

[ CASE REPORT ]

## Cerebral Infarction with Pulmonary Thromboembolism Due to Immobilization

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### Abstract:

Arterial and venous thrombi can coexist without preexisting conditions, such as malignant disease, thrombotic predisposition, or arteriovenous shunt. We herein report a case of acute cerebral infarction and pulmonary thromboembolism in the absence of underlying disease. A 71-year-old woman presented with left hemiplegia. On an examination, her oxygen saturation was 91% on ambient air despite the absence of chest symptoms and clear lung fields on a chest radiograph. The patient was finally diagnosed with acute cerebral infarction caused by large artery atherosclerosis and acute pulmonary thromboembolism due to deep vein thrombosis, consequent to immobilization for three days after the onset of cerebral infarction.

**Key words:** arterial thrombus, venous thrombus, cerebral infarction, immobilization, pulmonary thromboembolism, venous thromboembolism

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### Introduction

Although venous thromboembolism, presenting as deep vein thrombosis and its complication with pulmonary thromboembolism, is sometimes associated with stroke and has a high mortality rate (1-4), the significance of its risk can be underestimated. An immobile state in a patient due to a stroke is a potential cause of venous thromboembolism (4, 5). In addition, the coexistence of thrombi in both the arterial and venous systems is possible under specific conditions, such as malignant disease (6, 7), thrombotic predisposition (8, 9), or arteriovenous shunt (10, 11). A systematic evaluation for these underlying conditions is essential for the secondary prevention of stroke and venous thromboembolism.

We herein report a case of acute cerebral infarction caused by large artery atherosclerosis and pulmonary thromboembolism with no evidence of underlying disease. In this case, deep vein thrombosis consequent to immobilization for three days after cerebral infarction onset was considered the cause of pulmonary thromboembolism. Early detection and

treatment of existing pulmonary thromboembolism may help prevent further deterioration.

