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【 CASE REPORT 】

A Long-term Survival Case of Pulmonary Tumor Thrombotic Microangiopathy due to Gastric Cancer Confirmed by the Early Diagnosis based on a Transbronchial Lung Biopsy

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Abstract:

Pulmonary tumor thrombotic microangiopathy (PTTM) is an acute, progressive, and fatal disease. PTTM manifests as subacute respiratory failure with pulmonary hypertension, progressive right-sided heart failure, and sudden death. An antemortem diagnosis of PTTM is very difficult to obtain, and many patients die within several weeks. We herein report a case of PTTM diagnosed based on a transbronchial lung biopsy. In this case, we finally diagnosed PTTM due to gastric cancer because of its histological identity. The patient was administered chemotherapy, including angiogenesis inhibitors, against gastric cancer at an early age and survived for a long time.

Key words: pulmonary tumor thrombotic microangiopathy, transbronchial lung biopsy, gastric cancer, angiogenesis inhibitor

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Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) was established by von Herbay et al. in 1990 (1) and characterized by acute progressive pulmonary hypertension and tumor embolism in small pulmonary arteries observed on histopathological images that differ from normal hematogenous pulmonary metastases or large tumor embolisms (simple vascular occlusions by tumors). Widespread tumor emboli of small arteries and arterioles induce thrombus formation and fibrocellular and fibromuscular intimal proliferation (2). According to some reports, 0.9-3.3% of patients who undergo an autopsy after cancer death are diagnosed with PTTM (1, 3, 4).

Because of the rapid progression of PTTM, most patients cannot be diagnosed while alive. The most common primary malignancy is gastric cancer, which is often poorly differentiated adenocarcinoma (1, 4). There are many unexplained aspects of this entity because PTTM is an acute, progressive, and fatal disease.

We herein report a case of PTTM due to gastric cancer diagnosed based on a transbronchial lung biopsy (TBLB) in a patient who survived for a long time thanks to the early initiation of chemotherapy, which was able to inhibit the progression of pulmonary hypertension.

Case Report

A 68-year-old-man was a former smoker of 1 pack of cigarettes per day for 27 years and had a history of type II diabetes. In early November 2017, dry cough occurred and worsened gradually. He visited his primary care doctor and underwent chest computed tomography (CT), which revealed some abnormalities. His serum tests also showed elevated levels of C-reactive protein (CRP). He was prescribed levofloxacin, but his symptoms persisted. Thereafter, he was referred to our hospital for further examinations and treat-

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Table 1. the Serum Test Results at the Initial Visit.

WBC	4,500 /μL	Na	141.5 mEq/dL
Neut	55.2 %	K	4.87 mEq/dL
Eo	5.1 %	CK	370 U/L
Baso	0.9 %	CK-MB	14 U/L
Mono	6.7 %	HbA1c	6.4 %
Lymp	32.1 %	Alb	4.8 g/dL
RBC	441×10^4 /μL	CRP	0.9 mg/dL
Hb	13.9 g/dL	BNP	5 pg/mL
Plt	24.7×10^4 /μL	ACE	4.4 pg/mL
AST	28 U/L	T-SPOT	(-)
ALT	25 U/L	anti MAC antibody	(-)
ALP	290 U/L	βD-Glucan	7 pg/mL
LDH	207 U/L		
γ-GTP	20 U/L		
BUN	18.9 mg/dL		
Cre	0.98 mg/dL		

WBC: white blood cell, Neut: neutrophil, Eo: eosinophil, Baso: basophil, Mono: monocyte, Lymp: lymphocyte, RBC: red blood cell, Hb: hemoglobin, Plt: platelet count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, γ-GTP: γ-glutamyl transpeptidase, BUN: blood urea nitrogen, Cre: creatinine, CK: creatine kinase, CK-MB: creatine kinase MB, HbA1c: hemoglobin A1c, Alb: albumin, CRP: C-reactive protein, BNP: brain natriuretic peptide, ACE: angiotensin converting enzyme, T-SPOT: T-SPOT®-TB, anti MAC antibody: anti-micobacteria antibody, βD-Glucan: beta-d-glucan

