Pulmonary Tumor Thrombotic Microangiopathy Diagnosed Antemortem and Treated with Combination Chemotherapy

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Abstract

A 29-year-old man developed a persistent dry cough. Chest high-resolution computed tomography (HRCT) revealed centrilobular ultrafine granular shadows scattered in all lung fields. A lung biopsy with video-assisted thoracoscopic surgery revealed findings compatible with pulmonary tumor thrombotic microangiopathy (PTTM). However, the primary tumor was not identified. Combination chemotherapy with S-1 and cisplatin decreased his cough and improved the chest HRCT findings. The illness, however, gradually became difficult to control. He eventually developed pulmonary hypertension and died. Typically, an antemortem diagnosis of PTTM cannot be made. In this case, the diagnosis of PTTM and combination chemotherapy improved the chest HRCT findings, respiratory symptoms, and prognosis.

Key words: pulmonary tumor thrombotic microangiopathy, cancer of unknown primary, pulmonary hypertension, combination chemotherapy

(Intern Med 51: 2767-2770, 2012)
(DOI: 10.2169/internalmedicine.51.7682)

Introduction

The concept of pulmonary tumor thrombotic microangiopathy (PTTM) as a condition related to malignant tumors was proposed in 1990 by von Herbay et al. (1). In PTTM cases, the endothelial attachment of multiple microscopic tumor emboli induces fibrocellular and fibromuscular intimal proliferation of small pulmonary arteries and arterioles combined with secondary thrombosis, which leads to a massive reduction of the pulmonary vascular bed and result in pulmonary hypertension. An antemortem diagnosis of PTTM is very difficult, because the findings on chest computed tomography (CT) are often trivial or non-specific, and the condition rapidly progresses to death.

We herein report a case of PTTM diagnosed prior to the development of pulmonary hypertension, which responded to combination chemotherapy.

Case Report

The patient was a 29-year-old Japanese man with a history of infantile asthma until the age of 10 years and no history of smoking. He had worked in the forestry industry for six years before this episode. In June 2007, he developed a dry cough. The symptoms worsened, and he was prescribed an antitussive medication by a local doctor, but the cough failed to improve. In September 2007, he was referred to our hospital. His cough did not show any notable characteristics and persisted throughout the day. However, he showed normal auscultation findings and no fever. His oxygen saturation level was 98% (room air), and he showed normal results for electrocardiography (ECG) and sputum culture. Blood biochemical examinations revealed moderately increased levels of C-reactive protein (5.85 mg/dL) and a slight abnormality in the coagulation and fibrinolytic system (D-dimer, 3.1 μg/mL). Chest radiography, contrast-enhanced CT and high-resolution CT (HRCT) of the chest did not re-
reveal any abnormalities. Diseases such as cough variant asthma and gastroesophageal reflux were suspected, and therefore, he received inhaled corticosteroids, inhaled β2 agonists, and proton pump inhibitors, in addition to the anti-tussive agents, but these agents had no effect.

We attempted to perform bronchoscopy to exclude the presence of bronchial lesions, such as those from tuberculosis of the bronchus, while the patient was under sedation, but his severe coughing prevented the procedure from being completed. In November 2007, another chest HRCT was performed, which revealed centrilobular ultrafine granular shadows scattered in all lung fields (Fig. 1a). Blood biochemical examinations revealed elevated levels of carbohydrate antigen 19-9 (CA19-9) (1,288 U/mL). However, the serum carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA), and pro-gastrin-releasing peptide (Pro-GRP) concentrations were within the normal range. The patient’s cough continued to worsen, at times making speaking difficult. To determine the cause of the severe cough, a lung biopsy from the lingular segment of left lung was performed by video-assisted thoracoscopic surgery (VATS). This procedure revealed signet-ring cell carcinoma in the peripheral pulmonary arteries, marked endothelial fibrocytic hyperplasia in the arterioles, and organized thrombogenesis (Fig. 2). PTTM was diagnosed on the basis of these pathological findings.

Immunohistochemical staining of the tumors showed positive results for cytokeratin (AE1/AE3), cytokeratin 7, cytokeratin 20, and CA19-9 and a negative result for thyroid transcription factor-1 (TTF-1). Upper and lower gastrointestinal endoscopies and a full-body contrast-enhanced CT scan were performed to identify the primary lesion, but no abnormal findings were obtained. An examination by 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed accumulations in the third and fourth cervical vertebrae, thus suggesting metastasis. An ECG examination was performed at this time, and it yielded normal results, and a transthoracic echocardiogram revealed normal pulmonary artery pressure. We decided to treat him for PTTM caused by cancer of an unknown primary. Chemotherapy with S-1 (tegafur/gimeracil/oteracil potassium, 120 mg/body; day 1-21) and cisplatin (60 mg/m²; day 8) was initiated to treat the PTTM. The severity of the cough rapidly decreased after the initiation of chemotherapy. Chest HRCT performed after three courses of chemotherapy showed that the ultrafine innumerable granular shadows in the centrilobular lung fields had almost disappeared (Fig. 1b).

