

Pulmonary Tumor Thrombotic Microangiopathy Caused by a Parotid Tumor: Early Antemortem Diagnosis and Long-term Survival

Haruka Toyonaga¹, Michiko Tsuchiya¹, Chikara Sakaguchi¹, Hitomi Ajimizu¹, Yosuke Nakanishi¹, Seiya Nishiyama¹, Noboru Morikawa¹, Yasuyuki Hayashi¹, Yukio Nagasaka¹ and Hiroshi Yasui²

Abstract

Pulmonary tumor thrombotic microangiopathy (PTTM) is a high-mortality disease that is difficult to diagnose clinically. Our patient was an 80-year-old woman who came to us due to symptoms of increasing dyspnea. A clinical evaluation showed that she had hypoxemia and pulmonary arterial hypertension without any abnormalities in the major pulmonary arteries, bronchi, or alveoli. A lung perfusion scan showed multiple wedge-shaped perfusion defects. Further examination revealed adenocarcinoma in her right parotid gland with metastasis to the submandibular lymph nodes. We diagnosed her to have PTTM caused by a parotid tumor. The patient survived for 11 months with chemotherapy. An early antemortem diagnosis by minimally invasive examinations will help PTTM patients to survive longer.

Key words: pulmonary tumor thrombotic microangiopathy, perfusion scan, pulmonary hypertension, antemortem diagnosis, salivary duct carcinoma of the parotid gland

(Intern Med 56: 67-71, 2017)

(DOI: [10.2169/internalmedicine.56.7439](https://doi.org/10.2169/internalmedicine.56.7439))

Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare form of metastatic cancer that causes progressive dyspnea and pulmonary arterial hypertension (PAH). Histopathologically, PTTM is characterized by tumor embolism, multiple microthrombi, and intimal myofibroblast proliferation in the pulmonary arteries and arterioles (1, 2).

An antemortem diagnosis of PTTM is difficult because the symptoms and clinical findings are not specific and the disease usually progresses rapidly. An autopsy study from the Mayo Clinic reported the mean interval between respiratory symptoms and death to be only one month (3).

Only a few cases have been reported to have survived for as long as a year with chemotherapy (4-9). We herein report a case of PTTM caused by salivary duct carcinoma. We made an antemortem diagnosis based on the clinical findings

rather early in the patient's disease process, and she therefore was able to survive for 11 months with chemotherapy.

Case Report

An 80-year-old woman was admitted to our hospital because of progressive dyspnea on exertion for the previous two months. She had been treated for hypertension and dyslipidemia. She had no known history of cancer. On admission, her oxygen saturation (SpO₂) was 94%, which decreased to 74% with exertion. Her body temperature was 37°C, heart rate was 82 beats per minute (regular), and blood pressure was 161/77 mmHg. Physical examination of her heart and chest showed no abnormality at that time. Several submental lymph nodes were palpable as rubbery, non-tender masses, and they measured less than 2 cm in size.

Arterial blood gas (ABG) on ambient air showed arterial

¹Respiratory Medicine, Rakuwakai Otowa Hospital, Japan and ²Department of Pathology, Rakuwakai Otowa Hospital, Japan

Received for publication March 18, 2016; Accepted for publication May 10, 2016

Correspondence to Dr. Michiko Tsuchiya, rakuwadr015@rakuwadr.com

Table. Laboratory Findings on Admission.

