Case Report

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Pulmonary tumour thrombotic microangiopathy presented as gastric signet ring cell carcinoma: A case report

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Abstract

Pulmonary tumour thrombotic microangiopathy (PTTM) is a rare complication of cancer characterized by widespread tumour cell emboli in small arteries and arterioles of the lung and often accompanied by microthrombi. We report a case of PTTM in a young Chinese woman that presented as gastric signet ring cell carcinoma. Although rare, PTTM should be considered in cancer patients with a rapidly progressing dyspnoea, chest computed tomography (CT) scan suggestive of pulmonary hypertension and diffuse pulmonary interstitial infiltration.

Keywords

Pulmonary tumour thrombotic microangiopathy, signet ring cell carcinoma, pulmonary hypertension, dyspnoea, gastric cancer

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Introduction

Pulmonary tumour thrombotic microangiopathy (PTTM) is a rare complication of metastatic cancer.[1,2] Clinically, it is characterized by dyspnoea and pulmonary hypertension.[3] Pathologically, widespread tumour cell invasion of small pulmonary arteries and arterioles of the lung can be seen which leads to vascular stenosis and thrombosis.[3] The radiological findings on

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computed tomography (CT) are typically diffuse centrilobular nodular opacities in a tree-in-bud pattern.[4,5] A rapid diagnosis of PTTM is essential because the time from onset of the disease to death is short.[1]

We report here on a young woman who presented with dyspnoea, pulmonary hypertension and right heart failure and was initially thought to have signet ring cell carcinoma of the stomach.

Case report

A 38-year-old Chinese woman presented to our hospital with a three-month history of progressive dyspnoea on exertion, cough with bloody sputum and chest pain. She had no fever, night sweats or weight loss. She had previously visited another hospital, where she was found to be hypoxemic (oxygen saturation 85%) and echocardiography had shown severe pulmonary hypertension (pulmonary artery pressure, 71 mm Hg). She was transferred to our hospital after diuretic treatment had failed.

The patient had no prior history of tuberculosis, had not travelled recently and had not been exposed to any respiratory irritants. She did not smoke or drink alcohol and had no history of abnormal gestation or births. On clinical examination, her temperature was 36.4°C, heart rate 88 beats/min, blood pressure 105/61 mmHg and oxygen saturation 85%. She had jugular venous distention, diminished breath sounds over the right lower lung, pronounced P2 heart sounds and mild pitting oedema of her lower extremities.

Blood tests showed that her white blood cells (10,290/mm^3), neutrophils (77%) and C-reactive protein levels (1.8 mg/l) were elevated. Her platelet count (149,000/mm^3), haemoglobin (12.2 g/dl), erythrocyte sedimentation rate (11 mm/h) and procalcitonin levels (0.05 ng/ml) were normal. In addition, she had elevated levels of D-dimer (4460 ng/ml), N-terminal pro brain natriuretic peptide (637.7 pg/ml), carcinoembryonic antigen (CEA; 21.9 ng/ml), cytokeratin 19 fragment (20.3 ng/ml), and tumour marker CA125 (62.2 U/ml).

Arterial blood gas analysis suggested type 1 respiratory failure (pH 7.4, PaO_2 52 mm Hg, $PaCO_2$ 38 mm Hg, bicarbonate [HCO_3] 24.7 mmol/l and oxygen saturation 85%). Other biochemical tests including indicators of rheumatology were negative.

A CT scan of the chest detected multiple patchy infiltrating shadows of mixed density distributed mostly around the hilum, interlobular septal thickening and moderate right pleural effusion enlargement of the main pulmonary artery (Figure 1a). The lymph nodes in the mediastinum and hilar regions were not enlarged. A CT pulmonary angiogram (CTPA) showed no evidence of pulmonary thromboembolism in any vessel (Figure 1b). Results of a transthoracic echocardiogram showed mild right ventricular dilatation (anteroposterior diameter 27 mm), severe pulmonary hypertension (71 mm Hg) and normal left ventricular (LV) systolic function (LV ejection fraction, 65%). On the first day of admission, these findings led to an initial diagnosis of severe pulmonary hypertension, pulmonary shadow, right pleural effusion and type 1 respiratory failure. Preliminary treatments included oxygen inhalation, preventive anticoagulation and diuretics and cardiotonic drugs to improve heart function.

