



A case of pulmonary tumor thrombotic microangiopathy associated with lung cancer diagnosed by cell-block immunohistochemistry of pulmonary microvascular cytology

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ABSTRACT

Pulmonary tumor thrombotic microangiopathy (PTTM) is rare but should be considered as a possible diagnosis in patients with cancer. In this case, PTTM induced by lung cancer was more accurately diagnosed using cell block immunohistochemistry of pulmonary microvascular cytology (PMC) because we could confirm that lung adenocarcinoma was the origin of PTTM by the positive result of TTF-1 for atypical cells in PMC. The PMC procedure was minimally invasive and safer than lung biopsy. We believe that the cell block technique of PMC should be considered as one diagnostic option in PTTM.

1. Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) is a clinicopathologic disease entity in which tumor cells embolize to the pulmonary vasculature and cause a series of maladaptive reactions including activation of coagulation and fibrocellular intimal thickening [1]. The subsequent stenosis of blood vessels leads to pulmonary hypertension and eventual death [2]. Because the patient can rapidly progress to respiratory failure and/or right heart failure, the diagnosis of PTTM is often made postmortem. Recent reports have shown that pulmonary microvascular cytology (PMC) may be useful in the antemortem diagnosis of PTTM [3,4].

The challenges of obtaining a diagnosis from cytology include indistinct morphological details, overlapping or overcrowding of cells, abundance of inflammatory cells, a paucity of representative cells, and cell losses or changes [5]. To overcome these limitations, cell block technique was developed to provide better tissue architecture and morphological features for differentiating between malignant and non-malignant cells and for further processing via special stains and immunohistochemistry [6]. We report a case of PTTM induced by lung cancer that was more accurately diagnosed using cell block immunohistochemistry of PMC.

1.1. Case report

A 75-year-old never-smoking woman had a medical history of chronic kidney disease (CKD) (estimated glomerular filtration rate of about 10 mL/min/1.73 m² for the past 1 year) without dialysis. At a checkup, some abnormality was found on her chest X-ray, so she had to return for a complete physical. She was subsequently diagnosed as having lung adenocarcinoma of clinical stage III B [cT2aN3M0]. Because of her severe CKD, and after treatments were discussed with her and her husband, she first underwent radiation therapy for bilateral hilar and mediastinal lymph node metastases to prevent constriction of her esophagus. However, in the middle of radiation therapy (30 Gy of a 50-Gy scheduled dose administered), she developed dyspnea and was hospitalized at our hospital. On admission, her initial peripheral arterial oxygen saturation was 90%, and blood gas analysis showed a PaO₂ of 68.2 Torr and PaCO₂ of 18.5 Torr on room air, indicating hypoxemia. Her laboratory data revealed anemia and thrombocytopenia. Serum LDH was elevated at 478 IU/L, D-dimer at 31.2 μg/mL, and BNP at 129.5 pg/mL. Chest computed tomography (CT) scan showed mild dilation of the pulmonary arteries and a slightly mosaic appearance (Fig. 1A–C) along with a mass lesion of the left lingual lobe as the primary lung cancer (Fig. 1B). We could not perform contrast-enhanced CT because of

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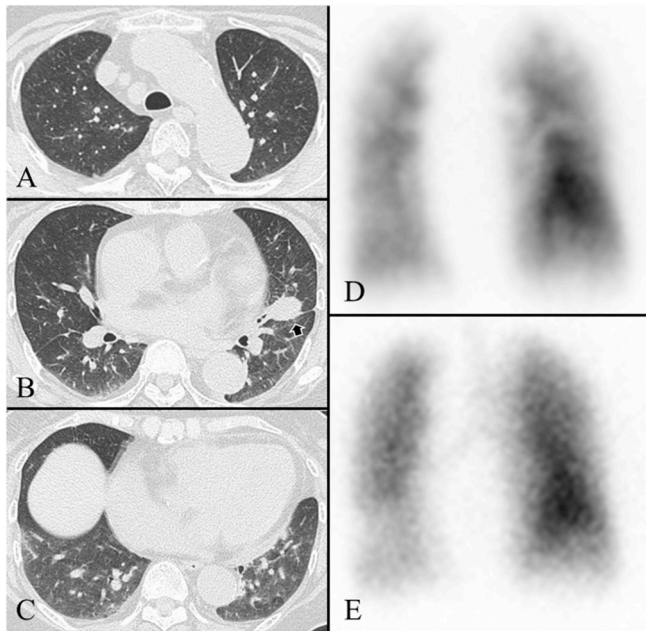


Fig. 1. Chest computed tomography scan showed mild dilation of the pulmonary arteries and slightly mosaic appearance (A–C) and a mass lesion (closed arrow) in the left lingual lobe as the primary lung cancer (B). Lung scintigraphy using ^{99m}Tc -MAA (D) and ^{81m}Kr (E) showed multiple peripheral mismatching perfusion defects.

her renal failure. From these findings, we suspected acute pulmonary thromboembolism and began heparin therapy. On hospital day 2, pulmonary scintigraphy using ^{99m}Tc -MAA and ^{81m}Kr showed multiple mismatching perfusion defects (Fig. 1D and E). On hospital day 4, considering the differential diagnosis of PTTM and intravascular lymphoma, PMC was performed, for which a Swan-Ganz catheter was inserted and located in the right pulmonary artery wedge position. The mean pulmonary capillary wedge pressure was 11 mmHg, mean pulmonary artery pressure was 43 mmHg, and cardiac output was 4.65 L/min, which indicated pulmonary hypertension without left cardiac failure. PMC revealed papillary clusters of atypical cells. In addition, cell block technique using PMC samples showed the atypical cells to be positive for TTF-1 staining (Fig. 2A–C). Because her thyroid showed no radiological abnormalities, we diagnosed the patient as having PTTM with lung adenocarcinoma. Unfortunately, her pulmonary hypertension rapidly progressed, and she died due to severe right heart failure on hospital day 11.

