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Vascular tree-in-bud sign in pulmonary tumour thrombotic microangiopathy (PTTM): CT findings for a difficult radiological early antemortem diagnosis

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To the editor,

Pulmonary tumour thrombotic microangiopathy (PTTM) is a rare clinic-pathological disease entity in which the tumour cells embolize into the pulmonary vasculature inducing thrombotic microangiopathy. Although it has been observed in 0.9%-3.3% of autopsy case studies with extra-thoracic malignancies, rarely is it diagnosed antemortem (1). PTTM should be suspected in the appropriate clinical setting and confirmed by lung biopsy, that demonstrates pulmonary tumour emboli within pulmonary vasculature surrounded by fibrin deposition and fibrocellular intimal proliferation (Figure 1). The pathogenesis remains to be clarified, but it is known that embolization of tumoral cells into the pulmonary vessels induces endothelial damage leading to stenosis and thrombosis. Different neoplasms reported have been associated with PTTM, but adenocarcinomas are the most frequently related. Gastric cancer is the most commonly associated malignancy (up to 26%), but it is not the only one: it is followed by breast (21%), prostate (13%), and lung (10%) carcinoma. Although less frequent, PTTM has also been observed in renal cell carcinoma, bladder, ovarian and hepatocellular carcinoma. We have collected 8 cases of PTTM diagnosed in our Radiology Emergency Department in patients with suspect pulmonary embolism and a history of active cancer disease, in the period between 2014 and the end of 2022. It is not well known why gastric carcinoma is more frequently associated with PTTM: the median age of a patient diagnosed with gastric cancer is around 50-70 years, as well as with our patients (median age 62.2 years, between 50 to 78 years). Six (75%) of our cases had previous gastric cancer diagnoses, following the literature (2).

Patients with PTTM can present with different symptoms such as weakness, pain, fever, weight loss, and respiratory symptoms, mimicking other different syndromes such as pulmonary hypertension, right heart failure, or organ dysfunction. However, these clinical symptoms are nonspecific, and making a diagnosis is tricky.

Although it is extremely difficult to diagnose PTTM before death, this could be suspected in cancer patients with acute worsening respiratory insufficiency and the absence of embolism in major pulmonary arteries on enhanced CT scans. Our patients had a cancer history but no radiological evidence of pulmonary embolism at CT scans, according to literature: instead, they had various abnormalities in lungs high-resolution CT (HRCT). Chest radiograph often shows diffuse reticular and nodular opacities. HRCT commonly shows interlobular septal thickening and ground-glass centrilobular micronodules

