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Case Report

Pulmonary Tumor Thrombotic Microangiopathy Induced by Prostate Cancer

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Pulmonary tumor thrombotic microangiopathy (PTTM) is a fatal, malignancy-related respiratory complication; we herein report a PTTM case induced by metastatic prostate cancer. An 81-year-old Japanese man developed dyspnea. High-resolution computed tomography (HRCT) revealed ground-glass opacities spread across bilateral lung fields. Pulmonary microvascular aspiration cytology detected prostate cancer cells. As PTTM was highly suspected, docetaxel chemotherapy was performed immediately. His respiratory condition and HRCT findings improved temporarily, but he died approx. 6 weeks after admission. Autopsy showed fibrocellular intimal proliferation of small pulmonary arterioles, which confirmed the diagnosis of PTTM induced by prostate cancer. As in the present case, it is often difficult to confirm the presence of not only tumor embolization but also fibrocellular intimal proliferation before the patient's death.

Key words: autopsy, dyspnea, prostate neoplasm, metastatic lung cancer, thrombotic microangiopathy

Pulmonary tumor thrombotic microangiopathy (PTTM), a rare clinicopathological entity causing pulmonary hypertension in cancer patients, was first reported by von Herbay *et al.* in 1990 [1]. There are several reports of PTTM from Japan where the prevalence of gastric cancer is high, because gastric cancer is the malignancy that is most commonly associated with PTTM [2]. We report the fourth case of PTTM originating from metastatic prostate cancer.

Case Presentation

An 81-year-old Japanese man with a history of old myocardial infarction and chronic obstructive pulmonary disease had been clinically diagnosed with prostate cancer approx. 8 years prior to his present admission (serum prostate-specific antigen [PSA] level 51.3 ng/mL, clinical stage T3bN0M0) and was treated with combined androgen blockade. However, the disease progressed gradually over the next 7 years and became castration resistant. Radiological assessment revealed multiple bone metastases. Although we recommended chemotherapy, he voluntarily discontinued his follow-up visits. Six months later, he was admitted to our hospital with dyspnea of a few days' duration, and loss of appetite that started 2 months previously.

On admission, the patient was afebrile, with a blood pressure at 154/71 mmHg and a heart rate of 80 beats/min. Peripheral oxygen saturation was 90% on room air. His PSA level was highly elevated at 696.2 ng/mL; alkaline phosphatase was 7,672 U/L,

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fibrin degradation product was 31 μg/dL, and the D-dimer level was 9.5 μg/dL. Arterial blood gas measurement indicated hypoxemia (PaO_2 50.0 mmHg and $PaCO_2$ 32.0 mmHg) on room air. An electrocardiogram showed complete right bundle branch block. The tricuspid regurgitation pressure gradient shown by echocardiogram was 34 mmHg (normal, <30 mmHg), suggesting pulmonary hypertension.

Chest radiography demonstrated ground-glass opacities (GGOs) and patchy shadows on both bilateral middle and lower lung fields. Contrast-enhanced high-resolution computed tomography (HRCT), which had previously shown only emphysema change, revealed the progression of diffuse bone metastases and GGOs as well as micronodular opacities diffusely spread across bilateral lung fields (Fig. 1); however there was no evident pulmonary embolism. Lung perfusion scintigraphy showed bilateral multiple subsegmental defects (Fig. 2). On right heart catheterization on Day 8, the mean pulmonary arterial pressure was elevated to 21 mmHg but did not meet the criteria for pulmonary hypertension (mean pulmonary artery pressure ≥25 mmHg).

PSA stain-positive adenocarcinoma was detected by pulmonary microvascular aspiration cytology. This finding suggested that the cells originated from the prostate cancer (Fig. 3). On transbronchial lung biopsy (TBLB), tumor cells were detected in small vessels in the stromal tissue (Fig. 4). Pulmonary embolism caused by tumor or thrombosis, and lymphangiosis carcinomatosa were differential diagnoses based on these findings. A definitive diagnosis was difficult to determine at that time. However, we strongly suspected PTTM induced by prostate in light of the following: the rapid progressive dyspnea, hypoxemia, the marked increase

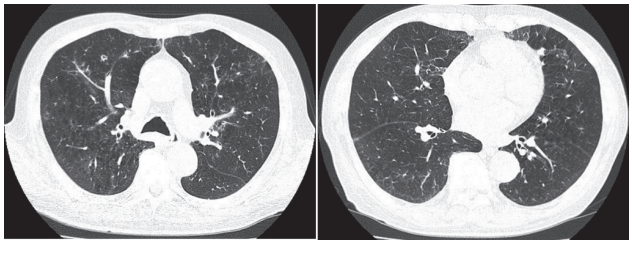

Fig. 1 Chest HRCT scan on admission showed GGOs, small granular shadows, consolidations, and bronchial wall thickenings in bilateral lungs diffusely.

