

Retroperitoneal hematoma in patients with COVID-19 infection during anticoagulant therapy: A case series and literature review

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Abstract

Due to the hypercoagulable status of patients with severe COVID-19 infection, anticoagulants are often used to prevent thrombosis. However, these agents may cause bleeding events such as retroperitoneal hematoma (RPH). We report here on six patients with COVID-19 who developed RPH during treatment. Early evidence of bleeding led to confirmatory diagnosis with imaging. Four patients recovered with supportive treatment (IV fluids and blood transfusions) and two patients recovered by angioembolization. RPH should be considered in COVID patients on anticoagulants as soon as haemoglobin or blood pressure falls. Further studies are required to provide guidance and recommendations on use of anticoagulants in critically ill patients with COVID-19.

Keywords

COVID-19, Hematoma, Anticoagulants, Retroperitoneal Space,

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Background

The novel coronavirus epidemic of 2019 (COVID-19) resulted in a global public health emergency. According to the WHO, the overall prevalence of the disease as of

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November 2021 was 253.78 million and its mortality was 5 million.^{1,2} In addition to respiratory issues, COVID-19 has been linked to extrapulmonary symptoms and consequences.² In critically ill patients, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may cause a hypercoagulable condition, which can lead to thrombotic events in a variety of organs (e.g., pulmonary embolism).³ As a consequence, prophylactic anticoagulation has been explored as a treatment option.³⁻⁶ However, reports have emerged of COVID-19 patients developing retroperitoneal haemorrhage (RPH) while on anticoagulation therapy⁷⁻⁹ or when extracorporeal membrane oxygenation was performed.¹⁰ In this report, we describe six cases of RPH in patients with COVID-19 who were receiving anticoagulant prophylaxis or treatment and review literature describing similar reports.

Methods

COVID-19 infection was verified in six patients using reverse transcriptase–polymerase chain reaction (RT-PCR) tests on nasopharyngeal swab samples. The patients were admitted to a single teaching referral hospital and had no previous history or indication of severe injuries. The reporting of this study conforms to CARE guidelines.¹¹ Signed informed consent was obtained from the patients for publishing their anonymised data. The study was retrospective and so exempt from ethical committee approval. Data were extracted from patient notes.

Case reports

Patient 1

A man in his late 40s presented to the clinic with shortness of breath and cough. His past medical history included presence of a renal stone on his right kidney. His current

symptoms had started eight days before his hospital admission. Vital signs on admission showed a body temperature of 38°C, blood pressure (BP) of 110/80 mmHg, heart rate (HR) of 90 beats/min, and respiratory rate (RR) of 22 breaths/min. Blood oxygen saturation (SpO₂) was 85% and his body mass index (BMI) was 26 kg/m². Four days after admission, his condition worsened and he was admitted to intensive care unit (ICU). Prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), and platelet count all were within the normal laboratory ranges. Chest computed tomography (CT) scan showed bilateral peripheral ground glass and consolidative opacities. Based on the Iran Ministry of Health and Medical Education protocols, standard treatment of COVID-19 was started. Due to the possibility of COVID-19 hypercoagulable condition, he was started subcutaneous enoxaparin 80 mg bd. After 10 days in ICU, he had right costovertebral angle pain. Tachycardia and BP 90/60 mmHg were recorded. His haemoglobin (Hb) level had dropped from 12 g/dl to 9.5 g/dl. A CT scan of his abdomen and pelvis showed a RPH (5.7 × 6.0 cm) in the right psoas muscle. The anticoagulation therapy was stopped and the patient was resuscitated with packed red blood cells (RBC) and intravenous (IV) fluids. The patient's health progressively improved, and he was discharged from hospital after 20 days.

Patient 2

A 70-year-old man with no previous medical history presented to the clinic with a 10-day history of myalgia, malaise, and fever. On hospital admission, the patient had a body temperature of 38°C, BP of 140/80 mmHg, HR of 100 beats/min, RR of 20 breaths/min, and SpO₂ 84%. His Hb level was 11 g/dl, and his D-dimer level was within normal limits. Following a chest CT scan that showed

bilateral areas of ground glass and consolidative opacities, COVID-19 pneumonia was diagnosed. The patient was started on standard treatment for COVID-19 and was admitted to ICU because of severe respiratory distress. In addition, subcutaneous enoxaparin 80 mg bd was administered. On Day 12 of his stay, the patient started to complain of left flank and inguinal pain. A physical examination showed tachycardia and hypotension (BP, 90/70 mmHg), but abdominal inspection revealed nothing unusual. His Hb level had decreased to 7 g/dl. A contrast-enhanced CT scan of his abdomen and pelvis showed a hematoma in the left iliopsoas muscle. Anticoagulation therapy was discontinued, and the patient received packed RBCs and IV fluids and fresh frozen plasma (FFP). Following CT scan images, that showed expanding RPH (Figure 1A) and the patient's unstable status, angioembolization was performed (Figure 1B). The patient's condition gradually improved and he was discharged from hospital on Day 18.

