

# Pulmonary micro-tumor emboli resulting in paradoxical emboli: a case report

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## Abstract

Pulmonary tumor embolism (PTE) is a rare manifestation of cancer. It is characterized by the presence of tumor cell emboli in the pulmonary arterioles and capillaries leading to an elevation of pulmonary vascular resistance. The ante-mortem diagnosis is difficult. We report a case of PTE associated with recurrent breast cancer that presented with neurological symptoms due to paradoxical cerebral embolism.

## Keywords

pulmonary tumor emboli, pulmonary hypertension, breast cancer

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## Introduction

Pulmonary tumor embolism (PTE) is a rare manifestation of cancers that was first described in 1897 by Schmidt<sup>1</sup> in an autopsy study and was later associated with subacute cor pulmonale in 1937.<sup>2</sup> It is characterized by the presence of tumor cell emboli in the pulmonary arterioles, causing microthrombi, occlusion, and, eventually, remodeling of the pulmonary arterioles resulting in pulmonary hypertension (PH).<sup>3</sup> Here, we report the first case of PTE due to recurrent breast cancer associated with paradoxical cerebral embolism.

## Case report

A 60-year-old Caucasian woman was admitted to our hospital because of new-onset neurological symptoms. She had a history of invasive “triple negative” (i.e. negative for estrogen and progesterone receptors and HER2/neu) breast adenocarcinoma stage pT2N1M0 diagnosed three years earlier. She was initially treated with surgery, radiotherapy, and adjuvant chemotherapy with no evidence of recurrence on last follow-up. She was also known for hypertension, dyslipidemia, and type 2 diabetes. The patient reported a

two-month history of progressive dyspnea and asthenia. She had consulted to the emergency ward two weeks before admission. A computed tomography pulmonary angiography (CTPA) revealed no evidence of pulmonary embolism, but a transthoracic echocardiogram showed isolated PH (estimated systolic pulmonary pressure of 58 mmHg) with no evidence of patent foramen ovale. Because of mild abnormalities on ventilation/perfusion scan (Fig. 1), she was prescribed rivaroxaban. When she presented to our institution, the patient was confused and drowsy. Her blood pressure was 117/82 mmHg, whereas her heart rate was 123 bpm. Peripheral oxygen saturation was 92% despite 5 L/min of oxygen. Jugular veins were distended bilaterally. Neurologic examination revealed central left-sided facial weakness, weakness of the left upper and lower limbs as well as truncular ataxia. Physical exam was otherwise unremarkable. Laboratory results showed anemia

