American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias

This Joint Statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS Board of Directors, June 2001 and by The ERS Executive Committee, June 2001

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Despite the considerable progress in the classification of the idiopathic interstitial pneumonias (IIPs), the lack of an international standard has resulted in variable and confusing diagnostic criteria and terminology. The advent of high-resolution computerized tomography, the narrowed pathologic definition of usual interstitial pneumonia (UIP) and recognition of the prognostic importance of separating UIP from other IIP patterns have profoundly changed the approach to the IIPs. This is an international Consensus Statement defining the clinical manifestations, pathology, and radiologic features of patients with IIP. The major objectives of this statement are to standardize the classification of the idiopathic interstitial pneumonias (IIPs) and to establish a uniform set of definitions and criteria for the diagnosis of IIPs. The targeted specialties are pulmonologists, radiologists, and pathologists. A multidisciplinary core panel was responsible for review of background articles and writing of the document. In addition, this group reviewed the clinical, radiologic, and pathologic aspects of a wide spectrum of cases of diffuse parenchymal interstitial lung diseases to establish a uniform and consistent approach to these diseases and to clarify the terminology, definitions, and descriptions used in routine clinical practice. The final statement was drafted after a series of meetings of the entire committee. The level of evidence for the recommendations made in this statement is largely that of expert opinion developed by consensus. This classification of IIPs includes seven clinico–radiologic–pathologic entities: idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, acute interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, and lymphoid interstitial pneumonia. The need for dynamic interaction between pathologists, radiologists, and pulmonologists to accurately diagnose these disorders is emphasized. The level of evidence for the recommendations made in this Statement is largely that of expert opinion developed by consensus. This Statement is an integrated clinical, radiologic, and pathologic approach to the classification of the IIPs. Use of this international multidisciplinary classification will provide a standardized nomenclature and diagnostic criteria for IIP. This Statement provides a framework for the future study of these entities.

Members of this multidisciplinary core panel writing committee had no direct commercial associations related to the preparation of this statement.

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EXECUTIVE SUMMARY

The American Thoracic Society and European Respiratory Society sponsored this project to standardize classification of the idiopathic interstitial pneumonias (IIPs), a subset of acute and chronic lung disorders collectively referred to as interstitial lung diseases or diffuse parenchymal lung diseases of unknown etiology. Major progress has been made in our understanding of the clinical, radiological, and pathological manifestations of these disorders. Consequently it was felt that an international multidisciplinary Consensus Statement was needed to establish a uniform set of definitions and criteria for the diagnosis of IIPs.

Objectives

This is an international Consensus Statement defining the clinical manifestations, pathology, and radiologic features of patients with IIP. This Statement has been produced as a collaborative effort from the American Thoracic Society (ATS) and the European Respiratory Society (ERS). The purpose of this Consensus Statement is to provide an integrated clinical, radiologic, and pathologic approach to classification of the clinicopathological entities within the IIP group that has bearing on clinical course and prognosis. The targeted specialties are pulmonologists, radiologists, and pathologists.

Participants

Panel members are expert clinicians, radiologists, and pathologists in adult pulmonary diseases. The supporting associations nominated panel members. The co-chairs were selected by the ATS. Panel members were selected because of special interest and expertise in diffuse parenchymal lung disease and to provide an international range of expertise. The panel was divided into a core group and a reviewer group (*see* Appendix).

Evidence

The core group was responsible for review of background articles that discussed the existing scientific evidence. Relevant articles from the medical literature were identified by a MedLine search (1966 to December 1998) of English language articles or articles with English abstracts, the bibliographies of the articles retrieved, and the committee members' files.

In addition, this group reviewed the clinical history, chest-imaging studies including chest radiograph and high-resolution computerized tomography (HRCT) scans, and lung biopsy slides from a wide spectrum of cases of diffuse parenchymal lung disease. The core group established a uniform and consistent approach to these diseases and clarified the terminology, definitions, and descriptions used in routine clinical practice. The final Statement was drafted after a series of meetings of the entire committee.

The level of evidence for the recommendations made in this Statement is largely that of expert opinion developed by consensus. The best evidence is from well-conducted cohort studies. There is no supportive evidence from well-conducted randomized controlled trials.

Validation

The draft document was reviewed by a large and diverse reviewer group, which provided additional expert input. Peer reviewers identified by the ATS and ERS subjected the final document to external review. It was submitted for review and approval to the governing bodies of the ATS and ERS.

Key Messages

1. The *idiopathic interstitial pneumonias* (IIPs) comprise a number of clinicopathological entities, which are sufficiently different from one another to be designated as separate disease entities. As a group they can be distinguished from other forms of diffuse parenchymal lung disease by clinical methods including history, physical examination, chest radiology and laboratory studies, and pathology.
2. These conditions are rare and few physicians have substantial experience with their diagnosis and management.
3. The new ATS/ERS classification proposed in this document comprises the following clinicopathologic entities in order of relative frequency: idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), and lymphoid interstitial pneumonia (LIP).
4. NSIP is an area of uncertainty that requires further definition. The panel recommended that the use of the term NSIP be considered as a *provisional diagnosis* until there is further clarity on the nature of the corresponding clinical condition. Under the auspices of the ATS, a multidisciplinary panel is reviewing clinical cases of NSIP from around the world. When published (expected in late 2002), this review will be used to better characterize this entity and to determine its relationship to IPF, hypersensitivity pneumonitis, COP, DIP, and LIP.
5. Achieving a correct diagnosis is a dynamic process. During the diagnostic work-up of patients with an IIP, the diagnosis may need to be revised, as more details of history are obtained, when new associations are discovered, or when results of bronchoalveolar lavage, transbronchial biopsy (where appropriate), and surgical lung biopsy become available. It is particularly important to re-evaluate the patient in a search for a specific etiology when NSIP, diffuse alveolar damage (DAD), and LIP are found on lung biopsy. The final diagnosis should be rendered only after the pulmonologist, radiologist, and pathologist have reviewed all of the clinical, radiological, and pathological data obtained from the patient.
6. In order to clarify the relationship between the historical pathologic and clinical terms that have been used for these entities, the new classification defines a set of histologic patterns that provide the basis for a final clinico–radiologic–pathologic diagnosis. Because the histologic patterns seen by pathologists usually allow for better separation of these entities than the imaging patterns seen by radiologists, these histologic patterns provide the primary basis for the various categories of IIP and serve as the foundation for the classification.
7. In the absence of contraindications, surgical lung biopsy is advised in patients with suspected IIP who do not show a classic clinical and HRCT picture of IPF/usual interstitial pneumonia (UIP). The availability of less invasive surgery in the form of video-assisted thoracoscopic lung biopsy has made it more acceptable for clinicians to recommend surgical biopsy to their patients with diffuse parenchymal lung disease. Surgical lung biopsies should be obtained from more than one lobe of the lung.
8. It is recommended that the term *pattern* be added to the IIP designations when referring to the lung biopsy pathologic pattern, to distinguish it from the clinico–radiologic–pathologic diagnosis (e.g., NSIP, DIP, or LIP).
9. High-resolution computerized tomography (HRCT) scans are indicated for all but a small proportion of patients for whom a specific diagnosis is strongly suggested on the basis of the standard chest radiograph. Careful attention to technique is necessary to assure diagnostic accuracy. The

HRCT images should be obtained in accordance with established guidelines and interpreted by a radiologist experienced in the evaluation of diffuse lung diseases.

10. The primary role of HRCT is to separate patients with typical findings of IPF/UIP from those with the less specific findings associated with other idiopathic interstitial pneumonias.
11. Transbronchial biopsies are not useful in the diagnosis of most of the IIPs, with the exception of DAD/AIP, and occasionally organizing pneumonia (OP)/COP. The primary role of transbronchial biopsies is to exclude sarcoidosis and certain infections. Bronchoalveolar lavage is not always required in the assessment of the IIPs.
12. The final diagnosis should be rendered only after the pulmonologist, radiologist, and pathologist have reviewed all of the clinical, radiological, and pathological data obtained from the patient.
13. Trials of therapy should be discouraged until a concerted effort has been made to establish a firm diagnosis based on the integrated approach proposed in this document. These criteria should provide an international standard as the basis for future studies and publications on the subject of IIP.

INTRODUCTION

The idiopathic interstitial pneumonias (IIPs) are a group of diffuse parenchymal lung diseases (DPLDs), a group also described as interstitial lung diseases (Figure 1). The IIPs are a heterogeneous group of nonneoplastic disorders resulting from damage to the lung parenchyma by varying patterns of inflammation and fibrosis. The interstitium includes the space between the epithelial and endothelial basement membranes and it is the primary site of injury in the IIPs. However, these disorders frequently affect not only the interstitium, but also the airspaces, peripheral airways, and vessels along with their respective epithelial and endothelial linings (1).

Diffuse lung diseases such as emphysema or chronic obstructive lung disease (COPD), bronchiolitis, and pulmonary hypertension are excluded from this discussion. Some categories of diffuse parenchymal lung diseases such as those associated with occupational or environmental exposures and/or collagen vascular disease, granulomatous lung disorders such as sarcoidosis, and a further group comprising several rare forms of DPLD with distinctive and well-defined clinicopathologic features such as lymphangioleiomyomatosis (LAM), pulmonary Langerhans' cell histiocytosis, and eosinophilic pneumonia are also excluded. The IIPs described herein comprise a number of clinicopathologic entities, which are sufficiently different from one another to be designated as separate disease entities. As a group they can be distinguished from other forms of diffuse parenchymal lung disease by clinical methods including history, physical examination, chest radiology and laboratory studies, and pathology.

Idiopathic indicates unknown cause and *interstitial pneumonia* refers to involvement of the lung parenchyma by varying combinations of fibrosis and inflammation, in contrast to airspace disease typically seen in bacterial pneumonia. The *idiopathic interstitial pneumonias* include the entities of idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), and lymphocytic interstitial pneumonia (LIP). For the purposes of this document, the following terms are viewed as synonymous: *idiopathic* and *cryptogenic* as well as *pneumonia* and *pneumonitis*.

RATIONALE FOR A CHANGE IN THE APPROACH TO CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS

1. The terminology applied to the IIPs has been confusing. Clinicians in different countries have employed varied terms such as *idiopathic pulmonary fibrosis* (IPF) in the United States and *cryptogenic fibrosing alveolitis* (CFA) or "lone CFA" (CFA not associated with the presence of collagen vascular disease) (2, 3) in the United Kingdom, or idiopathic interstitial pneumonia in Japan (4). These represent clinically defined disease entities that historically have included a range of histologic patterns (5, 6).
2. In clinical practice, patients are commonly misclassified as having an IIP because of inadequate history taking. In addition, an increasing number of associations between the development of DPLD and occupational, environmental, and drug exposures are being described (7–9). For these reasons, during the diagnostic work-up of the IIPs, a diagnosis may need to be revised at several stages, as more details of history are obtained, when new associations are discovered, or when results of bronchoalveolar lavage, transbronchial biopsy (where appropriate), and surgical lung biopsy become available.
3. These conditions are rare and few physicians have substantial experience with their diagnosis and management. A reported overall prevalence of interstitial lung disease in New

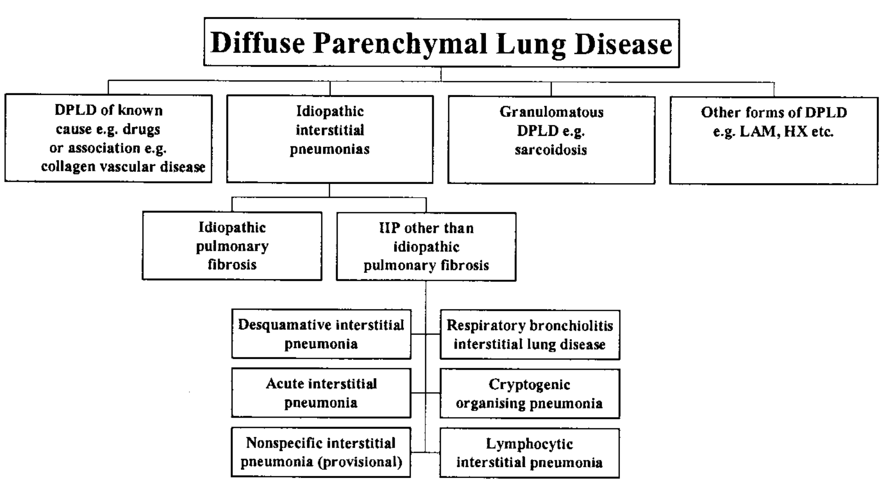

Figure 1. Diffuse parenchymal lung diseases (DPLDs) consist of disorders of known causes (collagen vascular disease, environmental or drug related) as well as disorders of unknown cause. The latter include idiopathic interstitial pneumonias (IIPs), granulomatous lung disorders (e.g., sarcoidosis), and other forms of interstitial lung disease (ILD) including lymphangioleiomyomatosis (LAM), pulmonary Langerhans' cell histiocytosis/histiocytosis X (HX), and eosinophilic pneumonia. The most important distinction among the idiopathic interstitial pneumonias is that between idiopathic pulmonary fibrosis and the other interstitial pneumonias (IPs), which include nonspecific interstitial pneumonia (a provisional term), desquamative interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease, acute interstitial pneumonia, cryptogenic organizing pneumonia, and lymphocytic interstitial pneumonia.

