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PET-NEGATIVE LUNG ADENOCARCINOMA ARISING WITHIN A BENIGN-APPEARING PULMONARY BULLA: A RARE CASE OF SYNCHRONOUS PRIMARY LUNG CANCERS

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ABSTRACT

Lung cancer associated with cystic airspaces (LC-CAS) represents an uncommon and often under-recognized presentation of lung adenocarcinoma in which tumor growth occurs within or along the wall of a pre-existing cystic airspace, including emphysematous bullae. Because these lesions may appear as thin-walled benign structures on CT and may lack fluorodeoxyglucose (FDG) uptake on PET/CT, they pose a significant diagnostic challenge.

We describe a rare case of synchronous primary lung adenocarcinomas in a 75-year-old man: a PET-avid solid mass in the left lower lobe and a second PET-negative invasive adenocarcinoma arising along the wall of an apical pulmonary bulla in the left upper lobe. Despite its benign radiologic appearance and absence of metabolic activity, histopathology confirmed the presence of invasive malignancy.

This case highlights that PET negativity does not reliably exclude malignancy in cystic lung lesions and underscores the necessity of meticulous CT evaluation and multidisciplinary correlation to prevent delayed or missed diagnosis.

Keywords: Lung adenocarcinoma; pulmonary bulla; cystic airspace; PET-negative; synchronous primary lung cancer.

1. INTRODUCTION

Lung adenocarcinoma is the most common subtype of non–small cell lung cancer and is increasingly detected incidentally with high-resolution CT and PET/CT[1]. A small subset of these tumors arises in association with pre-existing cystic airspaces, a presentation referred to as lung cancer associated with cystic airspaces (LC-CAS), accounting for approximately 3–4% of primary lung cancers[2].

LC-CAS refers to malignancies that develop within or adjacent to cystic airspaces, including both true pulmonary cysts and emphysematous bullae[2],[3]. Although pulmonary bullae are frequently regarded as benign structural changes—particularly in elderly patients—carcinoma may arise along their walls. Because these lesions may retain a thin wall and lack an obvious solid component, they can closely mimic benign airspaces on CT. Suspicious imaging features include asymmetric wall thickening, mural nodules, irregular margins, or surrounding ground-glass opacity[2]. Importantly, the absence of FDG uptake on PET/CT does not reliably exclude malignancy, especially in lesions with low tumor cellularity or predominant lepidic growth[4].

We report a rare case of synchronous primary lung adenocarcinomas in a 75-year-old man, including a PET-avid solid tumor in the left lower lobe and a second PET-negative invasive adenocarcinoma arising along the wall of a benign-appearing apical pulmonary bulla. This report aims to highlight the diagnostic challenges associated with LC-CAS and to emphasize the importance of careful evaluation of cystic airspaces, even when metabolically inactive.

2. CASE REPORT

A 75-year-old man with no prior history of malignancy and no active smoking history presented with chronic, nonspecific back discomfort. He denied any known chronic lung disease. Physical examination and laboratory findings were unremarkable.

A non-contrast chest CT performed for symptom evaluation incidentally revealed a well-defined 3.2-cm

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solid mass in segment S10 of the left lower lobe, in close contact with the mediastinal pleura but separated from the descending thoracic aorta by a preserved fat plane (Figure 1).

