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【 CASE REPORT 】

Spontaneous Muscle Hematoma in Japanese Patients with Severe COVID-19 Treated with Unfractionated Heparin: Two Case Reports

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Abstract:

In hospitalized coronavirus disease 2019 (COVID-19) patients, anticoagulation therapy is administered to prevent thrombosis. However, anticoagulation sometimes causes bleeding complications. We herein report two Japanese cases of severe COVID-19 in which spontaneous muscle hematomas (SMH) developed under therapeutic anticoagulation with unfractionated heparin. Although the activated partial prothrombin time was within the optimal range, contrast-enhanced computed tomography (CECT) revealed SMH in the bilateral iliopsoas muscles in both cases, which required emergent transcatheter embolization. Close monitoring of the coagulation system and the early diagnosis of bleeding complications through CECT are needed in severe COVID-19 patients treated with anticoagulants.

Key words: COVID-19, spontaneous muscle hematoma, therapeutic anticoagulation, vascular dysfunction, unfractionated heparin

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Introduction

Since the first report of a cluster of pneumonia in Wuhan, China, coronavirus disease 2019 (COVID-19) has rapidly spread worldwide (1). The spectrum of clinical manifestations of COVID-19 ranges from a fever, cough, and dyspnea to pneumonia, acute respiratory distress syndrome, and even respiratory failure (2). In addition, extrapulmonary complications, such as myocardial injury, arrhythmia, and acute renal injury, which sometimes result in death, have been reported (3).

Since patients with severe COVID-19 have an increased risk of advancing to a hypercoagulable state, anticoagulation therapy is recommended for all hospitalized COVID-19 patients according to the National Heart, Lung, and Blood Institute guideline (4). However, whether low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) should be used for anticoagulation remains controversial (5, 6). Recent studies have reported that anticoagulation with LMWH can cause bleeding complications, such as spontaneous muscle hematoma (SMH) (7-11). However, whether or not this hemorrhaging also occurs under anticoagulation with UFH and in individuals other than Caucasians, as reported, are unknown.

We herein report two Japanese patients who developed bilateral iliopsoas hematomas under therapeutic anticoagulation therapy with UFH and who required transcatheter arterial embolization (TAE) during treatment for severe COVID-19.

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Table. **Blood Test Findings at Admission and When Hematoma was Identified.**

	Case 1		Case 2		Reference range
	Admission	Event*	Admission	Event*	
Days after COVID-19 onset	7	35	8	20	
Creatinine (mg/dL)	0.60	0.69	1.18	0.82	0.65-1.07
Ferritin (ng/mL)	806	522	1,567	1,776	50-200
CRP (mg/dL)	6.06	13.80	5.80	1.56	0.00-0.14
WBC (/μL)	6,660	32,380	9,020	10,090	3,700-8,000
Eosinophil (/μL)	0	80	0	110	
Hemoglobin (g/dL)	14.8	7.5	15.8	13.4	13.0-16.5
Platelet (10^4/μL)	15.9	20.6	14.6	28.3	15.0-45.0
PT (s)	11.5	13.8	11.7	13.4	10.5-13.2
PT-INR	1.01	1.23	1.03	1.19	0.90-1.10
APTT (s)	22.8	58.6	32.5	40.0	25.0-40.0
D-dimer (μg/mL)	3.9	2.6	0.5	1.5	0.0-1.0

*Both samples were taken while unfractionated heparin was being administered.

COVID-19: coronavirus disease 2019, CRP: C-reactive protein, WBC: white blood cell, PT: prothrombin time, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time

Case Reports

Case 1

This patient was a 48-year-old Japanese man with a medical history of asthma and diabetes mellitus. He was referred to our hospital with a fever, malaise, and cough that persisted for 1 week. On admission, his body weight was 71.5 kg, and his oxygen saturation was 92% under 5 L/min of oxygen provided by nasal cannula. The results of blood tests performed at admission are shown in Table.

Real-time polymerase chain reaction (RT-PCR) of a nasopharyngeal swab detected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and he was diagnosed with severe COVID-19 (4). Remdesivir, dexamethasone (6 mg/day), and tocilizumab treatment was initiated, with the patient in a prone position for 16 h/day, but his respiratory failure did not improve. He was intubated on the 3rd day and underwent tracheostomy on the 15th day of hospitalization. Since his serum D-dimer level was elevated (4.0 μg/mL) on the 6th day, intravenous UFH was administered. UFH dose was increased to 32,000 U/day (18.6 U/kg/h) to keep his serum activated partial thromboplastin time (APTT) within 40-60 s. Bedside rehabilitation was initiated simultaneously.

