Utility of Core Needle Biopsies and Transbronchial Biopsies for Diagnosing Nonneoplastic Lung Diseases

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Sampling error in small biopsies is a reality in the practice of lung pathology. Although the yield of these samples varies from high (sarcoidosis) to low (obliterative bronchiolitis) depending on the availability of image guidance and the size and distribution of the lesion being sampled, any type of pathology can be missed by any sampling method for a variety of reasons. This phenomenon is especially common when the lesion is nonneoplastic and patchy. Pathologists who deal with small lung biopsies must also be cognizant of a wide variety of artefacts and nonspecific changes that need to be mentally subtracted from the overall histologic picture before a specific abnormality is detected. Even in cases where specific pathologic abnormalities are identified, their clinical impact may be enhanced, diminished, or modified by the clinical and radiologic context. For example, in the correct clinical context, a minute solitary nonspecific nonnecrotizing granuloma may be interpreted by the clinician as being supportive of sarcoidosis. On the other hand, a highly specific finding such as particles of food/vegetable material within lung parenchyma accompanied by the appropriate inflammatory reaction, may be downplayed or ignored because the clinical setting is deemed to be atypical or incompatible.

Nonneoplastic lesions can be missed or inadequately sampled by transbronchial lung biopsies, and occasionally even by core needle biopsies. Although the yield of the latter procedure is enhanced by computed tomography (CT) guidance and by the fact that a nodule or mass is relatively discrete and easier to sample than an ill-defined infiltrate, the fact that a needle is within a lesion radiologically is no guarantee of success (“the needle may be in the mass, but the mass is not in the needle”). Biopsies may obtain numerous cores and sample abundant tissue, all of which may prove to be normal lung, pleura, or skeletal muscle from the chest wall. Even when an adequate amount of abnormal tissue is present in the sample, the pathologic findings may be nonspecific or nondiagnostic. Given this background, it is important not to miss specific nonneoplastic findings when they are present, as their recognition can obviate the need for a second procedure, which is often an invasive surgical lung biopsy. While most pathologists are aware of the importance of findings such as granulomas or organisms, less common findings can be missed or misinterpreted, impacting patient care. Indeed, from the point of view of the patient and the bronchoscopist, a “nondiagnostic bronch” represents a poor outcome. The aim of this review is to provide surgical pathologists and pathology trainees with menus of specific nonneoplastic entities that can be diagnosed in small lung biopsies. The first part of the review will address core needle biopsies, while the second will focus on transbronchial lung biopsies. Table 1 offers a menu of nonneoplastic diagnoses that can be made in core needle biopsies of lung nodules, with examples illustrated in Figures 1 through 4. Table 2 provides a menu of nonneoplastic diseases that can be diagnosed by transbronchial lung biopsies. Selected entities are illustrated and illustrate some of these entities as they appear in small lung biopsies.

Data Sources.—Published literature and the authors’ experience with small lung biopsies for diagnosis of nonneoplastic lung diseases.

Conclusions.—Although sampling error imposes some limitations, core needle biopsies and transbronchial lung biopsies can contribute to the diagnosis of a variety of nonneoplastic lung diseases and reduce the need for invasive surgical intervention.
Necrotizing granulomatous inflammation is the most common specific finding in core needle biopsies of lung nodules. A recent multi-institution study of 500 cases of lung granulomas from 7 countries demonstrated that the type of organism found within necrotizing granulomas in lung biopsies and resections varies greatly by geographic setting, reflecting the mycobacterial or fungal endemic in the area where the biopsy is performed. Acid-fast bacteria (AFB) are the most common organisms in necrotizing granulomas in large swaths of the developing world. In core needle biopsies, they are most commonly identified within the necrotic center of the lesion. Tips for finding AFB have been published recently, one of the most important being that adequate time should be devoted to hunting for organisms by using at least an ×40 objective lens. We have seen many examples in which a cursory scan at low magnification has missed mycobacterial organisms. In any type of lung biopsy, AFB can be very few in number and nonuniformly distributed. Therefore, the absence of AFB in a small sample does not exclude the possibility of mycobacterial infection. Several studies clearly demonstrate the fact that mycobacterial cultures can be positive even when no organisms are detected by histology. The converse is also true, that is, mycobacteria can be identified by histologic examination in cases where cultures are negative. The reader should also be aware that in some settings in developed Western nations, nontuberculous mycobacteria (NTM)—most commonly Mycobacterium avium complex (MAC)—are more common in necrotizing granulomas of the lung than Mycobacterium tuberculosis. It is worth noting that the presence of AFB within necrotizing granulomas does not necessarily imply tuberculosis, since NTM can cause identical pathologic findings. The only definitive means for differentiating between M. tuberculosis and NTM are microbiologic cultures and polymerase chain reaction (PCR). Submitting a portion of biopsied tissue for cultures is an obvious solution to this problem, but in the authors’ experience tissue for core needle biopsies is often not submitted for cultures, especially when a neoplasm is suspected clinically. In such cases, interventional radiologists usually submit the entire sample in formalin for histopathology. Although formalin-fixed material cannot be used for cultures for obvious reasons, PCR for mycobacteria can be attempted on formalin-fixed, paraffin-embedded tissue. This usually requires send-out to a specialized reference laboratory, with a turnaround time of at least a few days. In general, the lower the number of AFB seen in the biopsy sample, the lower the yield of PCR. If PCR fails or if PCR testing is not available, an additional diagnostic procedure may be required to obtain fresh tissue for cultures. Bronchoscopy with bronchial washings and bronchoalveolar lavage (BAL) is especially effective for this purpose.

Infections Caused by Fungal Hyphae

Core needle biopsies can be used to diagnose lung infections caused by fungal hyphae, most commonly Fusarium. Several studies have shown that the presence of mycetomas is highly suggestive of fungal infection. Invasive aspergillosis is a frequent cause of death in patients with leukemia, lymphoma, and solid tumors. Aspergillus is a ubiquitous fungus that can cause both allergic and invasive disease. The presence of aspergillomas in lung biopsies can be used to diagnose invasive aspergillosis. In patients with chronic lung disease, these hyphae can appear identical. For this reason, we use the term fungal hyphae in pathology reports rather than Aspergillus unless the organism has been proven to be Aspergillus by prior microbiologic cultures.

