Benign Mimics of Malignancy in Pulmonary Pathology

Jeffrey L. Myers, M.D.

Department of Pathology, the University of Michigan, Ann Arbor, MI

Introduction
There are a variety of predictable circumstances in which benign lung lesions are at risk of being interpreted as malignant neoplastic processes. This brief overview will focus on three of them chosen because of their relative frequency in cases received for consultation. The most common diagnostic challenge is separating hyperplasia and/or metaplasia of non-neoplastic respiratory epithelium from adenocarcinoma, especially on small biopsies. This includes organizing pneumonia which may occasionally mimic either epithelial or non-epithelial neoplasms when it presents as a localized process. Benign lung neoplasms are occasionally confused with malignant lesions; sclerosing hemangioma and multiple carcinoid tumorlets are the chief constituents of this second category of mimics. Finally, benign pleural disease is sometimes difficult to distinguish from either early epithelial mesothelioma or desmoplastic variants of sarcomatous mesothelioma and is a common cause for consultation even among expert reviewers.

Epithelial hyperplasia and metaplasia
Hyperplastic and metaplastic epithelium arising from bronchi, bronchioles, and/or distal alveolar septa is a constant in virtually all forms of non-neoplastic lung diseases, but often the histologic context is sufficiently distinctive (eg, acute bronchopneumonia) to allow easy separation from neoplastic processes. In other cases knowledge of the clinical circumstances, especially the radiologic distribution of disease, can be extremely helpful in resolving what might otherwise be a challenging histopathologic diagnoses. Occasionally, however, it is difficult to resolve the distinction between non-neoplastic and neoplastic proliferations with confidence on the basis of histology alone especially when the clinical context is either unknown or confounding.

Chronic fibrotic conditions are perhaps the most common category of non-neoplastic lung disease in which epithelial proliferations may mimic malignancy. In a classic review focusing on a potential link between atypical epithelial proliferations and carcinogenesis, Meyer and Liebow suggested that a “more important background lesion for atypical proliferation than such focal scarring as is related to organized granulomas, infarcts or trauma is chronic interstitial pneumonia.” Epithelial proliferations in fibrotic lung disease most likely to mimic malignancy are typically derived from bronchiolar epithelium and can be divided into two main categories: honeycomb change and peribronchiolar metaplasia (PBM).

Honeycomb change is a form of architectural distortion common in usual interstitial pneumonia (UIP) and occasionally seen as a final common pathway in other forms of diffuse fibrotic lung disease. Honeycomb change comprises bronchiolectasis in distally scarred and collapsed lung resulting in cystic, ectatic spaces lined by columnar epithelium. The cystic air spaces may contain various forms of cellular and acellular detritus, often including acute and chronic inflammatory cells. The lining epithelium typically includes ciliated and non-ciliated columnar cells including goblet cells. If severely inflamed the lining epithelium may show variably
degrees of cytologic atypia in the form of nuclear enlargement and prominent nucleoli. Squamous metaplasia is uncommon, occurring primarily in patients with superimposed diffuse alveolar damage in the context of acute exacerbation of idiopathic pulmonary fibrosis (IPF). Recognizing a well differentiated adenocarcinoma against this backdrop is sometimes challenging and hinges on recognition of a monomorphic population of non-ciliated epithelium with mild to moderate cytologic atypia that includes vesicular chromatin and areas of either an invasive growth pattern or early architecture complexity in the form of nuclear crowding and incipient papillations.

Peribronchiolar metaplasia (PBM) refers to a combination of fibrosis and epithelial hyperplasia involving bronchioles and peribronchiolar alveolar septa. The phenomenon has been described using a number of terms (e.g., airway-centered interstitial fibrosis) in various clinical, radiologic and histopathologic contexts. PBM is, therefore, not specific but when extensive may mimic non-mucinous bronchioloalveolar carcinoma (adenocarcinoma in-situ) or atypical adenomatous hyperplasia (AAH), a putative adenocarcinoma precursor although its role in carcinogenesis remains controversial. Key to separating these entities is recognition of not only a polymorphic population of relatively bland bronchiolar epithelial cells in PBM but also the histopathologic background. PBM is associated with fibrosis and sometimes smooth muscle hyperplasia in peribronchiolar interstitium and is rarely, if ever, a solitary lesion.

