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 fever, 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 >2 years.

On admission, her temperature was 36.7°C, her pulse was regular at 70 b.p.m., 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 her 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 mm Hg), PaO₂ 9.3 kPa (69.4 mm Hg), and A-aDO₂ 4.2 kPa (31.5 mm Hg). 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 the thrombin-antithrombin III complex was 7.0 (normal value ≤ 3.0) ng/ml. Fibrinogen and fibrinogen degradation products were within their normal ranges. The results of pulmonary function tests were: VC 1.86 liters, %VC 69.1%, FEV_{1.0} 1.88 liters, FEV_{1.0}% 100.0%, DLCO 8.37 ml/mm/mm Hg, and %DLCO 51.4%. Echo- and electrocardiograms disclosed no findings of cardiac failure or pulmonary hypertension.

Chest radiography showed multiple nodular opacities in both 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 (fig. 1a). Wedge-shaped or irregularly shaped nodular opacities suggesting pulmonary infarction were also seen in subpleural distribution (fig. 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 (fig. 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. Pathologically, 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?

Fig. 1. a, b Thin-section CT images of the chest obtained using 1-mm collimation: lung window settings disclose 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: 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.

Diagnosis: Pulmonary Tumor Thrombotic Microangiopathy

Fig. 2. Serial sections of the TBLB specimens from right B⁴ stained with hematoxylin-eosin (HE), elastic van Gieson (EVG) and estrogen receptor, respectively. **a** The small muscular arteries are obstructed with thrombi and intimal thickening. In the thickened intima, entrapped atypical cells are observed (arrow; HE). **b** EVG staining highlights two arteries with elastic laminae, which are obstructed by thrombi and intimal thickening. **c** Immunohistochemical staining for estrogen receptor showing weakly positive staining in the nuclei of atypical cells entrapped in the thrombus and intimal thickening (arrowheads). Scale bar = 100 μm.

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 and progesterone receptors was seen in the breast and lung tissue. Reevaluating the lung specimen in light of this evidence, the small arteries and arterioles were obstructed with organized thrombi and intima proliferation (fig. 2). Findings of recanalization were also seen.

On the 19th day after 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 with tumor-related microangiopathic lesions in small pulmonary arteries and arterioles [1]. PTTM is detected in 0.9–3.3% autopsies of patients with malignant tumors [1, 2]. Although PTTM is relatively well discussed in a number of case reports, the diagnosis of PTTM was made overwhelmingly on autopsy [3–7], and cases of PTTM

with antemortem diagnosis, 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 disease extent and progression were mild and very slow, i.e. she visited our hospital before her general condition had become critical.

Because PTTM occurs mainly in small arteries and arterioles, cases showing minute or almost normal radiographic findings are occasionally reported [3, 6]. Thin-section CT findings of PTTM have been described in only 2 case reports in the English literature previously; they had multiple small nodules and centrilobular branching opacities located predominantly just under the pleura [9, 10]. In cases of pulmonary hypertension, prominent pulmonary arteries are commonly detected [6, 9].

Histologically, 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 directly occlude affected vessels, but they induce local activation of coagulation, release of inflammatory mediators, and fibrocellular intimal proliferation, leading 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 case of PTTM with unknown primary malignant lesion, immunohistochemical staining for CK7, CK20,

TTF-1, and hormone receptors has been reported to be useful in providing a clue regarding 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 immunohistochemical study 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 other previously reported case 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 PTTM. Coagulation tends to be activated in patients with cancer [15], and similar to the treatment of cancer-associated venous thrombosis, low-molecular-weight heparin, which provides a good predictable anticoagulant response [16], is generally recommended in order 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 regarding the diagnosis of PTTM.

Key Words

Breast cancer • Pulmonary tumor • Thrombotic microangiopathy • Transbronchial lung biopsy

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