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Pulmonary Tumor Thrombotic Microangiopathy with Administration of Pulmonary Vasodilator Resulting in Clinical Improvement Prior to Final Diagnosis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Female, 80-year-old
Final Diagnosis: Pulmonary tumor thrombotic microangiopathy
Symptoms: Dyspnea
Medication: —
Clinical Procedure: Diagnostic therapy
Specialty: Cardiology

Objective: Rare disease

Background: The pathophysiology of pulmonary tumor thrombotic microangiopathy (PTTM) was recently revealed by autopsy. Considered rare, we suggest that this fatal disease is not rare, but has not been diagnosed pre-mortem. Some patients with pulmonary thromboembolism with unknown thrombus source or with sudden death have been treated for malignant carcinoma. We report a patient with PTTM who was successfully rescued acutely by treatment with soluble guanylate cyclase (sGC), resulting in appropriate palliative care.

Case Report: An 80-year-old Japanese woman was transferred to our emergency room for severe dyspnea owing to type I respiratory failure. Her clinical findings indicated pulmonary thromboembolism, but we found no thrombus in either the pulmonary artery or inferior vena cava. However, we incidentally found gallbladder cancer with peritoneal metastases. These findings raised the suspicion of PTTM. We began concurrent sGC and direct oral anticoagulant (DOAC) on the assumption that PTTM had occurred, while performing peripheral pulmonary artery sampling for cytology, and pulmonary perfusion scintigraphy. Cytology revealed several aplastic cells; consequently, we finally diagnosed PTTM. Because she did not wish to undergo examination and active treatment for carcinoma, we initiated palliative care while continuing sGC. She was able to spend time with her family for more than 100 days, without dyspnea.

Conclusions: We must recognize PTTM, which is a lesser-known disease, and introduce diagnostic therapy with a pulmonary vasodilator, such as sGC, immediately, when we suspect PTTM, leading to appropriate clinical care.

Keywords: Carcinoma • Palliative Care • Pulmonary Embolism • Thrombotic Microangiopathies

Abbreviations: **sGC** – soluble guanylate cyclase; **DOAC** – direct oral anticoagulant; **A-a Do2** – alveolar arterial difference of oxygen; **FDP** – fibrinogen degradation products; **BNP** – brain natriuretic peptide; **BGA** – blood gas analysis; **TRPG** – tricuspid regurgitation pressure gradient; **EF** – ejection fraction; **LA** – left atrial; **E peak** – early diastolic ventricular filling velocity; **A peak** – late diastolic ventricular filling velocity; **PTE** – pulmonary thromboembolism; **CT** – computed tomography; **PCWP** – precapillary wedge pressure

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/933867

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Background

Pulmonary tumor thrombotic microangiopathy (PTTM) is a fatal disease process in which pulmonary hypertension (PH) occurs with malignant disease. The pathophysiology of PTTM indicates a form of pulmonary artery tumor embolism resulting in microangiopathy, which is activation of the coagulation cascade, formation of fibrin clots, and fibrinocellular intimal proliferation of small pulmonary arteries [1]. An autopsy study from the Mayo Clinic reported the mean interval between respiratory symptoms and death as only 1 month [2]. According to previous reports, among unselected autopsy case series of patients with carcinoma, 1.4-7.7% of the patients had pulmonary tumor emboli, and 4.1% had fatal multiple pulmonary emboli [2,3]. Most people with this disease are diagnosed postmortem by autopsy and not ante-mortem, probably owing to a lack of established diagnostic criteria and rapid progression resulting in death before detailed examinations [4].

The purpose of this report was to recommend a pulmonary vasodilator immediately when one suspects PTTM, which can mitigate severe respiratory failure and lead to appropriate clinical care in patients with advanced carcinoma.

We report a case of PTTM diagnosed acutely, in which we improved the patient's quality of life by administering the pulmonary vasodilator, soluble guanylate cyclase (sGC), as a diagnostic therapy [5].

