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Pulmonary Tumor Thrombotic Microangiopathy by Lung Adenocarcinoma

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Abstract:

Pulmonary tumor thrombotic microangiopathy, which was established as a disease entity by von Herbay *et al*, is an uncommon cancer-related complication. The most common disease associated with pulmonary tumor thrombotic microangiopathy is poorly differentiated adenocarcinoma of the stomach, and cancers other than gastric cancers are very rare. We present a case of pulmonary tumor thrombotic microangiopathy caused by lung adenocarcinoma which was found in a 61-year-old Japanese woman. She was taken suffering from general fatigue without any history of cancers. Two-days after admission she suddenly complained of dyspnea and succumbed to pulmonary hypertension. Postmortem autopsy revealed that lung adenocarcinoma with multiple liver metastasis and intimal proliferation of pulmonary small arteries with or without tumor emboli, which were characteristics of pulmonary tumor thrombotic microangiopathy.

Key words: Adenocarcinoma, Pulmonary Hypertension, Lung Neoplasms, Liver, Dypnea.

Introduction

Pulmonary tumor thrombotic microangiopthy (PTTM) is a rare complication of malignant disease, which was first reported by von Hearbay *et al* [1]. An antemortem diagnosis of PTTM is extremely difficult, because the findings on chest computed tomography are very trivial or non-specific, and the patient rapidly deteriorates to death. Its histopathological characteristic is intimal proliferation in pulmonary small arteries and arterioles with or without tumor emboli, resulting in vascular stenosis. The most common disease associated with PTTM is poorly differentiated adenocarcinoma of the stomach, and carcinomas other than gastric carcinomas are very rare. We here report a postmortem autopsy case of PTTM caused by lung adenocarcinoma with multiple liver metastasis.

Case Report

The patient was a 61-year old Japanese woman

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who presented with general fatigue and loss of appetite lasting for 2 weeks. There was no significant past history. She was suffering from general fatigue with mild hypoxia with 90% of oxygen saturation in the room air. A chest computed tomography (CT) showed a moderate fine nodule attached to the chest wall in the left lower lung [Fig.1]. Laboratory tests revealed that elevated serum carcinoembryonicantigen (CEA) (174.7 ng/mL; range < 5.0) and cytokeratin 19 fragment (CYFRA) (310 ng/mL; range <3.5). A bronchoscopy was planned to be performed. However, 2-days after admission, her respiratory condition suddenly deteriorated with severe hypoxia. No abnormal breath sounds were heard on auscultation of the lung fields. Routine biochemistry tests were normal except for elevated plasma-fibrin degradation products (P-FDP) (123.7 µg/mL; range < 5.0) and strongly positive D-dimer (56.16 µg/mL; range <1.0). Transthoracic echocardiography indicated severe pulmonary hypertension with tricuspid regurgitation; estimated gradient pressure was approximately 60 mmHg [Fig. 2]. Due to clinical suspicion of pulmonary thromboembolism, she underwent contrast-enhanced CT of her chest, pelvis and thighs. Although the angiographic phase did not present any signs of pulmonary thromboembolism, the CT scan showed signs of acute cor pulmonale characterized by increased right heart chamber dimensions [Fig.3]. In the lung window, the CT scan showed diffuse centrilobular nodular opacities with ground-glass attenuation, associated with a tree-in-bud disseminated through her lung [Fig.4]. Her respiratory condition abruptly worsened to the bottom. She died on the third day after admission.

