Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.1796-18
Intern Med 58: 1311-1314, 2019
http://internmed.jp

【 CASE REPORT 】

Pulmonary Tumor Thrombotic Microangiopathy Mimicking Inhalation Lung Injury

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Abstract:
Pulmonary tumor thrombotic microangiopathy (PTTM) is a complication characterized by dyspnea, pulmonary hypertension, and occasionally sudden death. We encountered a man who developed PTTM and had an inhalation history of chemical herbicides and abnormal findings on chest computed tomography, mimicking chemical inhalation lung injury. He was diagnosed with PTTM with adenocarcinoma by a transbronchial lung biopsy and received chemotherapy and anticoagulant therapy. He survived for one month. An autopsy revealed primary gastric cancer with PTTM that can have a presentation similar to diffuse pulmonary diseases, including chemical inhalation lung injury. The examination of a biopsy specimen is crucial in such patients.

Key words: pulmonary tumor thrombotic microangiopathy, inhalation lung injury, signet ring cell carcinoma, gastric carcinoma, pulmonary hypertension

(Intern Med 58: 1311-1314, 2019)
(DOI: 10.2169/internalmedicine.1796-18)

Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare complication from cancer that refers to tumor cells within the pulmonary arteries and/or capillaries in pathologic lung samples, as first described by von Herbay et al. in 1990 (1). Most cases in the literature were diagnosed at an autopsy, and an antemortem diagnosis of PTTM is extremely difficult because of the rapid progression of pulmonary hypertension, right heart failure, and death, which generally occurs over a few days. There are only a few case reports in which the diagnosis of PTTM was made while the patient was still alive (2-4).

The other reason for the difficulty obtaining an early diagnosis of PTTM is the non-specific findings of chest computed tomography (CT), including diffuse micronodules and ground-glass opacity (5). Other diffuse pulmonary diseases, such as hypersensitivity pneumonitis, intravascular lymphoma, and chemical inhalation lung injury due to the inhalation of toxic elements, also display similar CT findings.

We herein report a patient with transbronchial lung biopsy (TBLB)-proven PTTM of metastatic signet ring cell carcinoma who had a dry cough and nodular findings on chest CT mimicking chlorine inhalation lung injury; the patient survived over one month with chemotherapy treatment.

Case Report

A 75-year-old man was admitted to our hospital with a progressive cough and weight loss of 3 kg in 1.5 months. Two months prior to admission, he had used chemical herbicides (chlorate herbicide) for farming. Two weeks after using chemical herbicides, he visited our clinic with an intermittent dry cough. The symptoms had not improved with symptomatic therapy such as antitussive medications. Suspecting that he might have hypersensitivity pneumonitis or chlorine inhalation lung injury, he was admitted to the hospital for both antigen avoidance and a further evaluation. He had a history of persistent atrial fibrillation but no other underlying chronic respiratory diseases and had not taken any medications that might influence his immune status. He had no history of smoking or alcohol abuse.

On admission, his blood pressure was 132/91 mmHg, and

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Received: July 7, 2018; Accepted: September 17, 2018; Advance Publication by J-STAGE: January 10, 2019
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his heart rate was 75 beats/min. His oxygen saturation level was 96% (room air), his respiratory rate was 16 breaths/min, and his body temperature was 35.3℃. No adventitious sounds were auscultated on heart and lung examinations. Laboratory tests showed abnormalities in coagulation and slightly elevated C-reactive protein levels (Table). Chest radiography showed reticulonodular opacities in the bilateral lungs. Chest CT demonstrated a centrilobular granular shadow in the bilateral lungs, interlobular septal thickening, and mediastinal lymphadenopathies (Fig. 1A); pulmonary thromboembolism was not detected (Fig. 1B). ^{18}F-Fluorodeoxyglucose-positron emission tomography (FDG-PET) showed a higher FDG uptake in the mediastinal lymph nodes than in the other lymph nodes. No other abnormal uptake was detected. A TBLB and endobronchial ultrasound-guided transbronchial needle aspiration were performed to retrieve a lung biopsy specimen, which revealed atypical cells occluding a small pulmonary artery. Immunohistochemical staining of the atypical cells suggested adenocarcinoma (Fig. 2). Furthermore, transbronchial needle aspiration (TBNA) of lymph node (#7, #11L, and #11s) biopsy specimens revealed massive metastasis of signet ring cell carcinoma. Although a trained endoscopist performed the gastroesophageal endoscopy, only a small red depression in the lower curvature of the stomach was detected, and the biopsy specimen showed atrophic gastritis without malignant findings (Fig. 3A). In addition, colonoscopy, a bone marrow biopsy, and PET-CT did not provide any indication of the primary lesion. Right heart catheterization confirmed severe pulmonary hypertension (mean PAWP 10 mmHg, mean PA 38 mmHg, RA 8 mmHg). Lung perfusion scintigraphy showed multiple small wedge-shaped defects in the bilateral lungs. Thus, the patient was diagnosed with PTTM of adenocarcinoma of unknown primary origin.

