ORIGINAL RESEARCH LETTER

Occult malignancy underlying a case of "hyperacute" onset of severe pulmonary hypertension

To the Editor:

"Tumoral pulmonary hypertension (PH)" includes several subtypes of conditions leading to abnormal levels of pulmonary artery or venous pressure occurring in patients with a current or previous malignancy. Pulmonary tumour "microvascular disease" includes both pulmonary tumour microembolism (PTE) and pulmonary tumour thrombotic microangiopathy (PTTM) that are likely to be part of the same spectrum disease [1]. PTE was described in early studies, and was defined as the occlusion of the pulmonary microvasculature by tumour cells and associated thrombi. Tumour thrombi are frequently formed by malignant cells, platelets and fibrin, and are highly resistant to recanalisation and lead to an irreversible obstruction. In many cases, they are associated with vascular tissue reaction characterised by extensive fibrocellular intimal hyperplasia of small pulmonary arteries initiated by tumour microemboli known as PTTM [1, 2]. Most reported cases of PTE occur in association with adenocarcinomas, including liver [3, 4], kidney, breast [5, 6], stomach [4, 7], bladder and choriocarcinoma [8]. In a handful of cases of PTE, estimated at 5% [9], the primary cancer is unknown. *Ante mortem* diagnosis of PTE is often challenging and the majorities of cases are identified as results of *post mortem* studies. This is especially true for a subset of patients with occult malignancy and acute onset of severe PH.

We report a case of fatal PTE occurring in a healthy young man who developed acute-onset respiratory failure due to severe PH refractory to intensive care supportive management.

A 38-year-old, previously healthy, male smoker of 10 pack-years who has never used anorectics complained of a 3-months history of a flu-like syndrome with dyspnoea, dry cough, fever and unintentional weight loss. He was sent to the emergency department due to his worsening symptoms and acute hypoxic respiratory failure was discovered (arterial blood gas analysis in room air: pH 7.46, oxygen tension (P_{O_2}) 49.8 mmHg and carbon dioxide tension (P_{CO_2}) 29.7 mmHg; and peripheral oxygen saturation (S_{pO_2}) 86%).

D-dimer serum level was elevated and computed tomography (CT) angiography showed no evidence of pulmonary thromboembolism but demonstrated a diffuse centrolobular nodular pattern. Transthoracic echocardiography demonstrated severely increased right ventricle cavity size and systolic pulmonary arterial pressure (sPAP) was estimated to be 50 mmHg. Blood cell counts revealed a normal white cell count. *Legionella* and pneumococcal urinary antigens, procalcitonin, HIV, cytomegalovirus, *Mycoplasma*, *Chlamydia*, and autoimmune serological tests were negative. Ventilation/perfusion lung scanning revealed multiple segmental perfusion defects. The patient was given antibiotics and subcutaneous low molecular weight heparin. 48 h later, due to the poor response of his rapidly progressive type I respiratory failure to oxygen therapy (arterial blood gas analysis on oxygen support at 15 L·min^{-1} with a reservoir: pH 7.45, P_{O_2} 55.6 mmHg and P_{CO_2} 32.7 mmHg; and S_{pO_2} 88.3%), helmet continuous positive airway pressure (CPAP) was quickly applied (CPAP 12 cmH_2O and inspiratory oxygen fraction 0.80). Unfortunately, after 12 h, respiratory distress developed due to profound hypoxaemia with haemodynamic instability (mean artery pressure <65 mmHg) despite CPAP, fluid resuscitation and amine support. The patient was urgently intubated and mechanically ventilated, transferred to the intensive care unit, and supported by means of

