

# Recurrent metastatic breast cancer manifesting as pulmonary tumor thrombotic microangiopathy with interstitial pulmonary fibrosis and infarcts: A clinicopathological correlation

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## ARTICLE INFO

### Keywords:

Pulmonary Tumor Thrombotic  
Microangiopathy  
Tumor embolism  
Pulmonary hypertension  
Cor pulmonale  
Ground-glass opacities  
Breast cancer

## ABSTRACT

Pulmonary Tumor Thrombotic Microangiopathy (PTTM) is a fatal complication of malignancy characterized by embolization of tumor cells to the pulmonary vasculature leading to a vascular reaction resulting in stenosis and pulmonary hypertension. Because the clinical manifestations of PTTM overlap with those of other entities, premortem diagnosis is challenging. We describe an unusual case of PTTM as the only clinical manifestation of recurrent metastatic breast cancer. A 50 year-old woman presented with hypoxemia and echocardiographic findings consistent with pulmonary hypertension and cor pulmonale. Correlation of premortem pulmonary imaging with autopsy histopathologic findings revealed that ill-defined ground-glass opacities identified on CT angiogram corresponded to areas of cellular interstitial fibrosis and widespread intrapulmonary tumor emboli involving predominantly small-sized arteries with associated florid intimal fibrosis. The radiologic nodularities and scattered peripheral wedge-shaped consolidations corresponded to evolving pulmonary infarcts on histopathology. Although retrospectively, the imaging findings were concordant with a spectrum of increasing severity of tumor embolization and vascular remodeling, the diagnosis of PTTM was not made premortem. PTTM is a rare entity that must be considered in cancer patients with unexplained hypoxemia, pulmonary hypertension and lung opacities on imaging.

## 1. Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) describes a morphologic pattern of lung injury that is characterized by thrombosis and remodeling of vessel walls due to the intrapulmonary vascular spreading of malignant cells. Widespread obliteration of small vessels is followed by interstitial fibrosis, pulmonary infarction, alveolar hemorrhage and an increase in the pulmonary vascular resistance that can progress to severe pulmonary hypertension, acute or subacute cor pulmonale, and potentially sudden death [1]. The utmost difficulty in diagnosing PTTM is the broad range of more common diagnoses with similar clinical presentation and imaging findings, including other causes of pulmonary thromboembolism, heart failure and interstitial lung diseases (ILD) [2]. With the purpose of increasing awareness of this lethal entity, and as an opportunity to correlate radiologic findings with histopathology, we present an unusual case of recurrent metastatic

breast cancer presenting as PTTM resembling ILD. Recognizing that PTTM can manifest with a spectrum of lung imaging abnormalities, including ground-glass opacities (GGO) and wedge-shaped areas of consolidation (WSAC), is relevant for its timely diagnosis and treatment.

## 2. Case report

A 50 year-old woman underwent left partial mastectomy for multifocal estrogen receptor (ER)+/progesterone receptor (PR)+/Her 2-invasive breast carcinoma (IBC), duct cell type, with multiple metastases to axillary lymph nodes. BRCA mutation testing was negative. The management included adjuvant chemo-radiotherapy followed by an aromatase inhibitor. Two years later, an ER+/PR-ductal carcinoma in situ (DCIS) in the same breast was detected and excised. At that time, a PET-CT scan ruled out metastatic disease. Six months later, the patient developed progressive dyspnea, cough with occasional blood streaking

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<https://doi.org/10.1016/j.rmcr.2019.100958>

Received 14 August 2019; Accepted 22 October 2019

Available online 23 October 2019

2213-0071/© 2019 The Authors.

