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Lung: Case Report

# Benign Lung Adenoma Mimicking an Adenocarcinoma With *EML4-ALK* Gene Fusion

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**Bronchiolar adenoma is a benign neoplastic process thought to be derived from the bronchiolar epithelium. Particularly in small biopsy specimens, this entity can mimic lung cancer with important implications for management. We report the case of a 33-year-old man with a right upper lobe lung nodule, with initial biopsy identifying an adenocarcinoma with *EML4-ALK* gene fusion. After being considered for neoadjuvant targeted therapy trials, the patient underwent a lobectomy. On postoperative histologic evaluation, the patient was found to have a benign bronchiolar adenoma.**

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Bronchiolar adenoma is a relatively new entity proposed by Chang and coworkers[1] now recognized as a provisional entity in the fifth edition of the World Health Organization classification of pulmonary tumors. The term refers to a benign neoplastic proliferation of cells similar in appearance to bronchiolar epithelium. Here we present a case of bronchiolar adenoma, specifically a ciliated muconodular papillary tumor, in a young man that mimicked a lung adenocarcinoma with echinoderm microtubule-associated protein-like 4 (*EML4*) and anaplastic lymphoma kinase (*ALK*) gene fusion.

A 33-year-old man presented to thoracic surgery clinic for workup of a solitary pulmonary nodule incidentally found on a nuclear myocardial perfusion scan performed in preparation for a bariatric surgical procedure. He had a past medical history of obesity and reactive airway disease. There was no tobacco use history and no family history of lung cancer.

A positron emission tomography scan revealed a 1.6-cm solid nodule in the right upper lobe, with a standardized uptake value maximum of 2.3, but was otherwise negative for suspicious lesions. A follow-up computed tomography scan performed 1 month later showed a 1.7-cm nodule, which was interpreted as a possible lung neoplasm (Figure 1). Computed tomography-guided core biopsy demonstrated alveolar spaces and small acinar structures lined by hyperchromatic, mildly atypical nuclei suggestive of adenocarcinoma. The patient was diagnosed with clinical stage T1b N0 M0, stage IA2 non-small cell lung cancer (NSCLC).

Given his young age and lack of environmental and behavioral risk factors, it was thought that his tumor likely had a targetable gene mutation, and his biopsy specimen was sent for next-generation sequencing for potential enrollment in a therapeutic targeted therapy clinical trial. Molecular analysis demonstrated an *EML4-ALK* fusion. He was screened for a trial of neoadjuvant targeted therapy in patients with *ALK* mutation but was ineligible because of clinical stage <II.

The patient proceeded with an uncomplicated, minimally invasive right upper lobectomy (Figure 2) with mediastinal lymphadenectomy. On final pathologic examination, it was determined to be bronchiolar adenoma/ciliated muconodular papillary tumor, with no malignant transformation. The tumor had a heterogeneous appearance, in part composed of papillae (Figure 3A) lined by bland, mucinous, columnar epithelium with rare ciliated cells (Figure 3B). Other parts of the lesion were composed of an acinar-like proliferation with flat to cuboidal epithelium, few mucinous cells, stromal fibrosis between glands, inflammation, and focal nuclear atypia (Figure 3C). Focally, clusters of neoplastic cells resembling micropapillae were present within alveoli at the periphery of the lesion (Figure 3D). There was abundant extravasated mucin in the adjacent alveolar air spaces. Immunohistochemical staining for p63 highlighted a basal epithelial layer throughout the lesion. The luminal cells showed variable, weak expression of thyroid transcription factor 1 (TTF-1).

The acinar areas and detached intra-alveolar clusters were initially concerning for a mucinous adenocarcinoma. However, these features were discordant with the overall noninfiltrative nature of the lesion, the cytologically bland cells, and the bronchiolar phenotype with $p63^+$ basal cells throughout. These findings along with

