Spontaneous muscle hematomas presenting with hemorrhagic shock in critically ill patients with SARS-CoV-2 pneumonia

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ABSTRACT

Background: Spontaneous muscle hematomas (SMH) are rare but potentially life-threatening. We report three patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia who developed hemorrhagic shock, due to large SMHs, during their intensive care unit stay.

Case Presentation: All the patients were receiving mechanical ventilation and anticoagulation therapy with enoxaparin. The bleeding was located in the gluteal muscles in two of the patients and in the iliopsoas muscle with retroperitoneal extension in the other. Anemia and hemodynamic instability were the main signs; however, because of their gradual onset, they were initially confused with the anemia of the critically ill patient and sepsis related to secondary infections. All received conservative medical treatment, but unfortunately one patient died within hours of diagnosis.

Conclusion: This report highlights that clinicians should also be alert to major spontaneous hemorrhage in patients with SARS-CoV-2 infection. Since it is a novel disease, a possible association with bleeding events cannot be disregarded and, on the contrary, should be considered, particularly to determine the appropriate use of anticoagulation in this type of patients.

Keywords: Coronavirus, COVID-19, SARS-CoV-2, muscle hematomas, hemorrhagic shock, retroperitoneal bleeding.

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Background

Due to current worldwide outbreak of the novel coronavirus identified in Wuhan at the end of 2019, severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), many patients have required intensive care unit (ICU) admission in a rate that varies from 5% to 12% of all positive cases [1]. Although the main reason for this admission has been the development of pneumonia and acute respiratory distress syndrome (ARDS), other complications have also been reported, such as acute kidney injury (AKI), sepsis, cardiac injury, encephalopathy, and thromboembolic events [2,3].

Spontaneous muscle hematoma (SMH) is an uncommon but potentially life-threatening condition. Most times, these hematomas affect the abdominal wall or the gluteal muscles [4] but they can diffuse into the peritoneal or retroperitoneal space [5]. Several risk factors have been described, including anticoagulant treatment, old age, hemodialysis, and others [4,5].

We report three cases of SMH presenting with hemorrhagic shock, in critically ill patients with SARS-CoV-2 pneumonia admitted in our ICU.

Case Presentation

Patient characteristics and laboratory findings are listed in Table 1.

Case 1

72-year-old male suffering from dyslipidemia and type 2 diabetes mellitus. The day of admission in our unit, he required invasive mechanical ventilation. Prophylactic anticoagulation with enoxaparin 40 mg twice a day was started after a marked increase in D-dimer levels (8,000 ng/ml) on day 4. No other organ failures were observed, and weaning from mechanical ventilation was started on day 10. The next day, the patient developed hemodynamic instability, acute anemia (Figure 1), and signs of abdominal pain during the physical examination. A contrast abdominal computed tomography (CT) scan showed a massive hematoma in the right iliopsoas and retroperitoneal space (Figure 2). Following multiple blood transfusions, fluid replacement, vasoactive support, and administration of protamine; the patient experienced significant recovery in the successive days.

Table 1. *Patient characteristics and laboratory findings.*

CASE	1	2	3
Age (years)	72	73	72
Bleeding location	Right iliopsoas and retroperitoneal hematoma	Right pelvis, gluteal and thigh muscles	Right gluteal and upper thigh muscles
Anticoagulant initiation (day of admission in ICU)	4th day	6th day	9th day
Dose of enoxaparin	40 mg/12 hours	60 mg/12 hours	80 mg/12 hours
Length of stay until diagnosis (days)	11	17	59
Prone position sessions	4	2	4
INR	1.01	1.08	1.06
aPTT (seconds)	29.1	44.5	25.3
Anti-factor Xa levels (UI/ml)	0.53	1.4	0.72
Platelets (mcl)	319.000	276.000	433.000
Initial Hb level (g/dl)	14.1	12.7	14.6
Lowest Hb level (g/dl)	7.9	6.1	6.4
Number of RBC transfusions	8	11	9
Outcome	Survival	Death	Survival

*ICU: Intensive c*are *u*nit, INR: Prothrombin time International normalized ratio, *aPTT*: Activated partial thromboplastin time, RBC: *R*ed blood cells.

