CT-Histologic Correlation of the ATS/ERS 2002 Classification of Idiopathic Interstitial Pneumonias

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The American Thoracic Society and the European Respiratory Society 2002 classification defines the histologic patterns that provide the basis for a clinico-radiologic-pathologic diagnosis of an idiopathic interstitial pneumonia. Idiopathic pulmonary fibrosis is the clinical term for usual interstitial pneumonia, the characteristic histologic pattern is interstitial fibrosis with temporal heterogeneity, and the radiologic pattern is basal and subpleural areas of ground-glass and reticular attenuation and honeycomb pattern. Nonspecific interstitial pneumonia has cellular or fibrosing patterns of chronic inflammation with temporal homogeneity; the radiologic pattern is subpleural and basal areas of ground-glass and reticular attenuation. Lymphoid interstitial pneumonia results from lymphocyte interstitial infiltration; CT demonstrates ground-glass attenuation and nodular interlobular septal thickening. Respiratory bronchiolitis–associated interstitial lung disease is characterized by bronchiocentric alveolar macrophage accumulation; CT shows centrilobular ground-glass attenuation. Desquamative interstitial pneumonia is characterized by alveolar macrophage accumulation with predominantly lower zone ground-glass attenuation seen on CT scans. Cryptogenic organizing pneumonia is characterized radiologically by peribronchial ground-glass attenuation and subpleural consolidation. Acute interstitial pneumonia is the clinical term for idiopathic diffuse alveolar damage; the exudative phase is characterized radiologically by diffuse ground-glass attenuation and dependent consolidation, with the additional feature of lung architectural distortion in the organizing phase. Ideally, diagnosis of an idiopathic interstitial pneumonia should be rendered only after all clinico-radiologic-pathologic data have been reviewed.

INDEX TERMS: Bronchiolitis obliterans organizing pneumonia, 60.79 • Lung, CT, 60.12118 • Lung, interstitial disease, 60.79 • Pneumonia, acute interstitial, 60.7921 • Pneumonia, desquamative interstitial, 60.793 • Pneumonia, lymphocytic interstitial, 60.795 • Pneumonia, nonspecific interstitial and fibrosis, 60.795 • Pneumonia, usual interstitial, 60.792

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Introduction

Liebow and Carrington (1) provided the framework for the histologic classification of the idiopathic interstitial pneumonias in 1969. They described five types of interstitial pneumonia: usual interstitial pneumonia, bronchiolitis obliterans interstitial pneumonia with diffuse alveolar damage, desquamative interstitial pneumonia, lym- phocytic interstitial pneumonia, and giant cell interstitial pneumonia. The evolution of this classification over time included adding respiratory bronchiolitis interstitial lung disease (2), bronchiolitis obliterans organizing pneumonia (3), acute interstitial pneumonia, and nonspecific interstitial pneumonia (2,3). Giant cell interstitial pneumonia was dropped from the classification because it results from hard metal pneumoconiosis. Some authors do not consider respiratory bronchiolitis and desquamative interstitial pneumonia to be idiopathic interstitial pneumonias. These diseases have a strong association with smoking, with des- quamative interstitial pneumonia being on the same spectrum as respiratory bronchiolitis–associ- ated interstitial lung disease, albeit the extreme form (4). However, there may be an idiopathic variety of these two entities (5).

The development of a new classification of the idiopathic interstitial pneumonias was prompted by the publication of large series of patients with idiopathic interstitial pneumonia (6,7), availability of the more acceptable video-assisted thoracoscopic lung biopsy (8,9), widespread use and understanding of high-resolution computed tomog- raphy (CT) (10,11), and renewed interest in the pathogenesis of idiopathic interstitial pneumo- nias because of new therapeutic developments (12,13). The American Thoracic Society and the European Respiratory Society have issued a consen- sus statement that defines a set of histologic patterns that provides the basis for a final clinicoradiologic-pathologic diagnosis of idiopathic interstitial pneumonia (14). The new classification includes seven designations: (a) idiopathic pulmon- ary fibrosis (IPF) (also known as usual inter-stitial pneumonia [UIP]), (b) nonspecific interstitial pneumonia (NSIP), (c) lymphoid interstitial pneumonia (LIP), (d) respiratory bronchiolitis–associated interstitial lung disease (RB-ILD), (e) desquamative interstitial pneumonia (DIP), (f) cryptogenic organizing pneumonia (COP) (formerly known as bronchiolitis obliterans organ-izing pneumonia), and (g) acute interstitial pneumonia (AIP).

