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Retroperitoneal Hematoma During Prophylactic Dose of Heparin Therapy for Coronavirus Disease 2019

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We report a case of retroperitoneal hematoma during prophylactic heparin therapy for coronavirus disease 2019 (COVID-19). A 79-year-old man was diagnosed with COVID-19 pneumonia with possible exacerbation of fibrotic hypersensitivity pneumonia. He received a prophylactic dose of subcutaneous heparin therapy, methylprednisolone pulse therapy and Intravenous remdesivir but developed a spontaneous iliopsoas muscle hematoma, and transcatheter arterial embolization was performed. Even with a prophylactic dose of subcutaneous heparin therapy, the course should be carefully monitored, especially in patients with preexisting risk factors for hemorrhagic complications. Once retroperitoneal hematoma develops, aggressive procedures, such as transcatheter arterial embolization, should be considered to avoid fatal outcomes.

Key words: COVID-19, Retroperitoneal hematoma, Unfractionated heparin, Hemorrhagic complication

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been associated with poor outcomes, not only due to pneumonia and severe respiratory failure, but also with an increased risk of thrombotic diseases. Anticoagulant therapy with heparin has been recommended for all hospitalized patients with COVID-19 [1]; however, it causes major bleeding in 1.9% and 3.8% of non-critically and critically ill patients with COVID-19, respectively [1, 2]. In a recent trial of the treatment of acute venous thromboembolism (VTE) with unfractionated heparin (UFH), the frequency of major bleeding was less than 3% and even less with low-molecular-weight heparin (LMWH) in patients with no COVID-19 [3–5]. These data suggest that patients with severe COVID-19 are also susceptible to major bleeding during anticoagulant therapy, although hemorrhagic complications have not been fully investigated.

Retroperitoneal hematoma is a fatal hemorrhagic complication of anticoagulant therapy, and patients with COVID-19, especially those receiving therapeutic doses of heparin or antiplatelet therapy, are at a high risk [6]. Herein, we report a case of iliopsoas hematoma during the treatment of COVID-19 with a low (prophylactic) dose of heparin. This report highlights the need to identify the risk factors for hemorrhagic complications and carefully monitor the course of anticoagulant therapy.

CASE REPORT

A 79-year-old man was hospitalized due to sudden-onset dyspnea and fever three days after his daughter was diagnosed with COVID-19. He had a history of hypertension, type 2 diabetes mellitus, chronic obstructive pulmonary disease, and fibrotic hypersensitivity pneumonia (treated with nintedanib 200 mg/day for 2 weeks). He was vaccinated for COVID-19 three times. On admission, he had fever (38.9°C), tachycardia, and tachypnea with 95% saturation of percutaneous oxygen under six liters of oxygen via a face mask. Fine crackles were audible in both lower lung fields. No edema or swelling was observed in the lower extremity. Peripheral blood cell counts were 8.7×10^3 /μL for leukocytes, 14.6 g/dL for hemoglobin, 12.7×10^3 /μL for platelets. Serum laboratory tests demonstrated mild liver dysfunction and an increase in D-dimer (1.9 μg/mL) and C-reactive protein (4.81 mg/dL). Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) antigen test was positive in the nasopharyngeal swab. Chest computed tomography (CT) revealed diffuse reticulation without honeycombing and newly appeared ground-glass opacities in the bilateral lower lobes (Fig. 1A, B). The patient was diagnosed with COVID-19 pneumonia with a possible exacerbation of fibrotic hypersensitivity pneumonia.