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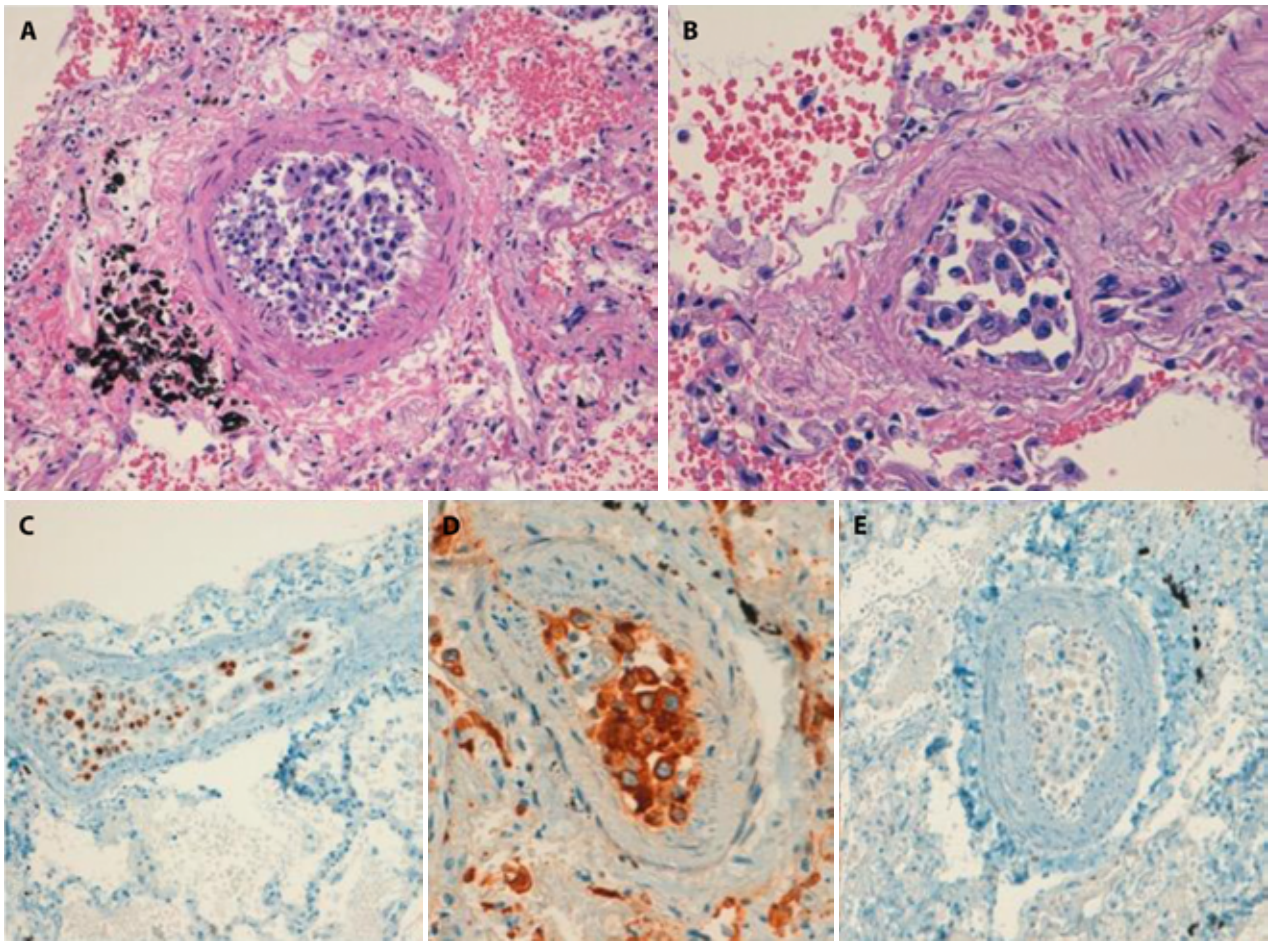

Figure 1. Histopathological findings of pulmonary tumour thrombotic microangiopathy. (a) 200x and (b) 400x Haematoxylin Eosin staining of lung tissue showing carcinoma cells in pulmonary arterioles. Carcinoma cells were positive for (c) cytokeratin AE1/AE3 and (d) p63 and negative (e) for cytokeratin CK5/6.

(representing fibrocellular intimal hyperplasia of pulmonary arteries in response to embolized tumour cells). Mediastinal and hilar lymphadenopathies are common findings, as malignancy spreads.

Recently the so-called "vascular tree-in-bud pattern" has been described in HRCT findings in PTTM. Typically, tree-in-bud pattern consists of the association of centrilobular nodules at the extremity of branching linear opacities (caused by dilatation and filling of the small airways) and has been described exclusively in small airways disease, but it not should no longer be considered specific for bronchiolar disease (3). Because pulmonary arteries are parallel to the bronchi, this pattern should also be seen in arterial disorders characterized by vascular dilatation or filling by tumour cells (Figure 2). Meanwhile, there is growing evidence of another type of vascular tree-in-bud due to SARS-CoV-2 infection, which causes significant vascular damage, leading to pulmonary angiopathy (4). Two of our cases (28%) at the onset of symptoms also tested positive for Sars-Cov2 infection. Chest CT findings of pulmonary embolism and right heart failure are evidenced by right ventricular enlargement, prominent pulmonary artery trunk, deviation of the interventricular septum, and reflux of contrast into the inferior vena cava (sensitivity 87%; specificity of 89%). All of our patients showed a vascular tree-in-bud pattern, associated with ground-glass opacities and diffuse inter-intralobular septal thickening and clear radiological signs of right heart failure.