Patient 3

A woman in her late 50s, with a history of hypertension, presented to the clinic with a 11-day history of myalgia, malaise, and

fever. Vital signs on admission showed a body temperature of 38°C, BP of 130/75 mmHg, HR of 110 beats/min, RR of 22 breaths/min and SpO₂ 89%. Initial laboratory tests showed a Hb level of 12.5 g/dl and an elevated D-dimer level of 4800 ng/ml. On suspicion of pulmonary thromboembolism (PTE), a pulmonary CT angiogram was performed and diagnosed. The patient was admitted to ICU and subcutaneous enoxaparin 60 mg bd was administered. On Day 7, although her BP was normal (115/70 mmHg), her Hb level had decreased to 8.9 g/dl. An emergency contrast abdominal and pelvic CT scan showed a RPH along the iliopsoas muscle, on the right side. Her anticoagulation therapy was stopped and she received packed RBCs and IV fluids. Her Hb level increased and her vital signs stabilized. The patient's respiratory condition improved, and she was discharged from hospital on day 23 on rivaroxaban 20 mg qd for six months.

Patient 4

A 60-year-old woman with no previous medical history presented to the clinic with shortness of breath and a productive cough. Her vital signs on admission were body temperature 38°C, BP 120/70 mmHg,

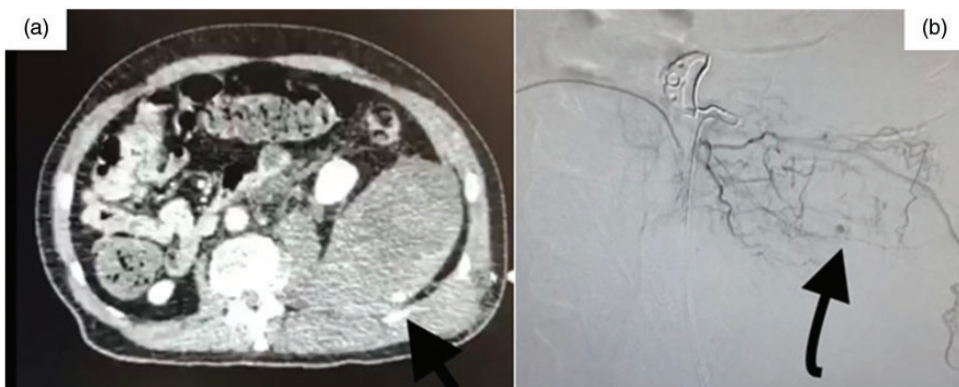


Figure 1. Imaging results from Patient 2: (a) Site of contrast extravasation in the computed tomography (CT) scan and (b) Site of contrast extravasation (black arrow) seen during angioembolization.

HR 105 beats/min, RR 20 breaths/min and SpO₂ 85%. Laboratory test results showed Hb 14.6 g/dl and D-dimer 3600 ng/ml; her PT, aPTT, INR, and platelet counts were all within normal ranges. Pitting oedema on her right upper limb was discovered on physical examination, and Doppler ultrasound indicated acute thrombosis in the right radial vein. Standard treatment for COVID-19 was initiated plus an intravenous infusion of heparin 1000 U/h. On Day 10, the patient's Hb level fell to 9.5 g/dl, her BP was 110/70 mmHg and HR 90 beats/min. Imaging studies showed a RPH (7.0 × 3.0 cm) in the right psoas muscle. Anticoagulation therapy was discontinued and the patient was managed with IV fluids. Her Hb levels gradually increased, her vital signs stabilized and she was discharged on Day 19 on apixaban 5 mg bd.

Patient 5

A man in his late 80 s, with a previous history of hypertension (treated with losartan 25 mg qd) and ischemic stroke (treated with warfarin 5 mg qd and aspirin 80 mg qd) presented with shortness of breath, a productive cough, and decreased level of consciousness. His vital signs on admission were body temperature 38°C, BP 120/70 mmHg, HR 105 beats/min, RR 20 breaths/min and SpO₂ 85%. Laboratory test results showed Hb 13.2 g/dl and serum creatinine 1.2 mg/dl; his PT, aPTT, and platelet counts were all within normal ranges and his INR was 2.3. An electrocardiogram (ECG) indicated an atrial fibrillation rhythm. Chest CT scan showed bilateral diffuse ground glass and consolidative opacities were observed. The patient was started on standard COVID-19 treatment and his previous anticoagulant therapy was continued. He was admitted to ICU due to his condition. On Day 3, his serum creatinine had increase to 1.9 mg/dl and his Hb had fallen to 9.5 g/dl. Abdominopelvic sonography indicated a

large hematoma in the right psoas muscle. Anticoagulation therapy was discontinued and he was managed with IV fluids and packed RBCs. His Hb level increased, his vital signs stabilized and his condition improved; he was discharged from hospital on Day 25 on apixaban 2.5 mg bd.

