Antemortem Diagnosis of Pulmonary Tumor Thrombotic Microangiopathy in a Patient with Recurrent Breast Cancer: An Autopsy Case Report

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Objective: Herein, we report a case of a patient with recurrent breast cancer who was diagnosed antemortem with pulmonary tumor thrombotic microangiopathy (PTTM) using wedge aspiration cytology of the pulmonary artery after breast cancer surgery.
Case summary: The patient was a 50-year-old woman who underwent mastectomy and axillary lymph node dissection for stage IIIA (T3N2M0) triple-negative left breast cancer. Postoperative follow-up was performed with radiotherapy and anticancer chemotherapy. Seventeen months after the surgery, the patient was hospitalized for right heart failure and diagnosed with pulmonary arterial hypertension. The patient was diagnosed with PTTM following the detection of malignant cells in the pulmonary artery using wedge aspiration cytology. Anti-pulmonary hypertension therapy was administered; however, the patient did not respond and died 26 days after admission.
Autopsy revealed multiple microscopic tumor emboli in the pulmonary artery. In portions of the pulmonary artery without embolization, fibro-cellular intimal hyperplasia and stenosis were observed. Tumor embolism was expressed for CK7+/CK20-, consistent with the primary breast cancer.
Discussion: Since the primary pathophysiology of PTTM entails narrowing due to fibro-cellular intimal hyperplasia rather than multiple tumor thrombi, the efficacy of chemotherapy combined with vasodilators is discussed.

Key words: Breast cancer, Pulmonary tumor thrombotic microangiopathy, Pulmonary tumor embolism, Pulmonary wedge aspiration cytology, Autopsy

INTRODUCTION

Pulmonary tumor thrombotic microangiopathy (PTTM) is a condition that was first described by von Herbay *et al*. in 1990 [1]. It is often characterized by rapid progression of respiratory failure due to pulmonary arterial hypertension caused by tumor thrombi in the micro-vessels of the pulmonary artery, and its prognosis remains poor. Pathologically, PTTM is characterized by tumor thrombi and fibro-cellular intimal hyperplasia in the peripheral pulmonary artery. With regard to clinical manifestations, it is essential to differentiate between chronic thromboembolic pulmonary hypertension and PTTM. While the former progresses at a gradual rate, the latter progresses rapidly, often within weeks.

Approximately 90% of patients with PTTM die within a month of diagnosis [2], highlighting the importance of early diagnosis. Nevertheless, it is often challenging to provide an antemortem diagnosis of PTTM. Although a definitive diagnosis requires cytological and histological examinations, the diagnosis could be often established only by an autopsy. Because invasive tests, such as computed tomography (CT)-guided lung, transbronchial lung, and surgical lung biopsies, are not feasible because of poor general conditions of the patients. Diagnosis based on aspiration cytology of the pulmonary artery has recently been reported [3, 4].

Herein, we report a case of a patient with recurrent breast cancer who was diagnosed antemortem with PTTM using pulmonary wedge aspiration cytology.

CASE PRESENTATION

A 50-year-old premenopausal woman diagnosed with left breast cancer underwent mastectomy and axillary lymph node dissection. The results of the postoperative pathological examination from other hospital were as follows: breast cancer stage IIIA (T3N2M0), triple-negative invasive ductal breast cancer (papillo-tubular carcinoma with micropapillary component), and a ki67 rate of 70%.

As postoperative treatment, the patient was administered radiation therapy and chemotherapy (four cycles

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Table 1 laboratory data on admission

			Alb	3.6	g/dl	CK	200	U/l
WBC	8900	/μl	AST	203	U/l	Total- Bilirubin	2	mg/dl
RBC	4.99	10^6/μl	ALT	209	U/l	Direct-Bilirubin	0.4	mg/dl
Hb	14.5	g/dl	LDH	1373	U/l	CRP	0.537	mg/dl
Ht	42.7	%	ALP	697	U/l	NH3	29	μg/dl
Plt	8.5	10^4/μl	γ-GTP	313	U/l	BNP	1210	pg/ml
APTT	29	sec	Cre	0.96	mg/dl	cardiac troponin T	0.05	ng/ml
PT	15.1	sec	BUN	41	mg/dl	AFP	1.3	ng/mL
INR	1.36		Na	143	mEq/dl	PIVKA-2	18	mAU/mL
D-dimer	21	μg/ml	K	5.3	mEq/dl	CEA	5.4	ng/mL
			Cl	108	mEq/dl	CA15-3	665.3	U/l

