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CASE REPORT

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Pulmonary tumor thrombotic microangiopathy due to early gastric carcinoma in a patient with no antemortem findings suggestive of primary malignancy

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Abstract

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare and critical malignancy-related disease characterized by acute progressive pulmonary hypertension (PH). In most cases of PTTM, the cancer can be diagnosed in advance. Identification of the primary cancer is valuable for PTTM diagnosis. Here, we present the case of a patient with PTTM due to early gastric carcinoma in whom the diagnosis of malignant cancer was not revealed until macroscopic autopsy findings. This case highlights the importance of recognizing causative occult early gastric cancer leading to PTTM in cases of acute progressive PH.

KEYWORDS

autopsy, gastric cancer, pulmonary hypertension, pulmonary pathology, pulmonary tumor thrombotic microangiopathy

INTRODUCTION

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare and fatal disease commonly observed in patients with metastatic adenocarcinoma. PTTM was first reported by von Herbay *et al.* and is histologically characterized by fibrocellular intimal proliferation of the small pulmonary arteries.[1,2] The pathophysiology involves the release of inflammatory cytokines or proliferative factors such as vascular endothelial and platelet-derived growth factors in cancer cells, which cause thrombosis and fibroproliferative changes in the vascular lumen.[2,3] Antemortem diagnosis of PTTM is challenging because of its aggressive clinical course. Recognizing primary cancer and its metastasis on imaging is essential for recognizing PTTM. Here, we report a case of PTTM due to early gastric cancer (EGC) (signet ring cell carcinoma [SRCC]) without antemortem malignancy findings which was diagnosed only after autopsy pathological microscopic examination.

CASE DESCRIPTION

A 78-year-old woman was referred to our hospital with rapidly worsening dyspnea. Echocardiography revealed significant right heart dilatation and ventricular septum flattening suggesting severe pulmonary hypertension (PH),

which was not observed 4 months prior in a local hospital. The patient history was remarkable for breast cancer 10 years prior, which was in complete remission after chemoradiation therapy and left-sided lumpectomy. Physical examination findings included blood pressure, 102/56 mmHg; heart rate, 78 beats per minute; respiratory rate, 16 per minute; and an oxygen saturation of 96% with 4 L/min oxygen. Further examination revealed jugular vein distension, a fixed splitting second heart sound, clear chest sounds, and peripheral edema. Laboratory tests showed elevated brain natriuretic peptide (1407 pg/mL) and D-dimer levels (2.4 μg/mL). Tricuspid regurgitation peak gradient was 81 mmHg in the echocardiography test. Contrast-enhanced computed tomography (CT) revealed dilatation of the main pulmonary artery; however, lymphadenopathy, interstitial pneumonia, or cancer were not observed. Dual-energy CT imaging revealed wedge-shaped iodine-deficient and diffusely impaired lung perfusion (Figure 1a–c). Lung ventilation-perfusion scintigraphy showed a mismatched heterogenous pattern with numerous peripheral perfusion defects. These findings suggested chronic thromboembolic pulmonary hypertension (CTEPH). The patient's status worsened despite intravenous dobutamine therapy. Severe clinical deterioration required increased dobutamine

