

Diagnostic Approach to the Patient With Diffuse Lung Disease

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Detecting diffuse lung infiltrates on chest radiography is a common clinical problem. Many diverse pathological processes can cause diffuse lung disease. The presentation of these diseases can vary from acute to chronic and includes a wide array of radiological patterns that are optimally evaluated on high-resolution computed tomography of the chest. In diagnosing diffuse lung disease, it is helpful to focus on a few pivotal parameters to narrow the broad differential diagnosis. We describe the diagnostic approach to a patient with diffuse lung disease using the

following key parameters: tempo of the pathological process, characteristics of the radiological pattern, and clinical context.

Mayo Clin Proc. 2002;77:1221-1227

BOOP = bronchiolitis obliterans with organizing pneumonia; CT = computed tomography; DIP = desquamative interstitial pneumonia; HRCT = high-resolution CT; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis

Many different disease processes may present with diffuse lung shadowing on chest radiography (Figure 1). These processes include infection, neoplasm, pulmonary edema, hemorrhage, environmental and occupational lung diseases, drug-induced lung disease, aspiration pneumonia, many forms of interstitial lung diseases (ILDs), and others. "Diffuse" implies involvement of all lobes of both lungs, but the process need not affect all lobes or all lung regions uniformly. Although most disorders with diffuse lung shadowing will be parenchymal processes (the focus of this article), some airway diseases such as bronchiectasis and cystic fibrosis may present with diffuse lung infiltrates.¹ Similarly, some vascular disorders such as pulmonary veno-occlusive disease are associated with diffuse lung infiltrates and may be mistaken for ILD.²

Chest radiography is usually the first method of detecting a diffuse lung process, but several caveats should be noted. In up to 10% of cases, the chest radiograph may look normal despite the presence of a diffuse parenchymal lung disease, especially early in the disease course.³⁻⁶ In addition, the pattern of opacities seen on chest radiography may be interpreted differently when compared with the pattern seen on high-resolution computed tomography (HRCT) of the chest or pathological examination.³ This is because

standard chest radiographs present a 2-dimensional summation of overlapping shadows at relatively low-contrast resolution obtained from a 3-dimensional structure, the thorax. For example, pulmonary lymphangioleiomyomatosis may present as predominantly linear densities on chest radiography, whereas HRCT shows a diffuse cystic lung disease. Thus, classifying radiographic opacities on the basis of chest radiographic appearance may be misleading at times.

Computed tomography of the chest can be extremely useful when chest radiographs provide insufficient information to answer important clinical questions about diagnosis, extent of disease, and prognosis.³ Conventional computed tomography (CT) of the chest examines 7- to 10-mm slices obtained at 10-mm intervals. High-resolution CT examines 1.0- to 1.5-mm slices at 10-mm intervals using a high-spatial-frequency reconstruction algorithm and illustrates lung parenchymal details better than conventional CT. Scans are done at full inspiration in the supine patient.^{3,7} Prone positioning may be helpful in distinguishing gravity-dependent atelectasis in the dorsal bases seen on supine images from early changes of idiopathic pulmonary fibrosis (IPF).^{3,8} Expiration images may be helpful in evaluating the mosaic pattern (patchwork of lung regions of varied radiological attenuation) and patients with obstructive lung diseases.⁸⁻¹⁰

In patients with suspected diffuse parenchymal lung disease (based on clinical findings, chest radiography, or pulmonary function abnormalities), indications for HRCT of the chest include detecting lung disease in the presence of normal or equivocal chest radiographic findings; identifying the pattern, distribution, and extent of radiographic opacities; diagnosing bronchiectasis; and identifying associated features such as lymphadenopathy.^{3,8} More accurate

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This study was supported in part by Mayo institutional funds and the Robert N. Brewer Family Foundation.

A question-and-answer section appears at the end of this article.

