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LETTER TO THE EDITOR
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A case of rapidly progressive fatal pulmonary hypertension in a patient with metastatic bladder cancer: reflections on the early recognition of pulmonary tumour thrombotic microangiopathy

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Pulmonary tumour thrombotic microangiopathy (PTTM) is a rare but under-recognised cause of rapidly progressive pulmonary hypertension (PH) and cor pulmonale, characterised by diffuse obstruction of small pulmonary arteries by metastatic tumour cells. These tumour emboli lead to obstructive intimal proliferation and *in situ* thrombosis within the pulmonary vasculature, further compromising the overall permeability of the pulmonary vascular bed and exacerbating PH.[1] The clinical and imaging manifestations of PTTM often overlap with those of other causes of PH, including chronic thromboembolic PH, pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis, often leading to diagnostic delays.

The patient was a 74-year-old man diagnosed with high-grade urothelial carcinoma of the bladder in September 2023, followed by laparoscopic radical cystectomy and ileal neobladder construction. He then received four cycles of pembrolizumab monotherapy as adjuvant treatment. In April 2024, tumour markers (CEA, CA 125, CA 19-9, CYFRA 21-1) were elevated and magnetic resonance imaging showed metastatic lesions in the liver, abdominal cavity, skull base and vertebrae. First-line treatment for metastatic cancer was initiated with six cycles of carboplatin, gemcitabine and durvalumab, followed by two cycles of maintenance durvalumab alone.

On 10 November 2024, he was hospitalized due to symptoms of headache and lumbar back pain, where he received anticoagulation and local radiotherapy to the skull base. Physical examination revealed tachycardia and tachypnea, with a loud P_2 noted on auscultation. His baseline oxygen saturation was 95%. On 14 November 2024, anticoagulants were discontinued due to grade 2 nasal bleeding, and hemostatic treatment was administered with batroxobin, Yunnan Baiyao. Four days later, he developed severe exertional dyspnea and significant hypoxemia (SpO_2 of 73% on room air).

Laboratory results indicated coagulation abnormalities (D-dimer elevated to 7.76 μg/mL, fibrin degradation products increased to 42.95 mg/L), hematological changes (platelets were reduced to 20×10^9/μL and leukocytes increased to 12.15×10^9/μL, hemoglobin was 117 g/L), and markedly elevated lactate dehydrogenase (1784 U/L). Electrocardiogram showed signs of right ventricular volume overload with S_IQ_{III} pattern (Figure 1). Two-dimensional transthoracic echocardiography revealed right atrial and right ventricular dilatation, right ventricular dysfunction, moderate tricuspid regurgitation, and a pulmonary artery systolic pressure of 95.7 mmHg (normal range: 15–25 mmHg) (Figure 2).

Chest computed tomography demonstrated newly scattered ground-glass opacities in the subpleural regions of both lungs (Figure 3, red arrows) and multiple metastatic lesions in the ribs and thoracic vertebrae. Computed tomography pulmonary arteriography indicated a 12 mm hypodense filling defect in the artery of the posterior basal segment of the left lower lung, and signs of PH: dilated main pulmonary artery (32 mm), mildly dilated right atrium and right ventricle with flattening of the interventricular septum (Figure 4). No deep vein thrombosis was seen on ultr-

