

Subacute right heart failure revealing three simultaneous causes of post-embolic pulmonary hypertension in metastatic dissemination of breast cancer

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Abstract

A 72-year-old woman with history of breast cancer only treated surgically was referred to our department for pulmonary hypertension (PH) suspicion. Echocardiogram revealed elevated right ventricular systolic pressure. Computed tomography (CT) angiogram showed no pulmonary embolism (PE), but lung scan revealed two ventilation-perfusion mismatch areas. Right cardiac catheterization established precapillary PH. Despite treatment with PH specific therapy (sildenafil, ambrisentan, and epoprostenol), her condition worsened rapidly with acute right heart failure (RHF). She died 22 days after admission. Post-mortem microscopic examination showed a rare combination of PH etiologies consistent with metastasis of breast cancer in pulmonary vasculature including the rare pulmonary tumour thrombotic microangiopathy (PTTM).

Keywords Pulmonary hypertension; Carcinomatosis lymphangitis; Pulmonary tumor thrombotic microangiopathy; Right heart failure; Cardiogenic shock; Tumor cell embolic; Pulmonary embolism; Dyspnea; Death

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Introduction

Among the many causes of dyspnea associated with PH in a patient with history of cancer, paraneoplastic thrombotic PE is the most common aetiology and must be considered in priority.

But tumour cells can metastasize in the pulmonary vasculature in three mechanisms: occlusion of the small pulmonary arteries, pulmonary tumour thrombotic microangiopathy, or reach the lymphatic system.

Case report

A 72-year-old woman was admitted to a hospital 2 months ago for exercise-induced dyspnea. She had history of left breast cancer pT2pN1M0 treated 2 years before with

mastectomy, chemotherapy, and chest radiation. A first echocardiogram revealed normal right ventricular systolic pressure. D-dimer serum level was elevated, so a CT angiogram was performed and showed no evidence of pulmonary embolism, whereas ventilation perfusion lung scan revealed two perfusion defects throughout superior lobes with normal ventilation. Distal PE was suspected, and oral anticoagulation therapy was initiated and the patient discharged.

Two months later, an echocardiogram revealed elevated right ventricular systolic pressure at 78 mmHg. The right ventricle was moderately dilated (30 mm), non-hypertrophic, with good systolic function. The left atrium was non-dilated, and no valvulopathy was seen. Thus, she was referred to our department for post-embolic PH suspicion.

Physical examination was unremarkable including pulmonary auscultation and no sign of cardiac dysfunction. She had severe hypoxemia of 52 mmHg, a pH of 7.46, a pCO₂ of

34, and HCO_3^- of 24 mmol/L with 10 L/min of oxygen. Initial cardiac brain natriuretic peptide was normal.

The pulmonary function tests, the viral serologies, and the immune checkup were normal. A second chest CT showed non-specific ground-glass opacities and lung fibrosis consistent with previous radiation therapy but no sign of PE, nor interlobular septal thickening, adenopathy, or mass.

Right cardiac catheterization established precapillary PH with mean PA pressure of 48 mmHg and not elevated pulmonary wedge pressure (4 mmHg). Atrial pressure was low (5 mmHg), cardiac output was normal (2.66 L/min/m²), and pulmonary vascular resistance were increased at 8.6 Wood units. No cytologic study was performed.

A specific PH tritherapy was administrated (sildenafil, ambrisartan, and epoprostenol), but her condition worsened rapidly with acute RHF, respiratory distress, acute renal failure, and microangiopathic hemolytic anaemia. In this context, in absence of diagnostic, we decided to withhold invasive ventilator support. The patient died 22 days after admission.

The autopsy showed three etiologies of PH consistent with hematogenous metastasis of breast cancer in pulmonary vasculature: carcinomatous cell inside lymph vessels (lymphangitis carcinomatosa) (*Figure 1*), tumour cell embolization inside small arteries (tumour cells emboli) (*Figure 2*) and pulmonary tumour thrombotic microangiopathy (PTTM) (*Figures 3 and 4*). This latter is histologically characterized by intimal and medial fibromuscular thickening with accumulation of carcinomatous cells in the residual lumen of the small arteries and arterioles.

Discussion

PTTM is a rare and lethal complication related to metastatic cancer. It was first described in 1990 in 3.3% of an autopsic

Figure 1 (Haematoxylin and eosin): tumour cells inside lymph vessels (black arrow); pleura (dotted arrow).

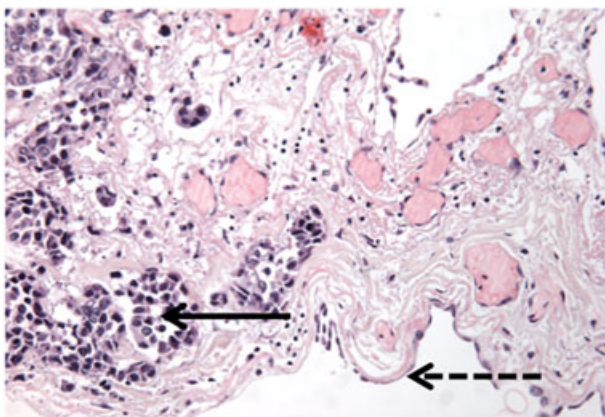


Figure 2 (Haematoxylin and eosin): tumour cells inside arteriole lumen. Non-hypertrophic arteriole wall.