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in sputum, weight loss, hypoxemia and spontaneous ecchymoses on both knees. Laboratory tests showed severe thrombocytopenia (16,000 cells/ $\mu$ L, range of reference [RR]: 150–450), normocytic normochromic anemia (hemoglobin 10.4 g/dL, RR: 12–16), and elevation of LDH (1297 U/L, RR: 84–246), PT (16.3 sec, RR: 10–13.5), INR (1.3, RR: 0.8–1.2), D-dimer (12.59  $\mu$ g/mL, RR: 0.27–0.50), fibrinogen (530 mg/dL, RR: 200–400), erythrocyte sedimentation rate (70 mm/hour, RR: 0–20), C-reactive protein (34 mg/dL, RR: 0–3), CA 15.3 (145 U/mL, RR: 0.50–32.4), and cancer antigen 27.29 (198 U/mL, RR: <38). White blood cell count, haptoglobin, aPTT, creatinine, electrolytes, and anion gap were within normal limits. A peripheral smear revealed schistocytes and dacryocytes. NT-pro BNP was elevated (4916 pg/mL, RR: 1–300) with an echocardiogram reporting dilation of the right ventricle chamber, severely increased pulmonary pressures (RVSP: 54 mmHg, RR: <25), and normal left ventricular function (LVEF: 65%).

Pulmonary thromboembolism was ruled out by a CT pulmonary angiogram, which showed multifocal ill-defined GGO and small pulmonary nodularities with scattered peripheral WSAC, absent in the CT scan performed 6 months ago (Fig. 1). Microbiology, toxicology and rheumatologic workup were all negative. The patient was admitted and treated with antibiotics and steroids; however, her symptoms did not improve. On hospitalization course, the platelet count remained low despite multiple transfusions (114,000 to 24,000/ $\mu$ L). She underwent a bronchoalveolar lavage (BAL) revealing blood in the airways and no evidence of atypical cells. A repeat PET-CT scan, performed in the fourth hospitalization week, showed avid uptake in L1, L4, T11 and in the left iliac bone. These lesions also exhibited enhancing in contrast MRI and nuclear medicine (NM) bone joint imaging (Fig. 2). Of note, the GGO tracking along bronchovascular bundles worsened when compared to the admission chest CT scan (Fig. 1d). After one month of hospitalization, the patient's shortness of breath worsened, she underwent cardiac arrest and expired.

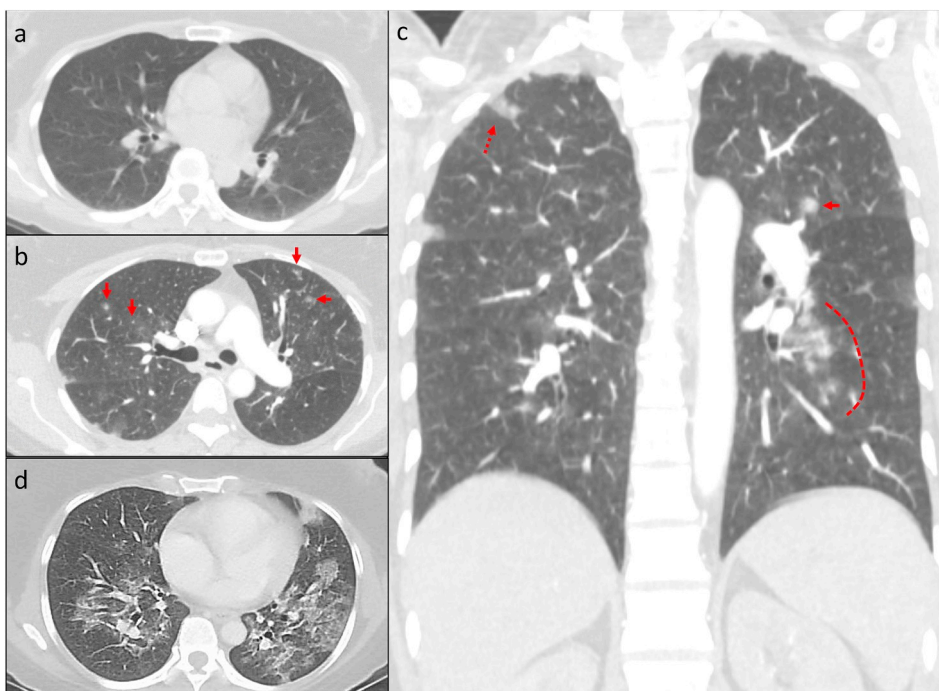
A full autopsy was performed revealing pulmonary congestion (right lung: 660 g, RR: 360–570; left lung: 750 g, RR: 325–480) with no gross evidence of pulmonary thromboemboli. Microscopically, widespread recent and organizing pulmonary tumor emboli were identified involving predominantly small-sized intraparenchymal arteries, with associated florid intimal fibrosis and luminal occlusion. The tumor cells