### Table 1. Nonneoplastic Diagnoses That Can Be Made in Core Needle Biopsies of Lung Nodules/Masses

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Granulomas caused by infection (mostly necrotizing granulomas)</td>
<td>Tuberculosis and nontuberculous mycobacterial infections, Aspergillus, Histoplasmosis, Cryptococcosis, Blastomyces, Coccidioidomycosis, Nocardiosis, Sarcoidosis, Particulate matter aspiration, Granulomatosis with polyangiitis, Apical cap, Radiation-related scar, Organizing pneumonia, Intrapulmonary lymph node, Acute bronchopneumonia and abscess, Pulmonary Langerhans cell histiocytosis, Nodular amyloidosis, Light chain deposition disease, Pulmonary hyalinizing granuloma</td>
</tr>
<tr>
<td>Granulomatous inflammation, noninfectious</td>
<td></td>
</tr>
<tr>
<td>Scars</td>
<td></td>
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<tr>
<td>Others</td>
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* Data derived from Mukhopadhyay and Doxtader et al.

in Figures 5 through 15. Table 3 provides examples of terminology in pathology reports on these samples.

NONNEOPLASTIC DIAGNOSES THAT CAN BE MADE IN CORE NEEDLE BIOPSIES OF LUNG NODULES OR MASSES

Core needle biopsies of the lung are percutaneous transthoracic biopsies typically performed under CT guidance (CT fluoroscopy or cone-beam CT) by a radiologist, the aim being to sample localized peripheral lung lesions, most commonly nodules or masses. In most instances, the clinical differential diagnosis includes a neoplasm. In biopsies where neoplastic cells are not found, the next question that arises is whether a specific nonneoplastic diagnosis can be made that would explain the presence of a lung nodule or mass. To answer this question, it is helpful to have a list of nonneoplastic abnormalities that may manifest as lung nodules or masses. This issue was specifically addressed in a recent study by Doxtader et al., which provided details of the histologic features in these samples. A menu of possible diagnoses based on this study and the authors’ experience is shown in Table 1. In a separate large series of cases in which core needle biopsies of the lung were compared to fine-needle aspirates, the rate of identification of specific benign lesions was significantly higher with the former.
Figure 1. Cryptococcosis in a core needle biopsy. The patient was receiving corticosteroids and methotrexate for sarcoidosis and was diagnosed with cryptococcal meningitis and a lung nodule. A, Fungal yeasts with light gray walls are visible on hematoxylin-eosin. Most are surrounded by a clear space (arrows). B, On a Grocott methenamine silver stain, marked size variation is characteristic (note size difference between yeasts indicated by long and short arrows) (original magnification ×400 [A and B]).

Figure 2. Coccidioides spherules in core needle biopsy of a solitary lung mass from an elderly nonsmoker who spent his winters in Arizona. A, A spherical structure suggestive of a fungal organism (arrow) is visible within necrotic debris (arrowhead). B, The structure is a spherule containing endospores, diagnostic of Coccidioides. Cultures were positive for Coccidioides organisms (hematoxylin-eosin, original magnifications ×20 [A] and ×1000/oil immersion objective [B]).

Figure 3. Organizing pneumonia in a core needle biopsy. A, Fibroblast plugs follow the contours of the airspaces as they move from one alveolar lumen to the next (arrows). The clustered arrangement of the plugs helps to differentiate them from fibroblast foci. Branching and serpiginous shapes are typical (arrowhead indicates a branch point). B, At high magnification, fibroblast plugs can be mistaken for fibroblast foci, the latter being a feature of
Infections Caused by Fungal Yeasts and Yeastlike Fungi

Granulomatous infections caused by fungal yeasts commonly manifest as peripheral lung nodules and can be sampled by core needle biopsies.3 The 4 major fungi associated with lung nodules (usually necrotizing granulomas) are Histoplasma, Cryptococcus, Blastomyces, and Coccidioides organisms. Unlike fungal hyphae, morphologic identification of fungal yeasts and yeastlike fungi in necrotizing granulomas of the lung is feasible in most cases, and correlates well with cultures. In some cases, fungal yeasts may be present in tissue (sometimes in large numbers) but may not grow in cultures. This situation is most commonly encountered with solitary histoplasmosmas of the lung, which invariably contain nonviable Histoplasma yeasts that almost never grow in cultures, even when large numbers of organisms are identified in tissue by histology.2,3,5,7,8,10 In many areas in the United States where histoplasmosis is endemic, lung nodules characterized by necrotizing granulomas are the hallmark of remote or “healed” lung infection in immunocompetent individuals. In core needle biopsies, these lesions consist predominantly of necrosis and can be misinterpreted as an infarct or as tumor necrosis if the subtle rim of epithelioid histiocytes is not appreciated.11,12 The necrosis contains variable numbers of uniform, tiny, oval-to-tapered yeasts with occasional narrow-based budding, diagnostic of Histoplasma.7 The organisms are visible within necrosis on Grocott methenamine silver (GMS) but cannot be seen in the same areas on hematoxylin–eosin (H&E)–stained sections.10 Periodic acid–Schiff—generally a good stain for fungal organisms—is suboptimal for this form of histoplasmosis, since nonviable organisms stain very lightly or not at all and may be missed. Rarely, the disseminated form of histoplasmosis (discussed in detail in the section on transbronchial biopsies) can be sampled by core needle biopsies. Another fungal infection that can be diagnosed in core needle biopsies is cryptococcosis (Figure 1, A and B). It features organisms that are visible on H&E within histiocytes and multinucleated giant cells as well as within necrosis as faintly staining round yeasts with light gray cell walls surrounded by a clear space (Figure 1, A). Both necrotizing and nonnecrotizing granulomas can be encountered, and multinucleated giant cells can be numerous. The GMS stain is useful for highlighting the remarkable size variation and fragmentation that are hallmarks of this organism (Figure 1, B).7 The mucicarmine stain helps to confirm the diagnosis when positive, but absence of staining does not exclude the diagnosis. Blastomyces organisms can also be identified on core needle biopsies. The classic tissue reaction is a mix of supplicative (neutrophil-rich) and granulomatous inflammation. The organisms are larger than Histoplasma or Cryptococcus organisms and are characterized by broad-based budding, double-contoured cell walls, and purple nuclear material. Coccidioides spherules with or without endospores can be identified by core needle biopsy within necrosis (Figure 2, A and B) or in granulomas or giant cells. Cases with a mix of spherules and endospores can be confidently diagnosed, but differentiation from Blastomyces is often difficult or impossible.