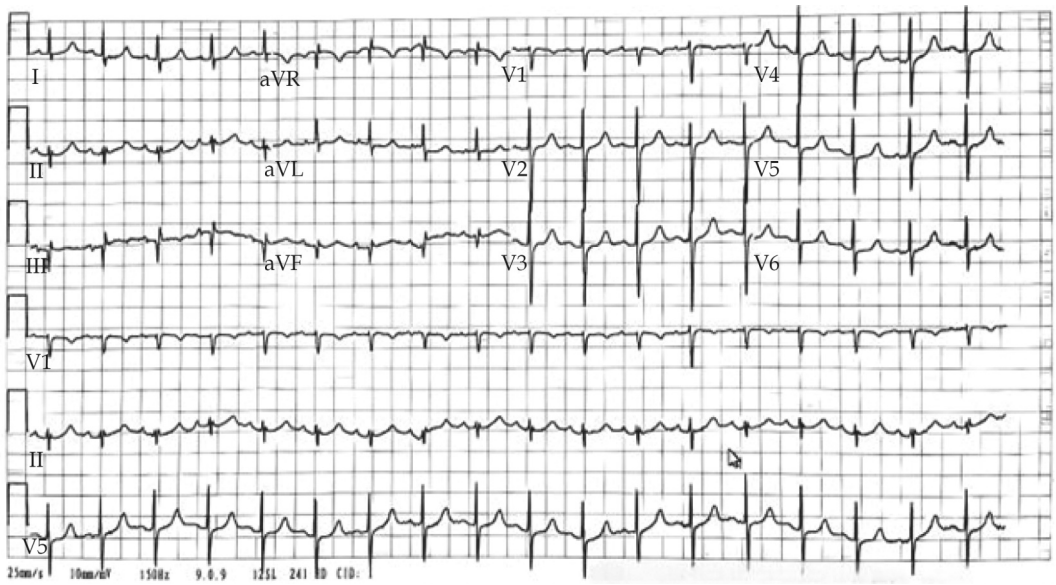

Figure 1 Electrocardiogram showing signs of right ventricular volume overload of type S_IQ_{III}.

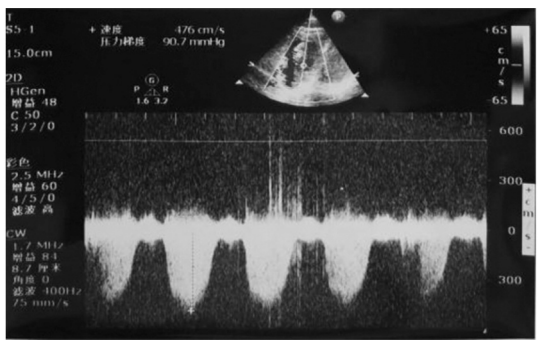

Figure 2 Initial two-dimensional transthoracic echocardiogram showing moderate tricuspid regurgitation with a pulmonary artery systolic pressure of 95.7 mmHg.

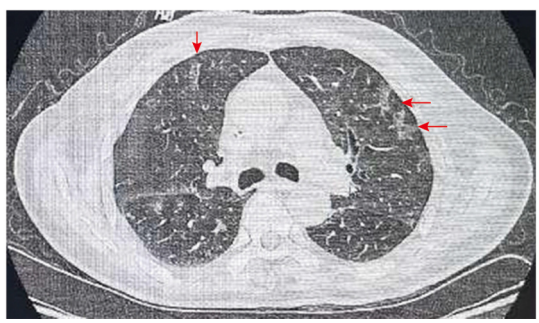

Figure 3 Chest computed tomography scan showing scattered ground-glass opacities in the subpleural regions of both lungs (red arrows).

asound. While checkpoint inhibitor pneumonitis with superimposed infection was suspected, the etiology of the PH remained unclear.

The patient was treated with meropenem, low-molecular-weight heparin, methylprednisolone, erythropoietin and ambrisentan. During treatment, oxygen supplementation via nasal cannula, high-flow oxygen therapy and non-invasive ventilation were used to achieve SpO_2 levels between 70% and 90%. Arterial blood gas analysis showed a low oxygen partial pressure of 72 mmHg, a carbon dioxide partial pressure of 22.5 mmHg and an SpO_2 of 92.5%, indicating respiratory alkalosis (pH = 7.46).

The following day, the patient presented with severe PH (with echocardiography showing a pulmonary artery systolic pressure increase to 125 mmHg) (Figure 5) and acute hypoxaemia. Despite treatment, including mechanical ventilation and circulatory support, the patient eventually succumbed.

With the increasing incidence of cancer, the identification and management of cancer-associated thrombotic microangiopathy has become an urgent priority. PTTM is a rare but potentially fatal cancer-associated thrombotic microangiopathy that typically presents with rapidly progressive dyspnoea and unexplained PH.[2] The resulting PH is primarily due to vascular histopathological changes and secondary thrombosis, rather than large tumour emboli directly obstructing the vessels.

