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Histopathology of pulmonary thromboembolism in a patient with Behçet's disease

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ABSTRACT

Pulmonary involvement in vascular Behçet's disease (BD) (VBD) is a serious manifestation. Among the pulmonary manifestations, pulmonary embolism is considered a rare manifestation because deep vein thrombosis (DVT) has been thought to detach from the vessel wall, whereas pulmonary thrombus has been suggested to result from in situ pulmonary arteritis.

In this case report, we present histopathological evidence of pulmonary embolism derived from DVT in an autopsy case of VBD. This observation emphasises that DVT causes pulmonary embolism in BD, indicating that anticoagulants are required for its prevention.

Introduction

Behçet's disease (BD) is a chronic recurrent inflammatory disease of unknown aetiology, characterised by recurrent oral aphthous ulcers, ocular disease, skin lesions, and genital ulcers (1). Pulmonary artery involvement is a life-threatening complication that presents with aneurysm and thrombosis (2). Pulmonary embolism (PE) is a rare manifestation, whereas pulmonary thrombus is formed due to *in situ* pulmonary arteritis (3, 4). In addition, although PE is generally a consequence of deep vein thrombosis (DVT), a common comorbidity in vascular BD (VBD), DVT does not usually detach from the vessel wall in VBD (3, 5-7).

Herein, we provide histopathological evidence of PE caused by inferior vena cava (IVC) thrombus in an autopsied patient who died of acute pulmonary artery obstruction.

Case report

A 37-year-old man with vasculo- and entero-BD was admitted to our hospital with an acute attack of dyspnoea during lymphocyte apheresis therapy. Four years before admission, he was hospitalised due to chest pain and syncope caused by PE and DVT; therefore, an umbrella filter was inserted into the IVC and warfarin administration was initiated. There were no thrombotic predispositions, including protein C, protein S, and antithrombin III deficiency, and antiphospholipid antibody syndrome. Subsequently, he was diagnosed with BD based on the development of an oral aphthous ulcer, folliculitis, and genital ulcer. These symptoms met the 2014 international BD criteria (8), and were complicated with colitis. Before this admission, he was treated with 25 mg/day prednisolone, 10 mg/week methotrexate, 1.0 mg/day colchicine, 3 g/day salazosulfapyridine, 4 mg/day warfarin, and lymphocyte apheresis therapy.

Examination at admission revealed a body temperature of 36.4°C; pulse rate, 104 bpm; blood pressure, 120/80 mmHg; and percutaneous oxygen saturation (SpO2), 94% on room air. His heart and lung sounds were clear. Laboratory findings showed a white blood cell count of 13,400/μL; C-reactive protein, 23.8 mg/L; and D-dimer, 25.0 μg/mL. Chest and abdominal computed tomography (CT) showed enhancement defects in the bilateral pulmonary arteries and IVC (Fig. 1A-B). Lung perfusion scintigraphy revealed multiple perfusion defects (Fig. 1C).

He was diagnosed with recurrent PE, and unfractionated heparin was administered. His condition showed improvement; however, 7 days after admission, he suddenly complained of dyspnoea after walking with low blood pressure and severe hypoxemia. Chest CT showed exacerbated enlargement of the right pulmonary artery, suggesting repeated PE. Although ventilator management and administration of tissue plasminogen activator were started, he died 8 days after admission.

Autopsy findings

Autopsy within 7 h of death showed obstruction with multiple massive thrombi in the bilateral pulmonary arteries extending into the segmental arteries (Fig. 1D). In the IVC, floating thrombus formation was observed measuring 10 cm from the inserted filter on the distal side, whereas no thrombus was found either in the proximal IVC from the filter or on the filter (Fig. 1E). It should be noted that there was no obvious thrombus in any area other than the IVC.

Histological studies revealed two main types of pathological changes in the pulmonary artery. One was formation of thrombi covering the thickened fi-

