A Wolf’s in Sheep’s Clothing
Lung Cancers with Benign Features on CT

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Objectives

• Illustrate atypical features and ambiguous imaging findings in cases of biopsy-proven lung cancers.

• Propose strategies to avoid misclassifying lung cancers as benign lesions.

• Discuss how data in this era of lung cancer screening and volumetric CT provides insight into the many manifestations of lung cancer.
50 F, 45 pack-year smoking history with nodule on chest radiograph.

There is a large calcification in this nodule.

**Are you certain this is a granuloma?**

Path→ poorly differentiated adenocarcinoma (ADC) with fibrogranulomas and hilar lymph node metastasis.

Note ipsilateral enlarged hilar lymph nodes with minimal calcification.

Coronal reformatted CT. Note eccentric (inferior) position of the calcification.
Pseudo-central Calcification

- 1\textsuperscript{st} : Evaluate the pattern of calcification.
- 2\textsuperscript{nd} : Use orthogonal planes to characterize their location. Eccentric location can be missed if only evaluated on axial plane.
- Beware of “too much tissue” in a calcified nodule.
- Granulomas do not become cancer. Cancers engulf them.
- While up to 13\% of lung cancers can contain calcification, it occurs in only 2\% of those smaller than 3 cm\textsuperscript{1}.
Non-small cell lung cancer engulfing a granuloma

Calcification is eccentric, and there is extensive soft tissue. 

Companion case (CC) 1. Poorly differentiated ADC with central calcification. Note extensive amount of tissue around the calcification (A). Spiculations present on lung windows should raise suspicion (B). There is sequela of old granulomatous disease with calcified mediastinal lymph nodes and calcified left lower lobe nodule (C). Nodes were FDG PET negative, and cancer was resected.

Teaching Points
- Rarely, cancers contain calcification.
- Evaluate calcification pattern in all planes.
- If a calcified nodule has disproportionate soft tissue, look for common cancer features (e.g. spiculations, lymphadenopathy).

CC 2. Non-small cell lung cancer engulfing a granuloma
Calcification is eccentric, and there is extensive soft tissue.
Endocavitary nodule at baseline. There is a crescent of air below the nodule, making it nondependant. Are you confident calling this nodule an aspergilloma?

Path: Non-small cell lung carcinoma.

At 1 month, note how the nodule is larger, and the crescent of air inferiorly disappears.
Endocavitary Filling Defect Pseudo-Aspergilloma

- Confirm nodule is dependent in the cavity (crescent of air underneath).
- Prone/decubitus CT may help. Aspergillomas are mobile while tumors should not change position\(^2\).
- Aspergillomas may grow but typically do so very slowly.
- If CT with positional change is not helpful and no comparison available, short term (3 month) follow-up could be considered.
Emphysema with Focal Wall Thickening

68-year-old asymptomatic F. Notice how the walls of the cystic area become thicker. Some thicker areas are ground-glass (yellow arrow) and some are solid (green arrow).

*Would you call this inflammation?*

**Path:** Adenocarcinoma
Cyst with Focal Wall Thickening

Classic Teaching was...

<table>
<thead>
<tr>
<th></th>
<th>&lt; 1 mm</th>
<th>≤ 4 mm</th>
<th>5-15 mm</th>
<th>&gt; 15 mm</th>
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<tbody>
<tr>
<td>Benign</td>
<td>Usually Benign (92%)</td>
<td>Indeterminate 51% benign 49% malignant</td>
<td>Usually Malignant 95%</td>
<td></td>
</tr>
</tbody>
</table>

Note this study was done using radiography not CT!

Can you guess which two examples represent biopsy-proven cancers?

* Squamous Cell Carcinoma

Woodring et al. 3
This retrospective study based on I-ELCAP* describes the behavior of lung cancers associated with cystic spaces.

Progressive wall thickening and appearance of a nodule was evident between 12-118 months (median 35).

Of the cancers diagnosed on follow up exams, median wall thickness was 8 mm at diagnosis, progressed from 1 mm at baseline.

Median wall thickness of the cancers diagnosed at baseline was 4 mm.

Of all the cancers: 77% solid nodules; 23% subsolid nodules.

Out of 13 cases where the cystic space was observed over time: the diameter of this space got smaller in 5/13, was stable in 2/13, and became larger in 6/13.

*International Early Lung Cancer Action Program
67-year-old F with persistent cough. Right upper lobe abnormality on chest radiograph evaluated with CT. Are you certain this linear opacity on axial images represents atelectasis?

Note how the opacity has volume on orthogonal views. It is also related to a cystic space on sagittal reformat.

Path → Adenocarcinoma
Linear/Band-like Opacities

- Opacities (including ground-glass) should be evaluated in multiple planes.
- Scar or atelectasis should remain linear in orthogonal planes.
- Shaggy or irregular margins or adjacent cystic area are additional warning signs of potential malignancy.
NSCLC: Note the irregular margins and the cystic space. Although the opacity is linear, these are signs of potential malignancy.
Fat Attenuation Nodule on CT

77-year-old F
New nodule on chest radiograph.

Nodule has central low density.

Single point region of interest (ROI) measures fat density, whereas circular ROI with multiple pixels does not.

Are you confident calling this nodule a hamartoma?

Path: Adenosquamous carcinoma.
Hamartomas VDT* > 450 days\textsuperscript{5}. New or rapidly growing nodules should prompt biopsy.

Macroscopic fat visual assessment most reliable method of diagnosis. Fat attenuation pixels in the inner two-thirds of the lesion $\rightarrow$ specificity 100\%\textsuperscript{6}.

Proposed threshold density of -33 HU (ROI with $\geq$ 8 pixels) has accuracy, sensitivity and specificity of 95.3\%, 100\%, and 96.3\%\textsuperscript{7}. Single point ROI measurement is not reliable.