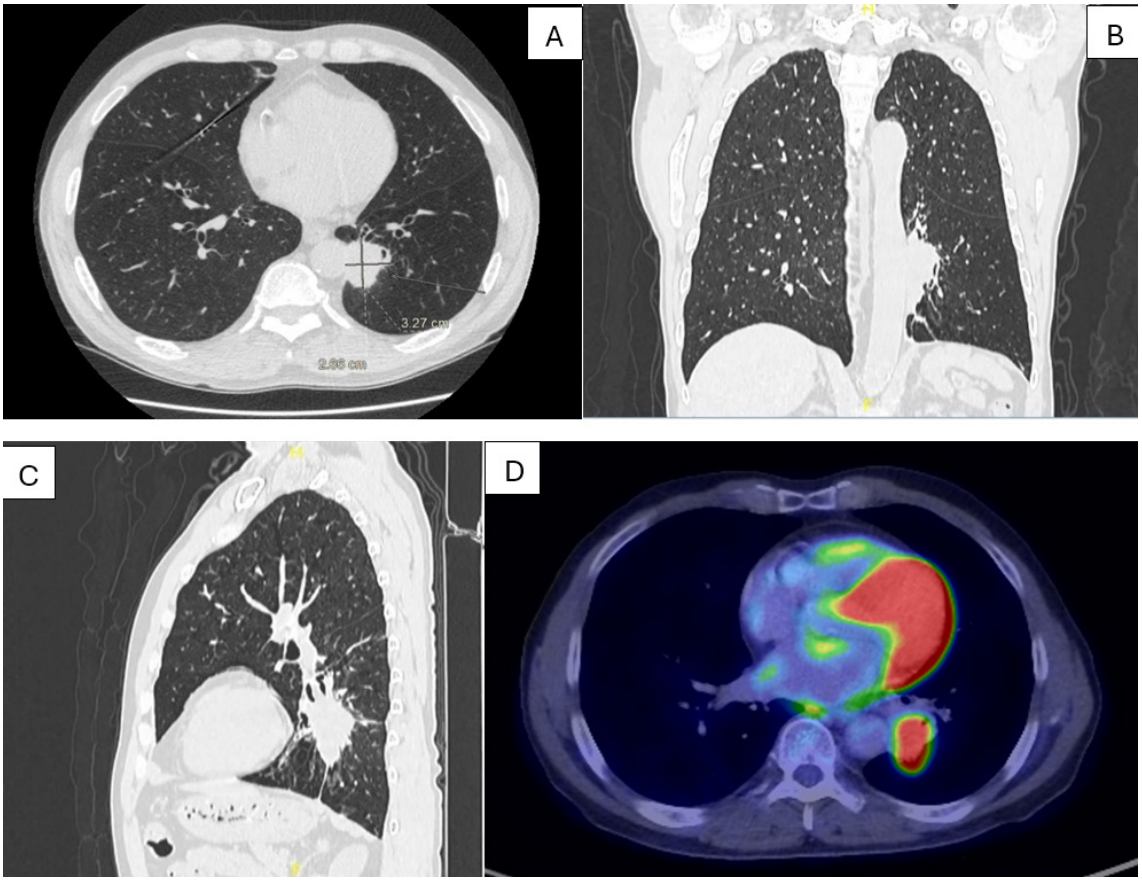

Figure 1. (A–C) Non-contrast chest CT scan (axial, coronal, sagittal views) showing a 3.2 cm solid, well-defined pulmonary mass in segment S10 of the left lower lobe, abutting the mediastinal pleura and adjacent to the descending thoracic aorta. The fat plane between the mass and the aorta is preserved. (D) PET/CT scan demonstrating intense FDG uptake in the left lower lobe mass with a SUVmax of 10.6.

Additional CT findings included several small bilateral pulmonary nodules, patchy ground-glass opacities, mild interstitial thickening, and multiple thin-walled emphysematous bullae in the apical region of the left upper lobe. Among these, a 14.6 mm thin-walled apical bulla demonstrated no focal wall thickening or internal nodularity (Figure 2). PET/CT showed intense FDG uptake in the left lower lobe mass (SUVmax 10.6), with suspected involvement of the left inferior pulmonary vein. In contrast, the apical bullae demonstrated no abnormal FDG uptake.

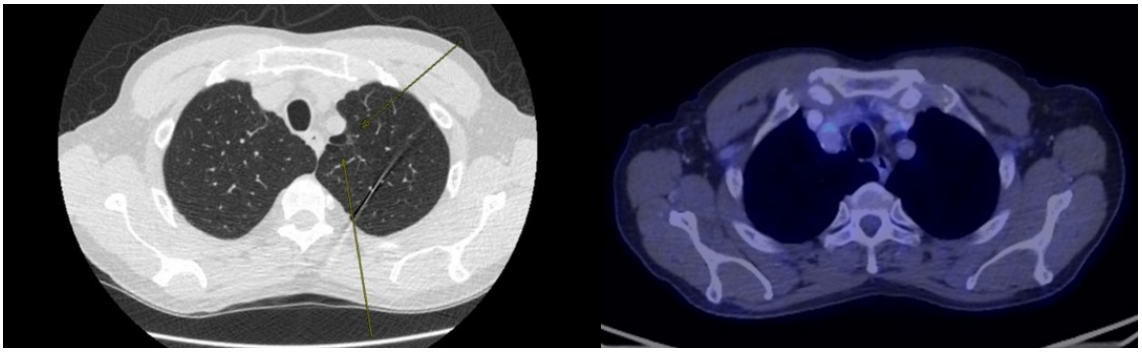

Figure 2. (A) Non-contrast chest CT (axial view) demonstrating multiple thin-walled emphysematous bullae in the apical segment of the left upper lobe. The largest bulla measures approximately 14.6 mm in diameter and shows no focal wall thickening or internal nodularity. (B) PET/CT scan showing no abnormal FDG uptake within these bullous changes.

A transthoracic core needle biopsy confirmed invasive adenocarcinoma with an acinar growth pattern, and the tumor was staged clinically as cT2bN0M0 (AJCC 9th edition). After multidisciplinary discussion, the patient underwent video-assisted thoracoscopic surgery (VATS) with left lower lobectomy and systematic mediastinal lymph node dissection (Figure 3).

