Rare findings of spontaneous hemothorax and small subpleural lung hematoma in a COVID-19 patient: A case report

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Abstract
Hemothorax (HT) and pulmonary hematoma represent rare complications of anticoagulant therapy. We present a rare case of a 53-year-old man with COVID-19 pneumonia who showed, in a follow-up computed tomography (CT) scan 13 days after hospitalization, a left HT and a small hyperdense area in a subpleural location and compatible with a small subpleural hematoma. This patient was being treated with a subcutaneous administration of low-molecular-weight heparin (100UI/kg/BID). No vascular malformations were visualized on the CT pulmonary angiography. Herein, we report the first case of both a spontaneous HT and a lung subpleural hematoma in a COVID-19 patient, probably caused by anticoagulant therapy.

Keywords
SARS-CoV-2, COVID-19, anticoagulant therapy, hemothorax, subpleural pulmonary

Introduction
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the novel coronavirus responsible for the global pandemic of coronavirus disease 2019 (COVID-19). COVID-19's manifestations vary from asymptomatic cases to pneumonia and gastrointestinal and neurological symptoms.1 The lung is a preferred site for the virus.

However, emerging research has focused on a vasculo-centric theory of COVID-19 suggested by the endothelial dysfunctions, thrombosis, and dysregulated inflammation usually found in this novel disease.2 Some COVID-19 patients undergo anticoagulant therapy to mitigate the increased risk of venous thrombosis and pulmonary lung embolism.3 However, there are emerging complications of anticoagulant treatment in COVID-19 patients such as muscular hematomas and arterial bleeding.4,5

Hemothorax (HT) and pulmonary hematoma (PH) are usually secondary to chest trauma.6,7 Spontaneous HT is a rare and life-threatening condition that can be caused by...
tumors, arteriovenous malformations, pulmonary emboli, endometriosis, and neurofibromatosis.8,9 Spontaneous HT due to anticoagulant therapy such as that with warfarin, apixaban, and low-molecular-weight heparin (LMWH) has only emerged in case reports.8,9 Spontaneous PH is extremely rare, and its possible causes include anticoagulation therapy, thrombocytopenia, and congenital disorders.10

In this case report, we present the first, to our knowledge, case of spontaneous subpleural PH with HT in a COVID-19 patient who underwent anticoagulant therapy without any history of trauma or iatrogenic causes.

Case presentation

A 53-year-old man, who was a physiotherapist and worked in a rehabilitation center, came into our hospital’s emergency room for worsening dyspnea and fever (38.5°), with an O₂ saturation level of 88%. He suffered from arterial hypertension and was under treatment with Cardicor (1.25 mg once daily orally) and Norvasc (10 mg once daily orally). He reported one contact with a patient who had tested positive for COVID-19 a few days before the onset of his symptoms. However, the laboratory blood tests continued to show a mild decrease in Hb (11.5 mg/dl), with D-dimer in the normal range (0.45 mg/L).

In this case, the patient complained of thoracic pain on the left side, and a chest CT was performed on Day 15 of the hospitalization. In this case, the patient was positive for COVID-19 a few days before the onset of his symptoms.

Blood tests revealed a slightly low hemoglobin (Hb) value of 12.5 g/dL (normal range, 13.0–16.5 mg/dL) with a standard mean cell volume value of 86.3 FL (normal range, 82–93.5 FL), normal white blood cell count of 11.9 × 10³/μL (normal range, 4.00–11.00 × 10³/μL), normal platelet count (301.000/mm³) (normal range, 150,000–400,000/mm³), an elevated D-dimer level (9.02 mg/L) (normal range, 0.45–3.5 mg/L), as was the international normalized ratio (INR), with a value of 1.43 (normal range, 0.85–1.17). C-reactive protein was also elevated, at 0.85 mg/dL (normal range, 0–5 mg/dL), and there was a mild elevation of liver transaminases and ferritin (458.40 ng/mL). The other laboratory values were in the normal ranges.

NS/OP swabs were taken in the emergency room to test for SARS-CoV-2 with reverse transcriptase–polymerase chain reaction (RT-PCR).

Chest computed tomography (CT) with pulmonary angiography acquisitions (CTPA) was also conducted in the emergency room to rule out any lung embolisms. The chest CT showed features typical of COVID-19 pneumonia with multifocal areas of ground glass (GGO) in a crazy paving pattern with a central and peripheral distribution and a moderate visual extension (Fig. 1) based on the CT-severity score (CT-SS 16/25) proposed by Pan et al.11 Small vessel enlargement and pleural thickness were also present. No lung arterial embolism was found.

The NS/OP swabs resulted in positive for SARS-CoV-2 after 2 hours of the CT results.

Serology via a chemiluminescent immunoassay revealed the presence of both SARS-CoV-2 IgM (48.30 AU/mL) and IgG (32.33 AU/mL).

Oxygen therapy and the prone position were necessary after the worsening of his clinical respiratory condition.

After 13 days, the patient showed two consecutive negative RT-PCR results for SARS-CoV-2.

The examination was completed by an angiography study that did not reveal any arterial bleeding or vascular malformations.

A CT-guided intercostal drainage was immediately performed to improve the patient’s clinical conditions, which removed 300 mL of hematic pleural fluid (with a hematocrit >50% of the blood hematocrit). A chest CT scan after 5 days showed the reduction of the HT (Fig. 3), with a slight pneumothorax, and a small reduction in the density (40 HU) of the previous small subpleural hyperdense area, compatible with a lung subpleural hemotema, was observed (Fig. 3).