Table. Laboratory Data on Admission.

Hematology		Biochemistry	
WBC	5,300 /μL	TP	7.5 g/dL
Neutro	69.3 %	Alb	3.5 g/dL
Eosino	2.4 %	AST	23 IU/L
Baso	0.6 %	ALT	29 IU/L
Mono	8.6 %	LDH	227 IU/L
Lymph	19.1 %	ALP	168 IU/L
RBC	456×10^4 /μL	T-bil	1 mg/dL
Hb	13.8 g/dL	BUN	14 mg/dL
Ht	39.8 %	Cre	0.8 mg/dL
Blood coagulation		Glu	89 mg/dL
Plt	14.6×10^4	CRP	2.97 mg/dL
PT(INR)	1.1	BNP	109.1 pg/mL
APTT	33.3 sec	KL-6	277 U/mL
D-dimer	8.7 μg/mL		
Bronchoalveolar lavage		Blood arterial gas (Room air)	
Cell count	250,000 /mL	pH	7.409
Neutro	6 %	$PaCO_2$	34.9 mmHg
Lymph	8 %	PO_2	73.5 mmHg
Eosino	1 %	HCO_3^-	21.6 mmol/L
Macrophage	85 %	BE	-2.3 mmol/L

WBC: white blood cell, Neutro: neutrophils, Eosino: eosinophils, Baso: basophils, Mono: monocytes, Lymph: lymphocytes, RBC: red blood cell, Hb: hemogurobin, Ht: hematocrit, Plt: platelet, PT (INR): prothrombin time (international normalized ratio), APTT: activated partial thromboplastin time, TP: total protein, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatese, T-bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine, Glu: glucose, CRP: C reactive protein, BNP: brain natriuretic peptide, KL-6: Krebs von den Lungen-6, BE: base excess

The patient received chemotherapy with carboplatin [area under the concentration-time curve (AUC): 5] and paclitaxel (180 mg/m^2) administered intravenously every 3 weeks, starting from the eighth hospital day, for adenocarcinoma of unknown primary origin, and he started heparinization for anticoagulation. His cough and shortness of breath improved slightly after the first course of chemotherapy. After 25 days of admission, the patient's serum D-dimer level had gradually decreased from 8.6 μg/mL to 1.8 μg/mL. On the 28th day, transthoracic echocardiography measured a continued high right ventricular pressure (60 mmHg), which was almost the same as that at the initiation of chemotherapy (58 mmHg), although chest CT showed a slight reduction in the centrilobular granular shadow. Following this, 5 L of oxygen

