International Cancer Conference Journal (2023) 12:1–6
https://doi.org/10.1007/s13691-022-00566-7

CASE REPORT

Antemortem diagnosis of pulmonary tumor thrombotic microangiopathy associated with gastric cancer and response to immediate chemotherapy

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Received: 31 March 2022 / Accepted: 5 July 2022 / Published online: 29 July 2022

Abstract

Pulmonary tumor thrombotic microangiopathy is a rare and fatal complication of cancer that features widespread tumor cell-derived embolisms in the small arteries and arterioles of the lung and is often associated with thrombus formation. We describe the case of a 43-year-old woman who was hospitalized with cough and respiratory distress that lasted for 2 months. Computed tomography findings demonstrated multiple areas of interlobular septal thickening and ground-glass opacities in both lungs. Transthoracic echocardiography demonstrated a D-shaped left ventricle suggesting right heart overload, and pulmonary blood flow scintigraphy revealed multiple small, peripheral, and patchy areas of reduced blood flow. Upper gastrointestinal endoscopy revealed a signet-ring carcinoma. The patient was diagnosed with pulmonary tumor thrombotic microangiopathy based on her clinical presentation and treatment with tegafur, gimeracil oteracil potassium, oxaliplatin, and an anticoagulant was initiated on the 3rd day after admission. The symptoms improved rapidly after treatment initiation. The patient was discharged 28 days after initiation of chemotherapy without the need for supplemental oxygen. This case suggests that the immediate use of chemotherapy and anticoagulants for treating pulmonary tumor thrombotic microangiopathy may improve patient survival.

Keywords Gastric cancer · Pulmonary hypertension · Pulmonary tumor thrombotic microangiopathy · Signet-ring carcinoma

Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare form of pulmonary arterial embolism caused by tumor cells. In PTTM cases, the endothelial attachments of multiple microscopic tumor cell emboli induce fibrocellular intimal proliferation of small pulmonary arteries and arterioles combined with secondary thrombosis, resulting in pulmonary arteriole stenosis or obstruction, which causes pulmonary hypertension (PH), leading to acute or subacute cor pulmonale and respiratory failure [1].

An antemortem PTTM diagnosis is difficult because the chest computed tomography (CT) findings are often trivial or non-specific, and the disease rapidly progresses to death. In a previous study, 7 of 103 patients were pathologically diagnosed with PTTM while still alive [2], and their prognosis was unclear; however, few patients had a survived for several months. We report the case of a patient with PTTM associated with gastric cancer who was diagnosed antemortem and responded to immediate chemotherapy. Written informed consent was obtained from the patient for publishing this case report and any accompanying images.

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Case report

A 43-year-old woman presented to a different hospital 1 month prior with complaints of productive cough lasting for 2 months and dyspnea interfering with her daily life (Hugh–Jones IV) that progressed rapidly 1 week before admission to our hospital. Contrast-enhanced CT and upper gastrointestinal endoscopy were performed. She was diagnosed with gastric cancer and referred to our hospital for advanced respiratory failure. Upon clinical examination, her temperature, heart rate, blood pressure, and oxygen saturation were 36.7 °C, 109 beats/min, 100/66 mmHg, and 90%, respectively. Blood tests indicated that inflammatory markers were slightly elevated—white blood cell count (7690/mm^3), neutrophil count (78%), C-reactive protein levels (0.61 mg/L), and procalcitonin levels (0.02 ng/mL). She demonstrated slight abnormalities in the coagulation and fibrinolytic systems with D-dimer levels at 3.8 μg/mL (normal: < 1 μg/mL). N-terminal pro-brain natriuretic peptide (NT-proBNP; 316 pg/mL), carcinoembryonic antigen (2.6 ng/mL), cytokeratin 19 fragment (137 ng/mL) were elevated. Chest radiography revealed multiple bilateral granular shadows (Fig. 1). Contrast-enhanced CT demonstrated multiple areas of interlobular septal thickening and ground-glass opacities in both lungs, which were not observed 3 weeks prior, and intra-abdominal lymphadenopathy (Fig. 2). No visible pulmonary embolisms were observed. Upper gastrointestinal endoscopy revealed a 5 cm sized 0–IIc depressed-type lesion on the posterior wall of the lower body of the stomach (Fig. 3a). The pathological diagnosis was signet-ring cell carcinoma (Fig. 3b). Hypoxemia worsened rapidly after admission (SpO_2: 88% with a nasal cannula delivering 2 L/min), and PTTM associated with gastric cancer was suspected based on the imaging findings, demonstrating shadows of the rapidly developing bilateral lung fields. Pulmonary blood flow scintigraphy revealed multiple wedge-shaped or small peripheral patchy areas with reduced blood flow (Fig. 4a). Transthoracic echocardiography revealed normal left ventricular systolic function with an ejection fraction of 64%; however, significant enlargement of the right ventricle and atrium, compressed D-shaped left ventricle