WBC	4,700 / μ L	LDH	254 U/L	sIL-2R	714 U/mL
Neutro	67.5 %	ALP	239 U/L	BNP	54.7 pg/mL
Lymph	23.7 %	γ -GTP	30 U/L	ANA	< 1:40
Mono	6.2 %	BUN	8.4 mg/dL	PR3-ANCA	<1.0 U/mL
Eosino	1.5 %	Cre	0.46 mg/dL	MPO-ANCA	<1.0 U/mL
Baso	1.1 %	Na	136 mEq/L	KL-6	516 U/mL
RBC	398×10^4 / μ L	K	4.3 mEq/L	SP-D	138 ng/L
Hb	13 g/dL	INR	0.98	SP-A	34.2 ng/mL
Plt	19.9×10^4 / μ L	APTT	29.9 sec	ACE	13.4 U/L
TP	6.9 g/dL	D-dimer	1.0 μ g/mL	<ABG analysis>	
Alb	4.2 g/dL	CEA	4.7 ng/dL	pH	7.43
T-Bil	0.9 mg/dL	Pro GRP	60.1 pg/mL	PaCO ₂	35 Torr
AST	33 U/L	CYFRA	<1.0 ng/mL	PaO ₂	64 Torr
ALT	37 U/L	CA19-9	6.5 U/mL	HCO ₃	23.2 mmol/L

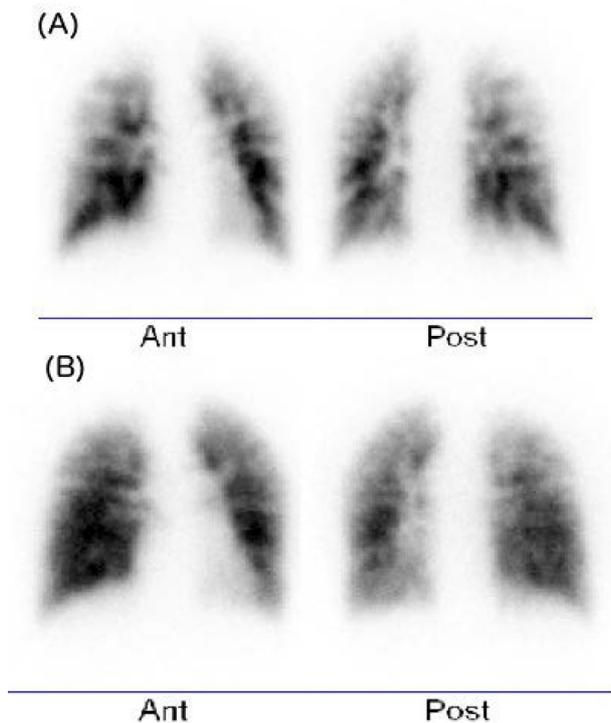


Figure 1. Lung perfusion scans. (A) Panel A showed multiple subsegmental peripheral defects before chemotherapy. (B) The multiple defects improved after chemotherapy.

oxygen tension (PaO₂) of 64 mmHg and alveolar-arterial oxygen tension difference (AaDO₂) of 43 mmHg (Table). Chest X-rays, electrocardiography (ECG), and ultrasound cardiography (UCG) showed no abnormality. Pulmonary function tests showed a decreased diffusing capacity (%DL_{CO}; 74%). A high-resolution computed tomography (HRCT) scan showed almost no abnormalities in the lung fields and a contrast-enhanced CT scan showed no findings of pulmonary embolism. Transbronchial lung biopsy (TBLB) and bronchoalveolar lavage revealed no evidence of disease, including malignancy.

As this patient showed a decreased diffusing capacity

without any parenchymal lung abnormalities, we suspected that she had problems in her pulmonary circulation. We could exclude pulmonary thromboembolism by contrast-enhanced CT. These findings indicated that this patient had peripheral pulmonary vascular disease. A lung perfusion scan was performed and revealed multiple wedge-shaped subsegmental defects (Fig. 1A). From these findings, we considered PTTM to be a possible cause of her illness.

Her serum tumor markers and immunological tests were normal (Table). Upper gastrointestinal endoscopy and mammography revealed no evidence of malignancy. Positron emission tomography (PET)-CT showed an abnormal uptake in her right deep neck with a maximal standardized uptake value (SUV_{max}) of 3.8. There were no remarkable uptakes in the lung fields.

MRI of the head and neck showed a right parotid mass that had invaded the parapharyngeal space, medial pterygoid muscle, and mandibular bone. A biopsy of the submandibular lymph nodes revealed metastatic adenocarcinoma, and an immunohistochemical examination showed cytokeratin 7 (CK7) and gross cystic disease fluid protein 15 (GCDFFP15) to both be positive. These findings were compatible with salivary duct carcinoma. We diagnosed her to have PTTM caused by adenocarcinoma of the parotid gland according to these radiological and pathological findings. We could not perform a biopsy directly from the parotid gland because its location was deep and difficult to approach.

