

# Intravascular Small Cell Carcinoma Disguised as Pulmonary Embolism

Ariel Rokach MD MHA<sup>1,6</sup>, Sarit Hochberg-Klein MD<sup>5,6</sup>, Nissim Arish MD<sup>1,6</sup>, Victoria Doviner MD<sup>2,6</sup>, Rachel Bar-Shalom MD<sup>3,6</sup>, Yehonatan Turner MD<sup>3,6</sup>, Norman Heching MD<sup>4,6</sup>, and Samuel N. Heyman MD<sup>5,6</sup>

<sup>1</sup>Pulmonary Institute and Departments of <sup>2</sup>Pathology, <sup>3</sup>Nuclear Medicine, and <sup>4</sup>Oncology, Shaare Zedek Medical Center, Jerusalem, Israel

<sup>5</sup>Department of Medicine, Hadassah-Hebrew University Medical Center, Mount Scopus, Jerusalem, Israel

<sup>6</sup>Hebrew University–Hadassah Medical School, Jerusalem, Israel

**KEY WORDS:** D-dimer, intravascular, malignancy, neuroendocrine tumor, thromboembolism  
*IMAJ 2021; 23: 52–54*

Pulmonary thromboembolism (PE) is a common disease entity with protean manifestations [1]. Yet it is often asymptomatic or presents with subtle symptoms, leading to misdiagnosis or under-diagnosis. Thus, PE detection remains a formidable challenge in clinical practice with failed identification often leading to grave outcome. Contrast-enhanced computed tomography (CT) became the gold standard in the diagnosis of PE, and once recognized, other diagnostic tools, including D-dimer blood test, pulmonary ventilation-perfusion scan or venous Doppler-ultrasound study (Duplex) are needless [1].

Yet, filling defects within the pulmonary vasculature, once detected, are not unequivocally diagnostic for thromboemboli. We report a patient presented with pleuritic pain and with filling defects on CT compatible with PE, that were found to represent primary intravascular small cell carcinoma.

## PATIENT DESCRIPTION

A 63-year-old previously healthy female non-smoker complained of left pleuritic chest pain and night sweats for a month. The patient denied dyspnea, cough, fever, palpitations, or symptoms of venous thrombosis. Chest X-rays performed by

her family practitioner disclosed left lung opacities and she was treated with antibiotics for presumed community acquired pneumonia for 2 weeks without improvement and was therefore referred to the emergency department.

Physical examination was unremarkable, other than a few crackles on the lower left hemithorax, which were compatible with radiological findings in the left lower lobe and lingula. Contrast-enhanced CT was performed, considering a wide range of differential diagnoses, including non-resolving infections, as well as malignant, inflammatory, and thromboembolic disorders. It revealed filling defects within the left main pulmonary artery, accompanied with consolidations compatible with pulmonary embolus and infarction [Figure 1A]. The unusual presentation and the peculiar confluent filling defect within the left pulmonary vasculature, without additional scattered defects elsewhere, led us to challenge the diagnosis: Indeed, D-dimer test, performed immediately on admission (before the development of false-positive results along the hospitalization course) was normal, suggesting a non-thrombotic lesion. Furthermore, the pulmonary filling defect remained unchanged during 2 weeks on anticoagulation. <sup>18</sup>F-fluorodeoxyglucose positron-emission tomography/computed tomography (<sup>18</sup>F-FDG PET/CT) scan showed pathological uptake in the left pulmonary artery [Figure 1B] and in the cerebral frontal lobe. Magnetic resonance imaging confirmed

the brain metastasis. Endovascular biopsy from the pulmonary artery revealed poorly differentiated neuroendocrine carcinoma, small-cell type [Figure 1C]. Chemotherapy was initiated (etoposide and carboplatin) and the brain lesion was irradiated, with subsequent resolution of these lesions on follow-up PET/CT scans [Figure 1B]. The patient has been in partial remission on checkpoint immune inhibitors for over 2 years.