PTTM is a rare condition, with recent systematic reviews suggesting an incidence of approximately 1.4%–3.3% in cancer patients.[3] Due to its rapid progression, PTTM can be fatal before a definitive diagnosis is made, leading to significant underdiagnosis.[4,5] However, autopsy studies have shown that up to 26% of patients with solid tumours have tumour emboli in the pulmonary microcircula-

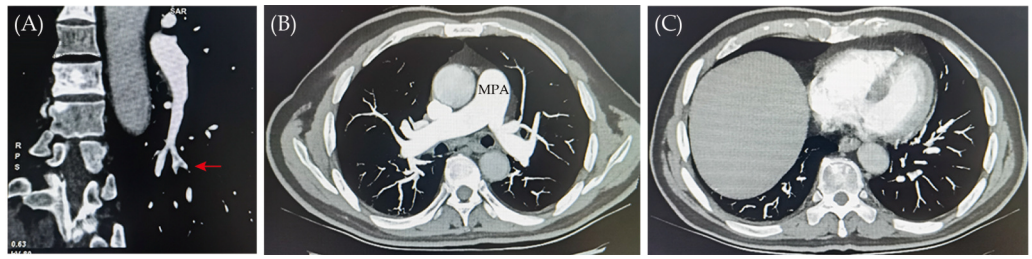

Figure 4 Computed tomography pulmonary arteriography showing a 12 mm hypodense filling defect in the artery of the posterior basal segment of the left lower lung (A) (red arrow) and signs of pulmonary hypertension: dilated main pulmonary artery of 32 mm (B), mildly dilated right atrium and mildly dilated right ventricle with flattening of the interventricular septum (C).

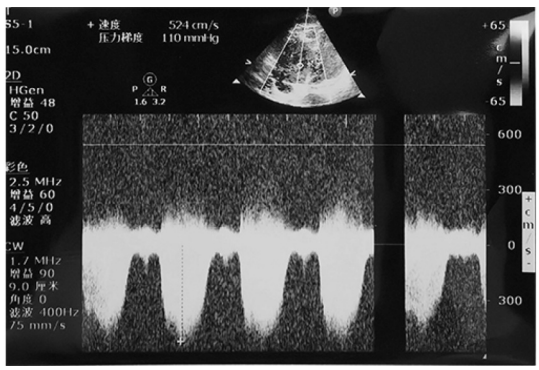

Figure 5 Two-dimensional transthoracic echocardiogram at terminal stage showing severe tricuspid regurgitation with a pulmonary artery systolic pressure of 125 mmHg.

tion.[6] In addition, the clinical and imaging manifestations of PTTM overlap with those of other causes of PH, including chronic thromboembolic PH, pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis,[3] complicating the diagnostic process and increasing the likelihood of misdiagnosis. Therefore, the true incidence of PTTM may be higher than reported. Due to the rarity of this condition, most of the published literature consists of case reports or small case series, with few cohort analyses; consequently, most clinicians lack sufficient awareness, leading to frequent diagnostic errors. The initial misdiagnosis of this patient as checkpoint inhibitor pneumonitis is a reflection of this clinical reality.

Although the patient was diagnosed with checkpoint inhibitor pneumonitis based on his primary disease, medication history and lung imaging features, the rapidly progressive PH could not be adequately explained. Retrospectively, his key features included: (1) unexplained, rapidly progressive dyspnoea in a patient with metastatic cancer; (2) echocardiographic evidence of rapidly progressive PH without a clear precipitating factor; (3) chest computed tomography showed no significant pulmonary artery thrombosis; and (4) unexplained severe thrombocytopenia. Therefore, we considered PTTM to be the most likely cause of PH. Currently, the diagnosis of PTTM still requires histological examination, which may delay treatment. Recent studies have shown that if PTTM is diagnosed early enough, specific chemotherapy and PH treatments can reduce intimal proliferation, improve symptoms and prolong survival.[1,7,8] Current evidence suggests that in cases of unexplained PH, further investigations such as a lung ventilation-perfusion scan, right heart catheterisation or lung biopsy should be performed. However, the feasibility of performing lung biopsy in critically ill patients is low. Therefore, future efforts should focus on a comprehensive assessment of medical history, imaging and laboratory tests to enable earlier diagnosis and treatment in such patients.

At present, improved knowledge dissemination and clinical awareness, especially in patients with a history of cancer and PH, are key to promoting the diagnosis and management of PTTM. To improve survival in patients with PTTM, further research is needed to expand diagnostic tools and therapeutic strategies.

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