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Figure 1. Chest radiograph of a patient with bird fancier's disease shows diffuse infiltrative lung disease characterized by numerous poorly circumscribed nodular opacities.

and detailed assessment of pulmonary parenchymal abnormalities by HRCT allows refinement of differential diagnosis and a more confident diagnosis.^{3,7,8} If the findings are sufficiently characteristic of a specific diagnosis, HRCT may obviate a lung biopsy.^{3,7,8,11} When a biopsy is needed, HRCT of the chest may guide the selection of the appropriate biopsy procedure and locate optimal sites for biopsy.^{3,7,8,11}

A clinician trying to determine the best diagnostic approach to a patient with diffuse lung infiltrates detected on chest radiography or HRCT should focus on 3 pivotal parameters to narrow the differential diagnosis and guide the diagnostic evaluation: (1) tempo of the disease process (acute vs chronic), (2) radiological pattern, and (3) clinical context (Table 1). These same features also help the clinician determine the diagnostic approach to a patient with any type of lung infiltrates.

Table 1. Pivotal Parameters in the Diagnosis of Diffuse Lung Disease

Tempo of disease
Radiological pattern
Pattern of opacities
Distribution
Associated radiological findings
Clinical context

TEMPO OF DISEASE

For the initial assessment of a patient with diffuse parenchymal lung disease, the clinician should first ascertain the tempo of the pathological process. The duration and progression of potentially relevant symptoms and signs are important to this assessment. In addition to the pertinent account of symptom progression, the assessment of tempo is facilitated by reviewing previous chest radiographs or CT scans, when available. In a patient with rapidly progressive symptoms and bilateral lung infiltrates, initial management may need to include hospitalization and institution of empirical therapy.

Acute (less than 4 to 6 weeks in duration) diffuse lung diseases most commonly include infection (pneumonia), pulmonary edema (cardiogenic or noncardiogenic), pulmonary hemorrhage, or aspiration.^{12,13} In addition, some diffuse infiltrative lung diseases or ILDs (most of which are chronic) may present acutely; these include hypersensitivity pneumonitis,¹⁴ drug-induced lung disease,^{15,16} pneumonitis related to toxic exposures (eg, silo filler's disease),¹⁷ acute eosinophilic pneumonia,¹⁸ acute interstitial pneumonia,¹⁹ and cryptogenic organizing pneumonia (also called idiopathic bronchiolitis obliterans with organizing pneumonia [BOOP])^{20,21} (Table 2).

Most chronic diffuse lung diseases are ILDs and represent a heterogeneous category of many distinct clinicopathologic entities.^{7,11,22} These disorders generally have a slow tempo of progression over many months or even years. The most common ILDs are IPF, sarcoidosis, ILD associated with connective tissue disorders, pneumoconioses, hypersensitivity pneumonitis, and drug-induced diseases.^{11,22}

RADIOLOGICAL PATTERN

The components of the radiological pattern that help the clinician diagnose diffuse lung disease include the pattern of opacities (consolidation, reticular, etc), distribution, and associated findings (Table 2). High-resolution CT is generally needed to decipher the underlying radiological pattern accurately for reasons already discussed, particularly for opacities other than consolidation seen on chest radiography.

Consolidation

Airspace consolidation or alveolar filling is characterized by indistinct margins, the tendency to coalesce, and the presence of air bronchogram or silhouette sign (effacement of an anatomical soft-tissue border due to adjacent consolidation) (Figure 2).^{3,7,8} Increased attenuation obscures the underlying vasculature. Airspace consolidation may be caused by accumulated water, blood, pus, cells, and other material. Diffuse alveolar infiltrates may be acute or chronic.

Diffuse alveolar infiltrates occurring acutely are usually due to pneumonia, pulmonary edema, acute respiratory distress syndrome, pulmonary hemorrhage, aspiration, or drug reactions.^{12,13} Less commonly encountered are acute hypersensitivity pneumonitis,¹⁴ acute eosinophilic pneumonia,¹⁸ and cryptogenic organizing pneumonia.^{20,21} In contrast, the presence of diffuse alveolar infiltrates for weeks to months may represent chronic infection, lymphoma, or advanced bronchioloalveolar carcinoma. In addition, several forms of ILDs may present with persistent alveolar infiltrates, including cryptogenic organizing pneumonia,^{20,21} chronic eosinophilic pneumonia,²¹ pulmonary alveolar proteinosis,²³ and sarcoidosis (rarely).²⁴ Patchy, peripheral areas of airspace consolidation are characteristic of chronic eosinophilic pneumonia and of cryptogenic organizing pneumonia.^{20,21}

