

Case Report: Iliopsoas Hematoma during the Clinical Course of Severe COVID-19 in Two Male Patients

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Abstract. Anticoagulation plays a major role in reducing the risk of systematic thrombosis in patients with severe COVID-19. Serious hemorrhagic complications, such as intracranial hemorrhage, have also been recognized. However, intra-abdominal hemorrhage is under-recognized because of its rare occurrence, despite high mortality. Here, we discuss two cases of spontaneous iliopsoas hematoma (IPH) likely caused by anticoagulants during the clinical course of COVID-19. We also explored published case reports to identify clinical characteristics of IPH in COVID-19 patients. The use of anticoagulants may increase the risk of lethal IPH among COVID-19 patients because of scarce data on optimal dosage and adequate monitoring of anticoagulant effects. Rapid diagnosis and timely intervention are crucial to ensure good patient outcomes.

INTRODUCTION

As awareness of COVID-19-associated coagulopathy increases, thrombotic manifestations are implicated in mortality.^{1,2} A recent multicenter retrospective study from the United States reported a thrombotic complication rate was 9.5%, despite standard prophylactic anticoagulation dose.³ Furthermore, hemorrhagic events among COVID-19 patients have been recognized. The overall proportion of patients with bleeding complications range from 4.8% to 8%, of which approximately 3.5% had major bleeding.^{3,4}

Herein, we describe two cases of life-threatening iliopsoas hematoma (IPH) during the clinical course of COVID-19. Both cases were recovering from acute respiratory distress syndrome owing to COVID-19 when they developed IPH. Moreover, they were receiving anticoagulants to prevent thrombosis. This report highlights IPH as a serious hemorrhagic complication in severe COVID-19 patients treated with anti-thrombotic agents.

CASE REPORT

Case 1. A 62-year-old man was referred to our institution because of a 4-day history of fever, productive cough, and fatigue. Results of real-time PCR for SARS-CoV-2 performed for a nasal swab were positive.

On admission, his temperature was 37.2°C; blood pressure, 148/76 mmHg; heart rate, 100 beats/minute; respiratory rate, 24 breaths/minute; oxygen saturation (SpO₂), 91–94% in ambient air; and ratio of arterial oxygen partial pressure to fractional inspired oxygen (P/F ratio), 316. Chest computed tomography (CT) on admission revealed ground-glass opacities in the bilateral peripheral lung fields, and laboratory findings were leukocyte count, 6.8 (normal, 3.3–8.6) × 10⁹/L with 76.9% neutrophils; lymphocyte percentage, 18.3% (normal, 26–46%); platelet count, 178 (normal, 158–348) × 10³/μL; interleukin-6 level, 89.1 pg/mL (cutoff < 4.0 pg/mL);

C-reactive protein (CRP) level, 5.53 mg/dL (cutoff < 0.14 mg/dL); ferritin level, 537.1 (normal, 50–200) ng/mL; D-dimer level, 0.5 μg/mL (cutoff < 1.0 μg/mL); and fibrinogen level, 611 (normal, 180–350) mg/dL.

We prescribed favipiravir (loading dose of 1,800 mg on day 1, followed by 400 mg twice daily for 13 days), dexamethasone (6.6 mg/day intravenously administered for 10 days), and nafamostat (100 mg/day). Despite initial treatment, 10 L of oxygen supplementation was required to maintain SpO₂ > 90% for the first 3 days after admission. Hence, tocilizumab (8 mg/kg) was intravenously administered on days 3 and 4. Hypoxia continued to worsen; thus, the patient was intubated and transferred to the intensive care unit (ICU). Recombinant human soluble thrombomodulin (rhsTM; 12,800 U twice daily) was administered to prevent thrombosis. After 5 days in the ICU, he fully recovered from acute respiratory failure, extubated, and returned to the ward on day 9. On the same day, rhsTM was replaced with daily subcutaneous enoxaparin (40 mg).

