

[ CASE REPORT ]

## Ischemic Stroke Due to Heparin-induced Thrombocytopenia during Severe COVID-19 Infection

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### Abstract:

A 53-year-old woman with severe coronavirus disease 2019 (COVID-19) pneumonia was admitted and treated with intravenous unfractionated heparin for thromboprophylaxis under general anesthesia with mechanical ventilation. She developed right hemiparesis after hospitalization due to a large hemorrhagic infarction. Her platelet count decreased from 243,000/ $\mu$ L at administration to 121,000/ $\mu$ L. Anti-platelet factor 4-heparin antibody testing was positive according to a latex immunoturbidimetric assay. She was therefore diagnosed with heparin-induced thrombocytopenia. We immediately stopped the heparin and started argatroban; the platelet count recovered, and thrombosis did not relapse. Physicians should consider heparin-induced thrombocytopenia as a cause of ischemic stroke in patients with COVID-19 infection.

**Key words:** heparin-induced thrombocytopenia, COVID-19, ischemic stroke

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### Introduction

In patients with coronavirus disease 2019 (COVID-19) infection, immunothrombosis contributes to the pathogenesis (1). Immunothrombosis is a biological defense mechanism by which neutrophils and monocytes interact with platelets and the coagulation cascade to form thrombi to prevent systemic infection (1). However, when immunothrombosis is uncontrolled under the condition of severe COVID-19 infection, excessive promotion of thrombus formation through inflammation, cytokine storms, and endothelial dysfunction can result in both venous and arterial thrombotic events (2, 3). The incidence of venous thromboembolism is up to 20% in COVID-19 patients and higher in intensive-care unit (ICU) than in non-ICU patients (4).

An observational study showed that prophylactic anticoagulation for patients with COVID-19 within 24 hours of admission reduced cumulative 30-day mortality compared to

patients without anticoagulation (5). Based on these data, to prevent venous thromboembolism in critically ill patients with COVID-19, guidelines recommend that patients who require ICU-level care receive a prophylactic dose of heparin (6, 7). However, heparin administration can paradoxically cause thrombosis due to heparin-induced thrombocytopenia.

We herein report a case of ischemic stroke associated with heparin-induced thrombocytopenia during prophylactic heparin administration for severe COVID-19 infection.

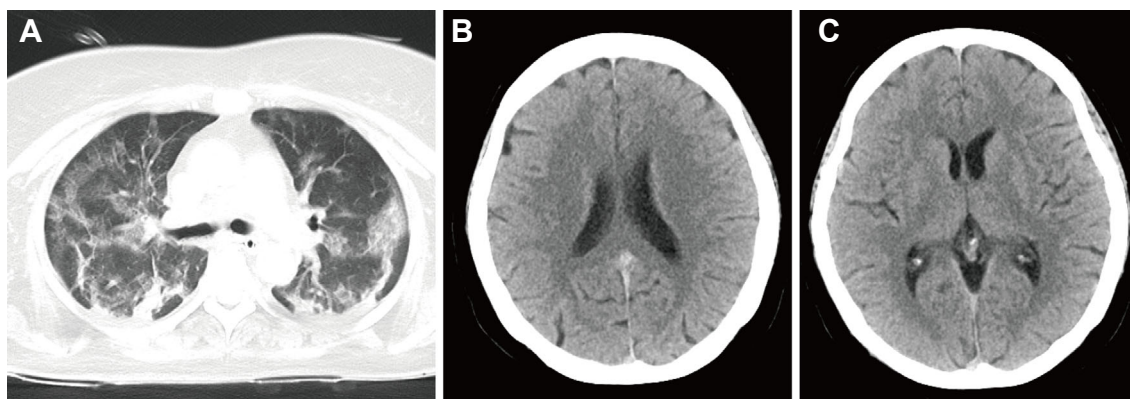
### Case Report

A 53-year-old woman with a body mass index of 32.9 kg/m<sup>2</sup> was referred to our hospital for COVID-19 pneumonia 6 days after testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection. She had not received the SARS-CoV-2 vaccine. She had a medical history of uncontrolled type 2 diabetes mellitus, and no history

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**Figure 1.** (A) Chest computed tomography (CT) scan showed bilateral pneumonia on admission. (B, C) Head CT scan findings were normal on admission.

of heparin use.