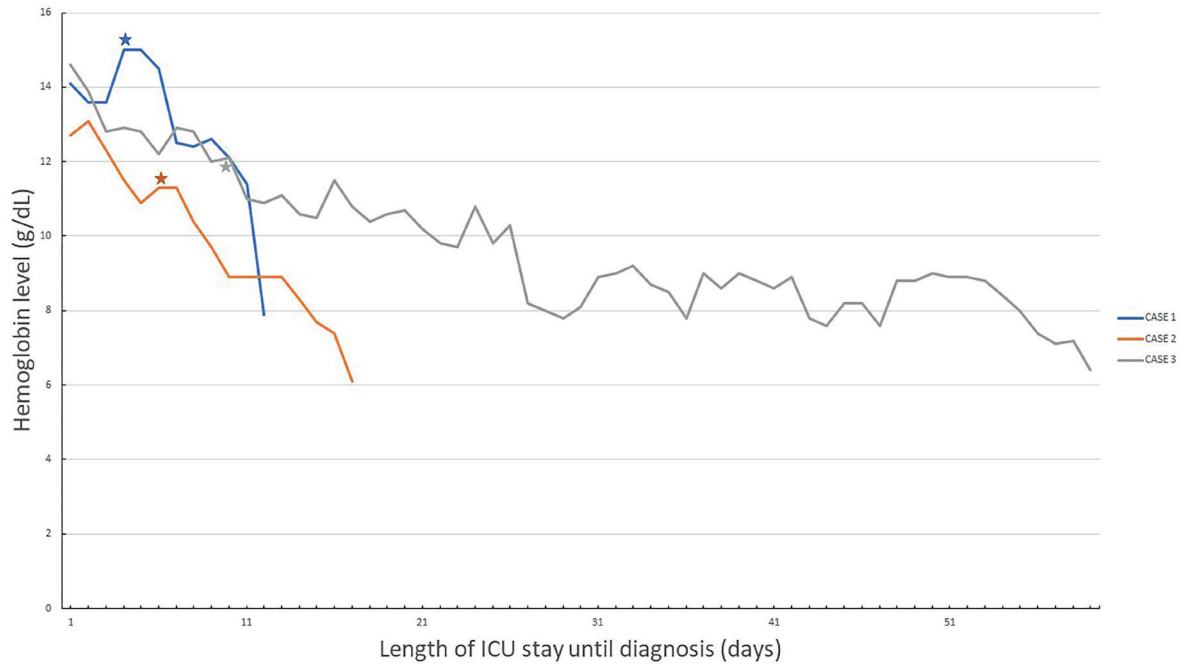

Figure 1. *Timeline of the Hb levels during ICU stay. Stars indicate the day of anticoagulant therapy initiation.*

Case 2

73-year-old man with a history of hypertension and glucose intolerance who was admitted in our ICU for acute respiratory failure requiring intubation, and mechanical ventilation. During his ICU stay, he also developed hemodynamic instability, AKI, and atrial fibrillation; hence, noradrenaline, continuous venovenous hemodiafiltration, and enoxaparin 60 mg twice a day were initiated, respectively. During the first 15 days of admission, all organ failures improved, therefore, ventilator weaning was started. On day 16, a decreased hemoglobin (Hb) level of 7.4 g/dl was observed (Figure 1) followed by a progressive hypotension. A contrast CT of the abdomen and pelvis demonstrated a large hematoma in the right hemipelvis, gluteal and upper thigh muscles (Figure 2). Urgent anti-factor Xa assay revealed a supratherapeutic level of 1.4 IU/ml. The clinical status of the patient steadily deteriorated thereafter despite vasoactive support, volume resuscitation, packed red blood cells and plasma

