



Case report

Diffuse alveolar damage associated with pulmonary thromboembolism

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ABSTRACT

In contrast to other internal organs, pulmonary arterial hypoperfusion does not always show ischemic changes in the lung parenchyma. Pulmonary thromboembolism (PTE)-related lung injury is extremely rare except in the case of pulmonary infarctions, in which PTE occasionally causes necrosis of the parenchyma. We describe the case of an 86-year-old woman who presented with respiratory failure and bilateral ground-glass opacity predominantly the upper lobes. Autopsy revealed a saddle-shaped old organized thrombi in the main pulmonary artery, relatively fresh thrombi in both pulmonary arteries, and localized diffuse alveolar damage (DAD) in the bilateral upper lung fields. The hypoperfused regions resulting from the thromboembolism anatomically coincided with the pulmonary lesion where DAD was identified. Although PTE is not regarded as a causal factor of DAD, it might induce DAD as a result of hypoperfusion in limited cases.

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1. Introduction

Lung parenchyma distal to pulmonary thromboembolism (PTE) is normal or shows mild atelectasis, minimal intra-alveolar hemorrhage, edema, and infarction.¹ Moreover, except in the case of pulmonary infarction, PTE-related lung injury is extremely rare. Diffuse alveolar damage (DAD) is a nonspecific pathological finding of acute lung injury that can be caused by infectious agents, inhalants, drugs, shock, sepsis, or exposure to radiation.^{2,3} To the best of our knowledge, PTE is not regarded as the causal factor of DAD. Here we report a case in which causal association between PTE and DAD was suspected.

2. Case report

An 86-year-old woman with a history of chronic heart failure was referred to our institution with dyspnea. She had a smoking history of 1 pack cigarettes/day but had stopped smoking a year ago. She had no history of respiratory diseases. Physical examination revealed bilateral fine inspiratory crackles on auscultation. Peripheral edema and clubbing were not observed.

The results of laboratory studies were as follows: leukocytes, 6500/ μ L; hemoglobin, 12.4 g/dL; hematocrit, 36.3%; platelets, $11.0 \times 10^4/\mu$ L;

blood urea nitrogen, 27.1 mg/dL; creatinine, 1.02 mg/dL; C-reactive protein, 6.99 mg/dL; brain natriuretic protein, 634 pg/mL; KL-6, 2697 U/mL; and D-dimer, 4.3 μ g/mL. Other abnormalities including autoantibodies and coagulation abnormalities were not detected. Chest radiography showed bilateral ground-glass opacities predominantly the upper lobes (Fig. 1A). Chest computed tomography showed dilatation of the pulmonary trunk with a maximal diameter of 4.5 cm (Fig. 1B). Bronchial dilatation, honeycombing, and pleural effusion were not observed (Fig. 1C). Echocardiography revealed normal right ventricular size with good left cardiac function (58%). Doppler-determined peak systolic tricuspid pressure gradient was not elevated (25 mmHg).

On admission, acute respiratory distress syndrome, which was predominant in the upper lobe, and atypical pneumonia were suspected. Therefore, we intravenously administered high doses of methylprednisolone (1000 mg/day) and ciprofloxacin (600 mg/day). However, the patient's condition deteriorated, and she suffered severe respiratory distress. She was not willing to receive advanced mechanical ventilation and died on the 10th day of admission. We obtained informed consent for autopsy.

Autopsy revealed that an old saddle-shaped organized thrombus had extended from the main pulmonary artery to both pulmonary arteries (Fig. 2A and B). Relatively fresh organizing thrombi, which were pathologically presumed to emerge before the onset of symptoms, extended along the wall of pulmonary arteries from the origin of both pulmonary arteries to the bifurcation of A6; however,