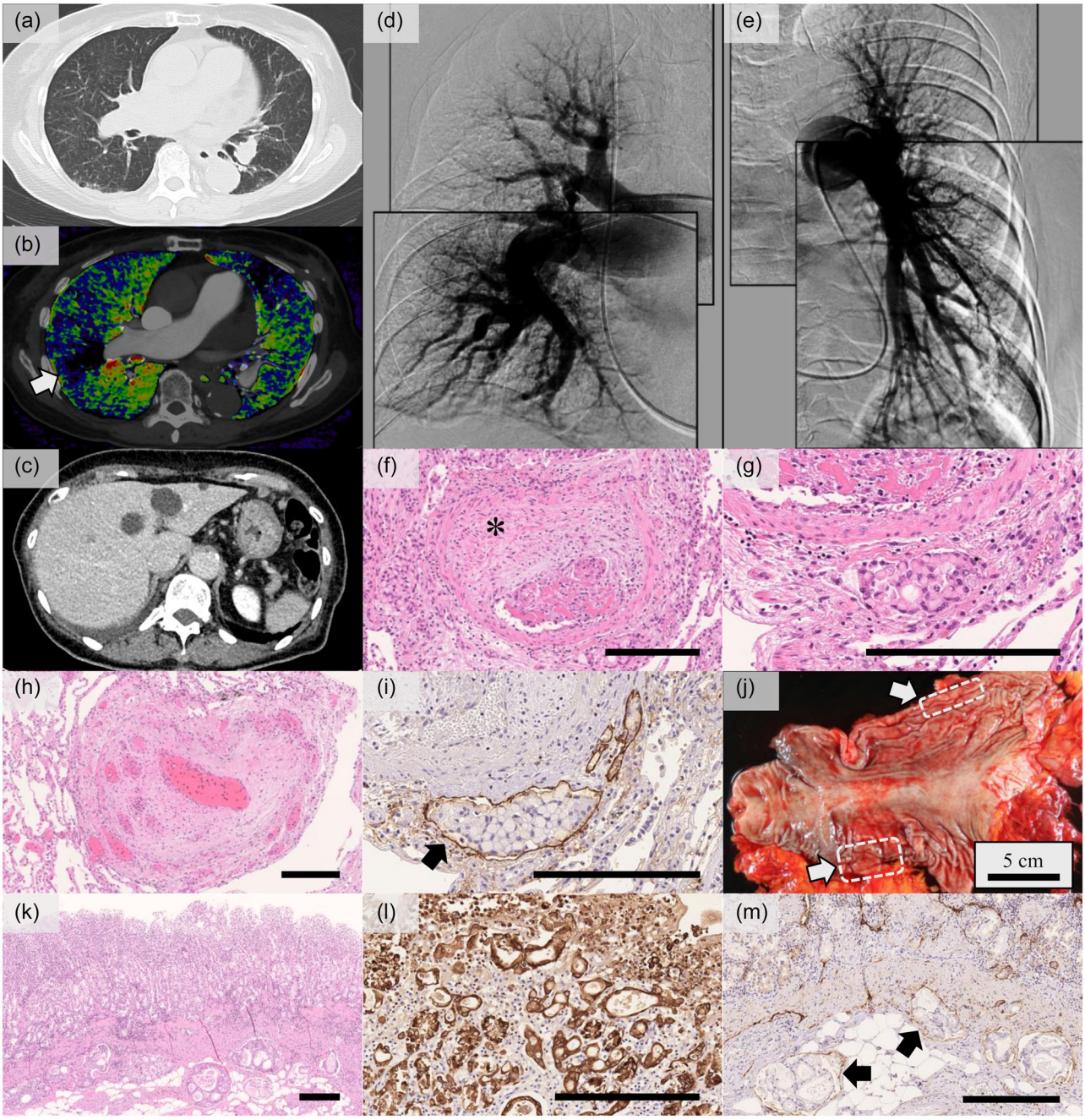

FIGURE 1 (See caption on next page).

infusion and noninvasive positive pressure ventilation. Right heart catheterization showed severe precapillary PH, with mean pulmonary artery pressure of 60 mmHg, pulmonary vascular resistance of 32.9 wood units, and cardiac index of 0.95 L/min/m^2. Pulmonary angiography demonstrated delayed pulmonary blood flow and poor subpleural perfusion diffusely (Figure 1d,e). Typical CTEPH lesions were not observed. Soon after the catheterization test, the patient experienced cardiopulmonary arrest. Despite prompt multidisciplinary treatment including extracorporeal cardiopulmonary resuscitation, the patient died on Day 8.

An autopsy was performed with the consent of the patient's family. Pathological findings of the pulmonary artery showed intravascular cancer cells, fibrin thrombi, intimal fibrocellular proliferation with recanalization, and significant luminal stenosis with an organized thrombus (Figure 1f–i). These findings are consistent with PTTM. The cancer was diagnosed as SRCC. However, macroscopic survey or premortem CT imaging had not revealed the primary lesion. Further microscopic pathological evaluation of multiple gastric serial sections revealed that the primary cancer was an early gastric SRCC spreading from the lamina propria to the submucosa with lymphatic invasion, and the pathological TNM staging was classified as pT1bN1M1 (Figure 1j–m). No pathological findings indicated other malignant tumors, such as recurrent breast cancer.

DISCUSSION

Diagnosing PTTM is often delayed because of clinical and radiographic overlap with other diseases that mimic the causes of PH like CTEPH. A previous survey reported that less than 10% of PTTM cases were diagnosed before death using biopsy.[1] Laboratory analyses of some cases of PTTM have shown anemia, thrombocytopenia, and elevated D-dimer, with no specific markers for PTTM.[4] Chest CT in PTTM commonly demonstrates ground-glass opacities, tree-in-bud opacities, nodules, and septal thickening, indicating intimal fibrocellular hyperplasia of the small pulmonary arteries. Mediastinal or hilar lymphadenopathy is also frequently observed. However, these findings are not specific to PTTM. Similarly, the ventilation perfusion scan is unlikely to distinguish PTTM from CTEPH because of similar findings of mismatched peripheral perfusion defects.[5] Although we recognized the possibility of PTTM based on the patient's history of breast cancer and rapid clinical deterioration in the present case, the absence of primary cancer on CT imaging and findings similar to those of CTEPH made antemortem diagnosis difficult.

