The many faces of pulmonary tumor embolism

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Learning objectives

1. To give an overview of the clinical findings.
2. To illustrate the CT and pathological findings.
3. To emphasize the differential diagnosis
Background

Pulmonary tumor emboli (PTE) are grouped into two main categories: large, proximal emboli and smaller emboli in the microvasculature. Although usually considered rare, PTE are found in up to 26% of autopsies of patients who die from cancer. Autopsy often reveals intravascular pulmonary metastases, particularly in patients with choriocarcinoma or breast, stomach, liver, kidney, lung, or prostate cancer.

Tumor emboli in the pulmonary arteries may manifest with various patterns on CT, depending on the size of the vessels affected. Occasionally, pulmonary tumor embolism may be the first sign of occult malignancy, mainly in patients presenting pulmonary tumor thrombotic microangiopathy (PTTM).

PTTM is rare; histologically, it is characterized by proliferation of intimal myofibroblasts in the small pulmonary arterioles, induced by tumor microemboli. Patients develop rapidly progressive and severe cardiopulmonary failure, usually leading to death.
Findings and procedure details

Clinical findings:

The clinical presentation of PTE depends on the number of vessels affected; patients may be asymptomatic or, in the case of disseminated PTTM, present significant dyspnea.

The main clinical sign is subacute, progressive dyspnea with hypoxemia and tachycardia, but its course may also be acute. Clinically, PTE and pulmonary thromboembolism are nearly indistinguishable, and PTE is often mistaken for thromboembolism.

Pulmonary tumor microembolism is an under-recognized cause of respiratory failure in patients with cancer.

The mean age of PTTM patients is 52.4 years and men are affected more frequently than women.

PTTM causes increased vascular resistance, resulting in severe clinical manifestations, including a new onset of dyspnea, acute worsening of chronic dyspnea, rapidly deteriorating hypoxia, pulmonary hypertension (PH), right-side-heart failure with cor pulmonale, and sudden death. PTTM can occur in patients with widespread incurable cancer, a history of malignant disease, or occasionally as the first symptom of occult malignancy.

Because antemortem diagnosis of PTTM is rare and difficult, knowledge is largely derived from postmortem examinations.

Miyano et al. reported an interesting case in which PTTM was diagnosed antemortem, and the patient survived after chemotherapy. The patient had not developed PH. This case emphasizes the clinical importance of antemortem diagnosis and management of PTTM before PH develops.

Radiological findings:

The radiologic diagnosis of PTE is difficult because the findings are often minimal or nonspecific.

Chest plain films could show nonspecific bilateral pulmonary opacities or small nodules (due to the beaded arteries or the vascular tree-in-bud sign) Fig. 1 on page 7, Fig. 2 on page 7.

On CT scans, PTE may manifest with various patterns, depending on the size of the vessels affected:
• Large emboli in the main, lobar, or segmental pulmonary arteries cause filling defects that mimic acute pulmonary thromboembolism.
• Small emboli that affect subsegmental arteries produce multifocal dilation or beading of vessels. **Fig. 3 on page 8, Fig. 4 on page 9, Fig. 5 on page 10, Fig. 6 on page 11.**
• Microscopic emboli (PTTM) cause consolidation, ground-glass opacity, small nodules, and a vascular tree-in-bud appearance (due to the involvement of the secondary pulmonary lobule arterioles) as well as signs of PH and of malignancy (lymphadenopathy, masses, etc). Case 1 **(Fig. 7 on page 12, Fig. 8 on page 13, Fig. 9 on page 14, Fig. 10 on page 15, Fig. 11 on page 16, Fig. 12 on page 17.)** and case 2 **(Fig. 13 on page 18, Fig. 14 on page 19, Fig. 15 on page 20, Fig. 16 on page 21, Fig. 17 on page 22, Fig. 18 on page 23, Fig. 19 on page 24 ).**

The tree-in-bud pattern, widely described in disorders of the small airways, consists of centrilobular nodules at the tips of branching linear opacities. Diverse entities manifest with this pattern on CT. When bronchial thickening is present and multiplanar reconstructions show filled distal bronchial structures, the tree-in-bud pattern points to bronchial disease.

The tree-in-bud pattern can also have vascular causes, such as distal PTTM. Thin slices and MIP reconstructions are essential to show dilations of the distal pulmonary arteries. Another feature that helps in the differential diagnosis with tree-in-bud due to bronchial disease is the lack of changes in the bronchi.

In patients with dyspnea, the tree-in-bud sign should prompt a search for signs of PH (dilation of central pulmonary arteries and repercussion in the right heart chambers) and signs of malignancy.

Ventilation-perfusion lung scans may be useful, usually demonstrating multiple distal perfusion defects.