Case Report

An 80-year-old Japanese woman suffered dyspnea and palpitations for several days. Because her symptoms worsened, she was transferred to the emergency room of South Miyagi Medical Center, Miyagi, Japan. She had a history of hypertension and hyperlipidemia, which were under medical control, and breast cancer, which was in complete remission following surgical treatment 30 years earlier. She did not smoke or drink alcohol. Her clinical findings in the emergency room were as follows: blood pressure (BP), 107/55 mmHg; heart rate, 96 beats/min; respiratory rate, 24 breaths/min; and oxygen saturation (SpO2), 85% on 2 L/min of O2. She had no fever, cough, or edema. Chest X-rays showed an enlarged pulmonary artery, protrusion of the right second arch, and interstitial shadows in both lung fields, but no other significant findings, such as pleural effusion, infiltration shadows, and enhancement of pulmonary vascular shadows. Electrocardiography (ECG) showed sinus tachycardia at a rate of 100 beats per min and negative T waves in leads V1-4. Arterial blood gas analysis (BGA) showed type 1 respiratory failure: pH, 7.49; P_{O2}, 50.5 mmHg; P_{CO2}, 29.5 mmHg; HCO_3, 22.0 mmol/l; Lac, 2.0 mmol/l, and calculated A-a DO2 >100 mmHg. Laboratory testing revealed the following: WBC, 10 600/µl; FDP, 6.3 µg/ml; LDH, 294 U/L; BNP, 114 pg/ml; and troponin I, 26 pg/ml. Transthoracic echocardiography showed right ventricular enlargement: 24 cm^2 end-diastolic area and 19 cm^2 end-systolic area. The trans-tricuspid pressure gradient (TRPG), which indicates estimated systolic pulmonary artery pressure, was 90 mmHg, and the diameter of the inferior vena cava (IVC) was 19 mm. In comparison, left ventricular wall motion was normal, with an LV ejection fraction (EF) of 71%. The left atrial (LA) dimension was 30 mm, early diastolic left ventricular filling velocity (E peak) was 73 cm/s, late diastolic left ventricular filling velocity (A peak) was 134 cm/s, and the ventricular filling velocity ratio was 0.54. These echocardiographic findings indicated the presence of right cardiac overload but no left cardiac overload.

The clinical, biochemical, and physiological findings suggested that pulmonary artery hypertension was the cause of the hypoxia, with resultant dyspnea and palpitations. These findings strongly suggested a diagnosis of pulmonary thromboembolism (PTE). We then performed enhanced computed tomography (CT) from the chest to the lower limbs. However, we identified no findings responsible for the severe desaturation (ie, defect in the main pulmonary artery or visible peripheral pulmonary arteries) (**Figure 1A**), and we found no venous thrombosis in the lower limbs and inferior vena cava. We found mild ground-glass opacity and consolidation in the right inferior lung lobe, although this finding was not responsible for the desaturation (**Figure 1B**). Incidentally, we found a 20-mm tumor image in the gallbladder and periaortic lymphadenopathy on the CT image, which strongly indicated gallbladder carcinoma with concurrent carcinomatous peritonitis (**Figure 1C, 1D**). Thus, we suspected PTTM rather than PTE, and that PTTM likely originated from advanced gallbladder carcinoma leading to pulmonary hypertension. In addition, we did not find other visible abnormal findings on the CT image, which led us to suspect malignant diseases such as advanced gastric cancer. Several reports show that gastric cancer is the usual origin of PTTM, but we did not perform fiberoptic gastrointestinal endoscopy because of the poor condition of the patient. The patient was admitted to the intensive care unit and was administered 4 L/min of O_2 with a nasal canula and direct oral anticoagulant (DOAC) therapy with 30 mg/day of edoxaban, in accordance with the standard dose for PTE. On day 2 of admission, we performed a pressure study using a Swan-Ganz catheter, and confirmed precapillary hypertension: the precapillary wedge pressure (PCWP) was 12 mmHg, and the mean pulmonary artery pressure was 42 mmHg. Furthermore, we obtained a 50-ml blood sample for cytology from the right pulmonary capillary vessel by balloon inflation of the Swan-Ganz catheter. On day 3, we administered a pulmonary vasodilator: 3 mg/day of riociguat, orally, which was the standard dose, without waiting for the cytology results, adding to the DOAC, to mitigate the respiratory failure. Also, we started

