Clinical History: A 65-year-old non-smoking woman presented with a history of cough, exertional dyspnea, and occasional wheezing. Frontal chest radiography (Figure 1) was performed.

Figure 1. Admission chest x-ray.

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

1. The frontal chest radiograph is normal
2. The frontal chest radiograph is non-specifically abnormal
3. The frontal chest radiograph shows numerous small nodules, consistent with a “miliary” pattern
4. The frontal chest radiograph shows significant right lung volume loss, suggesting endobronchial obstruction
5. The frontal chest radiograph shows diffuse fibrotic lung disease
Correct!

2. The frontal chest radiograph is non-specifically abnormal

The frontal chest radiograph shows some potential abnormalities, and therefore is not completely normal, but the findings are minor and non-specific. The chest radiography shows some increased opacity in the medial right apex, which may reflect thyroid enlargement or tortuous vascularity. Faint nodular opacity is present in the medial right base, although clear evidence of a mass is not seen. A clear, active cardiopulmonary process is not readily identifiable. A small nodular ["miliary"] pattern is not present. No “hard” features of significant volume loss- such as fissure displacement, bronchial displacement, rib narrowing, etc. are seen. Features of a diffuse fibrotic process such as architectural distortion, coarse reticulation, honeycombing, and clear traction bronchiectasis are not present.

Clinical Course: The patient subsequently underwent thoracic CT (Figure 2).

Figure 2. Representative images from the thoracic CT scan.

Regarding the thoracic CT, which of the following statements is most accurate?

1. The thoracic CT findings are most suggestive of an active, non-infectious alveolitis
2. The thoracic CT findings suggest a diffuse fibrotic lung disease
3. The thoracic CT findings suggest a process primarily producing airway obstruction
4. The thoracic CT findings suggest an active, diffuse pulmonary infection
5. The thoracic CT findings are most suggestive of multifocal pulmonary hemorrhage
Correct!

3. The thoracic CT findings suggest a process primarily producing airway obstruction

The thoracic CT shows diffuse bilateral inhomogeneous lung opacity (areas of comparatively “white” and “black” lung parenchyma), small bilateral nodules (red arrowheads), airway thickening and bronchiectasis (red arrows), and a mass with calcification in the medial right lower lobe (yellow arrows) (Figure 3).

![Thoracic CT scan with arrows](image)

Figure 3. Thoracic CT scan with arrows (see text for description).

The inhomogeneous lung opacity manifests as geographic areas of increased and decreased lung opacity (yellow arrowheads), the latter representing areas of diminished perfusion due to hypoxic bronchoconstriction. The hyperattenuating areas represent normally perfused, or slightly hyperperfused, lung, which results from shunting of blood from the oligemic areas of lung. Some of the lung nodules are clearly associated with abnormal bronchi (panels B, E, F, G, and L). The medial right lower lobe mass is closely related to the right lower lobe medial basal segment bronchus.