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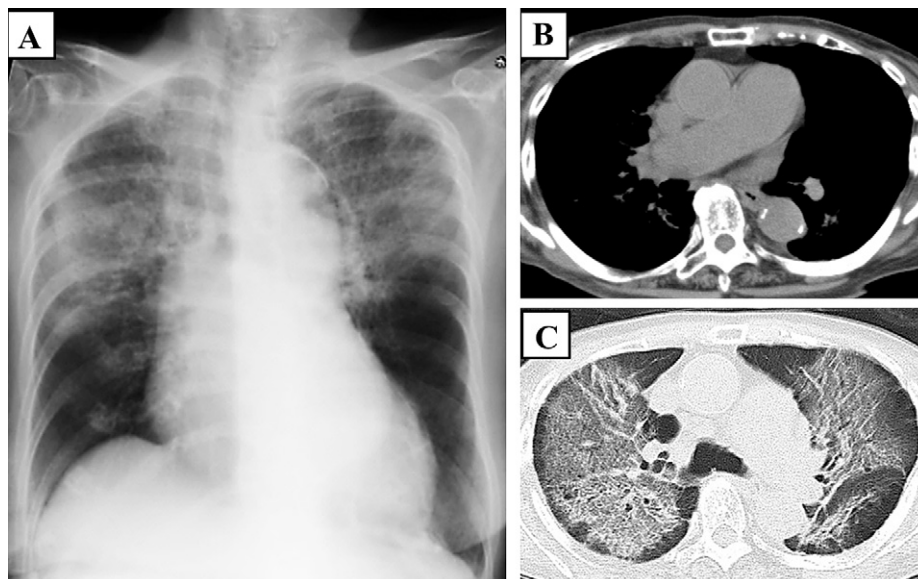


Fig. 1. A. Chest radiography showed bilateral ground-glass opacities predominantly the upper lobes. B. Chest computed tomography showed dilatation of the pulmonary trunk. C. Chest computed tomography showed ground-glass opacity without bronchial dilatation, honeycombing, and pleural effusion.

it did not reach both basal arteries, which perfused lower lobes (Fig. 2A and C). Segmental arteries were obstructed by relatively fresh thrombi in both pulmonary arteries incompletely. It was estimated that the thrombus caused pulmonary arterial hypoperfusion in right S1–6 and left S1–6.

Microscopic examination revealed many fibroblastic proliferation foci along the walls of the respiratory bronchioles and alveolar ducts (Fig. 3A). The alveolar ducts and alveoli were filled with fibroblastic proliferation (Fig. 3B). These features were found diffusely in right S1–6 and left S1–5 and were consistent with those of organizing DAD. Pulmonary infarction and lesions attributable to viral infection or other specific pathogens such as mycobacteria, fungi, and *Pneumocystis jiroveci* were absent. The hypoperfused regions caused by the thromboembolism anatomically coincided with the pulmonary lesion where DAD was identified.

3. Discussion

Lung parenchyma generally receives blood from the pulmonary arteries and bronchial circulation. Therefore, a pulmonary vascular occlusion does not always result in significant ischemic changes in the lung parenchyma.^{1,4–6} Meanwhile, pulmonary infarction, which is the most common form of PTE-related lung injury, is observed in limited cases.^{1,5,6} A likely mechanism is that the systemic to pulmonary flow from bronchial circulation, which is important in perfusing potentially ischemic regions distal to obstructions, might be reduced because of systemic arterial hypotension and pulmonary venous congestion.⁶ Therefore, profound hypoperfusion caused by interrupted dual circulation may have induced a pulmonary infarction. On the contrary, apart from pulmonary infarction, this case strongly indicated the causal association between

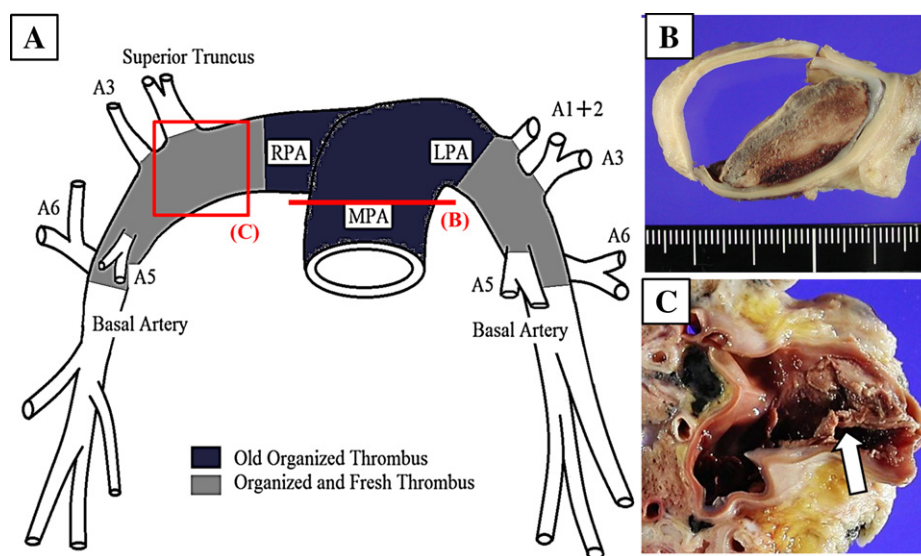


Fig. 2. A. An old organized thrombus had extended from the main pulmonary artery (MPA) to both pulmonary arteries, and organized and fresh thrombi extended from the origin of both pulmonary arteries to the bifurcation of A6. B. A transverse cut surface of MPA showed an old organized thrombus. C. A coronal cut surface of right pulmonary artery showed relatively fresh organizing thrombi extended along the wall with web or bands (arrow). MPA = main pulmonary artery. RPA = right pulmonary artery. LPA = left pulmonary artery.