Mexico is 80.9 per 100,000 in males and 67.2 per 100,000 in females, corresponding with annual incidence rates of 31.5 per 100,000/yr in males and 26.1 per 100,000/yr in females (10). The IIPs are rare in children, but increase with advancing age. The prevalence of IPF in different series ranges from 6 to 14.6 per 100,000 persons (8, 10), but in those older than 75 yr the prevalence may exceed 175 per 100,000 (8).

4. Lung biopsies are not frequently obtained from patients with clinical evidence of interstitial lung disease (ILD) (11–15). This low biopsy rate has been attributed to the invasive nature of surgical biopsies and the fact that many patients with these diseases are viewed as too old or too frail to undergo biopsy. The practice of video-assisted thoracoscopic biopsy has resulted in an increase in surgical lung biopsy in some institutions because of decreased morbidity compared with a formal thoracotomy procedure. In addition, there is a lack of confidence in the diagnostic and predictive value of pathology, leading to a view that knowledge of the pathological findings does not alter the treatment approaches. Therefore, clinicians have commonly preferred to rely on a trial of therapy as a predictor of clinical course and prognosis rather than subject the patient to lung biopsy.
5. Pathology-based classifications have largely been developed from data derived from series of surgical (thoracoscopic or open) biopsies and postmortem examinations of lung tissue. Consequently they may represent only a small proportion of patients with these disorders because most patients with IIP do not undergo surgical lung biopsy (3, 10, 12). Occasionally, pathology case series have lacked sufficient supporting clinical and radiological data or have included patients with histories of exposure to occupational or environmental agents or systemic diseases associated with the development of ILD (16–18).
6. Clinicians frequently do not have access to the opinion of pathologists who are experienced in examining lung biopsies from patients with IIP. Further, a limited number of experts have been relied on to provide pathological identification of the lesions present.
7. Clinicians have frequently been confused by the descriptions provided in pathology reports, particularly when several patterns are described in a single biopsy.
8. It is not always clear, when the common terms are employed, whether they are being used as a pathologic or clinical term. For example, bronchiolitis obliterans organizing pneumonia (BOOP) is often assumed to indicate the idiopathic entity; however, it could represent a nonspecific histologic reaction that can occur in a wide variety of clinical settings. As a further example, a pathologist may recognize the histologic pattern of diffuse alveolar damage (DAD); however, the diagnosis of AIP requires additional clinical information to exclude potential etiologies (19). Much of the evaluation to exclude specific causes is likely to be completed after the lung biopsy has been signed out. Therefore the best diagnosis many pathologists may be able to make in cases of AIP is "DAD, etiology undetermined" with an added comment that the differential diagnosis may include AIP. For these reasons, the term *pattern* may be added to the designations that have the same term as that used for the clinicopathologic diagnosis (NSIP, DIP, and LIP) when referring to the lung biopsy pathologic pattern only.
9. Pathologists have generally tended to be "splitters" and clinicians tend to be "lumpers" (17). That is, pathologists have divided the IIPs into separate groups based on the histopathologic pattern found on biopsy. However, clinicians have commonly applied a single term that included several different pathologic patterns; for example, the term IPF has been applied to patients with interstitial lung diseases of unknown cause characterized pathologically by several different histologic patterns including DIP, UIP, and NSIP.

DEVELOPMENT OF A NEW CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIA

Several developments have prompted a review of the previous classification systems and encouraged the development of a new comprehensive clinical–radiologic and pathologic classification of the IIPs.

1. The publication of large series of patients with IIP with accompanying pathologic evaluation by experts in lung pathology has provided a clearer picture of the types of histopathologic patterns seen and their relationship to the patient's clinical course and responsiveness to treatment (20–23).
2. The availability of less invasive surgery in the form of video-assisted thoracoscopic lung biopsy has made it more acceptable for clinicians to recommend surgical biopsy to their patients (24–27). This has led to an increase in the frequency of surgical lung biopsy in some institutions.
3. The widespread use and improved understanding of the value of high-resolution computerized tomography (HRCT) scans in the evaluation of these diseases has led to improved understanding of the extent and severity of the lesions commonly present (26, 28–31).
4. The development of several new therapeutic approaches for the management of fibrotic lung diseases has prompted renewed interest in understanding the pathogenesis of these disorders (3, 32, 33).

Current Classification of IIP

Liebow and Carrington provided a landmark histologic classification of the chronic interstitial pneumonias in 1969 (34). Liebow and Carrington described five types of chronic interstitial pneumonia: usual interstitial pneumonia (UIP), bronchiolitis obliterans interstitial pneumonia and diffuse alveolar damage (BIP), desquamative interstitial pneumonia (DIP), lymphocytic interstitial pneumonia (LIP), and giant cell interstitial pneumonia (GIP). The evolution of this classification over time is presented in Table 1.

The classification schemes proposed by Liebow and Carrington (34), Müller and Colby (35), and Katzenstein (36) maintained UIP and DIP as separate types of lung diseases in contrast to the concepts of IPF and CFA, which regarded them as part of a single spectrum (3). However, LIP and GIP were dropped because many of the former were thought to develop into lymphomas and were therefore preferably classified as lymphoproliferative disorders, whereas many of the latter were found to be hard metal pneumoconioses. In addition, newly recognized entities including respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) (16), bronchiolitis obliterans organizing pneumonia (BOOP) (termed cryptogenic organizing pneumonia [COP] in some countries) (37, 38), acute interstitial pneumonia (AIP) (39), and nonspecific interstitial pneumonia (NSIP) (17) have been added to the classification of the IIPs (35, 40, 41).

New ATS/ERS Classification

The new ATS/ERS classification proposed in this document comprises the following clinicopathologic entities in the order of relative frequency: IPF/CFA, NSIP (provisional), COP, AIP, RB-ILD, DIP, and LIP (Table 2) (20, 41). The rationale for choosing these terms and including each entity is discussed in each respective section below. To clarify the relationship between the historical pathologic and clinical terms that have

TABLE 1. PREVIOUS CLASSIFICATIONS OF IDIOPATHIC INTERSTITIAL PNEUMONIAS

Liebow and Carrington (1969)*: Chronic Forms	Katzenstein (1997)†	Müller and Colby (1997)‡
Usual interstitial pneumonia	Usual interstitial pneumonia	Usual interstitial pneumonia
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia/ respiratory bronchiolitis interstitial lung disease	Desquamative interstitial pneumonia
Bronchiolitis obliterans interstitial pneumonia and diffuse alveolar damage		Bronchiolitis obliterans organizing pneumonia
	Acute interstitial pneumonia	Acute interstitial pneumonia
	Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia
Lymphoid interstitial pneumonia		
Giant cell interstitial pneumonia		

* *See* reference 34.
† *See* reference 36.
‡ *See* reference 35.

been used for these entities, the new classification defines a set of *histologic patterns* that provide the basis for a final *clinico–radiologic–pathologic diagnosis* (*CRP diagnosis*) (Table 2). Because the histologic patterns seen by pathologists allow for better separation of these entities than the imaging patterns seen by radiologists, these histologic patterns provide the primary basis for the various categories of IIP and serve as the foundation for the classification. However, the final clinicopathologic diagnosis, including the issue of whether the disorder is idiopathic, can be made only after careful correlation with clinical and radiologic features. Thus, the final diagnosis should be rendered only after the pulmonologist, radiologist, and pathologist have reviewed all of the clinical, radiological, and pathological data obtained from the patient.

PRINCIPLES GUIDING THE ASSESSMENT OF PATIENTS WITH IDIOPATHIC INTERSTITIAL PNEUMONIAS

Before describing the features of each IIP, it is necessary to consider the principles that apply to the general assessment of patients with IIPs. The new classification of IIP is based on clinical, radiological, and pathological criteria.

The Diagnostic Process Is Dynamic

The process of achieving a diagnosis in a patient with IIP is dynamic, requiring close communication between clinician, radiologist, and pathologist. For example, a pathologist is at a disadvantage if asked to interpret a lung biopsy without a relevant history of clinical presentation, radiologic findings, occupational exposure, smoking status, and associated diseases. Also, once a pathologist has recognized a histologic pattern such as NSIP, the clinician needs to go back to the patient and check carefully for antigen exposure that could account for hypersensitivity pneumonitis, laboratory or clinical features of collagen vascular disease, and possible drug or toxic exposure. The practice of observing clinical and radiologic deterioration before obtaining biopsy is not helpful because it delays diagnosis, reduces the likelihood that the disease will be correctly identified, and not infrequently results in patients receiving unnecessary or inadequate treatment. For the same reasons, trials of therapy should be discouraged until a concerted effort has been made to establish a firm diagnosis based on this integrated approach.

Clinical Evaluation

The approach to patients with diffuse parenchymal lung disease begins with a careful history followed by physical examination, routine chest radiographs, and pulmonary function testing (Figure 2) (42). The assessment of the clinical history should include the nature of the first symptoms (usually breathlessness or cough), their progression, clinical course, and in particular the presence of comorbid disease such as collagen vascular disease or immunodeficiency disorders such as infection with the human immunodeficiency virus (HIV). A record of environmental exposures including smoking status, drug use, and detailed occupational exposures with dates, duration of exposure, and a detailed description of work activities is essential. A history of previous malignancy and treatment for malignancy or a family history of lung disease may also be relevant.

On physical examination the presence of crackles and finger clubbing, although varying in frequency in different forms of IIP, provides a useful clue to the presence of an IIP. Joint swelling or tight skin may suggest collagen vascular disease. After obtaining the clinical history, a chest radiograph, and pulmonary function tests, the clinician should be in a position to decide whether the patient has a DPLD and whether a form of IIP needs to be considered (Figure 2). If the answer to the latter question is yes, an HRCT scan is usually indicated.

