Shirt-Sleeve or Scanning Magnification as an Aid to the Diagnosis of Commonly Encountered Medical Lung Diseases

Eugene J. Mark, MD; Ruchira Ruangchira-Urai, MD; Richard L. Kradin, MD

Shirt-sleeve magnification (holding a slide over a white sleeve) and low-power magnification serve as useful adjuncts in the general categorization of noninfectious medical lung disease. This article divides medical lung disease into chronic and acute, where the temporality is determined first by clinical circumstances and then confirmed by histopathology. The low-power patterns of various lung diseases overlap, sometimes greatly. Nevertheless, classic examples of chronic disease can be sorted as linear, nodular filling, nodular dispersed, nodular lymphangitic, or cystic patterns at shirt-sleeve or low-power magnification. Classic examples of acute disease generally produce a solidifying pattern at shirt-sleeve or low-power magnification, which can be followed by a determination as to whether alveolar filling is principally fibrotic or principally fluid or cells at higher magnification. This article gives a simple system for the categorization of medical lung disease by this approach, with an emphasis on the most common diseases to be encountered in a general surgical pathology practice. In our experience, this system also proves useful in arriving at some therapeutic decisions.

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Every histologic examination of a slide begins with picking up the slide. Sometimes, considerable information can be gleaned from looking at the slide before putting it on the stage of the microscope. In the case of wedge biopsies of lung, because the normal lung contains air and is relatively clear on a slide, disease patterns can be apparent at shirt-sleeve magnification (holding a slide over a white sleeve) and may provide useful information for an initial differential diagnosis. The usefulness of this approach is the subject of this report. It deals with lung specimens obtained by thoracoscopy or thoracotomy where sufficient tissue (approximately 1 cm² or greater) is available for such observation. It is based on light microscopy and staining with hematoxylin-eosin. This is a selection of common pulmonary diseases. It does not include infectious diseases, emphysema, chronic bronchitis, congenital diseases, or malignancy.

RADIOGRAPHIC-PATHOLOGIC CORRELATION OF PATTERNS IN MEDICAL LUNG DISEASE

Recent advances in high-resolution computed tomography of the chest have led in some cases to increased diagnostic acumen of lung diseases based on the radiographic findings. The different radiographic patterns include the following: solitary airspace shadow, multifocal airspace shadow, widespread airspace shadow, solitary pulmonary nodule, multiple pulmonary nodules, diffuse bilateral small nodular opacities, bilateral reticulonodular opacities, ground glass opacities, and consolidation.¹⁻⁴ Refinements of these patterns also exist. For instance, interstitial patterns can be further subdivided into thickened interlobular or intralobular septa, subpleural honeycomb pattern, peribulbar thickening, and intersecting linear opacities.¹ Such radiographic pattern analysis can lead the clinician to diagnoses of both interstitial and consolidative diseases with greater or lesser degrees of certainty. Etiologic diagnoses and activity of disease usually require histologic and other studies, including microbiologic and serologic investigations. The distinction between a pattern and an etiology must be kept in mind.

This article is not about radiographic-pathologic correlations in medical lung disease. There are many articles and books on this subject.¹⁻⁴ However, extraction of information at a macroscopic level of lung pathology is a relatively neglected exercise, as surgical pathology generally does not lend itself to such study. A wedge biopsy of lung may contain from 1 to 4 cm² of tissue on the slide and thereby include several acini and more than one secondary lobule.⁵ This can allow for comparison to radiologic patterns.

Analysis of a wedge biopsy of lung at shirt-sleeve magnification is not a substitute for either the radiologic pattern, microscopy, or radiologic-pathologic correlation. On the other hand, the patterns that can be observed at shirt-
Figure 1. Usual interstitial pneumonitis, diffuse interstitial thickening involving entire specimen and accentuation of scar beneath pleura (between arrows) with microcystic spaces of honeycomb change (hematoxylin-eosin, shirt-sleeve magnification).

Figure 2. Usual interstitial pneumonitis, subpleural fibrosis with honeycomb (H) change, as well as spatial and temporal heterogeneity with regions of scarring (S) (eosinophilic collagen) and regions of inflammatory infiltrate (I) (hematoxylin-eosin, original magnification ×20).

Figure 3. Atelectatic scar, band of dense solid scar (S) beneath the pleura without microcystic change and sharply demarcated from relatively normal subjacent lung (L) (hematoxylin-eosin, shirt-sleeve magnification).

