October 2016 Imaging Case of the Month

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Clinical History: A 35-year-old woman presented with a several month history of slowly worsening shortness of breath and dry cough. Laboratory data, include white blood cell count and serum chemistries were within normal limits. Oxygen saturation on room air was 99%.

Frontal and lateral chest radiographs (Figure 1) were performed.

Figure 1. Frontal (A) and lateral (B) radiographs.

Which of the following statements regarding the chest radiograph is **most accurate**?

1. Frontal and lateral chest radiography appears normal
2. Frontal and lateral chest radiography shows abnormally diminished lung volumes
3. Frontal and lateral chest radiography shows bilateral peribronchial and mediastinal lymph node enlargement
4. Frontal and lateral chest radiography shows cardiomegaly
5. Frontal and lateral chest radiography shows upper lobe bilateral linear and reticular abnormalities

Correct!

5. Frontal and lateral chest radiography shows upper lobe bilateral linear and reticular abnormalities

On initial review the frontal and lateral chest radiographs superficially appear normal. There is no evidence of peribronchial or mediastinal lymph node enlargement, the lung volumes appear normal, and the heart size is normal. However, upon close inspection, faint reticular and nodular opacities are visualized in the upper lobes bilaterally in a fairly symmetric fashion (Figure 2).

Figure 2. Close up of frontal radiograph. Faint, symmetric, bilateral upper lobe reticular and nodular opacities (arrowheads) are present.

The patient's past medical history was unremarkable- no history of diabetes, heart disease, or malignancy was noted. Approximately a year earlier, she had experienced a chemical burn at her employment that involved her hands, but seemed to extend more proximally along her arms, and involved her thighs and legs as well. The skin affected showed peeling, and persisted, eventually transitioning to a white, popular, pruritic rash. She was a lifelong non-smoker.

Which of the following would be **most useful** for the evaluation of this patient?

1. Dermatologic consultation
2. Flexible fiberoptic bronchoscopy
3. Pulmonary function testing
4. Repeat frontal chest radiography
5. Right heart catheterization

Correct!

1. Dermatologic consultation

Repeat chest radiography could be of some use, particularly if the previously noted pulmonary opacities have resolved- in that case, there would be no need to pursue the chest abnormalities further. Obtaining pulmonary function testing could be of benefit as well, although normal results would not negate the fact that chest imaging abnormalities have been noted and require further assessment. Bronchoscopic evaluation is similarly not an incorrect choice, but may be a premature, given that further non-invasive investigation could provide information sufficient to obviate an invasive procedure. Right heart catheterization is not indicated- nothing thus far points towards pulmonary vascular disease or pulmonary hypertension. Dermatologic consultation may be the best choice, among those listed, for further assessment at this point. While the patient's skin complaints may be unrelated to the chest radiographic abnormalities, occasionally disorders affecting the lungs may have dermatologic manifestations and, if this is the case for this patient, a unifying diagnosis may be provided without further exposure to ionizing radiation through diagnostic imaging or invasive tissue sampling. Dermatologic consultation prompted skin biopsy, which showed chronic inflammation and was clearly abnormal but not diagnostic of a particular entity. The patient was re-evaluated and her rash persisted (Figure 3), and repeat chest radiography (not shown) was unchanged from presentation.

Figure 3: Skin lesions on the calf, thigh, and near the elbow

The patient subsequently underwent pulmonary function testing showed a total lung capacity of 88% predicted, a forced vital capacity of 90% predicted, and a forced expiratory volume in 1 second of 95%. Diffusion capacity was 94% predicted.

Which of the following is the **most appropriate** next step for the evaluation of this patient?

1. ^{68}Ga -citrate scintigraphy
2. Flexible fiberoptic bronchoscopy
3. Mediastinoscopy
4. Unenhanced high-resolution chest CT
5. Ventilation – perfusion scintigraphy

Correct!

4. Unenhanced high-resolution chest CT

Among the choices listed, unenhanced high-resolution thoracic CT (HRCT) is the best choice. HRCT would be the most useful examination to confirm that the abnormalities detected at chest radiography persist, and, assuming they do, to characterize these opacities. ^{68}Ga -citrate imaging can be used for diffuse lung diseases, but typically in the context of a more widespread alveolitis, not small nodular opacities. Flexible fiberoptic bronchoscopy could be of benefit for this patient, but is invasive and HRCT results could inform if this procedure is even indicated, and, if so, where best to attempt tissue sampling. $^{99\text{m}}\text{Tc}$ -MAA ventilation – perfusion scanning is used to assess pulmonary blood flow, typically for thromboembolic disease assessment or in the context of pre-operative testing for differential pulmonary blood flow assessment, but neither consideration is relevant to this patient. Mediastinoscopy is commonly employed to sample paratracheal or anterior subcarinal lymph node stations, often in the context of lung cancer staging, but occasionally to establish a diagnosis for patients with enlarged lymph nodes or masses in these areas, but neither situation is germane to this patient's presentation.

The patient underwent unenhanced HRCT (Figure 4).

Figure 4. Axial high-resolution chest CT images through the upper lungs.

Which of the following is **correct** regarding the description of the thoracic CT findings?

1. HRCT shows diffuse, small nodules consistent with a *centrilobular* distribution
2. HRCT shows multifocal bilateral areas of lobular consolidation with air bronchogram formation
3. HRCT shows multifocal bronchiectasis
4. HRCT shows numerous randomly scattered small nodules consistent with a *miliary* distribution
5. HRCT shows patchy, small nodules consistent with a *perilymphatic* distribution

Correct!