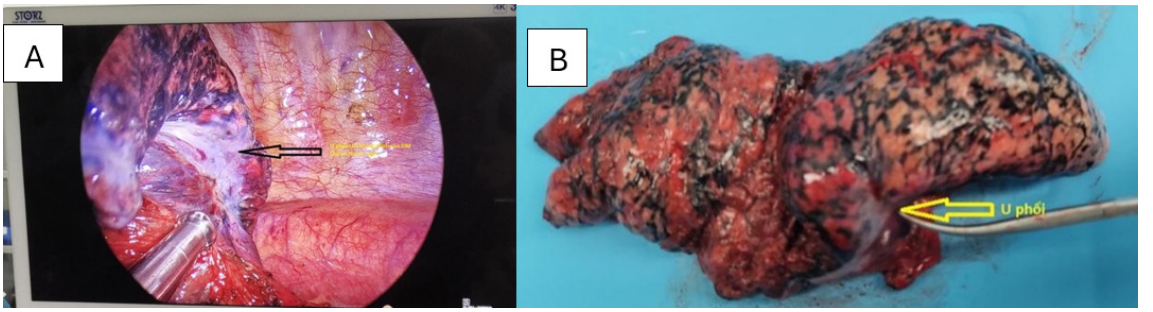

Figure 3. (A) Intraoperative view during video-assisted thoracoscopic surgery (VATS) demonstrating a well-circumscribed mass in the left lower lobe, located beneath the visceral pleura, without adhesions to the chest wall or the descending thoracic aorta. (B) Gross pathological specimen of the resected tumor, measuring approximately 5.5 cm in greatest dimension, showing marked visceral pleural retraction over the tumor surface.

During surgery, multiple apical bullae were observed in the left upper lobe. Although they appeared benign on inspection and palpation, a prophylactic wedge resection was performed to reduce the risk of postoperative pneumothorax (Figure 4).

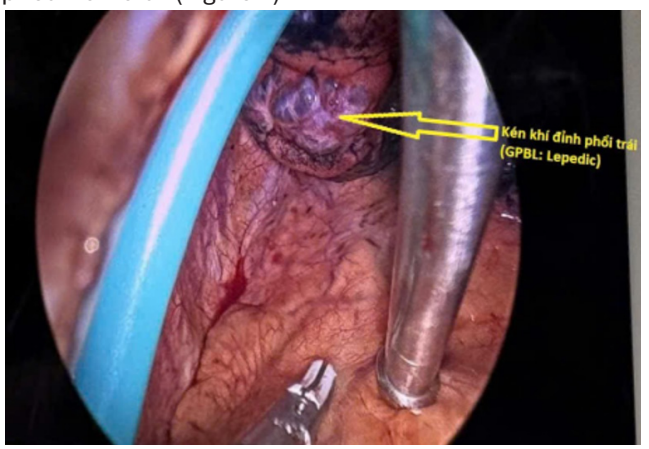

Figure 4. Intraoperative view showing multiple apical bullae in the left upper lobe.

Histopathologic examination of the left lower lobe mass revealed a moderately differentiated invasive adenocarcinoma, predominantly acinar (90%) with minor papillary and solid components. Lymphovascular and perineural invasion were present, and two of twenty lymph nodes (stations 7 and 10L) contained metastatic carcinoma, yielding a final pathologic stage of pT2bN2aM0.

Unexpectedly, histologic evaluation of the resected apical bulla demonstrated a second primary invasive adenocarcinoma measuring 15 mm in invasive size. The tumor exhibited a mixed lepidic (50%) and acinar (50%) growth pattern and was graded as moderately differentiated (G2). No lymphovascular, perineural, or pleural invasion was identified. The invasive component was completely excised; however, the lepidic component extended to the parenchymal margin, resulting in an R1 resection. No lymph nodes were sampled from the upper lobe.

A subsequent multidisciplinary review determined that the two tumors represented synchronous primary lung adenocarcinomas rather than intrapulmonary metastasis. This conclusion was supported by their distinct anatomic locations (different lobes), differing predominant histologic patterns, and discordant metabolic behavior on PET/CT, fulfilling the Martini–Melamed criteria [7]. The patient received adjuvant radiotherapy to the left upper lobe surgical bed due to the R1 margin and remains under close oncologic follow-up.

3. DISCUSSION

Lung cancer associated with cystic airspaces (LC-CAS) represents an uncommon imaging–pathologic presentation of lung carcinoma in which tumor growth occurs within or along the wall of a pre-existing cystic airspace.[2][3] This entity includes malignancies arising in association with both true pulmonary cysts and emphysematous bullae. Because these air-containing spaces are often interpreted as benign structural changes—particularly in elderly patients—early malignant involvement of the cyst or bulla wall may be overlooked. [2][5][3]

In the present case, the upper-lobe lesion appeared as a 14.6-mm thin-walled apical bulla without focal wall thickening or mural nodularity on CT and demonstrated no FDG uptake on PET/CT. Despite its benign radiologic appearance and absent metabolic activity, histopathologic examination revealed invasive adenocarcinoma growing along the bulla wall. This illustrates how LC-CAS may evade detection, even in patients already undergoing evaluation for a known primary lung malignancy.

