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【 CASE REPORT 】

A Rare Case of Pulmonary Tumor Thrombotic Microangiopathy Associated with Micropapillary Urothelial Carcinoma of the Urinary Bladder: An Autopsy Case

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Abstract:
A 70-year-old woman was hospitalized with dyspnea. A transthoracic echocardiogram indicated an elevated systolic pulmonary artery pressure, and the cytology specimens obtained using a pulmonary artery catheter confirmed adenocarcinoma metastasis. Diffusion-weighted whole-body imaging with background body signal suppression (DWIBS) detected high-signal-intensity lesions in the urinary bladder. The patient died of respiratory failure and a postmortem examination was performed. Tumor cells in the bladder were immunohistochemically positive for GATA3, indicating micropapillary urothelial carcinoma, which is a rare variant of urothelial carcinoma and considered an adenocarcinoma subtype. This case is the first autopsy case of pulmonary tumor thrombotic microangiopathy (PTTM) associated with micropapillary urothelial carcinoma of the urinary bladder.

Key words: pulmonary tumor thrombotic microangiopathy (PTTM), micropapillary urothelial carcinoma, diffusion-weighted whole-body imaging with background body signal suppression (DWIBS), MRI

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Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare and fatal pulmonary complication observed in cancer patients. It is characterized by tumor cell activation of coagulation, the induction of inflammation, and the production of growth factors that stimulate fibrocellular intimal thickening and small vessel thrombi, which is associated with the development of pulmonary hypertension, resulting in acute respiratory failure (1-3). PTTM is mainly associated with adenocarcinoma of the stomach, pancreas, breast, lung, and liver; however, a few cases of PTTM related to urothelial carcinoma of the urinary bladder have also been reported (4). Furthermore, micropapillary urothelial carcinoma is a rare variant of urothelial carcinoma and is considered an adenocarcinoma subtype.

We herein report a rare autopsy case of PTTM associated with micropapillary urothelial carcinoma of the urinary bladder. In our patient, diffusion-weighted whole-body imaging with background body signal suppression (DWIBS) was useful for detecting a bladder tumor as the primary lesion site.

Case Report

A 70-year-old woman with no cancer history was hospitalized with dyspnea that had persisted for 1 month. Upon admission, her initial peripheral arterial oxygen saturation was 91%, and blood gas analyses revealed a PaO_2 of 63.2 mmHg and a $PaCO_2$ of 34 mmHg with a nasal cannula delivering 3 L/min of oxygen. Considering the observed pro-