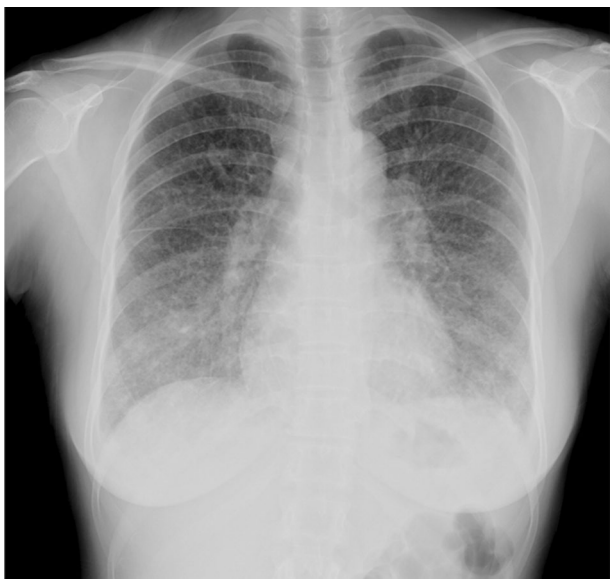

Fig. 1 Chest radiographic findings showing multiple bilateral granular shadows

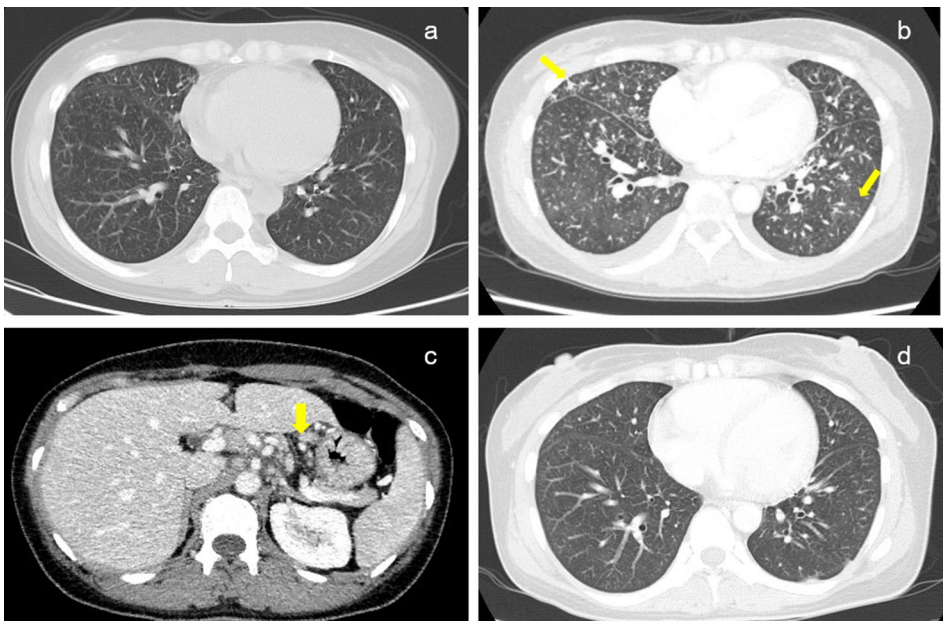

Fig. 2 Chest computed tomography image showing progressive multiple lung shadows. **a** At 3 weeks before admission. **b** On admission day; arrows show interlobular septal thickening and ground-glass opacities. **c** Swelling of the lymph nodes on the lesser curvature side of the stomach; arrows present intra-abdominal lymphadenopathy. **d** At 1 month after discharge, chest computed tomography findings showed improvement in the bilateral lung field shadows