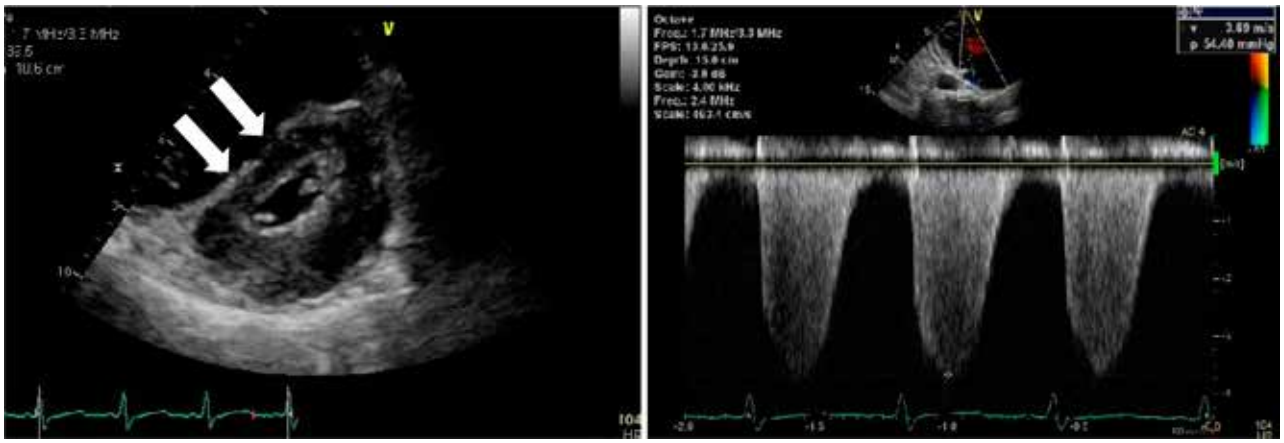

Fig. 1 Echocardiography on admission.
Echocardiography strongly suggests a flattening of the interventricular septum (white arrows), dilation of the inferior vena cava, tricuspid regurgitation pressure gradient of 54 mmHg, and pulmonary arterial hypertension.

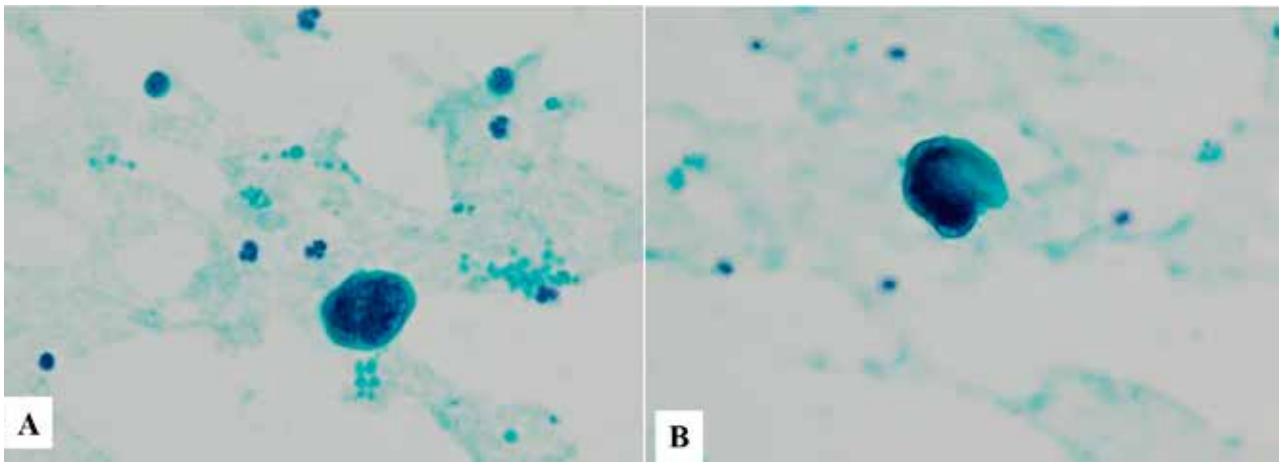

Fig.2 Aspiration cytology finding from the swanz-ganz catheter.
(A) Cytologically, a single neoplastic large cell of cleaved nuclei with high N/C ratio was shown. (Papanicolaou staining, Magnification × 400)
(B) Note the hyperchromatic pattern of bizarre and eccentric nuclei. (Papanicolaou staining, Magnification × 400)

of epirubicin plus cyclophosphamide and four cycles of docetaxel). Subsequently, the patient visited our hospital for treatment every three months.