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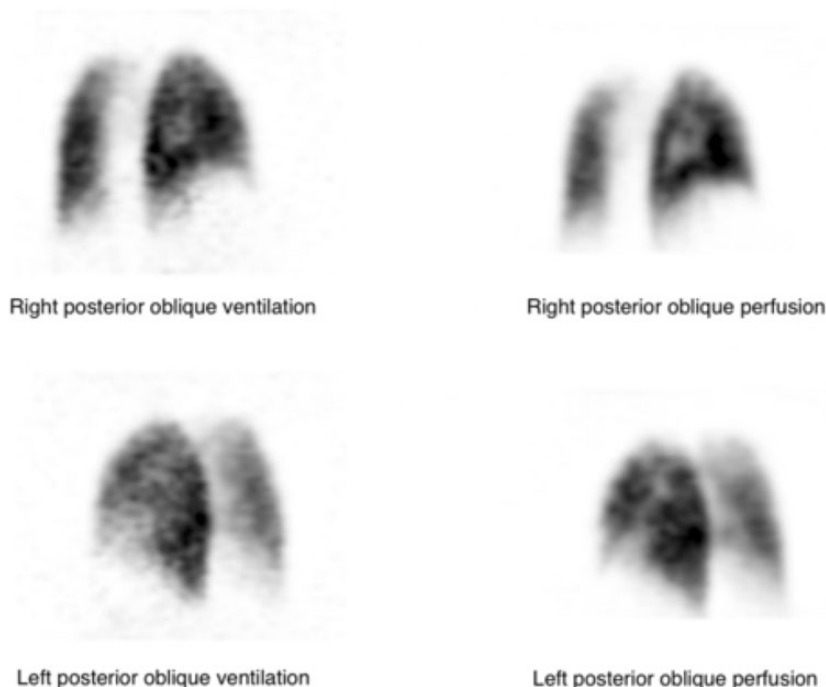
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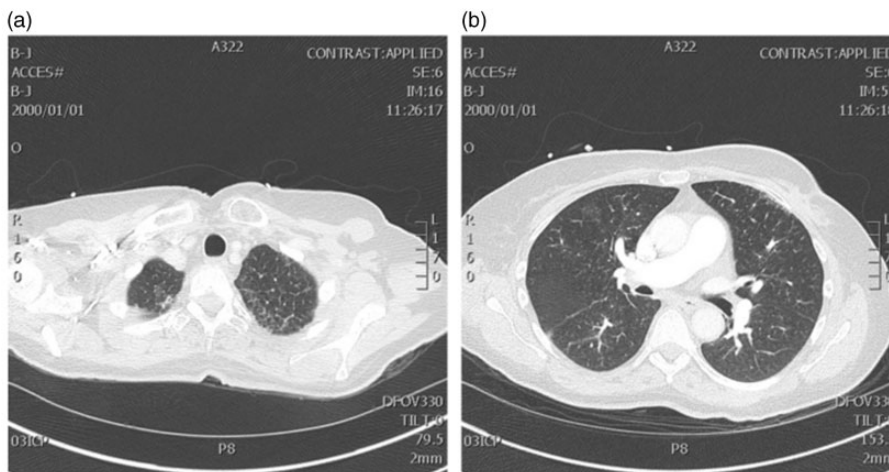
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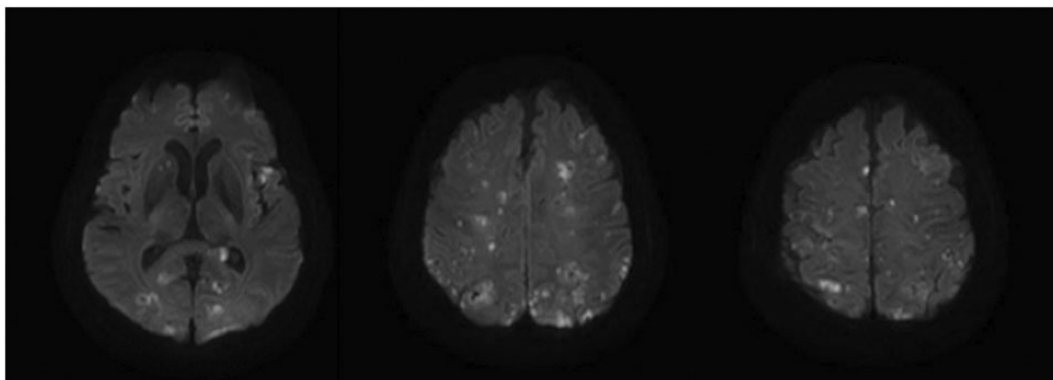
**Fig. 1.** Ventilation perfusion scan showing mild abnormalities on ventilation/perfusion scan.