Intravenous remdesivir (200 mg on the first day, followed by 100 mg every 24 hours for four days), 5000 units of subcutaneous UFH twice daily, and methylprednisolone pulse therapy (1000 mg/day for 3 days) followed by high-dose oral prednisolone (50 mg/day) were started. His dyspnea and saturation oximetry/fraction of inhaled oxygen gradually improved, with improved permeability of the bilateral lung fields on the chest radiographs (Fig. 2). However, he started experiencing pain and numbness in his left thigh on

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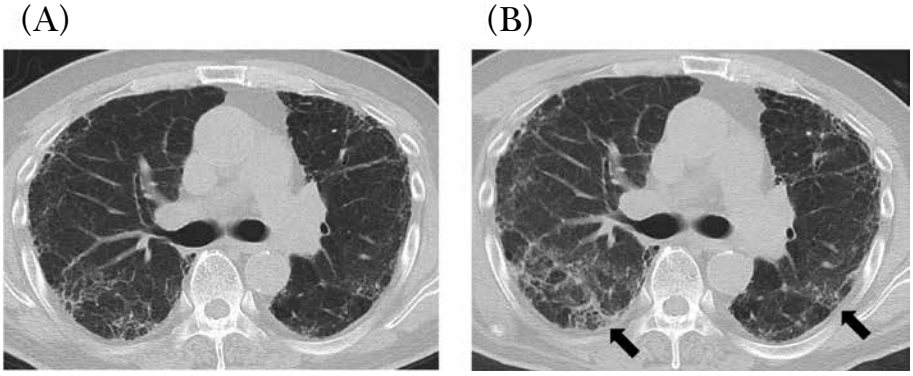

Fig. 1 Chest computed tomography scan two weeks before the patient was hospitalized (A) and on admission (B).
Diffuse reticulation without honeycombing had been observed in the bilateral lower lobes prior to admission, whereas, ground-glass opacities (black arrow) newly appeared on admission in the bilateral lower lobes.