The typical thoracic CT features of non-infectious alveolitis include ground-glass opacity and/or consolidation, with or without fine reticulation, all of which are largely absent in this case. There is bilateral inhomogeneous lung opacity, which manifests as areas of increased and decreased pulmonary parenchymal attenuation. The areas of increased attenuation resemble ground-glass opacity, but in fact represent normally, or mildly hyperperfused, possibly also atelectatic, lung; the areas of decreased attenuation represent oligemic lung, and are often referred to as *mosaic perfusion*. The
parenchymal oligemia in mosaic perfusion occurs as the result of the presence of pulmonary artery obstruction or, more commonly, hypoxic vasoconstriction resulting from airway obstruction. The pulmonary parenchyma subtended by abnormal airways is poorly ventilated in patients with large and/or small airway diseases, and, as a result, the blood supply to these lung regions gets diverted from these abnormal areas to areas of more appropriately ventilated lung. This situation results in geographic areas of pulmonary parenchymal perfusion, referred to as mosaic perfusion. Because much of pulmonary parenchymal attenuation at thoracic CT is due to pulmonary blood flow, any condition that redistributes blood flow has the potential to affect lung parenchymal attenuation at CT. Therefore, the areas of decreased attenuation in this setting represent areas of diminished blood flow, whereas the more hyperattenuating areas represent areas of normally perfused, or hyperperfused, lung parenchyma. The inhomogeneous lung opacity is further accentuated by the presence of air trapping, which manifests as low attenuation at inspiratory thoracic CT. When the inhomogeneous lung opacity accentuates at post-expiratory CT [e.g., the “white” areas become “whiter” and the “black” areas become “blacker”], air-trapping is considered to be the cause of the mosaic perfusion at inspiratory thoracic CT. When this accentuation does not occur at post-expiratory CT, pulmonary artery obstruction may be the cause of the mosaic perfusion. The thoracic CT in this case shows large airway abnormalities and inhomogeneous lung opacity, which suggests an abnormality related to airflow obstruction, indicating that choice “c” is the best answer. Pulmonary hemorrhage usually presents as multifocal ground-glass opacity, perhaps with areas of consolidation, associated with smooth interlobular septal thickening- such findings are not present in this case. Typical features of fibrotic lung disease at thoracic CT- traction bronchiectasis, reticulation, linear opacity, architectural distortion, and honeycombing- are not seen. Diffuse pulmonary infection is technically possible, but areas of ground-glass opacity and consolidation, commonly seen with infection, are not seen, and findings suggesting focal bronchiolitis- such as small, clustered nodules with branching morphologies- are not present.

What is the appropriate next step for the evaluation / management of this patient?

1. Serial thoracic CT observation
2. Bronchoscopy with transbronchial biopsy / bronchoalveolar lavage
3. Transthoracic percutaneous lung biopsy
4. Whole-body FDG-PET imaging
5. Thoracic MRI
Correct!

2. Bronchoscopy with transbronchial biopsy / bronchoalveolar lavage

Given the close association of the right lower lobe mass with the right lower lobe medial basal bronchus, and the other features suggesting a diffuse large and small airway process, bronchoscopy with transbronchial biopsy / bronchoalveolar lavage is the most appropriate step for the evaluation of this patient. Transthoracic percutaneous lung biopsy could be considered to establish the etiology of the dominant mass in the right lower lobe, but, in general, bronchoscopy may be considered for the first step in the approach of a lesion when a clear relationship to a major airway is present, as in this patient. Transthoracic percutaneous lung biopsy may then be reserved for patients in whom bronchosscopic evaluation was unrevealing. Thoracic MRI offers no value for the diagnosis of the lung nodules and airway disease in this patient, beyond that already known through thoracic CT. Serial thoracic CT would also not be appropriate given that a lung mass is present and other diffuse pulmonary / airway abnormalities are present in the setting of active symptoms. Finally, whole-body FDG-PET could be considered for the evaluation of the right lower lobe lesion, but that lesion contains calcium and is closely associated with an airway, which specifically suggests the diagnosis of carcinoid tumor. Because FDG-PET results may be false negative in carcinoid tumors, and elevated tracer uptake would prompt a tissue diagnosis for this lesion anyway, FDG-PET is unlikely to provide management-altering information at this point in this patient's evaluation.

The patient subsequently underwent bronchoscopy with transbronchial biopsy of the right lower lobe lesion. What is the most likely diagnosis?

1. Metastatic disease, probably from a bone- or chondroid matrix forming tumor, given the increased attenuation in the right lower lob mass
2. Multiple spindle cell tumors due to benign metastasizing leiomyomas
3. Carcinoid tumor with diffuse neuroendocrine cell hyperplasia.
4. Pulmonary lymphomatoid granulomatosis
5. Pulmonary vasculitis due to granulomatosis / ANCA-associated granulomatous vasculitis with polyangiitis (previously known as Wegener’s granulomatosis)
Correct!

