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Case Report

A Case of Recurrent Breast Cancer Identified by Pulmonary Tumor Thrombotic Microangiopathy

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Keywords
Pulmonary tumor thrombotic microangiopathy · Breast cancer · Recurrence · Dyspnea

Abstract
Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare, cancer-related, pulmonary complication that causes hypoxia and pulmonary hypertension. We report on a 42-year-old woman who was diagnosed with recurrent breast cancer that was detected due to the presence of PTTM. Eleven months after surgery for heterochronous bilateral cancer of the left breast, she developed progressive dyspnea but computerized tomography showed no pulmonary thromboembolism, and a transthoracic echocardiography revealed mild pulmonary hypertension. She was diagnosed with PTTM by cytology from pulmonary artery catheterization and perfusion lung scintigraphy. Also, the patients complained of back pain after admission, bone scintigraphy showed multiple bone metastases. Despite the early diagnosis of PTTM, her platelet count decreased, her performance status rapidly deteriorated, and her dyspnea worsened. Thus, we could not treat her with chemotherapy. She died due to respira-

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tory failure 19 days after admission. To the best of our knowledge, this is the first report of recurrent breast cancer identified by the manifestation of PTTM. Although PTTM is a rare phenomenon, it should be considered in the differential diagnosis of acute dyspnea or pulmonary hypertension in patients with breast cancer. Furthermore, upon diagnosis, the patient should be referred to a cardiologist as soon as possible.

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Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare, cancer-related, pulmonary complication that causes hypoxia, pulmonary hypertension, and heart failure. It rarely occurs in patients with metastatic or recurrent breast cancer. However, to the best of our knowledge, there are no reports of PTTM as the first symptom of recurrent breast cancer.

Case Report

A now 42-year-old woman underwent resection of the right breast and axillary lymph node dissection, and subsequently received the following adjuvant chemotherapy: CAF (cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, and fluoropyrimidine 500 mg/m^2 for 6 cycles) and goserelin followed by UFT (uftoral, ftorafur, and tegafur-uracil) for 2 years. Then, 12 years after surgery, she noticed a mass in her left breast and was subsequently diagnosed with heterochronous bilateral breast cancer. Mastectomy was performed on the left breast, and her axillary lymph nodes were also dissected. The histology of the left breast showed scirrhous carcinoma, which included spindle cell carcinoma, and all nodes were positive (21/21). She received adjuvant chemotherapy that consisted of 75 mg/m^2 docetaxel and 600 mg/m^2 cyclophosphamide for 4 cycles, and then radiation therapy for 5 weeks. Routine follow-up, which included a blood examination every month and lymph node ultrasound every 3 months, detected no recurrence of the tumor.

Eleven months postoperatively, she went to her local hospital due to a 5-day history of dyspnea. X-ray examination and electrocardiography revealed no abnormalities in her chest or heart. However, the dyspnea worsened and she returned 3 days later. Since her SpO_2 was 80% (room air), she was admitted to another hospital. Computerized tomography (CT) showed no pulmonary thromboembolism (Fig. 1). Furthermore, a transthoracic echocardiogram showed normal left ventricular systolic function (left ventricular ejection fraction, 70%). Right ventricular and atrial enlargement suggested mild pulmonary hypertension with an estimated right ventricular systolic pressure of 47 mm Hg. Therefore, pulmonary artery catheterization was performed. Pulmonary arterial pressure was measured at 32/22 (27) mm Hg, and the cardiac index was 2.40 L/min/m^2. Wedged pulmonary artery blood cell sampling showed histologically malignant cells, which led to the diagnosis of PTTM (Fig. 2).

The patient was then transferred to our hospital. On admission, her body temperature was 36.4°C, blood pressure 99/66 mm Hg, heart rate 85 beats per min, and SpO_2 94% (nasal O_2 1L). Electocardiography showed only sinus tachycardia, and a chest radiogram revealed no significant abnormalities. Arterial blood gas analysis in 2 L nasal O_2 revealed hypoxemia: pH 7.430, pCO_2 41.0 mm Hg, pO_2 70.7 mm Hg, HCO^{3-} 26.6 mmol/L, and base excess 2.1 (room air). Further laboratory examination showed the following: white blood cells 5,500/mm^3 with normal differential counts, hemoglobin 12.9 g/dL, platelets 60,000/mm^3, total bilirubin 0.8 mg/dL (normal, 0.4–1.5 mg/dL), aspartate aminotransferase 60 IU/L

(normal, 13–30 IU/L), alanine aminotransferase 15 IU/L (normal, 7–23 IU/L), lactate dehydrogenase 1,186 IU/L (normal, 124–222 IU/L), C-reactive protein 1.24 mg/dL (normal, 0–0.14 mg/dL), and B-type natriuretic peptide 32.8 pg/mL (normal, 0–19.5 pg/mL). A blood coagulation test showed that D-dimer was elevated to 10.15 μg/mL (normal, <0.49 μg/mL), and fibrin degradation products were also elevated to 31.43 μg/mL (normal, <10 μg/mL), suggesting a micro-thromboembolism disease.