TABLE 2. HISTOLOGIC AND CLINICAL CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS*

Histologic Patterns	Clinical–Radiologic–Pathologic Diagnosis
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis
Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia (provisional)†
Organizing pneumonia	Cryptogenic organizing pneumonia‡
Diffuse alveolar damage	Acute interstitial pneumonia
Respiratory bronchiolitis	Respiratory bronchiolitis interstitial lung disease
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Lymphoid interstitial pneumonia	Lymphoid interstitial pneumonia

* **Unclassifiable interstitial pneumonia**: Some cases are unclassifiable for a variety of reasons (*see* text).
† This group represents a heterogeneous group with poorly characterized clinical and radiologic features that needs further study.
‡ COP is the preferred term, but it is synonymous with idiopathic bronchiolitis obliterans organizing pneumonia.

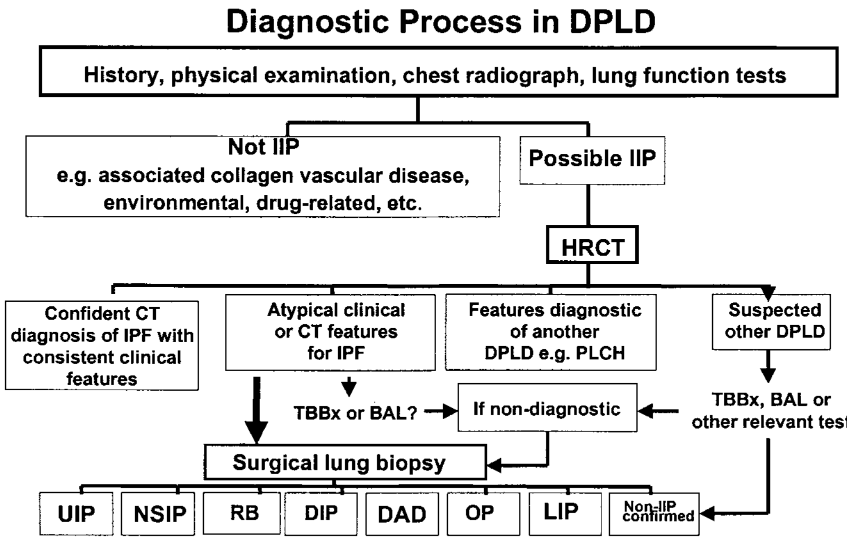

Figure 2. The diagnostic process in diffuse pulmonary lung diseases (DPLDs) begins with a clinical evaluation that includes a history, physical examination, chest radiograph, and lung function tests. On the basis of this information, the patients may be divided into two groups: cases that do not represent idiopathic interstitial pneumonia (IIP), owing to recognition of associated conditions or underlying exposures, and cases that could represent IIP. Patients in the latter category typically receive a high-resolution computerized tomography (HRCT) scan. This generally results in four categories of patients: (*1*) those with distinctive features that allow for a confident diagnosis of idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP) in the appropriate clinical setting, (*2*) those with atypical clinical or CT features for IPF, (*3*) those with features diagnostic of another DPLD such as pulmonary Langerhans' cell histiocytosis (PLCH), and (*4*) those with suspected other forms of DPLD. Although many patients will go directly to surgical lung biopsy, some patients may undergo transbronchial biopsy (TBBx) or bronchoalveolar lavage (BAL). If these findings are nondiagnostic a surgical lung biopsy may be necessary to separate the various IIPs from non-IIP DPLD.

Radiological Evaluation

HRCT has become an integral part of the evaluation of the patient with idiopathic interstitial pneumonia (Figure 2 and Table 3). HRCT is indicated for all but a small proportion of patients for whom a specific diagnosis is strongly suggested by the standard chest radiograph. Careful attention to technique is necessary to assure diagnostic accuracy. HRCT images should be performed in accordance with established guidelines (43, 44) and interpreted by a radiologist experienced in the evaluation of diffuse lung diseases (45).

When interpreting the HRCT scan of a patient with diffuse lung disease, the radiologist must first determine the presence or absence of a pattern typical of UIP (Figure 2). In more than 50% of cases suspected to be IPF/UIP, the presence of typical clinical and HRCT features of UIP, when identified by expert clinicians and radiologists, is sufficiently characteristic to allow a confident diagnosis and eliminate the need for surgical lung biopsy (31, 42). The HRCT may also provide clues to non-IIP disorders such as sarcoidosis (46), hypersensitivity pneumonitis (47), lymphangioleiomyomatosis (48), Langerhans' cell histiocytosis (48), and pulmonary alveolar proteinosis (49), and may prompt the selection of bronchoscopy (usually with both bronchoalveolar lavage and transbronchial biopsy) in preference to proceeding to a surgical lung biopsy. Therefore, the primary role of HRCT is to separate patients with UIP from those with non-UIP lesions or those with less specific findings associated with other idiopathic interstitial pneumonias (NSIP, RB-ILD, DIP, and AIP).

TABLE 3. RADIOLOGIC FEATURES AND DIFFERENTIAL DIAGNOSIS OF IDIOPATHIC INTERSTITIAL PNEUMONIAS

Clinical Diagnosis	Histologic Pattern	Usual Radiographic Features	Typical Distribution on CT	Typical CT Findings	CT Differential Diagnosis
IPF/CFA	UIP	Basal-predominant reticular abnormality with volume loss	Peripheral, subpleural, basal	Reticular, honeycombing Traction bronchiectasis/bronchiolectasis; architectural distortion. Focal ground glass	Asbestosis Collagen vascular disease Hypersensitivity pneumonitis Sarcoidosis
NSIP, provisional	NSIP	Ground glass and reticular opacity	Peripheral, subpleural, basal, symmetric	Ground glass attenuation Irregular lines Consolidation	UIP, DIP, COP Hypersensitivity pneumonitis
COP	OP	Patchy bilateral consolidation	Subpleural/peribronchial	Patchy consolidation and/or nodules	Infection, vasculitis, sarcoidosis, alveolar carcinoma, lymphoma, eosinophilic pneumonia, NSIP
AIP	DAD	Progressive diffuse ground glass density/consolidation	Diffuse	Consolidation and ground glass opacity, often with lobular sparing. Traction bronchiectasis later	Hydrostatic edema Pneumonia Acute eosinophilic pneumonia
DIP	DIP	Ground glass opacity	Lower zone, peripheral predominance in most	Ground glass attenuation Reticular lines	RB-ILD Hypersensitivity pneumonitis Sarcoidosis, PCP
RB-ILD	RB	Bronchial wall thickening; ground glass opacity	Diffuse	Bronchial wall thickening Centrilobular nodules Patchy ground glass opacity	DIP NSIP Hypersensitivity pneumonitis
LIP	LIP	Reticular opacities, nodules	Diffuse	Centrilobular nodules, ground glass attenuation, septal and bronchovascular thickening, thin-walled cysts	Sarcoidosis, lymphangitic carcinoma, Langerhans' cell histiocytosis

Definition of abbreviations: AIP = acute interstitial pneumonia; CFA = cryptogenic fibrosing alveolitis; COP = cryptogenic OP; DAD = diffuse alveolar damage; DIP = desquamative interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; LIP = lymphoid interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; PCP = *Pneumocystis carinii* pneumonia; RB-ILD = respiratory bronchiolitis-associated interstitial lung disease; UIP = usual interstitial pneumonia.

A confident radiologic diagnosis of UIP on HRCT is based on a bilateral, predominantly basal, predominantly subpleural, reticular pattern, associated with subpleural cysts (honeycombing) and/or traction bronchiectasis (31, 42). The abnormality decreases gradually in extent on serial scans from the base to the apex of the lungs. Consolidation and nodules are absent. When the radiologic diagnosis of UIP is based on these findings, it is correct in more than 90% of cases (30, 31, 42). However, when the CT findings are "atypical" (e.g., upper lobe or peribronchovascular predominance, predominant ground glass abnormality or micronodules), or when there is one or more "atypical" clinical features (e.g., young age, inconclusive exposure history, lack of dyspnea, absence of restrictive lung function defect, or presence of marked lymphocytosis on bronchoalveolar lavage [BAL]), then biopsy is indicated. The primary role of HRCT is to separate patients with typical findings of IPF from those with the less specific findings associated with other idiopathic interstitial pneumonias.

Role of Surgical Lung Biopsy

A surgical lung biopsy is necessary for a *confident clinicopathologic* diagnosis except in cases with a typical clinical–radiological picture of UIP/IPF. This is not to say that a biopsy is always necessary to make a *clinical* diagnosis (Table 4). Pathology is least helpful when obtained late in the course of the illness or after commencement of treatment.

The benefits of obtaining a surgical lung biopsy can be briefly summarized as follows:

1. Establishment of a firm clinicopathologic diagnosis allows the patient and clinician to make more informed decisions about therapy.
2. Almost all of the current treatments for the IIPs have potentially serious risks and side effects, and it is not reasonable to expose patients to these risks in the presence of diagnostic uncertainty.
3. Detection of fibrotic processes related to specific exposures can have important compensation implications for the patient, and important public health consequences for the community; for example, asbestosis.

Although a highly probable diagnosis of IPF can be made without a lung biopsy, a *definitive* diagnosis of IPF and of the other forms of IIP can be established only with the aid of a surgical lung biopsy (Figure 2). In most cases the biopsy provides definitive classification of patients into the recognized histologic patterns of UIP, NSIP, OP, DAD, DIP, respiratory bronchiolitis (RB), and LIP. It also allows for confirmation or exclusion of an alternative diagnosis such as sarcoidosis, hypersensitivity pneumonitis, LAM, or lymphangitic carcinoma, or suggests the presence of an occupational disease such as hard metal disease. In lung biopsy specimens with moderate or marked acute and/or chronic inflammation, it is useful to perform special stains to exclude infectious organisms.

Several issues relating to lung biopsies for diagnosis of IIPs need to be considered.

1. The role of transbronchial biopsies in the diagnosis of the IIPs in most cases is to exclude sarcoidosis, neoplasms, and certain infections. In some cases with classic clinical and radiologic features of COP (50, 51) or AIP the histologic diagnosis of an OP or DAD pattern, respectively, may be viewed as confirmatory on a bronchoscopic biopsy specimen (*see* below).
2. It can be helpful to have surgical lung biopsies from more than one lobe of the lung (52, 53). In addition, if the lung shows severe fibrosis with honeycombing the biopsy specimen should not be taken from the worst-looking areas because these frequently show nonspecific changes. However, if the lung does not show severe fibrosis or honeycombing grossly the surgeon should take the biopsy from the abnormal areas of the lung. HRCT scanning may guide the surgeon to the most optimal biopsy sites (54). Ideally the lung biopsy should include the full spectrum of the gross appearance, including honeycomb foci, because these confirm severe fibrosis, one of the criteria for UIP. The surgeon must also attempt to avoid deflation of the specimen through clamping, as this complicates interpretation of histological findings. Specimen atelectasis can be corrected by inflating lung biopsies with formalin either by injection with a syringe or by gently shaking thin slices of the lung biopsy specimen in the specimen container before paraffin processing (55). An effort should be made to communicate these issues to the thoracic surgeon.
3. In a small proportion of cases the pathologic diagnosis may need to be revised in the light of an unexpected clinical course, identification of a potential cause for lung fibrosis, or response to treatment. Periodic review should include re-examination of the original lung biopsy and radiologic material in addition to the data from the clinical follow-up.
4. In patients with biopsies from multiple lobes, sometimes the second or third lobe may show a different pattern than the first, for example, a UIP pattern in the lower lobe and an NSIP pattern in the upper lobe. An article by Flaherty and coworkers indicates that if a UIP pattern is present in one of the lobes and an NSIP pattern is present in one or more of the other lobes, the clinical behavior is similar to that of IPF (53). For this reason UIP is the default pattern in such a case. Although uncommon, one lobe may show a pattern of ill-defined fibrosis simulating UIP and another lobe may show a "specific" lesion such as a granulomatous reaction or asbestos bodies. In such a case, the diagnosis is that most consistent with the specific histologic finding, that is, for the above-described examples, sarcoidosis or hypersensitivity pneumonitis or asbestosis.