On the 27th day of hospitalization, he presented with right lumbago, extension-based pain in the right lower leg, and numbness in the right thigh. Hypotension (81/59 mmHg) and remarkable anemia appeared on the 29th day (Table). Contrast-enhanced computed tomography (CECT) of the abdomen and pelvis revealed bilateral hematomas of the iliopsoas muscles and extravasation of contrast medium (Figure A, B). Intravenous UFH was immediately discontinued, and emergent TAE of the bilateral lumbar arteries was performed. The hematomas showed no evidence of further expansion after the procedure, and anemia and hypotension improved after transfusion and other supportive therapy. Anticoagulation was not resumed, but no apparent thrombosis has been identified. Rehabilitation was restarted, and he was discharged home on the 60th day of hospitalization.

Case 2

This patient was a 60-year-old Japanese man with a medical history of diabetes mellitus, renal insufficiency, hypertension, and gastroesophageal reflex disease. After 1 week of a fever and cough, RT-PCR revealed SARS-CoV-2 positivity and dexamethasone (6 mg/day) treatment was initiated. He was referred to our hospital the following day, when his body weight was 71.6 kg and oxygen saturation was 93% under 15 L/min of oxygen provided by a reservoir mask. He was diagnosed with severe COVID-19 and promptly intubated. Results of blood tests performed at admission are shown in Table. Remdesivir and baricitinib were added to dexamethasone, with the patient maintained in a prone position. During intubation, 14,000 U/day (8.1 U/kg/h) of UFH was administered intravenously due to elevated D-dimer (3.8 μg/mL), and rehabilitation was started. He was extubated on the 8th day, and rehabilitation was intensified with the patient in a standing position.

On the 10th day of hospitalization, extension-based pain that was not relieved by painkillers appeared in the left lower leg. Hypotension (90/74 mmHg) appeared on the 13th day, but anemia only progressed slightly (Table). On the 13 th day, CECT of the abdomen and pelvis identified bilateral iliopsoas hematomas (Figure C, D). Intravenous UFH was discontinued, and emergent TAE of the bilateral iliolumbar arteries and left iliac circumflex artery was performed. After a lack of further expansion of the hematomas was confirmed, he was discharged home with oxygen therapy on the 22nd day of hospitalization. No apparent thrombosis has been observed without anticoagulation therapy.

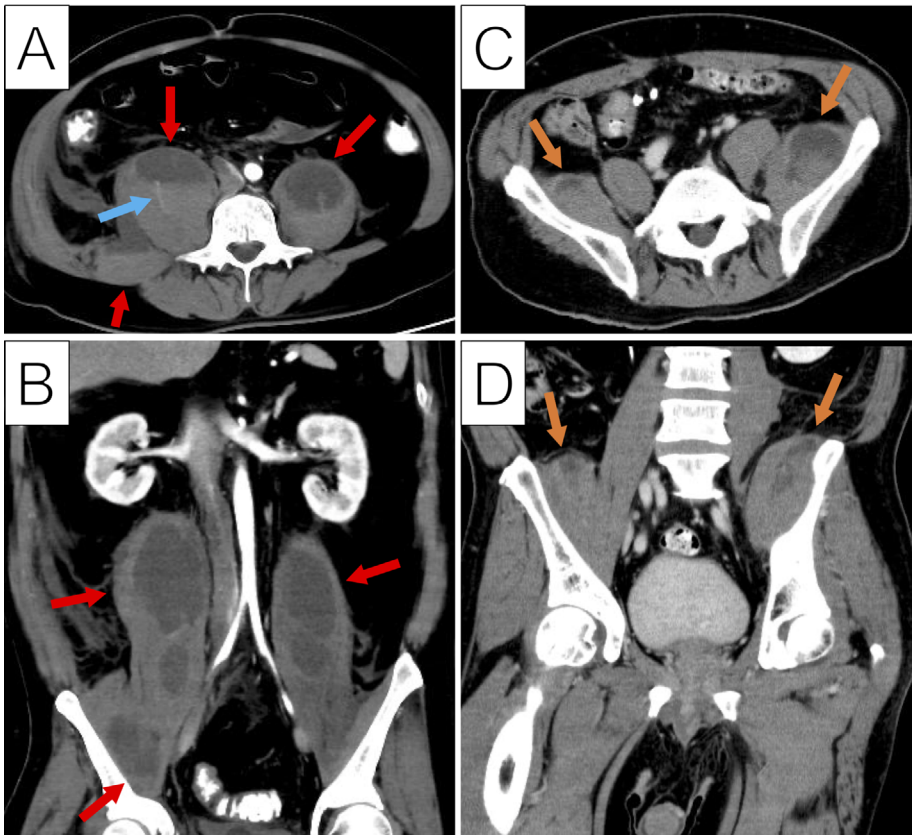

Figure. **Radiological findings in two cases. Axial (A) and coronal sections (B) of the CECT arterial phase in Case 1 revealed bilateral iliopsoas hematomas (red arrows) and extravasation of contrast medium (blue arrow). Similarly, axial (C) and coronal sections (D) of the CECT equilibrium phase in Case 2 showed bilateral iliopsoas hematomas (orange arrows). CECT: contrast-enhanced computed tomography**