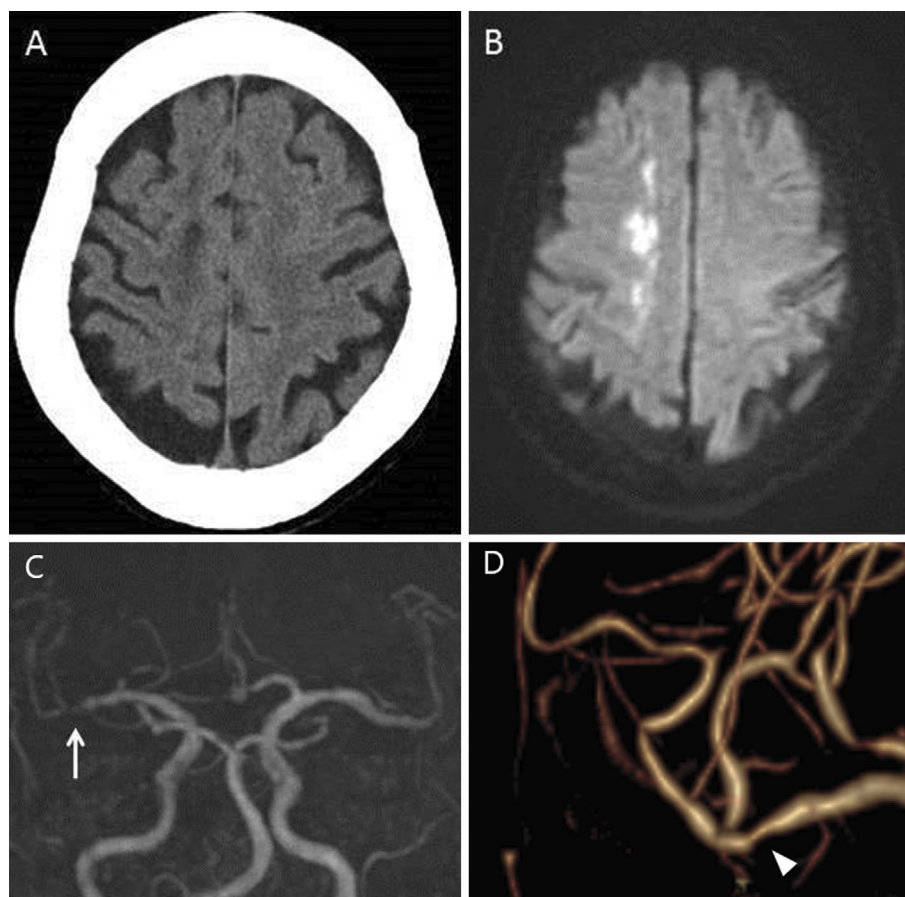
### Case Report

A 71-year-old woman was transferred to the emergency room of our hospital due to left hemiplegia. The patient had been in her normal state of health until three days before presentation, when paralysis of the left arm and leg developed. The patient reportedly noticed the occurrence of left hemiplegia but did not seek medical care, choosing instead to stay at home with the support of her husband. On the day of her arrival at hospital, her son found her having difficulty sitting and called an ambulance. She did not report any shortness of breathing, hemoptysis, chest pain, or leg pain. On taking her history, we learned that the patient had been lying down on her left side for three days since the hemiplegia had occurred. She reported that she had not experienced any prior physical trauma or loss of consciousness. Her medical history was unremarkable, and she was not taking any medications. The patient did not drink, smoke, or use illicit drugs and had no known allergies.

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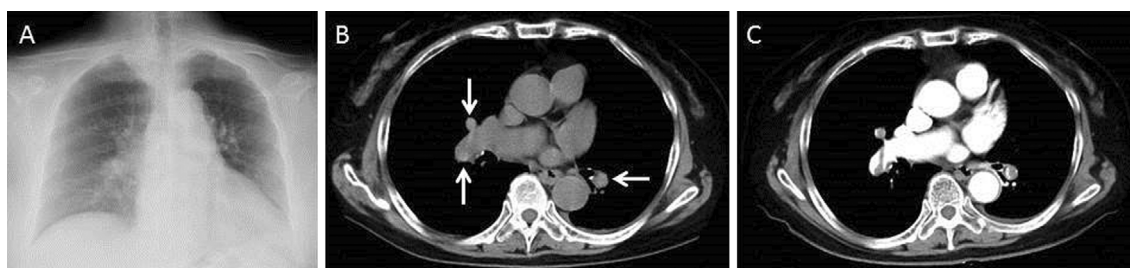
**Figure 1.** Images of the brain. An axial CT image of the brain shows a low-signal area in the right frontoparietal lobe (A). An increased signal intensity is present in the same area on diffusion-weighted MRI (B). MR angiography shows an irregularity in the right middle cerebral artery (C, arrow), with the distal portion showing low perfusion. CT angiography also shows localized narrowing in the same area, suggesting atherosclerotic stenosis (D, arrowhead).

On arrival, she was found to have a Glasgow Coma Scale of 14 (E4V4M6). Her blood pressure was 149/108 mmHg, her pulse was 111 beats per minute, her body temperature was 37.5°C, her respiratory rate was 18 breaths per minute, and her oxygen saturation was 91% while breathing ambient air. Her lungs were clear to auscultation without signs of wheezing or rales. Her left leg had noticeable unilateral pitting edema without Homan's sign. Her pupils were equal in size (2.0 mm in diameter), round, and reactive to light. Using manual muscle testing, her strength was rated 1 out of 5 for both the left arm and the left leg. In addition, her ability to sense light touch was decreased on the left side of the body. The remainder of the physical examinations, including cranial nerve testing, were normal.

Electrocardiography showed a normal sinus rhythm without abnormal Q waves or QT prolongation. Anteroposterior chest radiography was normal, except for a slight enlargement of the pulmonary artery. Her white cell count was 5,500/ $\mu$ L with 70.1% neutrophils, her hemoglobin was 12.1 g/dL, and her platelet count was 215,000/ $\mu$ L. In addition, her C-reactive protein was 1.10 mg/dL, and her blood glucose was 123 mg/dL. Both urea nitrogen and creatinine levels were within the normal range, as were electrolytes and

the results of the liver function and thyroid tests. Both her D-dimer (14.1  $\mu$ g/mL, reference value,  $\leq$ 1.0) and brain natriuretic peptide (52.5 pg/mL, reference value,  $\leq$ 18.4) levels were elevated.