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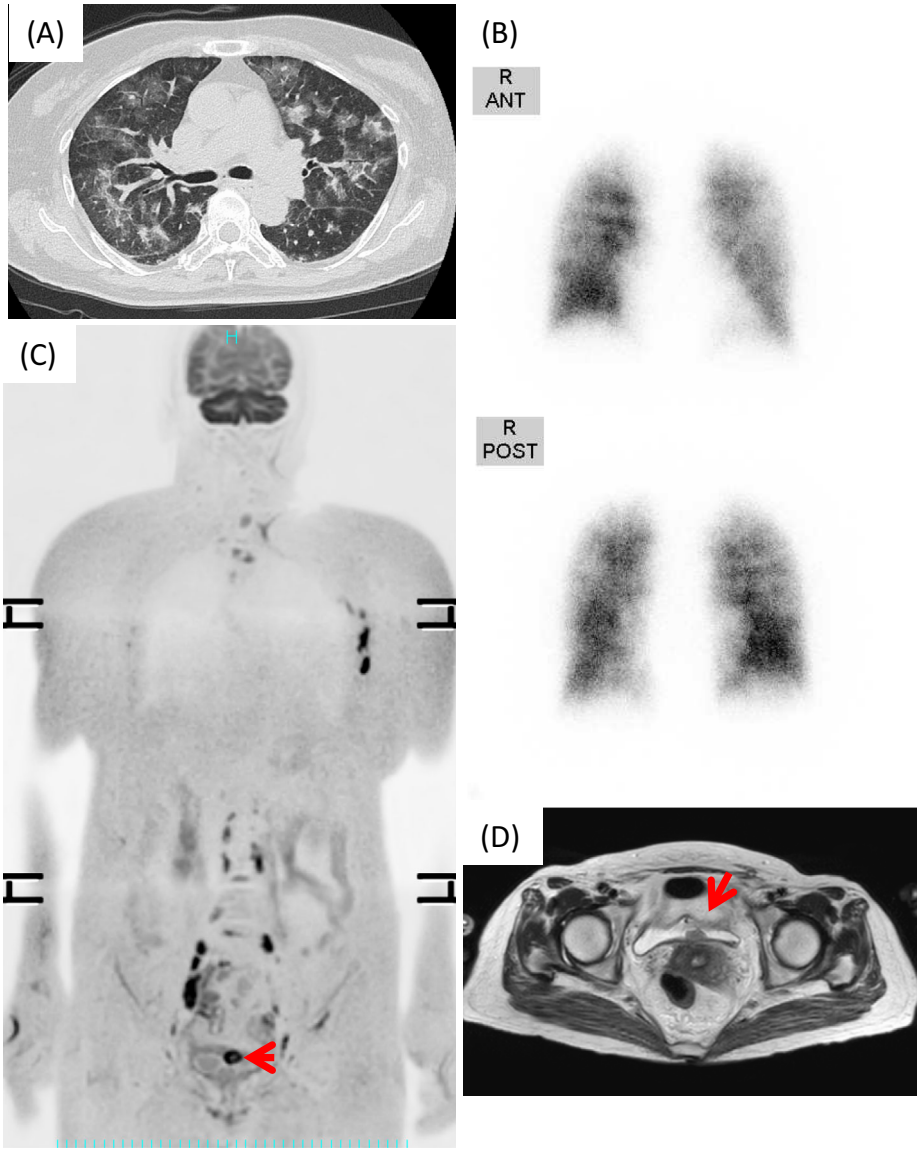

Figure 1. **(A) Contrast-enhanced chest CT revealing diffuse patchy infiltrates in the bilateral lung fields. (B) Lung perfusion scintigraphy using ^{99m}Tc-MAA showing multiple peripheral perfusion defects in the bilateral lungs. (C) Whole-body DWI showing high-signal-intensity regions in the urinary bladder (arrow), left axillary lymph nodes, and intraabdominal lymph nodes. (D) T2-weighted imaging showing a mass lesion on the urinary bladder wall, consistent with the high-signal-intensity region on whole-body DWI (arrow).**

gressive hypoxia and bloody sputum, we intubated and ventilated the patient on the second hospitalization day. She had elevated serum lactate dehydrogenase (LDH) levels at 614 IU/L, D-dimer levels at 5.9 μg/mL, and brain natriuretic peptide (BNP) levels at 237.5 pg/mL.

A transthoracic echocardiogram indicated an elevated systolic pulmonary artery pressure of 82 mmHg. Contrast-enhanced computed tomography (CT) revealed diffuse patchy infiltrates in the bilateral lung fields and enlarged left axillary lymph nodes without obvious pulmonary embolism (Fig. 1A). However, perfusion scintigraphy using ^{99m}Tc-MAA and 81mKr revealed multiple bilateral perfusion defects in the lungs (Fig. 1B). The levels of several tumor markers associated with adenocarcinoma were notably elevated, for example, CA19-9 (100,302 U/mL) and CA125 (3,290 U/mL). Taken together, these findings suggested PTTM associated with adenocarcinoma.

To confirm this diagnosis, we performed a pulmonary microvascular cytology (PMC) assessment, a lymph node biopsy, and DWIBS. Right heart catheterization revealed an elevated systolic pulmonary artery pressure of 79 mmHg, similar to the transthoracic echocardiogram. The cytology specimens obtained using both a pulmonary artery catheter and a needle biopsy confirmed adenocarcinoma metastasis (Fig. 2A). DWIBS did not reveal any abnormal findings in the lungs but did detect high-signal-intensity lesions in the patient's urinary bladder, multiple lymph nodes, and bones (Fig. 1C, D). Very few atypical cells were detected on a urine cytology examination.