The patient complained of increasing exertional dyspnea, and a further decrease of SpO₂ at rest was noted within a month after admission. A split of the second heart sound (S₂) at the apex, a clinical sign of pulmonary hypertension, had become apparent by this time. ECG showed new-onset T-wave inversion in leads II, III, aVf, and V1-5. UCG at this time revealed tricuspid regurgitation with a pressure gradient (TRPG) of 57 mmHg, right ventricular dilatation, and flattening of the interventricular septum. These findings suggested that the patient had significant pulmonary hypertension. HRCT showed dilatation of the peripheral pulmonary arteries and a diffuse patchy distribution of ground-glass

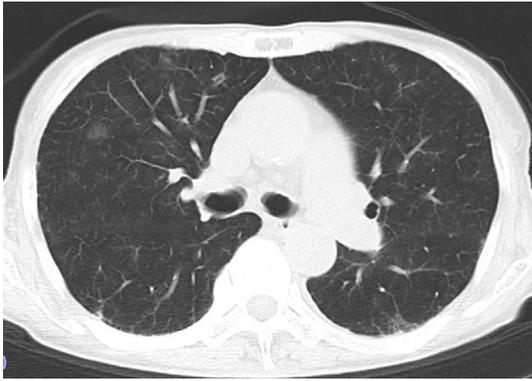


Figure 2. Chest CT one month after admission revealed dilatation of the peripheral arteries and diffuse ground-glass opacities.

opacity (GGO) in the bilateral lung fields (Fig. 2). Enhanced CT revealed no findings of pulmonary emboli or deep vein thrombosis of the lower extremities. Based on these findings we considered the cause of pulmonary hypertension to be diffuse pulmonary embolization at the peripheral pulmonary arteries, which was compatible with the findings of PTTM.

Although the diagnosis of PTTM was not pathologically definitive, we started chemotherapy with paclitaxel (PTX; 170 mg/m²)/carboplatin (CBDCA; AUC 4.5). Dyspnea and the physical signs of PAH improved gradually during the first two weeks after starting chemotherapy, and a decrease of TRPG was found after another two weeks. The defects in the lung perfusion scan also showed some improvement (Fig. 1B). Two months after the first course of chemotherapy, her symptoms deteriorated again with the increase of TRPG. We treated her with five courses of PTX/CBDCA and a course of docetaxel (DOC). Her symptoms and the findings of PAH first improved, but then deteriorated repeatedly (Fig. 3). Eleven months after her initial visit, severe dyspnea, hypoxia and pulmonary hypertension developed and she died suddenly on her way to the restroom.

Autopsy findings of her lung showed multiple tumor embolisms, thrombus formation, recanalization, and intimal fibrocellular proliferation in the muscular pulmonary arteries measuring from 100 to 200 μ m in diameter (Fig. 4). The diagnosis of PTTM was made pathologically. Salivary duct carcinoma with lymphovascular invasion was found in her right parotid gland and it was considered to be the primary lesion of PTTM. Her heart showed significant dilation and thickening of the right ventricle, and her other organs were congestive, which suggested that significant PAH and right-sided heart failure were the causes of death. Slight alveolar wall thickening and inflammatory cell infiltration with hyaline membrane formation was observed focally. There were almost no tumor cells in these alveoli.

Discussion

In this case, the patient was clinically diagnosed to have PTTM without a histological confirmation of the lung le-

sion. A formerly healthy elderly woman presented with progressive dyspnea and hypoxemia with increased AaDO₂ and decreased DLCO without any abnormalities in the lung parenchyma based on the findings of HRCT and TBLB specimens. No cardiac or pulmonary shunts nor pulmonary emboli in the major pulmonary arteries were found. We estimated that the main cause of hypoxemia was most likely located in the peripheral pulmonary circulation. A lung perfusion scan showed diffuse wedge-shaped defects. These findings suggested the clinical diagnosis of PTTM.