Figure 4. Usual interstitial pneumonitis, active fibroblastic focus (F) characteristic of the disease, as myxoid fibrosis forms a pillow upon an alveolar wall distinct from the underlying older collagen (C) (hematoxylin-eosin, original magnification ×100).

Figure 5. Atelectatic scar, band of old fibroelastic scar (S) without any temporal or spatial variation, without any inflammation, and sharply delineated from underlying unremarkable lung (L) (hematoxylin-eosin, original magnification ×20).
sleeve magnification can help to quickly narrow the focus and serve as a teaching aid.

**MEDICAL LUNG DISEASE: THE BIG PICTURE ON THE GLASS SLIDE**

Shirt-sleeve magnification can approach medical lung disease as linear, lobular filling, nodular dispersed, nodular lymphangitic, and cystic for chronic disease or consolidation due to florid active fibrosis or fluid and cells for acute disease (Table 1). Chronic and acute as general principles begin with the clinical story. The pathologist on initial histologic examination can categorize diseases as chronic conditions (eg, mature collagen, type of inflammation, architectural deformation) or acute conditions (eg, fibrin, granulocytes, hyaline membranes). On initial histologic examination, the pathologist can categorize alveolar consolidation either as principally proliferation of fibroblasts or principally fluid and cells. We here describe 7 possibilities based on knowledge of patterns and chronicity or acuteness. We here use the term "chronic" for a disease that is clinicopathologically months or years in duration and "acute" for a disease that is clinicopathologically days or a few weeks in duration.

**CHRONIC DISEASE**

**Chronic Disease, Linear**

The prototype for chronic linear disease in the context of this article is usual interstitial pneumonitis (UIP), a relatively common disease causing progressive respiratory failure, a disease that can be encountered as an occult finding at autopsy, and a disease that produces linear markings on chest radiographs as well as on a slide (Figure 1). In addition to producing linear markings, the disease is generally more advanced in the subpleural lung zone with honeycomb change, another facet that can be observed at low power (Figure 2). Scanning magnification of UIP shows the advanced fibrosis as well as the temporal and spatial heterogeneity characteristic of the disease (Figure 2). This should be contrasted with subpleural atelectatic scarring as is seen, for example, with pneumothorax, where no linear marking is present deep in the lung (Figure 3). One high-power corroborative of UIP is the active fibroblastic foci (Figure 4). This contrasts with the sometimes linear active fibrosis but forms a subpleural band in atelectatic fibrosis (Figure 5).

To the extent that it is possible, a firm diagnosis of UIP is crucial because of the prognostic import of the diagnosis. The macroscopic distribution of the disease sought on computed tomography is interstitial disease with subpleural accentuation, and these facets can be studied at shirt-sleeve magnification. As a paradigm of chronic linear disease, UIP heads the differential diagnosis. Further light microscopic examination is intended to supplement diagnostic features of UIP or their absence and thereby extend the differential diagnosis into the various other forms of interstitial pneumonitis and fibrosis, such as nonspecific interstitial pneumonitis (NSIP), airway-centered interstitial fibrosis (ACIF); desquamative interstitial pneumonia (DIP), interstitial pneumonitis due to infectious agents, or asbestosis. At shirt-sleeve magnification, NSIP may be indistinguishable from UIP. However, the absence of subpleural accentuation of the fibrosis and the absence of honeycomb change in a biopsy with diffuse interstitial fibrosis suggest NSIP (Figure 6 and 6, inset), which can be of a cellular form, a fibrotic form, or a combination of both forms.

Shirt-sleeve magnification of ACIF is, in one regard, a spatial reversal from UIP in that the greatest disease appears in the middle of the specimen rather than in the subpleural lung zone (Figure 7). Airway-centered interstitial fibrosis has fibrosis that concentrates around small conducting airways, involves alveolar walls more diffusely, and exhibits distal extension of respiratory epithelium from scarred bronchioles into adjacent alveoli (Figure 8), with the latter process also known as Lambertosis or peribronchiolar metaplasia.

**Chronic Disease, Lobular Filling**

Alveolar-filling diseases with consolidation typically are acute diseases and are described later in the article. One chronic disease that is characterized by alveolar filling by pigmented histiocytes with one lobule often more involved than another is DIP (Figure 9). Although DIP is, by terminology, an interstitial process, generally the fibrosis is not advanced but may be evident as increased interstitial markings on shirt-sleeve magnification (Figure 10). The histiocytes pack alveoli in the affected lobule (Figure 10, inset) and often have commingled eosinophils. Respiratory bronchiolitis-associated interstitial lung disease is generally considered as a continuum of DIP with lesser degrees of alveolar filling. Both diseases are seen essentially only in cigarette smokers.