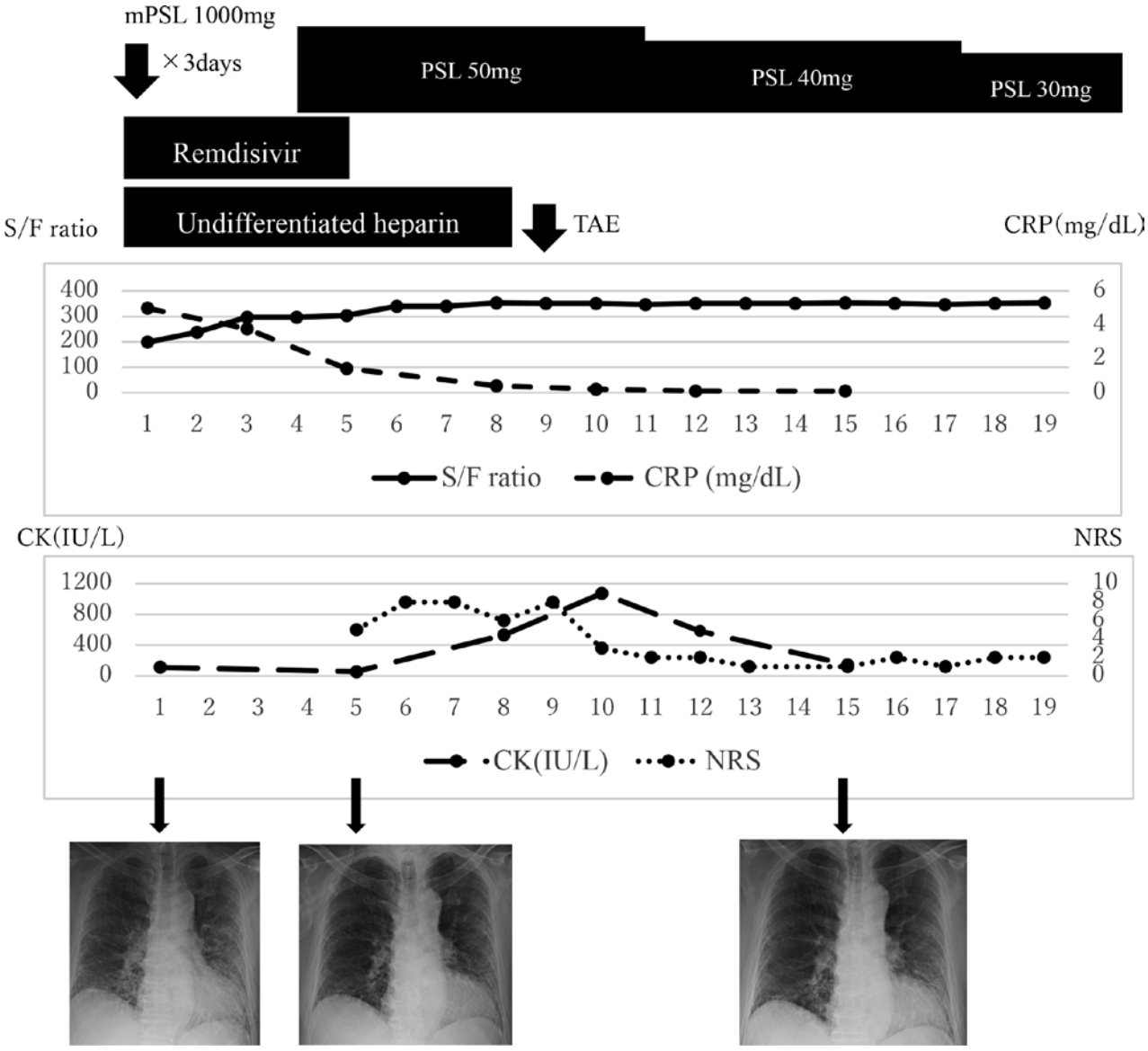

Fig. 2 Clinical course
S/F, Saturation of percutaneous oxygen/fraction of inhaled oxygen; CK, Creatine kinase in serum; CRP, C-reactive protein in serum; NRS, Numerical rating scale of numbness in the left thigh; mPSL, Methylprednisolone; PSL, Prednisolone; TAE, Transcatheter arterial embolization