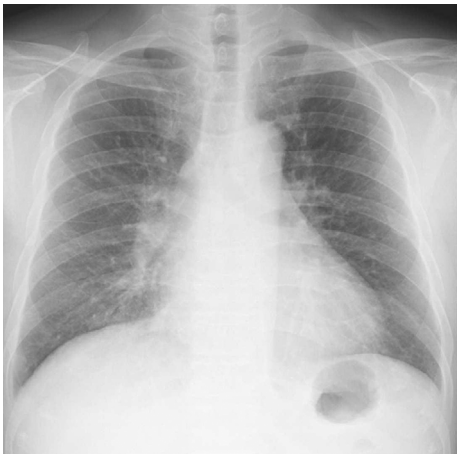

Figure 1. Chest radiography at the initial visit.

ments in mid-December, 2017.

There were no abnormalities on physical findings. A serum test showed no abnormalities except for the elevated level of CRP (0.9 mg/dL) (Table 1). Chest radiography showed mild heart enlargement and enhancement in pulmonary vascular shadow (Fig. 1). High-resolution computed tomography (HRCT) of the chest showed bronchial vascular bundle thickening, centrilobular nodules, and interlobular septal thickening on both sides. Uneven ground-glass opacity was present mainly on the right side; in addition, there was pleural effusion on both sides as well as pericardial effusion (Fig. 2). No abnormalities were noted on an electrocardiogram. Echocardiography showed a normal ejection fraction (66%) and mild elevation of the tricuspid regurgitation pressure gradient (TRPG; 36 mmHg). Based on these results, we did not strongly assume the possibility of the exacerbation of chronic heart failure.

For a further inspection, we conducted a TBLB of the right upper lobe, where HRCT showed centrilobular nodules and interlobular septal thickening more strongly. In a pathological image of the TBLB specimen, phloem-like or clumping adenocarcinoma cells were noted in the thick interstitial vessels and vessels of the alveolar wall but not in the lymphatic vessels (Fig. 3). Because a tumor embolism consisting of fibrin and tumor cells was noted, a pathologist in our hospital confirmed the diagnosis of PTTM. Immunostaining showed carbohydrate antigen 19-9(+), Mac5-AC(+), D2-40 (-), and thyroid transcription factor-1(-) (Fig. 4). Based on these results, we suspected that the primary tumor might be a gastric or pancreatobiliary cancer.

While we planned further inspections, he was referred to the emergency room of our hospital because of worsening dyspnea in early January 2018. HRCT showed increased pleural effusion and worse interlobular separation wall thickening on both sides than had been noted in the HRCT findings acquired previously (Fig. 5). Emergency hospitalization was implemented, and chest drain placement was conducted. Once hospitalized, he underwent upper gastrointestinal endoscopy for scrutiny. Ulcerative lesions were noted in the posterior wall of the stomach (Fig. 6). The biopsy result indicated moderately to poorly differentiated adenocarcinoma and signet-ring cell carcinoma, which was in agreement with the finding of adenocarcinoma cells on the TBLB (Fig. 7). Contrast-enhanced CT was performed to rule out pulmonary

