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Case report

Initial diagnosis and successful treatment of pulmonary tumor embolism manifesting as the first clinical sign of prostatic adenocarcinoma

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ABSTRACT

Although pulmonary tumor embolism (PTE) is a well-recognized end-stage form of pulmonary metastases at postmortem examination, the entity is rarely the first clinical sign of prostate cancer. Diagnosis of this condition in patients who have no previous history of malignancy is a challenge. Herein, we reported a 79-year-old man presented with progressive, unexplained dyspnea on exertion. Microscopic PTE coinciding with pulmonary lymphangitic carcinomatosis were readily recognized based on the presence of multifocal dilatation and beading of the peripheral pulmonary arteries with thickening of the bronchial walls and interlobular septa on the initial thin-section chest CT images. Pathologic examination of the transbronchial lung biopsy specimen revealed tumor emboli occluding both the small muscular pulmonary arteries and lymphatic vessels. These tumor cells were positive for prostatic specific antigen on immunohistochemical staining. The final diagnosis of prostatic adenocarcinoma was confirmed. Remarkable clinical and radiographic improvement was achieved following bilateral orchiectomies and anti-androgen treatment.

1. Introduction

Pulmonary tumor embolism (PTE) is considered a rare and end-stage manifestation of pulmonary metastases in patients with advanced cancer. The spectrum of PTE includes 1) macroscopic PTE involving main or large segmental pulmonary arteries; 2) microscopic PTE involving small pulmonary arteries, arterioles and capillaries; and 3) pulmonary tumor thrombotic microangiopathy (PTTM) [1–7]. Unlike large cell nests in microscopic PTE, PTTM is characterized by small or single metastatic tumor cells accompanied by fibrocellular intimal and/or muscular proliferation of the involved arteries [1,5,7].

The antemortem diagnosis of PTE, even in patients with established and advanced cancer, is often complicated and often misdiagnosed as pulmonary thromboembolism [5,6,8]. Moreover, PTE is rarely the first clinical sign of malignancy, especially in patients with prostate cancer [4].

Herein, we report an elderly man presenting with PTE coinciding with pulmonary lymphangitic carcinomatosis (PLC) as the first clinical sign of advanced prostatic adenocarcinoma. The diagnosis of this condition in a patient who has no previous history of malignancy is a challenge. Rapid recognition of this rare entity on the initial chest CT images as well as effective and timely delivery of appropriate treatment has led to a favorable patient outcome.

2. Case report

In November 2015, a 79-year-old man presented with progressive dyspnea on exertion for one month and cough with yellowish phlegm for 2 weeks. He was diagnosed as having acute bronchitis and was treated with clarithromycin and cough suppressant. Despite the partial

Abbreviations: CT, Computed tomography; PTE, Pulmonary tumor embolism; PTTM, Pulmonary tumor thrombotic microangiopathy; PLC, Pulmonary lymphangitic carcinomatosis; PSA, Prostatic specific antigen; VEGF, Vascular endothelial growth factor; PDGF, Platelet-derived growth factor.

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improvement of productive cough, his dyspnea worsened. He denied having other constitutional symptoms. He had a smoking history of 30 pack-years. His comorbid diseases included well-controlled type 2 diabetes mellitus, hypertension, and dyslipidemia. On examination, his breath sounds were normal upon auscultation, and no sign of pulmonary hypertension was observed. His oxygen saturation was 98% at ambient air. His 6-min walk test showed a walk distance of 265 m without desaturation. Spirometry was not performed. Complete blood count revealed hematocrit of 38% and white blood cell count of 5150 cells/μL (neutrophils, 54%). The serum D-dimer level was 4074 ng/mL. Other laboratory tests were within normal ranges.