**Pathological findings:**

In PTTM, tumor cells metastasize to the pulmonary vascular system at a microscopic level and adhere to the vascular endothelium. Isolated tumor cells or small clumps of cells can be seen within the lumen or attached to the endothelial layer. **Fig. 20 on page 25, Fig. 21 on page 26, Fig. 22 on page 27, Fig. 23 on page 28.**

Although tumor cells in PTTM invade the pulmonary vascular system and occlude the small arteries and arterioles, PTTM involves more than the simple mechanical obstruction of vessels. Tumor cells activate coagulation systems that release inflammatory mediators and growth factors like serotonin, vascular endothelial growth factor (VEGF), and osteopontin, resulting in deposition of platelets and fibrin, fibrocellular intimal proliferation,
and smooth muscle colonization. These processes lead to diffuse narrowing of the pulmonary arteriolar system and increased vascular resistance, resulting in marked PH.

Obstruction of small pulmonary arteries by intimal proliferation is often combined with secondary thrombosis at the surface of tumor emboli.

Although lymphangitis carcinomatosa is sometimes found together with PTTM, apparently there is no direct relation between the two.

In PTTM, tumor cells express VEGF and TF, and the TF-VEGF system, especially VEGF, seems to be involved in the pathogenesis of PTTM.

Whereas clinical manifestations of PTTM appear acutely or subacutely, fibrocellular and fibromuscular intimal proliferation build up over a relatively long time, so PTTM should be considered in biopsy interpretation, even when no known cancer is present.

**Differential diagnosis:**

The differential diagnosis of PTE should include:

- Pulmonary embolism
- Bronchial causes of the tree-in-bud pattern: peripheral airway diseases such as infection (bacterial, fungal, viral, or parasitic), congenital disorders, idiopathic disorders (obliterative bronchiolitis, panbronchiolitis), aspiration or inhalation of foreign substances, immunologic disorders, and connective tissue disorders.
- Other vascular causes of tree-in-bud: excipient lung disease, related to intravenous injection of oral tablets containing filler material (insoluble excipients such as starch, cellulose, or talc). Excipients can lodge into pulmonary arterioles and induce a potentially fatal foreign-body reaction. This excipient lung disease manifests on CT with a vascular tree-in-bud pattern associated with diffuse centrilobular nodules and signs of PH.
- Other causes of PH.

PTTM should be considered in the differential diagnosis of acute/subacute cor pulmonale and PH in patients with known cancer and in those without. MIP reformations are essential to visualize the vascular tree-in-bud.

The accompanying signs of malignancy provide a clue to the diagnosis.
Fig. 1: 81 year-old-woman with PTTM, was first admitted for recurrent asthma. Chest X-ray shows a nodular pattern and pulmonary infection was initially suspected. Treatment with antibiotics and a steroid was started. Nodular pattern is due to tree-in-bud appearance.

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Fig. 2: 51 years old man with PTTM. Arrives without previous clinical history for acute respiratory failure and syncope. Chest X-ray shows bilateral nonspecific opacities and micronodular pattern.

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Fig. 3: 71-year-old man with stage IV lung cancer and pulmonary metastases. Axial MIP CT image (lung window) show beaded arteries in the left lower lobe, indicating intravascular pulmonary metastases (red arrow)

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Fig. 4: 71-year-old man with stage IV lung cancer and pulmonary metastases. Sagittal MIP CT image (lung window) show beaded artery in the left lower lobe, indicating intravascular pulmonary metastases (red arrow)

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Fig. 5: 62-year-old woman with GIST tumor arrives for dyspnea. Axial MIP CT image (lung window) show small tumor emboli that affect subsegmental arteries (arrow). The finding of dilated and beaded peripheral pulmonary arteries in a patient with a known malignancy is highly suggestive of metastatic intravascular tumor emboli.

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**Fig. 6:** 62-year-old woman with GIST tumor arrives for dyspnea. Axial MIP CT image (lung window) show small tumor emboli that affect subsegmental arteries (arrows). The finding of dilated and beaded peripheral pulmonary arteries in a patient with a known malignancy is highly suggestive of metastatic intravascular tumor emboli.

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**Fig. 7:** 81 year-old-woman with PTTM, was first admitted for recurrent asthma. CT without contrast shows signs of pulmonary hypertension with significant dilation of pulmonary trunk.

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Fig. 8: 81 year-old-woman with PTTM, was first admitted for recurrent asthma. Thin-section pulmonary CT lung window, show multiple small nodules and tree-in-bud pattern (green arrows).

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Fig. 9: 81 year-old-woman with PTTM, was first admitted for recurrent asthma. Axial MIP CT image (lung window) reveals small nodules and a vascular tree-in-bud appearance (arrow) (the vascular tree-in-bud appearance is due to the involvement of the arterioles in the secondary pulmonary lobule). MIP reconstructions are essential to confirm a vascular tree-in-bud appearance.