The patient underwent further tests and right heart catheterization showed that her pulmonary arterial pressure (29 mm Hg), pulmonary vascular resistance (3.1 Wood units), and cardiac index (4.61/min/m^2) were elevated and her pulmonary arterial wedge pressure (3 mm Hg) was normal. These findings were compatible with a diagnosis of pulmonary hypertension. However, the increase in pulmonary arterial pressure was mild which was incompatible with severe dyspnoea and respiratory failure.

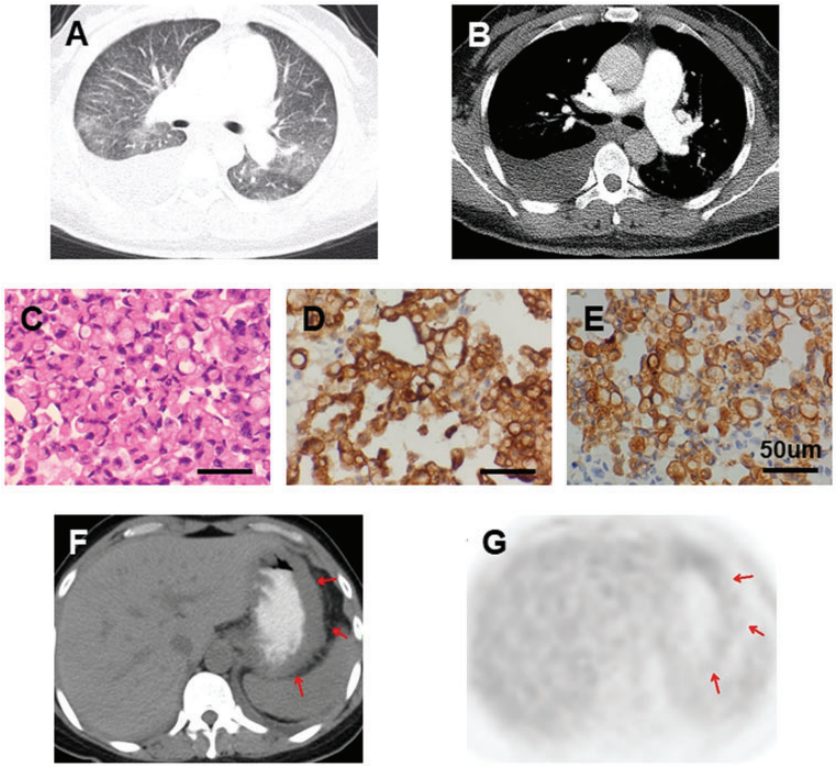

Figure 1. (a) A chest computed tomography (CT) scan demonstrating multiple patchy infiltrating shadows distributed mostly around the hilum, interlobular septal thickening and moderate right pleural effusions. (b) A computed tomography pulmonary angiogram (CTPA) showed no evidence of pulmonary thromboembolism. (c) Pleural fluid cytology showing malignant cells by hematoxylin-eosin staining (scale bar = 50 μm). (d) Immunocytochemistry showed the malignant cells were strongly immunoreactive for villin (scale bar = 50 μm). (e) Immunocytochemistry showed the malignant cells were strongly immunoreactive for cytokeratin 20 (CK20) (scale bar = 50 μm). (f) Computed tomography (CT) scan showing inhomogeneous thickening of the gastric side wall of the greater curvature of the stomach (red arrows). (g) Positron emission tomography using 18F-fluorodeoxyglucose (FDG-PET) showed a high FDG uptake in the gastric side wall of the greater curvature of the stomach (red arrows).