The initial chest radiograph revealed prominent bronchovascular markings with subtle reticulonodular opacities in the left upper zone and right lower zone. A volumetric high-resolution CT scan of the chest with intravenous contrast administration was subsequently performed. It revealed multifocal dilatation and beading of the segmental, subsegmental, and centrilobular pulmonary arteries with smooth or irregular thickening of either bronchial walls or interlobular septa in all pulmonary lobes (Fig. 1A and B). There were multiple enlarged mediastinal and hilar nodes. There was no evidence of discrete parenchymal nodule, pulmonary thromboembolism, or pulmonary hypertension. Multifocal areas of diminished perfusion were demonstrated on the post-processing CT color maps (Fig. 1C and D), automatically generated by pulmonary artery analysis application of Philips IntelliSpace Portal 7.0. These CT findings were highly suggestive of microscopic PTE with concomitant PLC and intrathoracic nodal metastases.

Without CT evidence of primary lung cancer, extrathoracic malignancy was sought out. Upper and lower gastrointestinal endoscopy showed only mild antral gastritis. Fiberoptic bronchoscopy showed no evidence of endobronchial lesion. Endobronchial ultrasound with transbronchial needle aspiration of the right paratracheal lymph node and transbronchial lung biopsy at the right middle lobe was performed. Cytologic examination of the lymph node specimen yielded a cluster of tumor cells characteristics of adenocarcinoma that aroused suspicion for metastatic prostate cancer. Pathological examination of the biopsied lung tissues confirmed the presence of clusters of adenocarcinoma within the small muscular pulmonary arteries and lymphatic vessels (Fig. 2A and B). Neither intimal proliferation nor thrombosis of the pulmonary arteries was demonstrated. Subsequent immunohistochemical staining showed that these tumor cells were positive for prostatic specific antigen (PSA) (Fig. 2C) but were negative for an antibody against vascular endothelial growth factor (VEGF) (Fig. 2D). His serum PSA level was 1825 ng/mL. Therefore, a CT scan of the whole abdomen was subsequently done and showed an enlarged prostate gland with an osteoblastic lesion involving the L3 vertebral body. No intraabdominal metastasis or lymphadenopathy was observed. Bone scintigraphy confirmed the presence of multiple bone metastases. Echocardiography showed no evidence of pulmonary hypertension. The diagnosis of advanced prostatic cancer with microscopic PTE, PLC, intrathoracic nodal, and bone metastases was established.

During the work-up, the patient had marked progression of clinical symptoms and bilateral pulmonary abnormalities identified on a follow-up chest radiograph. Following bilateral orchiectomy and anti-androgen (flutamide) treatment, the patient showed remarkable clinical and radiographic improvement (Fig. 3). The serum PSA level dropped to 1.08 ng/mL. He remained free of symptoms for almost 2 years.

In 2017, he presented to the hospital due to acute urinary retention requiring urethral dilatation and subsequent palliative transurethral prostatectomy. The follow-up chest CT showed a new small right lower lobe nodule, without evidence of PTE or PLC. In October 2018, he developed gross hematuria and obstructive uropathy. He received palliative care treatment and finally passed away 3 years after the initial presentation.

3. Discussion

Although the lungs are the common site of metastasis, PTE, and PLC are exceptionally rare, and either pattern is rarely the first clinical sign of prostate cancer [3,9–12].

Microscopic PTE and PTTM can coexist, and both can coincide with pulmonary PLC, which is defined as the presence of tumor emboli in the bronchovascular, interlobular septal, and subpleural lymphatic vessels [13]. Based on autopsy studies, the reported incidence of PTE ranges from 0.9% to 26% in patients with various malignancies, among which adenocarcinoma is the most common histologic subtype [1–5,7].