Despite the absence of abnormalities 14 months postoperatively, the patient visited our hospital for progressive dyspnea and difficulty walking 17 months after the surgery and was immediately hospitalized for hypoxemia and abnormal hepatic function disorder. The patient's vital signs and general condition on admission were as follows: clear consciousness; performance status 3; pulmonary hypertension World Health Organization functional class IV; height, 162 cm; weight, 49 kg; body temperature, 36.2 °C; blood pressure, 147/109 mmHg; pulse rate, 111/min; respiratory rate, 24/min; and SpO2, 95% (3 L/min, nasal cannula). Based on the following arterial blood gas analysis results — oxygen inhalation < 5 L/min (pH, 7.396, PaO2, 97.8 mmHg; PaCO2, 24.7 mmHg; HCO3, 14.3 mEq/L; and BE, -8.1 mmol/L). Blood tests revealed liver dysfunction, prolonged coagulation, and elevated

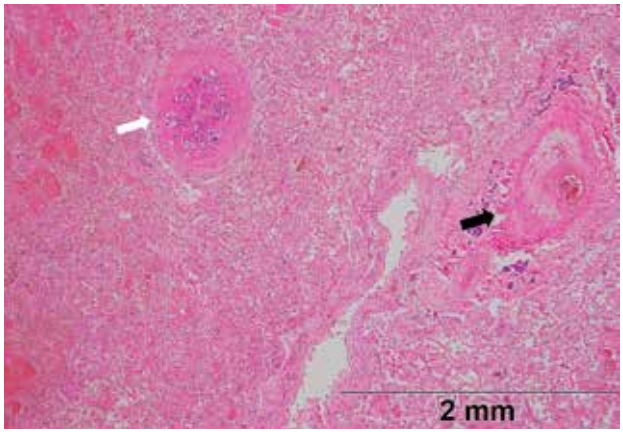

Fig.3 Low power view of pathological pulmonary finding (H.E staining).
Both cancerous occlusion (white arrow) and stenosis of thickened wall in the vessel (black arrow) could be simultaneously observed in the same field.

