CASE REPORT

How to Diagnose and Treat Pulmonary Tumor Thrombotic Microangiopathy

Hiroshi Onoda,1,2 MD, Teruhiko Imamura,1 MD, Kyoko Inao,3 MD and Koichiro Kinugawa,1 MD

Summary

We report here a 70-year-old female patient with a history of breast cancer who presented with dyspnea that had lasted for 2 weeks following a long-distance trip by bus. She was at first suspected of having a pulmonary embolism given the typical presentation, elevated D-dimer level, and enlargement of the right-side heart. However, her systemic condition deteriorated despite the initiation of anti-coagulation therapy. Given the absence of a major thrombus in the pulmonary major arteries but multiple low perfusion lesions in the periphery of the lungs, refractoriness to conventional therapy, an increase in tumor markers, and anaplastic cells demonstrated by aspiration cytology from the pulmonary artery, we diagnosed her as pulmonary tumor thrombotic microangiopathy (PTTM). She died on day 23 due to respiratory failure despite administration of inotropes and prostaglandin I2. The patient had an obvious history of malignancy, but we should emphasize that PTTM can develop even in patients with early-stage or completely cured malignancies. Although an early and definite diagnosis of PTTM is currently challenging, an optimal diagnostic and therapeutic strategy is warranted.

Key words: Anti-coagulation, Pulmonary hypertension, Pulmonary embolism

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare disease proposed by Herbay and colleagues in 19901) that is characterized by rapidly progressive pulmonary hypertension and hypoxia in patients with a history of malignancy.2) The first presentation might be similar to pulmonary embolism, whereas a prognosis of PTTM is much more serious with only days or weeks of survival. In this report, we present a patient with a history of breast cancer, in whom the differential diagnosis between PTTM and pulmonary embolism was difficult.

Case Report

A 70-year-old female patient was admitted to our institute presenting with progressive dyspnea for the previous two weeks following a long-distance trip by bus. She had right breast cancer with a history of surgery and chemotherapy with paclitaxel 4 years previously and bone metastases demonstrated by positron emission tomography one year ago. She had been coming to our hospital for chemotherapy for metastatic breast cancer. The pathological diagnosis was invasive ductal carcinoma.

Her blood pressure was 149/92 mmHg and her heart rate was 77 bpm. Blood gas at room air condition showed 33 torr of partial pressure of carbon dioxide and 54 torr of partial pressure of oxygen. The saturation of percutaneous oxygen was 99% under 6 L facial mask support. D-dimer was 24 μg/mL, fibrin/fibrinogen degradation product was 83 μg/mL, and fibrin monomer complex was > 150 μg/mL (Table). She had no chest pain or bilateral leg edema.

Chest X-rays showed slight cardiomegaly and the existence of a central venous port located on the right subclavian vein (Figure 1A). Electrocardiography showed normal sinus rhythm and a small q wave and inverted T wave in lead III (Figure 1B). Left ventricular end-diastolic diameter was 38 mm with an ejection fraction of 75%, whereas dilatation of the right-side heart with a left-sided shift of interventricular septum was observed by transthoracic echocardiography. Enhanced computed tomography showed no signs of deep venous thrombus or thrombus in major pulmonary arteries, whereas multiple sub-segmental low-perfusion lesions were observed at bilateral peripheral lung fields by the lung perfusion scintigraphy (Figure 2).

We suspected pulmonary microvascular thrombosis and therefore started continuous heparinization. Nevertheless, the desaturation did not improve. Pulmonary angiography showed no obstruction of the major pulmonary artery (Figure 3). Right heart catheterization showed a right ventricular end-diastolic pressure of 14 mmHg, mean pulmonary artery pressure of 52 mmHg, pulmonary capillary wedge pressure of 16 mmHg, and cardiac index of 1.9 L/minute/m². Tumor markers including CEA (from 15 to
110 ng/mL), CA 15-3 (from 41 to 305 U/mL), and ICTP (from 5.8 to 13.5 ng/mL) increased during the preceding 2 months. Aspiration cytology obtained from the pulmonary artery showed anaplastic cells (Figure 4). Based on a diagnosis of PTTM associated with breast cancer, we started a continuous infusion of inotropes and prostaglandin I2. Unfortunately, the patient died on day 23 due to respiratory failure.