On day 14, the patient complained about severe and sudden pain in his left lower back after physiotherapy. His blood pressure and pulse rates were 118/86 mmHg and 115 beats/minute, respectively. Hemoglobin levels dropped from 15.7 g/dL to 13.2 g/dL with an elevated D-dimer level of 2.6 μg/mL. Contrast-enhanced abdominal and pelvic CT showed a hematoma (6.5 × 10.5 cm) in the left iliopsoas muscle spreading to the retroperitoneal space with extravasation (Figure 1A). Urgent transarterial embolization (TAE) was performed by interventional radiologists. Extravasation was identified from the left L3 and L4 lumbar arteries and common iliac arteries. Those arteries were selectively catheterized with a five French Mickelson catheter through which gelatin sponge particles were placed for occlusion. After the procedure, no active contrast extravasation was observed. He received six packed red blood cell (PRBC) units with intravenous fluids because his hemoglobin levels dropped to 7.5 g/dL. He was discharged from the hospital with improved hemoglobin levels (12.6 g/dL) on day 33.

Case 2. A 79-year-old man presented with fever and general fatigue for 2 days and was transferred to our hospital owing to COVID-19-associated acute respiratory distress syndrome. A different general hospital administered favipiravir, dexamethasone,

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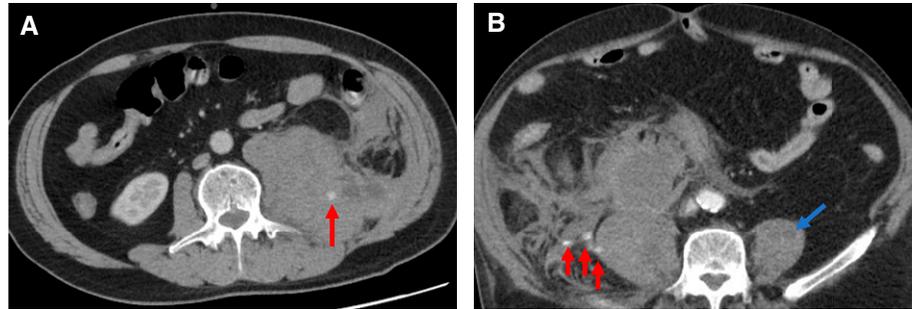


FIGURE 1. Contrast-enhanced computed tomography of the abdomen and pelvis. (A) Case 1: A massive hematoma with extravasation (red arrow) in the left iliopsoas muscle spreading to the retroperitoneal space is observed. (B) Case 2: The swollen right iliopsoas muscle with retroperitoneal hematoma and extravasation is observed (red arrow). A small low-density area (blue arrow) in the left iliopsoas muscle suggests a hematoma.

and subcutaneous unfractionated heparin (UFH) on referral day. Nevertheless, respiratory failure progressively worsened, and he was intubated.

Oxygen saturation was 95% under fraction of inspired oxygenation, 50%; P/F ratio 167; blood pressure, 132/65 mmHg; heart rate, 40 beats/minute; temperature, 38.4°C at the time of admission to our hospital. Initial laboratory findings were leukocyte count, $10.2 \times 10^9/L$ with 89.7% neutrophils; lymphocyte percentage, 5.6%; platelet count, $129 \times 10^3/\mu L$; CRP level, 2.9 mg/dL; D-dimer level, 0.6 $\mu g/mL$; and fibrinogen level, 285 mg/dL. Chest CT revealed bilateral ground-glass opacities with a small amount of pleural effusion.

Remdesivir (loading dose of 200 mg on day 1, followed by 100 mg once daily for 10 days), methylprednisolone (1,000 mg for 3 days) followed by dexamethasone (6.6 mg for 7 days), nafamostat (100 mg/day), and intravenous tocilizumab (two consecutive doses, 8 mg/kg) were administered. Intravenous UFH was also administered, with the dosage adjusted to meet the target-activated partial thromboplastin time (aPTT) range of 1.5–2.5 times the control value. The P/F ratio increased from 167 to 290 on day 10, and he was extubated.