Similar to the present case, up to 60% of patients having microscopic PTE and/or PTTM present with subacute or unexplained dyspnea on exertion that often progresses over a few days to months. Other presenting clinical symptoms and signs include cough, hemoptysis, pleuritic chest pain, hypoxia, and signs related to the primary malignancy [2,4,5,

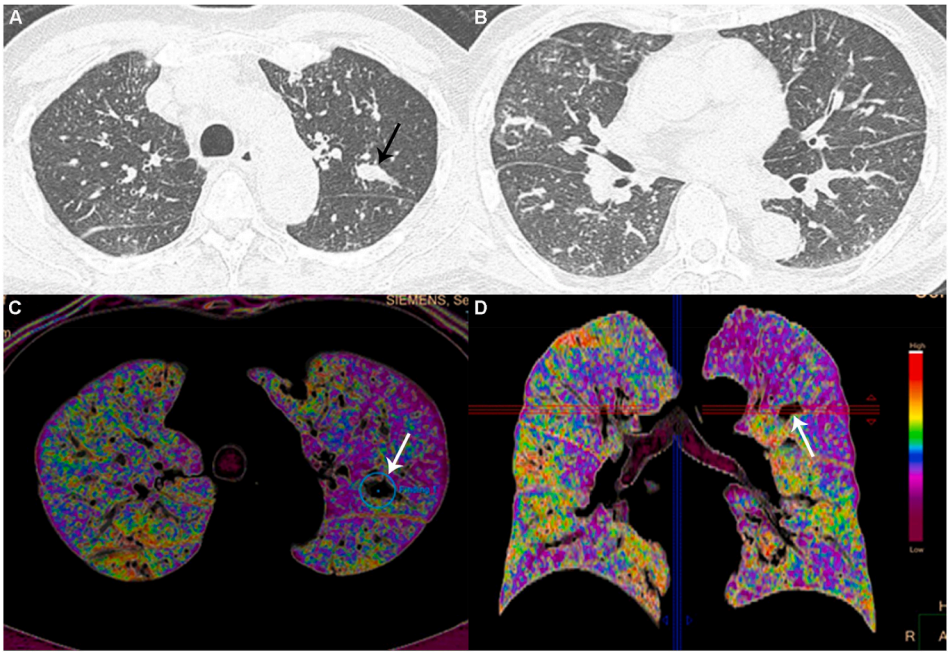

Fig. 1. A-D: Initial chest CT images with a lung-window setting (A and B) showing mosaic perfusion with multifocal dilatation and beading of the peripheral pulmonary vessels and thickening of bronchial walls and/or interlobular septa in all pulmonary lobes. Note nodular dilatation of the subsegmental pulmonary arterial branch mimicking a pulmonary parenchymal nodule (arrow in A) in the left upper lobe. The post-processing Hounsfield unit (HU)-based color maps of the axial (C) and coronal (D) contrast-enhanced CT images show marked heterogeneity of lung attenuation due to uneven perfusion, coded with different colors. As defined in the color bar in D, the multiple purple and blue-colored areas, most pronounced in the left upper lobe distal to the occluded artery (arrows in C and D), represent areas with low HU due to diminished perfusion. The green, yellow, orange and red-colored areas represent areas with higher HU or perfusion. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