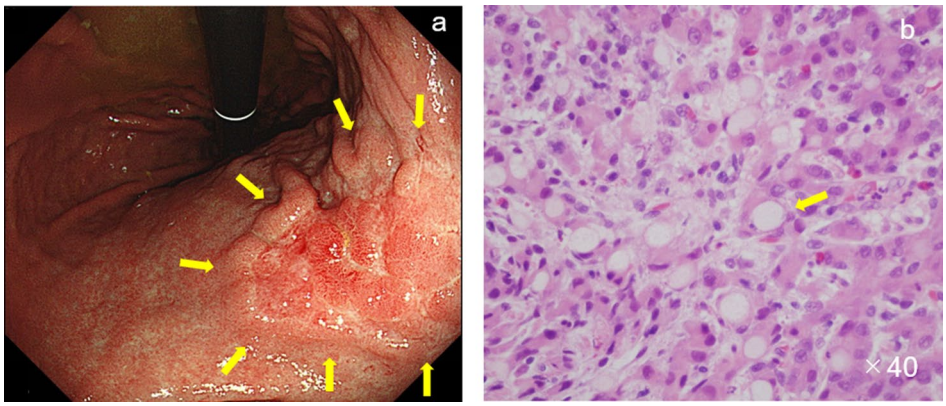

Fig. 3 **a** Upper gastrointestinal endoscopy image showing a 5 cm sized 0–IIc depressed-type lesion on the posterior wall of the lower body of the stomach. **b** The section of the lesion that was stained with hematoxylin and eosin staining showing poorly differentiated adenocarcinoma involving signet-ring cells (yellow arrows)

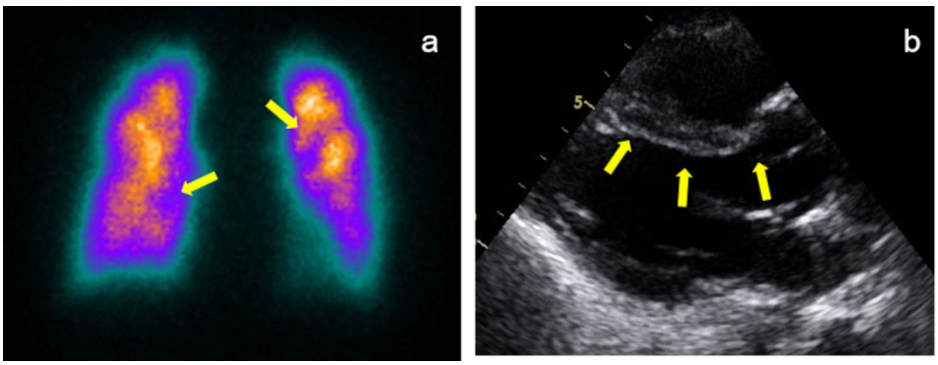

Fig. 4 Different imaging techniques used for diagnosing pulmonary tumor thrombotic microangiopathy. **a** Pulmonary blood flow scintigraphy image showing multiple wedge-shaped or small peripheral patchy areas of reduced blood flow. Red indicates high blood flow and blue indicates low blood flow. **b** Transthoracic echocardiogram showing a D-shaped left ventricle suggesting right heart overload

(Fig. 4b), and elevated tricuspid regurgitation pressure gradient (TRPG; 43 mmHg) were observed. Right heart catheterization was performed and confirmed significant PH (mean pulmonary arterial pressure, 44 mmHg; cardiac index, 2.1 L/min/m^2). Cytological examination using the Papanicolaou and Giemsa staining revealed that blood from the right heart catheter did not contain malignant cells. She was unable to tolerate bronchoscopy or lung biopsy because of dyspnea. Without a pathological diagnosis, we diagnosed PTTM based on the following clinical findings: (1) confirmation of gastric cancer, (2) acute progression of respiratory failure with severe PH, (3) no specific CT findings of pulmonary embolism or chronic thromboembolic PH, and (4) multiple subsegmental peripheral perfusion defects.