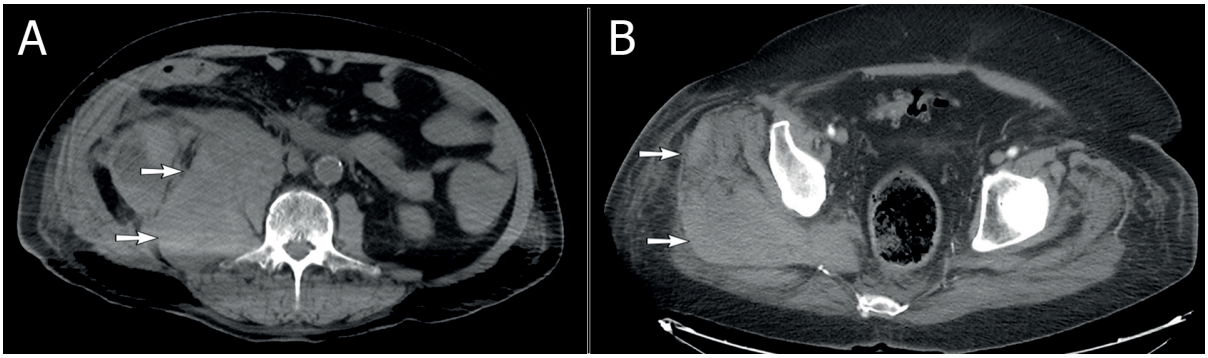

Figure 2. *Abdominopelvic CT demonstrating: (A) Right iliopsoas and retroperitoneal hematoma (white arrows) in Case 1 and (B) Large intramuscular hematoma in the right gluteal and upper thigh muscles (white arrows) in Case 2.*

transfusions, and reversal of anticoagulation with protamine. The patient died the next day.

Case 3

72-year-old male with a history of pulmonary embolism 14 years ago. The patient was admitted with severe respiratory insufficiency and treated with orotracheal intubation and mechanical ventilation. Due to his history of pulmonary embolism and rising D-dimer levels, anticoagulation therapy with enoxaparin was initiated on day 9 of admission. After an initial respiratory recovery, the patient was extubated on day 22; however, reintubation was performed 2 days later as a result of a respiratory failure. During the following 35 days, the patient experienced a significant respiratory deterioration, septic shock, AKI, and progressive anemia. On day 59, gradual hypotension was observed and laboratory examinations revealed a drop in Hb levels (6.4 g/dl). A contrast abdominopelvic CT scan demonstrated a voluminous hematoma in the right gluteal and upper thigh muscles. After conservative medical treatment including volume resuscitation, transfusion and noradrenaline infusion, the patient became clinically stable. Ten days later, a follow-up CT scan showed an important size reduction of the right gluteal and thigh hematomas, but also the development of a moderate size hematoma in the left upper thigh; however, this latter hematoma did not have any clinical repercussion.

Discussion

During the recent pandemic, between March and June 2020, 65 critically ill patients with SARS-CoV-2 pneumonia were admitted in our ICU. Three of them developed a SMH during their stay. This corresponds to an incidence of 4.6%, which is higher than reported in other cohorts [5-7]. All our patients were on therapeutic anticoagulation with enoxaparin. The development of SMH is significantly associated with anticoagulant treatment [4-7].

The estimated incidence of SMH in patients on anticoagulants is 0.6% [5]. In most cases, vitamin K antagonists or unfractionated heparin are involved. In rare cases, this complication occurs during treatment with low molecular weight heparin [4,6,7]. In addition, small hematomas are the most common and tend to resolve spontaneously; the bleeding seldom results in hemodynamic instability and requires or complicates ICU stays [5]. Very few studies have analyzed cases of SMH among patients hospitalized in ICU. In a multicentric study, it was reported an incidence of iliopsoas hematoma of 0.3% in patients admitted to ICU, they considered a cohort of patients who were diagnosed with iliopsoas hematoma at admission or while they were hospitalized in ICU (50 and 27 patients, respectively) [6]. They found that iliopsoas hematoma was related to anticoagulant therapy in 72% of the cases, particularly vitamin K antagonists and unfractionated heparin, and less frequently with low molecular weight heparin. Another similar study reported a slightly higher incidence of 0.38%, though they included only patients who developed iliopsoas hematoma after 72 hours past their ICU admission [7]. They also identified anticoagulant therapy as a main risk factor (95% of the cases), but unfractionated heparin was the anticoagulant drug used for all patients and no patient was treated with low molecular weight heparin.

At admission, standard prophylactic dose of enoxaparin was initiated in all of our patients; however, we escalated to therapeutic anticoagulation because of atrial fibrillation or elevated D-dimer levels. Thrombotic complications have been associated with elevations in D-dimer > 1,000 ng/ml [8], and in consequence, several investigators have recommended empiric escalation of anticoagulation in coronavirus disease 2019 (COVID-19) patients with elevated D-dimer levels but no known thrombotic complications [3,8]. Initial weight-based enoxaparin dose was used in our patients, additionally, anti-factor Xa levels were monitored regularly to ensure therapeutic levels of 0.5-1.2 IU/ml, particularly after changes in renal function. Only one patient was above the therapeutic range (1.4 UI/ml) at diagnosis, while the other two were on expected levels. SMH can occur in patients with therapeutic or supratherapeutic levels of anticoagulation [5-7], measured by the International normalized ratio (INR), in the case of vitamin K antagonists, and activated partial thromboplastin

time (aPTT), in the case of unfractionated heparin. No study has evaluated anti-factor Xa levels in patients with SMH receiving low molecular weight heparins.