## COMMENT

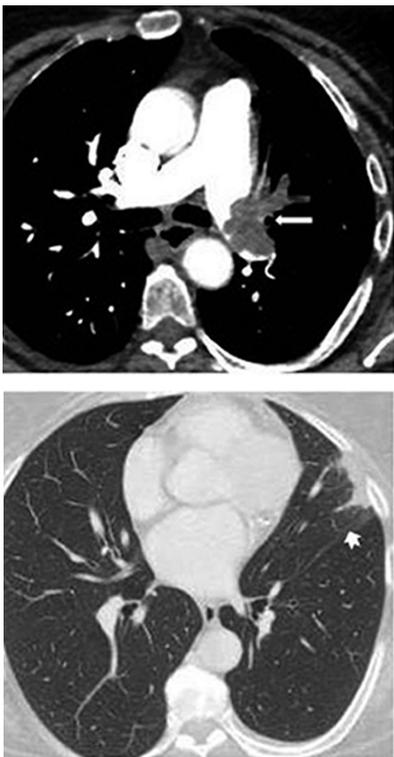
Thromboembolism is by far the most common cause of intraluminal filling defects detected by CT within the pulmonary vasculature [1]. Yet, other rare causes should be considered, such as in situ thrombus formation related to Behçet's disease with pulmonary vasculitis, embolized echinococcal daughter-cysts, or non-thrombotic malignant diseases.

Neoplastic involvement of the pulmonary trunk has diverse manifestations. Microvascular obliteration by intraluminal metastases may rarely occur, particularly in the case of mucinous adenocarcinoma [2]. They are not detected by contrast-enhanced imaging and are clinically manifested as progressive unexplained pulmonary hypertension.

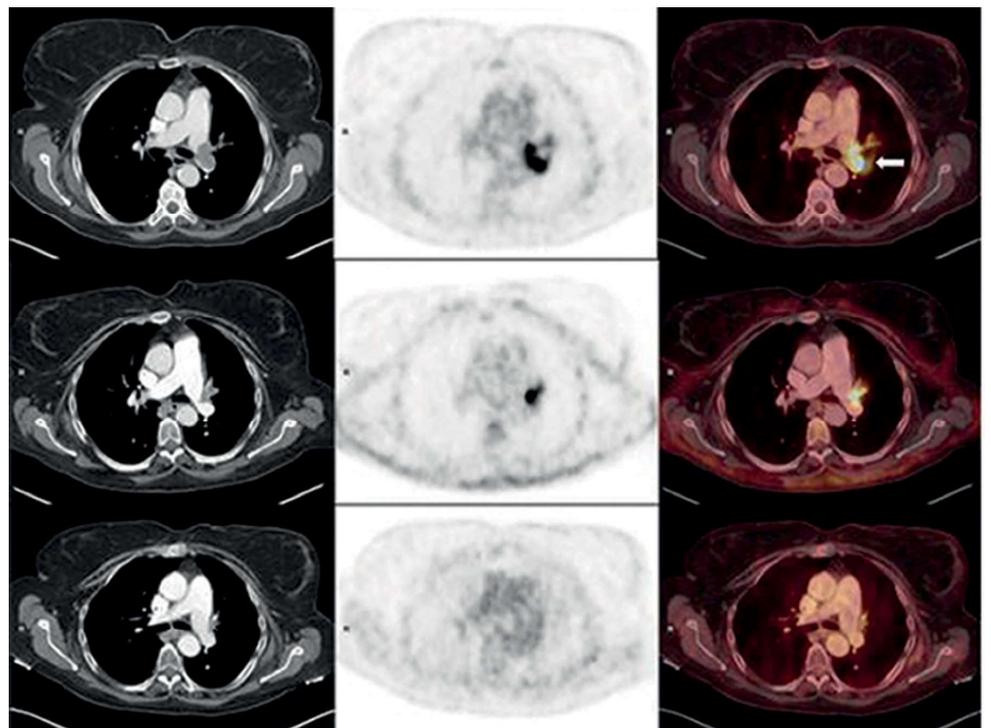
Occasionally, embolic venous spread to the pulmonary vasculature may originate from renal clear-cell carcinoma or right ventricular myxomas. Our case communication illustrates an additional rare pattern of pulmonary intravascular neo-