Organizing Pneumonia

Sampling of masslike consolidation or nonresolving localized opacities by core needle biopsy occasionally yields a lesion known as “organizing pneumonia,”3 characterized by the presence of fibroblast plugs (“Masson bodies”) within airspaces (Figure 3, A and B). These plugs are composed of fibroblasts in a pale-staining or lightly collagenized background (Figure 3, A), and are liable to be mistaken for fibroblast foci (a hallmark of usual interstitial pneumonia). In contrast to fibroblast foci, fibroblast plugs are often clustered (ie, multiple plugs lie adjacent to each other); are frequently located adjacent to small pulmonary arteries (Figure 3, B); have serpiginous, branching, or dumbbell-like shapes; and may contain inflammatory cells such as plasma cells and pigmented macrophages.2 Clinicians should be aware that organizing pneumonia can occur at the edge of other mass-forming processes such as neoplasms or infarcts. Whether a pathologic diagnosis of organizing pneumonia should be considered an adequate explanation for a mass or nodule therefore depends on the clinical context and radiologic findings.

Scars

Fibrous scars occasionally manifest radiologically as localized lung nodules and can be sampled with a core needle biopsy.3 The so-called pulmonary apical cap is a common type of scar found at the apices of the lungs. It is wedge shaped, the base being at the visceral pleura and the apex in the subpleural lung parenchyma. It has a characteristic elastotic appearance (similar to solar elastosis of the skin) and often contains entrapped lung epithelium or lymphoid aggregates. As the name suggests, radiation-related scars occur after radiation for malignancy.

Pulmonary Langerhans Cell Histiocytosis

Since most cases of pulmonary Langerhans cell histiocytosis—a disease of adult cigarette smokers—are diagnosed by surgical or transbronchial biopsies, it is not widely appreciated that this condition can be diagnosed by core needle biopsy. Core needle biopsies are not commonly used because the tiny nodules seen in this disease are thought to be too small to sample with this technique. However, it has been shown that the diagnosis can be made by core needle biopsy even when the nodules are as small as 5 mm (Figure 4, A through C).13 This diagnosis should be suspected when a heavy smoker presents with multiple tiny (millimeter–size) bilateral nodules (Figure 4, A). The stellate shape of the nodules that serves as an important clue to the diagnosis in surgical lung biopsies cannot be fully appreciated in needle biopsies. However, other diagnostic features remain appreciable, including sheets of Langerhans cells, variable numbers of eosinophils, and pigmented macrophages (Figure 4, B and C).

Other Specific Diagnoses

Miscellaneous causes of lung nodules diagnosable on core needle biopsy include intraparenchymal lymph node (often containing numerous dust-laden macrophages), abscesses (suppurative necrosis destroying lung architecture), nodular amyloidosis (deposits of amyloid associated with multinu-
Figure 4. Pulmonary Langerhans cell histiocytosis diagnosed by core needle biopsy of the lung. A, Chest computed tomogram shows multiple tiny bilateral millimeter-sized nodules. B, Computed tomography–guided core needle biopsy of one of the nodules shows a cellular infiltrate rich in eosinophils. C, At high magnification, one can appreciate sheets of Langerhans cells (arrows) (hematoxylin-eosin, original magnifications ×20 [B] and ×400 [C]).
tissue or skeletal muscle). Alternatively, the findings may consist of nonspecific chronic inflammation and/or fibrosis. Clearly, these findings do not account for the presence of a lung nodule or mass. Suggested wording in pathology reports in such cases is provided in Table 3. Depending on the characteristics of the nodule and the clinical setting, the clinician may elect to follow the lesion radiologically; obtain a repeated needle biopsy; use advanced bronchoscopic techniques such as electromagnetic navigation, ultrathin scope, or peripheral ultrasound; or proceed to surgical sampling.

NONNEOPLASTIC LUNG DISEASES THAT CAN BE DIAGNOSED IN TRANSBRONCHIAL LUNG BIOPSIES

Transbronchial lung biopsies are obtained by pulmonologists. The procedure involves introduction of a bronchoscope into the bronchial lumen, introduction of biopsy forceps through the bronchoscope, and subsequent piercing of the bronchus and extension of the biopsy forceps into alveolated lung in order to sample lesional tissue. The ideal sample should include 4 to 6 fragments of alveolated lung with or without fragments of bronchial wall.\(^\text{14}\) Fragments that contain both alveolated lung and bronchial wall are counted as the former. We generally include a brief description of the sample obtained in order to give the clinician a sense of the adequacy of the specimen (Table 3). The number of transbronchial biopsy specimens (fragments) obtained and the size of the forceps used depend on the clinical and radiologic setting. It is common practice to use larger forceps and obtain a greater number of fragments when a nonneoplastic condition is suspected. For diffuse parenchymal lung disease, the bronchoscopist may choose to sample more than 1 lobe of the same lung. Unlike core needle biopsies, other types of specimens such as bronchial washings, brushings, BAL, transbronchial needle aspirates, and endobronchial biopsies can be obtained to complement information obtained from the transbronchial biopsy sample and optimize the diagnostic yield.