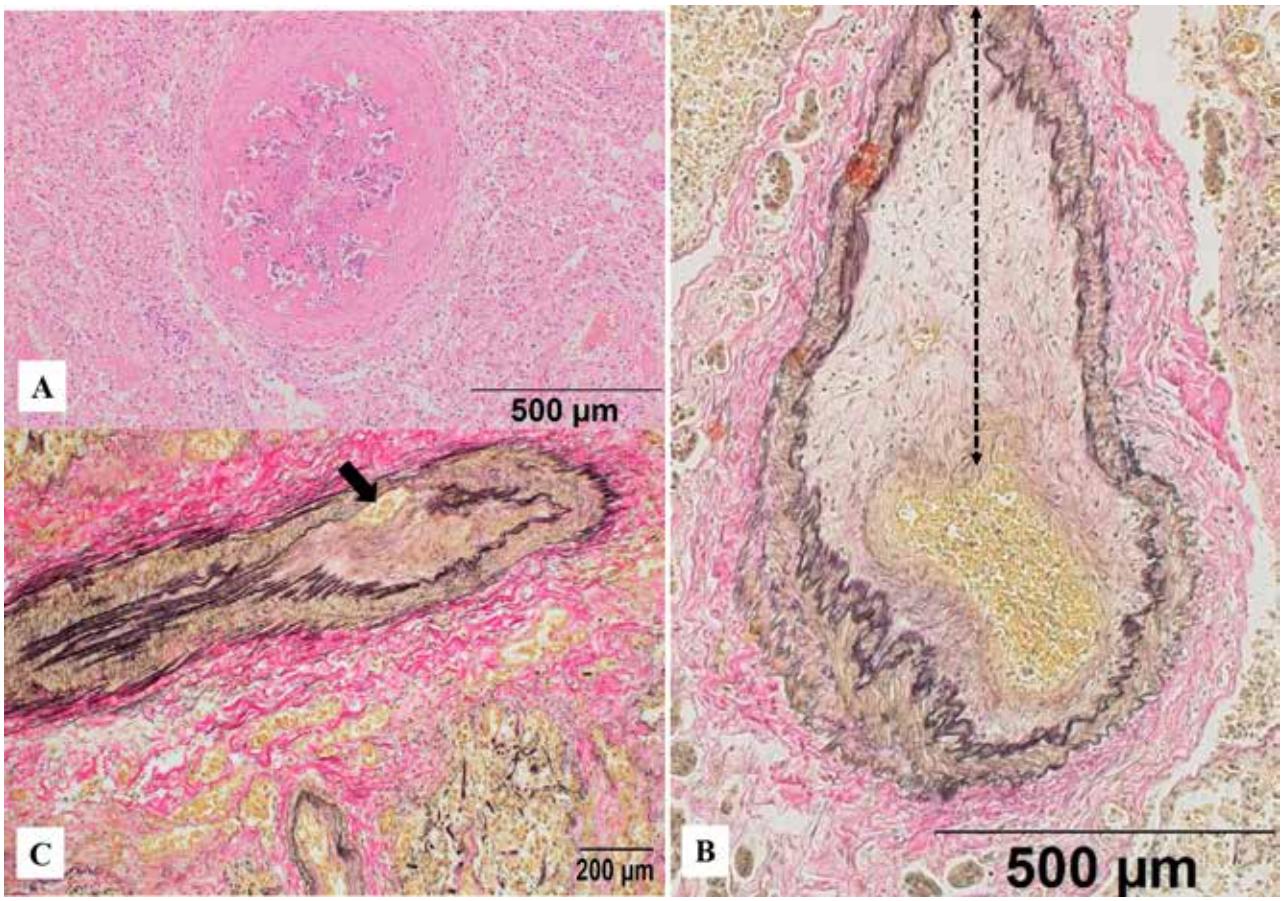

Fig. 4 High power view of pathological pulmonary artery. (A, H.E staining, B, C, EVG staining)
(A). As shown in high power view of Fig.3 (white arrow), there was shown small nests of cancer cells with cleft in the vessel, which could be estimated tumor emboli with necrosis.
(B) As shown in high power view of Fig.3 (black dot arrows), there was shown markedly fibrous intimal hyperplasia of vessel wall.
(C) Note the stenosis (black arrow) in the lumen of blood vessel, which indicates re-canalization from complete occlusion by non-tumorous thrombosis.

plasma brain natriuretic peptide and CA 15-3 levels (Table 1). Lung metastasis, pneumonia, and thrombus were not shown by enhanced CT scan.

It also revealed compression of the left ventricle due to right ventricular enlargement, suggesting pulmonary hypertension. Echocardiography revealed flattening of the interventricular septum, dilation of the inferior vena cava, and elevated tricuspid regurgitation pressure gradient of 54 mmHg, strongly suggesting the existence of pulmonary arterialhypertension (Fig. 1). Since right heart catheterization revealed an elevated mean pulmonary artery pressure of 37 mmHg and low pulmonary artery wedge pressure, the patient was diagnosed with pulmonary arterial hypertension.

The patient also suffered from organ failure due to right heart failure. The platelet count decreased rapidly from 100,000 to 29,000/μL within 24 h of admission owing to disseminated intravascular coagulation.

The patient exhibited acute worsening of respiratory insufficiency with a hypercoagulative state and absence of embolism in major pulmonary arteries on enhanced CT scans. Therefore, we performed pulmonary wedge