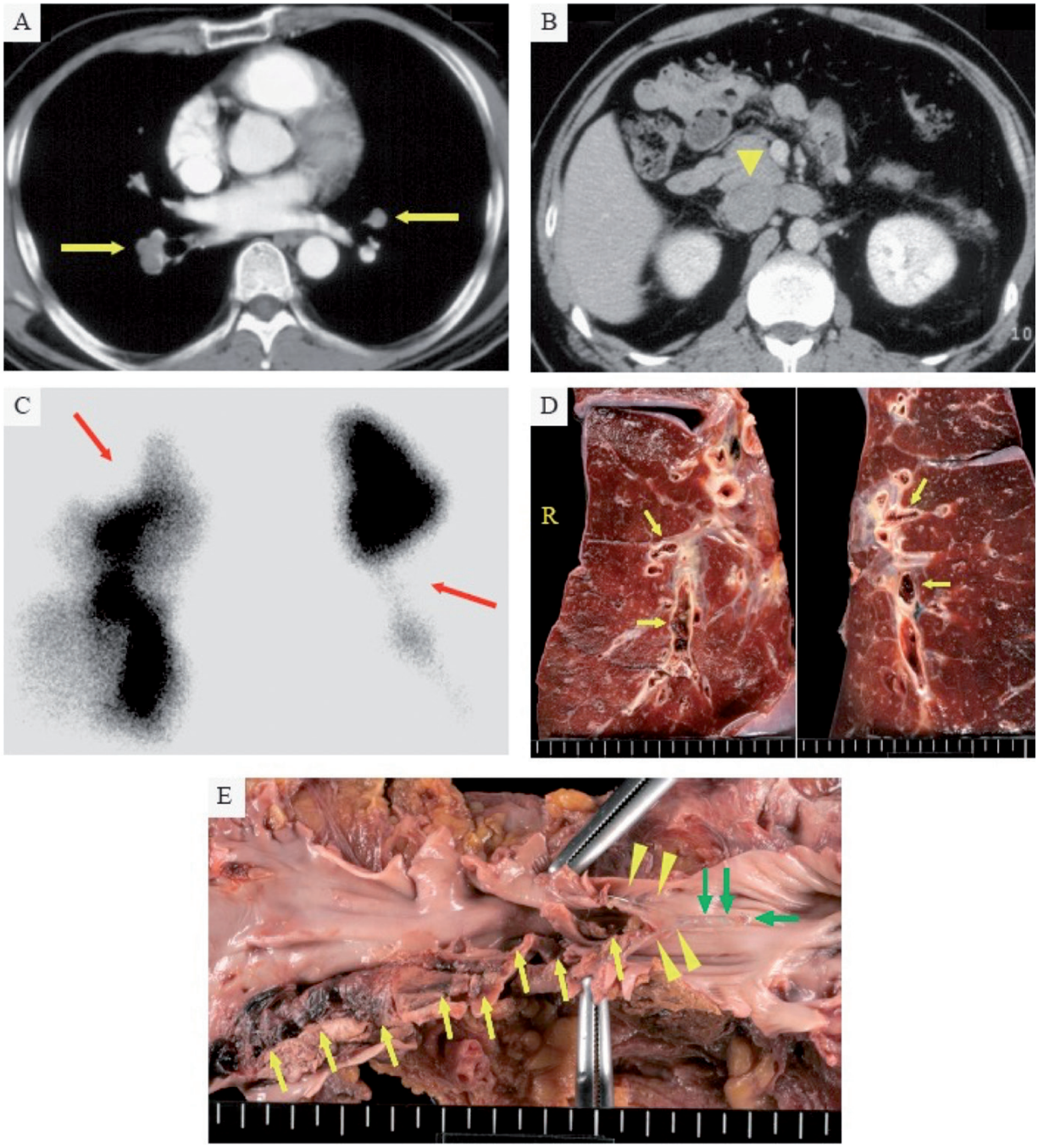

Fig. 1. CT, perfusion scintigraphy, and macroscopic findings in autopsy.
A: Contrast-enhanced chest and abdominal computed tomography (CT) scans showing pulmonary emboli (yellow arrows) in the bilateral pulmonary arteries and **B**: Deep vein thrombosis (yellow arrowhead) in the inferior vena cava (IVC).
C: Lung perfusion scintigraphy showing multiple perfusion defects (red arrows).
D: Near complete obstruction can in the bilateral pulmonary arteries extending into the segmental branches, which are completely occluded by massive emboli (yellow arrows). (E) *En face* IVC image; right of the image is the proximal side. There are no obvious trapped fragments of thrombi in the IVC filter (green arrows and yellow arrowheads indicate the head and legs of the filter, respectively) or thrombi formation in the IVC proximal from the IVC filter. Thrombi are observed distal from the IVC filter (yellow arrows).

brous intima, forming layer lesions with new thrombi continuously added to old thrombi without lumen obstruction (Fig. 2A-B). There was continuity between the intima and thrombus with inflammatory cell infiltration (Fig. 2C-D). These findings were consistent with those of pulmonary thrombosis. Accordingly, in the IVC, a thrombus with smooth edges arose from the intima with inflammatory cell infiltration at the border between the thrombus and intima, as was the case with pulmonary artery thrombosis (Fig. 2E). The thickened intima had an unclear border with the thrombus containing red and white thrombi (Fig. 2F).

