

Postmortem Diagnosis of Pulmonary Tumor Thrombotic Microangiopathy with Rapid Exacerbation in a Patient with Gastric Cancer: A Case Report

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Case report

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Abstract

Background: Pulmonary tumor thrombotic microangiopathy (PTTM) is a condition involving the development of pulmonary hypertension caused by the presence of microscopic tumor emboli of peripheral pulmonary arteries. Here, we report a case of rapidly exacerbating PTTM associated with gastric cancer, which was identified after the patient's death through a pathological autopsy.

Case presentation: Four days before a 52-year-old Asian woman, whose initial symptom was the occurrence of anterior chest pain while coughing, visited the emergency department of Gifu University Hospital, she had been diagnosed as having multiple osteolytic bone metastases throughout her body; for the detection of a primary lesion, she was scheduled to undergo combined positron emission tomography and computed tomography (CT) at a later date. However, she was unable to stand up, and consequently, she visited the emergency department. At the time of admission, the results of a physical examination revealed that while breathing room air, she had a percutaneous oxygen saturation level of 90% and cyanosis, and she was in a state of hemodynamic shock; laboratory-test data revealed the presence of elevated levels of fibrin degradation products and D-dimer in her blood. The results of chest CT were normal. She was admitted to the hospital's general ward for follow-up; however, she was soon in a further state of shock and respiratory failure. Electrocardiography revealed findings associated with right heart strain; however, contrast-enhanced CT did not reveal the presence of pulmonary embolism. She was transported to an intensive care unit of the hospital and treated for pulmonary hypertension; however, 45 h after her arrival at the hospital, she died of respiratory failure. A pathological autopsy revealed the presence of gastric cancer, tumor microemboli, and fibrous intimal thickening of the peripheral arteries of both lungs; thus, a diagnosis of PTTM was made.

Conclusion: In cases involving patients with carcinoma of unknown primary site and pulmonary hypertension, if CT scan rules out pulmonary embolism, emergency physicians and intensivists must consider the possibility of the patients having PTTM, which represents an oncologic emergency, and initiate the administration of chemotherapy as soon as possible.

Background

Pulmonary tumor thrombotic microangiopathy (PTTM) is a condition associated with pulmonary hypertension caused by the occurrence of tumor microembolism in peripheral pulmonary arteries, which leads to rapidly progressive pulmonary hypertension and respiratory failure. Since imaging findings for patients with PTTM do not reveal the presence of abnormalities in lung fields and the presence of major thrombi or emboli in pulmonary arteries, diagnosing PTTM early is difficult; in such patients, death often occurs a short while after the onset of symptoms. Herein, we have reported a case in which the presence of PTTM associated with gastric cancer in a patient was revealed through a pathological autopsy.

Case Presentation

A 52-year-old woman presented to her family doctor with a 20-day history of anterior chest pain while coughing. A full-body computed tomography (CT) scan revealed abnormal shadowing in her sternum, and 16 days after her visit to the family doctor, she visited the orthopedic department of Gifu University Hospital. She was diagnosed as having osteolytic bone metastasis along with partial sclerosis in the sternum, 11th thoracic vertebra, right 4th lumbar vertebra, right femoral head, and left iliac bone; she was scheduled to undergo combined positron emission tomography and CT at a later date. However, she was unable to stand up; consequently, 4 days after her visit to the orthopedic department, she visited the emergency department of our hospital. Upon her admission to the hospital, a physical examination revealed that she had a respiratory rate of 15 breaths/min, blood pressure of 88/43 mmHg, body temperature of 36.3°C, and heart rate of 116 beats/min; it also revealed that while breathing room air, she had cyanosis and a percutaneous oxygen saturation level of 90%. Furthermore, she was found to be in a state of hemodynamic shock without the use of catecholamine agonists. Her heart sounds were regular, and no heart murmurs were heard; additionally, her breath sounds were normal, and no rales were heard. An arterial blood gas test was performed, and its results are shown in Table 1. Laboratory-test data revealed that she had elevated levels of hepatobiliary enzymes; the level of fibrin degradation products in her blood was 37.7 µg/mL (normal level: ≤ 4.0 µg/mL), and that of D-dimer was 4.6 µg/mL (normal level: < 1.0 µg/mL) (Table 1). Electrocardiography only revealed that she had sinus tachycardia. The results of chest radiography and a plain chest CT scan were normal (Fig. 1).