The idiopathic interstitial pneumonias are a heterogeneous group of nonneoplastic disorders in which the lung parenchyma is damaged by varying patterns of inflammation and fibrosis. The interstitium includes the space between the epithelial and endothelial basement membranes and is the primary site of disease in the idiopathic interstitial pneumonias. These disorders also frequently affect the air spaces, peripheral airways, and vessels, as well as their respective epithelial and endothelial linings (15). The duration of symptoms from an interstitial pneumonia may be arbitrarily classified according to the duration of dyspnea and often a cough: acute symptoms are present for days to weeks; subacute, for less than 3 months; and chronic, for more than 3 months. The article summarizes the clinicoradiologic-pathologic features of the new classification and illustrates the CT and pathologic manifestations of each idiopathic interstitial pneumonia designation.

Chronic Forms of Idiopathic Interstitial Pneumonia

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is the archetype interstitial pneumonia and is the clinical term for an interstitial pneumonia of unknown cause associated with biopsy or autopsy findings that show a histologic pattern of usual interstitial pneumonia. The diagnosis of idiopathic pulmonary fibrosis requires the exclusion of other known causes of usual interstitial pneumonia, including use of toxic drugs, environmental exposure, and collagen vascular disease; characteristic chest radiographic or high-resolution CT abnormalities; and abnormal results from pulmonary function tests. The pulmonary function tests show lung restriction or impaired gas exchange, decreased $\text{PaO}_2$ with rest or exercise, or decreased diffusion capacity of the lung for carbon monoxide ($\text{DLCO}$).

A gradual onset of dyspnea is the prominent presenting symptom. Patients usually have a nonproductive cough that may be paroxysmal. Patients are typically older than 50 years of age. Velcro-type end-inspiratory crackles are heard on auscultation. Digital clubbing develops in 50% of patients. Bronchoalveolar lavage fluid contains an excess of neutrophils (16). Prognosis is poor, with a 2.5–3.5-year median length of survival from the time of diagnosis. Treatment options include corticosteroids, azathioprine, and lung transplantation. A promising new therapy is interferon-$\gamma$-1b that inhibits fibroblast proliferation and collagen synthesis. Preliminary work with this treatment suggests that it yields improvement in lung physi-
ology and survival (12,13); however, more work is necessary on this exciting development.

The most common chest radiographic abnormalities seen in patients with idiopathic pulmonary fibrosis are peripheral reticular areas of opacification (most marked posteriorly and at the lung bases), honeycomb pattern, and small lungs (17).

**CT Features.**—Idiopathic pulmonary fibrosis has characteristic manifestations on CT scans: reticular attenuation with interlobular septal thickening, architectural distortion with associated traction bronchiectasis and bronchiolectasis, a honeycomb pattern, and ground-glass attenuation (Fig 1a, 1b). The preceding abnormalities are predominantly basal and peripheral in distribution (10,18–22). The CT differential diagnosis of idiopathic pulmonary fibrosis includes usual interstitial pneumonia caused by asbestosis and collagen vascular disease, chronic hypersensitivity pneumonitis, and sarcoidosis, which occasionally can manifest with CT findings similar to those of idiopathic pulmonary fibrosis.
Histologic Features.—The histologic findings of idiopathic pulmonary fibrosis include dense fibrosis causing remodeling of lung architecture with frequent “honeycomb” change, fibroblastic foci typically scattered at the edges of dense scars, and fibrotic zones with temporal heterogeneity (with dense acellular collagen and scattered fibroblastic foci). Smooth muscle hyperplasia is often seen in areas of fibrosis (Fig 1c, 1d). These histologic features are frequently found in septa and beneath the pleura. There tends to be patchy lung involvement (7,23,24).