Although this review only addresses nonneoplastic lung diseases, it is worth noting that transbronchial biopsies occasionally sample unexpected malignancies in cases that appear nonneoplastic on clinical and radiologic grounds. The most classic example is lymphangitic carcinomatosis, but rarely lymphoma can also present with diffuse and bilateral lung opacities mimicking interstitial lung disease.\(^\text{15,16}\)

Mycobacterial Infections

A wide variety of infections can be diagnosed by transbronchial biopsies, the most common being mycobacterial and fungal (Figures 5 through 7; Table 2). As with core needle biopsies, transbronchial biopsies can contribute to the diagnosis of tuberculosis as well as NTM infection.\(^\text{6}\) Even when mycobacteria cannot be detected, the tissue reaction can be helpful in clinical decision-making. For example, in patients with suspected NTM infection, the finding of severe airway inflammation with granulomas can help to support the diagnosis, even if AFB are not

What If No Specific Diagnosis Can Be Made on a Core Needle Biopsy?

In some cases, the tissue sampled may be completely nonrepresentative, consisting only of fragments of normal lung, mesothelium-lined pleura, or chest wall (adipose

cleated giant cells), light chain deposition disease (similar to amyloid on H&E but negative for Congo red), and the rare entity known as pulmonary hyalinizing granuloma. The latter is not a true granulomatous lesion but instead is composed of dense bundles of hyalinized collagen.\(^\text{2}\)

Figure 6. Disseminated histoplasmosis in a transbronchial biopsy from a renal transplant recipient with bilateral ground-glass opacities. A, Very poorly formed granulomas are present within airspaces (long arrows). Organisms are only faintly visible at this magnification as tiny dots (short arrow). B, Under oil immersion, Histoplasma yeasts are visible within enlarged histiocytes on hematoxylin-eosin (arrows). Note eccentric chromatin dot in each yeast. Cultures were preliminarily reported as growing Histoplasma capsulatum 7 days after the biopsy diagnosis; final confirmation of culture results was obtained 2 weeks after the biopsy diagnosis (hematoxylin-eosin, original magnifications \(\times 200\) [A] and \(\times 1000\)/oil immersion [B]).
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Key Pathologic Findings and Clinical Notes</th>
</tr>
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<tbody>
<tr>
<td>Mycobacterial infections</td>
<td>Granulomatous inflammation, necrosis</td>
</tr>
<tr>
<td></td>
<td>Acid-fast bacteria</td>
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<tr>
<td></td>
<td>Clinical notes: highly variable clinical presentation. Cultures are required for confirmation of type of mycobacterium</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>Granulomatous inflammation and/or necrosis in most cases</td>
</tr>
<tr>
<td></td>
<td>Fungi: <em>Pneumocystis</em>, <em>Aspergillus</em>, <em>Histoplasma</em>, <em>Cryptococcus</em>, <em>Blastomyces</em>, <em>Coccidioides</em>, <em>Nocardia</em></td>
</tr>
<tr>
<td></td>
<td>Clinical notes: most of these infections can occur in immunocompetent individuals, and many can manifest as lung nodules that mimic lung cancer</td>
</tr>
<tr>
<td>Viral infections</td>
<td>Cytomegalovirus, adenovirus, herpes, measles</td>
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<tr>
<td></td>
<td>Clinical notes: variable presentation</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Well-formed nonnecrotizing granulomas in interstitium</td>
</tr>
<tr>
<td></td>
<td>Hyalinized fibrosis</td>
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<tr>
<td></td>
<td>Lung away from granulomas is normal</td>
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<td></td>
<td>Clinical notes: bilateral hilar/mediastinal lymphadenopathy and/or bilateral tiny lung nodules</td>
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<tr>
<td>Hypersensitivity pneumonitis</td>
<td>Lymphocytic infiltrate within interstitium and airway walls, occasional multinucleated giant cells or loose clusters of histiocytes</td>
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<td></td>
<td>Clinical notes: bilateral ground-glass opacities with air-trapping and mosaic attenuation. Typically occurs in never-smokers. Look for history of exposure to birds</td>
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<tr>
<td>Particulate matter aspiration</td>
<td>Most common particulate matter: food or vegetable particles (intact or degenerating); much less common: pill fillers</td>
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<td></td>
<td>Usual tissue reaction: multinucleated giant cells or histiocytes around or near aspirated particles. Other tissue reactions: acute or organizing pneumonia, acute or chronic inflammation in bronchiolar walls</td>
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<td></td>
<td>Clinical notes: often not suspected clinically. Can present as nodules or infiltrates, and can occur in any lobe. Look for history of recurrent pneumonia, and predisposing factors (esophageal/gastric abnormalities or surgery, narcotics or drugs of abuse, neurologic illnesses)</td>
</tr>
<tr>
<td>Talc granulomatosis (foreign body granulomas in interstitium, caused by intravenous injection of crushed oral pills)</td>
<td>Filler materials (microcrystalline cellulose, crospovidone or talc) within perivascular interstitium (alveolar septa), with adjacent foreign-body giant cell reaction</td>
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<td></td>
<td>Clinical notes: chronic use of opiates for chronic pain, venous access, multiple episodes of care at different hospitals</td>
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<tr>
<td>Pulmonary Langerhans cell histiocytosis</td>
<td>Stellate interstitial nodules containing sheets of Langerhans cells; these lesions often also contain pigmented (smoker's) macrophages, eosinophils, or lymphocytes</td>
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<td></td>
<td>Smoker's macrophages within airspaces in background lung</td>
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<td></td>
<td>Clinical notes: essentially all adults with this disease are smokers. Most cases that are biopsied have multiple bilateral millimeter-sized nodules clinically suggestive of metastatic tumor or miliary infection. Cases with nodules plus cysts on HRCT can be suspected or diagnosed by radiologists</td>
</tr>
<tr>
<td>Pulmonary alveolar proteinosis</td>
<td>Granular eosinophilic material within airspaces</td>
</tr>
<tr>
<td></td>
<td>Clinical notes: “Crazy-paving” pattern on high resolution chest CT is classic; imaging appears worse than clinical symptoms</td>
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<tr>
<td>Eosinophilic pneumonia</td>
<td>Eosinophils within airspaces (usually mixed with histiocytes and/or fibrinous exudates)</td>
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<td></td>
<td>Very common to also find numerous eosinophils within the interstitium and around small blood vessels</td>
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<td></td>
<td>Clinical notes: classic setting is eosinophilia in peripheral blood and peripheral lung infiltrates in young asthmatic individuals</td>
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<tr>
<td>Organizing pneumonia</td>
<td>Fibroblast plugs within airspaces</td>
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<td></td>
<td>Clues to differentiate from fibroblast foci: fibroblast plugs are clustered, serpiginous or branching, admixed with inflammatory cells, located adjacent to small artery</td>
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<tr>
<td></td>
<td>Clinical notes: often presents as “nonresolving pneumonia,” can manifest radiologically as infiltrate(s), opacity, nodule(s), or masslike consolidation</td>
</tr>
<tr>
<td>Diffuse alveolar damage</td>
<td>Hyaline membranes and/or diffuse alveolar septal fibroblast proliferation</td>
</tr>
<tr>
<td></td>
<td>Clinical notes: often, but not always, associated with acute respiratory failure. Radiologic picture is often misinterpreted as “pulmonary edema.” Cause is seldom evident from pathologic findings</td>
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</table>
demonstrable (Figure 5, A through C). This is because when MAC is isolated in sputum cultures, nonspecific colonization is often a concern, and the presence of an appropriate tissue reaction in the lung lends support to contention that the organism is truly pathogenic. A significant difference between transbronchial biopsies and core needle biopsies for the diagnosis of mycobacterial infections is that additional samples are often obtained along with transbronchial biopsies (bronchial washings, BAL, or bronchial brushings) and material is almost always submitted for cultures when infection is in the differential diagnosis, increasing the diagnostic yield.