Table 1
Laboratory Findings at The Time of Admission

<CBC>			<Biochemistry>		
WBC	8350	/uL	Total Protein	7.3	g/dL
RBC	5.36 x 10 ⁶	/uL	Albumin	4.3	g/dL
Hemoglobin	14.4	dL	Creatinine Kinase	81	g/dL
Hematocrit	53.4	%	Aspartate Transaminase	35	IU/L
Platelet	20.0 x 10 ⁴	uL	Alanine Transaminase	25	IU/L
<Coagulation Status>			Lactate Dehydrogenase	316	IU/L
APTT	24.8	sec	Alkaline Phosphatase	869	IU/L
PT-INR	0.99		Cholinesterase	390	IU/L
Fibrinogen	252	mg/dL	γ-Glutamyl Transpeptidase	26	IU/L
D-dimer	7.1	ug/mL	Creatinine	0.89	mg/dL
FDP	37.7	ug/mL	Blood Urea Nitrogen	12	mg/dL
AT III	107	%	Total Bilirubin	0.7	mg/dL
<Venous Blood Gas>			Sodium	137	mEq/L
F _I O ₂	0.21		Potassium	4.3	mEq/L
pH	7.405		Chlorine	99	mEq/L
PaCO ₂	27.6	mmHg	C-reactive protein	0.55	mg/dL
PaO ₂	70.3	mmHg	Blood Glucose	223	mg/dL
HCO ₃ ⁻	16.9	mmol/L	Hemoglobin A1c	5.8	%
Base Excess	-5.9				
Lactate	51	mg/dL			

She was admitted to a general ward of the hospital for examination and follow-up. Soon after her admission, she went into a state of shock, with a systolic blood pressure of 70 mmHg, and developed respiratory failure; therefore, we initiated the administration of oxygen to the patient. Two-dimensional transthoracic echocardiography revealed findings associated with right heart strain; however, contrast-enhanced CT did not reveal the presence of any obvious thrombus in the pulmonary arteries. Although she was receiving intensive care, and the administration of treatment for pulmonary hypertension had been initiated, she died of respiratory failure 45 h after her arrival at our hospital (Fig. 2). A pathological

autopsy revealed that the patient had gastric cancer, lymph node metastasis around the aorta, stomach, and pancreas, and bone metastases in the lumbar vertebrae. The autopsy revealed that the patient had no major tumor embolism; however, the presence of tumor microemboli and fibrous intimal thickening in the peripheral pulmonary arteries was detected (Fig. 3). Additionally, intestinal ischemia and the presence of microbleeds in the liver and cerebellum were detected. Finally, through a postmortem histopathological diagnosis, the patient was diagnosed as having PTTM.

Discussion And Conclusions

The findings in a case involving a patient with carcinoma of unknown primary site, who died due to rapidly progressive dyspnea and hypoxemia and was diagnosed after her death as having PTTM, have been highlighted in this report. With respect to cases involving patients with carcinoma of unknown primary site who have pulmonary hypertension, but in whom the presence of pulmonary embolism can be ruled, emergency physicians should remember and consider the possibility of the patients having PTTM, which represents an oncologic emergency.

