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【 CASE REPORT 】

Pulmonary Tumor Thrombotic Microangiopathy Due to Gastric Cancer Diagnosed Antemortem by a Cytological Examination of Aspirated Pulmonary Artery Blood

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Abstract:

A 66-year-old Japanese man receiving systemic chemotherapy for advanced gastric cancer presented with exertional dyspnea. D-dimer was elevated in the blood. Echocardiography revealed pulmonary hypertension, and a ventilation-perfusion scan indicated decreased perfusion in the bilateral lungs. Cardiac catheterization showed no evidence of pulmonary artery embolization and revealed cytologically confirmed adenocarcinoma. Thus, pulmonary tumor thrombotic microangiopathy (PTTM) was diagnosed. The patient died of respiratory failure on the 17th hospitalization day despite systemic chemotherapy. Retrospective serological testing revealed increased vascular endothelial growth factor in the pulmonary artery blood. This is a rare case with antemortem cytologically proven PTTM mediated by VEGF.

Key words: gastric cancer, pulmonary tumor thrombotic microangiopathy (PTTM), cardiac catheterization, vascular endothelial growth factor (VEGF)

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Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare complication of malignant tumors, characterized by severe pulmonary hypertension initiated by both fibrous intimal thickening caused by proliferation of intimal myofibroblasts of the small pulmonary arteries or arterioles and thrombo- or tumor-related microangiopathy in the lungs (1). It was previously reported that vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) were important for the pathogenesis of PTTM (2-4). However, its etiology remains poorly defined.

It is extremely difficult to diagnose PTTM even with high-efficiency imaging examinations, such as contrast-enhanced computed tomography (CT) (5), and invasive procedures or examinations cannot be tolerated by patients with PTTM because of their severe respiratory failure.

We herein report a patient with PTTM most likely mediated by VEGF, which we diagnosed by a cytological examination of aspirated pulmonary artery blood while the patient was still alive.

Case Report

A 66-year-old man presented to our hospital for a further investigation of back pain. He had no respiratory symptoms and no notable medical history.

Laboratory data indicated severe elevation of alkaline phosphatase (ALP) (2,328 U/L) and N-terminal crosslinking

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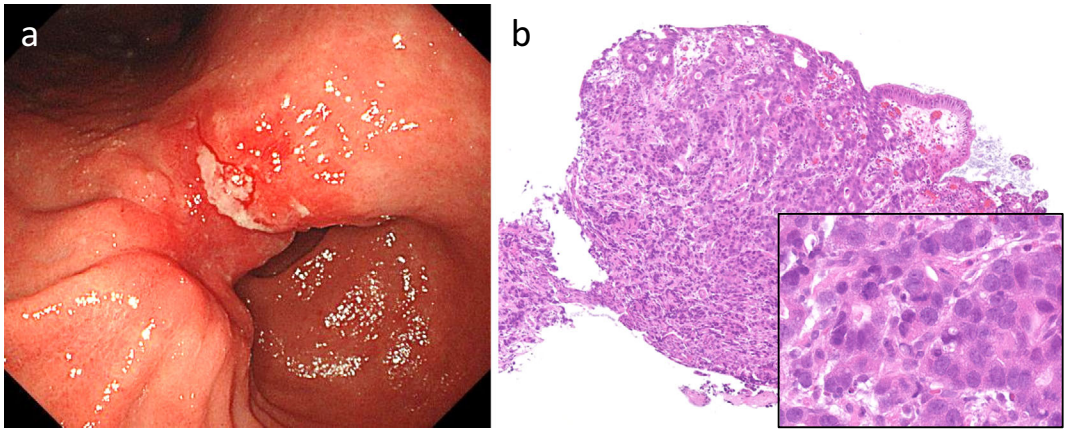

Figure 1. **EGD images at the first medical examination and pathological examination of the biopsy specimen. a: Gastric ulcer in the angle of the stomach. b: Moderately to poorly differentiated adenocarcinoma.**