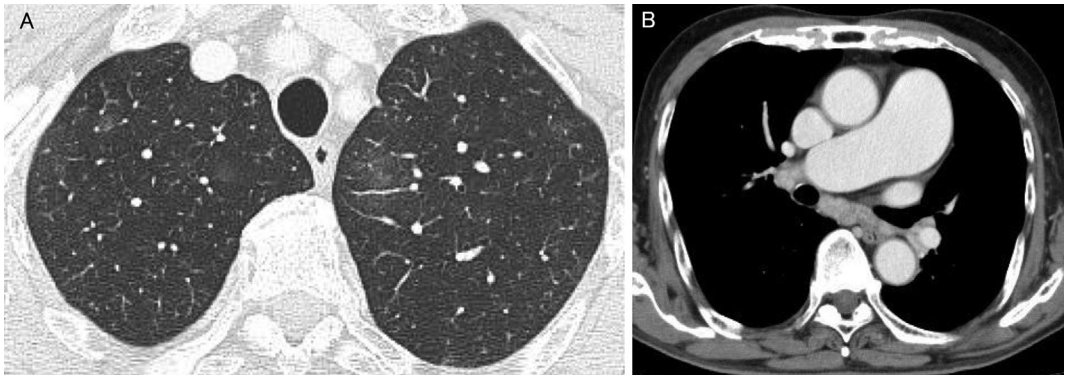

Figure 1. (A) Chest high-resolution computed tomography (CT) showed diffuse micronodules and ground-glass opacity in the centrilobular lung fields. (B) Contrast CT showed an enlarged pulmonary artery and mediastinal lymphadenopathy.

was required on the 34th day, and he suddenly died of cardiopulmonary arrest when he went to the bathroom by himself on the 35th day after admission.

An autopsy showed no macroscopic thrombi or tumor emboli in the central pulmonary arteries and no apparent tumor in the gastric mucosa. However, a microscopic examination revealed widespread tumor emboli in the peripheral small pulmonary arteries. Sections taken from the stomach showed that the tumor cells had crept under the submucosa, with 6 points of a maximum diameter of 1.8 mm at the mucous surface (Fig. 3B and C). The patient was therefore diagnosed with primary gastric cancer with PTTM.

Discussion

The present patient's history of inhalation of chlorine led us to a differential diagnosis of chemical inhalation lung injury. PTTM shows a variety of CT findings, including diffuse micronodules, that are similar to those observed with chlorine inhalation lung injuries (6). The clinical course of this patient provided an important lesson: a patient's clinical history may be misleading, and obtaining a pathological diagnosis is crucial in the management of diffuse lung disease.

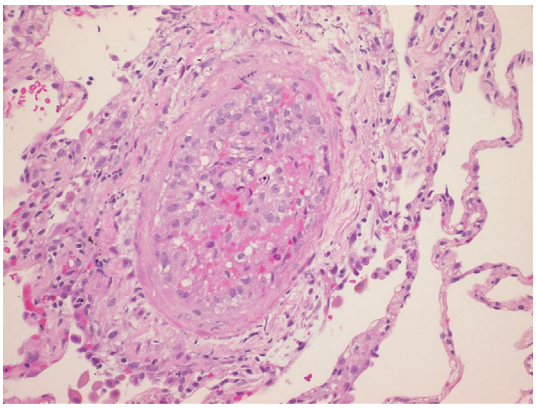

Figure 2. Occlusion of the small pulmonary artery with the adenocarcinoma cells and endothelial fibrocystic hyperplasia were determined by transbronchial lung biopsy specimens (Hematoxylin and Eosin staining, ×100).

PTTM is a rare manifestation of malignancy that has a poor prognosis. Based on the histological findings, PTTM is strongly associated with carcinomas, especially poorly differentiated adenocarcinomas (1, 7). The most frequent primary cancer complicated by PTTM is gastric cancer, followed by lung cancer, breast cancer, and cancers of unknown primary site (2). It is extremely difficult to make an antemortem diagnosis because of the rapid progression. The mean duration from the onset to admission is about 1 month, and the median survival of patients who die after admission is only 5 days (2). In addition, PTTM presents with non-specific radiological features, which also makes it difficult to diagnose (8). In previous reports, PTTM has been associated with a wide variety of radiological manifestations by chest CT, such as centrilobular nodules and ground-glass opacities, branching linear opacities, and interlobular septal thickening (8-10). It also shows a tree-in-bud centrilobular pattern, as pulmonary arteries that are occupied by tumor cells travel alongside small airways and share the same morphology (9). These radiological manifestations are also found in other diffuse pulmonary diseases, such as hypersensitive pneumonitis, intravascular lymphoma, and chemical-induced lung injury due to the inhalation of toxic elements (6, 11, 12). For these reasons, a diagnosis of PTTM while the patient is alive cannot be made easily or promptly. In fact, only a few cases of PTTM diagnosed prior to death exist in the literature (2-4, 13).