TABLE 4. ATS/ERS CRITERIA FOR DIAGNOSIS OF IDIOPATHIC PULMONARY FIBROSIS IN ABSENCE OF SURGICAL LUNG BIOPSY*†

Major Criteria
Exclusion of other known causes of ILD such as certain drug toxicities, environmental exposures, and connective tissue diseases
Abnormal pulmonary function studies that include evidence of restriction (reduced VC, often with an increased FEV_1/FVC ratio) and impaired gas exchange [increased $P(A–a)O_2$, decreased Pa_{O_2} with rest or exercise or decreased DL_{CO}]
Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans
Transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis
Minor Criteria
Age > 50 yr
Insidious onset of otherwise unexplained dyspnea on exertion
Duration of illness > 3 mo
Bibasilar, inspiratory crackles (dry or "Velcro"-type in quality)

Definition of abbreviations: BAL = bronchoalveolar lavage; DL_{CO} = diffusing capacity of the lung for CO; HRCT = high-resolution computerized tomography; ILD = interstitial lung disease; $P(A–a)O_2$ = alveolar–arterial pressure difference for O_2; VC = vital capacity.

* Reprinted by permission from Reference 60.

† In the immunocompetent adult, the presence of all of the major diagnostic criteria as well as at least three of the four minor criteria increases the likelihood of a correct clinical diagnosis of IPF.

Unclassifiable Interstitial Pneumonia

There is a small subset of patients with interstitial pneumonia that remains unclassifiable after extensive clinical, radiologic, and/or pathological examination. This guideline has resisted the creation of an additional nonclassifiable category because this is clinically unhelpful. However, it is standard in tumor classifications proposed by the World Health Organization to have an unclassifiable category, because there are cases when a specific pathologic diagnosis cannot be made (56). However this has not been fully addressed in the classification of interstitial pneumonia (57, 58). For interstitial lung diseases this situation often exists when some critical piece of data is unavailable or when there is a major discrepancy between the clinical, radiologic, and/or pathologic information. Some examples of reasons or circumstances under which a case may be unclassifiable include the following.

1. Inadequate clinical information.
2. Inadequate radiologic data.
3. An inadequate or nondiagnostic biopsy (e.g., because of small size or poor sampling).
4. The existence of a major discrepancy between clinical, radiologic, and pathologic findings.
5. Previous therapy resulting in alterations in the radiologic or histologic findings.
6. Discrepancy between histologic findings in different lobes that is not resolved after correlation with clinical and radiologic data. The issue of NSIP in one lobe and UIP in another lobe has been addressed elsewhere in this document. Another example is the coexistence of multiple histologic patterns; for example, a biopsy specimen from one lobe may show a UIP or NSIP pattern and other areas may show features of eosinophilic pneumonia, organizing pneumonia, or acute lung injury with fibrin and/or hyaline membranes. In such rare instances, one should rely on clinical findings and the most prominent radiologic findings to determine which of these possibilities appears to be the major/predominant lesion. This careful analysis will often result in a more specific clinico–radiologic–histologic diagnosis.

In summary, we propose that cases having any of the above-described unresolved issues to be called *unclassifiable interstitial pneumonia*. In this circumstance, the clinician would then need to embark on treatment based on the most probable diagnosis after detailed clinico–radiological–pathological case discussion with the pathologist and radiologist. Importantly, this category designation should not be used for cases of clearly defined NSIP or cases in which the distinction between the UIP and fibrosing NSIP patterns is difficult. In such cases, one should make the best possible diagnosis given the available information, realizing the differential diagnosis may be a challenge. Finally, the purpose of the concept of unclassifiable interstitial pneumonia is not to create an entity from which clinical studies might derive, but to emphasize the requirement for adequate clinical, radiologic, and pathologic information for classification and to acknowledge that uncertainty remains in individual cases.

Bronchoalveolar Lavage Fluid Evaluation

BAL is not always required in the assessment of the IIPs. However, if, as is commonly the case, it has been performed in the diagnostic work-up of diffuse parenchymal lung disease to exclude infection or tumor, the results may assist in the decision to perform a surgical biopsy and in distinguishing different forms of IIP (59). Although not diagnostic in IIP, a "typical" BAL cell pattern strengthens the clinical diagnosis and may contribute to the clinico–radiologic–pathologic assessment in difficult cases (1, 60–63). In rare instances, diagnostic features may be found, for example, in pulmonary alveolar proteinosis (64). BAL may also be suggestive of Langerhans' cell histiocytosis (1). The presence of hemosiderin-laden macrophages suggests alveolar hemorrhage. In addition, lipid-laden macrophages can be seen in a variety of settings including aspiration of material from the stomach or upper airway, oily liquids, and oil-based nasal instillation as well as lipid emboli or amiodarone therapy (1).

IDIOPATHIC PULMONARY FIBROSIS

The terms UIP and IPF have become more narrowly defined since they were originally proposed several decades ago (5, 65). The relationship between historically defined IPF (or lone CFA) and UIP has been described in an ATS Consensus Statement entitled "Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment" (60). According to the current definition, IPF is a distinctive type of chronic fibrosing interstitial pneumonia of unknown cause limited to the lungs and associated with a surgical lung biopsy showing a histologic pattern of UIP (60). In the presence of a surgical biopsy showing a UIP pattern the diagnosis of IPF requires (*1*) exclusion of other known causes of interstitial lung disease including drug toxicities, environmental exposures, and collagen vascular diseases, (*2*) characteristic abnormalities on conventional chest radiographs or high-resolution computed tomography (HRCT) scans as described below (60), and (*3*) abnormal pulmonary function studies showing restriction (reduced total lung capacity [TLC], or reduced vital capacity [VC] with a normal or increased FEV_1/FVC ratio) and/or impaired gas exchange [increased $P(A–a)O_2$ (alveolar–arterial pressure difference for O_2), decreased Pa_{O_2} with rest or exercise, or decreased DL_{CO} (diffusing capacity of the lung for CO)].

Definitive histologic diagnosis of IPF requires a surgical lung biopsy. The criteria for diagnosis of IPF in the absence of a surgical lung biopsy are summarized in Table 4 (60). In such cases the diagnosis of IPF is likely but not as certain as when a surgical lung biopsy also shows a UIP pattern. However, lung biopsy occasionally may also not be definitive. As mentioned above, this may arise when there is histologic heterogeneity in different lobes of the lung in IPF (53). So after correlating all the clinical, radiological, and pathological information, the final diagnosis may still be IPF in a patient with typical clinical–radiological IPF, even though a lung biopsy shows a fibrosing NSIP pattern.

Clinical Features

Onset of symptoms is usually gradual, with dyspnea the most prominent and disabling symptom (3). A nonproductive cough is usual and may be paroxysmal (60). It is often refractory to antitussive agents. The patient's age at onset is usually greater than 50 yr and IPF is slightly more common in males (3, 11). Constitutional symptoms are unusual. Digital clubbing develops in 25 to 50% of patients (3, 11), and Velcro-type fine end-inspiratory crackles that are initially confined to the basal areas are found on chest auscultation (60). These progress gradually to involve the entire lung. Features of right heart failure and peripheral edema develop only in the late stages. Most patients exhibit a restrictive pattern of ventilatory defect with a decrease in DL_{CO} and low resting Pa_{O_2}, which falls on exercise. Pulmonary function or chest radiographs may be normal or near normal in the early phase of IPF (66) In smokers and ex-smokers with IPF, coexistent chronic obstructive pulmonary disease may result in relatively higher lung volumes compared with never-smoking patients with IPF (60).

Clinical course. In most patients, symptoms have been present for more than 6 mo before presentation (3, 67). The clinical course is invariably one of gradual deterioration. Median length of survival from time of diagnosis varies between 2.5 and 3.5 yr (60, 68, 69). Occasionally, periods of rapid decline are recognized (70). These may represent accelerated disease, intercurrent viral infection with the development of organizing pneumonia, or diffuse alveolar damage (41). Improvement in lung physiology and radiologic abnormalities is rare (22).

Bronchoalveolar lavage features. Bronchoalveolar lavage fluid contains an excess of neutrophils, the proportions of which correspond to the extent of reticular change on HRCT (71). There may also be a mild or moderate increase in the percentage of eosinophils (1, 62). BAL cell counts, although correlating with severity of disease, do not predict prognosis (72). When eosinophils represent more than 20% of the count, consideration should be given to an eosinophilic lung disease (73). Lymphocytosis is not a feature of UIP, and counts above 15% should alert to an alternative diagnosis such as NSIP, COP, hypersensitivity pneumonitis, sarcoidosis, or other granulomatous lung disease (60).

Radiologic Features

The commonest chest radiographic abnormality in patients with IPF is peripheral reticular opacity, most marked at the bases, and often associated with honeycombing and lower lobe volume loss (Figure 3A and Table 3) (74, 75). In patients with associated upper lobe emphysema, the radiographic lung volumes may be normal or even increased. Chest radiographs may occasionally be normal in patients with IPF (66).

CT features. UIP is characterized on CT by the presence of reticular opacities, often associated with traction bronchiectasis (Table 3 and Figure 3B and 3C). Honeycombing is common (Figure 3B and 3C) (76). Ground glass attenuation is common, but is usually less extensive than reticular abnormality (26, 77). Architectural distortion, reflecting lung fibrosis, is often prominent. Lobar volume loss is seen with more advanced fibrosis. The distribution of UIP on CT is characteristically basal and peripheral, although often patchy (26, 78–80).

On serial scans in treated patients, the areas of ground glass attenuation may regress, but more commonly progress to fibrosis with honeycombing (Figure 4A and 4B) (81–83). Honeycomb cysts usually enlarge slowly over time (76).

CT–pathologic correlation. Reticular abnormality on CT correlates with fibrosis on histopathologic examination (26, 77). Honeycombing on CT correlates with honeycombing on biopsy. When ground glass attenuation is associated with reticular lines, traction bronchiectasis, or bronchiolectasis, it usually indicates histologic fibrosis. Isolated ground glass attenuation may correlate with evidence of interstitial inflammation, airspace filling by macrophages, patchy fibrosis, or a combination of these (26, 84, 85).

Radiologic differential diagnosis. The CT pattern of UIP due to IPF can be indistinguishable from that found in UIP due to asbestosis and to collagen vascular disease. The presence of pleural plaques or diffuse pleural thickening helps to distinguish asbestosis from IPF. Patients with chronic hypersensitivity pneumonitis (47, 86), or with end-stage sarcoidosis (87), may uncommonly develop a CT pattern similar to that of UIP. Hypersensitivity pneumonitis should be considered if poorly defined fine micronodules are seen, or if there is sparing of the lung bases. Sarcoidosis should be suspected if the cysts are large, or if peribronchovascular nodules are present.

Histologic Features

The key histologic features of the UIP pattern are architectural destruction, fibrosis often with honeycombing, scattered fibroblastic foci, patchy distribution and involvement of the periphery of the acinus or lobule (Figure 5A) (23, 40). It has a heterogeneous appearance at low magnification, with alternating areas of normal lung, interstitial inflammation, fibrosis, and honeycomb change (Table 5) (23, 40). The histological changes affect the peripheral subpleural parenchyma most severely. Interstitial inflammation is usually mild to moderate, patchy, and consists of an alveolar septal infiltrate of lymphocytes, plasma cells, and histiocytes associated with hyperplasia of Type II pneumocytes. The fibrotic zones show temporal heterogeneity with dense acellular collagen and scattered fibroblastic foci (Figure 5B and 5C). Areas of honeycomb change are composed of cystic fibrotic airspaces, which are frequently lined by bronchiolar epithelium and filled with mucin. Smooth muscle hyperplasia is commonly seen in areas of fibrosis and honeycomb change (88). Areas of relatively normal lung should be present in surgical biopsy specimens in order to exclude the presence of active lesions of other interstitial disorders. Otherwise the UIP pattern may be difficult to recognize and a pathologist may only be able to diagnose "severe fibrosis with honeycomb change." In some patients with a UIP pattern on lung biopsy, specimens from a second or third lobe of lung may not fulfill the histologic criteria for UIP and suggest other patterns such as NSIP. However, in such a setting the default pathologic diagnosis is UIP.