Linear or Reticular Pattern

Acute interstitial lung infiltrates seen on chest radiography are most commonly due to interstitial pulmonary edema or pneumonia.^{12,13} However, virtually any form of ILD can cause chronic interstitial lung infiltrates (Table 2). In this case, the pattern of opacities seen by HRCT and other features, including distribution of infiltrates, associated radiological findings, and clinical context, will help narrow the diagnostic possibilities.

The most common form of ILD is IPF, which is characterized by irregular linear opacities and honeycombing that involves mainly the subpleural regions predominantly in the lower lung zones (Figure 3).^{25,26} This pattern of opacities and the characteristic distribution of the opacities are more accurately depicted on HRCT than on chest radiography. Similar radiological features are seen in asbestosis (often with the addition of pleural plaques) and in connective tissue disease-related pulmonary fibrosis.²⁶ Chronic hypersensitivity pneumonitis may be confused with IPF but is usually associated with the presence of poorly defined centrilobular nodules and areas of ground-glass opacities, features usually not seen in IPF.^{14,27}

Nodular Pattern

In contrast to IPF, HRCT findings in sarcoidosis include nodules along bronchovascular bundles (lymphatic distribution), coarse linear opacities involving mainly the perihilar regions of middle or upper lung zones and the bilateral hilar and mediastinal adenopathy.^{24,28} A nodular pattern may also be seen with hypersensitivity pneumonitis, pneumoconioses, infections, respiratory bronchiolitis, metastases, and alveolar microlithiasis (Figure 4).⁸ For example, diffuse micronodular opacities (miliary pattern) may occur in disseminated tuberculosis, fungal infection, and metastatic disease.⁸ Nodular opacities of silicosis and

Table 2. Classification of Diffuse Lung Diseases According to Radiological Pattern

<i>Pattern of opacities</i>	
Consolidation	
Acute:	infection, acute respiratory distress syndrome, hemorrhage, aspiration, acute eosinophilic pneumonia, acute interstitial pneumonia, cryptogenic organizing pneumonia (also called idiopathic bronchiolitis obliterans with organizing pneumonia [BOOP])
Chronic:	chronic infections (tuberculosis, fungal), chronic eosinophilic pneumonia, cryptogenic organizing pneumonia, lymphoproliferative diseases, bronchioloalveolar carcinoma, pulmonary alveolar proteinosis, sarcoidosis (rarely)
Linear or reticular opacities	
Acute:	infections (viral, mycoplasma), pulmonary edema
Chronic:	idiopathic pulmonary fibrosis (IPF) or usual interstitial pneumonia, connective tissue disease-associated pulmonary fibrosis, asbestosis, sarcoidosis, hypersensitivity pneumonitis, drug-induced lung disease
Small nodules (round opacities <1 cm in diameter)	
Acute:	infections (disseminated tuberculosis, fungal or viral infections), hypersensitivity pneumonitis (poorly circumscribed, centrilobular)
Chronic:	sarcoidosis, hypersensitivity pneumonitis, silicosis, coal worker's pneumoconiosis, respiratory bronchiolitis, metastases, alveolar microlithiasis
Cystic airspaces	
Acute:	<i>Pneumocystis carinii</i> pneumonia, septic embolism
Chronic:	pulmonary Langerhans cell histiocytosis, pulmonary lymphangioleiomyomatosis, honeycomb lung caused by IPF or other disorders, metastatic disease (rare)
Ground-glass opacities	
Acute:	infections (<i>P carinii</i> , cytomegalovirus), pulmonary edema, hemorrhage, hypersensitivity pneumonitis, acute inhalational exposures, drug-induced lung diseases, acute interstitial pneumonia
Chronic:	nonspecific interstitial pneumonia (idiopathic or related to underlying diseases, eg, connective tissue diseases), respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, drug-induced lung diseases, pulmonary alveolar proteinosis
Thickened interlobular septa	
Acute:	pulmonary edema
Chronic:	lymphangitic carcinomatosis, pulmonary alveolar proteinosis, sarcoidosis, pulmonary veno-occlusive disease
Distribution	
Upper lung predominance:	pulmonary Langerhans cell histiocytosis, silicosis, coal worker's pneumoconiosis, carmustine-related pulmonary fibrosis, reactivation tuberculosis, <i>P carinii</i> pneumonia on pentamidine prophylaxis
Lower lung predominance:	IPF, pulmonary fibrosis associated with connective tissue diseases, asbestosis, chronic aspiration
Central (perihilar) predominance:	sarcoidosis, berylliosis
Peripheral predominance:	IPF, chronic eosinophilic pneumonia, cryptogenic organizing pneumonia (or idiopathic BOOP)
Associated findings	
Pleural effusion or thickening:	pulmonary edema, connective tissue diseases, asbestosis, lymphangitic carcinomatosis, lymphoma, lymphangioleiomyomatosis, drug-induced diseases
Lymphadenopathy:	infections, sarcoidosis, silicosis (sarcoidosis and silicosis may be associated with lymph nodes that are calcified in an eggshell pattern), berylliosis, lymphangitic carcinomatosis, lymphoma, lymphocytic interstitial pneumonia