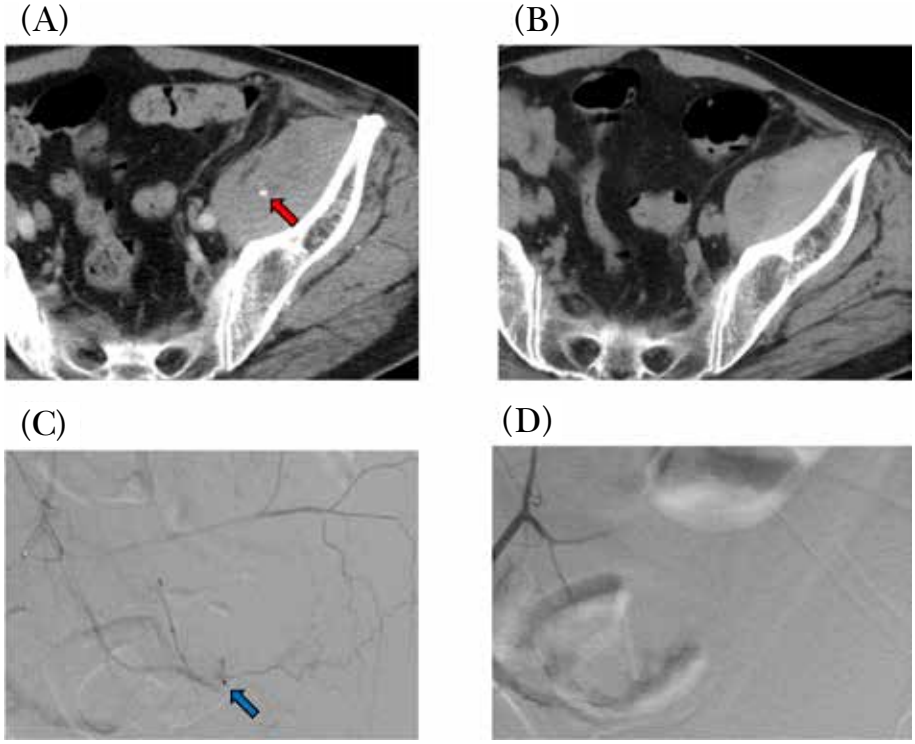

Fig. 3 Iliopsoas muscle hematoma
(A) Contrast enhanced computed tomography of the abdomen and pelvis on day 9 revealed a hematoma (67 mm × 59 mm) with extravasation (red arrow) in the left iliopsoas muscle spreading to the retroperitoneal space. (B) On day 15, the size of retroperitoneal hematoma reduced to 65 mm × 47 mm. (C) Selective angiogram shows active bleeding of the left ileo-lumbar artery (blue arrow). (D) Post-embolization angiogram shows a complete occlusion of the bleeding artery without any sign of extravasation.

day five. CT on day 9 demonstrated a hematoma in the left iliopsoas muscle with active extravasation into the retroperitoneal space (Fig. 3A). Although his vital signs were stable and no progression of anemia was observed, serum creatine kinase level was elevated to 531 IU/L. The platelet count was within the normal range (166×10^3 /mm^3) and there was no prolongation in the activated partial thromboplastin time (38 s) or prothrombin time (11.7 s), excluding the diagnosis of heparin-induced thrombocytopenia or disseminated intravascular coagulation due to COVID-19. The patient was diagnosed with femoral nerve palsy associated with a spontaneous iliopsoas muscle hematoma. The subcutaneous administration of heparin was discontinued, and transcatheter arterial embolization (TAE) using gelatin sponge was performed (Fig. 3C, D). After TAE, pain and numbness in the left thigh gradually disappeared. CT on day 15 demonstrated a reduced hematoma size in the retroperitoneum (Fig. 3B). No evidence of rebleeding was observed after 6 months.

DISCUSSION

Prophylactic doses of UFH or LMWH is recommended for hospitalized patients with COVID-19 because of the high rate of thrombosis, including VTE, myocardial infarction, and ischemic stroke [7]. However, a high rate of hemorrhagic complications (gastrointestinal and cerebral hemorrhage) has been reported in patients with COVID-19 receiving anticoagulant therapy [8]. Retroperitoneal hematoma is a serious hemorrhagic complication associated with anticoagulant or antiplatelet therapy. Although the etiology of spontaneous retroperitoneal hematoma has not been completely elucidated, diffuse angiopathy and arteriosclerosis of small retroperitoneal vessels may render them brittle and prone to rupture [9]. Other reports suggest that unrecognized minor trauma to the microcirculation can cause bleeding in presence of anticoagulants [10]. Spontaneous retroperitoneal hematoma develops in approximately 0.4% of hospitalized patients with COVID-19, and persistent strong cough may trigger blood vessel rupture [6]. Another possible hypothesis is direct damage to vascular endothelial cells expressing the angiotensin-converting enzyme 2 receptor, the receptor for SARS-CoV-2 [11].

Among reported 21 cases of retroperitoneal hematoma during heparin administration in patients with COVID-19, 76% were men with a median age of 61 years (Table 1) [6, 12–19]. More than 80% of patients had preexisting risk factors for retroperitoneal hematoma other than COVID-19, such as old age, hemodialysis, hypertension, or diabetes mellitus. The third quarter of patients received heparin at a therapeutic dose or in combination with antiplatelet therapy, whereas 24% of patients were treated with a prophylactic dose of heparin alone, as in the present case. The mortality rate was high (43%) even in patients treated with TAE. Among the five reported cases and the present one who developed retroperitoneal hematoma under anticoagulant therapy with a prophylactic dose of heparin alone (Table 2), two cases (33%) lacked any risk factors