**Fungal Infection**

*Pneumocystis* pneumonia is one of the most significant fungal infections diagnosed in transbronchial lung biopsies. Transbronchial biopsy is especially important in this infection because the organism cannot be cultured. Biopsies typically show a frothy material with dots within the airspaces accompanied by mild interstitial thickening. In some cases, this classic appearance is absent, however, and the histologic picture may consist of minimal and subtle interstitial thickening only. Because of this possibility, GMS staining should be performed for any severely immunocompromised patient, even in the absence of intra-alveolar froth. Careful examination of the GMS stain will occasionally yield rare *Pneumocystis* cysts. Histoplasmosis can also be diagnosed in transbronchial biopsies. Pulmonary histoplasmosis is most commonly sampled by core needle biopsy, but occasionally may be approached with a transbronchial lung biopsy. Rarely, in immunocompromised individuals, histoplasmosis does not manifest as necrotizing granulomatous inflammation (Figure 6, A and B). Instead, granulomas are poorly formed (Figure 6, A) or absent, and fungal yeasts can be seen within enlarged histiocytes on H&E (Figure 6, B). It has been shown that this finding in lung biopsies is not only diagnostic of histoplasmosis but also highly suggestive of the disseminated form of the disease. In contrast to histoplasmosomas, the organisms are viable, cultures are often positive, and the outcome is dismal.
unless antifungal therapy is initiated. As in needle biopsies, cryptococcosis can be diagnosed in transbronchial lung biopsies. Blastomycosis is less common than histoplasmosis or cryptococcosis (Figure 7, A through C). Masslike consolidation is a common radiologic finding (Figure 7, A). The tissue reaction features a mix of suppurative (abscess-like) and granulomatous inflammation, often in the form of granulomas with a suppurative center. Large fungal yeasts with double-contoured cell walls, broad-based budding, and purple nuclear material can be seen on H&E within the suppurative areas as well as within histiocytes and multinucleated giant cells (Figure 7, B and C). As with core needle biopsies, transbronchial biopsies are very useful for sampling infections caused by *Aspergillus* and other fungal hyphae, the most clinically significant being invasive aspergillosis.

**Noninfectious Lung Diseases With Granulomas**

Sarcoidosis and hypersensitivity pneumonitis are common indications for transbronchial lung biopsy (Figure 8, A and B). When sarcoidosis is suspected clinically, the pulmonologist may elect to additionally perform transbronchial needle aspiration and endobronchial biopsies in addition to transbronchial biopsies. The pathology of sarcoidosis in transbronchial biopsies is characterized by the presence of well-formed nonnecrotizing granulomas within the interstitium (Figure 8, A). When present, hyalinized fibrosis is an important clue to the diagnosis. Special staining for microorganisms (AFB and GMS) should be performed to exclude the possibility of mycobacterial or fungal infection. If these features are present in a patient with bilateral mediastinal adenopathy with or without bilateral lung nodules, our practice is to use the phrase “nonnecrotizing granulomas consistent with sarcoidosis.” The following link shows a digitally scanned whole slide image of a transbronchial biopsy from a case of sarcoidosis where this phrase was used in the diagnostic line of the pathology report: (http://epubdepot.clevelandclinic.org:82/CC/SM/2017-12/Sarcoidosis.svs/view.apml?X=0&Y=0&zoom=0.778400960162489; accessed February 2, 2018). However, in cases where granulomas are rare, necrosis is present, hyalinized fibrosis is absent, or granulomas are few or poorly formed, we prefer a descriptive diagnosis such as “granulomatous inflammation with focal necrosis.” The differential diagnosis in such cases includes mycobacterial or fungal infection, hypersensitivity pneumonitis, and hot tub lung. As shown in Figure 8, A, granulomas dominate the histologic picture in sarcoidosis. In contrast, hypersensitivity pneumonitis is characterized mainly by mild chronic inflammation within the interstitium, granulomas usually being few and difficult to find. In fact, isolated multinucleated giant cells are more common (Figure 8, B). Radiologic features on high-resolution CT can be helpful in corroborating the biopsy findings (see Table 2). Aspiration of particulate matter (mainly minute microscopic food particles) into the lung parenchyma can be accompanied by granulomas or giant cells, and is one of the most commonly missed nonneoplastic diagnoses in small lung biopsies. The key to the diagnosis is the

**Figure 7.** Blastomycosis in a transbronchial lung biopsy from a young man who was receiving infliximab for presumed sarcoidosis. A, Chest computed tomogram shows a large cavitary mass in the left upper lobe (arrow). B, Transbronchial biopsy shows fungal yeasts in a background of granulomatous inflammation (arrows). C, At high magnification, features diagnostic of Blastomyces become appreciable. Note broad-based bud (black arrow), purple nuclear material (arrowhead), and “double-contoured” cell wall (white arrow). There is considerable acute inflammation in the background. In the microbiology laboratory, the direct fungal examination showed spherical structures that were initially thought to be suggestive of endospores of *Coccidioides*. Blastomyces dermatitidis was subsequently isolated in cultures of bronchial washings, bronchoalveolar lavage, and transbronchial biopsy and confirmed by DNA gene probe (hematoxylin-eosin, original magnifications ×200 [B] and ×600 [C]).

