Dyspnea with a slow growing mass in the breast

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A 48-year-old Japanese woman presented with a 6-month history of increasing exertional dyspnea and dry cough. She denied fevers, night sweats, or weight loss. She was a nonsmoker. Her medical history was unremarkable except for the fact that she had been aware of a mass in her left breast for more than two years.

On admission, her temperature was 36.7°C, her pulse was regular at 70 bpm, and her respiratory rate was 16 breaths/min. Her lungs were clear on auscultation, and cardiac examination revealed no murmur or gallops. No edema or varicosities were seen in her lower extremities. A hard mass measuring up to 3 cm in diameter was palpable in the left breast. Oxygen saturation was 94% on room air. Arterial blood gases on room air were pH 7.404, PaCO₂ 5.5 kPa (40.9 mmHg), PaO₂ 9.3 kPa (69.4 mmHg), and A-aDO₂ 4.2 kPa (31.5 mmHg). On laboratory examination, the complete blood count and basic chemistries were within the normal ranges. D-dimer was 2.5 (normal value <1.0) μg/ml, and thrombin-antithrombin III complex (TAT) was 7.0 (normal value ≤3.0) ng/ml. Fibrinogen and fibrinogen degradation products were within their normal ranges. The results of pulmonary function testing were: VC 1.86l, %VC 69.1%, FEV₁ 1.88l, FEV₁% 100.0%, DLCO 8.37 ml/mm/mmHg, and %DLCO 51.4%. The echocardiogram and electrocardiogram showed no findings of cardiac failure or pulmonary hypertension.

Chest radiography showed multiple nodular opacities in bilateral peripheral lung fields. Thin-section CT of the chest revealed multiple tiny nodules and centrilobular branching opacities in the subpleural regions of both lung fields (Figure 1a). Wedge-shaped or irregularly shaped nodular opacities suggesting pulmonary infarction were also seen in a subpleural distribution (Figure 1b). On contrast-enhanced CT of the mediastinal window setting, a well-enhanced mass in the left breast, up to 3 cm in diameter, was seen (Figure 1c). No mediastinal or hilar lymphadenopathy was identified.
There were no pleural effusions.

The patient underwent bronchoscopy that showed normal endobronchial mucosa. Bronchoalveolar lavage was not diagnostic; no organisms or malignant cells were seen on lavage fluid stains, and the fluid was sterile.

Transbronchial lung biopsy (TBLB) was performed from right B4. On pathology, scattered thrombi involving small pulmonary arteries and arterioles were seen.

Simultaneously, a ventilation-perfusion lung scintigram was performed. Multiple minute defects in the peripheral lung fields just under the pleura were seen on the perfusion-scintigram, while the ventilation-scintigram showed normal ventilation.
In view of these findings, what is your diagnosis?

Diagnosis: Pulmonary tumor thrombotic microangiopathy (PTTM)

Discussion

In addition to the multiple thrombi in small pulmonary arteries, there were abnormal cells in the arterial lumen. Therefore, the existence of underlying malignancy was suspected, but the primary lesion was unknown at that time. Therefore, a core needle biopsy of the breast mass was performed, and the diagnosis of invasive ductal carcinoma was made. Immunohistochemically, strong reactivity for estrogen receptors and progesterone receptors was seen in the breast and lung tissue. Re-evaluating the lung specimen in the light of this evidence, the small arteries and arterioles were obstructed with organized thrombi and proliferated intima (Figure 2). Findings of re-canalization were also seen.

On the 19th day of admission, anticoagulant therapy with warfarin sodium was started. The patient was scheduled to have anticancer or hormone therapy within a short time, but she refused to receive further treatment. Thus, she never returned to our hospital, and we are not aware of her outcome at present.

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare type of pulmonary tumor embolism (PTE) with tumor-related microangiopathic lesions in small pulmonary arteries and arterioles [1]. PTTM is detected in 0.9 - 3.3% of autopsies of patients with malignant tumors [1, 2]. Although PTTM is relatively well discussed in a number of reported cases, the diagnosis of PTTM was made overwhelmingly on autopsy [3-7], and cases with PTTM diagnosed antemortem, including our present case, are very rare [8, 9].