At autopsy gross examination identified a yellowish-white nodule of 2 cm in diameter with pleural invasion in the left lower lobe [Fig.5]. Histopathological examination of the lung nodule showed poorly differentiated solid adenocarcinoma with mucin [Fig.6]. In all the other lung lesions

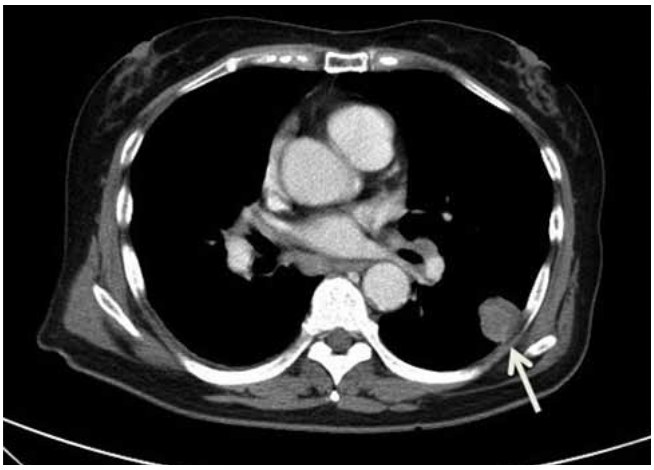

Fig.1: Chest computed tomography axial series with mediastinal window after infusion of intravenous contrast, showing ultrafine nodule in the left lower lung.

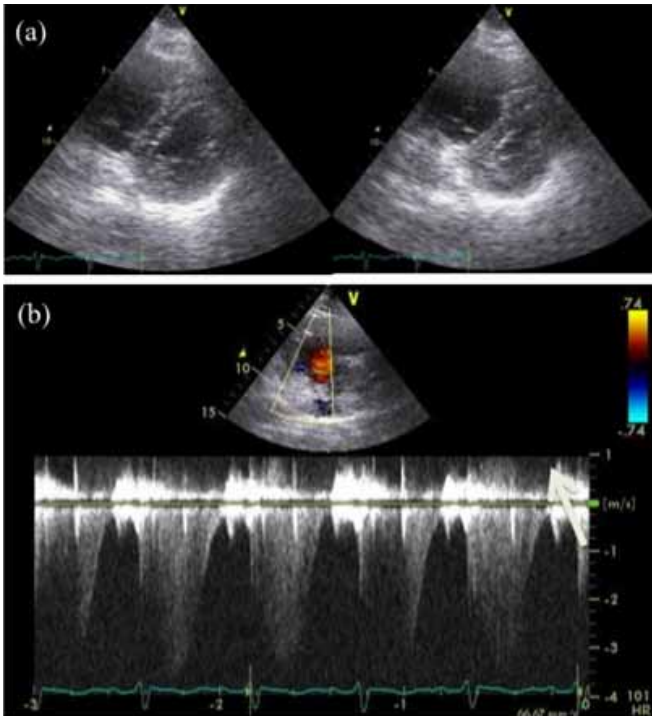

Fig.2: Echocardiography showed right ventricular dilation, flattening of interventricular septum in the left ventricle during diastolic phase (a), and severe pressure gradient estimated with tricuspid regurgitation (b).

prominent fibromuscular and/or fibrocellular intimal proliferation of small arteries and arterioles around 100 μm in diameter with or without tumor emboli, which caused marked luminal stenosis, was identified [Fig.7]. These characteristics are consistent with PTTM caused by lung adenocarcinoma.

Metastatic adenocarcinoma was identified diffusely in the liver. The immunohistochemical analyses revealed that the tumor cells both in liver and lung were positive for thyroid transcriptional factor -1 (TTF-1) [Fig.8].