Centrally necrotic lung cancers may rarely contain voxels of fat density.

* Volume doubling time
CC 1. Enlarging nodule along the staple margin in this patient with previously resected non-small cell lung carcinoma.

Notice the known recurrent cancer has central low density and measures fat. However, it is not the -33 HU threshold that is currently proposed.

Path: Adenosquamous carcinoma.
58-year-old M, immunosuppressed with severe pneumonia and respiratory symptoms. Symptoms improved with antibiotics.

Worsening cough and fatigue. Thought to have opportunistic infection. BAL* and cultures negative.

Would you attribute persistent and worsening consolidation to infection?

Path: Well-differentiated mucinous adenocarcinoma.

* Bronchoalveolar lavage
Consolidation

- Infection as a cause of consolidation should be symptomatic.
- Non improving consolidation after antimicrobial therapy requires further investigation.
- “Atypical” or fungal infection with negative cultures should be biopsied, avoiding necrotic areas.
- Although no clear guidelines, if patient > 50-years-old, consider follow-up radiograph. Allow 6-8 weeks between studies for radiographic improvement.
CC 1. 65-year-old M, former heavy smoker. Right lower lobe consolidation with air bronchograms in the absence of ongoing or recent respiratory symptoms.

Path: Invasive mucinous adenocarcinoma.
69-year-old F. Baseline lung cancer screening.

Notice there are segmental tree-in-bud nodules (*circle in A*) which prompted the search for a centrally obstructive lesion (B). Nodule is eroding into the bronchus (*arrows*).

**Do you routinely assess all airways?**

Path: Nonsmall cell lung carcinoma.
Central lesions and Tree-in-Bud Nodules

- Routine evaluation of each segmental bronchus reduces the chance of missed endobronchial lesions and central pulmonary nodules\(^8\).
- Locations for missed lung cancers on CT\(^9\).

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Endobronchial</td>
<td>67%</td>
</tr>
<tr>
<td>SPN*</td>
<td>13%</td>
</tr>
<tr>
<td>Peripheral</td>
<td>23%</td>
</tr>
<tr>
<td>All others</td>
<td>7%</td>
</tr>
<tr>
<td>Left lower lobe</td>
<td>7</td>
</tr>
<tr>
<td>Right lower lobe</td>
<td>4</td>
</tr>
<tr>
<td>Upper lobes</td>
<td>4</td>
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</tbody>
</table>

- Segmental tree-in-bud nodules should always trigger a search for a central endobronchial obstruction, particularly in non-dependent locations.
Tree-in-Bud Nodules

• Classically, clustered small (3-15 mm) nodules in a segment or subsegment typically indicate infectious or granulomatous process\textsuperscript{10}.

• Tree-in-bud opacities characteristically associated with cellular bronchiolitis (e.g. infection or aspiration).

• The presence of focal tree-in-bud nodules should prompt careful evaluation for central obstruction.
CC1. 65 M with acute dyspnea and pleuritic chest pain.

CT shows multiple pulmonary emboli (arrows in B,C).

Tree-in-bud nodules were seen on maximum intensity projection (D), prompting evaluation of the central airways.

Notice the abrupt cutoff of the anterior segment right upper lobe bronchus (E) and distal tree-in-bud (D).

The “pseudoembolus” (arrows in A) is an obstructed bronchus.

Path: Basaloid squamous cell carcinoma.
CC 2. 71-year-old F. Apparent nodule on chest radiograph accounted for by scattered small nodule in the right upper lobe and were felt to be inflammatory.

In retrospect, nodules were associated to a cystic space (arrows).

Patient had a stage IIB SCC, was treated with surgery and chemotherapy, and is currently free of disease.

Irregular mass at same location.

Path: Moderately differentiated squamous cell carcinoma.
48 F with recurrent pneumonias. Exam was called limited because of lack of IV contrast, and repeated.

Do you think the exam is limited? What if you follow the airways centrally?

- The left lower lobe bronchus is narrowed at its origin (arrows B)
- The mass is seen even without contrast (A)
- Vividly enhancing nodule after IV contrast (C)
- Octreoscan® showed uptake only in left hilum (D)

Pat: Typical carcinoid.
1. Carefully follow the airways (just as you evaluate the arteries in pulmonary embolism studies) to decrease the chance of missing a central lesion (endobronchial or not).
2. Tree-in-bud nodules should trigger an evaluation of the central airways in that segment.
3. Routinely evaluate abnormalities in orthogonal planes.
4. Not necessary to follow every cluster of tree-in-bud nodules. Necessity should be weighed against risk factors for lung cancer, presence of infectious symptoms, gastroesophageal reflux, hiatal hernia, or known aspiration.
Final case. 66-year-old M with constitutional symptoms. Cultures + for *M. gordonae*.

Notice how the central tissue does not move in lateral CT (C). Also, notice how irregular and thick the walls of the cavity are (A-C).
Teaching Points

This case illustrates other important teaching points already discussed:

1. Cancers can have “thin” walls.
2. These walls are usually irregular or nodular.
3. Routinely evaluate the walls in orthogonal planes.
4. Endocavitary nodule or tissue should move with changes in position. If this does not happen or you are not certain, follow up closely, or consider biopsy (of the walls, not the necrotic center).
Conclusions

• Increased use of chest CT can lead to increased detection of early-stage lung cancers with appearances that may be subtle and overlap with benign entities.

• We illustrate CT findings of lung cancers that closely mimic characteristics classically associated with benign entities and suggest methods to avoid these errors.

• Careful application of imaging criteria is needed to prevent misdiagnosis and lead to timely detection and treatment of lung cancer.


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