Perfusion lung scintigraphy showed multiple small peripheral perfusion defects in both lungs on the 7th day of admission (Fig. 3). An ultrasound of the heart showed normal left ventricular systolic function (left ventricular ejection fraction, 60.6%). Moderate pulmonary hypertension was observed with an estimated right ventricular systolic pressure of 51 mm Hg. Pulmonary artery catheterization was performed 5 days after the last examination. Pulmonary artery pressure was measured at 54/24 (36) mm Hg. The results of arterial blood gas analysis in room air revealed further hypoxemia: pH 7.477, pCO_2 36.0 mm Hg, pO_2 54.9 mm Hg, HCO^{3-} 26.6 mmol/L, and base excess 2.8 (room air). The patient also complained of back bone pain. Bone scintigraphy revealed that she had multiple bone metastases.

Treatment with chemotherapy was planned, but her platelet count decreased, her performance status rapidly deteriorated, and her dyspnea worsened. She died due to respiratory failure 19 days after admission. Since her family refused an autopsy, we could not obtain a histological sample of the lung.

Discussion

PTTM is a rare, cancer-related, pulmonary complication which triggers the development of hypoxia, pulmonary hypertension, and heart failure. However, the ante-mortem diagnosis of PTTM is very difficult. Von Herbay et al. [1] reported that 21 patients in 630 consecutive autopsy cases were diagnosed with PTTM (3.3%). According to their findings, all 21 patients with PTTM had carcinomas with distant metastasis, and 19 had adenocarcinomas in various organs. The most frequent cancer associated with PTTM was gastric cancer (11 of 41 cases, 26.8%). In contrast, PTTM was less frequent in breast and other cancers. They reported 2 of 72 cases (2.8%) with breast cancer. In another report, Okubo et al. [2] described 6 of 37 patients who died of gastric carcinoma associated with PTTM (16.2%). There are few cases of PTTM being diagnosed while the patients are alive. Fukada et al. [3, 4] reported 2 patients with PTTM who received chemotherapy for metastatic breast cancer. However, to our knowledge, there are no reports of recurrent breast cancer being diagnosed by the manifestation of PTTM.

In spite of the recent developments in morphometric and immunohistochemical analyses, the mechanism of PTTM remains unclear. Pathologically, PTTM is caused by the following: an obstruction of pulmonary arterioles by microembolisms caused by tumor cells, thrombus formation that is induced by the activation of thrombotic cascades on the surface of tumor embolisms, and the abnormal proliferation of vascular endothelial cells caused by growth factors that are induced by tumors [5]. Okubo et al. [2] reported a significant negative correlation between pulmonary arterial diameter and stenosis rate in 4 of 6 cases. They also performed a morphometric analysis of the pulmonary arteries and suggested that pulmonary arterial remodeling induced by carcinoma cell adhesion to the endothelium affects the status of pulmonary hypertension.

The clinical diagnosis of PTTM is extremely difficult [2, 6], and a standard diagnostic method for PTTM has not been established. In most cases, there is no evidence of pulmonary embolism on enhanced CT; however, ventilation-perfusion scanning may be useful for diagnosis. Regarding lung scintigraphy, multiple, subsegmental, mismatched defects are characteristic features of PTTM. In the future, pulmonary angiography may become the gold standard method for detecting PTTM. In our case and others, both pulmonary artery catheterization and wedged pulmonary arterial blood cell sampling have been used to diagnose PTTM [3, 4, 6, 7].

A standard treatment for PTTM has also not been established. Fukada et al. [3, 4] suggested that imatinib, a tyrosine kinase inhibitor of the PDGF receptor, may have led to the regression of pulmonary hypertension and pulmonary artery remodeling in PTTM. Miyano et al. [8] presented a PTTM patient with favorable clinical outcomes after a combination of imatinib and chemotherapy. They treated a patient who was diagnosed with distal gastrectomy 3 years prior using a single corticosteroid, an anticoagulant, and an oral anticancer drug. The patient received 0.05 mg/kg dexamethasone, 1.5 mg warfarin potassium, and 100 mg aspirin once a day. In addition, S-1 (Taiho Pharmaceutical Company Limited, Tokyo, Japan), a 4th-generation fluoropyrimidine that contains tegafur, 5-chloro-2,4-dihydroxypyridine (gimeracil), and potassium oxonate (oteracil), was administered orally twice daily for 21 consecutive days every 5 weeks at a dose of 35 mg/m^2 [9]. Cisplatin was planned to be given intravenously on day 8, but it was withdrawn due to her poor performance status. After 3 cycles of chemotherapy, the patient's symptoms disappeared, and serum VEGF and D-dimer concentrations decreased. Six months later, their patient appeared healthy without any respiratory symptoms.