The second type was complete obstruc-

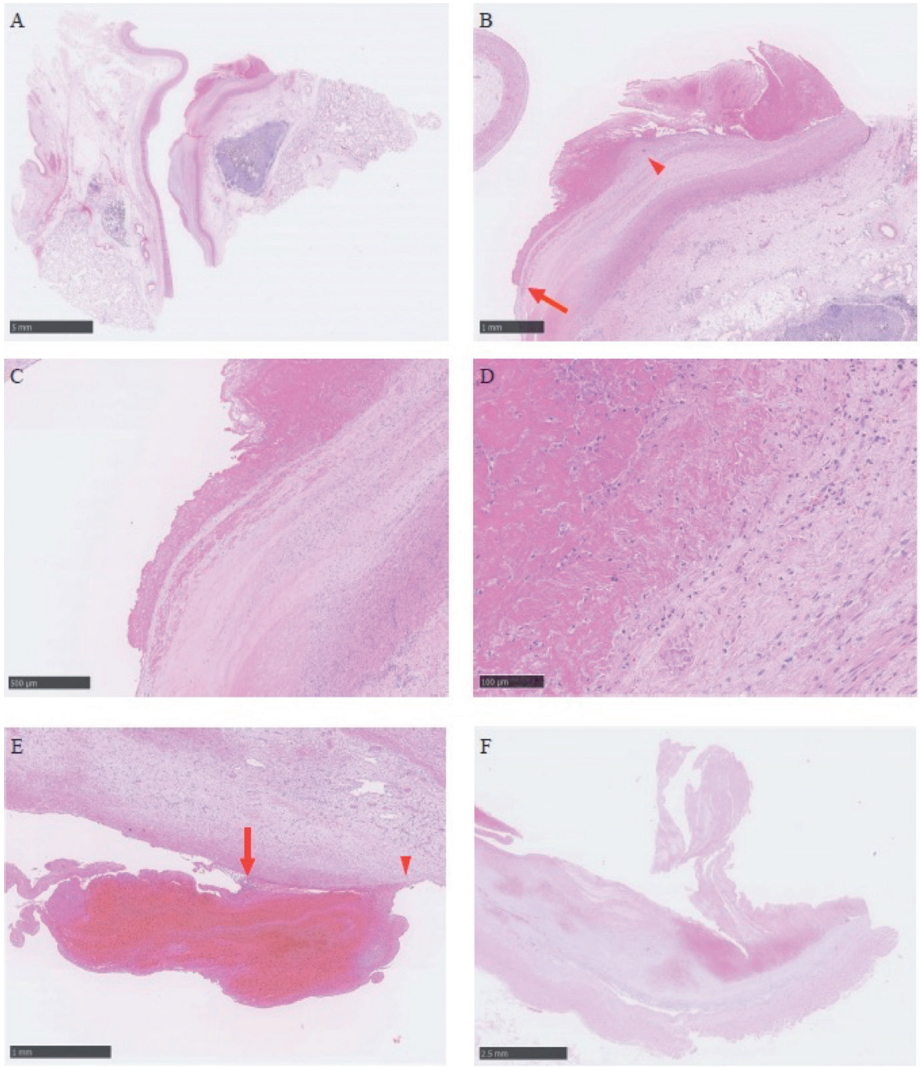

Fig. 2. Pulmonary artery thrombosis and inferior vena cava thrombosis.
A-**D**: Pulmonary artery thrombosis.
A: A pathology image with a loupe. Scale bar: 5 mm.
B: The layer thrombus covers the thickened fibrous intima. Scale bar: 1 mm.
C: The edge of the thrombus arising smoothly from the intima, which appears to have continuity (red arrow in B). Scale bar: 500 μm.
D: The borderline between the thrombus and the intima is unclear with inflammatory cell infiltration (red arrowhead in B). Scale bar: 100 μm.
E-**F**) Inferior vena cava thrombosis.
E) The partially free thrombus is adhered to the intima. The edge of thrombus arises smoothly from the intima, as is the case with the pulmonary thrombus (arrowhead), and inflammatory infiltration is observed in the thrombus and the intima (arrow). Scale bar: 1 mm.
F) The border between the thrombus and the intima is unclear and covered with red and white thrombi. Scale bar: 2.5 mm. Haematoxylin and eosin staining.