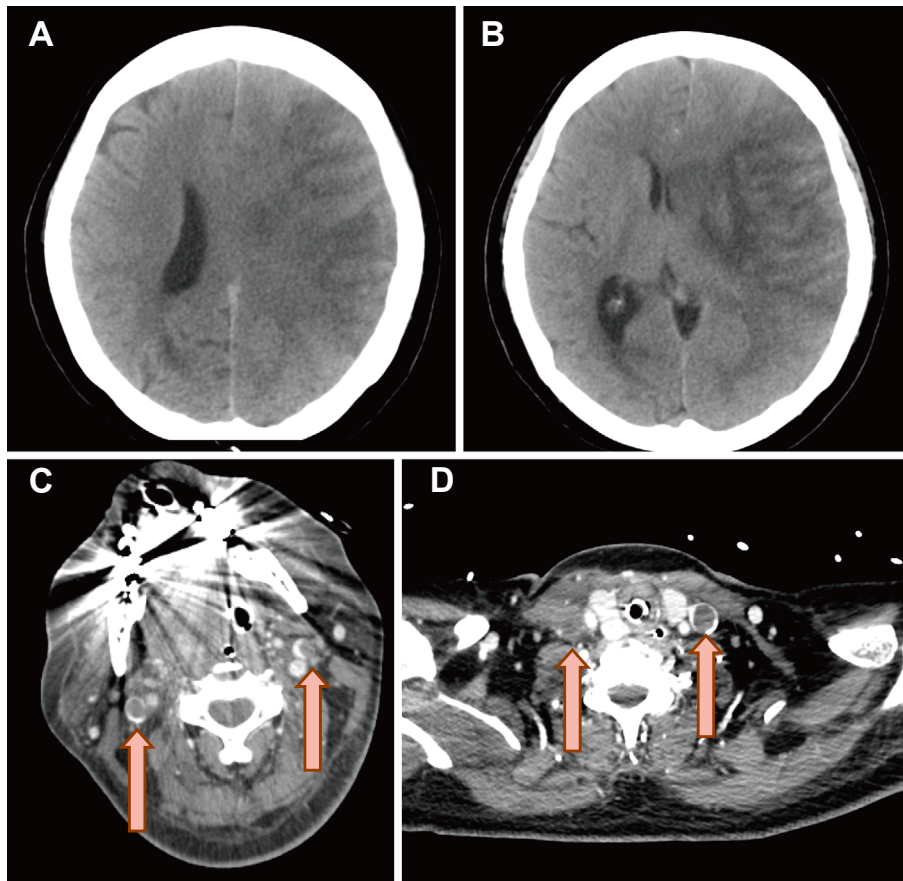
On admission, she was alert with a temperature of 37.3°C, blood pressure 121/100 mmHg, heart rate 98 beats per minute with normal sinus rhythm, respiratory rate of 21 per minute, and oxygen saturation of 88% despite supplemental oxygen administration (15 L/min). At the initial examination, she showed no neurological abnormalities. The laboratory findings were as follows: white blood cell count, 13,210/ $\mu$ L; platelet count, 243,000/ $\mu$ L; plasma C-reactive protein level, 12.04 mg/dL; plasma D-dimer level, 0.75  $\mu$ g/mL; and activated partial thromboplastin time (APTT), 29 seconds.

Whole-body computed tomography (CT) revealed bilateral interstitial pneumonia (Fig. 1a) and no brain abnormalities (Fig. 1b, c). She was immediately intubated and mechanically ventilated and then admitted to the ICU. She was started on an unfractionated heparin infusion at 400 IU/h for prophylaxis of venous thrombosis that was adjusted to maintain an APTT of 1.5-2 times the control value. She was treated with dexamethasone 6 mg once daily. She was also administered ivermectin and ampicillin-sulbactam, and then her respiratory status gradually improved. However, when sedation was withdrawn on day 7, her consciousness was not improved, and complete right hemiparesis was discovered on day 8. Brain CT on day 8 demonstrated a large cerebral infarction in the territory of the left middle cerebral artery (Fig. 2b, c). Brain CT angiography showed no occlusion or stenosis in the left intracranial internal carotid artery or middle cerebral artery. Contrast-enhanced CT revealed bilateral jugular vein thrombosis, in which central venous catheters for drug infusion including heparin were placed (Fig. 2c, d). In addition, systemic ultrasound examinations revealed acute thrombosis of the bilateral radial arteries, where arterial lines perfused with heparinized saline were placed. The platelet count decreased rapidly after 6 days of continuous intravenous heparin infusion and dropped from 243,000/ $\mu$ L at admission to 121,000/ $\mu$ L on day 8 (Fig. 3). She was clinically suspected of having heparin-induced thrombocytopenia as indicated by a 4T score, a pretest scoring system for heparin-induced thrombocytopenia, of 7