PTTM is a condition that was first described by Von Herbay et al. in 1990 [1]; it is a life-threatening disease because it is associated with the occurrence of severe respiratory failure with rapidly progressive pulmonary hypertension. Unlike pulmonary tumor embolism, PTTM is characterized by fibrous intimal thickening of peripheral pulmonary arteries, especially the small arteries. Clinically, it is difficult to differentiate between PTTM and pulmonary embolism; PTTM is often identified through pathological autopsies, and it is most commonly associated with gastric carcinoma [2]. Furthermore, other types of primary cancer that have been reported to be complicated by PTTM include breast cancer, tongue cancer, hepatocellular carcinoma, colorectal cancer, and prostate cancer [3]. RH Godbole et al. found that with respect to the main symptoms reported in 160 unique cases of PTTM, hypoxemia, dyspnea, abdominal pain, cough, and general pain were reported in 95%, 94 %, 86%, 85%, and 73% of the cases, respectively [3]. It has also been reported that in most cases of PTTM, there is an elevation in D-dimer levels, which makes it even more difficult to differentiate PTTM from pulmonary embolism [4]. Moreover, in cases of PTTM, the radiological findings obtained through chest CT, such as the presence of centrilobular nodules, ground-glass opacities, linear branching opacities, and interlobular septal thickening, are nonspecific [5–8].

In the present case, when the patient was admitted to the hospital, there was a mild elevation in the level of D-dimer in the patient's blood; however, chest CT did not reveal any significant findings, and we could not make a definitive diagnosis before the patient's death. Through the pathological autopsy performed in this case, over a wide area in both lungs, we observed the presence of arterial occlusions caused by microthrombi and tumor emboli that were present in pulmonary arterioles, accompanied by congestion and hemorrhage. Fibrous intimal thickening of the pulmonary arteries was also noticeable; this finding is typically associated with PTTM rather than pulmonary embolism. Although the pathogenesis of PTTM is still unclear, it is thought that an activation of the coagulation system and release of inflammatory mediators leads to the formation of microthrombi and fibrous intimal thickening of small arteries, which

in turn lead to the progression of pulmonary hypertension. It has also been reported that in cases of PTTM, there is a congregation of macrophages around blood vessels, and cell-to-cell signaling via osteopontin and CD44 is thought to contribute significantly to the pathogenesis of PTTM [2]. As mentioned previously, PTTM progresses rapidly, and reports indicate that in cases of PTTM, the average duration from the onset of PTTM in a patient to the patient's admission to a hospital is about 1 month, and in fatal cases, the median survival time is only 5 days [9]. Therefore, in many cases of PTTM, PTTM is diagnosed after the patients have already died; so far, in only a few reported cases of PTTM, patients were diagnosed and treated while they were still alive. Pulmonary microvascular cytology with the study of samples drawn through a wedged pulmonary artery catheter is the most reasonable method for making a diagnosis when a patient is still alive, it has been reported that the sensitivity and specificity of this technique range from 80–88% and 82–94%, respectively [10, 11].

A unique case regarding a patient with PTTM has been reported previously; in this case, the patient survived for 7 months after receiving imatinib in addition to chemotherapy for signet-ring cell carcinoma [12]. Imatinib is a platelet-derived growth factor receptor-tyrosine kinase inhibitor that has the potential to cause reverse remodeling due to its proliferation-inhibitory, apoptosis-inducing, and vasoconstrictive effects. Several other cases involving the use of imatinib for the treatment of pulmonary hypertension caused by PTTM have been reported, suggesting that imatinib is effective not only for the treatment of the primary tumor but also for the treatment of pulmonary hypertension [13–15]. According to the guidelines of the European Society of Cardiology and the European Respiratory Society for the diagnosis and treatment of pulmonary hypertension, pulmonary arterial hypertension is included in group 1 of the Nice classification of pulmonary hypertension, and upfront combination therapy, such as treatment with diuretics, prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors, is recommended for patients who, according to the World Health Organization's functional classification of pulmonary hypertension, have class II pulmonary hypertension, which is often observed in intensive care units (this therapy should be considered for patients with class IIa disease and may be considered for patients with class IIb disease). However, pulmonary hypertension related to tumor embolism is included in group 5 of the Nice classification. To the best of our knowledge, no randomized controlled trials depicting the efficacy of drugs for the treatment of pulmonary hypertension associated with tumor embolism have been performed so far [16]. Other drugs such as corticosteroids and anticoagulants are easier to introduce and have been used in many cases; however, no clear effects have been observed [11, 17, 18].