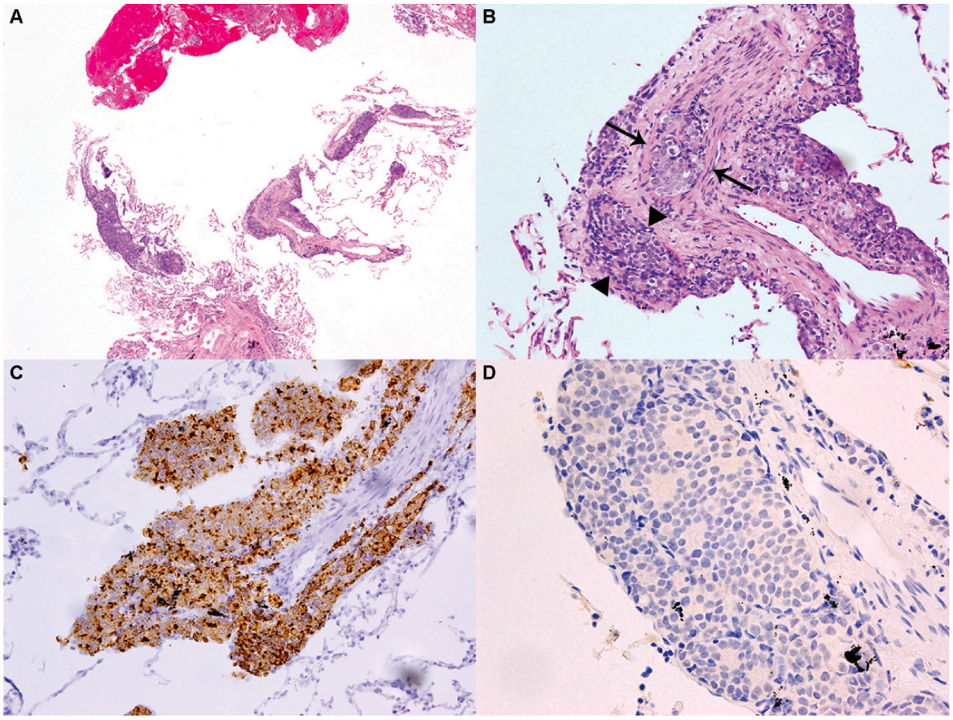

Fig. 2. A-D: Histologic examinations of lung tissues obtained by transbronchial lung biopsy with hematoxylin-eosin staining show a linear distribution of lymphangitic carcinomatosis (A, original magnification ×20) and clusters of tumor cells occluding small muscular pulmonary arteries (arrows) and lymphatic channels (arrowheads) (B, original magnification ×200). Immunohistochemical staining shows numerous neoplastic cells marked with PSA (C, original magnification ×200) and negative staining of neoplastic cells for VEGF (D, original magnification ×400).

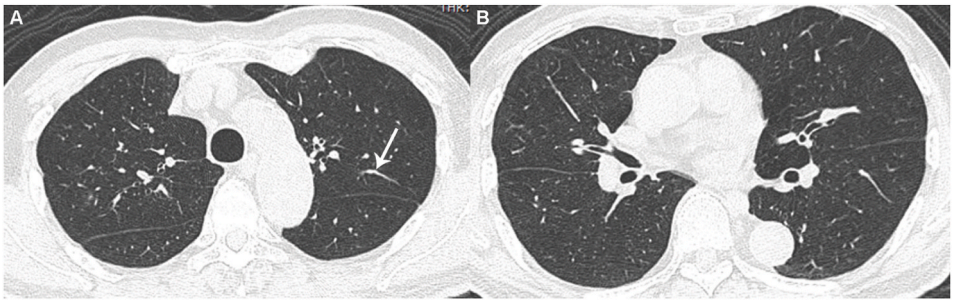

Fig. 3. A-B: Follow-up CT obtained 4 months after the treatment with a lung-window setting shows near-complete resolution of all previous abnormalities, including the previously dilated subsegmental pulmonary artery (arrow in A) in the left upper lobe.

7]. Unlike PLC, patients suffering from microscopic PTE and PTTM usually have symptoms more severe than what one would expect based on the physical examination and radiographic findings [2,3,5,14]. Regardless of treatment, patients with PTE typically progress rapidly to respiratory distress, pulmonary hypertension, right heart failure, and death [1,7,15].

Unlike the present case, initial chest radiographs are unremarkable in the majority of cases [2,3,5,10]. As the disease progresses, prominent bronchovascular markings, cardiomegaly, signs of pulmonary hypertension, lymphadenopathy, and pleural effusion may be seen [3,10].