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**Figure 6.** Nonspecific interstitial pneumonitis, accentuation of alveolar architecture due to interstitial fibrosis but no subpleural accentuation of scarring (hematoxylin-eosin, scanning magnification). Inset: Diffuse nature of the interstitial pneumonitis with relatively uniform rounding of alveolar airspaces (hematoxylin-eosin, original magnification ×10).

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**Table 1. Medical Lung Disease: The Big Picture on the Glass Slide**

<table>
<thead>
<tr>
<th>Chronic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear (interstitial, eg, UIP; Rx ineffective)</td>
</tr>
<tr>
<td>Lobular filling (eg, DIP/RBILD; Rx cessation of smoking)</td>
</tr>
<tr>
<td>Nodular dispersed (bronchiolar, eg, BOOP, aspiration, EG; Rx variably effective)</td>
</tr>
<tr>
<td>Nodular lymphangitic (eg, sarcoid; Rx variable depending on degree of scarring)</td>
</tr>
<tr>
<td>Cystic (eg, LAM, EG; Rx variable depending on degree of scarring)</td>
</tr>
<tr>
<td>Acute disease</td>
</tr>
<tr>
<td>Floridly fibrotic consolidation (eg, DAD; Rx ineffective unless etiology determined)</td>
</tr>
<tr>
<td>Fluid and cellular consolidation (eg, hemorrhage, edema, infections, eosinophilic pneumonia; Rx variable but potentially effective)</td>
</tr>
</tbody>
</table>

* UIP indicates usual interstitial pneumonitis; Rx, therapy; DIP, desquamative interstitial pneumonitis; RBILD, respiratory bronchiolitis-associated interstitial lung disease; BOOP, bronchiolitis obliterans–organizing pneumonia; EG, eosinophilic granuloma (Langerhans cell histiocytosis); LAM, lymphangioleiomyomatosis; and DAD, diffuse alveolar damage.
Figure 7. Airway-centered interstitial fibrosis, disease predominating in the middle of the specimen (between arrows) rather than in the subpleural lung zone (hematoxylin-eosin, shirt-sleeve magnification).

Figure 8. Airway-centered interstitial fibrosis, distorted bronchioles (B) with peribronchiolar fibrosis (F) extending into nearby interstitium as well as columnar epithelium lining abnormal distal airspaces (arrows) (hematoxylin-eosin, original magnification x20).

Figure 9. Desquamative interstitial pneumonia, lobular (L) eosinophilic consolidation with less alveolar filling around the most involved lobules and with interstitial (I) thickening visible in the less-involved areas (hematoxylin-eosin, shirt-sleeve magnification).

Figure 10. Desquamative interstitial pneumonia, alveolar filling by cells with no coarse interstitial fibrosis or architectural remodeling (hematoxylin-eosin, original magnification x10). Inset: Alveolus filled with pigmented histiocytes (hematoxylin-eosin, original magnification x200).
Chronic Disease, Nodular Dispersed

Nodularity can be described as to the number of nodules, their size, their discreteness, and their anatomic distribution. Perhaps the most common medical lung disease that enters into the differential diagnoses of dispersed nodules at shirt-sleeve magnification is bronchiolitis obliterans–organizing pneumonia (BOOP), also termed organizing pneumonia in the classification of the American Thoracic Society and European Respiratory Society. The nodules may be well demarcated and seemingly randomly dispersed (Figure 11). The elements of the obliterative bronchiolar process include a branching pattern and intra-bronchiolar fibrosis (often termed Masson bodies) and inflammation at higher power (Figure 12). Usual interstitial...
Figure 17. Sarcoidosis, several contiguous granulomas forming a line that signifies a lymphatic distribution (hematoxylin-eosin, original magnification ×200).

Figure 18. Langerhans cell histiocytosis, cystic spaces (C) in burned-out disease (hematoxylin-eosin, original magnification ×10).

Figure 19. Lymphangioleiomyomatosis, numerous cysts (C) of variable size distributed through the specimen (hematoxylin-eosin, shirt-sleeve magnification).

Figure 20. Lymphangioleiomyomatosis, proliferating abnormal smooth muscle cells (M) forming a nodule and walls of cysts (C) (hematoxylin-eosin, original magnification ×10). Inset: Fascicles of spindled smooth muscle cells are tightly packed together like sardines in a can (hematoxylin-eosin, original magnification ×200).

Figure 21.