Because there is no standard diagnostic approach for PTTM, if there is a sudden worsening of the respiratory status of a patient who has carcinoma of unknown primary site and pulmonary hypertension, emergency physicians and intensivists should remember and consider that in addition to the possibility of the patient having pulmonary embolism, the patient may have PTTM, which is an oncologic emergency. Furthermore, if a patient is suspected of having PTTM, we believe it is necessary to begin the administration of chemotherapy as soon as it is possible to do so according to the etiology of PTTM; additionally, it is important to continue to search for the primary cancer site in the patient.

Abbreviations

PTTM: pulmonary tumor thrombotic microangiopathy

CT: computed tomography

Declarations

Ethics approval and consent to participate

In Japan, approval from an ethics committee is not required for the reporting of cases. This case was reported in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the government of Japan.

Consent for publication

Written informed consent was obtained from the patient's legal guardians for the publication of this case report and any accompanying images. A copy of the consent form is available for the Editor-in-Chief of *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* to review.

Availability of data and materials

The datasets obtained and analyzed during this case and for writing of this report are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

RK, KK, H Okada, GY, T Miura, H Oiwa, YM, YK, RY, T Miyake, TD, TY, and SY treated the patient. TK, HT and AH performed the autopsy. RK and KK wrote the manuscript. H Okada revised and edited the manuscript. All authors have read and approved the final manuscript.