were positive for cytokeratins (AE1/AE3 and CAM5.2) and showed nuclear immunoreactivity for GATA-3, supporting a carcinoma of mammary origin. The carcinoma disseminated throughout the intrapulmonary vasculature in the form of intraluminal clusters and by lymphangitic spread, without definitive parenchymal invasion. Additionally, the obliteration of pulmonary arterioles was associated with cellular interstitial fibrosis, intra-alveolar hemorrhage and early infarction, explaining the lung CT abnormalities identified premortem (Figs. 3 and 4). The heart and coronary vessels were unremarkable. Additional findings included metastatic breast cancer to the thoracolumbar spine (Fig. 2) and liver.

### 3. Discussion

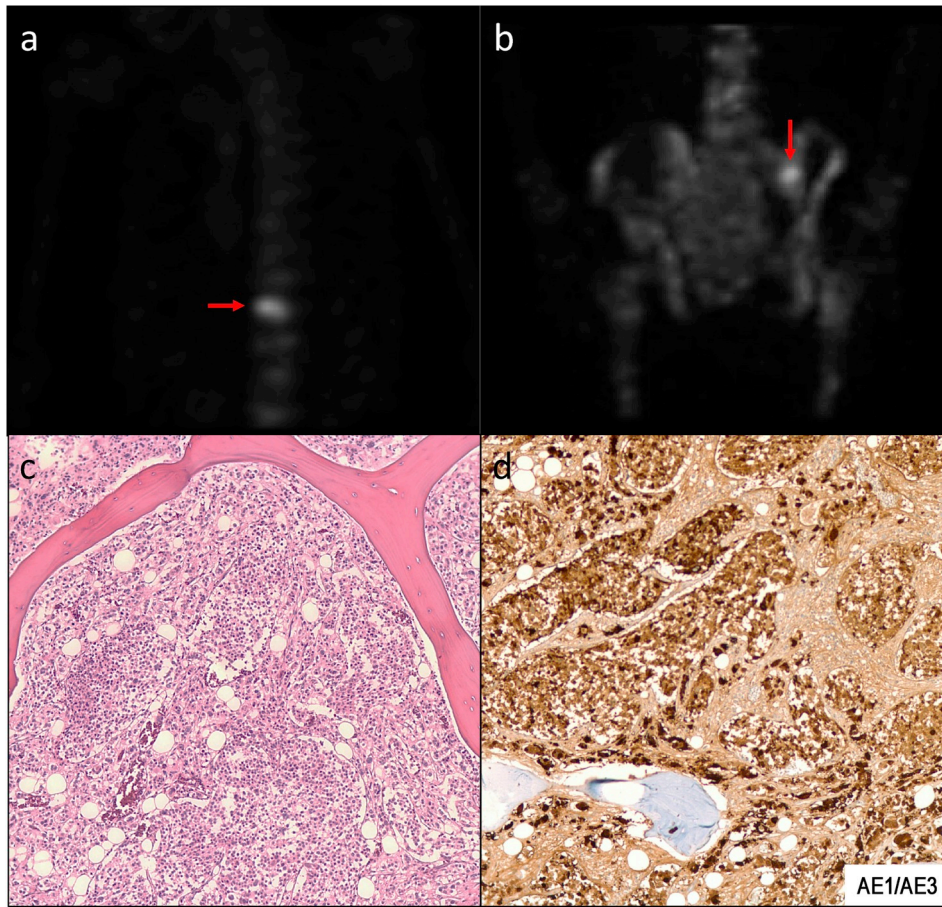
The autopsy findings were those of PTTM caused by disseminated breast cancer. PTTM can be considered a form of pulmonary embolism, in which malignant cells spread throughout the intrapulmonary arterial tree, causing occlusion and subsequent sudden death by severe pulmonary hypertension [2]. PTTM can be the only manifestation of tumor recurrence and evolves rapidly; therefore, it is rarely diagnosed premortem. The exact incidence of PTTM is unknown, but two postmortem studies reported an incidence of 1.4% and 3.3%, in series of 2215 and 630 consecutive carcinoma cases, respectively [1,3]. PTTM is mainly described as a fatal complication of gastric adenocarcinomas, especially those harboring signet-ring cells [4]. Breast cancer is the second most common cancer associated with PTTM [5]. Although data regarding PTTM in the setting of breast cancer is very limited, some authors have concluded that early recognition of PTTM could potentially be associated with prolonged survival when targeted therapy is available [6,7]. If left untreated, patients with PTTM usually do not survive beyond three months [5,6].