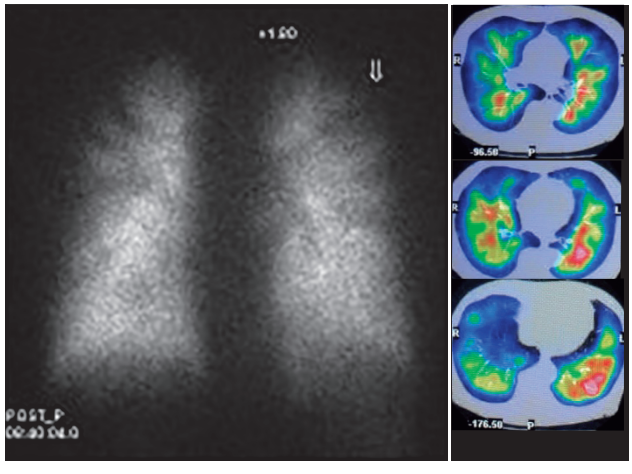

Fig. 2 Lung perfusion scintigraphy showed multiple subsegmental defects.

Fig. 3 Pulmonary microvascular cytology detected PSA stain-positive adenocarcinoma.

in PSA, the hypercoagulable condition, the tendency of increasing pulmonary artery pressure, no macroscopic pulmonary tumor emboli in the contrast-enhanced CT, multiple subsegmental defects shown by lung perfusion scintigraphy, the presence of PSA stain-positive adenocarcinoma detected by TBLB, and the pulmonary aspiration cytology results.

Therefore, chemotherapy with docetaxel (55 mg/m^2) on Day 10 was performed for prostate cancer. At the time, the patient's only subjective symptom was dyspnea on exertion, and his oxygen saturation level was approx. 95% on 4 L/min of O_2. Immediately after chemotherapy, his condition improved somewhat. His oxygen saturation level increased to approx. 98% at rest on 4 L/min of O_2. The oxygen dose could not be decreased, because of oxygen desaturation on exertion. On Day 28, HRCT revealed the improvement of the GGOs and micronodular opacities (Fig. 5), and the tricuspid regurgitation pressure gradient by echocardiogram decreased from 34 mmHg to 30 mmHg. Nevertheless, the patient's general condition had gradually worsened due to febrile neutropenia on Day 18, and pseudomembranous enterocolitis was observed on Day 21. After each improvement was observed, we debated the necessity of administering additional chemotherapy, and the second round with docetaxel (37 mg/m^2) was performed on Day 38. Nevertheless, the patient's respiratory status deteriorated rapidly on Day 40, and he died of the primary disease on Day 41.

On autopsy, the patient's lungs showed bilateral congestive edema; however tumor lesions on the macroscopic cut surface and inflammation of the lungs were not detected. The histological examination of the lung revealed tumor emboli from prostate cancer, fibrocellular intimal proliferation, and stenosis and recanalization at the lung arterioles (Fig. 6). A definitive diagnosis of PTTM derived from prostate adenocarcinoma was made based on the autopsy findings.

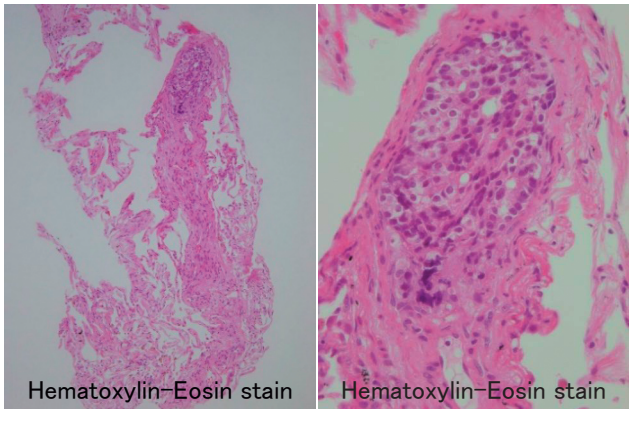

Fig. 4 Histological examination of a transbronchial lung biopsy specimen showed tumor cells in small vessels of the stromal tissue.

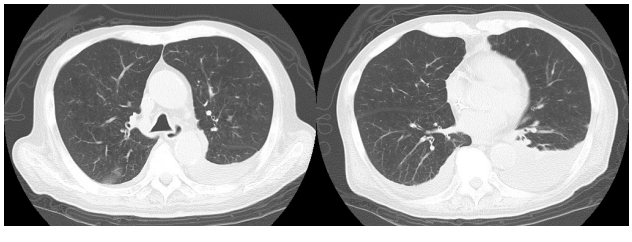

Fig. 5 HRCT scan on Day 28 showed improvement of the GGOs, small granular shadows, consolidations, and bronchial wall thickenings in bilateral lungs, and an increase of bilateral pleural effusion.