However, the efficacy and safety in combining imatinib and other chemotherapies for the treatment of metastatic breast cancer have not been established, and their effects remain unclear. A report from a multi-institutional phase 2 study examined imatinib, mesylate, and gemcitabine for first-line treatment of advanced pancreatic cancer [10]. All patients received the following therapies in a 21-day cycle: 1,200 mg/m^2 gemcitabine was administered on days 3 and 10; 400 mg imatinib was administered orally on days 1–5 and 8–12. A total of 44 patients were enrolled, and the median number of cycles completed was 3. Common adverse effects included neutropenia, nausea, anemia, and fatigue. Fifty percent of the patients had grade 3 or higher thrombocytopenia, and 17% had grade 3 or higher thrombocytopenia. Significant nonhematological toxicity related to treatment were grade 3 or higher dehydration in 9%, grade 3 or higher rash in 9%, grade 3 or higher fatigue in 6%, grade 3 or higher nausea in 6%, and grade 3 or higher renal failure in 2%. Clinically significant grade 1 and 2 toxicities included edema and rash in 4% and 6%, respectively. Overall, half of the patients required dose reduction.

In our case, since the patient's pulmonary hypertension was mild, we reasoned that there would be no merit in administering imatinib. We intended to treat her with chemotherapy; however, her respiratory condition and performance status worsened rapidly, and she developed grade 3 thrombocytopenia. Despite the early detection of PTTM, we could not administer effective treatments to the patient.

Conclusion

To the best of our knowledge, this is the first report of recurrent breast cancer detected by the manifestation of PTTM. PTTM is a fatal, cancer-related, pulmonary complication due

to its extremely rapid progression. Although PTTM is a rare phenomenon, it should be considered in the differential diagnosis of acute dyspnea or pulmonary hypertension in patients with breast cancer. Furthermore, upon diagnosis, the patient should be referred to a cardiologist as soon as possible.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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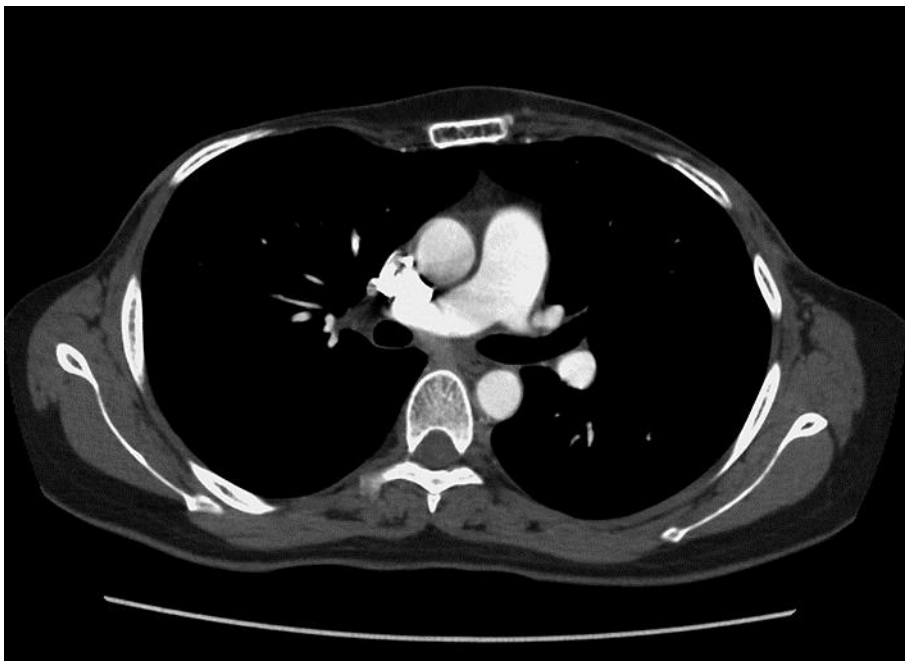

Fig. 1. Enhanced computed tomography showed no evidence of pulmonary thromboembolism.