Several CT morphologic patterns of LC-CAS have been described, but the classification proposed by Mascalchi et al. is the most widely adopted (Figure 5) [2]. While these patterns aid recognition, early-stage lesions

may lack overt solid components and instead mimic simple benign bullae. Consequently, diagnosis may depend on interval morphologic change or incidental surgical resection, as occurred in our patient.

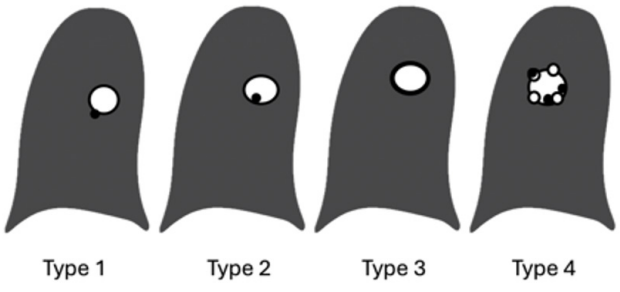

Figure 5: Four morphological patterns of cystic and cavitary lung cancer as classified by Mascalchi et al.[2]:

Type 1: *a nodule extruding from the wall of the cavitary lesion;*

Type 2: *a nodule protruding into the cystic lumen;*

Type 3: *focal or diffuse thickening of the cyst wall and/or associated soft-tissue density;*

Type 4: *a soft-tissue–density component intermixed within clusters of cystic or cavitary spaces.*

The pathogenesis of LC-CAS remains debated. Mascalchi et al. and Farooqi et al. proposed malignant transformation within the wall of a pre-existing cystic airspace, particularly in the context of emphysematous change or chronic lung injury [2][3]. Fintelmann et al., in contrast, suggested that early tumor growth may induce cystic remodeling through airway obstruction or parenchymal destruction [5]. In our patient, carcinoma was identified along the wall of a pre-existing emphysematous bulla; however, it cannot be definitively determined whether malignant transformation preceded cystic remodeling or vice versa.

A key feature of this case is the absence of FDG uptake in the upper-lobe lesion despite its invasive size of 15 mm. False-negative PET findings in lung adenocarcinoma are well documented, particularly in tumors with low cellular density, predominant lepidic growth pattern, or preservation of alveolar architecture.[4] In cyst-associated tumors, neoplastic cells may be distributed thinly along the bulla wall rather than forming a compact solid mass, thereby reducing overall metabolic activity. In addition, partial-volume effects may further decrease detectable FDG uptake in lesions with thin or peripheral tumor distribution. Therefore, PET negativity should not be interpreted as evidence of benignity in cystic lung lesions.

Management of isolated cystic lung lesions remains challenging, as no dedicated guidelines exist for purely cystic nodules. Suspicious CT features—including progressive wall thickening, development of internal nodularity, surrounding ground-glass opacity, or interval enlargement—should prompt closer surveillance. [3][5] In the absence of specific recommendations, management generally follows established guidelines for indeterminate pulmonary nodules, such as those of the Fleischner Society[6].

In this case, the cystic lesion was excised incidentally during prophylactic wedge resection and was unexpectedly diagnosed as a second primary adenocarcinoma. The distinct anatomic location, differing predominant histologic pattern, and discordant metabolic behavior supported the diagnosis of synchronous primary lung cancers according to the Martini–Melamed criteria .[7]

Overall, LC-CAS can closely mimic benign cystic lung lesions and may be metabolically silent on PET/CT. Careful CT evaluation of cystic airspaces, particularly in patients with known or suspected lung cancer, is essential to avoid delayed or missed diagnosis.

4. CONCLUSION

This case demonstrates that thin-walled emphysematous bullae, even when radiologically benign-appearing and PET-negative, may harbor invasive lung adenocarcinoma. As part of the spectrum of lung cancer associated with cystic airspaces (LC-CAS), such lesions can mimic simple benign airspaces and may lack detectable FDG uptake despite invasive histology.

In patients with known or suspected lung cancer, careful evaluation of cystic airspaces—including assessment of subtle wall changes and interval evolution—is essential. PET negativity should not provide false reassurance. Multidisciplinary correlation and appropriate imaging follow-up remain critical to prevent missed or delayed diagnosis of synchronous primary lung cancers.

Ethics

The study was conducted in accordance with the ethical regulations of Vinmec Times City International Hospital. The patient provided written informed consent for the publication of de-identified clinical information and images. The hospital granted permission for the use of clinical data. The authors declare no conflicts of interest.

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