Although chest CT scan or CT angiography is often reported to be normal or nondiagnostic, multifocal dilatation and beading of either central or peripheral pulmonary arteries, similar to the present case, have been reported to be characteristic findings in PTE and PTTM [2, 4–8,16]. Pulmonary infarction may occur as a wedge-shaped pleural based consolidation or ground-glass opacity with its apex directed towards the pulmonary hilum or, rarely, as a thin-walled cavity [17]. Of note, distinguishing between dilated, beaded pulmonary arteries in microscopic PTE and/or PTTM and a tree-in-bud pattern reflecting dilated, mucus-filled bronchioles in bronchiolar disease can be challenging [7,8,14,16]. Careful analysis of thin-section chest CT images obtained with volumetric acquisition can help provide the correct diagnosis because signs of airway inflammation with mucus plugging of the airway lumens are often observed in bronchiolar disease, but are not usually seen in microscopic PTE or PTTM. The relationship with the proximal arteries can be depicted on CT images reconstructed by using maximum intensity projection [14]. Moreover, microscopic PTE and PTTM can lead to perfusion defects and right ventricular strain. Perfusion defects can be demonstrated on a ventilation/perfusion lung scan using medical isotopes and scintigraphy [2,4,5,7,18–20] or on multi-detector single-energy or dual-energy CT using image post-processing tools [21].

Because PLC often coincides with either microscopic PTE or PTTM [2–5,7,11], the presence of characteristic CT findings of PLC (smooth, nodular or irregular thickening of interlobular septa and/or bronchial wall and associated intrathoracic lymphadenopathy [12,13]) in addition to dilated beaded peripheral pulmonary arteries and perfusion defects can serve as a clue for diagnosing microscopic PTE or PTTM, akin to the present case.

Pathological examination of the lungs remains the gold standard in the diagnosis of PTE. Tissue diagnosis can be obtained by transbronchial lung biopsy [15,19], transthoracic needle biopsy under a CT guidance [7], or pulmonary microvascular cytology [2,4,5,15]. If the diagnosis remains inconclusive, an open lung biopsy may be required [2,4,5].

Nevertheless, patients who suffer from either severe pulmonary hypertension or instability of hemodynamics may develop fatal postoperative complications [14].

Because of the difficulty in making the diagnosis antemortem and a limited understanding of the specific cellular and molecular mechanisms, a guideline for the treatment of this rare entity has not yet been established. The treatment usually targets the primary malignancy [2,4,15,16,19]. Recent studies show that patients with PTTM may have higher levels of VEGF, tissue factor, platelet-derived growth factor (PDGF), and osteopontin than patients with microscopic PTE [1,7]. Hence, these patients might also benefit from treatment with tyrosine kinase inhibitor for PDGF receptors (Imatinib) [18–20]. Our patient was treated with bilateral orchiectomy and anti-androgen therapy, which resulted in remarkable clinical and radiographic improvement. The patient was alive for 3 years after the initial presentation, longer than the reported median survival (9 days) in patients with PTE [1,7,16,18–20]. Besides prompt diagnosis and effective treatment, the favorable outcome in our patient might also be attributed to the fact that he did not yet develop PTTM or pulmonary hypertension.

4. Conclusion

In conclusion, we have reported the first patient with the initial diagnosis and successful treatment of microscopic PTE coinciding with PLC, which are unexpected and rare clinical presentations of advanced prostate cancer. The presence of dilated and beaded pulmonary arteries on CT in a patient presenting with subacute and unexplained dyspnea should not be misinterpreted as the so-called tree-in-pattern caused by bronchiolar diseases. Despite being an unusual cause of PTE, prostate cancer, a potentially curable disease, should be considered in the differential diagnosis of adenocarcinoma of unknown origin in men. Awareness and early recognition of this rare entity will reduce diagnostic delay and lead to the effective and timely delivery of appropriate treatment and favorable patient outcomes.

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Declaration of competing interest

All authors declare no conflicts of interest.

CRediT authorship contribution statement

Tananchai Petnak: Conceptualization, Visualization, Writing - original draft, Writing - review & editing. **Thitiporn Suwatanapongched:** Conceptualization, Visualization, Writing - review & editing, Supervision, Project administration. **Wipawi Klaisuban:** Resources, Writing - review & editing. **Chayanin Nitiwarangkul:** Resources, Writing - review & editing. **Prapaporn Pornsuriyasak:** Resources, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101163.

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