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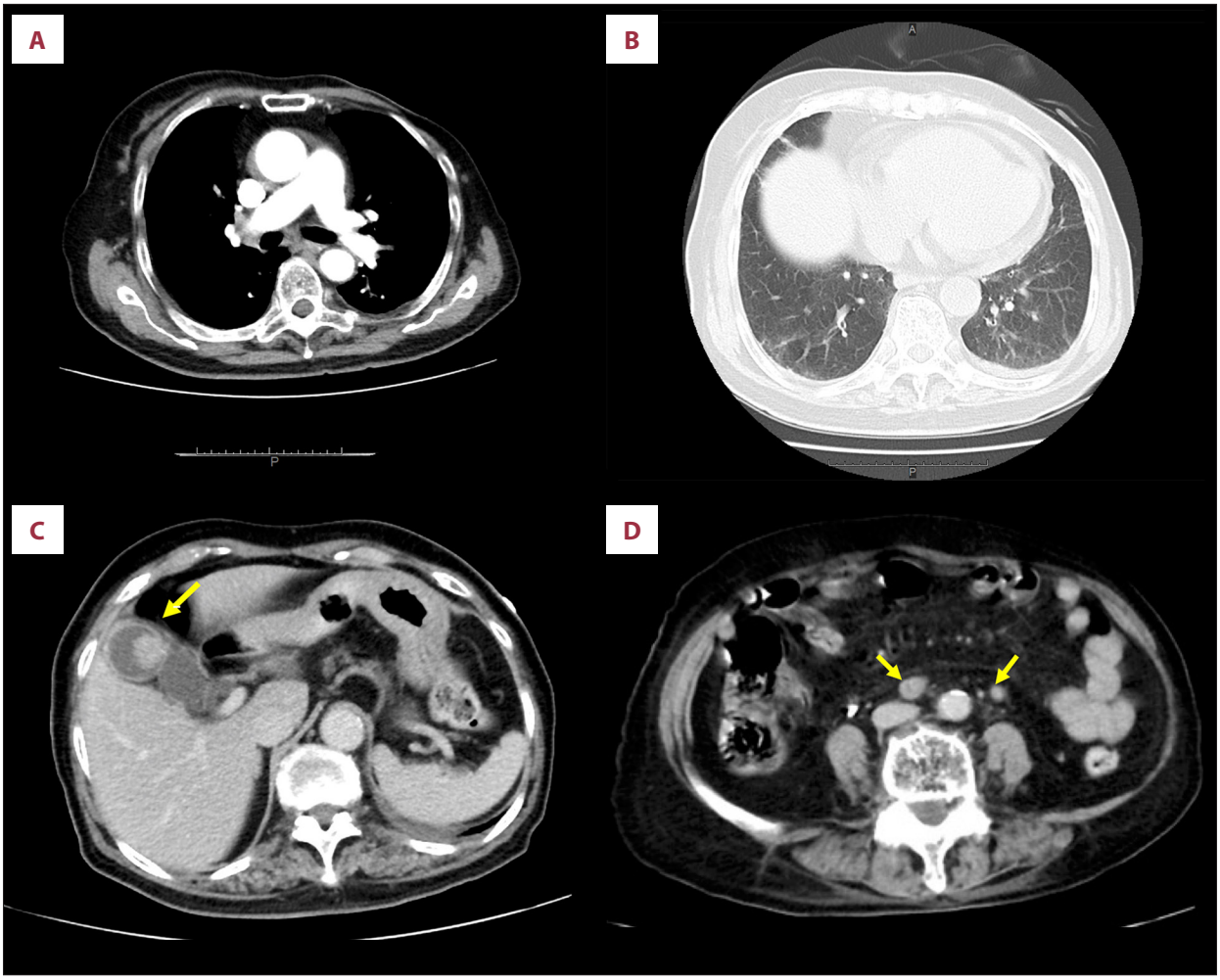

Figure 1. (**A**) Enhanced chest CT findings. (**B**) Plain chest CT findings (pulmonary window setting). (**C**) Enhanced abdominal CT findings. The yellow arrow indicates advanced gallbladder carcinoma. (**D**) Enhanced abdominal CT findings. The yellow arrow indicates carcinomatous peritonitis.

dobutamine with 2 ug/kg/min on the same day of sGC administration since blood pressure had decreased to 90/55 mmHg, probably due to the influence of sGC. On the same day, we performed pulmonary perfusion scintigraphy, and we found multiple wedge-shaped defects bilaterally, which indicated that the patient's hypoxia was due to multiple segmental pulmonary blood malperfusion (**Figure 2**).