After extubation, blood pressure gradually decreased with tachycardia. Moreover, he complained of gradual worsening pain in the right lower back since extubation. His hemoglobin levels decreased from 12.2 g/dL to 9.7 g/dL, suggesting hemorrhagic hypovolemic shock. His platelet count was $158 \times 10^3/\mu L$; aPTT, 42.1 (normal, 23.5–35) seconds; D-dimer level, 2.2 $\mu g/mL$; and fibrinogen level, 167 mg/dL. Contrast-enhanced abdominal CT showed swelling of the right iliopsoas muscle with retroperitoneal hematoma, extravasation in the right psoas major muscle, and a small-density area in the left psoas major muscle (Figure 1B). Intravenous UFH infusion was immediately discontinued; TAE was urgently attempted with rapid volume replacement and four units of PRBC transfusion. However, he had cardiac arrest for 4 minutes during preoperative preparations. Although he responded to resuscitation, the second episode of cardiac arrest occurred within an hour. Because his family members did not want further resuscitation attempts, 18 hours after extubation, his death was confirmed.

DISCUSSION

The current case series showed the life-threatening IPH in two COVID-19 patients on either prophylactic or therapeutic dose of anticoagulants; whereas one patient was successfully

treated with TAE, the other patient died because of hemorrhagic hypovolemic shock.

Iliopsoas hematoma is defined as retroperitoneal hemorrhage involving the iliopsoas muscle. The incidence of spontaneous IPH during hospitalization ranges from 0.3% to 0.4%.^{5,6} The precise frequency of spontaneous IPH in COVID-19 patients remains unclear; however, eight case series have been reported (Table 1).^{7–13} Several specific predisposing factors, including anticoagulation therapy, advanced age, and hemodialysis, are associated with developing spontaneous IPH.⁵ Previous reports in addition to the current case series were consistent with this evidence. Furthermore, concurrent off-level use of rHsTM or nafamostat mesylate may have contributed to major bleeding events in our cases. Despite insufficient data, those agents had been administered as compassionate therapy to alleviate hypercoagulation and for their antiviral effects.^{14,15}

Apart from anticoagulants, microvascular vulnerability derived from atherosclerosis and microtrauma, including cough, could lead to retroperitoneal bleeding; however, pathology has not confirmed the hypothesis.⁵ Whether direct effects of SARS-CoV-2 on vascular endothelial cells cause hemorrhage events is uncertain. However, several hypotheses have been raised: the affinity of SARS-CoV-2 for angiotensin-converting enzyme 2 receptors on endothelial cells can directly damage vessels, causing vessel wall rupture.¹⁶ By contrast, renin-angiotensin-aldosterone system dysregulation may contribute to increased blood pressure, causing hemorrhagic events.¹⁶ Erdinc and Raina⁹ reported a COVID-19 patient who developed IPH without anticoagulants.

The mortality rate of patients with spontaneous IPH, which occurred during hospitalization, is estimated to be between 30% and 50%.^{5,6} Given the high mortality rate, physicians should pay careful attention to the disease's early signs. Thrombocytopenia (platelet count $< 150 \times 10^3$ cells/ μL) and elevated D-dimer levels ($> 2.5 \mu g/mL$) at initial presentation are predictive of hemorrhage-related complications during hospitalization.³ In fact, the initial platelet count in case 2 was 129×10^3 cells/ μL .