Discussion

PTTM, which is characterized by microscopic tumor embolization and fibrocellular intimal proliferation of small pulmonary arterioles, has a poor prognosis. The mean time from the onset of dyspnea to death is reported only 3-4 weeks [3, 4]. In the present case, the period from the appearance of symptoms to death was 6 weeks. We believe that the early treatment due to suspected illness contributed to the improvement of his symptoms and CT findings, and to the prolonged survival. The pathologic finding of fibrocellular intimal proliferation is necessary to confirm the diagnosis of

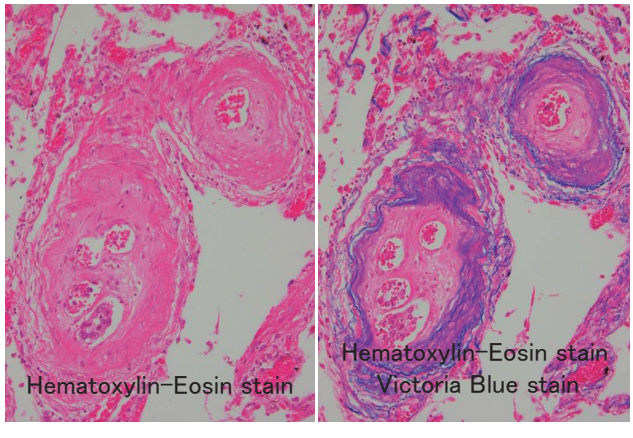

Fig. 6 Hematoxylin-eosin stain at the right upper lobe showed not only tumor emboli but also fibrocellular intimal proliferation, and recanalization of small pulmonary arterioles. Victoria Blue stain showed the thickening of subintimal elastic fibers.

PTTM; this proliferation is the result of marked activation of the coagulation system, either secondary to a direct attachment of tumor cells to the endothelium, or secondary to local thrombosis at the surface of tumor emboli, which is the hallmark of angiopathy [1]. Microangiopathy leads to a diffuse narrowing of the pulmonary arterioles and increased vascular resistance, resulting in secondary pulmonary hypertension.

PTTM is observed in 1.4-3.3% of consecutive autopsy cases of carcinoma [1, 3, 5]. The most common origin is stomach cancer, especially the poorly differentiated type; other origins include lung, breast, pancreas, and esophagus. To our knowledge, four known cases of PTTM originating from prostate cancer exist, including this case. Considering the previous reports, clinicians who encounter prostate cancer patients with a high Gleason score or with a marked rise in PSA, should keep the possibility of PTTM in mind [1, 6, 7]. An increasing number of PTTM cases induced by other tissue types, such as urothelial carcinoma, have been reported [8, 9].

The most common symptoms of PTTM are progressive dyspnea, coughing and hemoptysis [5]. These symptoms are attributed to pulmonary hypertension and right-sided heart failure. PTTM is thus often misdiagnosed as idiopathic pulmonary arterial hypertension. Chinen *et al.* reported that almost half of PTTM patients had developed pulmonary hypertension, or "features of increased pulmonary vascular resistance," and these patients died earlier [1, 4]. The clinical manifestation of end-stage PTTM is pulmonary hypertension. An early antemortem diagnosis before the development of pulmonary hypertension is thus very important [4, 10].

Nevertheless, the antemortem diagnosis of PTTM is extremely difficult. Antemortem PTTM has reportedly been diagnosed by video-assisted thoracic surgery, TBLB, or CT-guided lung biopsy [8-14]. von Herbay *et al.* emphasized the presence of both microscopic tumor emboli and fibrocellular intimal proliferation in the diagnosis of PTTM [1]. As in the present case, it is possible to confirm microscopic tumor emboli by TBLB or biopsy, but it is not possible to confirm the presence of fibrocellular intimal proliferation by TBLB or biopsy, and it is therefore often difficult to make a definite diagnosis. However, we strongly suspected PTTM induced by prostate cancer in light of the above-described findings. Because PTTM progressed rapidly if treatment is not provided, we initiated chemotherapy immediately before the patient exhibited pulmonary hypertension, and he achieved temporary improvement.

The radiologic diagnosis of PTTM has not been established because its findings are often minimal and nonspecific. In previous investigations, chest HRCT showed thickened interlobular septa, diffuse tree-in-bud opacities, or ground glass centrilobular micronodules [10, 11, 15-17]. These findings are not conclusive of PTTM because they can also be found in complicated lymphangiosis carcinomatosa [1]. Kayatani *et al.* reported that PTTM's ultrafine granular appearance on HRCT may be an early indicator of the disease [12]. In our patient's case, HRCT showed GGO and micronodular opacities diffusely spread across bilateral lung fields. These findings, along with the patient's symptoms, resolved temporarily upon chemotherapy. In addition, lymphangiosis carcinomatosa and inflammation of the lungs were ruled out at autopsy. Thus, findings of GGOs and micronodular opacities on HRCT may be attributed to the presence of PTTM.

The pathogenesis of PTTM starts with tumor emboli to the pulmonary vessels at the microscopic level. The emboli activate the coagulation system and release inflammatory mediators [2, 4, 10]. In the present case, docetaxel might have reduced the cancer cells and inhibited the coagulation cascade and inflammation.

In conclusion, PTTM is an under-recognized diagnosis and has an aggressive course once symptoms appear. Early antemortem diagnosis and treatment are very important before the patient develops pulmonary hypertension. Therefore, PTTM should be considered in all cancer patients with acute respiratory insufficiency, whose CT findings are minimal and nonspecific, including GGOs and micronodular opacities.

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