The clue in this case leading to a provisional diagnosis of PTTM was the discrepancy between not finding a thrombus on enhanced CT, and the presence of multi-segmental defects on pulmonary perfusion scintigraphy. According to these results, early introduction of a pulmonary vasodilator was justified. After administering sGC, the patient's dyspnea was gradually relieved, and oxygenation improved (**Figure 3**). BGA on day 14 revealed: pH, 7.45; P_{O2}, 89.7 mmHg, P_{CO2}: 46.4 mmHg; HCO_3, 32.0 mmol/l; Lac, 2.5 mmol/l; and calculated A-a Do2, 24 mmHg. Finally, the cytology results from the pulmonary capillary vessel sample revealed a few aplastic cells with irregular nuclear karyotypes, stained using Papanicolaou stain (**Figure 4**). With these results, we finally diagnosed PTTM. On day 12, we discontinued dobutamine because her blood pressure had been properly controlled. On day 16, we performed echocardiography, and confirmed that the TRPG had decreased dramatically to 50 mmHg from 90 mmHg at the first visit.

The patient and her family did not wish to pursue active treatment, including chemotherapy, and wished to initiate palliative care at their home. Because her activity level had improved and corresponded to a performance status of 3, she was discharged on day 17. After discharge, she continued taking sGC and DOAC and received home-visit medical care for 106 days until her death, without serious dyspnea.

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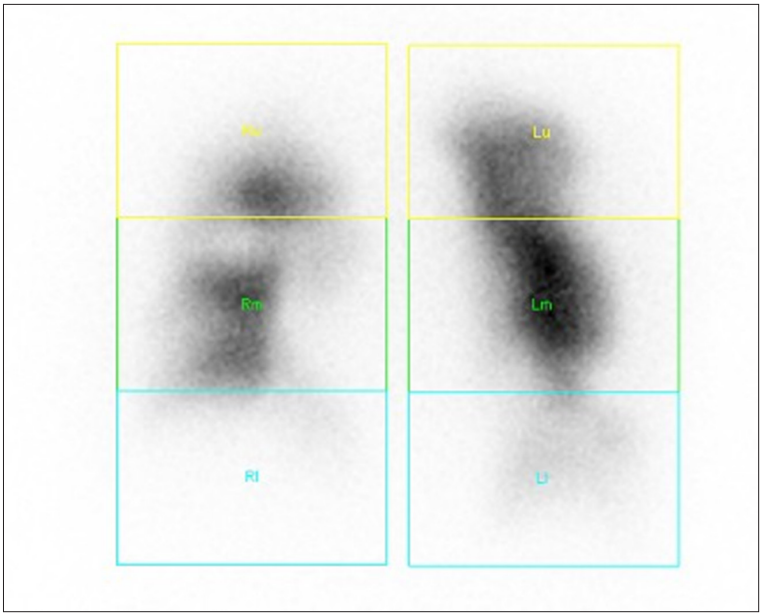

Figure 2. Pulmonary perfusion scintigraphy findings.

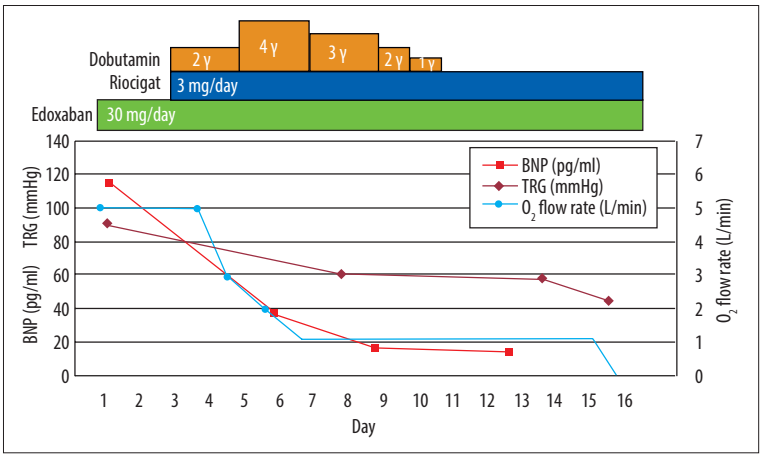

Figure 3. The patient's clinical course and laboratory data.