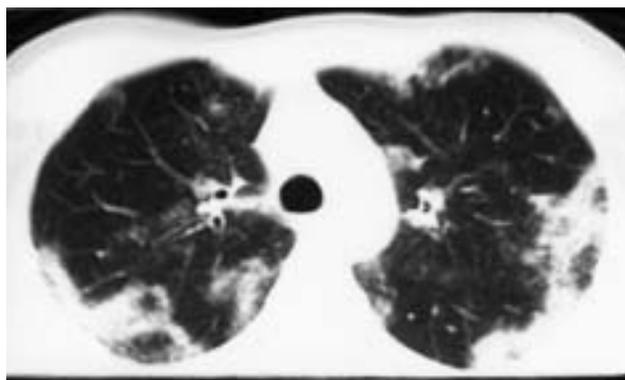


Figure 2. Computed tomographic scan of the chest shows characteristic findings of chronic eosinophilic pneumonia. Note multifocal regions of consolidation, which in this case have a typical distribution in the periphery of the lungs. Cryptogenic organizing pneumonia has a similar radiological appearance.

coal worker's pneumoconiosis are seen predominantly in the upper and middle lung zones.²⁷

Cystic Pattern

Diffuse cystic changes are seen in pulmonary lymphangiomyomatosis and pulmonary Langerhans cell histiocytosis (formerly called pulmonary eosinophilic granuloma or histiocytosis X) (Figure 5).^{29,30} Relative sparing of lung bases from cystic changes is seen in pulmonary Langerhans cell histiocytosis but not in pulmonary lymphangiomyomatosis.³⁰ Cystic airspaces seen in IPF (honeycombing) are predominantly in subpleural regions.^{25,26} Additionally, *Pneumocystis carinii* pneumonia, lymphocytic interstitial pneumonia, and septic embolism may be

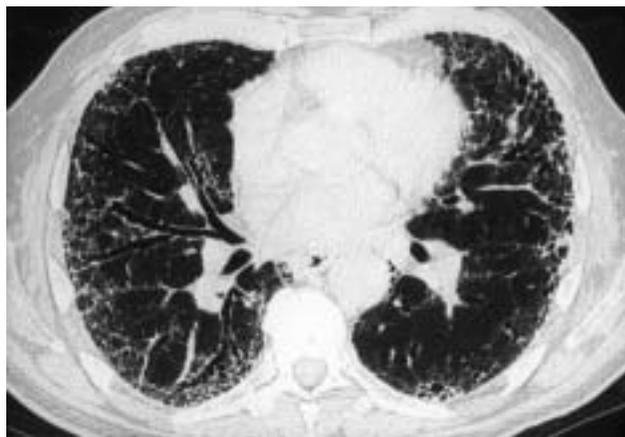


Figure 3. High-resolution computed tomographic scan of usual interstitial pneumonia. These findings are characteristic and include a honeycomb pattern with reticulation. A peripheral and basilar distribution is typical. Note regions of traction bronchiectasis. Reprinted from Ryu et al.²⁶

associated with scattered cystic lung lesions in the background of other opacities.⁸