Some radiologic findings can help clinicians to recognize PTTM, including septal thickening, non-solid centrilobular GGO, tree-in-bud sign, small semisolid nodularities, and WSAC, which represent a spectrum of increasing severity of tumor embolization and vascular remodeling, as seen in our case [5]. However, these abnormalities are also seen in a variety of ILDs. The diagnostic problem is aggravated by the fact that chemo- and radiotherapy used to treat breast cancer may

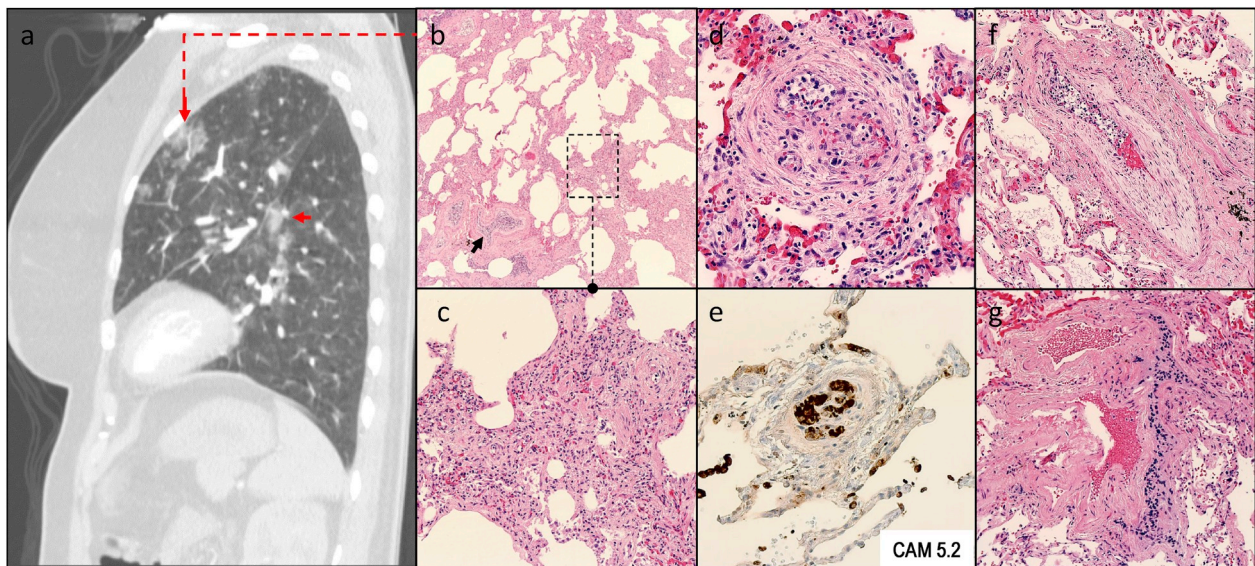


**Fig. 1. Non-contrast chest CT imaging findings associated with PTTM.** (a) Axial view at the level of the left atrium showing no abnormalities. This CT was part of a PET-CT scan performed 6 months prior to the CT pulmonary angiogram. (b) Axial view below the carina, showing multiple centrilobular nodules with discrete peripheral GGO opacities (arrows). (c) Coronal reconstruction view, through the anterior aspect of the thoracic spine, demonstrating multiple centrilobular nodules with peripheral prominent confluent GGO (discontinuous line) and peripheral wedge-shaped opacities (dashed arrow). (d) Axial view of a CT scan performed during the fourth hospitalization week revealing worsening GGO. All slices are shown in the lung window view.