To provide a better chance of a cure, six courses of chemotherapy were administered to the patient. The patient’s serum D-dimer levels returned to within the normal range, and the elevated serum CA19-9 (1,288 U/mL) level gradually decreased. However, 10 months after diagnosis, the

Figure 1. Chest high-resolution computed tomography (HRCT) findings. a) Innumerable ultrafine granular shadows in the centrilobular lung fields before chemotherapy. b) These shadows had almost disappeared after three courses of chemotherapy with S-1 and cisplatin.
cough reappeared. Chemotherapy with S-1 (120 mg/body; day 1-21) and gemcitabine (1,000 mg/m²; day 1, 8) was administered, and a therapeutic effect was observed again. However, the illness gradually became more difficult to control, and the patient’s condition was complicated by disseminated intravascular coagulation. An echocardiogram obtained showed pulmonary hypertension. The pulmonary hypertension progressed, the patient’s breathing rapidly deteriorated, and he died 15 months after the diagnosis.

Discussion

PTTM is characterized by the following phenomena: 1) the presence of tumor emboli in the small pulmonary arteries, 2) fibrocellular and fibromuscular intimal proliferation in the small pulmonary arteries, and 3) organization and recanalization of thrombi. The second finding is a particularly serious one, and is very different from simple pulmonary arterial tumor emboli. The presence of minute tumor emboli in the peripheral pulmonary arteries can cause damage to the vascular endothelium, leading to thrombus formation and accelerated coagulation. An echocardiogram obtained showed pulmonary hypertension. The pulmonary hypertension progressed, the patient’s breathing rapidly deteriorated, and he died 15 months after the diagnosis.

Autopsy data suggest that the most frequent primary site associated with PTTM is the stomach, with a few reports involving other organs (1, 3, 6-8). The tissue type is adenocarcinoma, particularly mucinous or signet-ring cell carcinoma (1, 4).

In our case, PTTM was identified using VATS and was effectively treated by chemotherapy. The primary site was unknown, but suspected to be the stomach or pancreas on the basis of immunohistochemical staining of the specimen from VATS, and previous reports of PTTM suggesting that the most frequent primary site is stomach (1). Based on this suspicion, we treated the patient with S-1 and cisplatin as first line and with S-1 and gemcitabine as second line therapy. Ours is the third case reported in English in which the diagnosis of PTTM was made while the patient was alive (2, 9), and this case is the first report in which combination chemotherapy achieved a therapeutic effect.

The clinical manifestations of end stage PTTM include cardio-respiratory failure due to progressive pulmonary hypertension. It is notable that there are some PTTM cases where patients develop a dry cough before heart failure (2, 10, 11, 12). In contrast to symptoms caused from pulmonary hypertension such as dyspnea, we presume that the cough appears relatively early in the course of PTTM, although not all PTTM patients develop it. A dramatic relief of cough was achieved by chemotherapy in our case, thus suggesting that the symptom was caused by PTTM. In patients with cough variant asthma, it was demonstrated that the VEGF levels in induced sputum samples are increased and related to airway hyperresponsiveness (13). Similarly, in PTTM cases, tumor cells express factors such as VEGF (2, 12, 14, 15), TF (15) or serotonin receptor type 2A (5-HT2A) (11). Some cytokines might induce airway hyperresponsiveness in some patients with PTTM, thus pos-
PTTM has been reported to present with a tree-in-bud pattern and ground-glass opacity in chest CT scans (10), but since previous reports have also included imaging findings from late-stage carcinoma and complicating lymphangiosis carcinomatosa, these cannot be said to be true imaging findings for PTTM itself. The lesions in PTTM are primarily located in the peripheral pulmonary arteries, and in this case, there was evidence of pathological thickening of the walls of the small pulmonary arteries. We believe that these findings are equivalent to the “ultrafine granular appearance” in the HRCT images. That is, since peripheral pulmonary arteries are accompanied by terminal bronchioles, the granular appearance presents in the form of centrilobular shadows. In addition, these granular shadows are reflection of the peripheral blood vessels, not the respiratory tract, and therefore, the border of the granular shadows is associated with almost no blurring. The “ultrafine granular appearance” in the HRCT images in this case can be considered to be one of the earliest signs of PTTM. Furthermore, these ultrafine granular shadows disappeared after combination chemotherapy.

Typically, a diagnosis of PTTM while the patient is alive cannot be made because of the sudden appearance of PTTM-induced severe pulmonary hypertension, which quickly leads to deterioration of the patient’s condition and death. It is very important to consider the possibility of PTTM before the appearance of pulmonary hypertension. Therefore, the early identification of PTTM on the basis of chest HRCT findings, malignant tumor history, coagulation system abnormalities, and the development of a stubborn dry cough is crucial. As observed in this case, with the diagnosis obtained through invasive tissue examinations, the fatal prognosis of PTTM could be improved by systemic chemotherapy.

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

References


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