Nonspecific Interstitial Pneumonia
The concept of nonspecific interstitial pneumonia is used to identify a group of interstitial lung disorders with a more favorable prognosis than that of idiopathic pulmonary fibrosis.

The clinical presentation of patients with nonspecific interstitial pneumonia, as well as the pathologic features as determined from surgical lung biopsy specimens, are as yet poorly defined. The mean age range of onset is 40–50 years. Duration of symptoms is 6 months to 3 years. Patients usually present with breathlessness, cough, and fatigue, with weight loss being reported in almost half of the cases. Crackles are heard on auscultation. Results from pulmonary function tests are milder but similar to those for idiopathic pulmonary fibrosis. Bronchoalveolar lavage fluid reveals an increase in the percentage of lymphocytes. The clinical course varies between complete recovery to stable symptoms and relapse in a number of cases (25,26). Treatment, when necessary, follows the same regimen as that used for idiopathic pulmonary fibrosis.

Chest radiography of a patient with nonspecific interstitial pneumonia demonstrates bilateral areas of reticular and ground-glass opacity in the lower lung zones (27).

CT Features.—Nonspecific interstitial pneumonia has characteristic manifestations on CT scans: ground-glass attenuation, irregular linear or reticular areas of attenuation with associated bronchiectasis and bronchiolectasis. Honeycomb lung and consolidation are seen infrequently (Fig 2a). Abnormalities are bilateral, symmetric, and subpleural in distribution (25,28,29). The CT differential diagnosis includes usual interstitial pneumonia, hypersensitivity pneumonitis, and sarcoidosis.

Histologic Features.—Nonspecific interstitial pneumonia manifests histologically with two different patterns: cellular or fibrosing. A case of nonspecific interstitial pneumonia will have varying degrees of cellular or fibrosing features (Fig 2b, 2c). The cellular pattern is characterized by mild to moderate interstitial chronic inflammation and interstitial fibrosis with loose fibrillar collagen. The fibrosing pattern is manifest as chronic interstitial inflammation obscured by interstitial fibrosis (with dense collagen), a temporal homogeneous pattern, and occasional focal honeycomb fibrosis (6,7,27).

Lymphoid Interstitial Pneumonia
Lymphoid interstitial pneumonia is a diffuse pulmonary lymphoid proliferation of involved areas with predominant interstitial changes. This condition must be differentiated from a related one, follicular bronchiolitis, which is a peribronchiolar lymphocytic infiltrate with germinal centers.

Lymphoid interstitial pneumonia is most often associated with collagen vascular disease, immunodeficiency, and Sjögren syndrome. Idiopathic lymphoid interstitial pneumonia is very rare. It is more common in women and in those who are 40–49 years old. An insidious onset of cough and dyspnea may be accompanied by fever, weight loss, and arthralgia. Because idiopathic lymphoid interstitial pneumonia rarely progresses to fibrosis, crackles and physiologic features of idiopathic interstitial pneumonia are absent or mild. Bronchoalveolar lavage fluid demonstrates many lymphocytes with no clonality (30). The most widely used treatment is corticosteroid therapy (31).

Chest radiographic patterns include basilar alveolar opacity or diffuse areas of opacity (32).
CT Features.—Lymphoid interstitial pneumonia often manifests with the following characteristics on CT scans: ground-glass attenuation, centrilobular and subpleural lung nodules with thickening of the interlobular septa, and peribronchovascular interstitium. Perivascular cysts are seen in some cases. These abnormalities may be regional or diffuse (Fig 3a, 3b) (33,34). The CT differential diagnosis includes hypersensitivity pneumonitis, sarcoidosis, and lymphangitic spread of tumor; the cystic abnormalities are reminiscent of those seen in Pneumocystis carinii pneumonia.
Histologic Features.—The histologic findings of lymphoid interstitial pneumonia include interstitial infiltration of involved areas including alveolar septa and bronchioles; infiltrates composed of mostly lymphocytes, plasma cells, and macrophages; and lymphoid follicles (Fig 3c, 3d). These histologic features have a predominantly alveolar septal distribution (14).