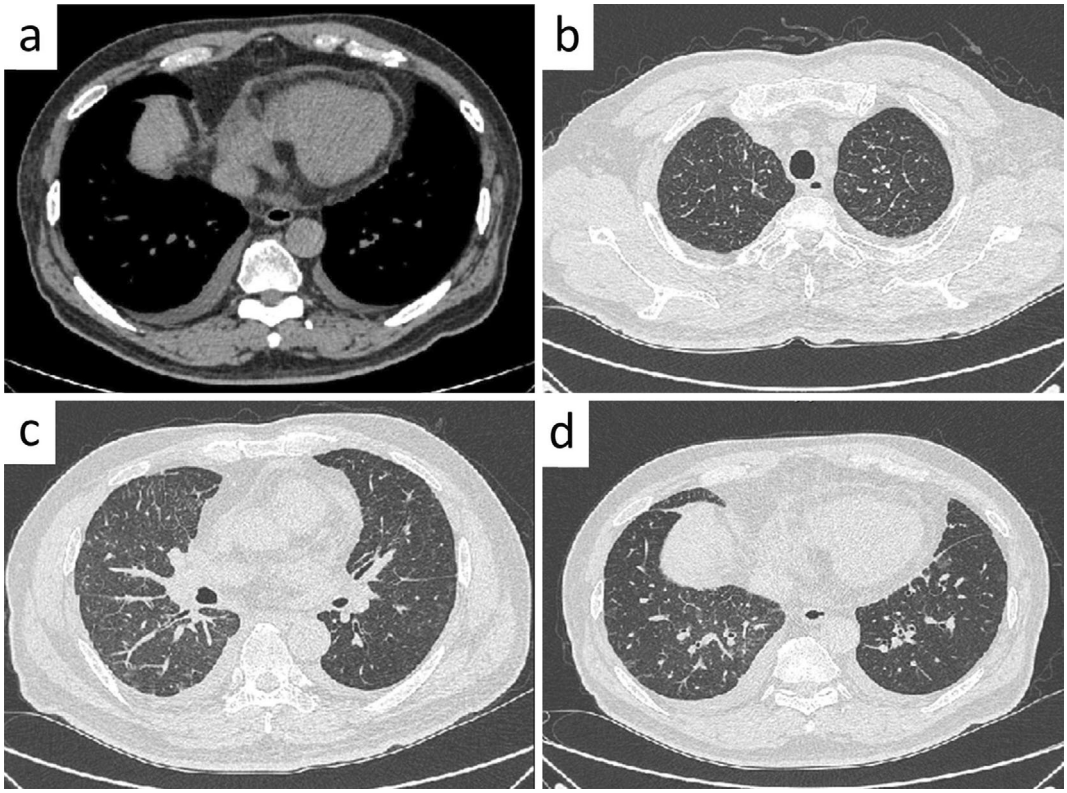

Figure 2. **High-resolution chest tomography at the initial visit. (a) The mediastinal window showed a small amount of pleural and pericardial fluid retention. (b) (c) (d) The lung window showed bronchial vascular bundle thickening, centrilobular nodules, and interlobular septal thickening on both sides.**

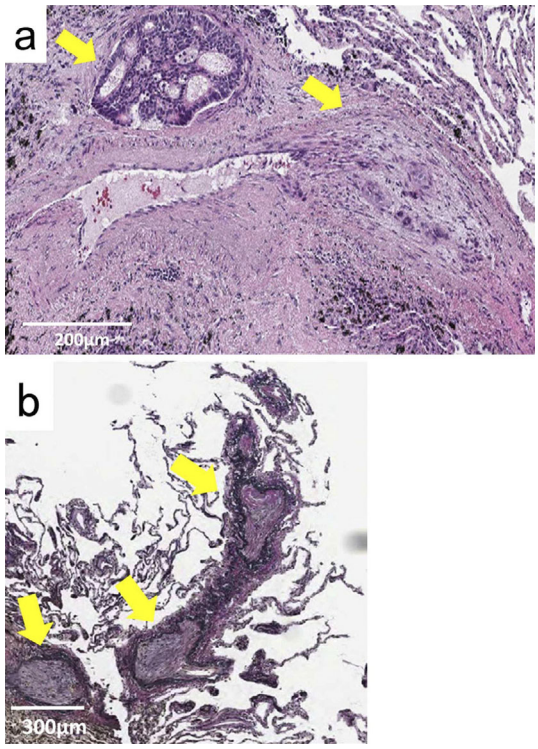

Figure 3. **The TBLB specimen showed vascular endothelial thickening and adenocarcinoma cells in small vessels (yellow arrows). (a) Hematoxylin and Eosin staining. (b) EVG staining. EVG: Verhoeff-Van Gieson, HE: Hematoxylin and Eosin staining, TBLB: transbronchial lung biopsy**

thromboembolism, but no thrombi were observed in the pulmonary artery (Fig. 8). Since the D-dimer level was also in the normal range, pulmonary thromboembolism was considered negative. Therefore, a definitive diagnosis of PTTM due to gastric cancer was made.