The patient's dyspnoea resulted in her being unable to tolerate a bronchoscopy or a lung biopsy and so she had a thoracentesis. Immunocytochemistry of the pleural effusions demonstrated that the tumour cells were strongly immunoreactive for the monoclonal antibodies, villin and cytokeratin 20 (CK20) (Figure 1c–e). The cells were negative for CDX-2, Wilms' tumour 1 (WT-1), calretinin, thyroid transcription factor-1 (TtF-1), napsin A and CA125 which supported a diagnosis of carcinoma probably originating from gastrointestinal tract. A CT scan of the abdominal region followed by positron emission tomography using 18F-fluorodeoxyglucose (FDG-PET) showed high FDG uptake in the gastric side wall of the greater curvature of the stomach (Figure 1f and 1g). Therefore, the presence of poorly differentiated adenocarcinoma in her pleural effusions and the morphologic features of gastric signet ring cell carcinoma led to an amended diagnosis of PTTM likely caused by gastric cancer. This

diagnosis was made on the 11th day after admission.

The patient was prescribed tegafur/gimeracil/oteracil potassium (S-1) combined with apatinib. However, she decided to return to her local hospital immediately and died of respiratory failure less than 24 hours after discharge from our hospital.

This case report did not require ethics committee approval. Written authorisation was obtained from the patient's family for publication of this case report.

Discussion

PTTM is a rare and lethal complication of cancer characterized by widespread tumour cell emboli in the small arteries and arterioles of the lung and often associated with thrombus formation; it is distinct from conventional tumour emboli in that fibrocellular intimal proliferation is present. PTTM was first described in 1990, where it was found in 3.3% cases in a retrospective study examining the autopsy findings from 630 consecutive cases with metastatic carcinoma.[1] PTTM is strongly associated with carcinomas, especially poorly differentiated signet-ring cancers of the stomach, with a post-mortem prevalence of 17–27%.[5] Other commonly associated malignancies with PTTM include lung, breast, colon, and pancreas.[5] Although the exact pathogenesis of PTTM remains unclear, several proteins have been implicated in its development. For example, vascular endothelial growth factor (VEGF) and tissue factor (TF) have been reported to be expressed more frequently in cancer cells leading to PTTM than those with traditional tumour emboli.[2,6] In addition, platelet-derived growth factor (PDGF)[7] and osteopontin (OPN)[8] have been suggested as factors involved in the development of PTTM but further studies are required to confirm their role.

The time from onset of PTTM to death is short and so an early diagnosis is essential. Indeed, it has been reported that the mean duration from onset to hospital admission is approximately one month and the median survival of patients who died after admission was only five days.[9] However, PTTM poses a difficult diagnostic problem not only because of its rapid progression but also because most of the definitive investigations are invasive and the degree of hypoxia precludes many of the tests. Although a chest CT scan can be helpful, it is insensitive.[4,5] By contrast, pulmonary artery catheterization and wedged pulmonary arterial blood cell sampling has been reported to have high sensitivity and specificity[10] and several studies have used the method successfully to confirm a diagnosis of PTTM.[10–13]

A standard treatment regimen for PTTM has not been established. Treatments for primary pulmonary hypertension such as endothelin antagonists, prostacyclin analogues, and phosphodiesterase type 5 inhibitors, may prove effective but data on their efficacy in PTTM are lacking.[10,14] Anticoagulation therapy has been used successfully in the short-term in one study but did not change the prognosis.[14] Imatinib, a tyrosine kinase inhibitor of the PDGF receptor, may be effective in selective cases of PTTM with tumour overexpression of PDGF, as in some gastric malignancies.[15] Another study observed a favourable clinical outcome using imatinib with chemotherapy,[16] further studies are required to establish the efficacy and safety of this combination treatment.[11]

In our case, the patient's young age and history of pulmonary hypertension misled our diagnosis. The presence of progressive dyspnoea, oedema and a CT scan that showed multiple patchy ground-glass shadows distributed around the hilum were compatible with a diagnosis of pulmonary hypertension and heart failure. Although

we originally suspected pulmonary hypertension, the inconsistent results from a right heart catheterization prompted us to perform further diagnostic tests. However, we were unable to obtain biopsy specimens of gastric mucosal tissue or lung tissue because of the patient's poor performance status. Furthermore, we missed the opportunity to obtain a wedged pulmonary arterial blood sample during right heart catheterization. Nevertheless, histopathological examinations of samples from a hydrothorax and results of FDG-PET assisted us in making a likely diagnosis of PTTM. We intended for her to receive anti-tumour therapy but her respiratory condition and performance status worsened rapidly and she died within 24 hours after discharge.