5. HRCT shows patchy, small nodules consistent with a perilymphatic distribution

The diagnostic value of HRCT for the assessment of pulmonary nodular diseases relies heavily on the distribution of the nodules relative to structures within the secondary pulmonary lobule, a diagnostic approach that was first recognized by pathologists as valuable for interpretation of biopsy and surgical histopathological specimens. HRCT technique allows imagers to extrapolate these pathological findings to imaging findings. Histopathologically, at least 4 nodule distributions within the secondary pulmonary lobule are recognized: *bronchiolocentric*, *angiocentric*, *lymphatic*, and, *random*. Nodules that are bronchiolocentric in distribution are related to the centrilobular and lobular bronchi, and angiocentric nodules are related to the pulmonary arteries within the secondary pulmonary lobule. Because the artery and bronchus are in very close proximity to one another within the secondary pulmonary lobule, both nodule types are located in or very near the center of the secondary pulmonary lobule, and these two distributions are not readily distinguished from one another on HRCT. So, bronchiolocentric and angiocentric nodule histopathological distributions are grouped together as *centrilobular* nodules. Thus, three distributions of nodules within the secondary pulmonary lobule are recognized on HRCT: *centrilobular*, *perilymphatic*, and *random* (Figure 5).

Figure 5. Small nodule distributions on HRCT: **Centrilobular**= nodules (arrowhead) approach, but typically space, costal and fissural pleural surfaces; **Perilymphatic**: nodules (arrowheads) contact costal and fissural pleural surfaces and are located along interlobular septae as well. The nodule distribution is typically *patchy*- normal lung regions are juxtaposed against abnormally infiltrated lung regions, and; **Random**: nodules (arrowheads) are seen along fissural surfaces but also appear centrilobular as well, and are *diffusely* distributed through the lungs bilaterally.

In this case, the nodules are noticeably distributed along pleural surfaces, particularly the right major fissure, and the distribution of the nodules is **patchy**- this latter term indicates abnormally infiltrated regions of lung are juxtaposed to relatively normal appearing lung, in contrast with a **diffuse** distribution, in which abnormally infiltrated lung is fairly widespread. The HRCT in this patient shows that the nodules are distributed along pleural surfaces and have a patchy distribution, which is most consistent overall with a perilymphatic nodule distribution. No consolidation with air bronchograms is evident and no bronchiectasis is seen.

Which of the following conditions are **associated with perilymphatic nodule formation** at HRCT?

1. Amyloidosis
2. Lymphocytic interstitial pneumonia
3. Pulmonary lymphangitic carcinomatosis
4. Sarcoidosis
5. All of the above

Correct!
5. All of the above

All of the above listed entities may produce perilymphatic nodules on HRCT studies. Among these disorders, sarcoidosis is the most common cause of perilymphatic nodules on HRCT.

At this point, which of the following tests would be **most useful** for establishing the diagnosis for this patient?

1. Bronchoscopic biopsy
2. Cervical mediastinoscopy
3. Medical pleuroscopy
4. Open surgical lung biopsy
5. Percutaneous transthoracic needle and core biopsy

Correct!

1. Bronchoscopic biopsy

Among the choices listed, bronchoscopic biopsy is the most appropriate. Cervical mediastinoscopy is useful for the evaluation of the mediastinum, particularly inferior to the carina, but would be of little use for a patient without mediastinal abnormalities. Medical pleuroscopy would not be useful for this patient as no pleural abnormalities are present. Open surgical lung biopsy would surely establish a diagnosis for this patient but is overly invasive at this point, and could be considered if transbronchial bronchoscopic biopsy is unrevealing and thoracoscopic lung biopsy cannot be performed. Percutaneous transthoracic needle and core biopsy is a very useful procedure for obtaining lung tissue for diagnosis, but is typically only employed for focal lung disorders, not diffuse lung diseases.

The patient underwent flexible fiberoptic bronchoscopy with transbronchial biopsy, which disclosed mixed inflammation with eosinophils and histiocytes. The histiocytes stained positively for CD1a, CD68, and S-100, with no staining for Factor XIII. These staining parameters were consistent with Langerhans cell histiocytosis. Further immunohistochemical analysis, however, showed no staining with CD207, which usually stains positive for LCH. Therefore the histopathological and immunohistochemical analysis was consistent with Indeterminate cell histiocytosis. Another biopsy of the focal skin lesions was performed and showed a similar staining pattern, with dendritic cell features showing extensive immunoreactivity for CD11c, HLA-DR, CD1a, and CD68, the latter consistent with macrophage differentiation. The final diagnosis was established as indeterminate cell histiocytosis, with multicentric disease.

Diagnosis: Non-Langerhans cell (intermediate cell) histiocytosis

Post-Script: Bone marrow biopsy, peripheral blood flow cytometry, nuclear skeletal scintigraphy, and CT of the abdomen and pelvis were performed and were normal. The patient was treated with methotrexate and ultraviolet light therapy for her skin lesions, and the skin lesions and nodules seen at thoracic CT (Figure 6) nearly completely resolved.

Figure 6. Repeat axial HRCT just over a year following the presentation HRCT (Figure 4) and following methotrexate therapy shows significant improvement in the nodular lung disease.

References

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