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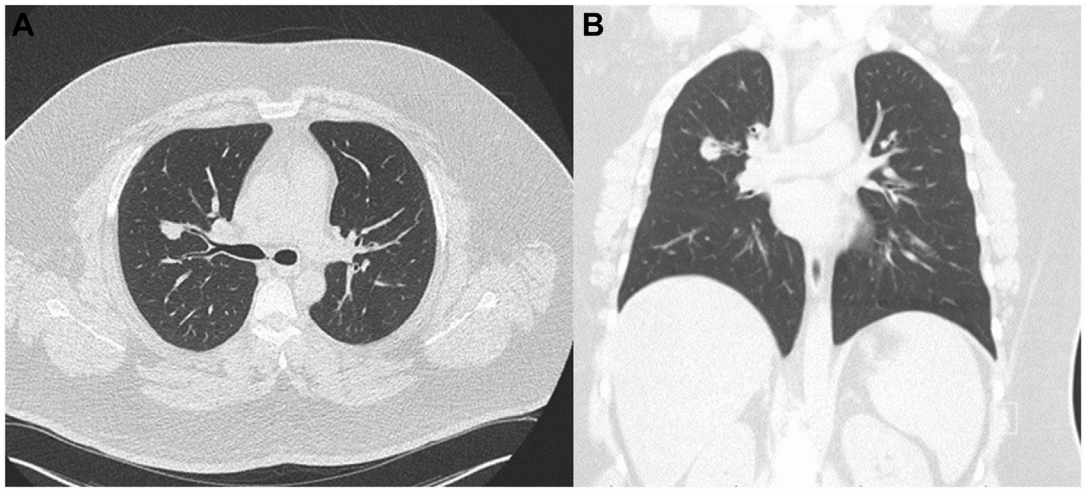


**FIGURE 1** (A) Axial and (B) coronal images on computed tomography of the chest.

the demographic and clinical characteristics of the patient were consistent with bronchiolar adenoma despite the presence of an *EML4-ALK* fusion.

## COMMENT

The term *bronchiolar adenoma* encompasses both the ciliated muconodular papillary tumor, which is thought to be derived from mucinous, ciliated, proximal-type bronchiolar epithelium, and adenomatous proliferations thought to be derived from the more distal bronchiolar epithelium that lacks prominent mucinous or ciliated cells. The unifying features of the spectrum of bronchiolar adenomas are that they are nodular, peripheral, biphasic proliferations composed of a continuous layer of basal cells (CK5/6$^{+}$, p63$^{+}$, p40$^{+}$) underlying luminal cells similar to bronchiolar epithelial cells. Proximal-type bronchiolar adenomas (or ciliated muconodular papillary tumors) are composed of ciliated and mucinous epithelium in a variety of architectural arrangements ranging from papillary projections to glandular or acinar-like structures. In distal-type bronchiolar adenoma, the luminal cells are cuboidal and resemble type 2 pneumocytes, with occasional cells resembling Clara cells. True desmoplasia or invasive acini would rule out the diagnosis, but as seen in this case, stromal fibrosis can mimic these changes and cause diagnostic difficulty. Clusters of tumor cells resembling micropapillary tufts are occasionally seen and can be mistaken for a micropapillary-type adenocarcinoma.

A serious potential pitfall in evaluating biopsy specimens and frozen sections of these lesions is mischaracterizing them as adenocarcinoma. Their growth pattern along alveolar walls and abundant mucin morphologically mimic mucinous adenocarcinoma. However, a continuous basal layer distinguishes them from adenocarcinoma. In addition, proximal-type bronchiolar adenomas typically do not show expression of TTF-1, unlike adenocarcinoma. Of note, distal-type bronchiolar adenomas often do show diffuse, strong expression of TTF-1 and occasionally napsin A (like the normal distal bronchiolar epithelium).

Molecular analysis of bronchiolar adenomas has shown several recurring driver mutations, including the most common *BRAF* V600E mutation as well as *EGFR*, *KRAS*, *AKT1*,[2] and *HRAS*.[1] A small number of prior studies have shown *ALK* rearrangements in bronchiolar adenomas.[3,4] In the cases with *ALK* rearrangement, the tumors were morphologically proximal-type bronchiolar adenomas, which is of interest as *ALK* rearrangement in lung adenocarcinoma is also associated with the presence of extracellular mucin or mucinous tumor cells.[5]

Our case demonstrates the potential difficulty in diagnosing and treating bronchiolar adenomas, especially in the era of precision medicine, and the new role of thoracic

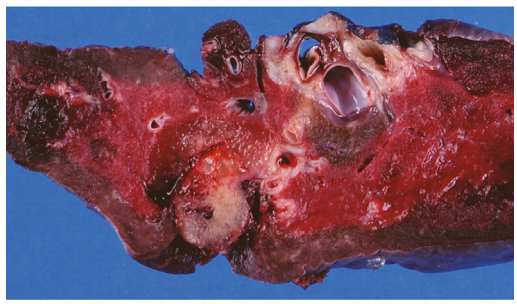

**FIGURE 2** Sectioning of the lobectomy specimen showed a 2-cm mass with a gray-tan, mucoid, focally hemorrhagic cut surface.