Ground-Glass Opacity

Ground-glass opacity refers to a hazy increase in lung attenuation through which pulmonary vessels may still be seen (Figure 6). Ground-glass opacity may be caused by a partial filling of the alveolar spaces or thickening of the interstitium. Differential diagnosis of ground-glass opacities includes infections, pulmonary edema, hypersensitivity pneumonitis, acute inhalational injuries, drug-induced lung diseases, nonspecific interstitial pneumonia, respiratory bronchiolitis-associated ILD, desquamative interstitial pneumonia (DIP), acute interstitial pneumonia, and pulmonary alveolar proteinosis.^{3,8}

Septal Pattern

Thickening of the interlobular septa may be caused by edema, lymphangitic tumor spread, or fibrosis (Figure 7).^{7,8} In lymphangitic spread of tumor, nodular or beaded thickening of the interlobular septa and bronchovascular bundles is present; nodularity is absent in septal thickening from pulmonary edema.^{7,8} Pleural effusion is commonly seen in both situations.

CLINICAL CONTEXT

To make sense of any clinical problem, integrating the clinical context is essential. This is certainly true of puzzling chest radiological abnormalities. After the tempo of the disease process and the radiological pattern have been integrated, the clinical context can further focus the differential diagnosis and guide subsequent evaluation. Specific features to be delineated in the clinical context include age, sex, smoking history, current and previous systemic illnesses, immunocompromising conditions, medications (including nonprescription items), environmental and occupational exposures, and family history.

Certain diffuse lung diseases are associated with characteristic epidemiological features. For example, pulmonary lymphangiomyomatosis occurs almost exclusively in women of reproductive age.²⁹ In contrast, IPF affects predominantly middle-aged and older subjects.^{25,26} Several ILDs, including pulmonary Langerhans cell histiocytosis,³⁰ respiratory bronchiolitis-associated ILD,³¹ and DIP,³¹ are strongly associated with cigarette smoking. Environmental or occupational exposures, as well as the use of medications and other drugs, need to be considered as possible causes of diffuse lung disease. Environmental or occupational exposure is important in the pathogenesis of hypersensitivity pneumonitis (farmer's lung disease, bird fancier's disease, etc), silo filler's disease (from nitrogen dioxide gas), asbestosis, silicosis, etc. Medications that cause

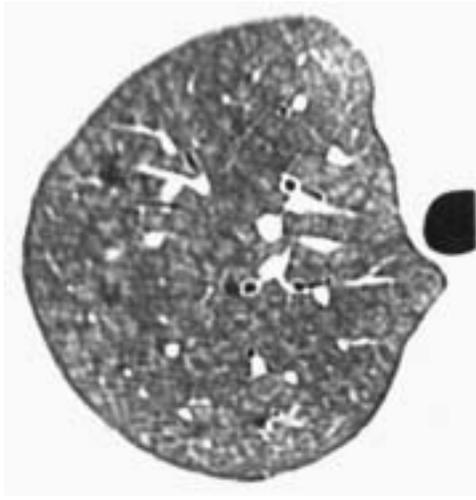


Figure 4. High-resolution computed tomographic scan of a patient with hypersensitivity pneumonitis. Note diffuse, poorly circumscribed nodular pattern with ground-glass attenuation. These findings are characteristic of subacute changes of hypersensitivity pneumonitis.

lung inflammation with the greatest frequency include nitrofurantoin, methotrexate, amiodarone, and bleomycin.¹⁶

Other facets of the patient's history and physical examination may provide clues to the nature of the diffuse lung disease. Preexisting diseases such as a connective tissue disorder or cancer may be relevant. Inheritable disorders such as tuberous sclerosis complex or neurofibromatosis should be elicited. The presence of "Velcro" crackles is nearly universal with IPF but uncommon with sarcoido-

sis.^{24,26} Similarly, digital clubbing is observed in up to two thirds of patients with IPF but is rare in patients with sarcoidosis. A history of recurrent pneumothorax is common in patients with pulmonary lymphangioleiomyomatosis and pulmonary Langerhans cell histiocytosis.^{29,30} Extrathoracic findings such as skin lesions may yield the diagnosis of sarcoidosis, dermatomyositis, or other diseases.