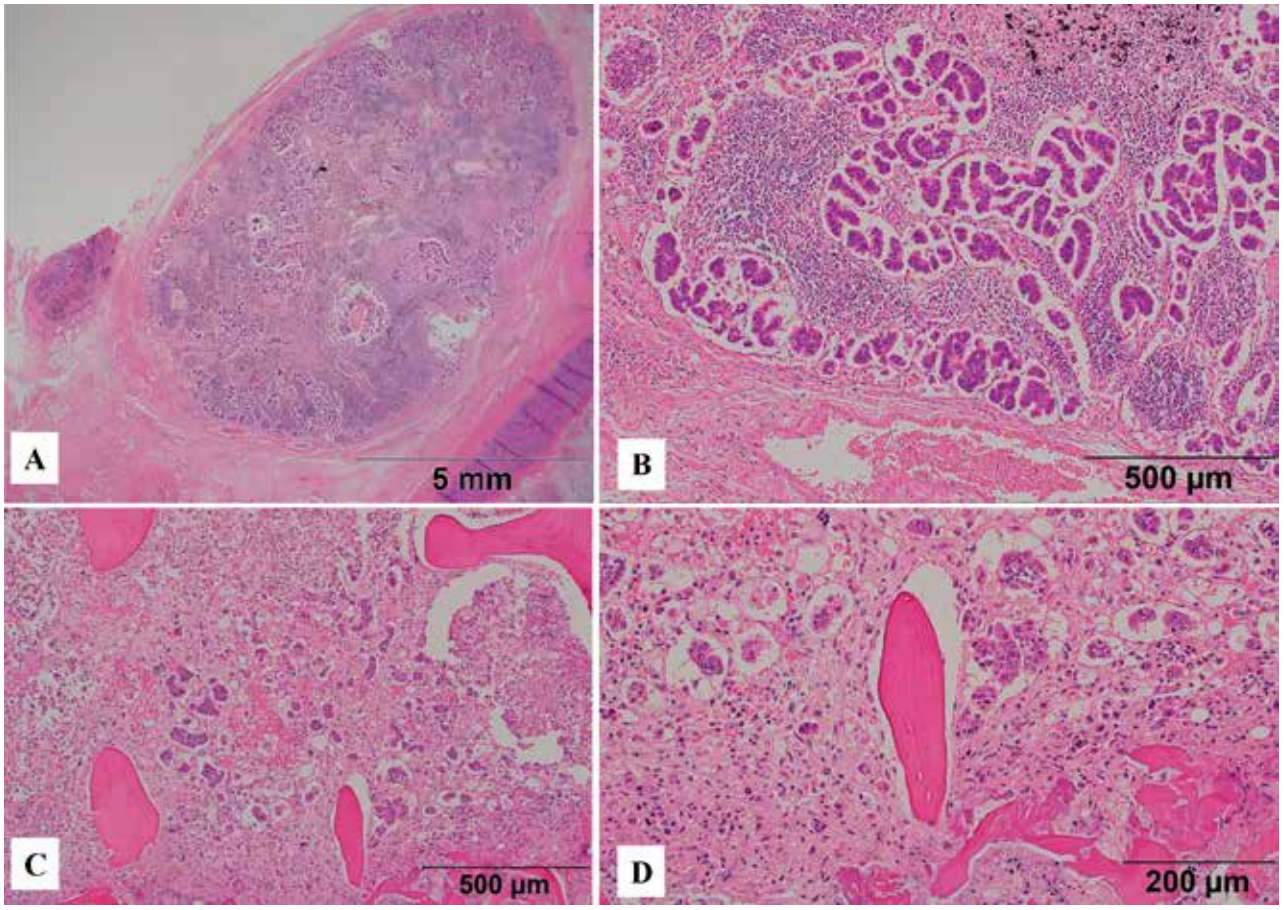

Fig. 5 Histopathological examination of hylar lymph nodes (A, B) and bone marrow (C, D) by hematoxylin and eosin staining.
(A)Microscopically, numerous cancer cell were occupied in the sinus node of lymphnode near the hyaline cartilage.
(B)Note an aggregation of small cancer nest with cleft. The feature was consistent with invasive micropapillary carcinoma of the breast.
(C)Microscopically, numerous cancer cells were occupied in the bonemarrow.
(D)Note invasive micropapillary cancer cells with cleft, which were the same morphological feature of Fig. 4A and 4B.

aspiration cytology trapped from the swan-ganz catheter during the second-time heart catheterization two days after the admission and were cytologically found the presence of a few malignant cells with enlarged nuclei and increased chromatin content (Fig. 2A, B). Based on the medical history of breast cancer, the patient was clinically diagnosed as PTTM. As the patient could not tolerate chemotherapy due to poor general conditions, the patient did not respond to the treatment and died 26 days after the admission.

The patient, who had rapidly developed fatal progression of respiratory failure, autopsy was performed with the consent of the family.

The pathological autopsy revealed severe systemic jaundice and edema. Most lung areas, except for the hilum, exhibited signs of necrosis and hemorrhage as well as the presence of hemorrhagic infarction. Multiple microscopic tumor emboli were also detected in the pulmonary artery (Fig3, White arrow, Fig4A), and stenosis by fibro-cellular intimal hyperplasia without embolization was observed in the blood vessels (Fig. 3 black arrow, Fig. 4B dot arrows). post-recanalization findings of the vascular lumen with severe stenosis were also obtained (Fig. 4C black arrow). The tumor thrombus was triple-negative (CK7+/CH20-) and were similar pattern to that of breast cancer. A few intravascular invasions were also detected in major organs, such as the heart, liver, stomach, jejunum, colon, spleen, and bilateral adrenal glands. Numerous lymph node metastases in the thoracic and abdominal cavities as well as cancer cell invasions of the lymphatic vessels in the lungs were observed (Fig. 5A, B). However, breast cancer cells exclusively infiltrated the bone marrow (Fig. 5C, D). The above results suggest that the direct cause of death was the presence of circulatory defects that occurred owing to the pathological condition of PTTM, which caused pulmonary hypertension, and right heart failure, which was induced by the formation of tumor thrombi and microangiopathy in the pulmonary artery.