Recent pathological studies have revealed the frequency of PTTM to be 1.4% of all the malignant tumors found in autopsied patients. The most frequent histological type was adenocarcinoma (93.3%), and the most frequent primary site was the stomach (60%) (10). We found only one reported case of PTTM caused by salivary duct carcinoma (SDC) in the literature (11). The reported patient died two months after the onset of dyspnea.

SDC is a rare and aggressive malignancy that accounts for 1-3% of all salivary malignancies. SDC most commonly affects men in their fifth and sixth decades of life. It presents as a rapidly growing mass with possibilities of early distant metastases and local recurrence (12). The treatment modalities are non-consensual because of the limited data and the median overall survival was 3.1 years in one series (13).

A radiological diagnosis of PTTM is difficult because the findings are often minimal or nonspecific. CT findings of PTTM may show peripheral wedge-shaped opacities, multifocal dilatation or beading of vessels, diffuse thickening of the interlobular septa, and enlarged central pulmonary arteries (14, 15). In our case, a patchy distribution of GGO was observed in the lung fields on chest CT when her dyspnea increased. Focal alveolar wall thickening and inflammatory cell infiltration with hyaline membrane formation were observed in the autopsy findings. These findings may indicate ischemic lung injury induced by PTTM and explain the pathogenesis of GGO.

There were no remarkable findings in lung fields on PET-CT in our case, although Tashima and colleagues reported that ¹⁸F-fluorodeoxyglucose (FDG)-PET images showed a multifocal abnormal FDG uptake in both lung fields (16). In lung perfusion scans, multiple small segmental defects throughout the bilateral lungs are reported to be characteristic of PTTM (6, 10, 17, 18), as was seen in this case.

Transbronchial lung biopsy (19), CT-guided lung biopsy (7), and video-assisted thoracic surgery (5) have been attempted for the pathological diagnosis of PTTM in patients who had a good performance status. Pulmonary microvascular cytology using a wedged pulmonary artery catheter has also been reported to be a useful diagnosis method (4, 20). These diagnostic procedures may be attempted when feasible.

Several cases of PTTM have been diagnosed early in their disease process. They were treated with anticancer drugs or molecular target drugs, and the patients survived for 7 to 15

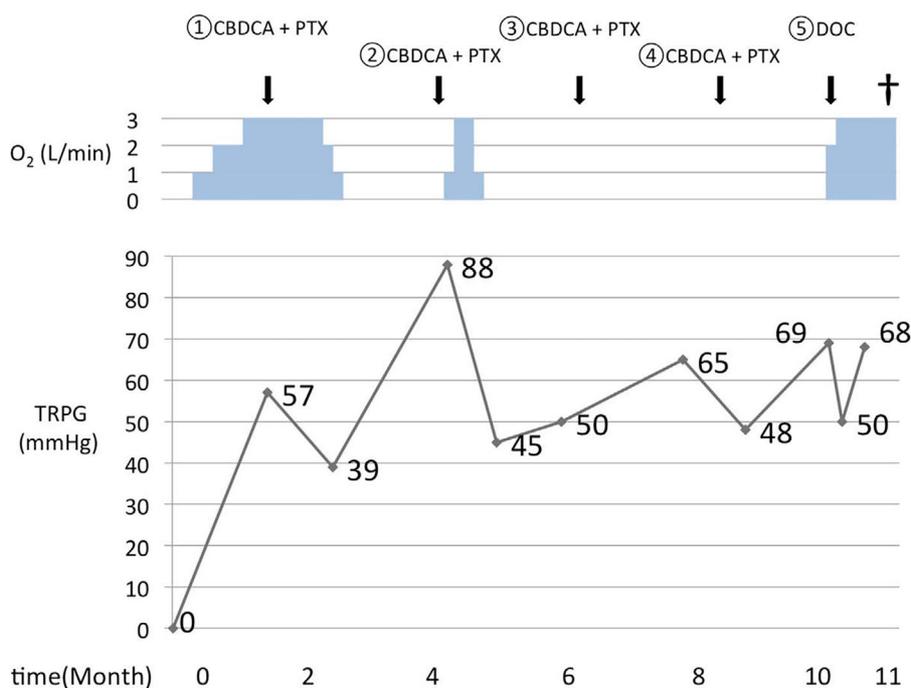


Figure 3. Time course of symptoms and treatments. TRPG and oxygenation improved after each course of chemotherapy (arrow).

