Rare disease

An autopsy case of acute cor pulmonale and paradoxical systemic embolism due to tumour cell microemboli in a patient with breast cancer

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Summary

A 62-year-old woman was admitted to our hospital because of severe respiratory distress. Diagnostic imaging studies suggested the existence of inexplicable cor pulmonale. Although we immediately sought the aetiology of her severe condition, she died suddenly on the fourth day after admission. Postmortem autopsy revealed tumour cell microemboli in the small pulmonary arteries. In addition, tumour cell embolisation identical to that in primary breast cancer cells was also observed in microvessels in systemic multiple organs, such as the liver, brain, kidneys, spleen, uterus, bone marrow and adrenal glands—with simultaneous findings of peripheral infarction. Systemic tumour cell embolism mediated through the patent foramen ovale superimposed on pulmonary tumour cell emboli (PTCE) is considered to be the mechanism underlying inexplicable cor pulmonale. The rapid aggravation of her condition terminated in death.

BACKGROUND

Pulmonary tumour cell embolism (PTCE) is reportedly an uncommon clinical manifestation in patients with malignant disease.¹ The prognosis is extremely poor after the onset of respiratory symptoms. The occlusion of the pulmonary microvasculature by tumour cells causes progressive respiratory failure. Unfortunately, microscopic tumour cell embolisation is rarely recognised before death because of the difficulty in diagnosis. In the present case, undiagnosed breast cancer was accompanied with diffuse PTCE that resulted in rapidly aggravating respiratory failure, leading to death on the fourth day after admission. Autopsy findings disclosed that tumour emboli were observed in pulmonary artery and also in systemic various organs. We experienced this unusual case and herein describe a patient with breast cancer in which the first clinical manifestation of acute cor pulmonale resulted from PTCE in combination with systemic tumour cell embolisation.

CASE PRESENTATION

A previously healthy 62-year-old woman developed dyspnoea and non-productive cough, 10 days before admission. Her chest symptom gradually aggravated. On the day of admission, a family member found her lying face-down on the floor, which prompted her family to call for an ambulance. In the emergency room, the administration of oxygen failed to improve oxygenation, and the patient was lethargic with respiratory distress. On physical examination, her blood pressure was 102/64 mm Hg, with tachycardia at 118 beats/min and tachypnoea at 26 respirations/min with nasal flaring. Her extremities exhibited pallor and cyanosis. Her oxygen saturation was 72% under oxygen supplementation of 10 l/min with a face mask. The pulmonary auscultation disclosed an almost

normal vesicular sound, whereas the pulmonic component of the second heart sound was accentuated, and a systolic murmur was audible along the right sternal border. Pedal and pretibial oedemas were not observed. There was no redness, hot sensation or swelling in the legs absence of deep venous thrombosis. A hard, palpable mass was present in the upper, outer quadrant of the right breast.

INVESTIGATIONS

Laboratory findings (table 1) demonstrated arterial hypoxaemia with respiratory alkalosis and elevated lactic acid. The alveolar-arterial oxygen difference increased to 67.2 mm Hg. White blood cell, C reactive protein and creatine kinase levels were elevated. Although D-dimer level had increased, the criterion for disseminated intravascular coagulation was not satisfied. The ECG demonstrated sinus tachycardia with an S1QIIITIII pattern and a negative T wave in the right precordial leads (figure 1). A chest x-ray (figure 2) revealed no pleural effusion and clear lung field. The cardiothoracic ratio was 56%. An echocardiogram showed dilatation of right ventricle and tricuspid regurgitation with preserved systolic function. Compression of the interventricular septum was observed in end-diastole. Thoracic CT demonstrated a mass in the right breast (figure 3A) and enlarged axillary lymph nodes. A macular shadow and small nodules under the pleura, without evidence of lymphangitis carcinomatosa, were found; however, these findings were non-specific. She had an almost normal air-filled lung (figure 3B). Thoracic-enhanced CT demonstrated that filling defects caused by thrombi were neither detected in the proximal pulmonary artery (figure 3C) nor in the deep veins of the lower extremities. Multiple low-density areas in the liver were also observed. Although an ECG and an echocardiogram suggested pulmonary thromboembolism, a contrast-enhanced