Hemodialysis, old age, hemostatic disorders, atheromatosis, diabetes, and increased abdominal pressure (sneezing, straining, coughing, and gagging) are among other known risk factors associated with SMH [4-6]. Whereas precise pathogenesis and pathophysiology of SMH is unknown, it is hypothesized that a microtrauma causing muscle and capillary tears is often related [4,5]. We believe that the advanced age and possible atherosclerosis, due to their cardiovascular risk factors, could have played an important role. One of the patients was receiving continuous venovenous hemodiafiltration, this may have been another contributing factor. In addition, as our patients presented ARDS and were on mechanical ventilation, patient-ventilator asynchronies, multiple aspiration of bronchial secretions, and repeated supine-prone postural changes could have been involved in muscle strain and blood vessel ruptures. Although changes in patient position are frequent in ICU, because of a work overload and expert staff shortage during the peak months of the coronavirus health crisis, there may have been some improper patient positioning that we were unaware.

We recognized hemorrhage in our patients on the basis of an important anemia and hemodynamic instability. However, these signs were initially confused with other entities. The progressive anemia was attributed to the common anemia of the critically ill patient; it was not until it reached unexpectedly low levels that we considered a possible bleeding. The presence of hemodynamic instability and need of vasopressors are also not uncommon in the critically ill patient, as sometimes they are associated to sedatives or other conditions different than hemorrhage. In our cases, when progressive hypotension and tachycardia appeared, the first diagnostic impression was the development of sepsis related to secondary infections (e.g., central line or ventilator-associated pneumonia), therefore, empiric antimicrobial therapy was initiated. Nonetheless, the association between a continuing hemodynamic deterioration and a persistent anemia despite transfusion, made us consider as a possible hemorrhage, and in consequence, an abdominopelvic contrast CT scan was performed. In our patients and in previous reports, the bleeding was located in the posterior region of the iliopsoas or gluteal muscles [5]. No signs of active bleeding, as active leaking of contrast or enhancement of the hematoma [5], were found in any of the patients; therefore, conservative medical treatment was performed in all of them.

A high incidence of acute thrombotic events has been described in patients with SARS-CoV-2 infection and, as a result, routine prophylactic or therapeutic anticoagulation has been widely recommended [3,9]. Nonetheless, bleeding complications are also significant and have been described even in absence of anticoagulation. It has been reported a major bleeding rate of 2.3% in noncritically ill patients and a 5.6% rate in the critically ill [8]. Among these bleeding events are gastrointestinal bleeding, pulmonary hemorrhage, epistaxis, and intracranial hemorrhage. Spontaneous arterial hemorrhage has also been communicated at a rate of 1.8%, with diagnostic angiography showing several different bleeding sites as lumbar, epigastric, gluteal, bronchial, thoracic and others [10]. However, very few cases of spontaneous muscle hematomas have been reported in general and in COVID-19 patients. In our experience, we had scarcely seen this complication in critically ill patients outside COVID-19.

This case report serves to highlight that clinicians should also be alert to major spontaneous hemorrhage in COVID-19 patients. In the presence of a persistent anemia and progressive hemodynamic deterioration, spontaneous muscle hematomas should be considered in the differential diagnosis, and thus an abdominopelvic CT scan. Moreover, a possible link between this new disease and hemorrhagic events cannot be dismissed and should be better clarified, specially to determine the appropriate use of anticoagulation.

What is new?

SMHs rarely present with hemorrhagic shock. As observed in these cases, this complication may not be promptly detected in critically ill SARS-Cov-2 patients; however, it should be considered in the presence of acute or gradual anemia.

List of Abbreviations

AKI	Acute kidney injury
aPTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
COVID-19	Coronavirus disease 2019
CT	Computed tomography
Hb	Hemoglobin
ICU	Intensive care unit
INR	International normalized ratio
SARS-Cov 2	Severe acute respiratory syndrome coronavirus 2
SMH	Spontaneous muscle hematoma

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Written informed consent for publication was obtained from the patients or next of kin.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Male. 72-73
2	**Final diagnosis**	SMHs
3	**Symptoms**	Anemia and hemodynamic instability
4	**Medications**	Blood transfusions, fluid replacement, vasoactive support, and administration of protamine.
5	**Clinical procedure**	Conservative medical treatment
6	**Specialty**	Critical Care