Acute or subacute progressive dyspnea with pulmonary hypertension is a typical
initial clinical presentation, and acute heart failure followed by severe pulmonary hypertension is the main cause of death [6, 8-11]. The current case presented with exertional dyspnea that had been progressive over a 6-month period. Slight hypoxemia was also seen, but findings of cardiac failure or pulmonary hypertension were not apparent. This may be because the extent and progression of the disease were mild and very slow, so that she visited our hospital before her general condition had become critical.

Because PTTM occurs mainly in small arteries and arterioles, cases with minute or almost normal radiographic findings are occasionally reported [3, 6]. Thin-section CT findings of PTTM have been previously described in only two case reports in the English literature; they had multiple small nodules and centrilobular branching opacities located predominantly just under the pleura [9, 10]. In cases with pulmonary hypertension, prominent pulmonary arteries are commonly detected [6, 9].

On histology, PTTM is characterized by widespread tumor emboli associated with fibrocellular intimal proliferation and thrombus formation in the small arteries and arterioles of the lungs [1]. The pathogenetic events start with metastases and adherence of small clusters of tumor cells to the pulmonary arterial system and adherence to the vascular endothelium at a microscopic level. Tumor emboli do not occlude affected vessels directly, but they induce local activation of coagulation, release of inflammatory mediators, and fibrocellular intimal proliferation, which lead to stenosis or occlusion of the vessel [1, 3, 5]. From this point of view, PTTM should be distinguished from tumor embolism [9], and to clarify the diagnosis, histological investigation is indispensable.

In a case of PTTM with an unknown primary malignant lesion, immunohistochemical staining with CK7, CK20, TTF-1, and hormone receptors has been reported to be useful in providing a clue to the nature of the primary lesion. It is also beneficial to confirm the relationship between the pulmonary findings and a known
malignancy [12, 13]. In the present case, pulmonary embolism appeared to be highly likely from the radiological findings, but immunological investigation of the tissue led to a prompt and accurate diagnosis.

In cases diagnosed antemortem, the diagnoses were made on the basis of surgical lung specimens or TBLB [8, 9]. Although TBLB is limited and not all abnormalities are present in the tissues obtained, TBLB can provide a clue to diagnose PTTM. Recently, pulmonary microvascular cytology using a pulmonary artery catheter has also been reported to be beneficial [14].

The standard treatment for PTTM has not yet been established [6]. The previously reported case that was diagnosed during life was successfully treated with aspirin, warfarin potassium, dexamethasone, and oral anticancer drug therapy [9], though it is not clear which had the best effect on the PTTM. Coagulation tends to be activated in patients with cancer [15], and as for the treatment of cancer-associated venous thrombosis, low molecular weight heparin (LMWH), which provides a good predictable anticoagulant response [16] is generally recommended so as to improve patient survival [17]. Thus, anticoagulant therapy may be effective in treating PTTM.

In summary, although PTTM is rare, it should be considered in the differential diagnosis of progressive dyspnea, even if malignancy is not apparent at the time of presentation. It is important to emphasize that TBLB can provide clues to make the diagnosis of PTTM.

**Key words**
pulmonary tumor thrombotic microangiopathy, breast cancer, transbronchial lung biopsy
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Figure legends

**Fig. 1.** (a and b) Thin-section CT images of the chest obtained using 1-mm collimation and lung window settings show multiple tiny nodules and centrilobular branching opacities in the subpleural regions of both lung fields (arrows). Wedge-shaped or irregularly shaped nodular opacities are also seen in a subpleural distribution (arrowhead). (c) Contrast-enhanced CT image of the chest obtained using 7-mm collimation and a mediastinal window setting shows a well-enhanced mass in the left breast, measuring up to 3 cm in diameter (arrow). No mediastinal or hilar lymphadenopathy is seen. There are no pleural effusions.

**Fig. 2.** TBLB specimens from right B4 show small pulmonary arteries. (a) The small muscular artery shows intimal thickening (hematoxylin and eosin stain (HE), x100) (insert, tumor cells in the arterial lumen (HE, x400). (b) The intimal thickening is highlighted by elastica van Gieson (EVG) stain (EVG, x100). (c) There is an arteriole showing re-canalization (EVG, x200). (d) One small arteriole has thrombus (EVG, x200).