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Figures

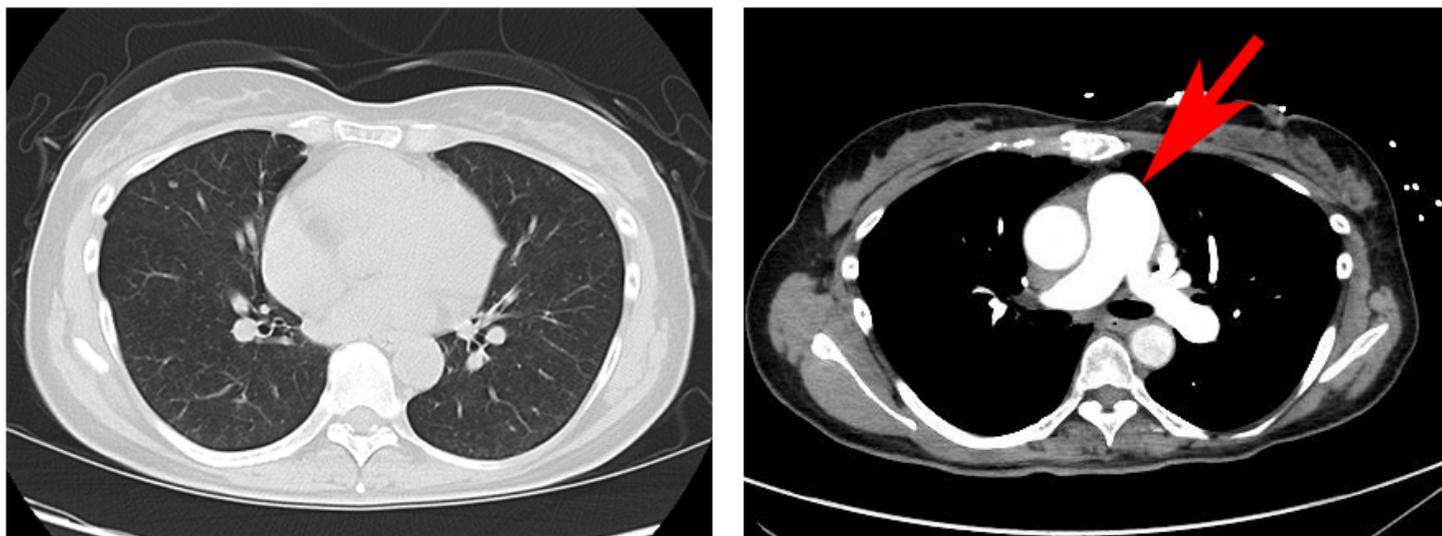


Figure 1

Results of computed tomography (CT) performed after the patient's arrival and admission to the hospital. Legend Left panel: result of thoracic CT performed after the patient's arrival to the hospital; no abnormal lesion was found. Right panel: thoracic contrast-enhanced CT performed after the patient's admission to

the hospital; no massive pulmonary thromboembolism or tumor emboli were found. Red arrow indicates that the diameter of aorta is enlarged.