Identifying the primary cancer is important for diagnosing PTTM. Gastric cancer is the most common primary lesion that causes PTTM.[2] EGC is defined as an adenocarcinoma restricted to the mucosa or submucosa, irrespective of lymph node metastasis. PTTM cases in EGC as primary lesions have rarely been reported; most of these are categorized as SRCC.[6,7] SRCC is highly associated with severe lymphatic infiltration, leading to the inflow of cancer cells into the pulmonary circulation via the thoracic duct. This pathophysiology is regarded as one of the primary reasons that gastric cancer is the leading cause of PTTM.[4] Notably, previous reported cases have described clinical findings before death that were suggestive of a primary malignancy, such as cervical, mediastinal, hilar, and abdominal lymphadenopathy, and metastasis to other organs, including the bone and ovalis. Some cases showed clinical findings despite endoscopy or macroscopic postmortem examination cannot detect stomach lesions.[6] To our knowledge, this is the first report of PTTM due to EGC without findings suggestive of primary cancer or metastasis in a living patient or via macroscopic autopsy. In our case,

FIGURE 1 Clinical images and pathological findings of the lung and stomach. (a) Contrast-enhanced computed tomography (CT) demonstrated the absence of lymphadenopathy, interstitial pneumonia, or lung cancer. (b) Dual-energy CT imaging revealed wedge-shaped areas of iodine deficiency (indicated by the white arrow) and diffuse impairment of lung perfusion. (c) Abdominal contrast-enhanced CT revealed liver cysts; however, no signs of malignancy or adenopathy were observed. (d) Pulmonary angiography (PAG) of right pulmonary artery. (e) PAG of left pulmonary artery. PAG did not reveal characteristic findings of chronic thromboembolic pulmonary hypertension, such as webs or bands. (f) Postmortem pathological examination showing pulmonary arterioles with adenocarcinoma cells, fibrin, and neutrophils. Asterisk denotes pulmonary artery intimal thickening (Hematoxylin and Eosin [H&E] stain). (g) Signet ring cells can be seen within and adjacent to the pulmonary artery (H&E stain). (h) The pulmonary artery shows organized thrombus and recanalization, representative findings of pulmonary tumor thrombotic microangiopathy (H&E stain; scale bar). (i) Tumor cell infiltration within the lymphatic vessels in the lungs (arrow) (D2-40 stain). (j) The macroscopic examination of the stomach did not reveal any evidence of malignancy. However, upon subsequent microscopic evaluation, a gastric tumor with a maximum diameter of 40 mm was identified. The region enclosed by the white dotted line corresponds to the occult tumor. During the grossing process in the pathological dissection, the gastric tumor inadvertently separated into two distinct parts. (k) Microscopic image of stomach reveals tumor cell infiltration to the submucosa, a finding of early gastric cancer (H&E stain). (l) Proliferation of irregularly fused glands and signet ring cells, representative findings of moderately to poorly differentiated adenocarcinoma of the stomach (Cytokeratin AE1/AE3 stain). (m) Tumor cell infiltration within the lymphatic vessels in the stomach (arrow) (D2-40 stain). The scale bar denotes 250 μm.

endoscopy was precluded by clinical illness, posing a limitation, though macroscopic pathological evaluation did not reveal EGC. Therefore, our case highlights EGC can develop into PTTM without suspicious findings on CT imaging or gross pathology.

In conclusion, although early recognition of PTTM is essential in patients with acute progressive PH for antemortem diagnosis of PTTM, it is challenging because clinical and radiographic findings overlap with differential diseases. Gastric carcinoma is the leading cause of PTTM. Therefore, imaging and endoscopic surveys should be performed to detect PTTM primary lesions. However, EGC can develop into PTTM despite the absence of findings suggestive of primary malignancy, as shown in our case. Understanding this diagnostic challenge will be helpful for early recognition of PTTM in patients with fulminant PH.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

This case report was conducted according to the World Medical Association Declaration of Helsinki. Informed consent for patient information and images to be published was provided by the patient's legally authorized representative.

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REFERENCES

1. Godbole RH, Saggar R, Kamangar N. Pulmonary tumor thrombotic microangiopathy: a systematic review. Pulm Circ. 2019;9(2):1–13.
2. von Herbay A, Illes A, Waldherr R, Otto HF. Pulmonary tumor thrombotic microangiopathy with pulmonary hypertension. Cancer. 1990;66(3):587–92.
3. Price LC, Seckl MJ, Dorfmüller P, Wort SJ. Tumoral pulmonary hypertension. Eur Respir Rev. 2019; 28(151): 180065.
4. Sato N, Tasaki T, Noguchi H, Irie K, Nakayama T. The pathological challenge of establishing a precise diagnosis for pulmonary tumour thrombotic microangiopathy: identification of new diagnostic criteria. Histopathology. 2019; 74(6): 892–901.
5. Ramakrishnan P, Dahiya G, Lindstrom M, Thenappan T. Pulmonary tumor thrombotic microangiopathy: exploration into current diagnostic aids and therapeutics. Pulm Circ. 2023;13(3):e12278.
6. Kawakami N, Moriya T, Kato R, Nakamura K, Saito H, Wakai Y, Saito K, Sakashita M. Pulmonary tumor thrombotic microangiopathy in occult early gastric cancer that was undetectable on upper endoscopy: a case report and review of similar cases. BMC Gastroenterol. 2021;21(1):423.
7. Tateishi A, Nakashima K, Hoshi K, Oyama Y, Ebisudani T, Misawa M, Aoshima M. Pulmonary tumor thrombotic microangiopathy mimicking inhalation lung injury. Intern Med. 2019;58(9):1311–4.

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