**Discussion**

**Diagnosis of PTTM:** Dyspnea as an acute onset following the long-distance trip and a history of malignancy led us to suspect deep vein thrombosis and pulmonary embolism. However, we ultimately diagnosed her as PTTM considering the absence of major arterial thrombosis, refractoriness to conventional therapies, an acute increase in tumor markers, and anaplastic cells obtained from the pulmonary artery.

PTTM, a disease with acute deoxygenation and pulmonary hypertension in patients with malignancy, was first proposed in 1990 by Herbay, et al.**1** PTTM should be clearly distinguished from tumor embolism. Disseminated tumor cells attached on endothelial cells of the pulmonary micro-vasculature emit cytokines, such as vascular endothelial growth factors and fibroblast growth factors, which facilitate the proliferation of fibroblasts and secondary thrombus formation, leading to diffuse injury of the pulmonary micro-vasculature.**3** The major origin of PTTM is adenocarcinoma, dominantly gastric cancer. Most PTTM develops in patients with advance-staged malignancies, while some are found in patients with early-stage or completely cured malignancies.**1,2,4** Given the acute course and difficulty to diagnose, most of the definitive diagnoses are made by autopsy.**5** Herbay, et al reported that 21 patients (3.3%) out of 630 consecutive autopsy cases with carcinoma were diagnosed with PTTM.**1**

For a definitive diagnosis, the existence of malignant cells should be confirmed, although it is often challenging given deteriorated respiratory function. A relatively less
Figure 2. Lung perfusion scintigraphy showing multiple sub-segmental low-perfusion lesions at the peripheral bilateral lung fields (see arrows).

Figure 3. Pulmonary angiography did not show abrupt vascular narrowing or obstruction of the major pulmonary artery.

Figure 4. Cytology with Periodic acid-Schiff stain (A) and Giemsa stain (B). Cells were aspirated from the pulmonary artery. Anaplastic cells with multinuclear morphology can be seen (arrows).
invasive procedure would be aspiration cytology obtained from the pulmonary artery via right heart catheterization, with 80-88% sensitivity and 82-94% specificity, as we did in this case. In this patient, we distinguished PTTM from a tumor embolism, which does not cause such a rapid progression of pulmonary hypertension that cannot be explained by focal thrombotic occlusion of the pulmonary vessel, as this patient experienced. Nevertheless, an autopsy would have been required for a definitive diagnosis of PTTM.

**Treatment of PTTM:** Several treatments have been proposed for PTTM, although there is no single established therapeutic strategy thus far. Thrombolytic and anti-coagulation therapies are conventional and usually performed, although they are not effective in most cases. Chemotherapies for the original malignancy might be effective. Other authors have proposed steroid therapy to inhibit the inflammatory reaction between disseminated tumor cells and the pulmonary micro-vasculature.

Several molecular targeted agents or anti-pulmonary hypertension agents have been reported, including imatinib (an inhibitor of platelet-derived growth factor receptor) and bevacizumab (an inhibitor of vascular endothelial growth factor), although they are off-label uses. We could not perform more intensive therapies beyond conventional anti-coagulation therapy due to the extensive deterioration of the systemic conditions. An early diagnosis of PTTM, although often difficult, might have let us select one of the more intensive therapies described above. Our patient had an obvious history of malignancy, however, we should emphasize that PTTM can develop even in patients with early-stage or completely cured malignancies. Further studies are warranted to construct an optimal therapeutic strategy for PTTM.

**Disclosure**

**Conflicts of interest:** There is no conflict of interest related to this manuscript.

**References**