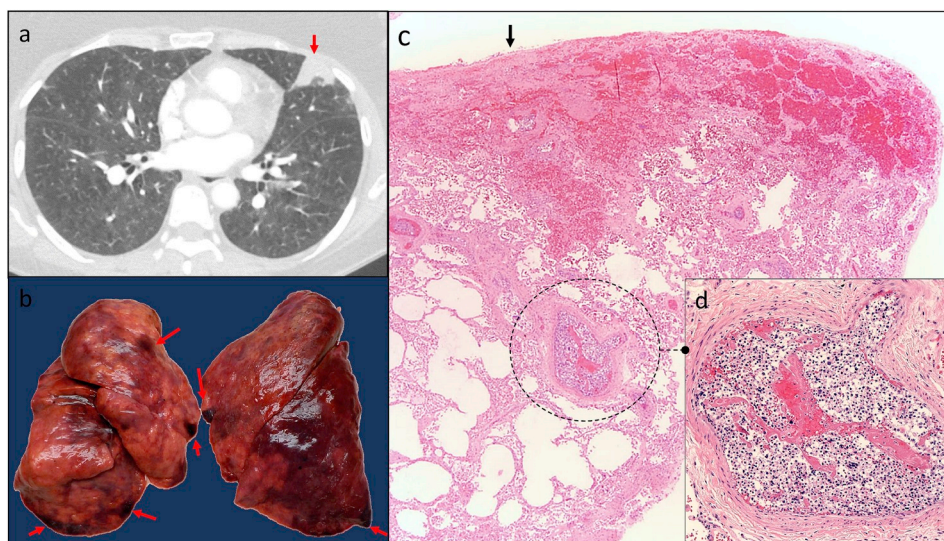


**Fig. 2. Radiologic findings and histopathology of metastatic carcinoma to the spine and left iliac bone.** (a, b) Technetium-99m NM bone images of the thoracolumbar spine and pelvis showing enhancing lesions in a lumbar vertebra and left iliac bone. (c) Bone marrow replaced by carcinoma, H&E (100×). (d) AE1/AE3 pancytokeratin immunohistochemistry highlighting the carcinoma cells (100×).



**Fig. 3. Lung histopathology corresponding to ground glass opacities on imaging.** (a) Sagittal non-contrast chest CT, lung window. Multiple centrilobular nodules with ground glass opacities in both the upper and lower lobes (arrows). (b) Alveolar wall thickening and tumor emboli (arrow, 50×). (c) Interstitial chronic inflammation (higher magnification 200×, dashed square in b). (d) Obliteration of a small-sized artery by intimal proliferation and carcinoma cells (400×). (e) CAM 5.2 cytokeratin highlighting carcinoma cells in the obliterated artery (400×). (f) Fibrointimal proliferation and tumor emboli in a medium-sized artery (200×). (g) Lymphangitic carcinomatosis (200×). b-d, f, and g: H&E staining.





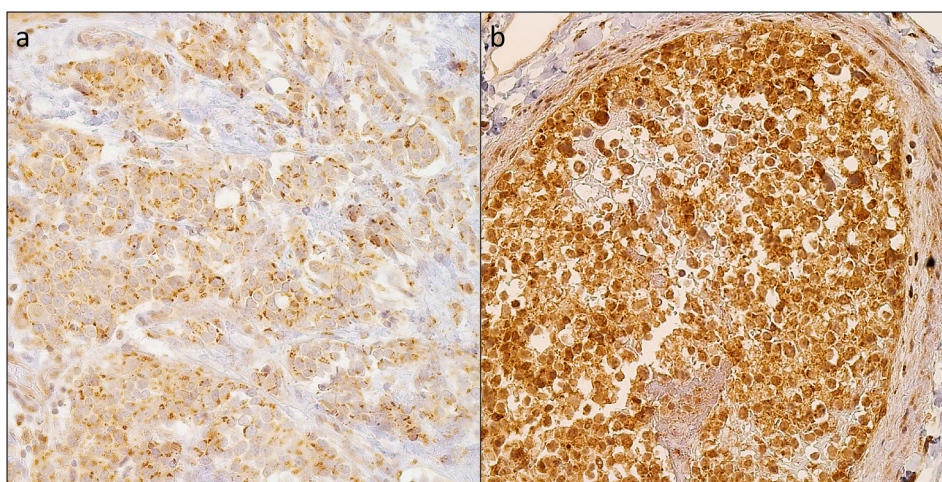
**Fig. 4.** Lung histopathology corresponding to peripheral wedge-shaped areas of consolidation on imaging. (a) Axial non-contrast chest CT, lung window. Peripheral wedge shaped density extending to the pleura (arrow). (b) Right and left lungs with numerous scattered peripheral wedge-shaped areas of hemorrhage. (c) These areas were evolving pulmonary infarcts (arrow, 25 $\times$ ). (d) Microscopic tumor embolus within a medium-sized pulmonary artery (dashed circle in b, 200 $\times$ ). b and c: H&E staining.