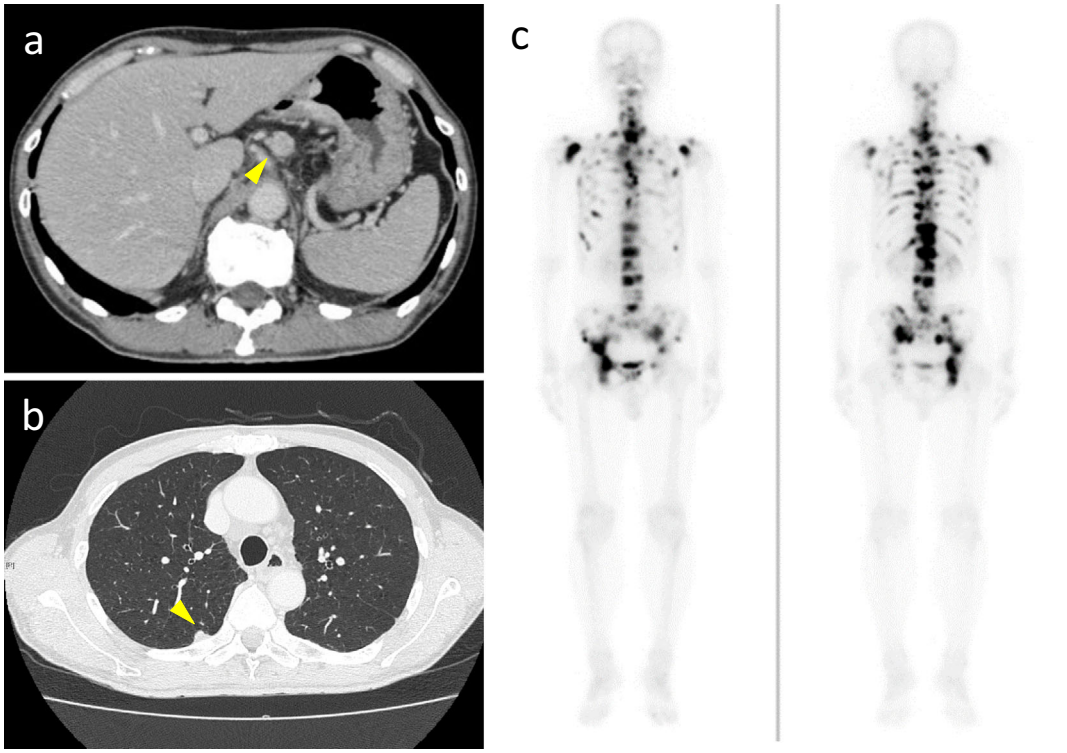

Figure 2. **Contrast-enhanced CT at the first examination. a: Swelling of the regional lymph node. b: Metastatic lung tumor in the right robe. c: Bone scintigraphy showing numerous whole-body bone metastases.**

telopeptide of type I collagen (NTX) (82.5 nmol/L), and elevation of fibrin degradation product (FDP) (34 μg/mL). Esophagogastroduodenoscopy revealed an ulcerative lesion in the gastric angle (Fig. 1a). A biopsy specimen obtained from the ulcer indicated moderately to poorly differentiated tubular adenocarcinoma (Fig. 1b). CT showed regional lymph node swelling (Fig. 2a) and lung metastases (Fig. 2b) with no evidence of vascular embolism. Bone scintigraphy showed multiple bone metastases (Fig. 2c). Therefore, a diagnosis of advanced gastric cancer cT3N1M1 PUL OSS at stage IV according to the Japanese classification of gastric carcinoma was made (6).

The patient then received S-1 and oxaliplatin (SOX) therapy, resulting in a decrease in the size of the metastatic lymph nodes after four courses. However, after the fifth course of SOX therapy, he presented again for an investigation of severe breathlessness.

At the time of this visit, his blood pressure was 134/79 mmHg, radial pulse rate 71 beats/min and percutaneous oxygen saturation 94% (room air). He had no anemia or chest-specific findings. Laboratory data showed thrombocytopenia and extremely elevated FDP (145 μg/mL); a blood gas

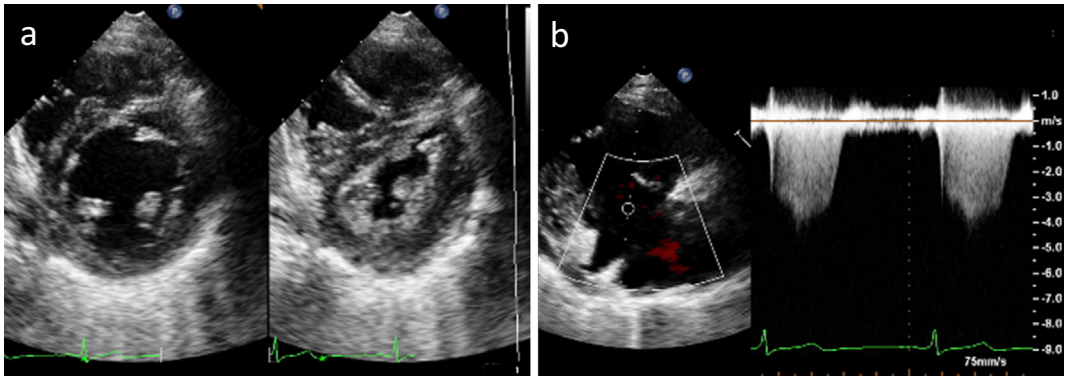

Figure 3. **Echocardiography at the time of consultation for a further examination of breathlessness. a: Dilated right ventricle with a compressed left ventricle at the diastolic phase (short-axis view). b: Estimated right ventricular systolic pressure of 67 mmHg.**