*Small Lung Biopsies for Nonneoplastic Disease—Mukhopadhyay & Mehta*
recognition of food particles, which are often degenerated (Figure 9, A and B). Unlike acute aspiration pneumonia that is commonly encountered at autopsy, food particles in biopsy specimens are seldom found within the lumens of bronchi or bronchioles. Instead, they are more commonly seen in the walls of bronchioles or in alveolar septa (interstitium) adjacent to small bronchioles (Figure 9, A). The inflammatory reaction is highly variable. With remote aspiration, an occasional multinucleated giant cell or a few histiocytes may be the only clues that the material is foreign. In more florid examples, there may be acute or organizing pneumonia with foreign-body giant cells, or severe chronic bronchiolitis (Figure 9, A). The differential diagnosis of granulomatous lesions that can be diagnosed by transbronchial biopsy also includes talc granulomatosis. This entity is caused by trapping of particles of “filler” material within alveolar septal capillaries and their subsequent seepage into the perivascular interstitium where they elicit a foreign-body giant cell response (Figure 10, A and B). These particles are usually derived from intravenous injection of crushed oral narcotic pills. Although the term talc granulomatosis persists for historical reasons, the filler materials more commonly encountered nowadays are microcrystalline cellulose and crospovidone. The strong birefringence of the former is a helpful diagnostic feature and can be recognized in transbronchial biopsies.

Noninfectious Causes of Lung Masses

Entities other than granulomatous infections and organizing pneumonia can occasionally cause masslike consolidation, and transbronchial biopsies of these lesions may be diagnostic. A classic example is exogenous lipid pneumonia, in which foamy macrophages with coarsely vacuolated cytoplasm accumulate within lung parenchyma. In some cases, the macrophages are more prominent within airspaces (Figure 11, A and B). In others, they extend into the alveolar septa and are associated with interstitial fibrosis. This entity commonly produces masslike lesions in the lower lobes, and is seen in individuals who aspirate oily liquids, the most common being laxatives for constipation.

Drug Toxicity

Transbronchial lung biopsies can play a role in the diagnosis of pulmonary toxicity caused by certain drugs. With some drugs (such as chemotherapeutic agents), the temporal relationship between the offending drug and subsequent lung injury may be fairly obvious. In other cases, atypical or subtle inflammatory reactions may be encountered, and the attribution of such reactions to drug toxicity may be problematic. Since pathologic findings are never pathognomonic of any type of drug toxicity, the determination that an inflammatory reaction is attributable to a drug depends on onset of radiologic abnormalities after initiation of drug therapy, exclusion of other etiologies (such as infection), and resolution of radiologic abnormalities following cessation of therapy with the suspected offending drug. In this analysis, transbronchial biopsies contribute by helping to exclude infection and in demonstrating an inflammatory response that could plausibly be linked to the drug in question. For example, amiodarone toxicity can be suspected in patients who are taking amiodarone and whose biopsies show intra-alveolar foamy macrophages in combination with organizing pneumonia, diffuse alveolar damage, or cellular interstitial infiltrates. Transbronchial lung biopsies may also play a role in the diagnosis of methotrexate toxicity, nitrofurantoin-induced interstitial pneumonia, and eosinophilic pneumonia. The following Web site is a useful resource when drug-induced lung disease is suspected: http://www.pneumotox.com (accessed February 22, 2018).

Airspace Diseases

Pulmonary alveolar proteinosis is the prototype of airspace diseases that can be sampled by transbronchial lung biopsy (Figure 12, A and B). The main pathologic finding is filling of airspaces by granular, eosinophilic proteinaceous material (Figure 12, A) containing “acicular spaces” and eosinophilic globules (Figure 12, B). The alveolar septa are normal in most cases. Another predominately airspace process amenable to transbronchial biopsy is eosinophilic pneumonia (Figure 13, A and B). It is characterized by the presence of numerous eosinophils within the airspaces, usually accompanied by macrophages and/or fibrinous material (Figure 13, A). Although the disease is defined by airspace eosinophils, interstitial eosinophils are also increased in number and occasionally dominate the histologic picture (Figure 13, B).

Diagnosis of Acute Lung Injury and Idiopathic Interstitial Pneumonias by Transbronchial Lung Biopsy

Both major forms of acute lung injury—diffuse alveolar damage and organizing pneumonia—are commonly encountered in transbronchial lung biopsies. Diffuse alveolar damage (Figure 14, A and B) may be seen in the acute stage, where it manifests as hyaline membranes (Figure 14, A), or in the organizing stage, in which hyaline membranes are infrequent or absent. In the latter, the most prominent feature is diffuse interstitial expansion by fibroblasts in a pale-staining background (Figure 14, B). The etiology of acute lung injury patterns is seldom discernible on histologic grounds.

Perhaps the most controversial issue regarding transbronchial lung biopsies is whether they can be used to diagnose usual interstitial pneumonia (UIP). Although Berbescu et al convincingly demonstrated in 2006 that features of UIP can be appreciated in these biopsies, the concept initially engendered much resistance. Subsequent studies by other investigators over the years have confirmed that UIP can be diagnosed in transbronchial biopsies, although the proportion of cases in which transbronchial biopsy findings can be considered diagnostic varies widely in these reports. As in surgical lung biopsies, the diagnosis of UIP requires a “patchwork pattern” characterized by alternation of interstitial fibrosis, scarring, and microscopic honeycomb change with normal lung. Fibroblast foci, when present, support the diagnosis. Unfortunately, it is uncommon to encounter a transbronchial lung biopsy that has sampled the entire constellation of findings required for a definitive diagnosis; one such case is illustrated in Figure 15, A and B.