In late January, 2018, S-1 (120 mg/m^2) and oxaliplatin (100 mg/m^2) were administered to eradicate the gastric cancer. However, the gastric cancer worsened, so the regimen of chemotherapy was changed to S-1 (80 mg/m^2), docetaxel (50 mg/m^2), and oxaliplatin (100 mg/m^2). After starting S-1, docetaxel, and oxaliplatin, his dyspnea disappeared gradually. This was because his pulmonary hypertension had improved, and the TRPG measured by echocardiography actually decreased from 36 mmHg to 23 mmHg. However, after four courses of S-1, docetaxel, and oxaliplatin, the progression of gastric cancer was confirmed, and his dyspnea worsened again. Echocardiography showed that the TRPG had increased from 23 to 41 mmHg. In late May, 2018, nab-paclitaxel (PTX) (100 mg/m^2) and ramucirumab (8 mg/kg) were initiated. There were no marked changes in dyspnea during the administration of nab-PTX and ramucirumab, and the TRPG decreased from 41 to 35 mmHg. We were able to stop the worsening of dyspnea and improve the pulmonary hypertension a little, but the development of gastric cancer was confirmed after two courses.

Therefore, irinotecan (70 mg/m^2) was initiated in mid-July, 2018. Soon after initiating irinotecan, his dyspnea