Figure 22.
pneumonitis and BOOP share some clinical and radiographic features, and this initial clinical differential diagnosis is common, but UIP generally does not produce nodules and BOOP generally does not produce linear disease, and this simple and important distinction can generally be made at shirt-sleeve magnification. Other causes of discrete nodular disease include aspiration (Figure 13) with focal pneumonia, bronchioalveolar carcinoma, or metastatic malignancy. A refinement of the nodular dispersed pattern is Langerhans cell histiocytosis, where characteristic starfish-shaped or stellate-shaped lesions are observed either on shirt-sleeve magnification (Figure 14) or at scanning magnification (Figure 15). The recognition of the Langerhans cells is observed at high power (Figure 15, inset).

**Chronic Disease, Nodular Lymphangitic**

The lymphatics course in two routes in the lung—first around bronchovascular bundles, and second within pleura and interlobular septa. Disease that selectively lies along lymphatic pathways can therefore produce the radiologic descriptions of peribronchial thickening, septal thickening, peribronchial thickening, or pleural thickening. The most commonly encountered lung disease in the United States that produces nodules in lymphangitic pattern is sarcoidosis. The linearity need not be continuous, and the nodules may be grouped (Figure 16). This linearity is best appreciated at shirt-sleeve or scanning magnification and cannot be appreciated on bronchoscopic biopsies or at high magnification of wedge biopsies. The lymphangitic distribution of the granulomas (Figure 17) aids in distinguishing sarcoidosis from infectious granulomatous diseases. Tuberculosis can be lymphangitic or miliary (ie, bloodborne or embolic), but sarcoidosis cannot be miliary. Other diseases that can appear in lymphangitic guise at low magnification include lymphangitic carcinoma, malignant lymphoma, silicosis, and fungal infections.

**Chronic Disease, Microcystic**

Radiographic analysis of cystic lung disease depends upon the age of the patient and which lobes are involved. The size of the cyst dictates whether an entire cyst can be represented on a wedge biopsy. Microcysts that are a few millimeters in diameter can be observed at low-power magnification and occur in various conditions. Two regularly enter into the differential diagnosis of medical lung disease. These two are burned-out Langerhans cell histiocytosis (Figure 18) and lymphangioleiomyomatosis (Figure 19). The diagnostic, densely packed, smooth muscle cells of lymphangioleiomyomatosis are appreciated at higher magnification as they create the wall of the cyst (Figure 20 and 20, inset). Other diseases with a cystic component and observable at shirt-sleeve magnification include emphysema, bronchiectasis, overinflation due to bronchiolar obstruction, and cystic adenomatoid malformation.

**ACUTE DISEASE**

**Acute Disease, Floridly Fibrotic Consolidation**

Consolidated lung at shirt-sleeve magnification means uniform opacity without air-containing parenchyma. Consolidated lung tissue encompasses a wide spectrum of disease, including infectious pneumonias, tumors, and scarring processes. In the context of patients with acute medical lung disease, we are addressing adult respiratory distress syndrome with airspace consolidation, which is the clinical scenario in which a wedge lung biopsy is performed and a speedy answer is expected of the surgical pathologist. Diffuse alveolar damage (DAD) is the common histopathologic finding in this scenario. The consolidation tinctorially will depend on its cellularity and connective tissue component, with floridly fibrotic consolidation being basophilic (Figure 21). Higher magnification shows the hyaline membranes (Figure 22), the proliferation of fibroblasts filling alveoli, and thrombosis of small blood vessels. Diffuse alveolar damage is used here as a pathologic diagnosis without regard as to whether the etiology is known. Clinical scenarios that can cause DAD and prompt a biopsy include sepsis, hypotension, aspiration, prolonged administration of oxygen, radiation, or drug reaction. Occasionally, the biopsy may contain morphologic clues to the etiology of the DAD (Table 2).

**Acute Disease, Fluid, and Cellular Consolidation**

Airspace consolidation can be due to fluid or cells. Foremost in clinical urgency among the fluids is blood, and...
Figure 23. Pulmonary hemorrhage, dense red consolidation due to blood, involving almost the entire specimen (hematoxylin-eosin, shirt-sleeve magnification). Inset: Alveoli are expanded by blood (hematoxylin-eosin, original magnification x20).

Figure 24. Pulmonary hemorrhage with capillaritis, alveolar wall widened by neutrophils and nuclear dust (N) and blood. Alveolar pneumocytes (P) on each side of the alveolar wall are hypertrophic (hematoxylin-eosin, original magnification x400).

Figure 25. Pulmonary edema, pale pink and in areas almost clear airspace filling (hematoxylin-eosin, shirt-sleeve magnification).