3. Carcinoid tumor with diffuse neuroendocrine cell hyperplasia

While one lesion with calcium or bone matrix is present within the right lower lobe, metastatic disease from a primary sarcoma forming either bone or chondroid matrix would be expected to produce multiple nodules with such features, and not a single right lower lobe nodule with calcium associated with large and small airway abnormalities. Similarly, benign metastasizing leiomyomas would manifest as multiple variably-sized nodules and / or masses, usually in a female patient with uterine leiomyomas or a history of hysterectomy for leiomyomas- such history was not provided in this case. Pulmonary lymphomatoid granulomatosis presents with multiple nodules or masses, with or without cavitation, but would not be expected to produce a nodule with calcification and diffuse large and small airway abnormalities. Finally, pulmonary vasculitis due to granulomatosis / ANCA-associated granulomatous vasculitis (formerly known as Wegener’s granulomatosis) usually manifests as multiple nodules or masses, often with cavitation, or multifocal pulmonary hemorrhage, at thoracic CT, rather than as a single partially calcified nodule with a background of large and small airway disease. The best answer is choice “3. Carcinoid tumor with diffuse neuroendocrine cell hyperplasia”.

Diagnosis: Diffuse idiopathic neuroendocrine cell hyperplasia

Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) I a rare condition recognized as a preinvasive precursor to carcinoid tumors and tumorlets. Coincident carcinoid tumors are seen in up to 40% of affected patients, and coexistent tumorlets are seen in more than two-thirds of patients as well. Histopathologically, DIPNECH presents with pulmonary neuroendocrine cell proliferation confined to the respiratory epithelium of large and small airways. The involvement is pronounced in small bronchi and bronchioles, but initially remains confined to the airway mucosa. When the neuroendocrine cell proliferation extends beyond the airway mucosa, and becomes extraluminal, the term tumorlet is employed. Somewhat arbitrarily, if a tumorlet exceeds 0.5 cm in diameter, the lesion is classified as a carcinoid tumor. Ultimately the small airway compromise that occurs in patients with DIPNECH may become widespread enough that clinical symptoms develop and the typical thoracic CT manifestations of small airway obstruction / constrictive bronchiolitis- are seen. Note, however, that neuroendocrine cell hyperplasia not uncommonly is encountered in the vicinity of peripheral carcinoid tumors, and thus the presence of such proliferation does not automatically establish the diagnosis of DIPNECH. In fact, the minority of patients with peripheral carcinoid tumors and pathologically-proven neuroendocrine cell hyperplasia will actually have clinical evidence of airflow obstruction.

DIPNECH presents over a fairly wide age range, but a female, middle-age predominance is recognized. Patients with DIPNECH may detected incidentally, when undergoing lung biopsy or resection for other reasons (typically the evaluation of a lung nodule), although most patients present with symptoms such as cough, dyspnea, and wheezing. Pulmonary function testing typically shows obstruction.
Chest radiographs are commonly non-specifically abnormal, showing one or more lung nodules and/or non-specific linear or reticular opacities. Thoracic CT often shows one or more small lung nodules and multifocal inhomogeneous lung opacity representing a combination of mosaic perfusion (the more lucent areas) and ground-glass attenuation (the higher attenuating areas). The inhomogeneous lung attenuation accentuates on post-expiratory imaging (meaning the lucent areas remain equally lucent or become more lucent, whereas the higher attenuation areas increase in attenuation) - this pattern indicates that the mosaic perfusion is due to air-trapping. Airway thickening and bronchiectasis are seen in the minority of patients.

The diagnosis of DIPNECH usually requires surgical lung biopsy, but can be established with bronchoscopy and transbronchial biopsy / bronchoalveolar lavage in some patients, in the proper clinical and imaging context. Bronchoscopy is often recommended prior to surgical lung biopsy to exclude competing diagnosis, such as infection or other more common diagnoses.

Patients are commonly treated with corticosteroids and bronchodilators and inhaled corticosteroid therapy. About 40% of affected patients remain stable, whereas about one-fourth of patients experiencing clinical deterioration, and the remaining showing improvement.

References