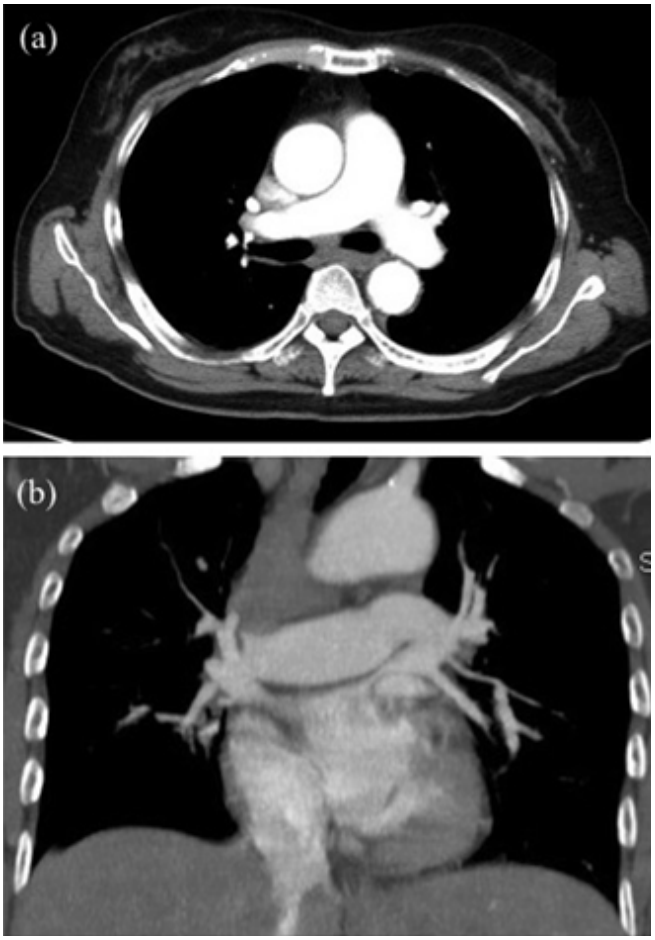

Fig.3: Chest computed tomography (CT) of angiographic phase, showing no signs of pulmonary thromboembolism: Axial series (a) and coronal series (b).

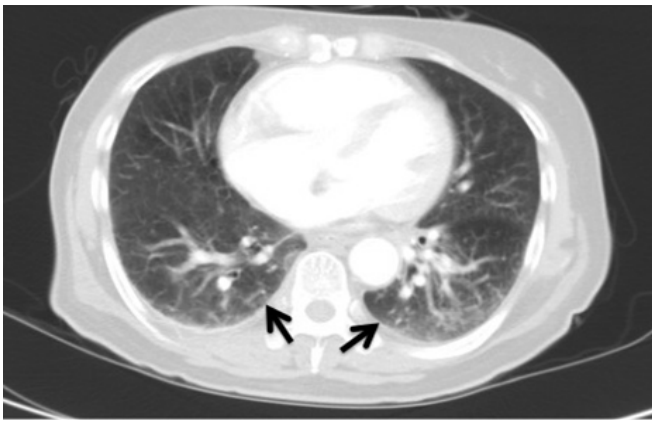

Fig.4: Chest CT axial series of the lower lobes with maximum intensity projection showing diffuse centrilobular nodular opacities with ground-glass attenuation associated with tree-in-bud pattern.

Fig.5: Cut surfaces of left lung. A single yellowish-white nodule of 2.0-2.5 cm in diameter in the left lower lung.No obvious gross metastases are seen.

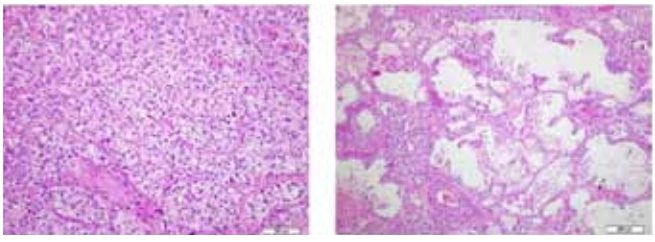

Fig.6: Histopathological findings of the lung nodule. Adenocarcinoma and solid adenocarcinoma with mucin. [Hematoxylin-Eosin (HE) double staining].

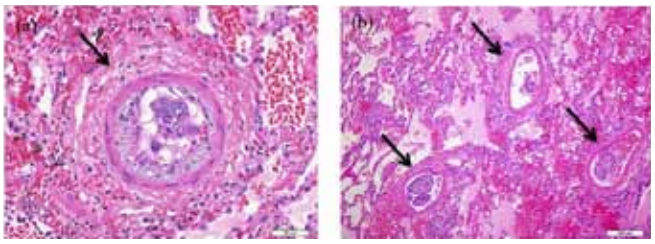

Fig.7: Microscopic findings of small pulmonary arteries and arterioles around 100 μm in diameter. Tumor embolus is accompanied by concentric fibrocellular and/or fibromuscular intimal proliferation. A thrombosed artery shows organization and recanalization [a, b; Hematoxylin-Eosin (HE) double staining].