The recent flurry of reports on transbronchial cryobiopsy has sparked renewed interest in the use of bronchoscopy for the diagnosis of UIP and other diffuse parenchymal lung diseases. This technique is similar in some ways to conventional transbronchial biopsy, a key difference being that the size of lung tissue obtained is larger, which is made possible by freezing the target lung tissue for a few seconds.
Figure 8. Sarcoidosis versus hypersensitivity pneumonitis in transbronchial biopsies. A, Interstitial granuloma in sarcoidosis (arrow). The granuloma is well formed and relatively large. It is surrounded by hyalinized fibrosis (arrowhead). B, Interstitial multinucleated giant cell in hypersensitivity pneumonitis (arrowhead). The giant cell contains a nonspecific endogenous inclusion (cholesterol cleft) and is present in a background of interstitial chronic inflammation composed mainly of lymphocytes. Note that the lymphocytic infiltrate is slightly accentuated near a bronchiole (short arrow) and tapers off away from the bronchiole (long arrow) (hematoxylin-eosin, original magnification ×200 [A and B]).

Figure 9. Particulate matter aspiration on transbronchial biopsy. The patient had a history of multiple strokes, chronic aspiration, and nodular ground-glass opacities. A, There is severe chronic inflammation around a bronchiole (arrow). Several eosinophilic particles are identifiable in the adjacent interstitium (arrowheads). B, One of the particles at high magnification. This is a severely degenerated food particle (hematoxylin-eosin, original magnifications ×40 [A] and ×200 [B]).

Figure 10. Talc granulomatosis. A, Tiny nodules expand the alveolar septa. Foreign material is visible within the nodules even at this low magnification. B, At high magnification, microcrystalline cellulose particles are identifiable within the interstitium (short arrow), surrounded by
Table 3. Sample Pathology Reports on Core Needle Biopsies of Lung and Transbronchial Lung Biopsy

<table>
<thead>
<tr>
<th>Biopsy Type and Diagnosis Type</th>
<th>Clinical History Provided on Requisition</th>
<th>Diagnosis (“line diagnosis”)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core needle biopsy, specific diagnosis</td>
<td>Neurosarcoidosis, concern for <em>Cryptococcus</em> infection</td>
<td>Lung, right upper lobe, needle biopsy - necrotizing granulomatous inflammation (numerous <em>Cryptococcus</em> yeasts present). (See comment).</td>
<td>Sections show necrotizing granulomatous inflammation with numerous <em>Cryptococcus</em> yeasts within the necrosis as well as in the granulomatous infiltrate. The organisms are visible on hematoxylin-eosin. Special stains will be reported in an addendum. The findings were discussed with Dr X on January 16, 2016. Addendum: A Grocott methenamine silver stain confirms the presence of numerous fungal yeasts, supporting the diagnosis. Mucicarmine shows very weak staining in occasional yeasts; the majority of organisms are negative. A Ziehl-Neelsen stain for mycobacteria is negative. The original diagnosis remains unchanged.</td>
</tr>
<tr>
<td>Core needle biopsy, nondiagnostic</td>
<td>Lung nodule</td>
<td>Lung, right lower lobe, needle biopsy - fragments of alveolated lung and pleura with no significant pathologic changes. (See comment).</td>
<td>This biopsy consists of tiny fragments of alveolated lung and minute strips of mesothelium-lined pleura. No granulomas or malignant cells are identified. The findings are nondiagnostic.</td>
</tr>
<tr>
<td>Transbronchial biopsy, specific diagnosis</td>
<td>Pulmonary infiltrate</td>
<td>Lung, right upper lobe, transbronchial biopsy - nonnecrotizing granulomas consistent with sarcoidosis. (See comment).</td>
<td>This biopsy consists of 5 fragments of alveolated lung parenchyma and 3 of bronchial wall. There are multiple nonnecrotizing granulomas within the bronchial wall and alveolar septa. The granulomas are well formed and associated with hyalinized fibrosis. Lung parenchyma away from the granulomas is normal. Special stains for microorganisms (AFB and GMS) are negative. The findings are consistent with sarcoidosis.</td>
</tr>
<tr>
<td>Transbronchial biopsy, nonspecific or nondiagnostic</td>
<td>Infiltrate</td>
<td>Lung, right upper lobe, transbronchial biopsy - minimal chronic inflammation. (See comment).</td>
<td>This biopsy consists of 3 fragments of alveolated lung parenchyma. There are a few lymphocytes in the bronchial mucosa. No granulomas or malignant cells are identified. The findings are nondiagnostic.</td>
</tr>
</tbody>
</table>

Abbreviations: AFB, acid-fast bacteria; GMS, Grocott methenamine silver.

* These are examples of actual pathology reports signed out by one of the authors. Exact phrasing varies from case to case depending on the pathologic findings as well as the clinical setting. There are many other valid and clinically valuable ways to phrase both the diagnosis and the comment.

Before biopsy with the aid of a cryoprobe. The frozen tissue is then removed with the bronchoscope. In addition to being larger than conventional transbronchial biopsy fragments, the tissue obtained in this manner is less prone to artefactual collapse and is thus easier to interpret. On the flip side, occasional serious complications have been reported, and questions regarding diagnostic yield persist. The hope is that this procedure will result in an increased diagnostic yield, compared to conventional transbronchial biopsy, and a lower complication rate than for surgical lung biopsy. Whether this expectation will come to fruition, and the settings where the use of this technique offer the most benefit, remain open questions.

Finally, pathologists should be wary of diagnosing nonspecific interstitial pneumonia (NSIP), lymphoid interstitial pneumonia, respiratory bronchiolitis–interstitial lung disease, or so-called desquamative interstitial pneumonia in transbronchial lung biopsies. These diagnoses are not reliable in small specimens because they can either be overturned or superseded by other pathologic findings that have not been sampled, or require detailed knowledge of the distribution of abnormalities that cannot be provided by a transbronchial biopsy. In some respects, all of these entities are diagnoses of exclusion that require extensive sampling that can only be provided by a surgical lung biopsy. For example, a transbronchial biopsy diagnosis of NSIP is unreliable because NSIP-like areas are common in UIP. Therefore, a transbronchial biopsy diagnosis of NSIP can easily be overturned by finding areas diagnostic of UIP in a larger specimen.