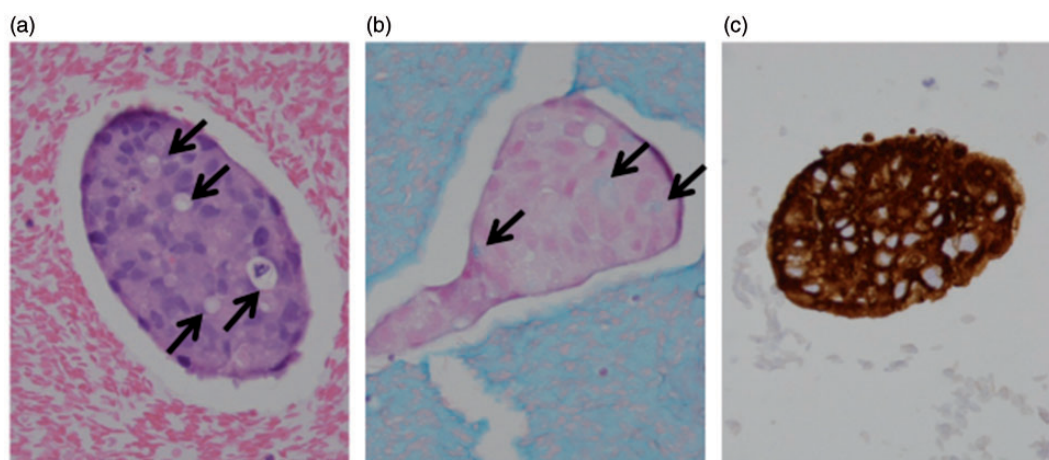
**Fig. 2.** CTPA showing non-specific ground-glass opacities with interlobular septal thickening at lungs' apex (a) associated with discrete diffuse ground-glass opacities throughout the lungs (b).

(hemoglobin 110 g/L), low platelet counts ( $59 \times 10^9/L$ ) with marked schistocytes on blood smear and signs of coagulopathy (INR 1.4, elevated D-dimers 12.83 ug/mL, decreased fibrinogen 0.63 g/L, and decreased haptoglobin 0.37 g/L). Troponin T levels were also elevated (402 ng/L,  $n < 14$ ) without ischemic changes on EKG. Transaminases and bilirubin were elevated, whereas GGT, ALP, sedimentation rate, creatinine, and autoimmune work-up were all normal. A second CTPA revealed subtle diffuse centrilobular ground glass opacities (Fig. 2) without evidence of pulmonary embolism. Brain magnetic resonance imaging (MRI)

confirmed multiple ischemic lesions in all vascular territories (Fig. 3). A patent foramen ovale with a right-to-left shunt and severe right ventricular dysfunction were seen on trans-esophageal echocardiogram; there was no intracardiac thrombus. Lower extremity venous Doppler ultrasound was normal. A Swan-Ganz catheterization then revealed pre-capillary pulmonary hypertension with an elevated mean pulmonary artery pressure (28 mmHg), decreased cardiac index ( $1.79 L/min/m^2$ ), elevated pulmonary vascular resistance ( $738 dyne.s.cm^{-5}$ ), and normal wedge (4 mmHg) and right atrial pressure (2 mmHg). Capillary cytology was



**Fig. 3.** Brain diffusion MRI showing multiple ischemic lesions measuring up to 8 mm in multiple vascular territories.



**Fig. 4.** Histology of tumor cells at high magnification (600 $\times$ ). On hematoxylin and eosin stain (a), clusters of tumor cells forming glands (arrows) were identified in a background of pulmonary capillary red blood cells. These glands contained mucin positive for Alcian Blue stain (b; arrows). Tumor cells were immunoreactive for cytokeratin 7 (c) but not for cytokeratin 20, estrogen receptors, progesterone receptors, mammaglobin, p40, and thyroid transcription factor-1 (not shown).

performed with the Swan-Ganz catheter in the wedged position and confirmed the presence of multiple clusters of tumor cells (Fig. 4) consistent with metastatic “triple negative” breast adenocarcinoma with hematogenous dissemination. A fluorodeoxyglucose-positron emission tomography (FDG-PET) scan documented diffuse hypercaptation of her bone marrow, but no signs of focal recurrence. A diagnosis of pulmonary tumor embolism (PTE) with paradoxical emboli was made. Because of poor general status, comfort care without chemotherapy was instituted and the patient died two weeks later in a palliative care home. No autopsy was performed in accordance with family wishes.