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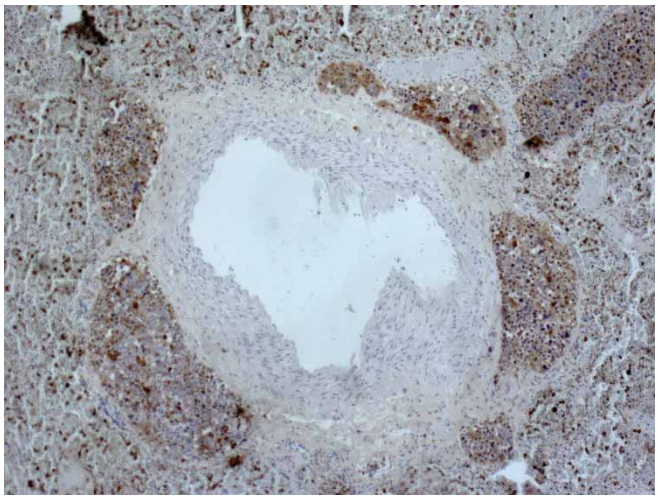

FIGURE 1 Multiple nests of neoplastic, undifferentiated cells within perivascular lymphatic vessels of the lung parenchyma. These cells show the following phenotype by immunohistochemistry: positivity for CKAE1/AE3 (shown), cytokeratin (CK)7, thyroid transcription factor-1, napsin, CK19 and CK8/18, and negativity for vimentin, CD45, myeloperoxidase, melan-A, p40, CK20, CDX-2, CD14, synaptophysin, PAX-8, GATA-3, inhibin, CD99, CD117, OCT3/4, CD30, PSA and racemase. CKAE1/AE3 stain, original magnification 10x.

venoarterial extracorporeal circulatory membrane oxygenation (ECMO-VA). The respiratory exchanges, despite a protective ventilation, appeared marginal.

A thoracic CT now showed a pattern of diffuse alveolar haemorrhage. Despite daily bronchoscopies for removal of blood bronchial clots, and the supportive care with both ECMO-VA and protective ventilation, after 15 days on ECMO-VA, the progressive decline in haemodynamic condition, the increase in the values of pulmonary pressure (sPAP 80 mmHg) and the uncontrollable bronchial bleeding led to the death of the patient. The autopsy examinations of both lungs' tissue revealed subverted parenchyma by bronchopulmonary abscess and by disseminated microscopic embolisation of the pulmonary circulation with haemorrhage and endoalveolar oedema. These endovascular foci of emboli completely occluding subsegmentary arteries contained undifferentiated epithelial tumour cells showing the following immunochemistry pattern: CKAE1/AE3, cytokeratin (CK)7, thyroid transcription factor-1 protein, CK19, CK8/18 and napsin (figure 1). These tumour cells were also found in pulmonary bilateral hilar lymph nodes and in the right adrenal gland. This pathological pattern is consistent with PTE due to occult malignant pulmonary vascular involvement.

Diagnosis of "microscopic tumour pulmonary embolism" in time is challenging due to the rapid development of lethal PH [10]. This condition has generally not been considered in the differential diagnosis of acute respiratory failure in patients with unknown malignant lesions [5]. According to the literature, the time from diagnosis of malignancy to development of respiratory symptoms is 14 months, but the mean interval between respiratory symptoms and death is only 1 month [1, 11]. In the case reported, the clinical decay was so rapid that it did not allow us to suspect PTE or to investigate an occult malignant tumour. In our opinion, the peculiar aspects of this case are: 1) the hyperacute onset with an interval of only 3 months between the start of symptoms and admission to hospital for severe hypoxaemia; 2) death from acute respiratory failure only 14 days after the hospital admission; and 3) the occult undiagnosed underlying malignancy.

With our case, we would like to emphasise the concept that microvascular pulmonary tumour embolism may clinically manifest as acute respiratory failure with PH, rapidly progressive, right-sided heart failure, and death. In rare conditions, in the absence of any causes of acute rapid right-heart failure also in patients without a cancer history, it is important to suspect microvascular pulmonary tumour embolism for rapidly respiratory deterioration particularly if there is no improvement with therapy despite extracorporeal circulatory assistance. In conclusion, we believe that investigations in a patient with new-onset PH should include screening for undiagnosed malignancy, even if this concept is not clearly found in the current PH guidelines [1, 12].

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