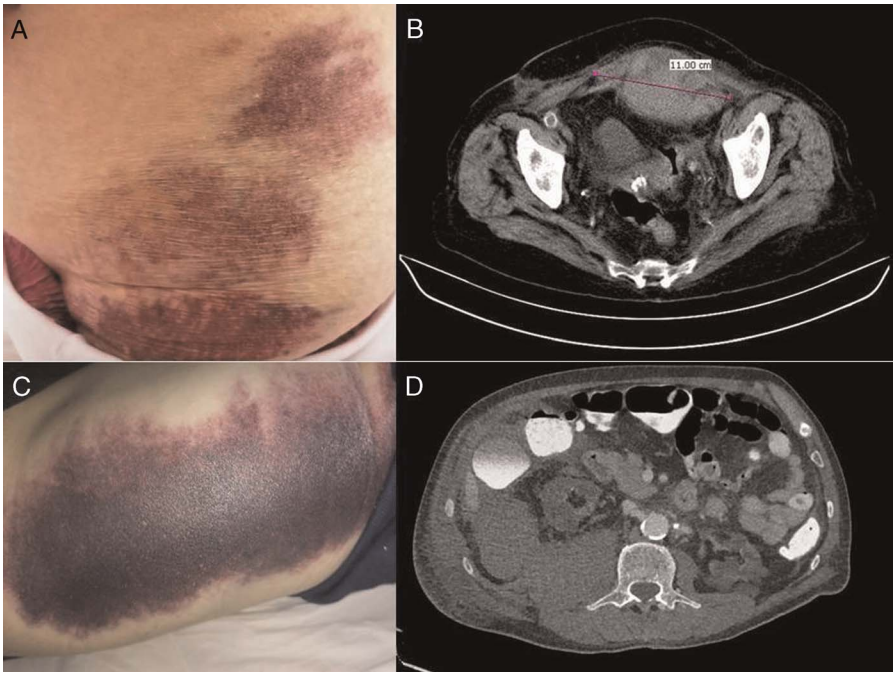

Figure 1. (A) Large ecchymosis extending from the left lower anterior abdominal wall to the external abdominal oblique muscles in a 76-year-old woman. (B) Abdominopelvic CT scan showing a large RSH unilaterally from the left internal and external oblique muscles to the left transversus abdominis muscle and subcutaneous fat tissues. (C) Massive right-sided ecchymosis in a 68-year-old autosomal dominant polycystic kidney disease patient. (D) Abdominopelvic CT angiography showing a large retroperitoneal hematoma in combination with a right-sided RSH, displacing the right kidney and compressing the inferior vena cava. CT = computed tomography; RSH = rectus sheath hematoma.

ischemic heart disease, peripheral arterial disease, and dyslipidemia. On admission, the patient was supported with high-flow nasal cannula oxygen and received combined therapy with dexamethasone, ceftriaxone, remdesivir, and enoxaparin at a prophylactic dose. The patient also underwent an intensified schedule of daily hemodialysis sessions to achieve optimal control of arterial blood pressure, uremia-associated variables, and resistant hyperkalemia. On day 14 of hospitalization, the patient experienced a bout of severe dry cough followed by a sudden, intense right flank pain accompanied by a palpable mass and signs of hypovolemic shock. A massive ecchymosis was observed the following day (Fig. 1C).

Subsequently, chest and abdominopelvic computed tomography angiography revealed severe deterioration of pulmonary involvement with extensive parenchymal condensation and a large retroperitoneal hematoma without evidence of active bleeding, in combination with a right-sided RSH (Fig. 1D). A complete blood workup showed severe anemia (hemoglobin level, 8.2 g/dL) and elevated levels of lactate dehydrogenase (962 IU/L), serum ferritin (1547 ng/mL), D-dimers (3.16 μg/mL), fibrinogen (745 mg/dL), and C-reactive protein (9.26 mg/dL). However, other coagulation parameters, platelet count, anti-factor Xa activity, and liver enzyme levels were within reference ranges. This patient received conservative therapy with bed rest, analgesics, withdrawal of LMWH, and red blood cell transfusions, but he died 6 days after bleeding due to septic complications.

Spontaneous RSH and retroperitoneal bleeding are rare types of soft tissue hematomas and abdominal bleeding, respectively. The aforementioned bleeding events are also well-documented anticoagulation-associated complications in patients with the following distinct characteristics: advanced age, female sex, hypertension, atherosclerosis, chronic kidney disease, collagen vascular disorders, systemic use of corticosteroids and immunosuppressant drugs, increased intra-abdominal pressure mainly due to severe flare-ups of cough, and inappropriate use of subcutaneous abdominal injections of LMWH with or without concomitant administration of antiplatelet agents.[14–16]

In conclusion, given that there is no concrete evidence for the dose and duration of LMWH administration in patients with SARS-CoV-2 infection, attention should be directed to the early recognition and management of major bleeding events in vulnerable subpopulations. An individualized approach should be considered, taking into account age, renal function, and various underlying comorbidities, to prevent not only early but also delayed and potentially life-threatening hemorrhagic complications at unusual sites.

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Statement of ethics

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