Figure 26. Pulmonary edema with translucent fluid (hematoxylin-eosin, original magnification x100).

Figure 27. Pulmonary alveolar proteinosis with opaque fluid when compared with edema fluid and with cracks and cholesterol clefts (arrows) and a cellular interstitial infiltrate (hematoxylin-eosin, original magnification x100).

Figure 28. Chronic eosinophilic pneumonia, airspace consolidation by cells and fibrosis (hematoxylin-eosin, shirt-sleeve magnification). Inset: Acute eosinophilic pneumonia, alveoli filled with eosinophils and histiocytes and fibrin (hematoxylin-eosin, original magnification x200).
this can be appreciated at shirt-sleeve magnification by the red color and the solidity and extent of consolidation (Figure 23). Expansion of alveolar airspaces (Figure 23, inset), as opposed to atelectasis with blood in compressed alveoli, is a useful feature in identifying hemorrhage from artefactual or operative or aspirated blood (Table 3). The most important element that the pathologist must recognize is capillaritis (Figure 24), since this morphologic diagnostisis may need to stand alone with or without confirmatory clinical or laboratory support.

Airspace consolidation can be due to other fluids. One such fluid is pulmonary edema, which will produce a pale pink consolidation on shirt-sleeve magnification if the protein content is high but may be virtually clear if the protein content is low (Figure 25). Edema fluid is translucent (Figure 26) compared with the alveolar fluid in pulmonary alveolar proteinosis, which has relative opacity (Figure 27) and granularity with cholesterol crystals. Alveolar consolidation as seen in pulmonary alveolar proteinosis generally presents as subacute or chronic disease but occasionally has a sudden clinical presentation.

Alveolar consolidation due to cells is classically seen in the pneumonias, where alveoli are filled with fibrin and inflammatory cells. This report does not deal further with the infectious diseases. A disease with alveolar filling by cells which does arise in the setting of medical disease is eosinophilic pneumonia, which can be either acute or chronic. Eosinophilic pneumonia is often patchy both radiographically and histologically, and it can cause lobular consolidation at shirt-sleeve magnification (Figure 28). Eosinophils and variable numbers of histiocytes expand alveoli (Figure 28, inset), with the proportion of eosinophils affected by corticosteroid therapy given prior to biopsy. Acute eosinophilic pneumonia often has a greater component of fibrin than chronic eosinophilic pneumonia, and blood and hyaline membranes also may be present.

A useful basic clinical differentiation can be achieved by categorizing alveolar-filling diseases as being fibrotic versus fluid or cells pending further investigative studies. Although positive end-expiratory pressure ventilation and other modalities are used in the treatment of DAD, survival of patients with DAD has improved only modestly over the years. This may be because of the variety of etiologies of DAD as well as the florid fibrosis which, once started, is difficult to stop. On the other hand, alveolar filling by hemorrhage due to capillaritis or bleeding diathesis is treatable, alveolar filling by edema is treatable depending on the etiology, alveolar filling by fibrin and neutrophils due to infection may be treatable with anti-biotics, and alveolar filling by eosinophils in the eosinophilic pneumonias is treated by corticosteroids.

**SUMMARY**

The exact diagnosis of medical lung disease cannot be made at shirt-sleeve or low-power magnification, but the diagnosis can be suspected in many instances. The basic patterns seen serve a useful purpose for both pathologists and pulmonologists. Paying attention to the biopsy at shirt-sleeve magnification establishes a visual habit of looking at all corners of the biopsy for thorough examination.

For therapeutic purposes, the principal differential diagnosis in most patients with chronic disease in the United States who come to have a wedge biopsy of lung is an interstitial pneumonitis, and particularly UIP versus BOOP or a form of organizing pneumonia, because the former cannot be effectively treated by correct medical management and the latter usually can be effectively treated.

This initial determination of linear or nodular dispersed is evident at shirt-sleeve magnification. Other low-power patterns of lobular filling, nodular lymphangitic, or cystic can represent less common conditions with variable means of treatment, including cessation of cigarette smoking and lung transplantation in addition to corticosteroids or other drugs.

For patients with acute disease, usually biopsied while in the intensive care unit, the generic clinical diagnosis of adult respiratory distress syndrome will usually be represented on biopsy at shirt-sleeve magnification as diffuse consolidation. Subdividing the consolidation at higher magnification into two general categories of fibrotic versus fluid or cells separates one condition, which has less effective therapy from all of the others, which have various possible etiologies but also more possibilities for therapeutice intervention.

**References**