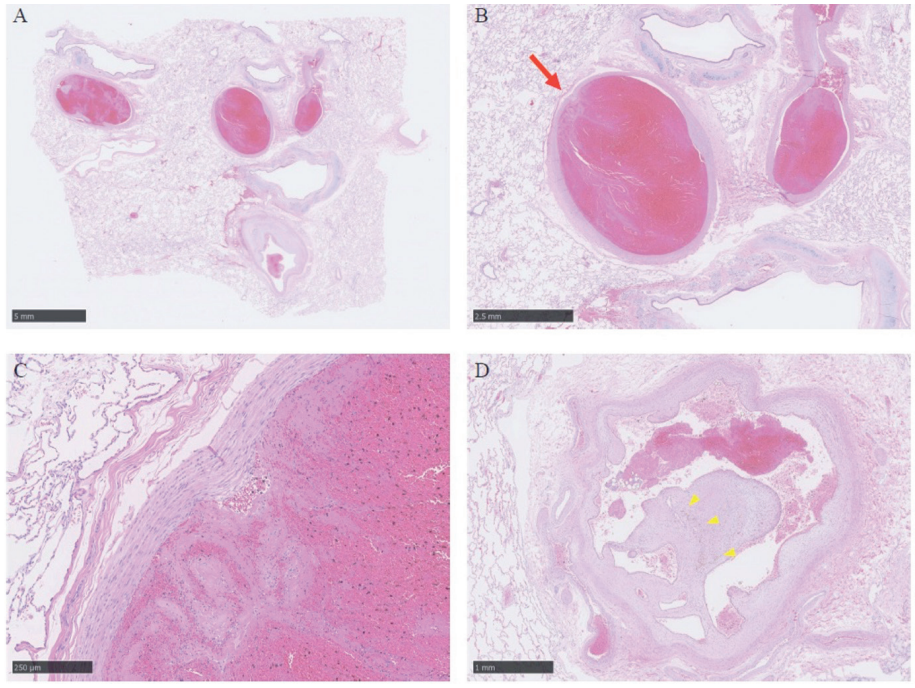

Fig. 3. Pulmonary artery embolism.
A: A pathology image with a loupe. Scale bar: 5 mm.
B: The thrombi consisting of fibrins and red blood cells occluding the lumen appear a clot formed at once. Scale bar: 2.5 mm.
C: The border between the emboli and the intima is clear, and there is no inflammatory cell infiltration (around red arrow in B). Scale bar: 2.5 μm.
D: The organised emboli with recanalisation and haemosiderin deposition (yellow arrowheads) and the fresh emboli in different section from A are seen. Scale bar: 1 mm. Haematoxylin and eosin staining.

tion of the lumen of the pulmonary artery by massive blood clots containing fibrin and red blood cells without prominent congestive pulmonary oedema (Fig. 3A-B). There was no continuity between the intima and thrombus with a clear borderline. Moreover, inflammatory cell infiltration was not observed around the border (Fig. 3C). These findings indicate that the clot was an embolus that migrated from outside the lung. In addition, some artery lumens included organised emboli that formed recanalisation and haemosiderin deposition, suggesting repeated PE (Fig. 3D).

These results indicate that the patient had both pulmonary thrombosis and PE. Complete obstruction of the pulmonary artery due to emboli was considered responsible for fatality in this patient.

Discussion

We reported the histopathology of pulmonary artery thrombosis and emboli in an autopsied BD patient who died from acute complete obstruction of the pulmonary arteries. To the best of our knowledge, this is the first histopathological report of PE in BD.

Obvious morphological differences in histopathology were noted between pulmonary artery thrombosis and emboli. Thrombosis formed a layer lesion covered with layers of thrombi without lumen occlusion, accompanied by inflammatory cell infiltration. In contrast, the emboli completely occluded the lumen without inflammatory cell infiltration. IVC thrombosis showed the same features as pulmonary thrombosis and was considered to be detached from the vessel wall as there was a free-floating segment of the thrombus.

The organised emboli with recanalisation and haemosiderin deposition indicate the presence of repeated PE in accordance with the clinical course. In the first attack of DVT and PE, no thrombotic predisposition was observed except for BD. Although it is possible that insertion of the IVC filter caused thrombus formation, autopsy findings did not reveal any detached thrombus caught by the filter or thrombus on its proximal side. These finding suggest that detached small fragments from the long thrombus of distal side of the IVC filter passed through the filter to cause PE. Of course, it is still possible that thrombus formed proximal of the filter was detached, although it appears unlikely from the macroscopic findings around the filter.

In our retrospective cohort from 1989 to 2009, seven of 42 patients with VBD had PE and DVT (9). Accordingly, there were several reports on the occurrence of PE in VBD (10, 11), suggesting that PE is not a rare condition in BD. This higher prevalence of PE than expected may also support the addition of anticoagulant therapy.

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