DISCUSSION

Von Herbay *et al.* performed consecutive autopsies on 3,300 patients and diagnosed PTTM in 21 (3.3%) out of 630 patients with solid tumors. Among these 21 patients with PTTM, there were 11 cases of gastric cancer, three cases of lung cancer, two cases of breast cancer, and one case each of colorectal, pancreatic, prostate, liver, and bladder cancers. Nineteen patients (90.5%) had an adenocarcinoma [1].

In a 2019 review of 160 patients with PTTM by Godbole *et al.*, the most common cancer was gastric

adenocarcinoma (n = 94, 59%), followed by breast cancer (n = 16, 10%), lung cancer (n = 10, 6.3%), urothelial carcinoma (n = 6, 3.8%), and ovarian cancer (n = 4, 2.5%). Fifty-seven (65%) and 31 (35%) patients had antemortem and postmortem diagnoses of malignant tumors, respectively. The mean duration from the diagnosis of a primary malignant tumor to PTTM onset in 21 patients was 3.5 years (median, 2 years; range, 0.1–12 years). In 127 patients (79%) with a postmortem diagnosis of PTTM, the mean duration from onset to death was 9.5 weeks (median, 3 weeks; range, < 0.5–88 weeks) [3].

A literature search on PubMed using "PTTM" and "breast cancer" as keywords only identified 10 studies. Out of the seven studies conducted in Japan, four were studies on patients with recurrent breast cancer and concurrent PTTM after radical surgery [5–8]. As with the patient in this case, another case report presented a patient with recurrent triple-negative papillo-tubular carcinoma involving a micropapillary component. The postoperative disease-free survival was one year [6]. Moreover, certain studies on HER2-positive breast cancer found four cycles of trastuzumab to be effective in achieving long-time survival [7].

In our case, the patient was diagnosed with PTTM after a micro-embolism was detected in the peripheral pulmonary artery. Because the micro-embolism induced the development of fibro-cellular intimal hyperplasia and pulmonary arterial hypertension, we presumed that imaging methods would be unable to detect recurrent lesions. Although a few bone metastases were observed at a microscopic level, the metastases were more extensive than that suggested by the diagnostic imaging results. Severe intrapulmonary lymphatic invasions suggested the metastases of cancer cells in the regional lymph nodes to the thoracic duct, superior vena cava, right heart, and pulmonary artery. Hemorrhagic infarction in PTTM is rare; nonetheless, in this case, it might have developed owing to anticoagulant use and veno-arterial extracorporeal membrane oxygenation.

Pathophysiologically, PTTM involves complex interactions between tumor cells, endothelial cells, smooth muscle cells, inflammatory cells, inflammatory mediators (including platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) released by tumor cells), tissue repair factors (osteopontin released by tumor cells, macrophages, and fibrous intimal cells), and coagulation activators (tissue factor released by tumor cells and endothelial cells) [3, 9–11]. Although the mechanisms are not clear, tumor and endothelial cells release TF during embolus formation in the pulmonary vasculature, thus initiating the coagulation cascade and formation of fibrin clots. Platelet aggregation occurs, and cytokines and chemokines are released, attracting macrophages to the inflammation site. It has been suggested that the infiltrated macrophages and TF further increase PDGF and VEGF levels, stimulating fibro-cellular intimal hyperplasia and neovascularization [9–11].

As PTTM is a disease in which pulmonary arterial hypertension is induced not only by the presence of a tumor thrombus but also by the narrowing of the peripheral pulmonary artery due to intimal hyperplasia, the use of chemotherapy combined with vasodilators may be effective. Owing to the involvement of PDGF and VEGF, certain studies have reported cases of patients who responded to targeted therapies such as bevacizumab and imatinib [3, 12]. Although a standard treatment for PTTM has not yet been established, the tyrosine-kinase inhibitor of the PDGF receptor, imatinib, may cause regression of pulmonary hypertension and pulmonary artery remodeling in PTTM. Therefore, further studies exploring this possibility need to be conducted.

CONCLUSION

Pulmonary wedge aspiration cytology is useful for diagnosis of PTTM. However, its therapy is still challenging.

CONFLICTS OF INTEREST

The authors state that they have no conflicts of interest.

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