## Discussion

PTE is characterized by the presence of tumor cell emboli in the pulmonary arterioles and capillaries leading to an elevation of pulmonary vascular resistance. Autopsy case series have estimated its prevalence to be 0.19–26% in association with solid cancers.<sup>4–7</sup> The prevalence of clinically significant

PTE, however, is unknown. Adenocarcinomas of the stomach, lung, colon, prostate, and breast are the primary tumors most commonly associated with PTE.<sup>4–7</sup> However, it has previously been reported in association with choriocarcinoma, as well as with renal and liver carcinoma. In one cancer case series, PTE was the cause of death in 3.6% of patients.<sup>5</sup>

Progressive dyspnea associated with subacute cor pulmonale, most commonly over a period of weeks to a few months, is the main clinical presentation. More rarely, cough, hemoptysis, and pleuritic chest pain have also been described.<sup>8,9</sup> The diagnosis of PTE is rarely established antemortem since few diagnostic modalities have been described over the years.<sup>10</sup> Surgical lung biopsy is the gold standard, but patients are often severely hypoxemic and hemodynamically compromised at presentation, therefore contraindicating the use of surgical lung biopsy in most cases. Transbronchial biopsy has been proposed as an alternative diagnostic test,<sup>11</sup> although severe PH represents a relative contraindication to this procedure due to the high risk of

bleeding.<sup>8</sup> Pulmonary microvascular cytology (PMC), a modality first used by Masson in 1979 to diagnose amniotic fluid embolism,<sup>12</sup> and later, to diagnose fat embolism and lymphangitic carcinomatosis,<sup>13</sup> has been proposed as another option to make the diagnosis of PTE. There is currently minimal data available regarding sensitivity and specificity of PMC because most of the literature pertaining to this procedure consists of case reports. In 1994, Abati et al.<sup>14</sup> published a case series of 21 patients who underwent PMC for investigation of suspected PTE. Nine patients had positive results for malignant cells. Only four diagnoses were confirmed by autopsy. The lone false-positive result was due to rare circulating lymphoma cells in the peripheral blood. The other 12 patients had negative PMC results (two were false negatives). More recently, Ishiguro et al.<sup>11</sup> evaluated the efficacy of this procedure using retrospective data from seven patients. PMC was positive in 2/4 patients with PTE and 2/3 patients with intravascular lymphoma. Nonetheless, the diagnosis of PTE is most commonly made at autopsy, which delineates whether the process has evolved into concomitant pulmonary tumor thrombotic microangiopathy that is characterized by fibrocellular intimal proliferation.<sup>11,15</sup>

With regards to imaging, multiple subsegmental perfusion defects on ventilation/perfusion scan, as described in this case, have been repeatedly described.<sup>16</sup> Conversely, CTPA characteristically reveals no sign of embolism, although PTE seen in the proximal pulmonary vasculature has been rarely described. In these cases, FDG-PET scan has been described to differentiate macroscopic PTE involving the main pulmonary artery from pulmonary thromboembolism.<sup>17</sup> Frequently, however, CTPA reveals indirect signs of PTE according to the size of tumor emboli, including a beaded aspect of the peripheral pulmonary arteries,<sup>18</sup> centrilobular nodules with a tree-in-bud pattern,<sup>19</sup> and non-specific ground-glass opacities.<sup>11</sup> It is noteworthy, however, that a normal CTPA alone cannot rule out a diagnosis of PTE.

The prognosis associated with PTE is very poor, patients usually die from cardiorespiratory failure in the days following admission. Treatment options are therefore limited. A consensus has emerged regarding the futility of anticoagulation. Although solumedrol has also been historically used, its impact on prognosis is likely to be limited. In rare cases, early chemotherapy and oncological surgery were associated with prolonged survival.<sup>20,21</sup> Regardless of the treatment, however, prognosis is currently poor. Earlier diagnosis is nonetheless essential to lengthen the therapeutic window in patients eligible for aggressive therapy. PTE should thus be considered in cancerous patients with unexplained dyspnea.

## Conclusion

PTE is a rare but devastating disease presenting as subacute cor pulmonale and in rare cases, as paradoxical embolism and neurological symptoms. While early diagnosis and

treatment are desirable, ante-mortem diagnosis is difficult. Pulmonary microvascular cytology for PMC may be used to confirm the diagnosis although its sensibility appears to be limited.

## Conflict of interest

The author(s) declare that there is no conflict of interest.

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