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Fig. 10: 81 year-old-woman with PTTM, was first admitted for recurrent asthma. Coronal MIP CT image (lung window) reveals small nodules and a vascular tree-in-bud appearance (the vascular tree-in-bud appearance is due to the involvement of the arterioles in the secondary pulmonary lobule). MIP reconstructions are essential to confirm a vascular tree-in-bud appearance.

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Fig. 11: 81 year-old-woman with PTTM, was first admitted for recurrent asthma. Coronal MIP CT image (lung window) reveals small nodules and a vascular tree-in-bud appearance (the vascular tree-in-bud appearance is due to the involvement of the arterioles in the secondary pulmonary lobule). MIP reconstructions are essential to confirm a vascular tree-in-bud appearance.

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Fig. 12: 81 year-old-woman with PTTM, was first admitted for recurrent asthma. Abdominal CT shows periaortic pathologic lymphadenopathy suggestive of malignancy. The histological findings reveal squamous carcinoma of gynecologic origin (cervix). The patient died two months later.

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**Fig. 13:** Pulmonary tumor thrombotic microangiopathy caused by unknown gastric tumour in a 51-year-old man. Thin CT-section (lung window) was described as a disorder of the small airways with diffuse centrilobular nodules and MIPs CT images were not done.

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Fig. 14: Pulmonary tumor thrombotic microangiopathy caused by unknown gastric tumour in a 51-year-old man. The patient died two days later and with the suspicious of PTTM, MIP CT images (lung window) were done and show diffuse vascular tree-in-bud pattern.

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Fig. 15: Pulmonary tumor thrombotic microangiopathy caused by unknown gastric tumour in a 51-year-old man. The patient died two days later and with the suspicious of PTTM, MIP CT images (lung window) were done and show diffuse vascular tree-in-bud pattern.

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Fig. 16: Pulmonary tumor thrombotic microangiopathy caused by unknown gastric tumour in a 51-year-old man. The patient died two days later and with the suspicious of PTTM, MIP CT images (lung window) were done and show diffuse vascular tree-in-bud pattern.

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Fig. 17: Pulmonary tumor thrombotic microangiopathy caused by unknown gastric tumour in a 51-year-old man. Contrast-enhanced pulmonary CT angiogram shows signs of pulmonary hypertension with dilation of pulmonary trunk (largest diameter compared with the ascending aorta diameter).

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Fig. 18: Pulmonary tumor thrombotic microangiopathy caused by gastric tumour in a 51-year-old man. Contrast-enhanced pulmonary CT angiogram shows signs of marked dilation of the right cavities with flattening of the interventricular septum.

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Fig. 19: Pulmonary tumor thrombotic microangiopathy caused by unknown gastric tumour in a 51-year-old man. CT (mediastinal window) shows pathologic mediastinum and axillary lymphadenopathy suggestive of malignancy (arrows). The patient died two days later and an autopsy was performed.

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Fig. 20: Pulmonary tumor thrombotic microangiopathy caused by unknown gastric tumour in a 51-year-old man. Histopathological findings of the lung specimens obtained at autopsy. Tumor embolism (black arrow) in the pulmonary arterioles with fibrocellular intimal proliferation (blue arrows). (Hematoxylin and Eosin staining, ×40)

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Fig. 21: Pulmonary tumor thrombotic microangiopathy caused by unknown gastric tumour in a 51-year-old man. Histopathological findings of the lung specimens obtained at autopsy. Neoplastic intravascular cells (asterisk)(Hematoxylin and Eosin staining, ×200).

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Fig. 22: Pulmonary tumor thrombotic microangiopathy caused by unknown gastric tumour in a 51-year-old man. Immunophenotype of the tumoral emboli consistent with gastric adenocarcinoma: CK7 positive (x200).

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Fig. 23: Pulmonary tumor thrombotic microangiopathy caused by unknown gastric tumour in a 51-year-old man. Immunophenotype of the tumoral emboli consistent with gastric adenocarcinoma: CK20 focally positive (x 200).

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Conclusion

The radiological diagnosis of PTE may be difficult, particularly in the case of PTTM (multiplanar and MIP reconstructions are essential); awareness of the clinical findings can help ensure timely and appropriate management as well as a more favorable prognosis.

PTTM is a rare condition with very high mortality. It should be distinguished from ordinary pulmonary thromboembolism and primary PH and should be considered in the differential diagnosis in patients with acute respiratory symptoms, especially in cases with an underlying cancer but also in those without.

PTTM requires interdisciplinary teamwork, with close collaboration between pathologists and clinicians.
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