**Transbronchial Lung Biopsies in Patients With Lung Transplant**

Although a detailed discussion of lung transplant-related pathology is beyond the scope of this review, it is worth noting that transbronchial biopsy is by far the most common pathologic sample used for the diagnosis of acute cellular rejection and obliterative bronchiolitis, since these patients are poor candidates for open lung biopsy.

**What If No Specific Diagnosis Can Be Made in a Transbronchial Biopsy?**

Our approach is to briefly state the pertinent findings and a few pertinent negatives. In most cases, we summarize the comment with a statement such as “the findings are multinucleated giant cells (long arrow) and foamy macrophages. As seen here, most of the particulate matter in talc granulomatosis is found in perivascular interstitium rather than within blood vessels (hematoxylin-eosin, original magnifications ×400 [A] and ×400 [B]).
Figure 11. Exogenous lipoid pneumonia in a transbronchial lung biopsy. A, Low magnification, showing an airspace-filling process. B, This alveolus is filled with foamy macrophages containing coarse vacuoles of varying sizes (arrow) (hematoxylin-eosin, original magnifications ×20 [A] and ×200 [B]).

Figure 12. Pulmonary alveolar proteinosis in a transbronchial lung biopsy. A, At low magnification, this fragment of alveolated lung shows filling of airspaces by eosinophilic material. B, The intra-alveolar material is coarsely granular and contains cholesterol cleft-like "acicular spaces" (arrow) and eosinophilic globules (arrowheads), both of which are diagnostically useful features (hematoxylin-eosin, original magnifications ×20 [A] and ×200 [B]).

Figure 13. Two examples of eosinophilic pneumonia in transbronchial biopsies. A, Numerous eosinophils are seen within airspaces. Note admixed macrophages. B, In this example, eosinophils are present within airspaces (arrow) but interstitial involvement is more striking (arrowheads) (hematoxylin-eosin, original magnifications ×400 [A] and ×200 [B]).
If the clinician has included a specific question or differential diagnosis on the pathology requisition, an attempt should be made to address these in the pathology report.

**Figure 14.** Diffuse alveolar damage in a transbronchial biopsy from a lung transplant recipient. A, Hyaline membranes are the hallmark of the acute phase. B, Organizing phase of diffuse alveolar damage from the same biopsy. Hyaline membranes are absent. The interstitium is expanded by fibroblasts in a pale background (hematoxylin-eosin, original magnifications ×100 [A] and ×200 [B]).

**Figure 15.** Usual interstitial pneumonia on transbronchial biopsy. A, A patchwork pattern is appreciable at low magnification. It is characterized by alternation of interstitial fibrosis (white arrow), architectural distortion, and microscopic honeycomb change (long black arrow) with normal lung (arrowhead). Fibroblast foci are present (short black arrow) in addition to collagen deposition. B, Another fragment from the same biopsy shows interstitial fibrosis with fibroblast foci (arrows) adjacent to normal lung (arrowheads) (hematoxylin-eosin, original magnification ×20 [A and B]).

nondiagnostic.” If the clinician has included a specific question or differential diagnosis on the pathology requisition, an attempt should be made to address these in the pathology report.

**IMPORTANCE OF CLINICAL AND RADIOLOGIC INFORMATION FOR INTERPRETATION OF TRANSBRONCHIAL LUNG BIOPSIES IN NONNEOPLASTIC LUNG DISEASE**

Clinical information is important for transbronchial biopsy interpretation in many ways. Knowing whether a lung lesion is a nodule/mass or an infiltrate is one of the most basic pieces of information that should be provided to the pathologist on the requisition form. Although pathologists look for all types of abnormalities in each biopsy, the significance of the findings observed can vary depending on whether the lesion is an infiltrate or a mass. If the patient is immunocompromised, this information should always be provided to the pathologist. This will ensure that subtle signs of infection are not missed, and it might alter the threshold at which the pathologist requests special stains for microorganisms. Transbronchial biopsies are thought to have a higher yield in immunocompromised hosts. As discussed above, some diagnoses (such as UIP) are very difficult to make in small biopsies. In such cases, knowledge of the radiologic findings is helpful. Pathologists are far more likely to make a diagnosis of UIP if the clinical setting is appropriate (73-year-old man with interstitial lung disease and basilar-predominant reticular opacities on high-resolution CT) than in highly improbable or discordant settings (23-year-old woman with pure ground-glass opacities). Occasionally, the presence of a highly suggestive clinical setting might justify some relaxation of pathologic criteria. For example, eosinophilic pneumonia is usually diagnosed when large numbers of eosinophils fill the airspaces. However, in a young individual with bilateral consolidation unresponsive to antibiotics, striking peripheral eosinophilia, and numerous eosinophils on BAL, one
might be justified in diagnosing eosinophilic pneumonia even if eosinophils are located predominantly within the interstitium rather than airspaces. Prior therapy can alter the pathologic picture. For example, eosinophilic pneumonia can regress dramatically after corticosteroid therapy. Some diagnostic labels in nonneoplastic lung disease are defined in such a way that they require an element of clinical judgement to be added to the pathologic diagnosis. For example, organizing pneumonia is a pathologic diagnosis but “cryptogenic” organizing pneumonia is a label that only clinicians can apply, since they are given leeway to decide if a particular etiology is plausible. For example, a clinician may decide that organizing pneumonia in a patient taking amiodarone is related to the drug, or that UIP in a particular patient is related to nitrofurantoin. Clearly, knowledge of the clinical history is required to make these judgements. Therefore, labels such as cryptogenic organizing pneumonia or idiopathic pulmonary fibrosis do not typically fall within the purview of the pathologist.

**CONCLUSIONS**

We hope that these lists/menus will be helpful for pathologists (especially pathology trainees and pathologists who are new in practice) when interpreting core needle biopsies or transbronchial lung biopsies that do not contain malignant cells. Recognition of these entities in small lung biopsies can spare patients the cost, discomfort, and risk associated with additional invasive testing.

**References**