Table 1

N = 21	
Patient characteristics	
Age, median (Interquartile range)	61 (69–79)
Male, %	76
Risk factors for retroperitoneal hematoma	
Age > 70 years, %	48
Hemodialysis, %	10
Hypertension, %	52
Diabetes mellitus, %	29
No risk factors other than COVID-19, %	19
Anticoagulation or antiplatelet therapy	
Prophylactic dose of heparin therapy alone, %	24
Prophylactic dose of heparin + antiplatelet therapy, %	24
Therapeutic doses of heparin therapy alone, %	38
Therapeutic dose of heparin + antiplatelet therapy, %	14
Treatment	
Transfusion, %	63
Transcatheter arterial embolization, %	38
Mortality, %	43

Table 2

Authors (reference #)	Age, Gender	Preexisting condition	Time to onset from diagnosed with COVID-19	Antiviral therapy	Anticoagulant therapy	Systemic steroid therapy	Treatment	Outcome
Present case	72, M	HT, COPD DM Fibrotic HP	5days	Remdesivir	Subcutaneous UFH (5000 unit twice daily)	Methylprednisolone (1000 mg)	TAE	Alive
Nakamura H, *et al.* (15)	62, M	None	14days	Favipiravir	Subcutaneous LMWH (40 mg once daily)	Dexamethasone (6.6 mg)	Transfusion	Alive
Mahboubi-Fooladi Z, *et al.* (12)	57, M	HT, DM, Hemodialysis	11days	None	Subcutaneous UFH (5000 unit thrice daily)	None	Transfusion	Died
Mahboubi-Fooladi Z, *et al.* (12)	51, F	None	10days	Remdesivir	Subcutaneous LMWH (60 mg once daily)	None	Transfusion	Died
Sottilotta G, *et al.* (13)	79, M	HT	14days	Hydroxy-chloroquine	Subcutaneous LMWH (60 mg twice daily)	None	None	Alive
Mansor, *et al.* (14)	50, F	HT, DM, Hemodialysis	15days	None	Subcutaneous LMWH (40 mg once daily)	Methylprednisolone (100 mg)	TAE	Died

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HP, hypersensitivity pneumonia; HT, hypertension; LMWH, lowmolecular-weight heparin; TAE, transcatheter arterial embolization; UFH; Unfractionated heparin

other than COVID-19 and three of them (50%) died, suggesting that COVID-19 alone is an important risk factor for fatal hemorrhagic complications such as retroperitoneal hematoma even under the prophylactic dose of heparin therapy.

In addition to the well-established risk factors for retroperitoneal hematoma, such as old age, hypertension, diabetes mellitus, and chronic kidney disease requiring hemodialysis [20–22], treatment with nintedanib for fibrotic hypersensitivity pneumonia could have triggered hemorrhagic complications in the present case. Nintedanib is a synthetic orally active tyrosine kinase inhibitor that targets receptors for platelet-derived growth factor, fibroblast growth factor, and vascular endothelial growth factor (VEGF). Nintedanib effectively prevents the decline in pulmonary function in advanced progressive fibrosing interstitial lung diseases; therefore, it is attracting attention as a drug that can inhibit the fibrotic process of COVID-19 [23]. However, mild hemorrhagic complications, such as epistaxis and subcutaneous bleeding, have been reported for this drug, possibly due to its inhibitory activity on the VEGF receptor [24, 25]. Importantly, an increased rate of hemorrhagic complications has been

reported with a combination of VEGF receptor tyrosine kinase inhibitors and anticoagulant therapy [26]. Although Grzesk *et al*. reported that the combination of nintedanib and direct oral anticoagulants does not increase the rate of hemorrhagic complications [27], physicians should be aware of possible hemorrhagic complications when nintedanib and anticoagulants are co-administered to patients with COVID-19.

In conclusion, we report a case of retroperitoneal hematoma during prophylactic heparin therapy for COVID-19. Even with a prophylactic dose of subcutaneous heparin therapy, the course should be carefully monitored, especially in patients with preexisting risk factors for hemorrhagic complications. Once retroperitoneal hematoma develops, aggressive procedures, such as TAE, should be considered to avoid fatal outcomes.

STATEMENT OF CONFLICT

The authors state that they have no conflict of interest (COI).

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