CLINICAL REVIEW

Significance of Atypical Cells on Lung Biopsy: A Case Series and Review of the Literature

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Case Review

Case 1
A 76-year-old female former 10-pack-year smoker presented with an abnormal chest x-ray. CT chest showed a 50 x 22 mm left upper lobe bronchovascular mass, concerning for granulomatous infection vs malignancy. Bronchoscopy with transbronchial cryobiopsy showed "atypical glands in a background of fibroelastotic scar tissue." Additional percutaneous CT-guided lung biopsy revealed "small fragments of lung tissue with minute focus of atypical pneumocytes with lepidic growth." Due to high suspicion for adenocarcinoma the patient underwent surgical resection and lobectomy was remarkable for a 5.2 cm invasive adenocarcinoma (pT3N0 - stage IIB).

Case 2
A 63-year-old female former 18-pack-year smoker presented with chronic cough. CT was remarkable for a 31 x 13 mm right upper lobe triangular shaped consolidation with air bronchograms, suspected sequela of prior infection. Bronchoscopy with transbronchial biopsy showed "atypical cells" on rapid on-site cytology, and pathology interpretation showed "fibrosis and chronic inflammation involving airway and surrounding lung tissue." Percutaneous CT-guided lung biopsy showed "minute focus of lung adenocarcinoma." Final pathologic diagnosis on lobectomy was 3.6 cm invasive adenocarcinoma (pT2aN0 - stage IB).

Case 3
A 77-year-old male former 30-pack-year smoker underwent lung cancer CT screening. A 16 x 12 mm spiculated left upper lobe lung nodule (lung RADS 4A) and CT-guided lung biopsy showed "atypical pneumocytes in a background of fibroelastic scar, chronic inflammation, and focal squamous metaplasia… within the spectrum of reactive changes. However, a well-differentiated component of an adenocarcinoma spectrum lesion was also in the differential." PET-CT scan showed a lung nodule with SUV 5.1, with invasion into the pulmonary artery. The patient underwent definitive stereotactic radiotherapy for stage IA2 lung adenocarcinoma.

Discussion

"Atypical" cells are often encountered on nondiagnostic lung biopsy, and may represent inadequately sampled malignancy, inflammation, or scarring.

Lung adenocarcinomas arise from cells of the lower respiratory tract: bronchial cells and pneumocytes. Lung adenocarcinomas evolve on a spectrum from adenomatous hyperplasia to adenocarcinoma-in-situ, minimally invasive adenocarcinoma, and invasive adenocarcinoma.[1] The morphology of benign bronchial cells changes in reaction to injuries including infection, radiation, chemotherapy, inhalational exposures, infarction, and interstitial lung disease.[2] In response to epithelial injury type 2 pneumocytes can show hyperplasia including nuclear enlargement and prominent nucleoli.[3] Reactive cells may be difficult to distinguish from adenocarcinoma. Pneumocyte hyperplasia and morphological alteration are also features of the lung adenocarcinoma spectrum, and type 2 pneumocyte surfactant vacuoles may mimic the mucin vacuoles of adenocarcinoma.[2] Features that support a diagnosis of malignancy rather than reactive atypia include monomorphic cells, clustering, formation of three-dimensional groups, plus a lack of background neutrophilic inflammatory cells.[2]

Similar to adenocarcinoma, squamous cell carcinoma exists in a continuum from squamous metaplasia to squamous dysplasia, in-situ carcinoma, and invasive squamous carcinoma. Squamous metaplasia can occur in response to injury including cigarette smoke, infection, radiation, and infarction.[3] While squamous metaplasia is benign, additional mutations may promote progression to carcinoma.[2] Squamous metaplasia may occur adjacent to fungal infections or granulomatous inflammation, and mimic cancer on biopsy. A greater degree of cellular undifferentiation is more clearly diagnostic for high-grade carcinoma.[2]

Cellular atypia on bronchioloalveolar lavage or lung biopsy is encountered frequently, and results must be interpreted with caution. In a study of BAL cytology, suspicious/atypical findings were ultimately diagnosed with benign disease in only 32% of cases (of which 40% were pulmonary infections). Serial studies showed cases with persisting atypia over 6 weeks represented adenocarcinoma-in-situ (previously termed bronchioloalveolar carcinoma).[4]

Peripheral lung lesions can be biopsied via percutaneous needle biopsy or via bronchoscopy (often guided by endobronchial ultrasound and/or electromagnetic navigation). A large retrospective study[5,6] of percutaneous needle lung biopsies reported 28% as nondiagnostic. Nondiagnostic results were more common in subsolid lesions vs solid lesions. Of the nondiagnostic