The clinical course of this patient provided us with an important lesson. PTTM should be considered in cancer patients with a rapidly progressing dyspnoea, chest CT scan compatible with pulmonary hypertension and diffuse pulmonary interstitial infiltration. In fact, pulmonary hypertension caused by PTTM is included within Group 5 category of the World Health Organization (WHO) pulmonary hypertension classification system.[17] Importantly, when there is doubt about PTTM diagnosis, a lung biopsy should be performed, even in young patients where malignancies are unexpected.

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Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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References

1. von Herbay A, Illes A, Waldherr R, et al. Pulmonary tumor thrombotic microangiopathy with pulmonary hypertension. *Cancer* 1990; 66: 587–592.
2. Uruga H, Fujii T, Kurosaki A, et al. Pulmonary tumor thrombotic microangiopathy: a clinical analysis of 30 autopsy cases. *Intern Med* 2013; 52: 1317–1323.
3. Belhassine M, Papakrivopoulou E, Venet C, et al. Gastric adenocarcinoma revealed by atypical pulmonary lymphangitic carcinomatosis. *J Gastrointest Oncol* 2018; 9: 1207–1212.
4. Franquet T, Gimenez A, Prats R, et al. Thrombotic microangiopathy of pulmonary tumors: a vascular cause of tree-in-bud pattern on CT. *AJR Am J Roentgenol* 2002; 179: 897–899.
5. Godbole R, Ghatol A, Betancourt J, et al. Pulmonary tumor thrombotic microangiopathy: clinical, radiologic, and histologic correlation. *J Clin Imaging Sci* 2015; 5: 44.
6. Chinen K, Kazumoto T, Ohkura Y, et al. Pulmonary tumor thrombotic microangiopathy caused by a gastric carcinoma expressing vascular endothelial growth factor and tissue factor. *Pathol Int* 2005; 55: 27–31.
7. 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* 2015; 56: 245–248.
8. Takahashi F, Kumasaka T, Nagaoka T, et al. Osteopontin expression in pulmonary tumor thrombotic microangiopathy caused

by gastric carcinoma. *Pathol Int* 2009; 59: 752–756.
9. Fujishiro T, Shuto K, Shiratori T, et al. A case report of pulmonary tumor thrombotic microangiopathy (PTTM) caused by esophageal squamous cell carcinoma. *Esophagus* 2013; 10: 247–251.
10. Keenan NG, Nicholson AG and Oldershaw PJ. Fatal acute pulmonary hypertension caused by pulmonary tumour thrombotic microangiopathy. *Int J Cardiol* 2008; 124: e11–13.
11. Abe T, Fukada I, Shiga T, et al. A case of recurrent breast cancer identified by pulmonary tumor thrombotic microangiopathy. *Case Rep Oncol* 2017; 10: 620–626.
12. Fukada I, Araki K, Minatsuki S, et al. Imatinib alleviated pulmonary hypertension caused by pulmonary tumor thrombotic microangiopathy in a patient with metastatic breast cancer. *Clin Breast Cancer* 2015; 15: e167–170.
13. Malani AK, Gupta C, Kutty AV, et al. Pulmonary tumor thrombotic microangiopathy from metastatic gallbladder carcinoma: an unusual cause of severe pulmonary hypertension. *Dig Dis Sci* 2007; 52: 555–557.
14. Kitamura A, Nishimura N, Jinta T, et al. 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; 2013: 259080.
15. Ogawa A, Yamadori I, Matsubara O, et al. Pulmonary tumor thrombotic microangiopathy with circulatory failure treated with imatinib. *Intern Med* 2013; 52: 1927–1930.
16. Miyano S, Izumi S, Takeda Y, et al. Pulmonary tumor thrombotic microangiopathy. *J Clin Oncol* 2007;25:597–599.
17. Kovacs G, Dumitrescu D, Barner A, et al. Definition, clinical classification and initial diagnosis of pulmonary hypertension: updated recommendations from the Cologne Consensus Conference 2018. *Int J Cardiol* 2018; 272S: 11–19.