2. Discussion

PTTM is known as a rare and severe cancer-related pulmonary complication with a prevalence of 1.4% in an autopsy series of patients

who died of cancer [7]. PTTM should be considered in the differential diagnosis of a patient presenting with pulmonary hypertension of unknown origin, especially if a known underlying carcinoma is present. We described a case of PTTM in which PMC detected tumor cells of lung adenocarcinoma.

Although earlier ante-mortem diagnosis is very difficult, PMC offers the possibility of improved prognosis of patients with PTTM by indicating the need for additional aggressive therapy of the underlying cancer (i.e., chemotherapy) and, potentially, the PTTM (i.e., by anti-proliferative approaches) [8]. Pathological diagnosis by lung biopsy remains the diagnostic gold standard for PTTM [9]. However, only limited numbers of patients with stable respiratory status can undergo a lung biopsy. In contrast, PMC could be a useful test to detect tumor cells localized to the pulmonary microvasculature in high-risk patients [4]. If a tissue biopsy is not available, the diagnosis of PTTM should be supported by a combination of PMC and clinical features of progressive acute pulmonary hypertension and/or disseminated intravascular coagulation, after excluding pulmonary thromboembolism by imaging studies as in our case [9]. In addition, this case highlights the potential diagnostic value of using cell block immunohistochemistry of PMC.

The diagnostic efficacy of the cell block technique was reported widely using cells isolated from bodily fluids or aspirates, particular in malignant disease [10,11]. Moreover, immunostaining of serial sections is commonly used for a definitive cytohistological diagnosis. In our patient, because of her severe CKD, we could not perform whole-body contrast-enhanced CT to explore for malignancy other than lung cancer. Moreover, clinically, we could not rule out the possibility of gastrointestinal malignancy, which is the most frequent cancer linked to PTTM. However, with additional analysis using the cell block technique, we could confirm that lung adenocarcinoma was the origin of the PTTM based on the positive result of TTF-1 for atypical cells in PMC.

In reality, the accurate diagnosis made did not improve the treatment of the PTTM in our patient because of the rapid and massive progression of her disease course. Chemotherapy has shown some success [12,13], but it takes time for chemotherapy to affect a malignancy. Unfortunately, our patient did not survive long enough for the chemotherapy to be effective. The pathogenesis of PTTM is related to the secretion of vascular remodeling factors including vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor (PDGF) [8]. Several reports suggest that imatinib, which blocks phosphorylation of the PDGF receptor and inhibits downstream cell growth, may extend survival in PTTM [8]. In one case report, the use of dexamethasone as an anti-inflammatory drug resulted in permanent resolution of PTTM related to gastric cancer [14]. A combined approach such as anti-inflammatory/anti-proliferative drugs and chemotherapy might improve the prognosis of PTTM. Although intervention with drug therapy is challenging in practice, further studies are warranted that focus on these treatments of PTTM.

In conclusion, we reported a case of PTTM induced by lung cancer that was more accurately diagnosed using cell block immunohistochemistry of PMC. The use of PMC samples prepared by cell block

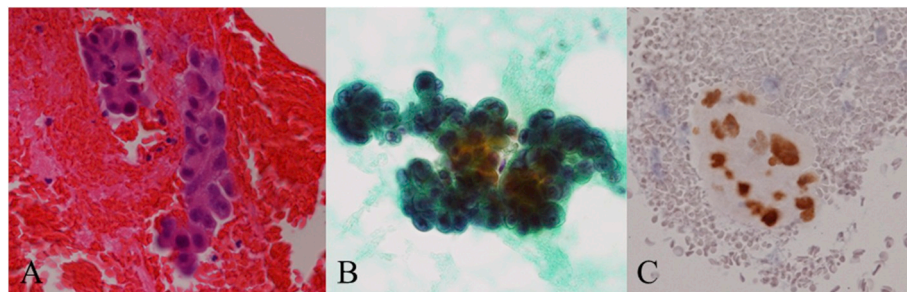


Fig. 2. Pulmonary microvascular cytology samples processed by the cell block technique. The samples showed atypical cells of lung adenocarcinoma (A: Hema-toxylin and eosin staining, B: Papanicolaou staining, C: TTF-1 staining).

immunohistochemistry represents a useful tool for the definitive diagnosis of PTTM. Because the PMC procedure was minimally invasive and safe, the cell block technique of PMC should be considered as one diagnostic option in PTTM.

Declaration of competing interest

The authors declare no Conflicts of Interest (COI) in association with this article.

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