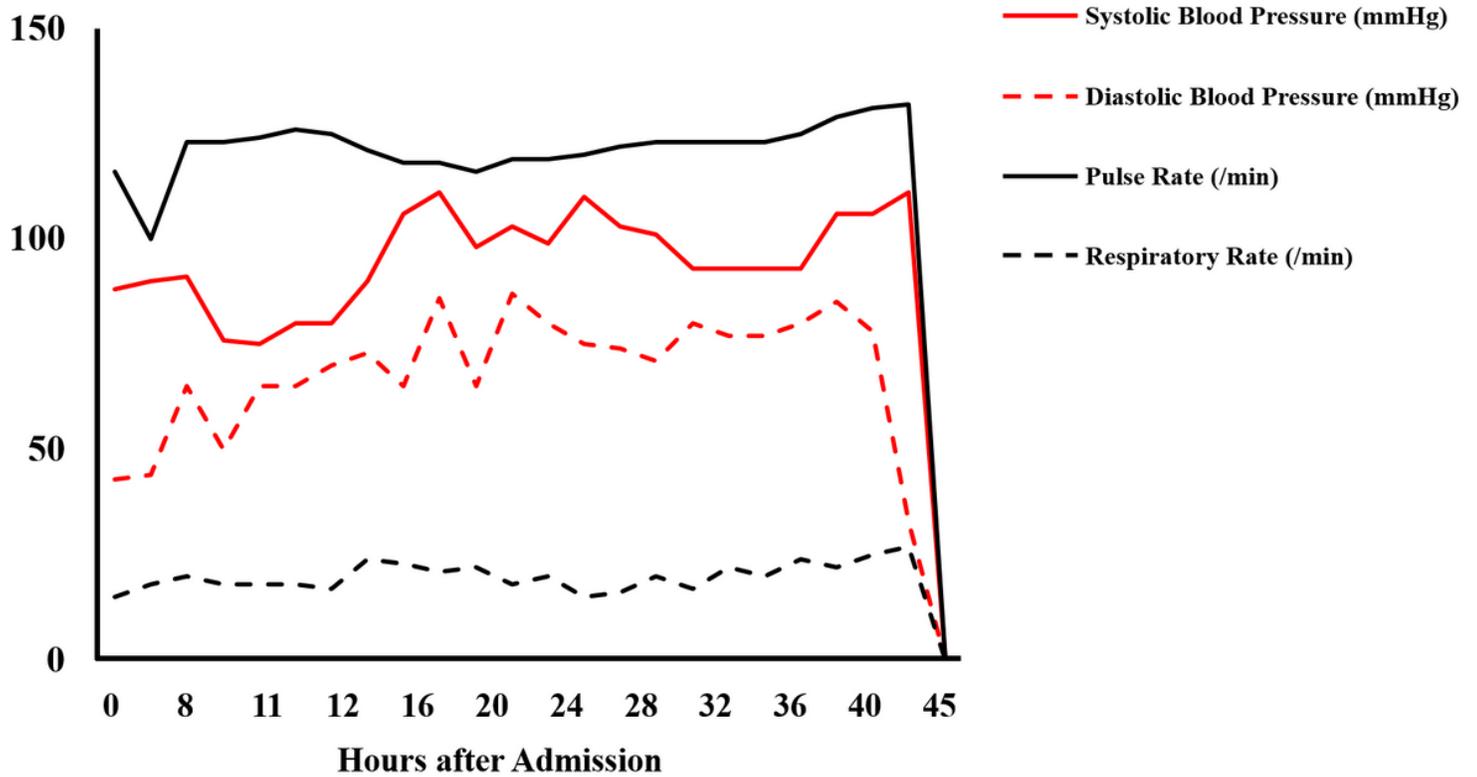


Figure 2

Summary of the clinical course in the reported case.

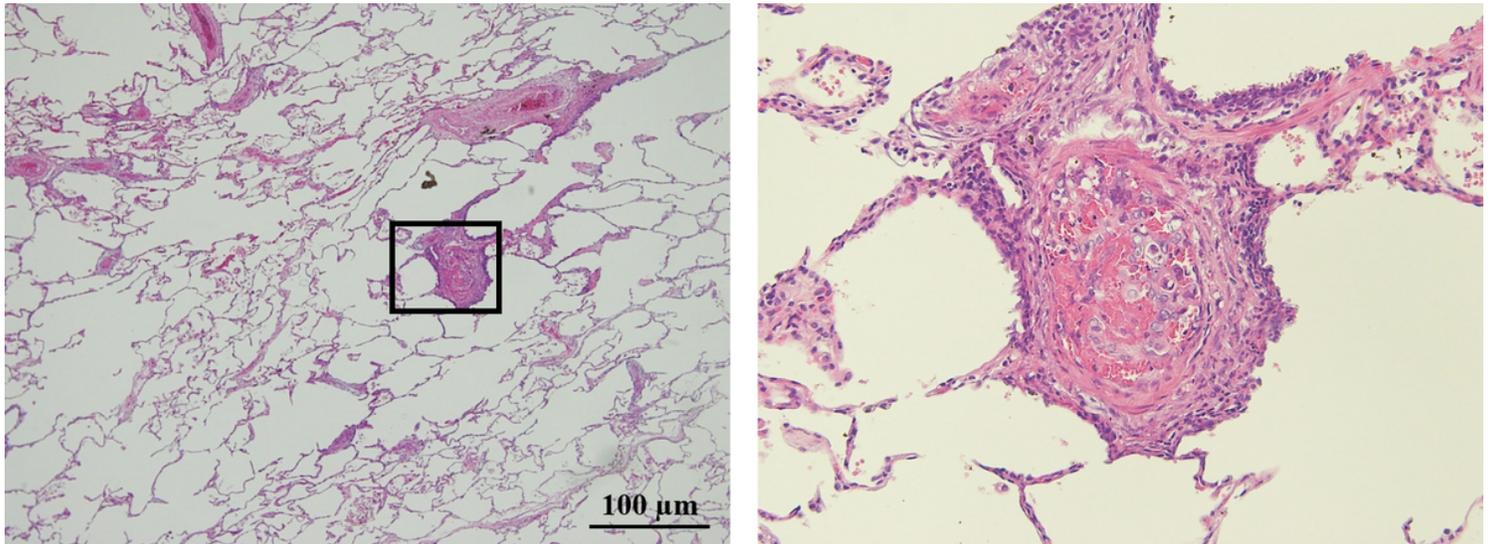


Figure 3

Images obtained during the pathological autopsy performed in the reported case. Legend Left panel: low-magnification image of the right upper lobe. Right panel: enlarged image of the black square in the left

panel of Figure 3; the presence of fibrous intimal thickening in the peripheral pulmonary arteries was observed.