Patient 6

A man in his late 70 s, with a history of hypertension was receiving aspirin 80 mg qd and heparin 7500 units subcutaneously tds because of acute coronary syndrome (ACS) and severe COVID disease. On Day 12 of his hospitalization, he had a severe drop in Hb and BP. A CT scan showed a large active RPH (12.0 × 11.0 × 11.0 cm) in the right psoas muscle that pulled the right kidney to the anterior. Anticoagulation therapy was discontinued and he was prescribed IV fluids and packed RBCs. However, the patient did not stabilize after receiving three units of RBCs and so underwent angioembolization. Following the intervention, the patient stabilized and was discharged from the hospital on Day 20.

Discussion

After recognizing the possibility of the involvement of SARS-COVID-2 in the occurrence of thrombotic complications such as microvascular thrombosis, venous thromboembolic disease, and stroke, anticoagulant therapy has commonly been used to prevent or treat COVID-19 patients.¹² While several guidelines recommend anticoagulants such as aspirin, enoxaparin, unfractionated heparin, fondaparinux, apixaban, rivoraxaban, and dabigatran, there is no consensus on the type and dose of anticoagulant to use and the duration of treatment.¹²⁻¹⁴ Moreover, it has been reported that patients with COVID-19 may have a prolonged activated partial-thromboplastin

Table 1. Summary of case studies reporting retroperitoneal hematoma in COVID-19 patients.

Study	Sex	Age	Previous medical history	Severity of COVID	Anticoagulant	Aspirin	Site of hematoma	Overt sign	Treatment	Outcome
Javid et al., 2021 ¹⁷	M	65y	DM; hypertension	Severe, ICU	Heparin, 5000 IU/6hr SC	-	Psoas muscle	Right flank pain	Volume resuscitation and conservative measures	Discharged
Patel et al., 2020 ⁸	M	69y	CAD; hypertension; T2DM	Severe, ICU	Enoxaparin, 1 mg/kg SC qd	80 mg qd	Right psoas muscle	Abdominal pain	IV fluids, PBC, vasopressors, anticoagulation, arterial embolization	Discharged
Hajian, 2022 ¹⁷	F	74y	Hypertension; right-sided renal atrophy	Severe, ICU	Enoxaparin, 60 mg SC bd	80 mg qd	Left retroperitoneal small bowel wall and mesentery hematoma	Unstable hemodynamic abdominal tenderness, rebound tenderness in the left side	PBC, FFP, laparotomy	Death
Ottewill, et al., 2021 ¹⁸	M	88y	Vascular dementia; atrial flutter; IHD	na	Enoxaparin, dose-adjusted	-	Rectus sheath	Right lower abdominal pain	Reversal of anti-coagulation with protamine sulphate	Discharged
	F	85y	na	na	Enoxaparin, dose-adjusted	-	Left side RPH arising from the iliacus muscle	na	Blood transfusion	Discharged
	M	66y	Obstructive sleep apnoea; PH; COPD; AF	-	Enoxaparin, dose-adjusted	-	Left iliacus muscle	Fall in BP and Hb	IV fluids, blood products and reversal of anti-coagulation	Death
Zhang et al., 2021 ¹⁹	M	71y	Hypertension	na	Heparin 25 U/kg infusion followed by bolus	-	RPH	Abdominal pain, fall in Hb	Anticoagulation stopped; PBC, FFP;	Discharged
	F	81y	Hypertension, DM	na	Heparin 25 U/kg infusion followed by bolus	-	RPH	Fall in Hb	Anticoagulation stopped; PBC, FFP;	Discharged
	M	62y	Rectal cancer	na	Heparin 50 U/kg infusion followed by bolus	-	Psoas muscle	Fall in BP and Hb	Anticoagulation stopped; PBC	Discharged
Teta et al., ²⁰	M	81y	Hypertension; hyperlipidaemia; hypothyroidism; COPD*	Severe, ICU	Enoxaparin, 40 mg SC bd then, 60 mg SC bd	325 mg qd	Left RPH	Obtunded, pale, and hypotensive	First conservatively, then, angioembolization	Death
Yeoh et al., 2021 ²¹	M	57y	None	Severe	Enoxaparin, 40 mg SC qd	-	Right psoas muscle	Hemodynamic instability with fall in Hb	PBC, FFP, 12 units of cryoprecipitate and 18 units of platelets	Discharged

(continued)

Table 1. Continued.