Respiratory Bronchiolitis–associated Interstitial Lung Disease
Respiratory bronchiolitis–associated interstitial lung disease is the clinical manifestation of an interstitial lung disease associated with the pathologic lesion of respiratory bronchiolitis, which is found in cigarette smokers. When respiratory bronchiolitis is symptomatic, the patient has abnormal results from pulmonary function tests and imaging studies.

Most patients with respiratory bronchiolitis–associated interstitial lung disease have mild
symptoms of dyspnea and cough. The disease usually affects current smokers 30–40 years old with more than 30 pack-years of cigarette smoking and has a male-to-female ratio of 2:1. Pulmonary function tests demonstrate a reduction in Dlco, as well as airway obstruction and restriction. Bronchoalveolar lavage fluid contains alveolar macrophages with golden, brown, or black pigment inclusions, findings that are indistinguishable from those seen in nonaffected smokers. Clinical course improves after cessation of smoking (35–37).

Chest radiography demonstrates thickening of the walls of the central and peripheral bronchi and areas of ground-glass opacity (38).

**Figure 4.** Respiratory bronchiolitis–associated interstitial lung disease in a 30-year-old woman. (a) High-resolution CT scan of the upper lobe demonstrates centrilobular ground-glass attenuation (arrows). (b) Photomicrograph (original magnification, ×40; hematoxylin–eosin stain) shows a terminal bronchiole filled with pigmented macrophages (a). (c) Photomicrograph (original magnification, ×50; hematoxylin–eosin stain) shows the “tobacco pigment” in macrophages (a) within alveolar ducts and alveoli. Collagenous scarring involves interstitium between alveoli. b = mild bronchiolar fibrosis, c = chronic inflammation.

**CT Features.**—Respiratory bronchiolitis–associated interstitial lung disease often manifests with the following characteristics on CT scans: centrilobular ground-glass nodules, thickening of central and peripheral airways with associated centrilobular emphysema and air trapping (Fig 4a). These findings appear predominantly in the upper lobes (37,38). The CT differential diagnosis of respiratory bronchiolitis–associated interstitial lung disease includes acute hypersensitivity pneumonitis, desquamative interstitial pneumonia, and nonspecific interstitial pneumonia.
Figure 5. Desquamative interstitial pneumonia in a 42-year-old man. (a) High-resolution CT scan of the upper lobes demonstrates diffuse ground-glass attenuation, a minor degree of interlobular septal thickening (arrow), and paraseptal emphysema. (b) High-resolution CT scan demonstrates a mosaic pattern of lung attenuation; the abnormal regions are manifested as ground-glass attenuation (arrows). (c) Photomicrograph (original magnification, ×12.5; hematoxylin-eosin stain) shows purple macrophages (a) filling the air spaces, interstitial fibrosis (b), and lymphoid aggregates (c). (d) Photomicrograph (original magnification, ×50; hematoxylin-eosin stain) reveals an alveolar duct that is filled and distended by pigmented macrophages with purple cytoplasm. Occasional eosinophils (d) and neutrophils are present amidst the macrophages. Interstitial fibrosis is present.
Histologic Features.—The histologic findings of respiratory bronchiolitis–associated interstitial lung disease include bronchiolocentric accumulation of pigmented alveolar macrophages with mild bronchiolar fibrosis and chronic inflammation (Fig 4b, 4c). Macrophages have dusty brown cytoplasm from the “tobacco pigment” (35,39).

Subacute Forms of Idiopathic Interstitial Pneumonia

Desquamative Interstitial Pneumonia

The term desquamative interstitial pneumonia is a misnomer because the dominant histologic feature is intraalveolar macrophage accumulation rather than desquamated pneumocytes. In most cases, desquamative interstitial pneumonia is associated with cigarette smoking and is thought to represent the end of a spectrum of respiratory bronchiolitis–associated interstitial lung disease.