**Figure 1.** Radiological and morphological findings

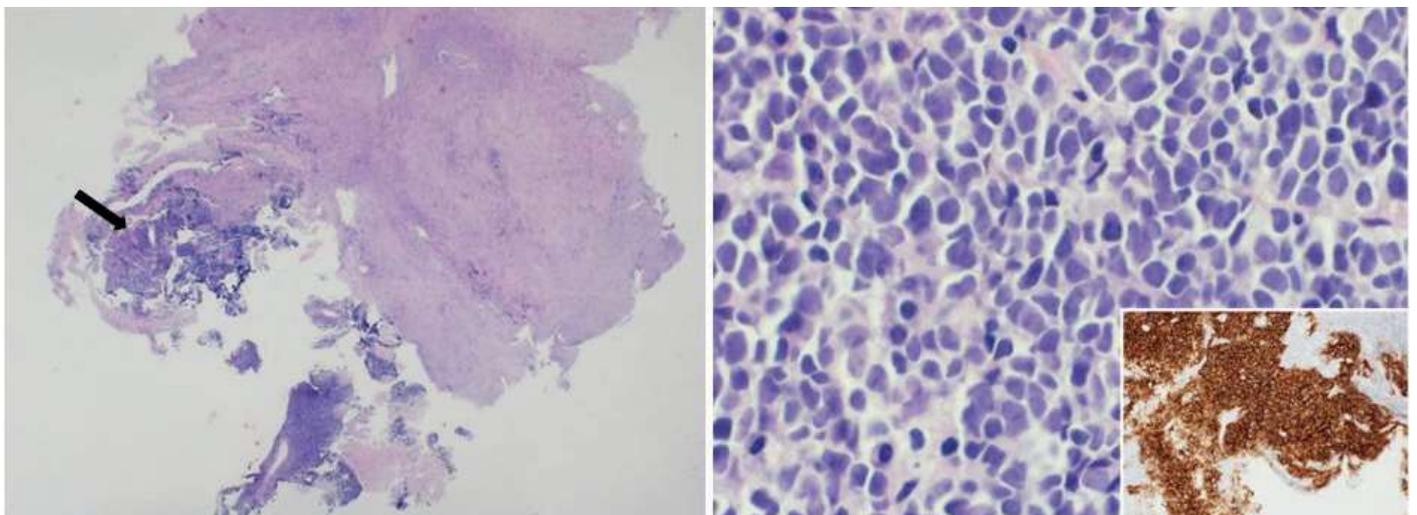
**[A]** Computed tomography scan disclosing a large confluent filling defect in the left main pulmonary artery (arrow), extending into lobar arteries, associated with peripheral consolidation-atelectasis of the left upper lobe (arrowhead)



**[B]** An Intense pathological uptake in a hypodense lobular process within the left main pulmonary artery and its lobar branches is demonstrated on axial computed tomography (CT) (left), <sup>18</sup>fluorodeoxyglucose positron-emission tomography (<sup>18</sup>FDG PET) (middle) and fused <sup>18</sup>FDG PET/CT (right, arrow) images at presentation (upper row), consistent with malignancy. Significant partial response with only residual pathological uptake within a smaller intravascular lesion is seen after 2 months of chemotherapy (cisplatin, etoposide) and chest irradiation of 45 Gray (middle row), followed by complete resolution of findings 4 months later (lower row). The brain metastasis resolved as well following irradiation of 30 Gray.



**[C]** Endovascular biopsy of pulmonary artery mass showing tumor fragments (arrow) attached to the intima (H&E, original magnification ×12.5). On large magnification the tumor cells exhibit morphological features typical for a small cell carcinoma (H&E, original magnification ×400). Inset: Immunostaining for CD56 establishes the neuroendocrine origin of the tumor cells (original magnification ×100)



plastic lesion, namely a primary intraluminal malignant process originating within the arterial wall. Pulmonary endovascular sarcoma has been encountered in most of these cases [3]. Our patient presented with small cell carcinoma of neuroendocrine origin forming a mass within the pulmonary artery, mimicking pulmonary embolus. To the best of our knowledge, only two comparable patients have been reported, so far [4,5], underscoring the very rare occurrence of this type of tumor arising within the pulmonary vasculature.