Despite the antemortem diagnosis of PTTM associated

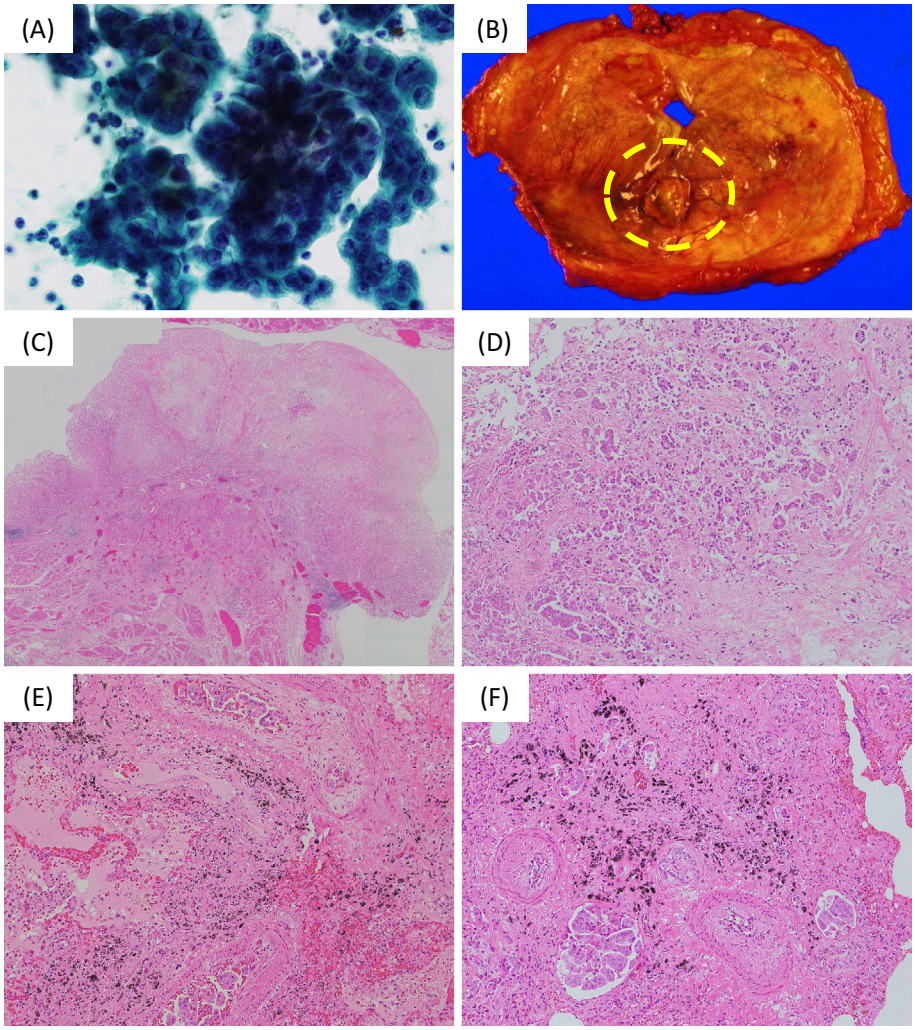

Figure 2. **(A) Pulmonary microvascular cytology samples containing atypical cells of adenocarcinoma (Papanicolaou staining). (B) Macroscopic findings from the specimen obtained by an autopsy revealing protruded lesion in the bladder (circle). (C) An autopsy specimen of the bladder showing a protruded lesion containing infiltration of atypical cells [Hematoxylin and Eosin (H&E) staining ×20]. (D) The atypical cells of the bladder forming a micropapillary architecture (H&E staining ×100). (E) (F) An autopsy specimen of the lungs showing widespread tumor embolism, fibrocellular intimal proliferation, and thrombus formation in the small arteries (H&E staining ×200).**

with adenocarcinoma and possible detection of the primary lesion site, the patient died of respiratory failure on the seventh hospitalization day, before a cystoscopy could be performed. Following a postmortem examination, histological tests revealed tumor cells in the bladder, similar to those found in the lymph node biopsy and PMC analysis (Fig. 2B-D). An immunohistochemical analysis revealed that the cells were CK7-, CK19- and GATA3-positive, indicating a pathological diagnosis of micropapillary urothelial carcinoma. Furthermore, the autopsy revealed a widespread tumor embolism, fibrocellular intimal proliferation, and thrombus formation in the small arteries, findings that were consistent with the PTTM diagnosis (Fig. 2E, F).