Desquamative interstitial pneumonia affects cigarette smokers 30–40 years old, with a male-to-female ratio 2:1. A slow onset of dyspnea and dry cough can progress to respiratory failure. Pulmonary function tests demonstrate a restrictive abnormality and decreased Dlco. Bronchoalveolar lavage fluid contains increased numbers of alveolar macrophages with granules of “smoker’s pigment.” The prognosis for patients with desquamative interstitial pneumonia is good with cessation of smoking and steroid therapy (40).

Chest radiography often demonstrates widespread areas of ground-glass opacity (41).

CT Features.—Desquamative interstitial pneumonia often manifests with the following characteristics on CT scans: ground-glass attenuation with occasional interlobular septal thickening having a peripheral and patchy or diffuse and uniform distribution (Fig 5a, 5b). These findings appear predominantly in the lower lung zones in the majority of cases (42). The CT differential diagnosis includes respiratory bronchiolitis–associated interstitial lung disease, acute or subacute hypersensitivity pneumonitis, sarcoidosis, and an infection such as P carinii pneumonia.

Histologic Features.—The histologic findings of desquamative interstitial pneumonia include lobular involvement of lung parenchyma with prominent accumulation of alveolar macrophages. Mild to moderate fibrotic thickening of alveolar septa is seen, with mild interstitial chronic inflammation including lymphoid aggregates and occasional eosinophils (Fig 5c, 5d) (35).

Cryptogenic Organizing Pneumonia

The organizing pneumonia pattern is often secondary to a known cause such as rheumatoid arthritis, viral pneumonia, or drug reactions. The term cryptogenic organizing pneumonia (formerly bronchiolitis obliterans organizing pneumonia) is used when the histologic features of the organizing pneumonia pattern are demonstrated and the cause is idiopathic.

Patients (mean age, 55 years old) usually present with variable degrees of productive cough and dyspnea and a short illness duration of less than 3 months. Weight loss, sweats, chills, intermittent fever, and myalgia are common. Localized or widespread crackles on auscultation are frequent. Elevated levels of erythrocyte sedimentation rate, C-reactive protein, and peripheral blood neutrophils are common. Bronchoalveolar lavage fluid contains an increased number and proportion of lymphocytes (43). Most patients recover completely after oral administration of corticosteroids. Relapse can occur.

The most common chest radiographic abnormality is bilateral or unilateral areas of patchy consolidation (17).

CT Features.—Cryptogenic organizing pneumonia manifests with the following characteristics on CT scans: consolidation and ground-glass attenuation with mild bronchial dilatation seen in regions of consolidation. The distribution is subpleural or peribronchial. Small centrilobular nodules are also seen (Fig 6a, 6b). The lower lung
zones are more frequently affected (44,45). The CT differential diagnosis includes alveolar cell carcinoma, lymphoma, vasculitis, sarcoidosis, and infection. When the consolidation is subpleural, chronic eosinophilic pneumonia should also be considered.

**Histologic Features.**—Cryptogenic organizing pneumonia manifests histologically with two different patterns: early phase and late phase. The features of early-phase cryptogenic organizing pneumonia include a localized lesion, centering on a bronchiole with involvement of alveolar ducts and alveoli. Lymphocytes and plasma cells are seen within a fibrous tuft in an airway. There is a relative preservation of lung architecture and
uniform temporal appearance with mild interstitial chronic inflammation (Fig 7). Late-phase cryptogenic organizing pneumonia has the appearance of intraluminal branching fibrosis in respiratory bronchioles and alveolar ducts and interstitial fibrosis (Fig 6c) (46–49).