Study	Sex	Age	Previous medical history	Severity of COVID	Anticoagulant	Aspirin	Site of hematoma	Overt sign	Treatment	Outcome
Mahboubi-Fooladi et al., 2021 ²²	F	65y	Hypertension; T2DM; dyslipidaemia; hypothyroidism	na	Enoxaparin, 40 mg SC qd	-	Right side pelvic/right rectus sheath	Abdominal pain	IV fluids, FFP, PBC	Discharged
	M	57y	Hypertension, T2DM; CKD	Severe, ICU	Heparin, 5000 IU/8hr SC	-	Left iliopsoas muscle	Abdominal pain	IV fluids, PBC, FFP	Death
	M	87y	Hypertension ^a	na	Enoxaparin, 1 mg/kg, SC, bd	-	Right iliopsoas muscle	Fall Hb	IV fluids, PBC	Death
	F	81y	Hypertension; IHD	Severe, ICU	Heparin, 5000 IU/12hr SC		Left side pelvic	Abdominal pain	IV fluids, PBC, FFP	Discharged
	F	51y	None	Severe, ICU	Enoxaparin, 60 mg SC, qd		Right iliopsoas muscle	Fall Hb	IV fluids, PBC, tranexamic acid	Death

*multi-organ failure on admission.

^aAcute thrombosis in the right common femoral vein on admission.

AF, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; F, female; FFP, fresh frozen plasma; Hb, haemoglobin; ICU, intensive care unit; IHD, ischemic heart disease; M, male; na, not available; PBC, packed red blood cells; PH, pulmonary hypertension; RPH, retroperitoneal hematoma; T2DM, type 2 diabetes mellitus.

time (aPTT), which may indicate a clotting factor deficiency or the presence of an inhibitor.¹⁵ Importantly, the risk of bleeding from anticoagulants in these patients has not been thoroughly evaluated.¹⁶

In the present report, we describe six COVID-positive patients who were treated with anticoagulants and developed retroperitoneal bleeding. The anticoagulation protocol for these patients was selected based on their hypercoagulable state due to COVID-19 or on their concomitant diseases. We searched PubMed and Google Scholar databases for similar case studies using “(Retroperitoneal hematoma) OR (Anticoagulation) AND (COVID-19) OR (SARS-CoV-2)” as keywords/terms. Our literature search identified eight articles that described 16 similar case studies (Table 1)^{7,8,17–22}. A review of these studies showed that the age of the six women and 10 men ranged from 51–88 years with 12 patients aged ≥ 65 years. Eight cases were described as severe and seven required transfers to ICU. Ten patients had been receiving enoxaparin and six patients heparin; symptoms often included abdominal pain and a fall in Hb and BP and the mortality rate was 38% (6/16).

The cause of RPH in COVID-19 patients while on anticoagulation therapy is unclear. Although uncommon, spontaneous RPH secondary to anticoagulant therapy is a well-known but self-limiting condition.¹⁶ In addition, the patients' concomitant conditions and previous medications may also influence bleeding times. Furthermore, the COVID disease itself may have directly or indirectly caused the bleeding complications. Significantly, there are no specific guidelines for treating RPH. If the patient's haemodynamics are normal, conservative treatment with coagulopathy correction, anticoagulant discontinuation, and supportive measures are recommended.²³ Patients with active bleeding may benefit from intra-arterial embolization. If the patient is

still bleeding profusely despite supportive measures and angioembolization, or has developed abdominal compartment syndrome due to RPH, open surgery is indicated.^{24,25}

Published studies have so far failed to suggest a safe drug or dose for anticoagulant therapy without any side effects. Moreover, although the possibility of thrombotic events after hospital discharge has not been investigated in COVID patients, some studies recommend continuation of anticoagulants after hospital discharge without defining dosage or duration.²⁶ Considering the pros and cons of anticoagulant therapy in COVID patients, it appears that this treatment should be limited to specific patients and should be prescribed with extreme caution in patients with severe disease. In addition, Hb and BP should be carefully monitored and RPH should be considered as soon as Hb or BP falls or if the patient complains of abdominal pain. Further studies are required to provide guidance and recommendations on use of anticoagulants in critically ill patients with COVID-19.

Declaration of conflicting interests


The authors declare that there are no conflicts of interest.

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