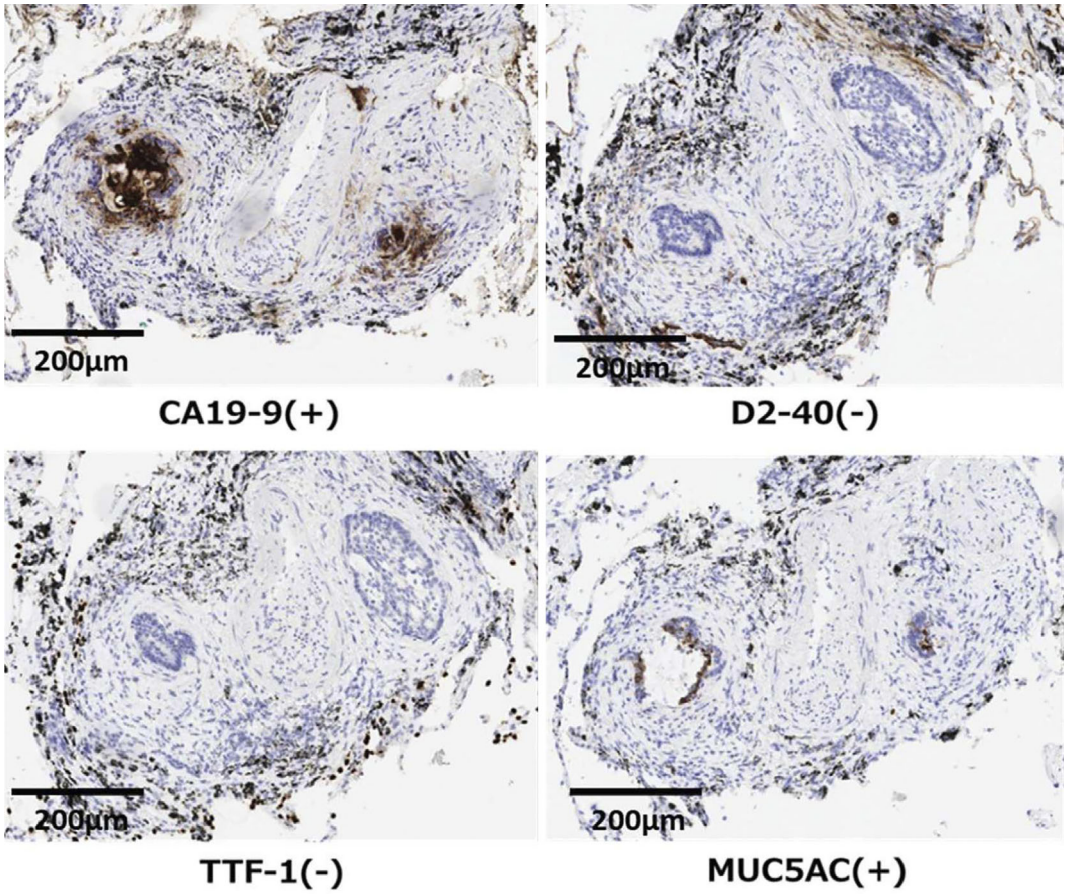

Figure 4. **Immunostaining of the TBLB specimen showed CA19-9 (+), Mac5-AC (+), D2-40 (-) and TTF-1 (-). CA19-9: carbohydrate antigen 19-9, TBLB: transbronchial lung biopsy, TTF-1: thyroid transcription factor-1**

worsened. Steroids and narcotics were prescribed to alleviate his symptoms. At the end of July 2018, his performance status was 4 owing to fatigue, anorexia, and dyspnea, so we decided to discontinue the chemotherapy and provide best supportive care. In late August, 2018, he passed away.

Discussion

PTTM is often diagnosed at a postmortem autopsy because of its rapid progression and poor prognosis. However, there are reports of 16 cases in which a diagnosis was able to be obtained before death and chemotherapy started, as in the present case (Table 2).

The diagnosis of PTTM has been made based on the cytological examination of aspirate from a wedged pulmonary artery catheter (5-9), video-assisted thoracoscopic surgery (10-13), a CT-guided biopsy (14), and a TBLB (15-20). Among these methods, a TBLB is the least invasive and simplest to perform. Considering the rapid progression of PTTM and the reduction in the physical burden, a TBLB should be attempted as the first step of inspection, as in the present case.

PTTM progresses rapidly, and the median prognosis is only 16.2 days (4). However, in cases wherein the diagnosis can be made while the patient is still alive, a relatively long-term survival is likely to be obtained by administering chemotherapy, as in the present case. This case achieved a long-term survival compared with previous cases that were able to be diagnosed with PTTM while living and start chemotherapy. According to the previous reports, the average survival after the diagnosis was 6.2 months, with a survival of only 4.0 months for patients with pulmonary hypertension at the time of the diagnosis (Table 2). In the present case, the survival after the diagnosis was 9.0 months despite the presence of pulmonary hypertension.

If CT abnormalities such as interlobular wall thickening and bronchial vascular thickening are observed, we suggest that bronchoscopy be performed at an early stage, considering the possibility of PTTM. This is because pulmonary hypertension progresses rapidly, and patients with PTTM are liable to die soon if not promptly managed. Thus, it is very important to diagnose patients before they develop severe pulmonary hypertension and initiate treatments as soon as possible. In our case, the TRPG was 36 mmHg when we diagnosed the patient with PTTM due to gastric cancer. We therefore believe that the main reason for the long-term survival was that we were able to initiate chemotherapy before the patient developed severe pulmonary hypertension.

In many PTTM cases, the vascular endothelial growth factor (VEGF) expression in tumor cells has been con-