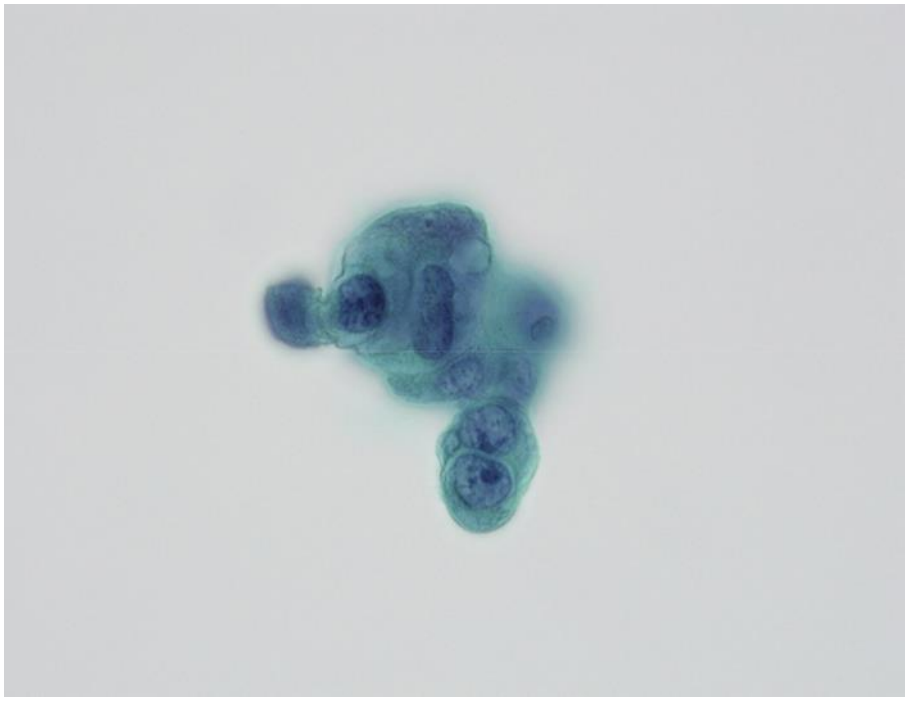

Fig. 2. Cytology of wedged pulmonary artery blood cell sampling proved the presence of adenocarcinoma cells (Papanicolaou stain). There were clusters of malignant epithelial cells. Focal glandular structures were present, and the nuclear/cytoplasm ratio was high. The cells had hyperchromatic nuclei, prominent nucleoli, and cell mutual inclusion.

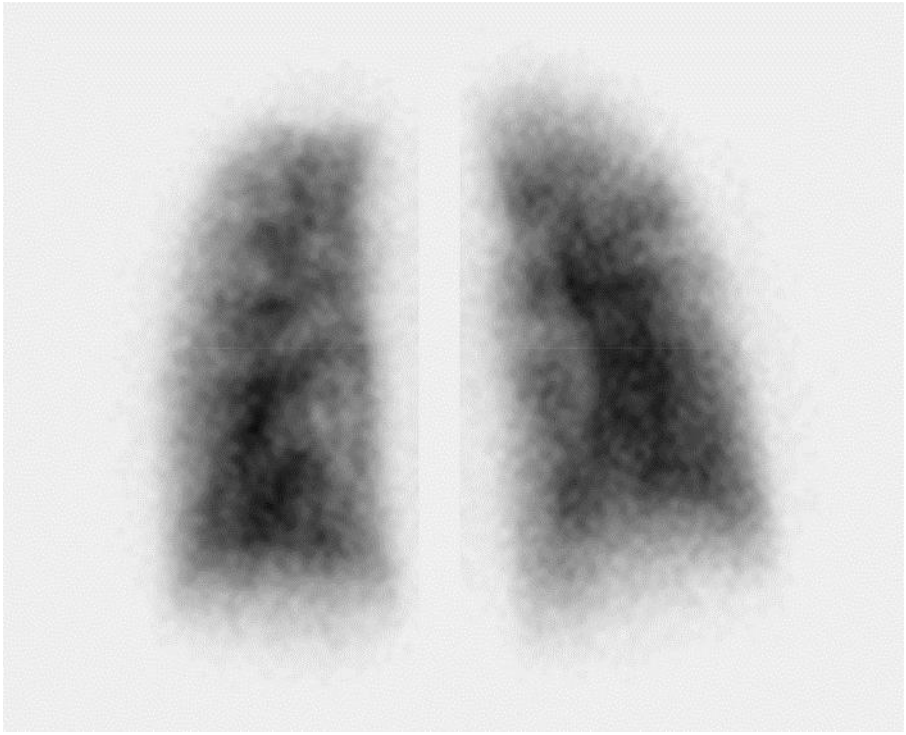

Fig. 3. Perfusion lung scintigraphy showed multiple small peripheral perfusion defects in both lungs.