We determined that immediate treatment was required. On the 3rd day after admission, chemotherapy was initiated with S-1 (tegafur/gimeracil/oteracil potassium, 120 mg/m^2; days 1–21) and oxaliplatin (130 mg/m^2; day 1). Anticoagulation therapy with continuous infusion of heparin (10,000–15,000 U/day) and morphine hydrochloride (20 mg/day) were administered for symptomatic relief. Three days after chemotherapy initiation, cough and hypoxemia rapidly decreased. NT-proBNP and TRPG levels decreased from day 5, and the second course of chemotherapy was maintained and administered 24 days after admission. On day 28, her respiratory distress symptoms improved (Hugh–Jones II), and she could continue her daily activities; she was discharged without supplemental oxygen. At discharge, NT-proBNP levels had improved from 316 to 58 pg/mL, and TRPG had improved from 43 to 22 mmHg. Additionally, imaging findings were improved after discharge (Fig. 2d). Five courses of S-1/oxaliplatin were maintained, and direct oral anticoagulant (Rivaroxaban) was administered in the outpatient department; however, 3 months after discharge, the patient was readmitted due to respiratory distress. Chest radiographic and CT examinations revealed multiple bilateral granular shadows similar to the previous findings. The NT-proBNP and TRPG levels had increased to 11,571 pg/mL and 52 mmHg, respectively. She was diagnosed with relapsed PTTM. The gastric cancer guidelines in Japan recommend a combination of paclitaxel and ramucirumab as a second-line treatment [3]. However, because of her poor general health condition, it was difficult to administer antitumor drugs. Therefore, ramucirumab (8 mg/kg) only was administered 3 days after re-admission. However, no

improvement was observed, and the patient died 3 days after ramucirumab initiation.

Discussion

PTTM is a rare and fatal complication of cancer featuring widespread tumor cell emboli in the small arteries and arterioles of the lung, resulting in thrombus formation. PTTM differs from conventional tumor embolisms by the presence of fibrocellular intimal proliferation [1]. It was first described in 1990 and detected in 3.3% of cancer cases in a retrospective study that examined 630 consecutive metastatic carcinoma cases [1]. Fujishiro et al. [2] reported 103 cases of PPTM; among which, gastric cancer was the most frequent (58 cases), followed by lung (10), breast (seven), unknown primary origin (five), ovaries (five), and bladder (four) cancer. The mean duration from PTTM onset to hospital admission was approximately 1 month, and the median survival after admission was only 5 days [2]. Recently, it has been reported that a prognosis of several months can be obtained by making an antemortem diagnosis and starting chemotherapy [4–8]. The time from PTTM onset to death is limited; hence, although it is clinically challenging, early diagnosis is essential for survival.

Several patients with PTTM have been diagnosed antemortem previously and undergone chemotherapy (Table 1) [4–20]. The median survival time was 90 days for patients who started treatment. Furthermore, all patients with satisfactory outcomes started treatment within 10 days after admission [5, 7, 13, 14, 18, 20]. Early treatment with imatinib was reported to be particularly effective [4, 5, 13, 20]. In our case, satisfactory results were obtained after chemotherapy for primary cancer 3 days after admission with 4 months of survival after treatment initiation. Furthermore, improved respiratory symptoms and general condition were observed.

Early PTTM diagnosis is critical. Chest CT may help demonstrate ground-glass opacification, septal thickening, nodules, and mediastinal/hilar lymphadenopathy; however, in our case, CT had a low specificity for diagnosing PTTM due to gastric cancer [21]. Although some specific imaging findings exist, it is vital to suspect PTTM based on various characteristics. PH is an important clinical sign of PTTM,

Table 1 Previously reported antemortem diagnoses of pulmonary tumor thrombotic microangiopathy and treatment details