cause lung injury, including radiation pneumonitis, pulmonary interstitial fibrosis, and cryptogenic pneumonia [8]. The role of modern imaging modalities for cancer detection, such as 18-fluorodeoxyglucose-PET scanning has not been studied in detail [5,9]. PET scanning is useful to identify metastatic disease elsewhere. The typical PTTM lesions, as in our case, can be non-avid on PET scan, and a negative result does not rule out PTTM [5].

Overall, PTTM persists underdiagnosed because a biopsy is rarely required to confirm any of its differential diagnoses, and patients may be in critical condition that contraindicates an invasive procedure. Video-assisted thoracic surgery (VATS) biopsy is the gold standard technique to obtain a diagnosis in cases of equivocal ILDs, and may be the ideal approach for patients who can tolerate this procedure. BAL is not useful since the tumor cells are contained within the intravascular compartment. Transbronchial or CT-guided lung needle biopsies have limited value, probably with a high false-negative rate, mainly because PTTM is not associated with the development of a mass-forming lesion. Pulmonary artery catheterization with pulmonary wedged aspiration cytology has shown promising results in the identification of intravascular tumor cells [10]. Currently, there is not enough evidence to support a standard method to confirm a PTTM diagnosis.

The mechanism of PTTM is poorly understood. Tumor microemboli

with an underlying intimal fibroblastic proliferation of intraparenchymal pulmonary arteries are the histopathologic hallmark of PTTM. It is thought that PTTM starts with the shedding of tumor cells, in the form of tumor clots, into the bloodstream from a primary or metastatic focus [1,3]. In the present case, the bone marrow metastases were most likely the source of tumor emboli. After carcinoma microemboli enter into the pulmonary circulation they anchor preferentially to small arteries. This affinity for intrapulmonary vessels could be related to specific tumoral adhesion molecules, or to other specific properties of native vessels such as vascular reactivity. The interaction of tumor with endothelial cells triggers the activation of pro-coagulant and fibrinolytic pathways resulting in consumption of coagulation factors and platelets, which can alter coagulation tests and cause thrombocytopenia [1]. Release of growth factors, including VEGF, stimulates the proliferation of endothelial cells and myofibroblasts. We found that in our case the carcinoma cells strongly expressed VEGF by immunohistochemistry (Fig. 5). Some authors suggest that growth factors are necessary for PTTM to develop fully [11]. Subsequent intimal thickening is associated with fragmentation of erythrocytes, seen as schistocytes on peripheral smears, due to shearing forces across narrowed vessels. Increase in the vascular resistance follows when there is extensive vascular occlusion, leading to lung injury, including alveolar hemorrhage, pulmonary



**Fig. 5.** Expression of vascular endothelial growth factor (VEGF) by immunohistochemistry in primary tumor (a) and tumor embolus (b). (a) Invasive breast carcinoma cells in the primary tumor (two and half years prior), expressing VEGF in a granular cytoplasmic pattern. (b) Tumor embolus composed of carcinoma cells (shown in Fig. 2c) showing stronger immunoreactivity for VEGF. All pictures shown at high magnification: 400 $\times$ .

infarction and fibrosis [1–4].

In conclusion, PTTM is among the deceptive clinical manifestations of metastatic breast cancer and must be considered early in the differential diagnosis of oncologic patients with unexplained hypoxemia, pulmonary hypertension and lung opacities on CT scan.

#### Funding acknowledgements

None to declare.

#### Author's contributions

C.A.F.A performed the autopsy and wrote the manuscript. D.T.W. and W.F.B. interpreted the radiologic studies. C.V. drafted the manuscript and was the primary pathologist.

#### Declaration of competing interest

The authors declare that they have no conflict of interest.

#### Acknowledgement

None to disclose.

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