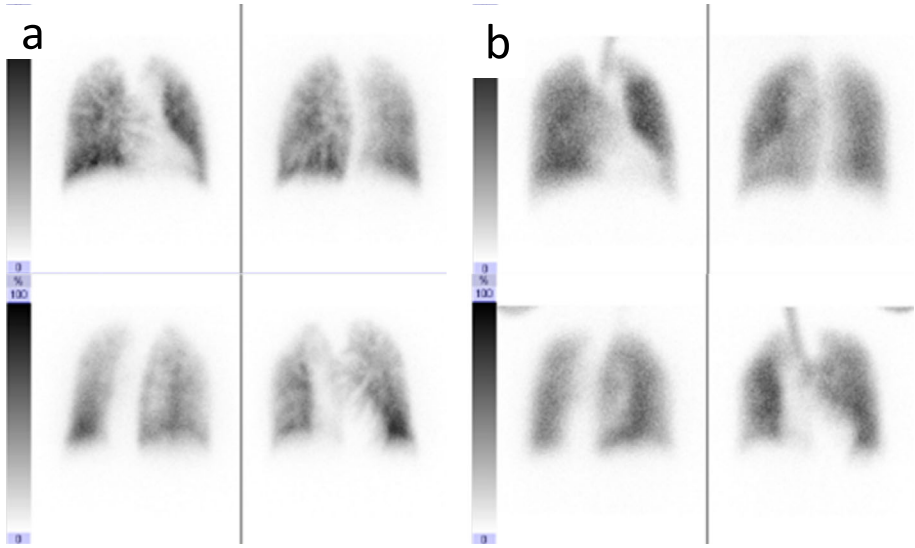

Figure 4. **Ventilation-perfusion scintigraphy on admission. a: Perfusion scintigraphy demonstrating a cuneiform defect of peripheral the pulmonary artery. b: Ventilation scintigraphy showing normal ventilation competence.**

analysis indicated respiratory alkalemia. An electrocardiogram showed a negative T wave in V_{1-4}, and echocardiography revealed paradoxical septal motion and severe pulmonary hypertension (estimated right ventricular systolic pressure was 67 mmHg) (Fig. 3a, b). Although contrast-enhanced CT showed no pulmonary thromboembolism, ventilation-perfusion mismatch was positive, as demonstrated by scintigraphy (Fig. 4a). It was assumed that the respiratory failure was the result of right ventricular failure due to PTTM, so right heart catheterization was performed. Pulmonary angiography also failed to identify any thromboembolism (Fig. 5a), and the pulmonary arterial pressure was 57/23 (35) mmHg, with a pulmonary capillary wedge pressure of 10 mmHg. Furthermore, a cytological examination of aspirated blood from the pulmonary artery revealed adenocarcinoma (Fig. 5b). Thus, PTTM was diagnosed.

After admission, the respiratory status and FDP level were temporarily improved (34 μg/mL) by the daily administration of dexamethasone. However, respiratory failure was exacerbated, and the FDP level increased again (109 μg/mL) on the fifth hospitalization day. Paclitaxel was administered as second-line systemic chemotherapy for advanced gastric cancer on the seventh hospitalization day. However, the patient ultimately died from respiratory failure due to PTTM on the 17th hospitalization day without any improvement in his general condition. Retrospective serological testing revealed increased VEGF (55 pg/mL) but not PDGF (undetectable) levels in the blood from the pulmonary artery.

Discussion

PTTM is acute or subacute-onset pulmonary thromboembolism caused by malignant tumors. Uruga et al. reported that among 2,215 consecutive Japanese autopsy carcinoma cases, 30 (1.4%) were diagnosed with definitive PTTM, the most frequent primary site of which was the stomach (60%) (2). Another report from Germany also indicated that PTTM was typically associated with poorly differentiated

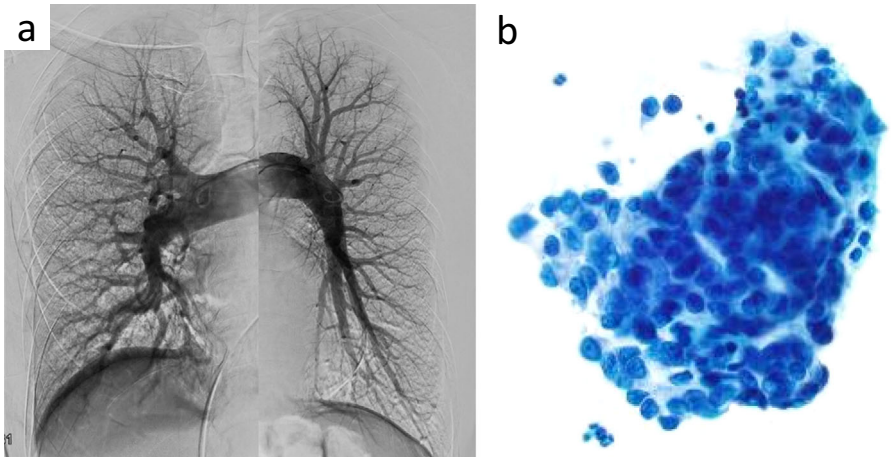

Figure 5. **a: Pulmonary angiogram showing no thromboembolism. b: Cytologically revealed adenocarcinoma in blood aspirated from the pulmonary artery.**