Computed tomography (CT) of the brain without contrast revealed a low-density area in the right frontoparietal lobe (Fig. 1A). Magnetic resonance imaging (MRI) of the head without contrast demonstrated a high signal intensity on diffusion-weighted images (Fig. 1B) and haziness in the right middle cerebral artery on angiography (Fig. 1C). Both findings were consistent with acute cerebral infarction in the region perfused by the right middle cerebral artery. Given that relatively low oxygen saturation was observed despite chest radiography showing clear lung fields (Fig. 2A), CT of the chest without contrast was also performed. CT showed slight enlargement of the pulmonary arteries in which hyperdensities were partially observed (Fig. 2B). CT of the whole body with contrast revealed contrast defects, not only in the right and left pulmonary arteries (Fig. 2C), but also in the left common femoral and popliteal veins. Transthoracic echocardiography showed a normal size and function of both ventricles, with hyperkinetic wall motion in the apex of the right ventricle [McConnell's sign (12)], a finding sug-



**Figure 2.** Images of the chest. An anteroposterior radiograph shows clear lung fields with slight enlargement of the right pulmonary artery (A). Note that luminal hyper densities were partially observed in the pulmonary arteries on CT without contrast (B, arrows). CT with contrast reveals multiple defects in the pulmonary artery (C). These defects coincide with the areas with a hyperdense lumen on non-contrast CT, findings consistent with acute pulmonary thromboembolism.

gestive of acute pulmonary thromboembolism. The estimated systolic pulmonary artery pressure was 65 mmHg.

The clinical course was uneventful, and medical treatment included anticoagulants (continuous intravenous heparin with an activated partial thromboplastin time of 35 to 45 seconds and later switched to 30 mg of edoxaban daily) and aspirin (100 mg daily). Holter-electrocardiography and prolonged bedside electrocardiograph monitoring over four weeks showed no evidence of arrhythmia that could lead to cerebral infarction, such as atrial fibrillation. Carotid artery stenosis was not detected by carotid ultrasound or magnetic resonance (MR) angiography. Transesophageal echocardiography with bubble contrast and the Valsalva maneuver showed no evidence of a right-to-left shunt, such as a patent foramen ovale. There was no evidence of thrombus in the heart, aortic atheroma (>4 mm), mobile aortic atheroma, or ulcerated aortic atheroma detected in this study. There was no mass lesion suggestive of pulmonary arteriovenous fistula, another kind of right-to-left shunt, detected on whole-body CT with contrast. Neither malignancy nor thrombotic predisposition (e.g., anticardiolipin antibody, antinuclear antibody, protein S and C deficiency, or antithrombin III deficiency) was found. CT angiography of the head, obtained about two weeks after admission, demonstrated a localized narrowing in the right middle cerebral artery, suggesting atherosclerotic stenosis (Fig. 1D). Follow-up transthoracic echocardiography performed approximately 2 weeks after admission revealed that the systolic pulmonary artery pressure had decreased to 33 mmHg. CT images obtained about three weeks after admission showed no thrombus present in the left leg but small thrombi present in the distal branches of the pulmonary arteries.

While some tests should be reassessed ideally for detecting latent causes of cerebral infarction undetected by present investigations, given the narrowing in the right middle cerebral artery and negative findings indicative of other causes, a diagnosis of acute cerebral infarction caused by large artery atherosclerosis, with acute pulmonary thromboembolism and deep vein thrombosis, was made. Clopidogrel (75 mg daily) was administered for the secondary prevention of cerebral infarction. The patient's left hemiplegia gradually improved,

and she was transferred to another hospital for further rehabilitation one month after admission.

## Discussion

Due to the patient's primary symptom of left hemiplegia, our initial diagnosis was acute cerebral infarction. After testing and imaging, she was later diagnosed as also having acute pulmonary thromboembolism with deep vein thrombosis. After carefully taking her history, it was revealed that three days of immobilization had occurred after the onset of cerebral infarction.

This case provides two important clinical suggestions. First, venous thromboembolism can coexist with cerebral infarction. In such cases, the early detection of venous thromboembolism and subsequent treatment are essential for preventing further deterioration. In addition, a systematic evaluation is necessary to determine if specific underlying conditions, such as thrombotic predisposition or arteriovenous shunt, are associated with the formation of the coexistent arterial and venous thrombi.

Venous thromboembolism is not uncommon, with an overall average age- and sex-adjusted annual incidence of 117 per 100,000 (deep vein thrombosis, 48 per 100,000; pulmonary thromboembolism, 69 per 100,000) (13). In a 15-year population-based, case-controlled study (14), more than 50% of all cases of venous thromboembolism could be attributed to institutionalization (hospitalization, 46% and nursing home residence, 13%). Of these cases, individual risk factors included malignancy (18%), trauma (12%), heart failure (10%), and indwelling devices (9%). However, none of these risk factors was observed in our patient, and she had never been institutionalized prior to this admission.