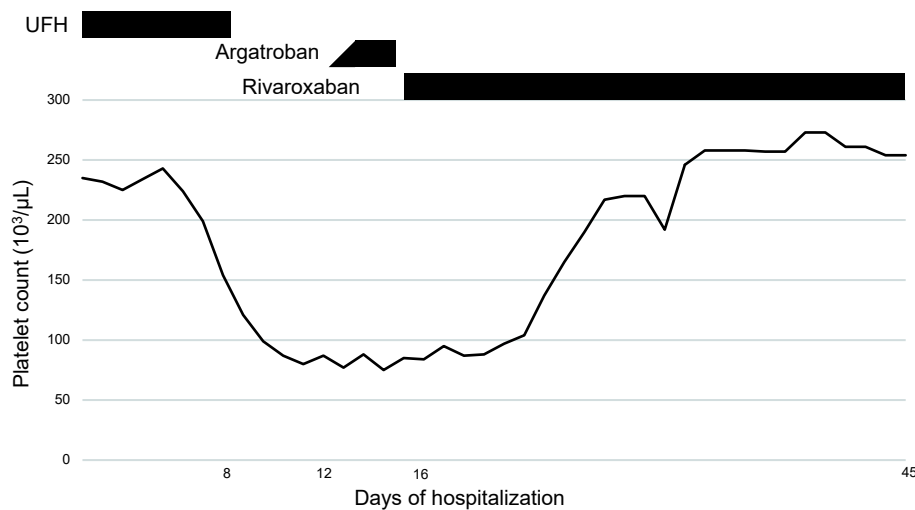
points (platelet count falling by 50% counting as 2 points, the onset of thrombocytopenia from day 6 counting as 2 points, new thrombosis counting as 2 points, and no other possible cause of the thrombocytopenia counting as 1 point), which indicated a high clinical probability of heparin-induced thrombocytopenia (8). A qualitative latex immunoturbidimetric assay to detect anti-platelet factor 4-heparin (anti-PF4/heparin) antibody [HemosIL<sup>®</sup> HIT-Ab (PF4-H)] was positive (>5 U/mL; cut-off value, 1 U/mL) on day 9.

An extensive workup for embolic sources, including electrocardiography monitoring, carotid ultrasonography, a transthoracic echocardiogram, and systemic CT angiogram, revealed no evidence of cardiogenic, atherosclerotic, or aortogenic embolic stroke. The laboratory findings after stroke were as follows: plasma D-dimer level, 3.44  $\mu$ g/mL; APTT, 29 seconds; antithrombin III, 111% (normal range 80-120%); protein C, 116% (normal range 70-135%); protein S, 82% (normal range 49-133%); anti-cardiolipin IgG <8 U/mL (normal range <10 U/mL); anti-beta2-glycoprotein I <1.3 U/mL (normal range <3.2 U/mL); and lupus anticoagulant 1.55 (normal range <1.3). The etiology of ischemic stroke was considered to involve an embolic mechanism due to heparin-induced thrombocytopenia for the following reasons: 1) a high pretest probability for heparin-induced thrombocytopenia with a 4T score of 7 points; 2) a positive anti-PF4/heparin antibody test result; and 3) the presence of thrombosis of bilateral jugular veins and radial arteries, where central and arterial lines flushing with heparin were placed.

The heparin infusion was immediately stopped after the diagnosis of ischemic stroke. Glycerin was started to reduce brain edema and continued until day 15. On day 12, anticoagulation with argatroban was started at 0.2  $\mu$ g/kg/min and increased to 0.6  $\mu$ g/kg/min. The anticoagulation was subsequently switched to rivaroxaban 30 mg/day on day 16. Her platelet count gradually increased after the withdrawal of heparin (Fig. 3) and recovered to 254,000/ $\mu$ L at discharge. Similarly, her plasma D-dimer level gradually decreased to 0.89  $\mu$ g/mL at discharge. A follow-up ultrasound examination performed on day 29 showed no thrombus in the jugular veins or radial arteries. Her respiratory symptoms gradu-



**Figure 2.** (A, B) Head computed tomography (CT) scan revealing a large infarction of the left middle cerebral artery territory on day 8. (C, D) Neck CT angiogram showing a filling defect of the bilateral internal jugular vein (arrows).



**Figure 3.** Platelet counts at admission and after anticoagulation. UFH: unfractionated heparin

ally improved, and she was withdrawn from the ventilator on day 23.

She had residual aphasia and severe right hemiparesis (modified Rankin scale score, 5) and was transferred to a rehabilitation hospital on day 45.