Diffuse alveolar damage (DAD) is a relatively nonspecific manifestation of catastrophic acute lung injury typically seen in the context of the adult respiratory distress syndrome (ARDS), acute interstitial pneumonia (Hamman-Rich disease) or acute exacerbation of antecedent diffuse fibrotic lung disease, most commonly UIP. Affected patients are usually profoundly hypoxemic requiring mechanical ventilation. As such the context is unlikely to be confused with malignancy. In the absence of supportive clinical data, however, the epithelial changes in DAD and to a lesser extent organizing pneumonia (also termed bronchiolitis obliterans organizing pneumonia or BOOP) can lead to an erroneous diagnosis of carcinoma. The atypical epithelial cells in DAD include not only bronchiolar epithelium, including squamous metaplasia, but also hyperplastic type II pneumocytes. On occasion the degree of cytologic atypia can be profound, especially in patients who have been treated with alkylating agents, and includes nuclear enlargement and prominent nucleoli. Cytoplasmic (Mallory’s) hyaline may be present and is sometimes helpful in identifying the cells of concern as non-neoplastic.

Benign neoplasms
Sclerosing hemangioma
Sclerosing hemangiomas (SH) are benign lung neoplasms derived from incompletely differentiated respiratory epithelium. Most present as asymptomatic peripheral lung nodules that tend to affect younger women. CT scans show well circumscribed round or oval subpleural nodules that may be PET positive. Central endobronchial examples are very uncommon. Multiple lesions occur in about 2% of patients. Rare reports of deposits in regional lymph nodes do not detract from the fundamentally benign behavior of these lesions; no metastases outside of regional lymph node deposits have been described and there are no tumor-associated deaths.
SH are well circumscribed subpleural nodules averaging two to three centimeters in diameter. The histological hallmark is a heterogeneous appearance resulting from both a mixture of cell types and highly variable growth patterns. Two populations of epithelial cells are a characteristic feature: 1) surface cuboidal cells derived from pneumocytes or Clara cells, and 2) pale interstitial round cells with an incompletely differentiated respiratory epithelial phenotype. The cells are arranged in various growth patterns that include a focally conspicuous sclerotic stroma that is often calcified. Pseudovascular blood-filled spaces occur in some cases and account for the term hemangioma, in this case a misnomer. The presence of bland cuboidal cells in solid nests and associated columnar cells with a papillary architecture sometimes results in diagnostic confusion with either carcinoid tumor or a well differentiated variant of adenocarcinoma. Lesions lacking the full range of histologic diversity characteristic of SH may be especially challenging at the time of frozen section.

**Multiple carcinoid tumorlets**

Tumorlets are arbitrarily defined as carcinoid tumors measuring no more than 0.5 cm in greatest dimension, and occupy a middle ground between neuroendocrine cell hyperplasia and typical carcinoid tumors in the lung. They may occur in isolation as incidental findings of no special significance, are common in certain forms of underlying lung disease such as bronchiectasis, and are present in as many as 25% of well sampled lungs resected for carcinoid tumors. Tumorlets are unlikely to mistaken for malignancy except in occasional patients being followed for other malignant neoplasms. Occasionally multiple carcinoid tumorlets can mimic the radiological appearance of metastases on computed tomography (CT) scans, and to the unwary pathologist may simulate lymphangitic metastases at the time of frozen section diagnosis.

**Mesothelial hyperplasia and fibrous pleurisy**

Distinguishing benign mesothelial proliferations from mesothelioma is a common driver for consultations on pleural biopsies. Lesions typically fall into one of three categories: hyperplasia of mesothelial cells in the setting of pleuritis, lesions of aggregated macrophages and mesothelial cells (“nodular histiocytic/mesothelial hyperplasia”), and fibrous pleurisy (chronic fibrosing pleuritis). In each of these the presence of absence of invasive behavior is the single most reliable criterion for separating benign from malignant lesions. While there is no single immunostain likely to be of value in distinguishing benign from malignant mesothelial proliferations, keratin stains can be helpful primarily in identifying the presence or absence of invasion. Other helpful histologic clues that favor malignancy include nodular stromal expansion, random (versus zonal) variation in cellularity, and necrosis. Homozygous p16 deletion assessed using fluorescence in situ hybridization (FISH) can be a useful adjunct, but is present in only about half of mesotheliomas and is therefore relatively insensitive even if highly specific.

**References**