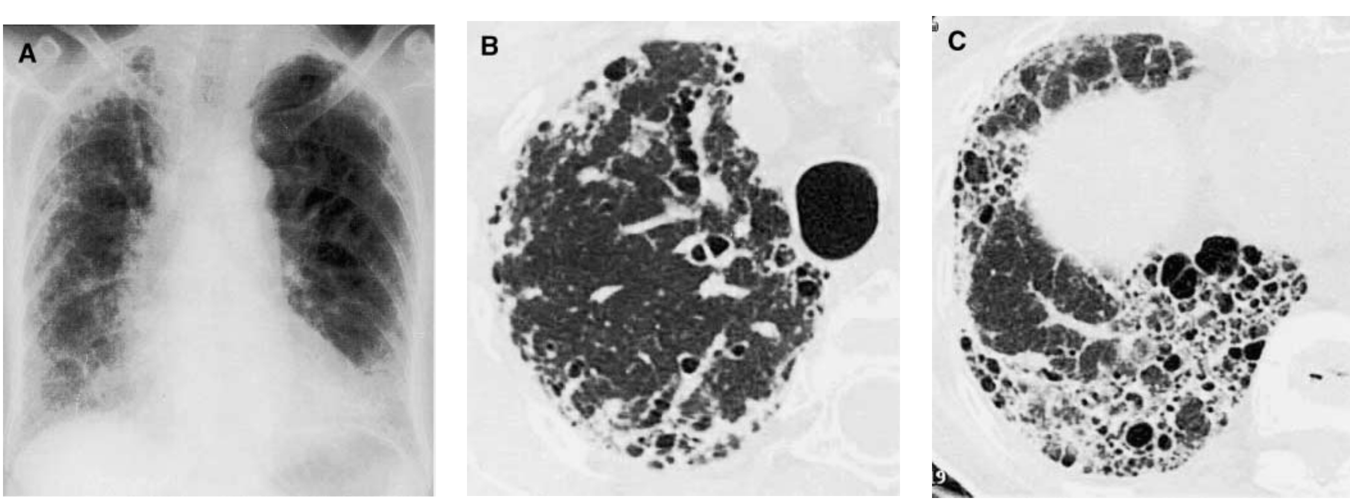

Figure 3. Idiopathic pulmonary fibrosis. (*A*) Chest radiograph shows typical peripheral reticular opacity, most marked at the bases, with honeycombing. Lower lobe volume loss (not present in this case) is also common. Chest radiographs may occasionally be normal in patients with IPF. (*B* and *C*) CT images show basal predominant, peripheral predominant reticular abnormality with traction bronchiectasis and honeycombing, typical of IPF.

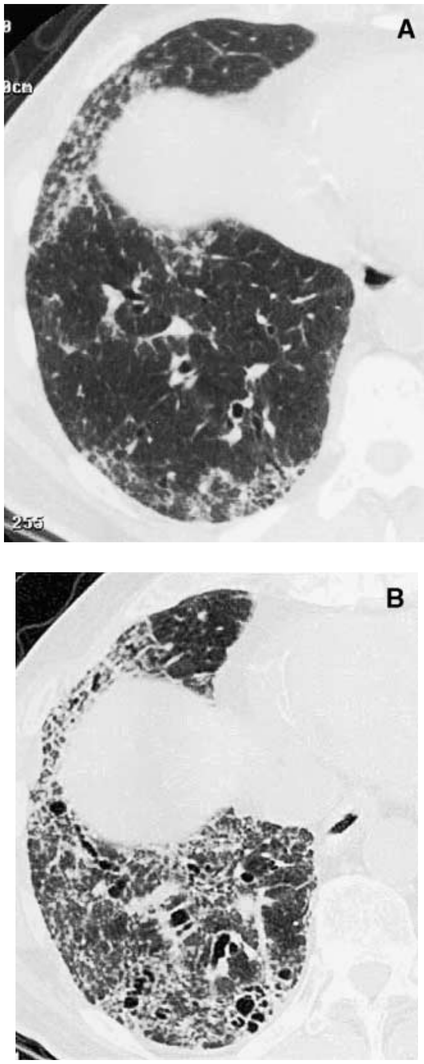

Figure 4. Progression of IPF in a 65-yr-old man. (*A* and *B*) CT scans obtained 20 mo apart show progression of lung fibrosis and honeycombing. Areas of ground glass opacity have progressed to reticular abnormality. Honeycomb cysts have enlarged, and the extent of disease has increased.

Patients who are biopsied during an accelerated phase of their illness may show a combination of UIP pattern and a variety of acute lesions. These include infection, prominent organizing pneumonia, DAD, and capillaritis. If no cause can be determined this may represent "accelerated decline of IPF" or acute exacerbation of IPF (70). A pattern of interstitial inflammation and fibrosis nearly indistinguishable from that seen in UIP can occur in patients with collagen vascular diseases, certain drug-induced lung diseass, chronic hypersensitivity pneumonitis, asbestosis, and familial IPF (Table 6). There is no single histologic finding that has shown a consistent correlation with treatment response or prognosis in IPF.

Histologic differential diagnosis. The differential diagnosis of the IIPs must be approached in two ways: histologically and clinically. In interpreting lung biopsies, the pathologist must address the differential diagnosis on the basis of the histologic pattern (89). A search should be made for histologic clues to a potential cause such as asbestos bodies, infectious agents, or other exogenous agents. The clinician must address most of the etiologic possibilities and in most cases ultimately determines whether the process is idiopathic.

The histologic differential diagnosis of the UIP pattern includes the histologic patterns of the other IIPs including fibrosing NSIP, DIP, OP, and DAD. With the narrowing of the histologic definition of the UIP pattern there are only a few clinical conditions that may cause an identical histologic pattern (Table 6). Lesions that can present histological features similar but not identical to UIP include asbestosis, collagen vascular disease, the fibrosing phase of hypersensitivity pneumonitis, radiation pneumonitis, and Hermansky–Pudlak syndrome.

IPF: Areas of Uncertainty

- Because the revised definition of IPF is more restrictive, previously reported series of cases need to be reviewed to establish the proportions of cases that would now be considered as non-UIP (and especially the cases that would be currently reclassified as NSIP).
- Do patients with histologic UIP who have an atypical CT pattern have different clinical features or clinical course? The true clinical course of confirmed IPF and the impact (if any) of treatment need to be defined.
- Is fibrosis in IPF another predisposing factor for lung carcinoma in addition to smoking?
- The pathogenesis of UIP needs to be defined.
- Histologic predictors of prognosis need to be sought.
- The characteristics and causes of accelerated IPF require study.
- The interobserver variability of pathological interpretation, particularly among general pathologists, needs to be defined.
- Is there a difference in the clinical features and prognosis of UIP in patients with IPF compared with those with known causes such as collagen vascular disease?

NONSPECIFIC INTERSTITIAL PNEUMONIA

The recognition that lung biopsy samples from some patients with idiopathic interstitial disease do not fit into any well-defined histologic patterns of idiopathic interstitial pneumonia led to proposals of the terms "unclassified interstitial pneumonia" by Kitaichi in 1990 (41) and NSIP by Katzenstein and Fiorelli in 1994 (17). The concept of NSIP has helped to identify a group of interstitial lung disorders with a more favorable prognosis and that need to be distinguished from IPF but that also differ from DIP, AIP, and COP (17, 18, 20, 21, 23, 35, 90). However, the term NSIP had also since the 1980s been used previously for noninfectious interstitial pneumonitis in HIV-infected patients (91–93).

Katzenstein and Fiorelli divided NSIP into three major subgroups based on the amount of inflammation and/or fibrosis in the lung biopsies: Group I, primarily with interstitial inflammation; Group II, with both inflammation and fibrosis; and Group III, primarily with fibrosis (17). In this study 39% of the patients with NSIP as a lung biopsy finding had a broad spectrum of associated conditions, such as collagen-vascular diseases (16%), slowly resolving DAD, and a variety of exposures (17).

In more recent publications the term NSIP has evolved from its original use, which was intended to indicate a histologic pattern with a variety of etiologies (17). Now it is almost exclusively used to identify a form of IIP (18, 20, 21, 35, 36, 40, 90, 94–96). However, the concept of an idiopathic form of NSIP presents a problem for the clinician because there is no recognized and distinctive clinical description for patients presenting with this histologic pattern on lung biopsy. Although these patients have a better prognosis than those with IPF, the clinician does not know this in advance. This improved prognosis has been observed in several studies and appears to cor-

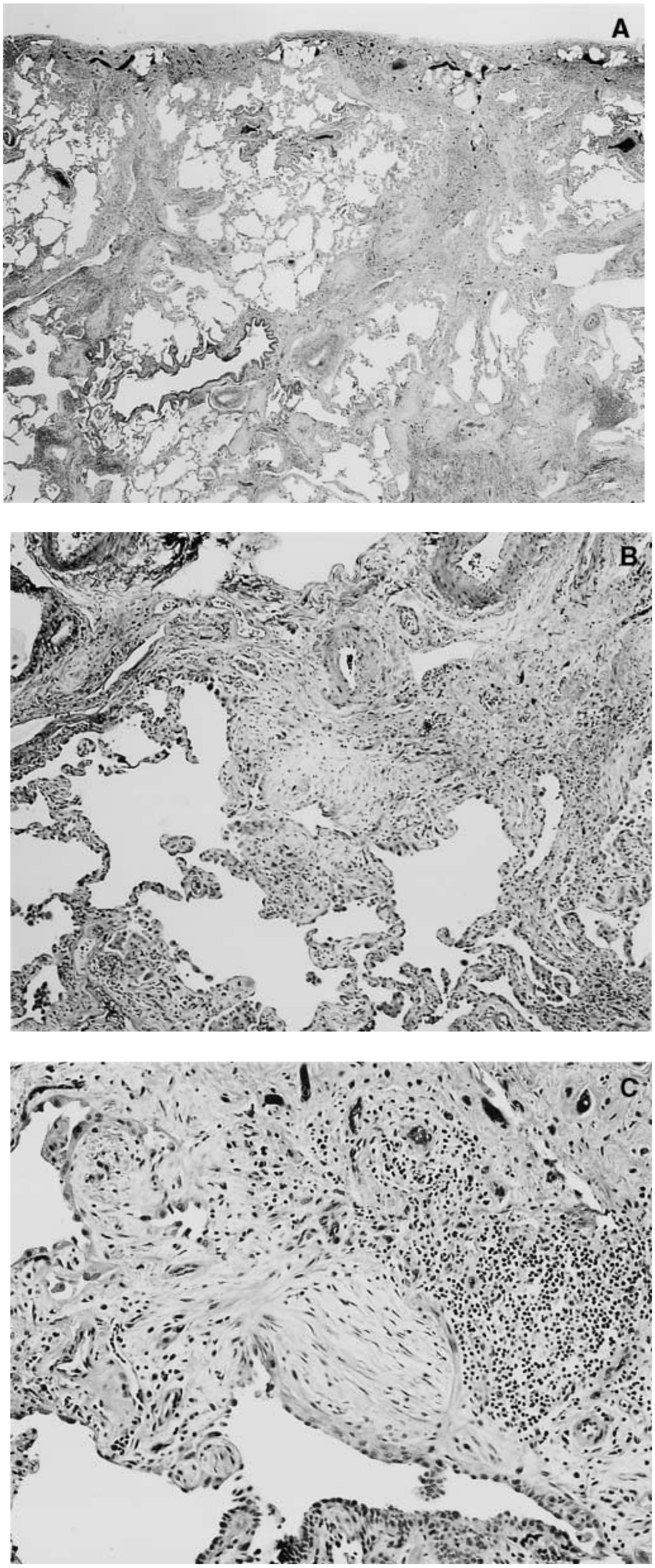

Figure 5. (*A*) Usual interstitial pneumonia pattern. Patchy fibrosis with remodeling of the lung architecture shows a striking subpleural distribution. Interstitial chronic inflammation is mild with a few lymphoid aggregates. Areas of "normal" lung are present that lack active lesions of other interstitial lung disorders. (*B*) There is marked fibrosis consisting of dense collagenous scarring with remodeling of the lung architecture and cystic changes. (*C*) The dense collagenous scar is juxtaposed with a fibroblastic focus of loose organizing connective tissue.