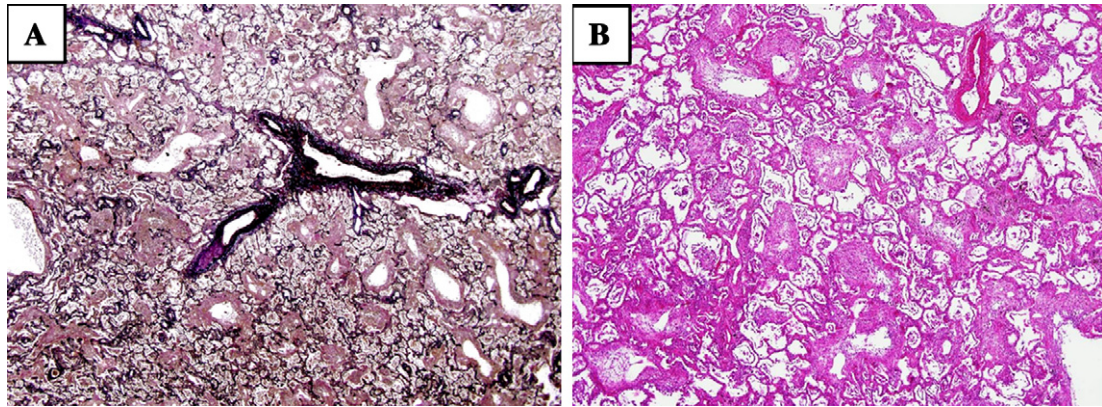


Fig. 3. A. Many foci of fibroblastic proliferation were found along the walls of respiratory bronchioles and alveolar ducts (Elastica van Gieson; original magnification, $\times 12.5$). B. Alveolar ducts and alveoli were filled with the fibroblastic proliferations (Hematoxylin–eosin; original magnification, $\times 40$).

PTE-induced pulmonary hypoperfusion and DAD. Even in the same origin, another mechanism might induce DAD, but not pulmonary infarction in limited cases.

The precise mechanism of alveolar epithelial cell injury in DAD is unclear; however, inflammatory cytokines, neutrophils, and platelet aggregates are considered to play a central role.² Actually, DAD is observed in ischemia/reperfusion after lung transplantation and is possibly caused by excessive secretion of inflammatory cytokines.^{2,7,8} Moreover, Zagorski et al. showed that excessive secretion of proinflammatory chemokines and neutrophil recruitment into alveoli are induced by pulmonary arterial occlusion even in the absence of reperfusion.⁸ These studies suggest that pulmonary arterial hypoperfusion itself is sufficient to induce a proinflammatory response, and that inflammatory mediators might be responsible for PTE-related DAD. In the present case, relatively fresh organizing thrombus induced hypoperfusion of the segmental artery and might have caused DAD in the bilateral upper lung fields, which is an uncommon form of DAD.

Pulmonary artery aneurysm (PAA) might have a certain role in the underlying cause for extensive thrombosis. In the present case, the pulmonary trunk was dilated with chronic pulmonary thromboembolism (CPTE); however, the compensatory dilatation for thrombotic stenosis is unlikely as the cause because of low systolic tricuspid pressure gradient. A few cases of low-pressure PAA have recently been reported.^{9,10} Low-pressure PAA are presumed to be caused by a combination of intrinsic arterial wall weakness and hemodynamic stress (*i.e.* right ventricular dysfunction secondary to volume overload), and might be a source of CPTE and recurrent emboli due to blood stasis and endothelial dysfunction.^{9,11} In the present case, no other underlying cause for the thromboembolic events was observed, and the patient's history included chronic right ventricular failure; therefore, extensive PTE may have been induced by low-pressure PAA.

In conclusion, DAD localized in bilateral upper lung fields was revealed by autopsy in the present case. Moreover, the hypoperfused regions caused by the thromboembolism anatomically

coincided with the pulmonary lesion where DAD was identified. In our opinion, excessive proinflammatory mediators induced by hypoperfusion might cause DAD. However, DAD was seldom observed in the PTE cases. Therefore, further cases are necessary to clarify this causal association.

Conflict of interest

All the authors do not have any conflict of interest to declare with regard to contents of the manuscript.

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