Discussion

We herein report a very rare autopsy case of PTTM associated with micropapillary urothelial carcinoma of the urinary bladder. Results obtained from DWIBS, which detected the primary bladder tumor and distant metastases, led to the consideration of PTTM, and this diagnosis was made antemortem by a PMC assessment.

PTTM, defined by Von Herbay et al. in 1990, is a rare and fatal cancer-related pulmonary complication, observed in 1.4% to 3.3% of autopsies of patients with malignant tumors (1, 5). PTTM is commonly associated with adenocarcinoma, particularly gastric adenocarcinoma (4, 5). However, in this case, despite the detection of adenocarcinoma using an antemortem lymph node biopsy and PMC analysis, the autopsy revealed that the PTTM had been associated with a micropapillary variant of urothelial carcinoma. Micropapillary urothelial carcinoma is a rare variant of urothelial carcinoma and is considered an adenocarcinoma subtype. Furthermore, it is regarded as highly aggressive and is associ-

ated with a poor prognosis (6). While a systematic review reported only six cases of PTTM associated with urothelial carcinoma of the urinary bladder, to our knowledge, the present case is the first one of micropapillary urothelial carcinoma (4). Most cases reported in the systematic review were diagnosed as PTTM postmortem; and one patient diagnosed antemortem had been previously diagnosed with urothelial carcinoma of the urinary bladder (1, 7-11). These findings suggest that it is very difficult to diagnose urothelial carcinoma as the PTTM site of origin in patients without a cancer history.

Although reports of antemortem cases of PTTM exist, patient outcomes remain poor due to the lack of a standard treatment (2, 4). A previous report revealed that the mean duration from the disease onset to hospital admission was approximately one month and that patients died a median of five days after admission (12). The antemortem diagnosis of PTTM is challenging due to the acute progression; in addition, there are no disease-specific symptoms or radiological features. In certain cases with no history of cancer, metastatic carcinoma is not diagnosed antemortem; rather, the condition is diagnosed as pulmonary hypertension of an unknown origin. For the antemortem diagnosis of PTTM, it is important to know whether or not the patient is a cancer-bearing patient.

Of note, recent reports on patients with PTTM have shown that chemotherapy targeting the primary cancer has improved the condition (2, 4), suggesting that the detection of the site of origin is an important step in the treatment process. In our patient, the elevated levels of several tumor markers and multiple high-signal lesions found using DWIBS prompted the performance of right heart catheterization and PMC, resulting in the antemortem diagnosis of PTTM. Although the treatment of PTTM and urothelial carcinoma could not be performed in this case, DWIBS accurately detected the primary site.

DWIBS, reported by Takahara et al. in 2004, is a unique concept of whole-body DWI (13). DWIBS is known to be useful for systemic tumor detection and staging as is positron emission tomography (PET) (14, 15). Regarding urinary bladder cancer, DWIBS may be more useful than PET for evaluating the primary lesion site, since a normal fluorine-18 deoxyglucose (FDG) accumulation in the urinary bladder may obscure the presence of urothelial carcinoma cells on a PET-CT (16). Few facilities are equipped with a PET-CT scanner, but MRI scanners are available in a relatively large number of facilities, and examinations can be performed even for intubated patients, as in the present case. For diseases in which the diagnosis must be made as promptly as possible, such as PTTM, MRI is a useful option for searching for tumor.

Given the above findings, we suggest that even if pathological analyses demonstrate the presence of an adenocarcinoma, urothelial carcinoma should not be ruled out as a potential diagnosis. Furthermore, as the detection of the site of origin is necessary for the rapid diagnosis and treatment of PTTM, we believe that DWIBS may be a useful strategy in such patients.

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

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