TABLE 5. HISTOLOGIC FEATURES OF USUAL INTERSTITIAL PNEUMONIA*

Key Histologic Features
Dense fibrosis causing remodeling of lung architecture with frequent "honeycomb" fibrosis
Fibroblastic foci typically scattered at the edges of dense scars
Patchy lung involvement
Frequent subpleural and paraseptal distribution
Pertinent Negative Findings
Lack of active lesions of other interstitial diseases (i.e., sarcoidosis or Langerhans' cell histiocytosis)
Lack of marked interstitial chronic inflammation
Granulomas: inconspicuous or absent
Lack of substantial inorganic dust deposits, i.e., asbestos bodies (except for carbon black pigment)
Lack of marked eosinophilia

* Adapted from Reference 23.

relate with differences in the dominant pathology, whether a cellular or fibrotic pattern of NSIP is present and dominates (17, 18, 20, 21, 23, 36, 40, 94, 95). Further subclassification may become necessary, but this remains an issue for further study. It is possible that specific occupational exposures may give rise to this pattern.

Importantly, the finding of an NSIP pattern on biopsy should prompt the clinician to redouble efforts to find potentially causative exposures. NSIP may be the presenting manifestation preceding the diagnosis of collagen vascular disease by several months or several years. The NSIP pattern may also be the lone histologic feature in a patient with hypersensitivity pneumonitis. Therefore, care should be taken to search for serological and other markers of the connective tissue diseases and a careful search for potential exposures is essential. It is possible that specific occupational exposures may give rise to this pattern.

After considerable debate regarding the best clinical term for patients with this histologic pattern, it was decided that use of the term NSIP was acceptable as a provisional measure until there is further clarity on the nature of the corresponding clinical condition. Although there are several reasons to be critical of the term NSIP, one advantage is that the name implies the uncertainty that prevails.

Clinical Features

The clinical features of patients with an NSIP pattern on surgical lung biopsy are poorly defined. NSIP probably represents a heterogeneous group of disorders and subsets of patients with different clinical courses are being recognized, but at this time there is no consensus about these.

The mean age of patients at onset of NSIP is a decade or more younger than patients with IPF (median age of onset is 40 and 50 yr in different case series) (18, 90) and unlike IPF may occur in children (17). There is neither sexual predominance nor association with cigarette smoking (18). Onset is

TABLE 6. CLINICAL CONDITIONS ASSOCIATED WITH USUAL INTERSTITIAL PNEUMONIA PATTERN

Idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis
Collagen vascular disease
Drug toxicity
Chronic hypersensitivity pneumonitis
Asbestosis
Familial idiopathic pulmonary fibrosis
Hermansky–Pudlak syndrome

usually gradual, but a minority of patients may have a subacute presentation. The median duration of symptoms before diagnosis is 18 and 31 mo in different series, but may be as short as 6 mo or as long as 3 yr (18, 90). Breathlessness, cough, and fatigue are usual symptoms, and almost half present with a history of weight loss (mean, 6 kg) (18). Constitutional symptoms such as fever are present in a minority and finger clubbing, which occurs in 10 to 35% of patients, is less common than it is in IPF. Crackles are initially predominantly basal but may be widespread. Inspiratory squeaks are found in some (18). Other clinical features are similar to those found in IPF. Lung function tests show similar but milder physiological abnormalities than those found in IPF; that is, a restrictive ventilatory defect in more than 90% of patients, mild airflow limitation in a minority, and reduced DL_{co} in all. Some patients may show moderate to severe physiological abnormalities. The KCO (CO transfer coefficient) is normal in about 50%. More than two-thirds develop hypoxemia during exercise.

Clinical course. The prognosis of NSIP is more variable than in IPF and appears to depend on the extent of fibrosis (17, 21, 23). Some patients experience almost complete recovery, and most of the remainder stabilize or improve on treatment. Relapse may occur (18). A minority of patients progress and die (17, 21, 23, 90).

Bronchoalveolar lavage features. Unlike in UIP, increases in the percentages of lymphocytes occur in about 50% of cases, and similar proportions also have increased numbers of neutrophils and/or eosinophils (18, 21, 97, 98). The presence of bronchoalveolar lavage lymphocytosis strengthens the suspicion of NSIP in conjunction with other findings, including HRCT and pulmonary function test results.

Radiologic Features

Chest radiographic features. NSIP typically shows bilateral pulmonary infiltrates and the lower lung zones are more frequently involved, although no large detailed analysis of the radiographic appearances of patients with NSIP exists. Of 97 reported cases, the chest radiograph was abnormal in 91 (94%) (17, 18, 94). Patchy parenchymal opacity was the most common radiographic feature in one study (94), but interstitial abnormalities have also been described (Table 3) (17).

CT features. Analysis of a total of 85 patients from three studies (18, 95, 99) shows that ground glass attenuation is the predominant finding in the majority of cases (Figure 6) and is the sole abnormality in about one-third of cases. It is most commonly bilateral and symmetrical with subpleural predominance. Irregular linear or reticular opacities are seen in approximately half of all cases, and may be associated with traction bronchiectasis. In general, honeycombing and consolidation are relatively infrequent. Differences among the three studies in the prevalence of honeycombing, consolidation nodules, and bronchovascular bundle thickening may reflect different study populations or different criteria for the inclusion of cases as NSIP. Fibrosing NSIP may be associated with HRCT evidence of honeycombing, and in such cases only the pathologist can make the distinction from the UIP pattern (21).

Of the limited number of patients with NSIP who have had follow-up CT examinations after treatment, the abnormalities of NSIP have generally improved in the majority.

Radiologic differential diagnosis. The CT differential diagnosis of patients with the pathologic pattern of NSIP depends on the dominant CT pattern exhibited. In a study of 50 patients (99), experienced observers considered the CT pattern indistinguishable from UIP in 32%, hypersensitivity pneumonitis in 20%, organizing pneumonia in 14%, and other diagnoses in 12%. In another investigation, the authors assessed the value of high-resolution CT in the differential diagnosis of 129 patients with histologically proven idiopathic interstitial pneumonias (100). Two independent observers were able to make a correct first choice diagnosis in more than 70% of cases of UIP and

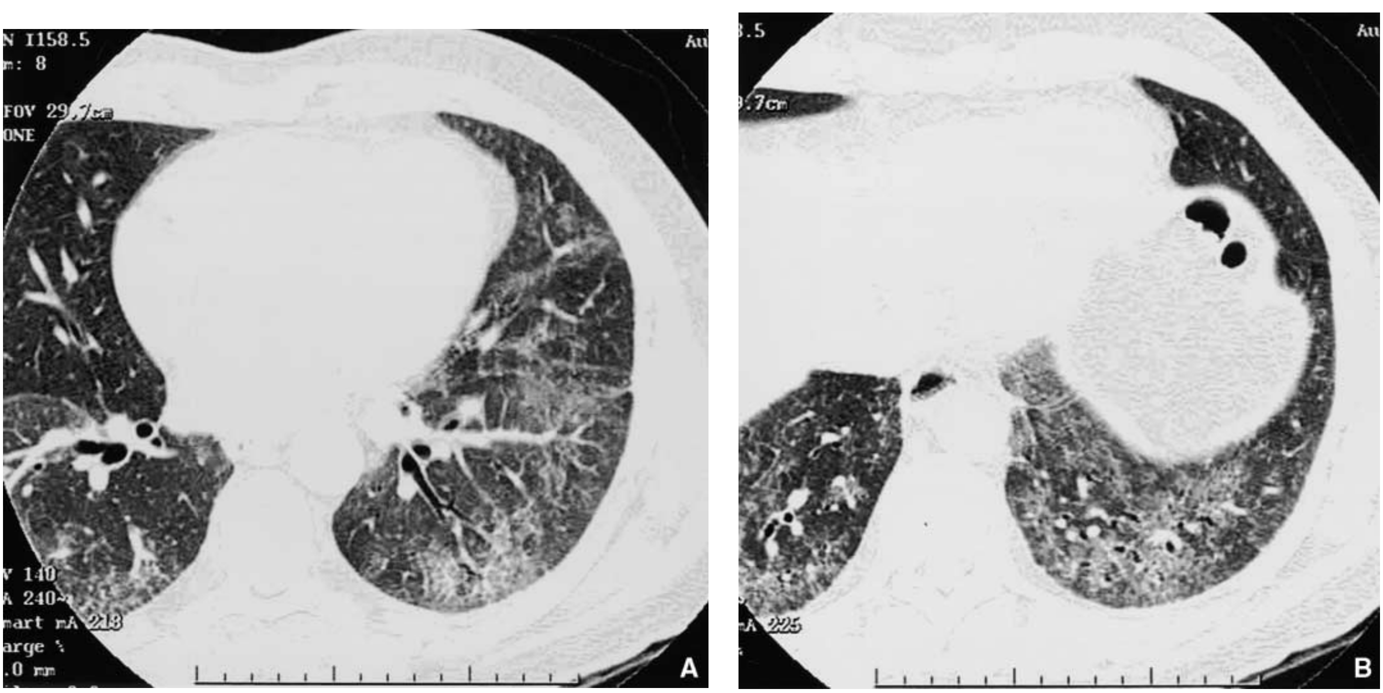

Figure 6. Nonspecific interstitial pneumonia. HRCT through the left lower lung shows extensive ground glass abnormality, with associated reticular abnormality and traction bronchiectasis. Histology showed a combination of inflammation and mild fibrosis.

COP, in more than 60% of cases of DIP and AIP, but in only 9% of cases of NSIP. In this study, NSIP was confused most often with DIP, and less often with COP and UIP. This study was retrospective, and subject to significant selection bias, because patients with classic CT changes of UIP generally did not undergo biopsy. Therefore these figures cannot be used to determine the accuracy of CT for differential diagnosis of the interstitial pneumonias. A study of 21 cases of UIP and 32 cases of NSIP found that an HRCT diagnosis of NSIP was associated with a sensitivity of 70% and a specificity of 63% and suggests that NSIP can be distinguished from UIP in most but not all cases by the presence of prominent ground glass attenuation (101).

CT–pathologic correlation. Ground glass attenuation corresponds to interstitial thickening due to varying amounts of interstitial inflammation and fibrosis (95). When irregular linear opacities and bronchial dilatation were present in areas of ground glass attenuation, interstitial fibrosis and microscopic honeycombing were seen on histology. Areas of consolidation correspond to areas of organizing pneumonia, with or without microscopic honeycombing.

Histologic Features

The NSIP pattern encompasses a broad spectrum of histologic features with varying degrees of alveolar wall inflammation or fibrosis (17, 21, 23). Lung biopsies may show predominantly interstitial inflammation or fibrosis or a combination of inflammation and fibrosis. The histologic features do not fit the histologic pattern of UIP, OP, DAD, DIP, or LIP. The histologic features and differential diagnosis of NSIP patterns are summarized in Tables 7 and 8.