One-third of patients with spontaneous IPH can present with Lenk's triad: severe flank pain, hemodynamic shock, and palpable mass.¹⁷ Monitoring the effects of anticoagulants is imperative to minimize the risk of hemorrhagic events; however, there are some inherent issues. Artzer et al.⁶ reported that severe adverse events could occur among patients treated with UFH despite optimal aPTT values. For case 2, aPTT values were within the target range. Regarding low-molecular-weight heparin, anti-factor Xa activity and thromboelastography may not

TABLE 1
Summary of case reports on iliopsoas hematoma in patients with COVID-19

Case no.	Reference	Age, years	Sex	Preexisting condition	Severity of COVID-19*	Anticoagulation at hemorrhage	Intervention for hemorrhage	Outcome	Comments
1.	Patel et al. ⁷	69	M	CAD, HTN, and type 2 DM	Severe	Therapeutic enoxaparin (1 mg/kg)	TAE	Alive	–
2.	Scialpi et al. ⁸	57	M	Non-Hodgkin's lymphoma	ND	ND	TAE	Alive	–
3.	Erdinc and Raina ⁹	58	F	HTN, obesity (BMI, 62 kg/m ²)	Severe	None	ND	Died	Acute DVT coincided
4.	Guo et al. ¹⁰	71	M	ND	Critical	ND, but presumably on anticoagulants because of ECMO	TAE	Alive	On ECMO
5.	Angileri et al. ¹¹	59	M	ND	Critical	Prophylactic enoxaparin (60 mg/day)	ND	ND	–
6.	Conti et al. ¹²	76	M	CAD and HTN	Severe	Prophylactic LMWH (6,000 UI/day)	TAE	ND	–
7.	Conti et al. ¹²	72	F	HTN	Severe	Therapeutic LMWH (100 UI/kg/bid)	TAE	ND	Acute DVT coincided
8.	Bargellini et al. ¹³	71	M	Atrial fibrillation	Severe	Prophylactic LMWH (6,000 UI/12 hours)	TAE	Alive	
9.	Case 1	62	M	None	Critical	Prophylactic enoxaparin (40 mg bid subcutaneous injection)	TAE	Alive	
10.	Case 2	79	M	HTN, obesity (BMI, 34.2 kg/m ²), type 2 DM	Critical	Therapeutic unfractionated heparin	TAE	Died	Died because of hypovolemic shock

bid = bis in die; BMI = body mass index; CAD = coronary artery disease; DM = diabetes; DVT = deep venous thrombosis; ECMO = extracorporeal membrane oxygenation; F = female; HTN = hypertension; LMWH = low-molecular-weight heparin; M = male; ND = not described; TAE = transarterial embolization.

* Severity of COVID-19 was defined as follows. Severe: individuals who have oxygen saturation < 94% on ambient air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen < 300 mmHg, respiratory frequency > 30 breaths/minute, or lung infiltrates > 50%. Critical: individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

be reliable for monitoring.¹⁸ Contrast-enhanced CT plays an important role in diagnosis, providing a wide range of information on volume, spatial extent, and compressive complications or extravasation.⁵

An effective anticoagulation therapy with low risk of bleeding is urgently required. Despite the lack of data, some experts have suggested intensified anticoagulation strategy such as using enoxaparin (0.5 mg/kg twice daily) because standard-dose prophylaxis may not prevent thrombosis.¹⁹ A recent observational study showed that compared with a prophylactic anticoagulant, a therapeutic dose of an anticoagulant had the tendency to lower the risk of mortality among hospitalized patients with COVID-19, but it showed an insignificant difference.²⁰ In addition, the therapeutic dose was associated with a higher risk of major hemorrhage than was prophylactic dose (3% versus 1.7%).

Although case reports are scarce for conclusion, our two cases, in addition to previous reports, suggest that COVID-19 patients treated with anticoagulants are at risk of IPH. The paucity of data on how to balance anticoagulation in COVID-19 patients may be attributed to hemorrhagic events. Until randomized trials prove the optimal anticoagulation treatment, there will be no clarity with respect to the ideal type and dose of anticoagulants for patients with COVID-19. If severe flank pain, along with anemia and hypovolemic signs, is present, CT should be used for evaluation.

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