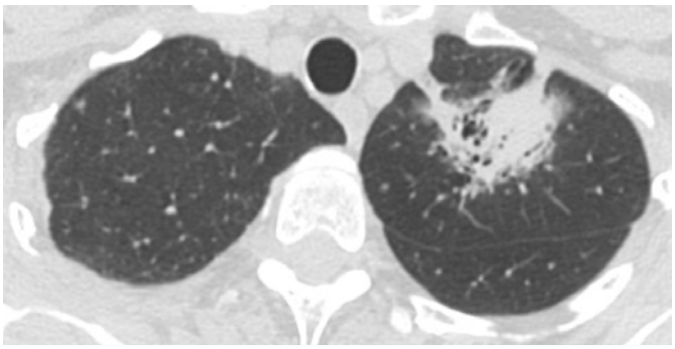
biopsies, 40% of lesions were ultimately found to be malignant. Age >65, female sex in those <65 years, the presence of emphysema, and subsolid density were significantly associated with a final diagnosis of malignancy. Definitive benign etiologies included granulomatous inflammation, abscess, and organizing pneumonia. Of the nondiagnostic biopsies with "atypical" cells, 90% were ultimately diagnosed as malignant. The samples with "insufficient specimen" also had significant rates of underlying malignancy with 47% later diagnosed with cancer. Of the biopsies with initially nondiagnostic results, 54% of repeat percutaneous needle biopsies were diagnostic.[6]

In another series of percutaneous lung biopsies, 75% of patients with atypia on lung biopsy were later diagnosed with cancer – 63% adenocarcinoma and 15% squamous cell carcinoma. More than half were diagnosed with cancer within 1 month, and >75% were diagnosed with cancer within 6 months. The radiographic features associated with subsequent diagnosis of malignancy were PET SUV>2.5, lung nodule size >3.5 cm, and mixed ground glass opacity. The most common benign diagnoses were pneumonia, fibrosis, and chronic inflammation.[5]

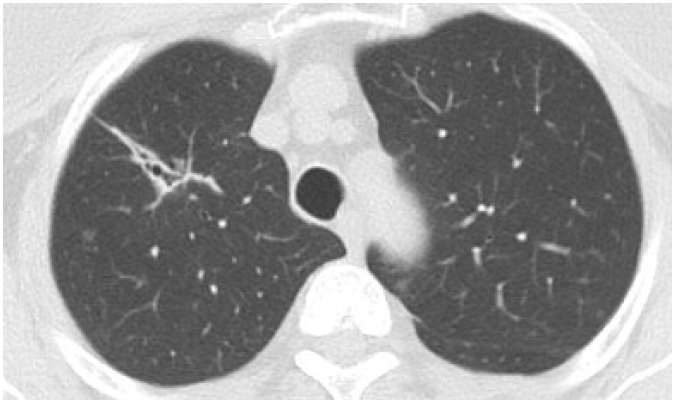
Bronchoscopic biopsies can also yield nondiagnostic results. A study of EBUS-guided transbronchial biopsies of peripheral pulmonary lesions, reported 7% nondiagnostic with "atypical cells." Of these cases, 73% were ultimately diagnosed with malignancy, more than half were adenocarcinoma. Atypical cells obtained from EBUS probe position adjacent to rather than within the lesion (likely representing suboptimal sampling) were associated with subsequent confirmed malignant diagnosis. The benign diagnoses included pneumonia, tuberculosis, and chronic inflammation.[7] A retrospective cohort of peripheral pulmonary lesions biopsied by navigational bronchoscopy reported atypia in 28% of nondiagnostic biopsies, of which 66% were diagnosed with malignancy within 2-year follow up. Adenocarcinoma was again the most common malignant diagnosis.[8]

In conclusion, the finding of "atypical" cells on lung biopsy, particularly from lesions with high pretest probability of malignancy (including concerning radiographic features such as subsolid density, larger size, and PET SUV>2.5, and in patients >65 years old) should further raise suspicion for malignancy. Prior studies report 75 to 90% of patients with atypical cells on lung biopsy are later diagnosed with cancer.[5-8] Patients should be appropriately counseled, and repeat biopsy or definitive resection should be considered to avoid treatment delays. Post-treatment reactive atypia changes related to radiation and chemotherapy may be particularly difficult to distinguish from persistent or recurrent carcinoma, and must be interpreted within the clinical context.[2]

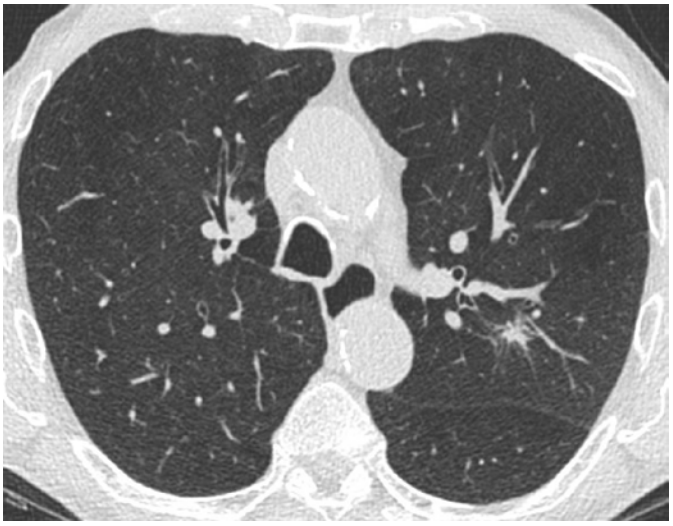
Figures



Case 1



Case 2



Case 3

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