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-
fraction (66%) and mild elevation of the tricuspid regurgita-
tion pressure gradient (TRPG; 36 mmHg). Based on these
results, we did not strongly assume the possibility of the ex-
acerbation 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 patho-
logical image of the TBLB specimen, phloem-like or clump-
ing adenocarcinoma cells were noted in the thick interstitial
vessels and vessels of the alveolar wall but not in the lym-
phatic 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
positive results. As a result, 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 thick-
ening on both sides than had been noted in the HRCT find-
ings acquired previously (Fig. 5). Emergency hospitalization
was implemented, and chest drain placement was conducted.
Once hospitalized, he underwent upper gastrointestinal endo-
scopy for scrutiny. Ulcerative lesions were noted in the pos-
terior wall of the stomach (Fig. 6). The biopsy result indi-
cated 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

tions in mid-December, 2017.

There were no abnormalities on physical findings. A se-
rum 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 pulmo-
nary vascular shadow (Fig. 1). High-resolution computed to-
mography (HRCT) of the chest showed bronchial vascular
bundle thickening, centrilobular nodules, and interlobular
septal thickening on both sides. Uneven ground-glass opac-
ity was present mainly on the right side; in addition, there
was pleural effusion on both sides as well as pericardial ef-
fusion (Fig. 2). No abnormalities were noted on an electro-
cardiogram. Echocardiography showed a normal ejection
fraction (66%) and mild elevation of the tricuspid regurgita-

Figure 1. Chest radiography at the initial visit.
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/m²) and oxaliplatin (100 mg/m²) were administered to eradicate the gastric cancer. However, the gastric cancer worsened, so the regimen of chemotherapy was changed to S-1 (80 mg/m²), docetaxel (50 mg/m²), and oxaliplatin (100 mg/m²). 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/m²) 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/m²) was initiated in mid-July, 2018. Soon after initiating irinotecan, his dyspnea

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
 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-

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

| Reference No. | Age | Sex | Primary site      | Diagnostic 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                      | +                                          | Fluourouracil, 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, bevacizubab            | 12                                     |
| (6)           | 61  | W   | Breast            | Pulmonary wedge aspiration| +                                          | Imanitinib                           | 1.5                                    |
| (12)          | 64  | M   | Stomach           | VATS                      | +                                          | Imatinib, s-1                         | 10.5                                   |
| (7)           | 77  | M   | Urinary 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.
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