Discussion

We reported two Japanese cases of severe COVID-19 in which bilateral iliopsoas hematomas developed during the clinical course, both of which required emergent TAE. The patients complained of symptoms such as leg extension-based pain or numbness before CECT revealed hematomas, suggesting hemorrhaging due to arterial disruption. Previous literature reported iliopsoas hematoma in Caucasian patients with severe COVID-19 treated with LMWH (8-11). The data from the 11 Caucasian patients described in 4 references revealed unilateral hematoma, with 8 patients receiving therapeutic doses of heparin and 5 requiring TAE. However, to our knowledge, few reports have described bilateral iliopsoas hematomas or SMH in other races or patients treated with UFH as an anticoagulant (12). In patients with COVID-19, SMH is an important complication, regardless of race or the type of anticoagulant administered.

A previous study indicated that known risk factors for SMH are cardiac or renal insufficiency, arteriosclerosis, hypertension, diabetes mellitus, and coagulation disorders, including when anticoagulants are used (13). Microtrauma of capillaries and muscles, such as in isometric muscle contraction, is believed to result in SMH development (14). In our cases, several reasons explained SMH occurrence. First, both of our patients had some risk factors of SMH: both had diabetes mellitus, and one had hypertension as well as renal insufficiency. Second, mobilization to a prone position and bedside rehabilitation can contribute to microvascular disruption and SMH (10). Another possible explanation for SMH was the tendency to bleed caused by UFH. However, in our cases, the targeted range of APTT was established at 40-60 s, and APTT was maintained within this optimal range in both cases when SMH developed. In one study, among patients treated with anticoagulation therapy who developed SMH, an overdose of anticoagulants occurred in approximately 30% (14). This suggests that the use of anticoagulants, even within the therapeutic range of APTT, can increase the risk for SMH.

In addition, it has been suggested that patients with COVID-19 are prone to bleeding due to various reasons. Disseminated intravascular coagulation (DIC) is frequently complicated with severe COVID-19, and enhanced-fibrinolytic-type DIC is particularly strongly associated with major bleeding (15). Thrombocytopenia is sometimes observed in patients with COVID-19 and is a predictor of bleeding complications (16). A previous study reported a

case of acquired von Willebrand disease in a patient with COVID-19, suggesting that an abnormal platelet function may contribute to a bleeding tendency in some cases (17). Furthermore, histopathological mechanisms may cause arterial rupture in severe COVID-19. SARS-CoV-2 is known to cause inflammatory cell infiltration along the vessel surface, which results in vasculitis. This vascular dysfunction may cause spontaneous bleeding due to arterial vulnerability (18, 19). A further pathological investigation and the accumulation of cases are needed to elucidate the mechanisms underlying bleeding complications in severe COVID-19.

Data on the use of anticoagulants at a therapeutic dose for severe COVID-19 patients are insufficient at present (4). Elevated serum D-dimer levels reflect a hypercoagulable state of COVID-19, so D-dimer may be a surrogate marker upon the introduction of anticoagulants at a therapeutic dose (16, 20). However, as in our cases, patients who receive UFH within the optimal range of APTT can develop bleeding complications, such as SMH. In clinical practice, clinicians should recognize the tendency to bleed in COVID-19 patients, and careful monitoring of the coagulation system and adjustment of anticoagulants are necessary to prevent bleeding complications, especially when therapeutic doses of anticoagulants are administered. Furthermore, if COVID-19 patients under anticoagulation therapy experience symptoms, such as leg extension-based pain, numbness in the lower extremities, or the development of anemia and hypotension, CECT should be immediately considered in order to rule out SMH. Emergent angiography should be also performed in case circulatory instability or extravasation is identified by CECT (14). Furthermore, whether rehabilitation or early mobilization should be initiated under anticoagulant treatment requires further determination.

In conclusion, we reported two Japanese COVID-19 cases in which bilateral iliopsoas hematomas developed during the clinical course. Clinicians should pay attention to bleeding complications, such as SMH, in severe COVID-19 patients under anticoagulation therapy. Close monitoring of their symptoms and coagulation system and early CECT-based diagnosis are needed to prevent and detect SMH.

The authors state that they have no Conflict of Interest (COI).

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