At the cellular end of the spectrum the NSIP pattern (Table 7) consists primarily of mild to moderate interstitial chronic inflammation, usually with lymphocytes and a few plasma cells (Figure 7) (17, 21, 23). The lung typically is uniformly involved, but the distribution of the lesions is often patchy. The interstitium around airways, blood vessels, interlobular septa, and pleura is sometimes involved. Dense fibrosis is inconspicuous or absent. Intra-alveolar organizing fibrosis may be seen in up to two-thirds of cases, but is considerably less than that seen in the organizing pneumonia pattern. Lymphoid aggregates are common.

At the fibrosing end of the spectrum the NSIP pattern consists of dense or loose interstitial fibrosis in varying degrees and the connective tissue is temporally homogeneous (Table 7 and Figure 8) (17, 23). Fibroblastic foci, the key lesion that gives the UIP pattern the appearance of temporal heterogeneity, are absent or inconspicuous (Table 7). In some cases the pattern of fibrosis is patchy in distribution, causing remodeling of the lung architecture (21). In other cases, this pattern differs from that of UIP in that there is more diffuse involvement of the lung with preserved alveolar architecture, but the alveolar septal interstitium is expanded by dense or loose fibrosis. Foci of honeycomb fibrosis and a mild degree of smooth muscle proliferation may be present but are not characteristic (21). Interstitial chronic inflammation is usually mild to moderate and consists mainly of lymphocytes and some plasma cells. However, some cases show a mixed fibrosing and cellular pattern with prominent interstitial chronic inflammation.

Histologic differential diagnosis. The histologic differential diagnosis for cases of NSIP with a cellular pattern includes the patterns of hypersensitivity pneumonitis, organizing pneumonia, LIP, resolving DAD, eosinophilic pneumonia, and fibrosing NSIP (17, 21, 23. 89). Hypersensitivity pneumonitis shows a pattern consisting of bronchiolocentric cellular interstitial pneumonia, scattered, poorly formed granulomas, and intralumenal organizing fibrosis (102, 103). The presence of loose, poorly formed granulomas in a case with a cellular NSIP pattern should raise concern to exclude hypersensitivity pneumonitis, infection, collagen vascular disease, or drug-induced pneumonitis. To help exclude infection the biopsy should be examined with special stains for fungi, *Pneumocystis carinii*, and acid-fast bacilli. The lymphoid infiltrate of the cellular NSIP pattern is less severe than the extensive diffuse alveolar septal infiltration observed in lymphocytic interstitial pneumonia.

The histologic differential diagnosis for cases of NSIP showing a fibrosing pattern includes the UIP pattern and fibrotic forms of other types of interstitial pneumonitis, including hypersensitivity pneumonitis, Langerhans' cell histiocytosis, DIP, organizing pneumonia, DAD, and sarcoidosis (17, 21, 23, 89). The most important difference between the fibrosing pattern of NSIP and UIP patterns is the temporal uniformity of the former, which contrasts with the variegated appearance of the connective tissue in the UIP pattern, in which dense collagen is associated with scattered fibroblastic foci. In most cases, the distinction between the cellular and fibrosing patterns of NSIP is not difficult. In some cases, the presence of dense interstitial fibrosis may be highlighted with connective tissue stains (e.g., the Masson trichrome stain or Movat stain).

Once the histologic differential diagnosis has been sorted out and a histologic pattern of NSIP determined, the clinician

TABLE 7. HISTOLOGIC FEATURES OF NONSPECIFIC INTERSTITIAL PNEUMONIA*

Key Histologic Features
Cellular pattern†
Mild to moderate interstitial chronic inflammation
Type II pneumocyte hyperplasia in areas of inflammation
Fibrosing pattern†
Dense or loose interstitial fibrosis lacking the temporal heterogeneity pattern and/or patchy features of UIP
Lung architecture may appear lost on examination of H&E-stained sections, but relatively preserved with elastic stains
Interstitial chronic inflammation—mild or moderate
Pertinent Negative Findings
Cellular pattern
Dense interstitial fibrosis: absent
Organizing pneumonia is not a prominent feature
Lack of diffuse severe alveolar septal inflammation
Fibrosing pattern
Temporal heterogeneity pattern: fibroblastic foci with dense fibrosis are inconspicuous or absent—this is especially important in cases with patchy involvement and subpleural or paraseptal distribution
Both patterns
Acute lung injury pattern, especially hyaline membranes: absent
Eosinophils: inconspicuous or absent
Granulomas: inconspicuous or absent
Lack of viral inclusions and organisms on special stains for organisms

Definition of abbreviations: H&E = hematoxylin–eosin; UIP = usual interstitial pneumonia.

* Adapted from Reference 23.

† There is a spectrum from cellular to fibrosing patterns, with some cases showing a combination of cellular and fibrosing features.

TABLE 8. CLINICAL CONDITIONS ASSOCIATED WITH NONSPECIFIC INTERSTITIAL PNEUMONIA HISTOLOGIC PATTERN*

No detectable cause (idiopathic NSIP)
Collagen vascular disease
Hypersensitivity pneumonitis
Drug-induced pneumonitis
Infection
Immunodeficiency including HIV infection

* Adapted from Reference 23.

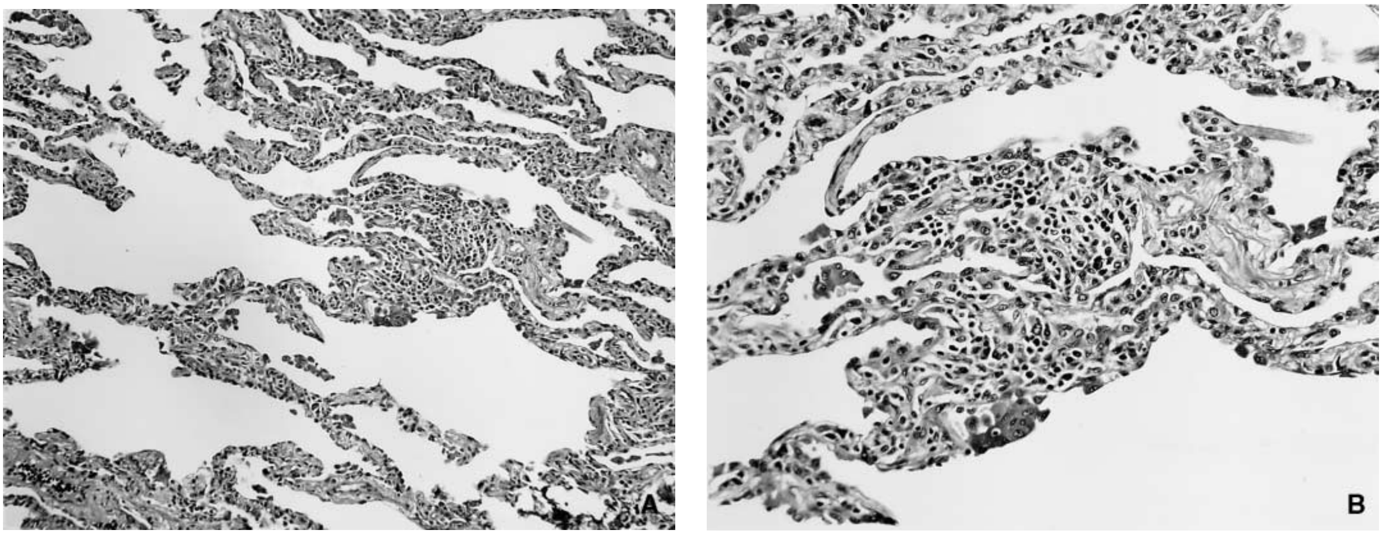

Figure 7. Nonspecific interstitial pneumonia, cellular pattern. (*A*) The interstitium is infiltrated by a moderate chronic inflammatory infiltrate. Fibrosis is absent. (*B*) The infiltrate consists of lymphocytes and plasma cells.

should re-evaluate the patient to exclude any of the clinical conditions that may be associated with NSIP (Table 8).

NSIP: Areas of Uncertainty

- In view of the uncertainty of NSIP as a clinical entity, it might be better termed "IIP-NSIP pattern" as a means of avoiding giving the term a disease status. Other terms considered include "IIP-NSIP variant."
- What are the incidence and prevalence of the disease?
- It is not clear whether clinical methods exist or can be devised to reliably distinguish cases of NSIP from other forms of IIP.
- In view of the variable pathology (range of cellularity and fibrosis) response to treatment and prognosis, is further subclassification warranted or possible?
- What accounts for the differences in radiographic patterns observed; for example, the presence of consolidation being recorded as common and rare in different series?
- What is the relationship between NSIP and UIP, if any?
- Are differences in imaging patterns and survival observed in different series accounted for by different selection or diagnostic criteria?

CRYPTOGENIC ORGANIZING PNEUMONIA

Cryptogenic organizing pneumonitis (COP) is a clinicopathologic entity described by Davison and coworkers in 1983 (38). In 1985, Epler and colleagues described the same entity under the term bronchiolitis obliterans organizing pneumonia (BOOP), and that latter term came into common usage (sometimes referred to as idiopathic BOOP) (37). The term cryptogenic organizing pneumonitis (COP) is preferred because it conveys the essential features of the syndrome described below and avoids confusion with airway diseases such as constrictive bronchiolitis obliterans, which can be problematic with the term BOOP. Features of the organizing pneumonia pattern are organization

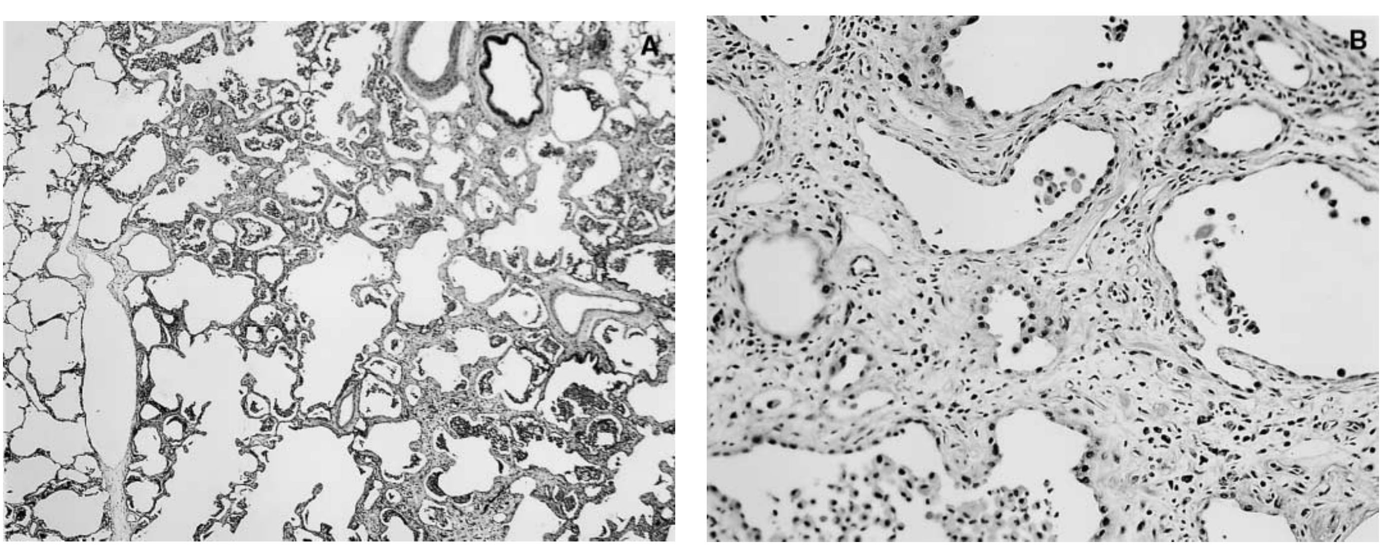

Figure 8. Nonspecific interstitial pneumonia, fibrosing pattern. (*A*) The alveolar walls show diffuse thickening by fibrosis and mild interstitial inflammation. No fibroblastic foci are present. (*B*) Nonspecific interstitial pneumonia, fibrosing pattern. The alveolar walls are thickened by dense collagen and a few lymphocytes and plasma cells.

within alveolar ducts and alveoli ("organizing pneumonia") with or without organization within bronchioles ("polypoid bronchiolitis obliterans"). Use of the generic term "organizing pneumonia" for this reaction pattern is suggested with modifiers as appropriate, for example, COP as described below, organizing pneumonia associated with rheumatoid arthritis, organizing pneumonia secondary to viral pneumonia, etc. In this context, organizing pneumonia is used for both infectious as well as noninfectious etiologies. Some of the well-known causes of the organizing pneumonia pattern are summarized in Table 9.