Discussion

COVID-19 is a new disease with systemic involvement, and the knowledge about it continues to evolve. Vascular damage and a dysregulation of the immune response, also known as “cytokine storms,” are described as typical events triggered by the virus’ actions.2,3 Clinical studies have
shown that patients with COVID-19 have increased fibrinogen, fibrin-degradation products, and D-dimer and these elevations were also found to be correlated with disease severity.\textsuperscript{2,3} Evidence of endothelial injuries is also described in autopsy reports,\textsuperscript{12} and the vascular damage can lead to a discrepancy between the preservation of lung compliance and the severity of the hypoxemia caused by ventilation/perfusion mismatch.\textsuperscript{2}

Various clinical studies in COVID-19 patients have shown that venous and arterial thromboembolisms result in an increased risk of morbidity and mortality, suggesting that the early administration of anticoagulant therapy to prevent these events is essential.\textsuperscript{3} On the other hand, emerging studies have reported muscular hematomas or arterial bleeding as possible complications of anticoagulant therapy.\textsuperscript{4,5} Some cases of spontaneous hematomas involving the

\textbf{Fig 1.} Images a, b, and c represent the lung window (W:1600 HU, L: −500 HU) of the baseline chest CT describing the multilobar COVID-19 pneumonia with a crazy paving pattern and with a peripheral and central distribution, with a CT-SS of 16/25. The left superior lobe and the right inferior lobe were more involved than the others. In the image, d represents the mediastinal window (W: 251 HU, L: 45 HU). No pleural effusion was seen on the left side.
The iliopsoas muscle, neck, abdominal wall, and chest wall have also been reported.\(^{13–15}\)

The risk of bleeding is relatively high in COVID-19 patients, especially in those who have received therapeutic anticoagulation treatment, and this condition is usually associated with an increased risk of mortality.\(^{16}\) However, Mattioli et al.\(^{4}\) reported a case of neck and upper chest spontaneous hematoma in an 84-year-old patient who was receiving prophylactic doses of LMWH.

Cerebral hemorrhagic complications and retroperitoneal and adrenal gland hemorrhages have also been described.\(^{17,18}\)

An emerging presentation of COVID-19 can also be hemoptysis.\(^{19,20}\) Peys et al.\(^{19}\) reported a case of a COVID-19 patient with an acute onset of hemoptysis and alveolar hemorrhage on CT. However, very few reports have described spontaneous HT as a possible complication of anticoagulant therapy in COVID-19 patients.\(^{21}\)

Hemothorax is defined as a collection of blood at different degrees of coagulation in the pleural space with a layered appearance also known as the “hematocrit sign.”\(^{22}\) Desnos et al.\(^{21}\) recently described 4 cases of COVID-19 acute respiratory syndrome (ARDS) patients who had received continuous infusions of unfractionated heparin at high preventive doses and who showed spontaneous HT on chest CT scans caused by pulmonary artery branch aneurysms, suggesting a vasculitis-like pathophysiological mechanism in these critically ill COVID-19 patients.

A CT scan is the modality of choice for visualizing COVID-19 pneumonia extension and its complications.\(^{23}\) Some visual semiquantitative and quantitative methods with CT-SS have been proposed as imaging tools for assessing COVID-19 pneumonia extension, with a possible role as predictors and prognostic indicators for COVID-19 outcomes.\(^{11,23}\) A CTPA can also rule out lung pulmonary embolism and reveal vascular malformations or any source of arterial bleeding.\(^{22,23}\)

Spontaneous PH appears on CT as a round hyperdense shape and can be caused by vessel rupture and subsequent hemorrhage, or it can occur in a preexisting cyst via angionecrosis and the erosion of the cystic wall.\(^{7,10,24,25}\) The treatment of PH is usually conservative,\(^{7}\) while the treatment of HT consists of chest tube drainage.

The microvascular damage usually found in COVID-19 patients with the use of anticoagulant therapy can explain both the HT and PH found in our patient.

In our patient, we had also earlier applied the prone position due to the onset of acute respiratory failure. Prone ventilation is an important strategy in managing severe ARDS associated with COVID-19 pneumonia, reducing the ventilation/perfusion mismatch by making the transpulmonary pressure more homogeneous and recruiting the non-aerated dorsal lung regions.\(^{26}\) Before the COVID-19 pandemic, the prone position had been reserved for only patients with ARDS who were ventilated mechanically.\(^{27,28}\)

However, studies emerging during the pandemic revealed that the prone position could also be considered applicable in the management of patients with acute respiratory failure related to moderate or severe COVID-19 pneumonia.\(^{27–29}\)
In conclusion, this case suggests how clinicians should pay attention not only to the risk of vascular complications in COVID-19 but also to the possible complications of anticoagulant therapy, highlighting that any decision on the type and dosing of anticoagulant agents should be individualized according to each case.

Authors contribution
Barbara Brogna drafted, edited, and conceptualized the manuscript and followed the CT examination of the patient. Annamaria Romano drafted the manuscript and followed the patient during the recovery. Loredana Tulullo drafted the clinical presentation in the manuscript and followed the patient during the recovery. Mariagrazia Montuori, Mariagrazia Nunziata, and Giuseppe Russo followed the patient during the hospitalization and reviewed the manuscript. Lanfranco Musto is the Head of the Radiology Department and revised the patient’s images and the manuscript.

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Ethical approval
All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the patients.

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