Reference	Year	Author	Primary site	Age	Sex	Diagnostic method	Beginning of treatment (days)[a]	Chemotherapy	Survival[b]
[9]	2007	Miyano	Stomach	64	F	TBLB, VATS	NA	S-1	7 months
[10]	2011	Ueda	Esophagus	60	M	TBLB	NA	Fluorouracil/nedaplatin	9 days
[11]	2012	Kayatani	Stomach or pancreas	29	M	VATS	NA	S1/cisplatin	15 months
[12]	2013	Kitamura	Breast	41	F	TBLB	NA	Irinotecan	3 months
[13]	2013	Ogawa	Stomach	47	F	TBLB	9	Imatinib	9 months
[4]	2014	Higo	Colon	61	M	NA	NA	Imatinib	12 months
[5]	2015	Minatsuki	Stomach	64	F	VATS	Several	Imatinib	12 months
[14]	2015	Fukada	Breast	61	F	Pulmonary wedge aspiration	9	Imatinib	2 months
[15]	2015	Yamakawa	Urinary bladder	77	M	Pulmonary wedge aspiration	8	Gemcitabine/paclitaxel	3 days
[16]	2016	Banno	Breast	70	F	Pulmonary wedge aspiration	13	Docetaxel	19 days
[17]	2016	Fukada	Breast	45	F	Pulmonary wedge aspiration	24	Imatinib	24 days
[6]	2016	Takahashi	Breast	65	F	VATS	NA	Trastuzumab	32 months
[7]	2017	Kubota	Stomach	56	F	NA	10	Imatinib	7 months
[18]	2018	Katayama	Prostate	81	M	TBLB, pulmonary wedge aspiration	10	Docetaxel	41 days
[19]	2019	Tateishi	Stomach	75	M	TBLB	8	Carboplatin/paclitaxel	1 month
[20]	2020	Yoshikawa	Breast	42	F	NA	4	Imatinib	3 months
[8]	2020	Imakura	Stomach	68	M	TBLB	20	S-1/oxaliplatin	7 months

F female, *M* male, *NA* not applicable, *S-1* tegafur, gimeracil oteracil potassium, *TBLB* tracsbronchial lung biopsy, *VATS* video-assisted thoracoscopic surgery

[a]The number of days between admission and the beginning of treatment for PTTM

[b]The number of days between treatment initiation and time of death

strongly contributing to a poor prognosis. The progression rapidity is likely related to the right ventricle's ability to compensate for the pressure and/or volume overload, and right heart catheterization is important for diagnosis and severity assessment [21]. Furthermore, wedged pulmonary arterial blood cell sampling has high sensitivity and specificity in diagnosing PTTM without a biopsy [22, 23]. In our case, the cytopathology results were negative in blood samples from the right heart catheter; however, right heart overload was diagnosed. Although a pathological diagnosis was not possible, we clinically diagnosed PTTM based on the CT findings, gastric cancer presence, decreased pulmonary blood flow, and right heart load results. The clinical antemortem diagnosis of PTTM was followed by immediate treatment, which made 4-month survival possible.

Several treatments have been attempted for patients diagnosed with or suspected PTTM (i.e., advanced PH therapy and administration of anti-neoplastic agents, anticoagulants, diuretics, and corticosteroids); to the best of our knowledge, a definitive treatment has not been established. Recently, imatinib, an inhibitor of platelet-derived growth factor receptor, which may have a role in reducing the vascular remodeling that promulgates PH, was reported as a therapeutic strategy for PTTM cases and should be studied extensively [5, 7, 13, 14, 20]. In our case, PTTM was improved after using anticoagulants and anticancer drugs other than imatinib. Moreover, vascular endothelial growth factor (VEGF) is suspected to be involved in PTTM and PH, and the VEGF inhibitors, bevacizumab and ramucirumab, are reported to improve PH [4, 8]. However, ramucirumab, a VEGF inhibitor, did not improve the patient outcome after relapse. Chemotherapy removes malignant cells from the pulmonary circulation and may reduce fibrointimal proliferation in PTTM. Here, S-1 and oxaliplatin therapies for treating gastric cancer were effective [3]. Although the chemotherapy regimen remains controversial, PTTM should be diagnosed as early as possible for treatment initiation.

In conclusion, we clinically diagnosed and treated PTTM in this patient. Immediate chemotherapy initiation was initially successful, suggesting that such treatment may extend the survival of patients with cancer and PTTM.

Acknowledgements We thank Editage (https://www.editage.com/) for editing a draft of this manuscript. The authors wish to thank Dr Masanori Kitamura at the Department of Pathology, Osaka International Cancer Institute, Osaka, Japan for assisting in submitting this article.

Author contributions All authors contributed to this manuscript. The first draft of the manuscript was written by KF, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the patient for publishing this case report and any accompanying images.