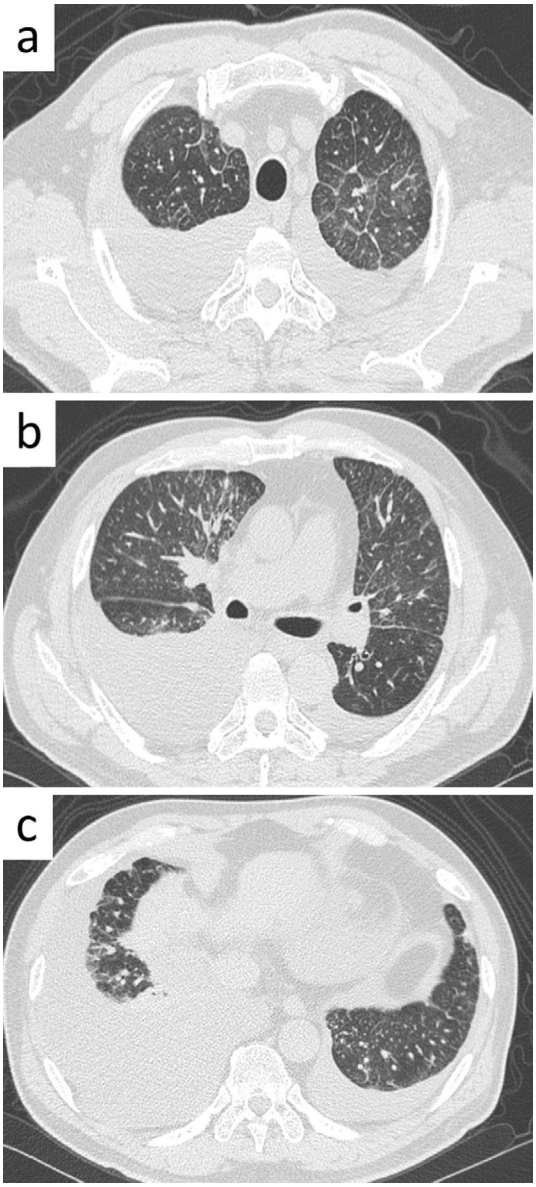

Figure 5. **High-resolution chest tomography at the emergency hospitalization. The lung window showed increased pleural effusion and worsening of interlobular separation wall thickening.**

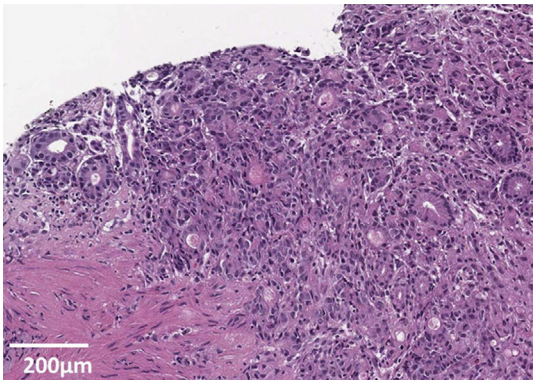

Figure 7. **A biopsy of the stomach showed moderately to poorly differentiated adenocarcinoma and signet-ring cell carcinoma.**

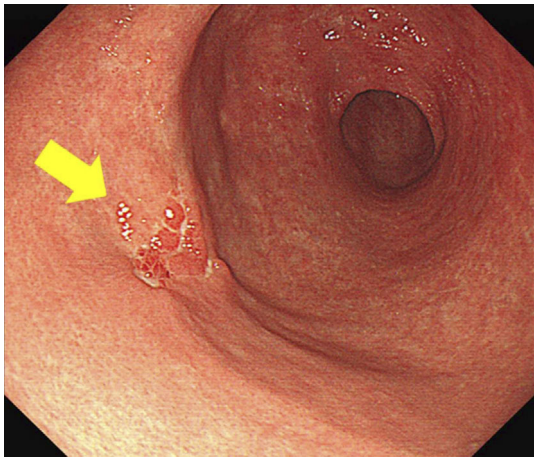

Figure 6. **Upper gastrointestinal endoscopy showed ulcerative lesions in the posterior wall of the stomach (yellow arrows).**