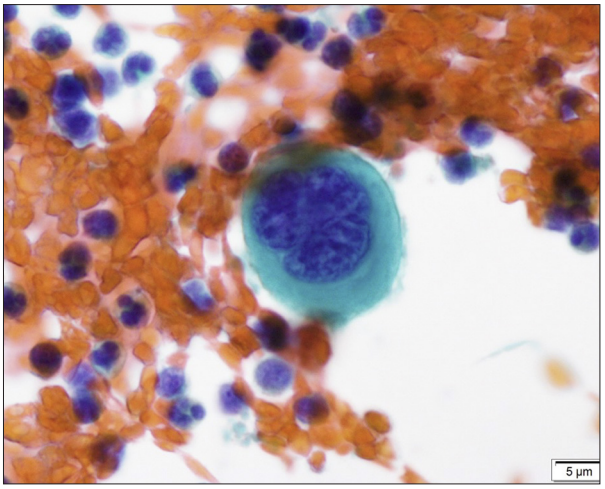

Figure 4. The cytology finding from a blood sample collected from a pulmonary peripheral artery (Papanicolaou stain).

Discussion

According to our experience in this case, we recommend the following management for PTTM to improve respiratory failure and lead to appropriate clinical care:

Introduce a Pulmonary Vasodilator

According to international guidelines, pulmonary hypertension (PH) owing to PTTM is included in class V, which contains heterogeneous etiologies. However, the diagnostic criteria and therapeutic strategy for the acute phase have not been established [4].

Hypoxia owing to PTTM evokes severe dyspnea and leads to critical respiratory failure, and possibly to systemic organ ischemia, all of which are associated with a poor prognosis. Our speculation according to the pathophysiology of PTTM

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is that dilating the pulmonary artery to address microangiopathy is reasonable to improve severe hypoxia. This therapy mitigates respiratory failure and systemic organ ischemia. Our selection of pulmonary vasodilator in this case was following to the guideline for treatment of pulmonary hypertension [5]. Riociguat, which is a first-generation sGC stimulator, has shown clinical benefit in pulmonary arterial hypertension and chronic thromboembolic hypertension (CTEPH), and sGC is one of the class 1 drugs for patients with CTEPH. Although there is no clear therapeutic guideline for PTTM, we chose to use sGC in the present patient, as we consider that PTTM is physiologically similar to CTEPH [6-8].

Although her blood pressure decreased with sGC, adding dobutamine was useful to maintain proper blood pressure. Notably, DOAC administration is necessary for patients with PTE, and this should not be discontinued in patients with PTTM. We suggest that DOAC combined with sGC is effective for improving pulmonary hypertension owing to PTTM, from a pathophysiological viewpoint.

Whereas several reports showed that chemotherapy targeting carcinoma in PTTM was effective, numerous other reports showed that chemotherapy generally reduces the patients' quality of life [9]. Therefore, we do not recommend chemotherapy in patients with PTTM whose physical status is insufficient to withstand chemotherapy.

Recommended Diagnostic Therapy

Clinical findings in PTTM are usually similar to those with PTE, and patients are sometimes misdiagnosed as having PTE regardless of the presence of venous thrombosis, resulting in death. Furthermore, as shown in our case, obtaining a definitive diagnose requires a fair amount of time. One report described a case of PTTM owing to gastric cancer that was revealed by cytology of a pulmonary blood sample; however, the patient died a few days after the final diagnosis because of rapidly worsening dyspnea [10]. In our case, although the clinical findings were similar to those of PTE, we suspected PTTM acutely, according to the CT findings, which indicated neither pulmonary artery thrombosis nor venous thrombosis, and the presence of advanced gallbladder carcinoma with peritoneal metastasis.

Introducing a therapy such as sGC, acutely, with a provisional diagnosis is challenging but important as critical care because of the need to mitigate respiratory failure. Furthermore, we consider that early diagnosis and therapeutic intervention, including with a pulmonary vasodilator, in this fatal disease may have contributed to extending our patient's life, with subsequent appropriate clinical care.

Conclusions

It is important to consider PTTM when we encounter patients whose clinical findings are similar to PTE but without an obvious thrombus origin. It is challenging, but we recommend administering a pulmonary vasodilator even under a provisional diagnosis to mitigate serious dyspnea and lead to appropriate clinical care.

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Department and Institution Where Work Was Done

This work was performed at the Department of Cardiology, South Miyagi Medical Center, Miyagi, Japan.

Declaration of Figures Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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