References

1. von Herbay A, Illes A, Waldherr R, Otto HF (1990) Pulmonary tumor thrombotic microangiopathy with pulmonary hypertension. Cancer 66:587–592
2. Fujishiro T, Shuto K, Shiratori T et al (2013) A case report of pulmonary tumor thrombotic microangiopathy (PTTM) caused by esophageal squamous cell carcinoma. Esophagus 10:247–251
3. Japanese Gastric Cancer Association (2018) Japanese gastric cancer treatment guidelines. Gastric Cancer 24:1–21
4. Higo K, Kubota K, Takeda A et al (2014) Successful antemortem diagnosis and treatment of pulmonary tumor thrombotic microangiopathy. Intern Med 53:2595–2599
5. Minatsuki S, Miura I, Yao A et al (2015) 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
6. Takahashi Y, Uruga H, Fujii T et al (2016) Antemortem diagnosis of pulmonary tumor thrombotic microangiopathy in a patient with recurrent breast cancer: a case report. BMC Cancer 16:666
7. Kubota K, Shinozaki T, Imai Y et al (2017) Imatinib dramatically alleviates pulmonary tumour thrombotic microangiopathy induced by gastric cancer. BMJ Case Rep 2017:bcr2017221032
8. Imakura T, Tezuka T, Inayama M et al (2020) A long-term survival case of pulmonary tumor thrombotic microangiopathy due to gastric cancer confirmed by the early diagnosis based on a transbronchial lung biopsy. Intern Med 59:1621–1627
9. Miyano S, Izumi S, Takeda Y et al (2007) Pulmonary tumor thrombotic microangiopathy. J Clin Oncol 25:597–599
10. Ueda A, Fuse N, Fujii S et al (2011) Pulmonary tumor thrombotic microangiopathy associated with esophageal squamous cell carcinoma. Intern Med 50:2807–2810
11. Kayatani H, Matsuo K, Ueda Y et al (2012) Pulmonary tumor thrombotic microangiopathy diagnosed antemortem and treated with combination chemotherapy. Intern Med 51:2767–2770
12. Kitamura A, Nishimura N, Jinta T et al (2013) A case of pulmonary tumor thrombotic microangiopathy diagnosed by transbronchial lung biopsy and treated with chemotherapy and long-term oxygen and anticoagulation therapies. Case Rep Pulmonol 2013:259080
13. Ogawa A, Yamadori I, Matsubara O et al (2013) Pulmonary tumor thrombotic microangiopathy with circulatory failure treated with imatinib. Intern Med 52:1927–1930
14. Fukada I, Araki K, Minatsuki S et al (2015) Imatinib alleviated pulmonary hypertension caused by pulmonary tumor thrombotic microangiopathy in a patient with metastatic breast cancer. Clin Breast Cancer 15:e167–e170
15. Yamakawa H, Yoshida M, Yamada M et al (2015) Pulmonary tumor thrombotic microangiopathy associated with urothelial

carcinoma of the urinary bladder: antemortem diagnosis by pulmonary microvascular cytology. Clin Case Rep 3:735–739
16. Banno A, Chiba K, Kasai H, Nagami K (2016) Ante-mortem diagnosis of pulmonary tumour thrombotic microangiopathy in a patient with unrecognised extramammary Paget's disease. BMJ Case Rep 2016:bcr2016216666
17. Fukada I, Araki K, Kobayashi K et al (2016) Imatinib could be a new strategy for pulmonary hypertension caused by pulmonary tumor thrombotic microangiopathy in metastatic breast cancer. Springerplus 5:1582
18. Katayama S, Takenaka T, Nakamura A et al (2018) Pulmonary tumor thrombotic microangiopathy induced by prostate cancer. Acta Med Okayama 72:309–313
19. Tateishi A, Nakashima K, Hoshi K et al (2019) Pulmonary tumor thrombotic microangiopathy mimicking inhalation lung injury. Intern Med 58:1311–1314
20. Yoshikawa S, Hara T, Suzuki M et al (2020) Imatinib dramatically improved pulmonary hypertension caused by pulmonary tumor thrombotic microangiopathy (PTTM) associated with metastatic breast cancer. Int Heart J 61:624–628
21. Godbole RH, Saggar R, Kamangar N (2019) Pulmonary tumor thrombotic microangiopathy: a systematic review. Pulm Circ 9:2045894019851000
22. Abati A, Landucci D, Danner RL, Solomon D (1994) Diagnosis of pulmonary microvascular metastases by cytologic evaluation of pulmonary artery catheter-derived blood specimens. Hum Pathol 25:257–262
23. Keenan NG, Nicholson AG, Oldershaw PJ (2008) Fatal acute pulmonary hypertension caused by pulmonary tumour thrombotic microangiopathy. Int J Cardiol 124:e11–e13