In immunocompromised patients, infection (especially *P carinii* pneumonia) is the most common cause of acute diffuse lung disease.³² The radiological pattern seen on HRCT can be extremely helpful in narrowing the differential diagnosis in this setting. For example, *P carinii* pneumonia usually presents as perihilar ground-glass opacities early in the course of disease.³² As the disease progresses, airspace consolidation and other features may appear. Invasive aspergillosis manifests nodules with a surrounding halo of ground-glass opacities that may evolve into necrotic infarction (air crescent formation).³²

In addition to clinical data obtained from the history and physical examination, laboratory tests and pulmonary function results may provide clues to the diagnosis. Peripheral eosinophilia is seen commonly in chronic eosinophilic pneumonia, and the presence of an underlying connective tissue disease may be further supported by positive serologic test results.²¹ Typically, pulmonary function testing shows a restrictive pattern with reduced diffusing capacity in ILD. Obstructive findings in a patient with diffuse lung infiltrates is uncommon but can be seen in patients with pulmonary lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis, hypersensitivity pneumonitis, and sarcoidosis.³³

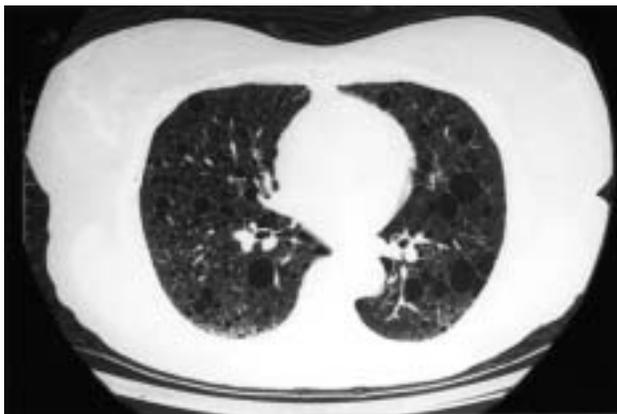


Figure 5. High-resolution computed tomographic scan of a patient with lymphangioleiomyomatosis. A diffuse pattern of well-circumscribed cysts is present throughout the lung. In lymphangioleiomyomatosis, the cysts have a diffuse homogeneous appearance throughout the lungs. The lung area between the cysts has a normal appearance on computed tomography.

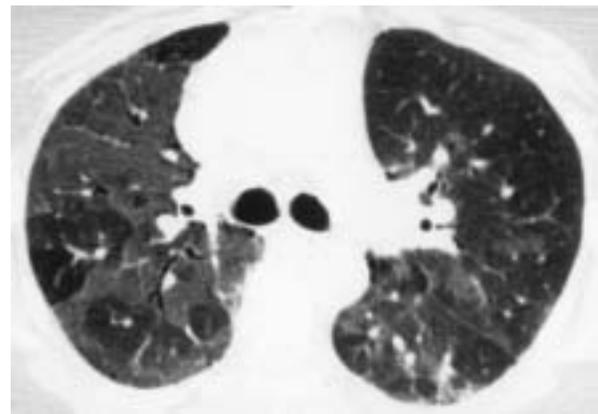


Figure 6. High-resolution computed tomographic scan of patient with desquamative interstitial pneumonia. Note mosaic pattern of ground-glass opacity. Several lobules are spared from this infiltration process. Note that in regions of ground-glass opacity, the vessels are visible, which is how ground-glass opacity is defined.