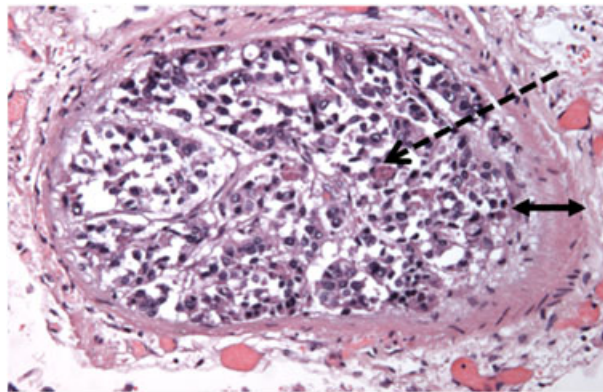


Figure 3 (Haematoxylin and eosin): tumour cells inside arteriole lumen (black arrow); intimal fibroblastic proliferation (black star); fibrin-rich thrombus (*); internal elastic lamina destruction.

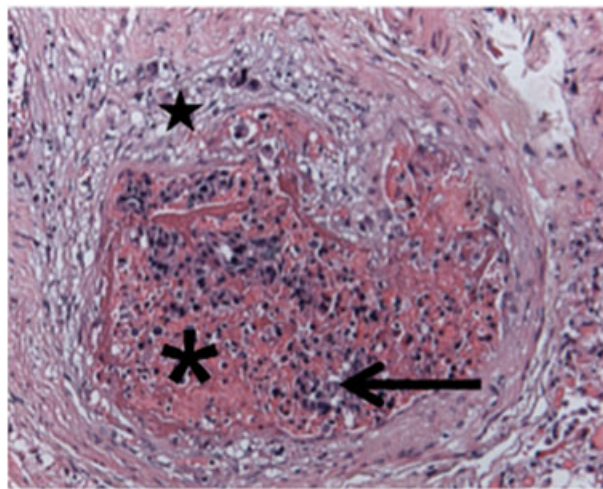
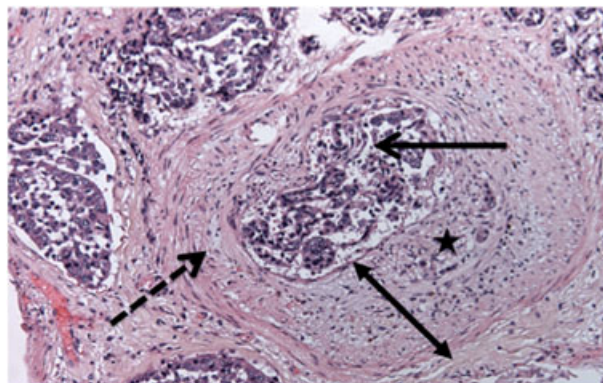


Figure 4 (Haematoxylin and eosin): tumour cells inside arteriole lumen (black arrow); intimal fibroblastic proliferation (black star); internal elastic lamina destruction (dotted black arrow); hypertrophic arteriole wall (double black arrow).



series of patients, who had died of metastatic adenocarcinoma, mostly of gastric origin.¹ Recently, a large case series estimated the incidence of 1.4% among 2215 autopsy patients with carcinoma and confirmed the stomach as the primary site of cancer associated with PTTM.

Patients usually present with dyspnea and RHF, sometimes with cough only. Most of the time, there is evidence of metastatic disease, but many occult cancers have been reported as in our description.

Previous studies have shown that tumour cells have the abilities to activate coagulation pathway and local thrombus formation and trigger fibroblastic intimal proliferation via production of cytokines such as tissue factor,² vascular growth factor, or platelet-derived growth factor.³ High VEGF expression associated with gastric cancer could explain the high incidence of PTTM. In addition to mechanical occlusion, these phenomena rapidly lead to arterioles remodelling and stenosis, increased pulmonary vascular resistance, and PH.

The tumoural cells are beyond the resolution of the CT angiogram, but their presence explains the perfusion defect on lung scan.

Recently, a tree-in-bud pattern, usually seen in bronchiolitis and characterized by small centrilobular nodules and branching linear opacities, was reported on thin-section CT of PTTM patients.⁴

Disseminated intravascular coagulation⁵ or cancer associated hemolytic anaemia has often been described consistent with elevated D-dimer.

Histologic antemortem diagnosis is very challenging because of the lightning deterioration after PH appearance. A study has estimated the median survival as 5 days from admission to hospital.⁶ PTTM may be identified using video-assisted thoracoscopic surgery, trans-bronchial biopsy, right heart catheterization, and CT-guided biopsy.⁷

In the rare antemortem diagnosis case, specific chemotherapy was administrated often associated with empiric treatment such as corticosteroids or anticoagulation. The best survival reported was 15 months probably because diagnosis was made prior to the development of PH.⁸

Chronic PE is the main cause of unexplained progressive dyspnea with precapillary PH in the context of cancer.

But when large proximal PE is absent in CT angiogram whereas lung scan show multiple perfusion defects, clinicians must consider other tumoural embolic causes in the differential, especially PTTM. Thereby, they will be able to perform pulmonary cytology or biopsy before the patient's condition deterioration. A rapid specific chemotherapy administration is the only way to improve the survival of patients.

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