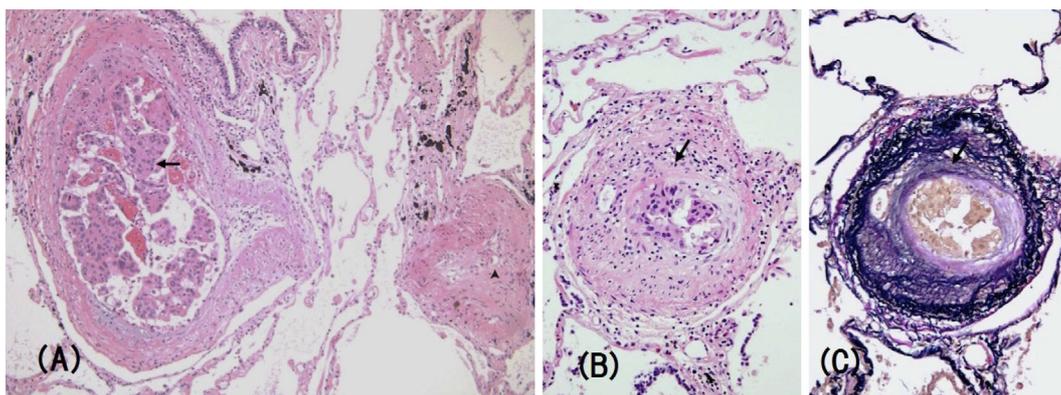


Figure 4. Autopsy specimens of the lung revealed evidence of PTTM. (A) Papillary clusters of tumor cells adhered to arterial intima and intimal fibrous thickening occlude arterial lumen (arrow). Thrombus formation and recanalization of the arteries (arrowhead) are also observed [Hematoxylin and Eosin (H&E) staining, $\times 200$] (B) Tumor cells and intimal fibrocellular proliferation occlude the arterial lumen (arrow) (H&E staining, $\times 400$) (C) Intimal fibrocellular proliferation. The surrounding alveolar walls are mostly normal. (elastica van Gieson stain, $\times 400$).

months (4-9, 19). As most patients with PTTM are diagnosed in advanced stages and with a poor performance status (PS), they are not candidates for chemotherapy. Some kinds of hormone therapies and molecular-targeted therapies may be useful for them because of their mild adverse effects and rapid response to the treatment.

When patients present with progressive hypoxemia and signs of PAH and also no significant findings on chest CT, we should thus consider PTTM. Lung perfusion scans will help diagnose PTTM. The search for the primary cancer lesion is also mandatory to establish an early antemortem diagnosis and select the optimal treatment.

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

References

1. von Herbay A, Illes A, Waldherr R, Otto HF. Pulmonary tumor thrombotic microangiopathy with pulmonary hypertension. *Cancer* **66**: 587-592, 1990.
2. Okubo Y, Wakayama M, Kitahara K, et al. Pulmonary tumor thrombotic microangiopathy induced by gastric carcinoma: morphometric and immunohistochemical analysis of six autopsy cases. *Diagn Pathol* **6**: 27, 2011.
3. Shields DJ, Edwards WD. Pulmonary hypertension attributable to neoplastic emboli: An autopsy study of 20 cases and a review of