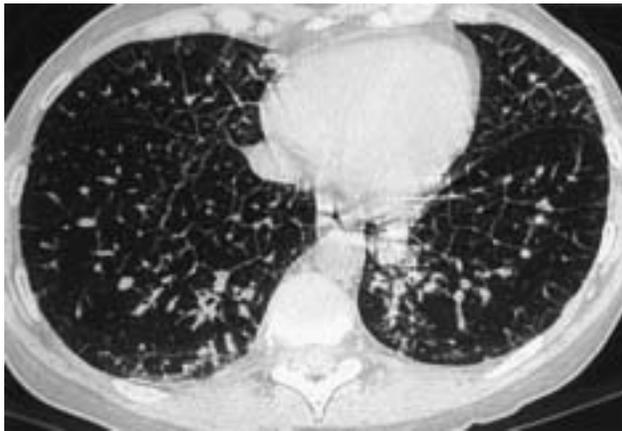


Figure 7. High-resolution computed tomographic scan shows a septal pattern due to lymphangitic carcinomatosis. Note thickening of interlobular septa, which defines secondary pulmonary lobules. Lymphangitic carcinomatosis tends to be more multifocal as opposed to cardiogenic edema, which tends to be more diffuse and with bilateral pleural effusions. The absence of marked nodularity involving the interlobular septa is uncharacteristic of lymphangitic carcinomatosis.

CONCLUSIONS

Diffuse lung disease can be caused by a large number of diverse disease processes. A methodical approach to a patient with diffuse lung disease can reduce a difficult diagnostic task and involves ascertaining pivotal parameters including tempo of the disease, radiographic pattern, and the clinical context. In many cases, correlation of these parameters may yield a working diagnosis that may or may not need to be verified by confirmatory diagnostic tests or lung biopsy. When a lung biopsy is needed, the method of biopsy (bronchoscopic or surgical) will be determined primarily by the likely diagnostic possibilities being entertained. Bronchoscopy with transbronchoscopic lung biopsy and bronchoalveolar lavage may be sufficient to diagnose infections, neoplastic processes, sarcoidosis, hypersensitivity pneumonitis, eosinophilic pneumonias, cryptogenic organizing pneumonia, pulmonary Langerhans cell histiocytosis, DIP, and pulmonary alveolar proteinosis. For other disorders such as IPF, surgical lung biopsy is required when histopathologic confirmation of the diagnosis is needed. Histopathologic diagnosis of these disorders requires a pattern recognition that is not achievable with transbronchoscopic biopsy.

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Questions About Diffuse Lung Disease

1. Which one of the following is not a feature of HRCT of the chest?
 - a. 1.0- to 1.5-mm slices
 - b. 10-mm intervals between obtained slices
 - c. High-spatial-frequency reconstruction algorithm
 - d. Standard scanning method in lung cancer staging
 - e. Useful in evaluating ILD
2. Which one of the following is not an indication for HRCT of the chest?
 - a. Detection of lung disease in the presence of normal chest radiographic findings
 - b. Detection of metastatic lung nodules
 - c. Diagnosis of bronchiectasis
 - d. Identification of pattern and distribution in ILD
 - e. Guidance in selecting the appropriate biopsy procedure and locating optimal site for biopsy
3. Which one of the following disorders is characterized by upper lung predominance of involvement?
 - a. Asbestosis
 - b. IPF
 - c. Chronic aspiration
 - d. Silicosis
 - e. Rheumatoid lung disease
4. Which one of the following is not a feature of *P carinii* pneumonia?
 - a. Peripheral lung predominance is common
 - b. Cystic changes may occur
 - c. Upper lung predominance may be seen
 - d. Ground-glass opacities are present
 - e. Acute presentation may occur
5. Which one of the following diseases or disorders does not present with cystic airspaces?
 - a. IPF
 - b. Pulmonary Langerhans cell histiocytosis
 - c. Pulmonary lymphangioleiomyomatosis
 - d. Septic embolism
 - e. Pulmonary alveolar proteinosis

Correct answers:

1. *d*, 2. *b*, 3. *d*, 4. *a*, 5. *e*