Noteworthy, a clinical suspicion regarding the neoplastic nature of the process had been adopted already at admission, based on the patient's symptoms, the absence of obvious predisposition to venous thromboembolism, the lack of symptoms suggesting venous thrombosis, and in particular the peculiar confluent pattern of the filling defect [Figure 1A] in the absence of additional scattered le-

sions within the pulmonary arterial ramifications.

Our suspicion was further strengthened by complementing our initial assessment using a D-dimer test. This diagnostic tool is usually used upstream in the diagnostic process of PE as an initial test before pulmonary angiogram. A negative D-dimer test is usually used to exclude PE when the pre-test probability for embolism is low [1], with highly specific true-negative results. As illustrated in our case report, D-dimer might also serve to exclude thromboembolic lesion when assessing already detected pulmonary intravascular defects with features suggesting a non-thrombotic nature.

#### CONCLUSIONS

We report on how intraluminal malignancies mimic pulmonary emboli, illustrating clinical clues. We suggest approaches in the diagnostic process.

#### Correspondence

Dr. S.N. Heyman

Dept. of Medicine, Hadassah-Hebrew University Medical Center, Mount Scopus, Jerusalem 91240, Israel  
Fax: (972-2) 584-4526

email: heyman@cc.huji.ac.il

#### References

1. Konstantinides S. Clinical practice. Acute pulmonary embolism. *N Engl J Med* 2008; 359 (26): 2804-13.
2. Pinckard JK, Wick MR. Tumor-related thrombotic pulmonary microangiopathy: review of pathologic findings and pathophysiologic mechanisms. *Ann Diagn Pathol* 2000; 4 (3): 154-7.
3. Srivali N, Yi ES, Ryu JH. Pulmonary artery sarcoma mimicking pulmonary embolism: a case series. *QJM* 2017; 110 (5): 283-6.
4. Kamigaki M, Yamazaki K, Tsujino I et al. Small cell carcinoma of the lung exclusively localized within the left descending pulmonary artery. *Chest* 2005; 127 (6): 2273-6.
5. Law T, Okiwelu L, Ardakani NM, et al. Unusual presentation of small cell lung cancer as a pulmonary tumour diagnosed after VATS pneumonectomy. *Heart Lung Circ* 2015; 24, Suppl1: e64.

**You are never too old to set another goal or to dream a new dream.**

C. S. Lewis (1898–1963), Irish novelist, scholar, and lay theologian

#### Capsule

### Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease

Adult-onset inflammatory syndromes often manifest with overlapping clinical features. Variants in ubiquitin-related genes, previously implicated in autoinflammatory disease, may define new disorders. Beck et al. identified 25 men with somatic mutations affecting methionine-41 (p.Met41) in *UBA1*, the major E1 enzyme that initiates ubiquitylation. (The gene *UBA1* lies on the X chromosome.) In such patients, an often fatal, treatment-refractory inflammatory syndrome develops in late adulthood, with fevers, cytopenias, characteristic vacuoles in myeloid and erythroid precursor cells, dysplastic bone marrow, neutrophilic cutaneous and pulmonary inflammation, chondritis, and vasculitis. Most of these 25 patients met clinical criteria for an inflammatory syndrome (relapsing polychondritis, Sweet's syndrome, polyarteritis nodosa, or giant-cell arteritis) or a hematologic condition (myelodysplastic syndrome or multiple myeloma)

or both. Mutations were found in more than half the hematopoietic stem cells, including peripheral-blood myeloid cells but not lymphocytes or fibroblasts. Mutations affecting p.Met41 resulted in loss of the canonical cytoplasmic isoform of *UBA1* and in expression of a novel, catalytically impaired isoform initiated at p.Met67. Mutant peripheral-blood cells showed decreased ubiquitylation and activated innate immune pathways. Knockout of the cytoplasmic *UBA1* isoform homologue in zebrafish caused systemic inflammation. Using a genotype-driven approach, the authors identified a disorder that connects seemingly unrelated adult-onset inflammatory syndromes, and named this disorder the VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome.

*N Engl J Med* 2020; 383: 2628

Eitan Israeli