- literature. *Cardiovasc Pathol* **1**: 279-287, 1992.
4. Higo K, Kubota K, Takeda A, Higashi M, Ohishi M. Successful antemortem diagnosis and treatment of pulmonary tumor thrombotic microangiopathy. *Intern Med* **53**: 2595-2599, 2014.
 5. Kayatani H, Matsuo K, Ueda Y, et al. Pulmonary tumor thrombotic microangiopathy diagnosed antemortem and treated with combination chemotherapy. *Intern Med* **51**: 2767-2770, 2012.
 6. Minatsuki S, Miura I, Yao A, et al. Platelet-derived growth factor receptor-tyrosine kinase inhibitor, imatinib, is effective for treating pulmonary hypertension induced by pulmonary tumor thrombotic microangiopathy. *Int Heart J* **56**: 245-248, 2015.
 7. Uruga H, Morokawa N, Enomoto T, et al. A case of pulmonary tumor thrombotic microangiopathy associated with lung adenocarcinoma diagnosed by CT-guided lung biopsy. *Nihon Kogyaku Gakkai Zasshi* **46**: 928-933, 2008 (in Japanese, Abstract in English).
 8. Miyano S, Izumi S, Takeda Y, et al. Pulmonary tumor thrombotic microangiopathy. *J Clin Oncol* **25**: 597-599, 2007.
 9. Ishiguro T, Takayanagi N, Ando M, Yanagisawa Y, Shimizu Y, Sugita Y. Pulmonary tumor thrombotic microangiopathy responding to chemotherapy. *Nihon Kogyaku Gakkai Zasshi* **49**: 681-687, 2011 (in Japanese, Abstract in English).
 10. Uruga H, Fujii T, Kurosaki A, et al. Pulmonary tumor thrombotic microangiopathy: a clinical analysis of 30 autopsy cases. *Intern Med* **52**: 1317-1323, 2013.
 11. Uruga H, Fujii T, Kurosaki A, et al. A case of pulmonary tumor thrombotic microangiopathy caused by carcinoma (salivary duct carcinoma) ex pleomorphic adenoma. *Nihon Kogyaku Gakkai Zasshi* **48**: 463-468, 2010 (in Japanese, Abstract in English).
 12. Mlika M, Kourda N, Zidi Y, et al. Salivary duct carcinoma of the parotid gland. *J Oral Maxillofac Pathol* **16**: 134-136, 2012.
 13. Gilbert MR, Sharma A, Schmitt NC, et al. A 20-year review of 75 cases of salivary duct carcinoma. *JAMA Otolaryngol Head Neck Surg* **142**: 489-495, 2016.
 14. Franquet T, Gimenez A, Prats R, Rodriguez-Arias JM, Rodriguez C. Thrombotic microangiopathy of pulmonary tumors: a vascular cause of tree-in-bud pattern on CT. *Am J Roentgenol* **179**: 897-899, 2002.
 15. Tack D, Nollevaux MC, Gevenois PA. Tree-in-bud pattern in neoplastic pulmonary emboli. *Am J Roentgenol* **176**: 1421-1422, 2001.
 16. Tashima Y, Abe K, Matsuo Y, et al. Pulmonary tumor thrombotic microangiopathy: FDG-PET/CT findings. *Clin Nucl Med* **34**: 175-177, 2009.
 17. Crane R, Rudd TG, Dail D. Tumor microembolism: pulmonary perfusion pattern. *J Nucl Med* **25**: 877-880, 1984.
 18. Iwamoto H, Sakai M, Yamane T, et al. A case of tumor microembolism diagnosed by perfusion scan and transbronchial lung biopsy. *Nihon Kogyaku Gakkai Zasshi* **47**: 687-691, 2009 (in Japanese, Abstract in English).
 19. Ogawa A, Yamadori I, Matsubara O, Matsubara H. Pulmonary tumor thrombotic microangiopathy with circulatory failure treated with imatinib. *Intern Med* **52**: 1927-1930, 2013.
 20. Yamakawa H, Yoshida M, Yamada M, et al. Pulmonary tumor thrombotic microangiopathy associated with urothelial carcinoma of the urinary bladder: antemortem diagnosis by pulmonary microvascular cytology. *Clin Case Rep* **3**: 735-739, 2015.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).