Table 1 Laboratory findings

BGA		CBC		Biochemistry		Coagulation	
pH	7.51	WBC	11900 / μ l	T-bil	0.8 mg/dl	PT	84%
PCO ₂	27 mm Hg	RBC	361 $\times 10^4$ / μ l	AST	163 U/l	PT-INR	1.11
PO ₂	49 mm Hg	Hb	11.4 g/dl	ALT	79 U/l	D dimer	2.7 μ g/ml
HCO ₃	21 mmol/l	Ht	33.4%	LDH	812 IU/l		
BE	−1	PLT	16.9 $\times 10^4$ / μ l	ALP	496 IU/l		
O ₂ saturation	86.1%			BUN	18 mg/dl		
Lac	26.0 mg/dl			Cre	0.66 mg/dl		
A-aDO ₂	67.25 mm Hg			TP	6.7 g/dl		
				ALB	3.3 g/dl		
				Na	140 mmol/l		
				K	3.4 mmol/l		
				Cl	104 mmol/l		
				Ca	8.3 mg/dl		
				AMY	31 U/l		
				CPK	539 IU/l		
				CK-MB	744 IU/l		
				BS	143 mg/dl		
				CRP	6.54 mg/l		

ALB, serum albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase transaminase; AMY, AST, aspartate aminotransferase; BE, BS; BUN, blood urea nitrogen; CBC, complete blood count; CK-MB, MB isoenzyme of creatine; CPK, creatine phosphokinase; CRP, C reactive protein; Hb, haemoglobin; Ht, LDH, lactate dehydrogenase; PLT, platelet; PT-INR, prothrombin time international normalized, ration; RBC, red blood count; TP, total serum protein; WBC, white blood count.

CT scan did not reveal any obvious thrombi, and diagnostic imaging found no pulmonary field abnormalities that could account for her severe respiratory failure.

DIFFERENTIAL DIAGNOSIS

Thromboembolism, granulomatous disease, infectious disease and tumour cell emboli of the pulmonary microvasculature were considered as differential diagnoses.

Diagnostic strategy was limited because of the patient's serious condition, and we could not establish an antemortem diagnosis.

TREATMENT

The patient was intravenously administered antibiotics, heparin and methylprednisolone, in addition to oxygen supplementation.

Figure 1 Electrocardiogram.

Figure 2 Chest x-ray.

OUTCOME AND FOLLOW-UP

Oxygen levels were initially stabilised at the time of hospitalisation by the administration of 12 litres of oxygen through a reservoir mask. However, oxygenation began to decrease on the second day, and her refractory hypoxia required respiratory support with positive-pressure ventilation. On the fourth day, she developed progressive hypoxaemia and systemic hypotension, leading to death. From

her clinical course, pulmonary microembolism caused by either thrombosis or tumours was thought to be the main cause of her illness. However, because of rapid deterioration, we were unable to make an antemortem diagnosis. An autopsy was immediately performed.

Postmortem autopsy findings are as follows: the patient's primary breast cancer was an invasive ductal carcinoma (scirrhous type) with invasive proliferation in alveolar and funicular arrangements (figure 4A). On both lungs, wide-ranging small pulmonary arteries exhibited luminal occlusion caused by tumour cell microemboli (figure 4B) with partial haemorrhagic infarction. In addition, tumour cell emboli were observed in the lymphatic vessels, and comorbid lymphangitis carcinomatosa was confirmed. Reactive fibrocellular intimal proliferation was not found. Tumour cell embolisation identical to the primary breast cancer cells was observed in microvessels in the liver, brain, kidneys, spleen, uterus, bone marrow and adrenal glands, with simultaneous findings of peripheral infarction. In the heart, although the right ventricle was enlarged, hypertrophy was not established. While no stenosis was found in the epicardial coronary vessels, tumour cell microemboli and diffuse myocardial infarction were observed (figure 4C). Patent foramen ovale (PFO) was also confirmed (figure 4D).

DISCUSSION

The patient was admitted to our hospital with progressive aggravation of respiratory failure and unexplained cor pulmonale and was later diagnosed with PTCE owing to scirrhous type of breast cancer on the basis of pathological diagnosis at autopsy. However, a contrast-enhanced CT scan did not show any obvious images of pulmonary thrombi, and diagnostic imaging showed no pulmonary

Figure 3 Enhanced CT. (A) Mass of right breast. (B) Almost normal air-filled lung. (C) No filling defects in the proximal pulmonary artery.