In the present case, the clinical course, including dry cough and centrilobular granular shadow on CT, was compatible with a diagnosis of chemical-induced lung injury, such as that induced by the inhalation of chemical herbicides (chlorate herbicide) for farming. Chlorine has intermediate solubility and is known to induce inhalation lung injury. CT of chemical-induced lung injury generally shows diffuse nodular opacities consistent with acute small airway injury and patchy areas of ground-glass attenuation (6, 11, 14). Although we originally suspected chemical-induced lung injury, an early TBLB was helpful for making a definitive diagnosis of PTTM, which allowed for the patient's immediate treatment. The primary site was unknown but was suspected to be the stomach or lung,

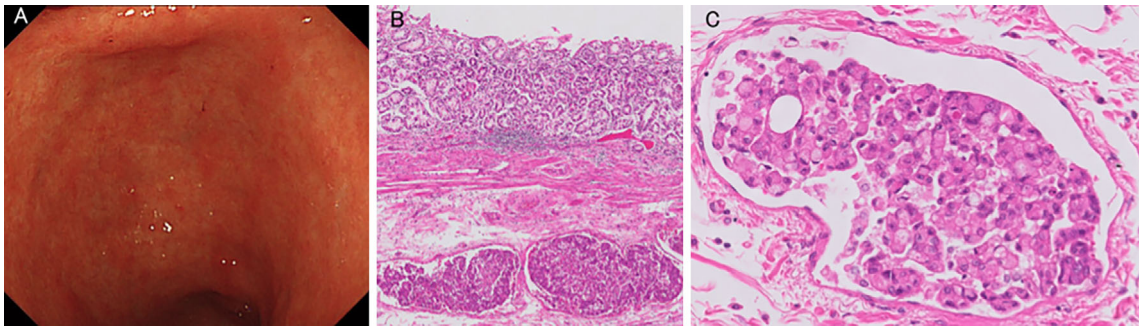

Figure 3. (A) Gastroesophageal endoscopy revealed only chronic gastritis. (B) Autopsy sections taken from the stomach showed that the tumor cells had crept under the submucosa. (C) Signet ring cell adenocarcinoma under the submucosa.

based on the immunohistochemical staining of the specimen from TBLB and TBNA. In addition, previous reports of PTTM have found that the most frequent primary sites are the stomach and lung (1, 2). Therefore, we started combination chemotherapy and anticoagulation therapy for adenocarcinoma of unknown primary site, which was proven to be gastric adenocarcinoma postmortem.

In the present case, we were unable to make an antemortem diagnosis of gastric cancer even after performing relevant evaluations using FDG-PET and gastroesophageal endoscopy. Gastroesophageal endoscopic observation and a biopsy specimen showed only atrophic gastritis without malignant findings. Occult primary gastric cancers similar to our case have been reported in previous studies and case reports on patients with Krukenberg tumor (15-17). In a previous study assessing 120 cases with Krukenberg tumors of the ovary, the primary site of only one patient could not be diagnosed among 38 cases of gastric origin, although repeated upper gastrointestinal radiographic and gastroscopic examinations were performed (15). In a case report of occult gastric cancer, no abnormal mucosa was detected, although repeated gastroesophageal endoscopies were performed by trained endoscopists. In that report, a random gastric biopsy from endoscopically normal-looking gastric mucosa revealed signet ring cell carcinoma (16). We were therefore able to make a postmortem diagnosis by examining small sections of the stomach.

A definitive treatment for PTTM has not been established. There are some case reports in which patients received systemic chemotherapy and anticoagulant therapy (3, 4). Kayatani et al. reported a patient with PTTM associated with cancer of unknown primary site who received systemic chemotherapy with tegafur-gimeracil-oteracil potassium and cisplatin and survived 15 months (3). According to the review by Fujishiro et al., comparing survivors and non-survivors, patients who had dyspnea-related PTTM before treatment had a poor prognosis (acute mortality of 80%) (2). We believe that the present patient had dyspnea before treatment; nevertheless, he was able to live over one month after admission because of the early diagnosis and combination chemotherapy and anticoagulant therapy.

In conclusion, we should be aware that PTTM can have a clinical and radiological presentation similar to that of other diffuse pulmonary diseases, including chemical inhalation lung injury. A pathological examination of biopsy specimens is crucial for such patients.

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

Acknowledgement

We thank Dr. Koichi Honma for making the diagnosis in this case.

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