Acute Forms of Idiopathic Interstitial Pneumonia

Acute Interstitial Pneumonia

Acute interstitial pneumonia is a rapidly progressive, organizing form of diffuse alveolar damage. Clinical features of this idiopathic disease include a wide age range, with a mean of 50 years old. Patients often have a history of a prior illness suggestive of a viral upper respiratory infection and present with myalgia, arthralgia, fever, chills, and malaise. Severe exertional dyspnea develops over days. The patient’s condition usually progresses to respiratory failure that requires mechanical ventilation and corticosteroid therapy, with the development of adult respiratory distress syndrome. Bronchoalveolar lavage fluid contains increased numbers of red blood cells, neutrophils, and occasionally lymphocytes (50). Death occurs in just over 50% of cases.

Chest radiography in acute interstitial pneumonia reveals bilateral air-space opacification with sparing of the costophrenic angles (51).

CT Features.—Acute interstitial pneumonia manifests with the following characteristics on CT scans: diffuse distribution of ground-glass attenuation with a mosaic pattern and consolidation (often in the dependent regions of the lungs). The organizing stage is associated with lung architectural distortion, traction bronchiectasis, and cysts (Figs 8a, 8b, 9a, 9b) (51–53). The CT differential diagnosis includes adult respiratory distress syndrome from known causes, widespread infection such as P carinii pneumonia, hydrostatic edema, hemorrhage, alveolar proteinosis, bronchioloalveolar cell carcinoma, and desquamative interstitial pneumonia.
Histologic Features.—The histologic findings of acute interstitial pneumonia include a diffuse distribution with a uniform temporal appearance. In the exudative phase, hyaline membranes, edema, and acute interstitial inflammation are also evident (Fig 8c). In the organizing phase, organizing fibrin, loose organizing fibrosis within alveolar lumens with incorporation within alveolar septa, and type II pneumocyte hyperplasia are seen (Fig 9c). Thrombi are common in small to medium-sized pulmonary arterioles. If the patient survives, the lung architecture may be partially restored. In other cases, the lungs have extensive fibrosis (50,54).

Use of Lung Biopsy
Transbronchial lung biopsies are not generally diagnostic in cases of idiopathic interstitial pneumonias, with the exception of diffuse alveolar damage and occasionally an organizing pneumonia. The primary role of transbronchial biopsy is to exclude sarcoidosis, certain infections, and neoplasia. In the absence of contraindications, surgical lung biopsy is advised in patients with suspected idiopathic interstitial pneumonia who do not show a classic clinical and high-resolution CT picture of idiopathic pulmonary fibrosis or usual interstitial pneumonia (14). Biopsy specimens should be obtained, preferably with video-assisted thoracoscopy, from more than one lobe.

Figure 8. Exudative phase of acute interstitial pneumonia in a 31-year-old woman. (a, b) High-resolution CT scans demonstrate diffuse ground-glass attenuation and minor interlobular septal thickening (arrows). (c) Photomicrograph (original magnification, ×50; hematoxylin-eosin stain) shows hyaline membranes (a) lining the alveolar ducts. b = acute interstitial inflammation.
Conclusions

The correct diagnosis of an idiopathic interstitial pneumonia is a dynamic process. The diagnosis may need to be revised as more details from the patient history or results from bronchoalveolar lavage fluid, transbronchial biopsy (when appropriate), and surgical lung biopsy become available. The final diagnosis of an idiopathic interstitial pneumonia should be rendered only after the pulmonologist, radiologist, and pathologist have reviewed all the data.

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References


Figure 9. Organizing phase of acute interstitial pneumonia in a 55-year-old man. (a) High-resolution CT scan demonstrates diffuse ground-glass attenuation, bronchiectasis, and bronchiolectasis (arrows). (b) High-resolution CT scan demonstrates diffuse ground-glass attenuation. A small amount of honeycomb lung affects the anterior part of the middle lobe (arrow). Small patches of consolidation affect the left lower lobe peripherally. (c) In the organizing phase, proliferative fibroblasts solidify the lung as they destroy alveolar architecture. Photomicrograph (original magnification, ×50; hematoxylin-eosin stain) shows fibrin (a) filling a few residual alveoli (b). Pneumocytes are hyperplastic (c). d = alveolar septa.


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