Figure 4 Histopathological findings. (A) Invasive ductal carcinoma with desmoplasia (scirrhous carcinoma). There was a proliferation of atypical cells forming a funicular or alveolar structure. (B) Diffuse microscopic tumoremboli in the small pulmonary arteries. (C) The myocardium had focal and diffuse infarctions due to microemboli. (D) Patent foramen ovale.

field abnormalities that could account for the observed respiratory failure. Arterial blood gas analysis suggested the presence of ventilation-perfusion mismatch or intracardiopulmonary shunt as the mechanism underlying severe hypoxaemia. However, the diagnostic strategy was limited by the serious condition of the patient, and we were unable to establish an antemortem diagnosis. A postmortem autopsy demonstrated that this case had the distinction of having a combination of two rare clinical entities: PTCE as the first clinical manifestation of breast cancer and paradoxical systemic tumour embolisation through the PFO.

PTCE, first reported by Schmidt¹ in 1897, is characterised by respiratory failure, hypoxia and right heart failure in the absence of pulmonary field abnormalities in patients with known malignancy. Kane *et al*² investigated 1085 postmortem cases associated with malignant tumour, and reported an incidence rate of PTCE of approximately 2.4%.

Respiratory failure is subacute and progressive, and prognosis is extremely poor after the onset of respiratory symptoms. The cancers in which PTCE occurs are often mucin-producing adenocarcinomas, such as lung cancer, gastric cancer and breast cancer,^{3 4} as in our case. Diagnostic strategies, such as an open lung biopsy or transbronchial lung biopsy, were limited by the severe condition of the patient. Pulmonary arterial cytology by Swan-Ganz catheter is reported to be a less invasive and effective technique for establishing a diagnosis.⁵ Acute diminution of pulmonary blood flow due to extensive tumour cell microembolisation may result in the extreme ventilation-perfusion mismatch that could be the mechanism underlying severe hypoxaemia in this case.

In the present case, PTCE as well as systemic tumour cell embolisation became evident upon postmortem

autopsy. Embolic particles which enter the pulmonary circulation are usually trapped by the pulmonary capillaries. In this case, tumour cell emboli were found in the lungs, as well as in multiple organs throughout the body. Paradoxical embolism caused by intracardiac shunt via PFO is thought to be the main cause of systemic tumour cell embolisation, as observed in this case.

PFO is common in the general population, and probe-patent PFO exists in 15–35% of the population, as reported in a review of over 9000 autopsy studies.⁶ PFO is a persistent valve-like connection between the right and left atria that—in most individuals—is closed by fibrous adhesions between the septum primum and the septum secundum during the first month of life.⁷ Right-to-left shunting across PFO is usually transient and without clinical significance. However, PFO has been implicated in the aetiology of a number of different pathologies, including cryptogenic stroke, decompression sickness in divers, platypnoea orthodeoxia and migraine with aura.^{7–11}

In many cases of systemic embolism mediated by PFO, right atrial pressure increases in early contractions with the Valsalva method or repeated coughing, and transient right-to-left shunts occur.⁸ This is believed to be sufficient to cause paradoxical embolism. Right-to-left shunts were also observed in 57% of 148 PFO patients when at rest and in 92% of patients when holding their breath or coughing.⁹ Therefore, even transient right-to-left shunting through a PFO can result in a paradoxical embolus. Haemodynamic changes that increase right-sided pressure by the pulmonary microembolism, as observed with our case, promote right-to-left shunting, resulting in systemic embolism. In addition, as another potential mechanism underlying severe hypoxaemia in this case, that is rapid elevation of pulmonary arterial pressure by antecedent PTCE may give

rise to the reopening of the foramen ovale—leading to systemic tumour cell embolisation and also to deoxygenated venous blood shunting.

The present case is exceptionally rare in that systemic tumour cell embolism was associated with PTCE mediated through the PFO. In this case, right heart pressure was increased by pulmonary hypertension caused by breast cancer microemboli. At the autopsy, we discovered wide-ranging microvascular pulmonary tumour cell emboli. There was neither right ventricular hypertrophy nor secondary change, including thrombus formation or fibromuscular intimal proliferation, associated with pulmonary tumour thrombotic microangiopathy.¹² Therefore, microembolisation of the pulmonary circulation may be an acute process in our case. Coexistence of acute PTCE and systemic microembolism of vital organs may account for the fulminant deterioration of the clinical course which was observed in this case.

Learning points

- ▶ Pulmonary tumour cell emboli (PTCE) is uncommon as the first clinical manifestation of malignant disease.
- ▶ PTCE is fatal after the onset of symptoms and is difficult to diagnose before death.
- ▶ We experienced a rare case with tumour embolism of the pulmonary microvasculature and subsequent systemic arterial tumour embolism through a patent foramen ovale.

Competing interests None.

Patient consent Obtained.

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