adenocarcinoma, especially that of gastric cancer (1, 2). Respiratory failure caused by PTTM progresses rapidly, and patients have an extremely poor prognosis, surviving for only a few days or weeks (2, 7). In the present case, with a markedly poor prognosis, the clinical course was typical of PTTM due to poorly differentiated gastric adenocarcinoma.

Because of the rarity and dramatically rapid exacerbation of PTTM, making an early diagnosis is extremely difficult, so almost all cases of PTTM have been confirmed postmortem (1, 2). While echocardiography and ventilation-perfusion scintigraphy are valuable for the low-invasive diagnosis of PTTM, it is difficult to obtain a definitive diagnosis due to the difficulty of excluding other differential diagnoses, such as lymphangiosis carcinomatosa and interstitial lung disease. A bronchoscopic or thoracoscopic biopsy is reportedly valuable for the pathological definitive diagnosis (8, 9), but few patients with PTTM are able to undergo such invasive diagnostic procedures because of their severe respiratory failure. A cytological examination with wedged pulmonary artery catheterization was reported to be useful for diagnosing PTTM, with a sensitivity of 80-88% and a specificity of 82-94% (10, 11). In the present case, right heart catheterization with minimum physical stress was also found to be useful for a definitive cytological diagnosis of PTTM and the assessment of the cardiac function, as well as for the exclusion of other differential diagnoses. Although whether or not to perform an invasive assessment for cases with severe respiratory failure in advanced stages of cancer remains controversial, a cytological examination using the pulmonary artery blood may be useful for making a definitive diagnosis of PTTM, especially in cases with unexplained respiratory disorders.

VEGF and PDGF are reportedly both involved in the pathogenesis of PTTM (2, 4, 12). VEGF is a cytokine produced by diverse epithelial lineages or inflammatory and hematopoietic cells and plays an important role in the induction, maintenance, and growth of vascular endothelial cells (13, 14). VEGF may be involved in the etiology of PTTM in cases where tumor cells are positive for VEGF according to immunohistochemistry and the serum concentration of VEGF is significantly increased (2, 10, 15). In the present case, the increased VEGF level in the pulmonary artery suggests that PTTM might have been induced by VEGF secreted from tumor cells. However, it was also reported that PDGF, which initiates tumor cell proliferation, invasion, and metastaticity, may play an important role, although in our case, no PDGF was detected in the blood aspirated from the pulmonary artery (2). This suggests that PDGF might not have been involved in the pathogenesis of PTTM in the present case.

Treatment strategies for PTTM are not well-established due to its rarity and severity. Imatinib, a PDGF receptor antagonist, may be an effective treatment for PTTM (15). Approximately 60% of patients with PTTM are positive for PDGF by immunohistochemistry (2). Although it has been proposed for "PDGF-positive" patients to be treated with imatinib, this is likely to be ineffective for "PDGF-negative" patients, as with our case. However, when tumor cells are immunohistochemically positive for VEGF (here, 96.6%), anti-VEGF drugs may be effective (2). Combination therapy with taxanes and ramucirumab, an anti-VEGF receptor (VEGFR)-2 antibody, is recommended for the second-line treatment of unresectable gastric cancer (16). In the present case, because our patient with a markedly increased FDP level was strongly suspected of being susceptible to systemic microthrombi, for which ramucirumab is contraindicated, he was treated only with paclitaxel. This was, however, ineffective for PTTM. Furthermore, the PTTM occurred suddenly, despite the clinical improvement of the gastric cancer on SOX therapy, suggesting that fibrous intimal thickening caused by tumor micro-embolism had been initiated a long time earlier and was not associated with the primary disease status. This course thus suggests that cytotoxic chemotherapy might be ineffective for PTTM.

Although the effectiveness of ramucirumab for PTTM remains unclear, the regional high levels of VEGF suggest that

this drug may have potential utility for treating VEGF-positive PTTM. Therefore, pulmonary artery catheterization should be promptly performed to determine the therapeutic strategy of choice for PTTM and whether or not imatinib and/or anti-VEGF/VEGFR antibody should be administered for cytologically confirmed PTTM.

The etiology of PTTM and treatment strategies for this syndrome with a very poor prognosis remain unclear, warranting large-scale and precise investigations, which will be challenging for this very rare disease.

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

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