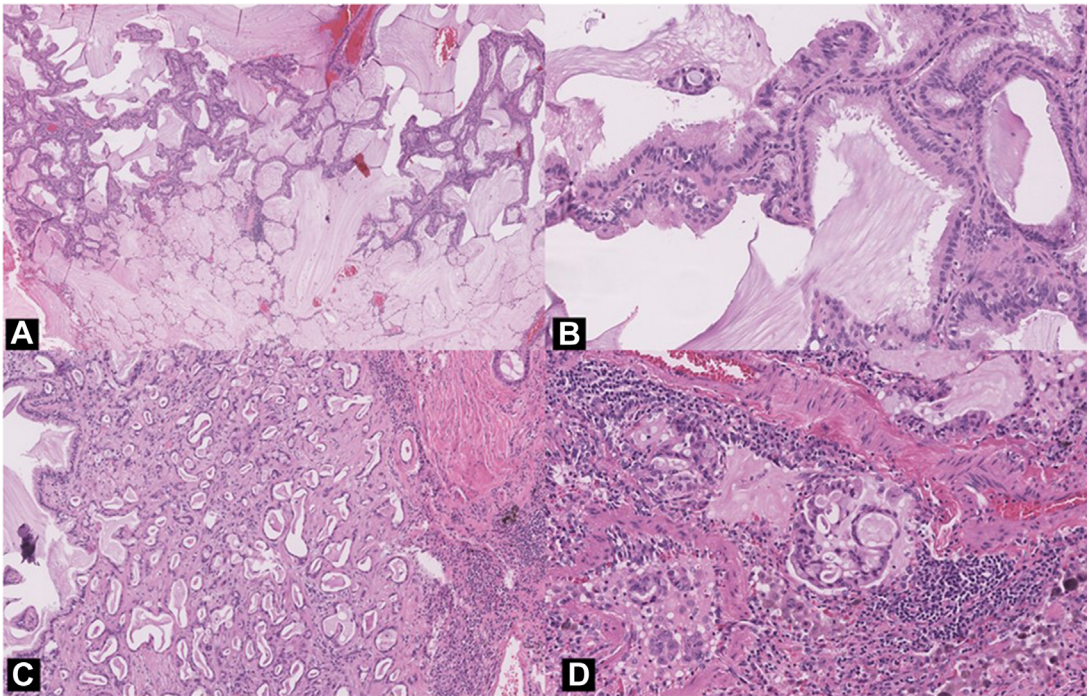


**FIGURE 3** (A) Papillary, mucinous portion of the tumor with abundant extravasated mucin (hematoxylin-eosin stain, magnification ×40). (B) Papillae lined by a bland, mucinous, columnar epithelium with rare ciliated cells (hematoxylin-eosin stain, magnification ×200). (C) Acinar-like portion of the tumor with a flat to cuboidal epithelium with few mucinous cells and stromal fibrosis between glands (hematoxylin-eosin stain, magnification ×100). (D) Focal clusters of neoplastic cells resembling micropapillae seen within alveoli at the periphery of the lesion (hematoxylin-eosin stain, magnification ×200).

surgeons in triaging patients with early-stage NSCLC with potential actionable mutations. This is a young patient with few risk factors for lung cancer, making a primary lung malignant neoplasm less likely; however, the initial biopsy was suggestive of adenocarcinoma. The patient potentially could have been enrolled in a therapeutic trial and have received systemic therapy for this lesion, which ultimately proved to be benign. In addition, there are multiple active trials evaluating neoadjuvant targeted therapy for early-stage NSCLC (eg, targeting *EGFR* and *ALK* mutations) that, depending on outcomes, could become Food and Drug Administration-approved standard of care.[6] Thoracic surgeons and oncologists should be aware of the existence of bronchiolar adenomas and consider them in their differential in patients who do not fit the classic risk profile for primary adenocarcinoma of the lung.

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## DISCLOSURES

The authors have no conflicts of interest to disclose.

## PATIENT CONSENT

Obtained.

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