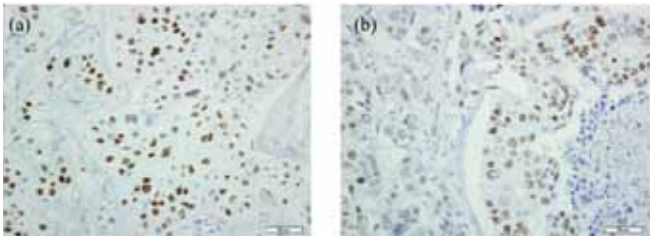

Fig.8: Immunohistochemical findings for thyroid transcriptional factor-1 (TTF-1) of tumor cells in lung (a) and liver (b).

Discussion

We here report a case of pulmonary tumor thrombotic microangiopathy (PTTM) caused by lung adenocarcinoma which was found in a 61-year-old Japanese woman. The patient developed rapidly progressive and fatal pulmonary hypertension. Postmortem autopsy revealed that lung adenocarcinoma with multiple liver metastasis and intimal proliferation of pulmonary small arteries with or without tumor emboli, which were characteristics of pulmonary tumor thrombotic microangiopathy.

PTTM is a very rare complication of malignancies commonly detected after death. It was first reported by von Herbay and his colleagues as a diffuse myofibroblast proliferation of small pulmonary arteries that cause severe pulmonary hypertension, leading cardiopulmonary failure and sudden death [2-6]. From the clinical point of view PTTM manifests with signs and symptoms of pulmonary hypertension which indicate progressive dyspnea, cough and hypoxia, as our patient presented. A cardiac evaluation may find signs of right-sided heart failure on electrocardiography and echocardiography. Deterioration inclinical condition occurs rapidly and patient generally expires before diagnostic confirmation and treatment [7].

Histopathologically PTTM is characterized by wide spread tumor embolism, microthrombi, and fibrocellular intimal hyperplasia of small pulmonary arteriesand arterioles [1,2]. Diffuse vascular occlusion in patients with PTTM results in increased pulmonary vascular resistance. Diffuse centrilobular nodular and a tree-in-bud pattern on chest CT is caused by the dilation and plugging of small airways by mucus and inflammatory material, which are often seen in patients with small airway disease. This pattern is seen in the present case and also in a few cases with PTTM [8,9]. This pattern might be the sign of a variety of pulmonary vascular abnormalities, including pulmonary tumor embolism and PTTM.

To best of our knowledge, only four cases of PTTM caused by lung carcinoma have been reported [1,10]. The histopathological typing of these cases is adenocarcinoma, as in the present case. Herbay *et al* reported that 19 of 21 carcinomas with PTTM (90.5%) were adenocarcinomas [1]. The reason why PTTM is more frequently associated with gastric cancers than non-gastric cancer and mostly associated with adenocarcinoma is unknown. In our case, bile duct adenocarcinoma is another candidate of diagnosis considering adenocarcinomais spread diffusely in her liver. However, consistency of positive TTF-1 between her lung and liver suggested primary and metastasis of adenocarcinoma.

PTTM rapidly progresses and is in most cases

fatal since almost all cases die within a week from onset. It is very important to consider the possibility of PTTM before the appearance of pulmonary hypertension. Katayama *et al* reported that antemortem diagnosis of PTTM is made prior to the development of pulmonary hypertension which responded to chemotherapy [11].

Conclusion

In conclusion, it is important to suspect PTTM as a differential diagnosis for rapidly progressing respiratory failure, not only in patients with cancer, but also in patients without a history of cancer. The early diagnosis of PTTM may lead to appropriate management.

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