## Discussion

Heparin-induced thrombocytopenia is an immune complication of heparin therapy caused by pathological anti-PF4/heparin antibodies. The binding of these antibodies to platelets leads to platelet activation and aggregation, causing

**Table.** Summary for Acute Ischemic Stroke Patients Associated with HIT in COVID-19.

Published reference	Age	Sex	Heparin at initial	Decrease in platelet counts at nadir (%)	4T score	Details of stroke	Alternative anticoagulation after HIT diagnosis	Hemorrhagic complications
(17)	63	M	LMWH	75	4	N/A	Danaparoid	N/A
(19)	63	M	UFH	67	8	N/A	Direct thrombin inhibitor	Gastrointestinal bleeding
(20)	65	F	LMWH	64	6	Left MCA M2 occlusion	Direct thrombin inhibitor	No
This case	53	F	UFH	68	7	Large left MCA region	Direct thrombin inhibitor	No

HIT: heparin-induced thrombocytopenia, LMWH: low molecular weight heparin, MCA: middle cerebral artery, UFH: unfractionated heparin

thrombocytopenia and thrombosis (9). Half of all patients who experience heparin-induced thrombocytopenia also develop thromboembolism (10). Venous thrombosis occurs more frequently than arterial thrombosis; however, a reported 3.1-5.8% of patients with heparin-induced thrombocytopenia develop ischemic stroke (11, 12). The diagnosis of heparin-induced thrombocytopenia is based on the combination of a compatible clinical picture and *in vitro* demonstration of heparin-dependent antibodies (13).

There are several available assays for diagnosing heparin-induced thrombocytopenia, including enzyme immunoassays, latex immunoturbidimetric assay, and functional assays, such as the serotonin release assay and heparin-induced platelet activation assay (14). In our hospital, we were unable to perform functional assays, which are considered the most specific (14), but the anti-PF4/heparin antibody titer according to the latex immunoturbidimetric assay was  $\geq 5$ , which is sufficient for a diagnosis of heparin-induced thrombocytopenia (15). Antiphospholipid syndrome may be another cause of ischemic stroke in this case, since lupus anticoagulant was weakly positive. Patients with COVID-19 reportedly often show positive results for antiphospholipid antibodies (16); however, unlike anti-cardiolipin IgG or anti-beta2-glycoprotein I, the association between lupus anticoagulant and thrombophilia has not been proven (16). Therefore, we considered her unlikely to suffer from antiphospholipid syndrome.

The combination of COVID-19 and heparin-induced thrombocytopenia may accelerate the hypercoagulable state. Previous reports of the prevalence of heparin-induced thrombocytopenia in patients with COVID-19 are controversial. Daviet et al. reported that 7 of 86 (8%) patients with severe COVID-19 admitted to the ICU were diagnosed with heparin-induced thrombocytopenia by a functional assay (17), and the higher prevalence of heparin-induced thrombocytopenia versus previous studies in the pre-COVID era may be explained by the PF4-linked activation of platelets by the excessive immune response (17). In contrast, Preti et al. reported that only 4 of 2,148 (0.18%) consecutive patients admitted to the ICU were diagnosed with heparin-induced thrombocytopenia (18). Further studies with

adjusted diagnostic methods and patient backgrounds are needed to clarify the associations between COVID-19 infection and the development of heparin-induced thrombocytopenia.

Including our case, four cases of ischemic stroke due to heparin-induced thrombocytopenia under the condition of COVID-19 infection have been published to date (Table) (17, 19, 20). Although the details of the stroke symptoms and prognosis were not described in the previous reports, our patient and the one reported by Madala et al. developed a large cerebral infarction (20). All patients were prescribed danaparoid or direct thrombin inhibitor after receiving the diagnosis of heparin-induced thrombocytopenia, and hemorrhagic complications were reported in only one patient with gastrointestinal bleeding (19). In our patient who received rivaroxaban after transition from argatroban, there was no relapse of thrombosis or bleeding events. In our case, the patient received rivaroxaban after transition from argatroban, according to the American Society of Hematology 2018 guidelines, in which direct oral anticoagulants are recommended for patients with HIT in the stable phase (21). Further studies regarding which antithrombotic drugs should be used and when will be needed to determine the appropriate use of antithrombotic drugs in patients with heparin-induced thrombocytopenia who have COVID-19 infection.

Although COVID-19 infection itself can cause ischemic stroke, when a patient with COVID-19 infection under prophylactic heparin therapy develops ischemic stroke, physicians should consider the possibility of heparin-induced thrombocytopenia-related thrombosis.

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

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