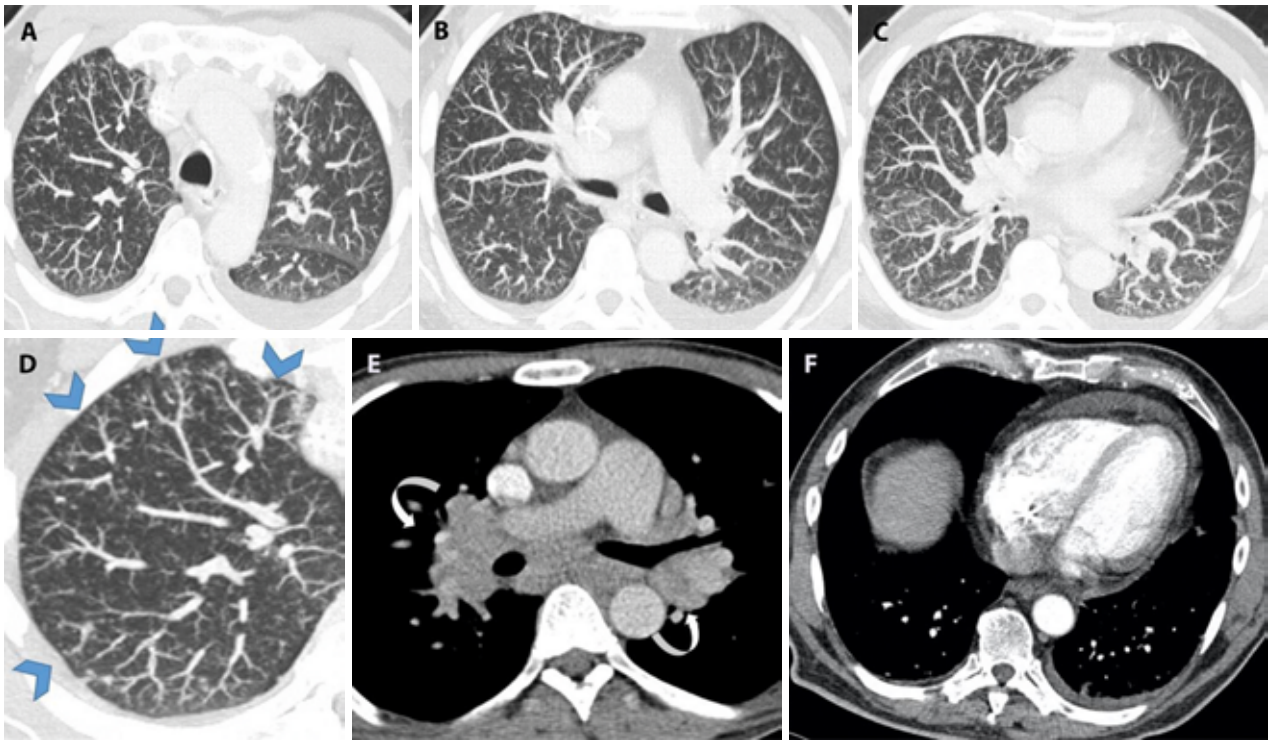

Figure 2. A 50-year-old male comes to our ED with a non-productive cough, dyspnoea for minimal effort, and marked asthenia. Axial MIP reconstructions (a-b-c-d) show better the vascular tree-in-bud pattern (blue arrowheads). Contrast-enhanced CT scan with a mediastinal window shows large bilateral lymphadenopathies (white arrows in "e"); right-heart enlargement and pericardial effusion are also visible (f).

Today, only the histopathological study allows to reach a definitive diagnosis, to make an early antemortem diagnosis. The biopsy is usually performed with wedge resection, VATS, CT-guided biopsy, or transbronchial access, if safely permissible depending on the patient's clinical symptoms and pulmonary pressures (5). None of our patients were eligible for these invasive diagnostic procedures because of the rapid worsening of dyspnoea and their bad performance status. Making an antemortem diagnosis or having high clinical-radiological suspicion of PTTM in addition to administering adequate treatment is mandatory for improving the prognoses of such patients. Although no definite treatment had been established, it is known that chemotherapy associated with anticoagulation protocols and corticosteroids may prolong the survival period. Treatment with Imatinib has been recently reported to be effective in patients with PTTM (6). Almost all patients (more than 90%) rapidly succumb to death due to severe hypoxia within one-two week after the onset of dyspnoea. All of our patients died after an average of 13.8 days after hospitalization.

Radiologists should remember that tumour microembolization in the pulmonary arteries may present with "vascular tree-in-bud" appearance, which should no longer be considered specific for bronchiolar disease. The search for primary cancer, if unknown, is mandatory to establish an early antemortem diagnosis and select optimal treatment, avoiding ineffective therapies. Furthermore, interdisciplinary research is essential, with a close collaboration between clinicians, radiologists, and pathologists.

Compliance with Ethical Standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

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