It is important to recognize that pulmonary thromboembolism may be associated with cerebral infarction. A large cohort study of 14,109,000 hospitalized acute ischemic stroke patients showed that 72,000 of the patients had also pulmonary thromboembolism (0.51%) (2). Another cohort study composed of 11,287 patients with acute ischemic stroke found that the incidence of clinically suspected pulmonary thromboembolism within 30 days of admission was

0.78% (3). In that study, patients with pulmonary thromboembolism had a higher mortality rate at discharge (31.5% vs. 12.7%) and were more likely to have cancer (29.2% vs. 9.9%) and a prothrombotic state (4.5% vs. 0.6%) than those without. A study using MR direct thrombus imaging also revealed that the incidence of clinical and subclinical pulmonary thromboembolism within 21 days of admission for acute ischemic stroke was 11.8% (4).

A similar condition, in which thrombi develop both in the arterial and venous systems, is observed in some disorders, such as cancer-related coagulopathy or Trousseau's syndrome (6, 7). Furthermore, antiphospholipid syndrome is a condition associated with thrombus formation in the arteriovenous system (8, 9). While the possibility of latent cancer cannot be completely dismissed, thrombotic predisposition including these conditions was ruled out in the current case. There was no evidence indicative of arteriovenous fistula in the lungs or other organs or underlying hereditary hemorrhagic telangiectasia (e.g., recurrent epistaxis and gastrointestinal bleeding, mucocutaneous telangiectasias, familial inheritance, presence of shunt in a bubble contrast echocardiogram, or mass lesion in imaging study) (11). Given the lack of evidence for a paradoxical brain embolism with right-to-left shunts, such as a patent foramen ovale or pulmonary arteriovenous fistula, we speculated that the underlying cause for acute pulmonary thromboembolism was deep vein thrombosis resulting from three days of immobilization after the onset of cerebral infarction.

A non-ambulatory status in the acute phase of ischemic stroke is associated with the occurrence of deep vein thrombosis and pulmonary thromboembolism (4). In a study of 30 patients with acute stroke and pulmonary thromboembolism, 11 patients had deep venous thrombosis (37%), invariably in the paralyzed leg (5). These findings suggest that immobility due to paralysis contributes to thrombus formation, which is a potential source of pulmonary thromboembolism, as observed in the current case. The site of thrombus formation in our patient, within the left common femoral and popliteal veins, can be explained by her left-sided recumbent posture after the onset of cerebral infarction.

The effect of immobilization duration on the risk for venous thromboembolism has not yet been confirmed, but we hypothesize that the risk likely increases with longer immobilization. In a meta-analysis of 4,055 long-distance travelers diagnosed with venous thromboembolism (15), a significant positive duration-risk relationship was identified. This risk was 18% higher for each 2-h increase in travel duration by any mode of transport. Given the present patient's immobilization over a period of three days, we speculate that her deep vein thrombosis had been provoked during this immobile period. It should also be noted that other factors known to accelerate thrombus formation, such as dehydration because of decreased appetite, may also have increased her risk after the onset of cerebral infarction.

Since the present patient had not been tested for pulmonary thromboembolism prior to this admission, it is possible

she was suffering from chronic thromboembolic pulmonary hypertension before the onset of cerebral infarction. However, the presence of this condition is unlikely, as both a positive McConnell's sign (12) and high-attenuation clots in the pulmonary arteries on non-contrast CT (16) were observed, indicating acute pulmonary thromboembolism. This is also consistent with her self-report of performing normal activities of daily living until three days before admission. In addition, the patient had not reported relevant symptoms, such as chest pain or shortness of breathing, during hospitalization. However, this does not completely rule out the possibility of an asymptomatic embolism, as a systematic review composed of 5,223 patients with deep vein thrombosis found the incidence of silent pulmonary thromboembolism was 32% (17).

In conclusion, we herein report a case of acute cerebral infarction associated with pulmonary thromboembolism due to deep vein thrombus that was caused by the patient being immobilized for three days after the onset of cerebral infarction. This case highlights the importance of attentiveness to venous thromboembolism with cerebral infarction and a systemic evaluation for possible underlying disorders to be differentiated, especially when patients do not seek medical care in the acute phase of immobilization.

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

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