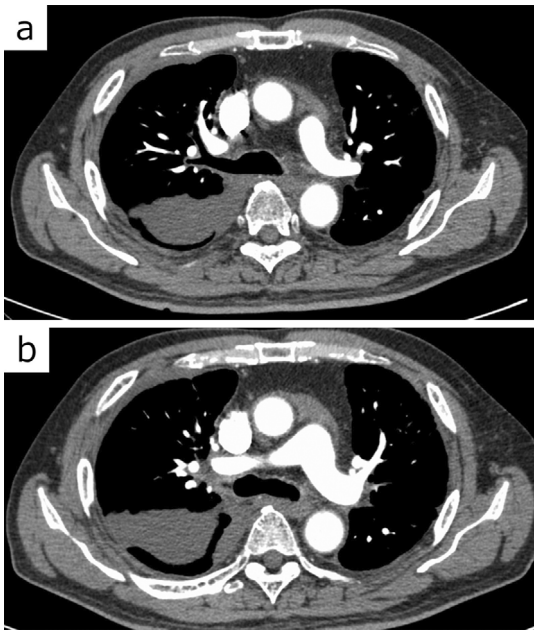

Figure 8. **Contrast-enhanced CT performed at the initiation of chemotherapy.**

firmed (2, 4, 21, 22). As such, VEGF is suspected to be involved in PTTM and pulmonary hypertension. Indeed, there is a case report that described a patient with PTTM diagnosed while still alive who received bevacizumab and experienced an improvement in their pulmonary hypertension (5). In our case, after initiating ramucirumab and nab-PTX, the TRPG decreased from 41 to 36 mmHg, and the worsening of dyspnea stopped; however, we were unable to stop the progression of gastric cancer. Although details are unknown, pulmonary hypertension may have been improved by the administration of ramucirumab in our case. On the other hand, ramucirumab also has side effects of pulmonary thromboembolism, which can exacerbate pulmonary hypertension. Given the successful response to bevacizumab and

Table 2. Reported Cases of Antemortem Diagnosis of PTTM and Initiation of Chemotherapy.

Reference No.	Age	Sex	Primary site	Diagnotic method of PTTM	Pulmonary hypertension (when diagnosed PTTM)	Chemotherapy	Survival after diagnosing PTTM (months)
(10)	64	M	Stomach	VATS	-	S-1	7
(14)	46	W	Lung	CT guided biopsy	+	Carboplatin, paclitaxel, gemcitabine	6
(15)	65	M	Unknown	TBLB	+	Cyclophosphamide, doxorubicin, vincristine	3
(16)	60	M	Esophagus	TBLB	+	Fluorouracil, nedaplatin	0.3
(11)	29	M	Unknown	VATS	-	S-1, cisplatin	15
(17)	47	W	Gastroduodenum	TBLB	+	Imatinib, s-1, 5-fluorouracil	9
(18)	41	W	Breast	TBLB	+	Irinotecan, s-1	3
(5)	61	M	Colon	Pulmonary wedge aspiration	+	Imatinib, s-1, bevacizuab	12
(6)	61	W	Breast	Pulmonary wedge aspiration	+	Imanitinb	1.5
(12)	64	M	Stomach	VATS	+	Imatinib, s-1	10.5
(7)	77	M	Uinary bladder	Pulmonary wedge aspiration	+	Gemcitabine, paclitaxel	0.1
(13)	65	W	Breast	VATS	-	Trastuzumab	32
(8)	70	M	Breast*	Pulmonary wedge aspiration	+	Docetaxel	0.6
(9)	45	W	Breast	Pulmonary wedge aspiration	+	Imatinib	0.8
(19)	81	M	Prostate	TBLB	-	Docetaxel	1
(20)	75	M	Stomach	TBLB	+	Carboplatin, paclitaxel	1

*He was diagnosed Paget's disease.

our case, it may be possible to consider ramucirumab as a treatment option for PTTM. To our knowledge, this is the first report of ramucirumab being used for PTTM.

If CT abnormalities, such as interlobular wall thickening and bronchial vascular thickening, are observed, the findings should be examined further, keeping in mind the possibility of PTTM. Although the effect on pulmonary hypertension is unknown, the use of a VEGF inhibitor or VEGF receptor inhibitor should be considered as one of the treatment options for PTTM.

The authors state that they have no Conflict of Interest (COI).

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