COP is included in the classification of IIP because of its idiopathic nature and the tendency on occasions to be confused with other forms of IIP in addition to the histologic features of alveolar septal infiltration by lymphoid cells with Type II pneumocyte hyperplasia in the involved areas (37, 104, 105).

Clinical Features

There is an equal sex distribution but nonsmokers outnumber smokers by 2:1. Mean age of onset is 55 yr (106, 107). Patients typically present with an illness of relatively short duration (median, less than 3 mo) with variable degrees of cough and dyspnea (106, 108). The cough may be productive of clear or discolored sputum. Symptoms usually follow a suspected but unconfirmed lower respiratory tract infection, and patients have often received at least one and frequently several courses of antibiotics. Continuing weight loss, sweats, chills, intermittent fever, and myalgia are common. Localized or more widespread crackles are frequently present, and rarely features of consolidation are found (106). Clubbing of fingers is absent. A markedly raised erythrocyte sedimentation rate (ESR), elevated C-reactive protein, and peripheral blood neutrophilia are common findings (106).

Lung function tests confirm a restrictive ventilatory pattern (usually mild to moderate) with a moderately reduced carbon monoxide transfer factor in most (74, 106, 108). Airflow obstruction is present in a minority and is thought to be an independent consequence of smoking. Mild resting hypoxemia may be present and reflects marked disturbance of gas exchange (106).

Clinical course. The majority of patients recover completely on administration of oral corticosteroids, but a significant number relapse within 1 to 3 mo when the corticosteroids are reduced (usually to below 15 mg/d) or stopped (37, 106). Prolonged treatment for 6 mo or longer is advised. A small proportion of patients recovers spontaneously (37). Rare cases previously classified as COP are reported to progress to respiratory failure and death. In some of these cases, additional features of diffuse interstitial fibrosis have been present, suggesting an alternative diagnosis including organizing pneumonia superimposed on a UIP lesion (acute exacerbation or accelerated decline of IPF) (107, 109–111).

COP may present in a variety of ways and if suspected on the basis of a typical clinical history and chest-imaging studies, the diagnosis may be confirmed by obtaining a transbronchial lung biopsy sample that shows consistent histopathologic features and does not show any features suggestive of another process and if the follow-up and response to therapy are appropriate (112).

Bronchoalveolar lavage features. BAL fluid contains increases in the total number and proportion of lymphocytes (lymphocyte percentages of up to 40% of total cells) (21, 108). The ratio of $CD4^+$ to $CD8^+$ cells is decreased, and the proportion of neutrophils (particularly in the early stages) and of eosinophils is frequently also increased (106, 108, 113, 114). A prominent increase in eosinophils should raise the consideration of eosinophilic pneumonia.

Radiologic Features

Chest radiographic features. The most common radiographic findings in COP are bilateral or unilateral areas of consolidation (Table 3) (74). The distribution is usually patchy but may be confined to the subpleural region in a minority of cases. Small nodular opacities are seen in 10–50% of cases. A minority of patients presents with a reticulonodular pattern (108). Large nodular opacities ($>$ 1 cm) are the presenting radiographic appearance in approximately 15% of cases. Lung volumes are normal in up to 75% of cases. The remaining patients demonstrate reduced lung volumes.

CT features. Areas of airspace consolidation are present on CT in 90% of patients with COP (Table 3 and Figure 9) (115, 116). CT demonstrates a subpleural or peribronchial distribution in up to 50% of cases. The lower lung zones are more frequently involved. Air bronchograms are a consistent finding when consolidation is present. Mild cylindrical bronchial dilatation is commonly evident in areas of consolidation. Small nodules ($<$ 10 mm) are usually seen along bronchovascular bundles and are evident in up to 50% of cases. Ground glass attenuation is present in about 60% of cases, usually associated with lung consolidation. Pleural effusions are rare.

Approximately 15% of patients with COP present with multiple large nodules (117). These nodules usually have an irregular margin (88%) with air bronchograms (45%). Ancillary findings include pleural tags (38%), spicules (35%), pleural thickening (33%), and parenchymal bands (25%).

The majority of patients with COP demonstrate radiographic improvement with treatment. However, the parenchymal abnormalities may regress or change in one area and even emerge in new locations without treatment. Most patients who respond to steroids show complete clearing or are left with small residual opacities. If reticular opacities are present on the chest radiograph of patients with COP, the patient is less likely to respond to steroids, and may progress to lung fibrosis (108).

Radiologic differential diagnosis. The radiographic differential diagnosis of COP in patients with areas of consolidation includes alveolar cell carcinoma, lymphoma, vasculitis, sarcoidosis, and infection (particularly tuberculosis or atypical mycobacterial infection). When the consolidation is subpleural, then the diagnosis of chronic eosinophilic pneumonia should be considered. Most of these diagnoses can be excluded by transbronchial biopsy. Those patients who present with multiple large masses have a differential diagnosis that includes metastatic lung tumor, lymphoma, and pulmonary infection including septic emboli. In the appropriate clinical context (consolidation increasing over several weeks despite antibiot-

TABLE 9. CLINICAL SETTINGS ASSOCIATED WITH ORGANIZING PNEUMONIA PATTERN

As an idiopathic process that may be a localized nodule or infiltrative lung disease (COP)
Organizing diffuse alveolar damage
Organizing infections
Organization distal to obstruction
Organizing aspiration pneumonia
Organizing drug reactions, fume, and toxic exposures
Collagen vascular disease
Extrinsic allergic alveolitis/hypersensitivity pneumonitis
Eosinophilic lung disease
Inflammatory bowel disease
As a secondary reaction in chronic bronchiolitis
As a reparative reaction around other processes (including abscesses, Wegener's granulomatosis, neoplasms, and others)

Definition of abbreviation: COP = crytogenic organizing pneumonia.

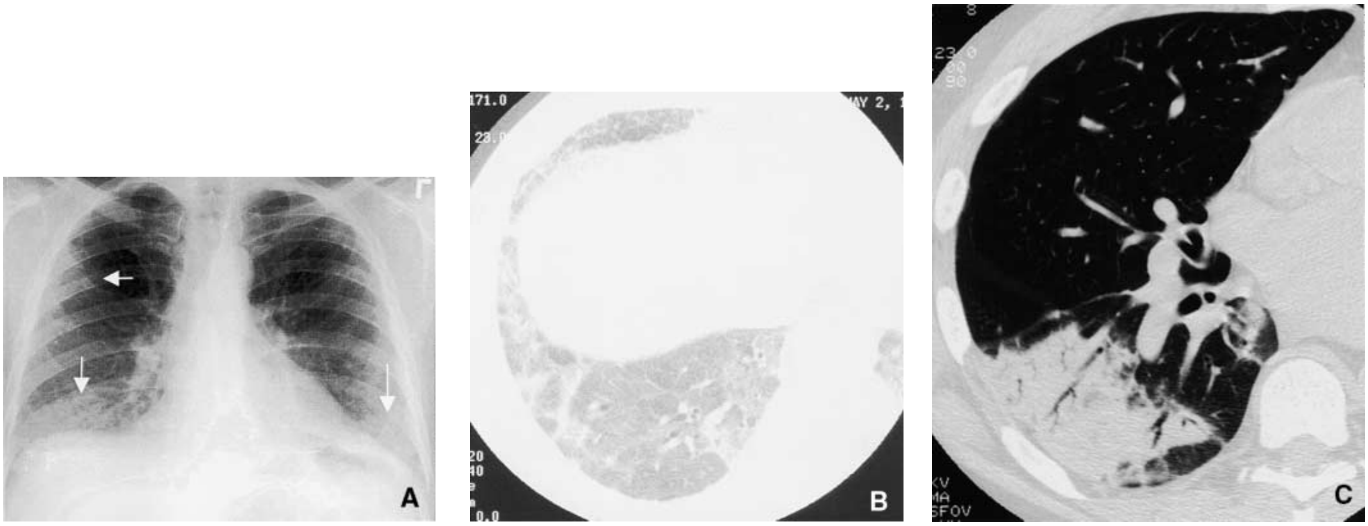

Figure 9. Cryptogenic organizing pneumonia. (*A*) Chest radiograph shows multifocal consolidation (*arrows*). (*B*) HRCT images through the lower lungs in the same patient show subpleural consolidation, ground glass abnormality, and reticular pattern. (*C*) HRCT in different patient shows a focal patch of subpleural consolidation with air bronchograms.

ics) a CT pattern of consolidation in a predominantly peribronchial or subpleural distribution is highly suggestive of COP. The combination of ground glass attenuation and cysts on CT should suggest either LIP or DIP.

Histologic Features

The organizing pneumonia pattern is a patchy process characterized primarily by organizing pneumonia involving alveolar ducts and alveoli with or without bronchiolar intralumenal polyps (Table 10 and Figure 10) (37, 89, 104, 107, 118). The connective tissue is all the same age. The majority of changes center on small airways. There is a mild associated interstitial inflammatory infiltrate, Type II cell metaplasia, and an increase in alveolar macrophages, some of which may be foamy. A small amount of airspace fibrin may be focally present. There is relative preservation of background lung architecture (37, 104, 107, 118).

Histological differential diagnosis. Histologic features strongly against the diagnosis of COP include airspace neutrophils, acute bronchiolitis, granulomas, necrosis, hyaline membranes, and prominent infiltration of eosinophils (89). The major histologic differential diagnostic considerations for the organizing pneumonia pattern include the DAD, NSIP, DIP, and UIP patterns. DAD is characterized by more uniform and diffuse lung injury with marked edematous thickening and organization in alveolar walls and, often, hyaline membranes (37, 104, 107, 118).

COP: Areas of Uncertainty

- What are the incidence and prevalence of the disease?
- What is the role of transbronchial lung biopsy in the diagnosis of COP?
- How frequent are relapses in patients with COP? What impact do recurrences have on long-term outcome?
- How does the timing of treatment alter the clinical course of patients with COP and the frequency of recurrences?
- Does spontaneous clinical improvement or resolution occur?
- What are the features that distinguish primary COP from secondary COP (that is associated with another process)?
- Why does this fibrotic process resolve, whereas the fibroblastic foci of the UIP lesion lead to progressive end-stage fibrosis?

ACUTE INTERSTITIAL PNEUMONIA

AIP is a rapidly progressive and histologically distinct form of interstitial pneumonia. The pathology is described as an organizing form of diffuse alveolar damage (DAD) indistinguishable from the histologic pattern found in acute respiratory distress syndrome (ARDS) caused by sepsis and shock. Some of the cases described by Hamman and Rich probably represented AIP (19, 119, 120). The term AIP is reserved for cases of unknown cause (39).

Clinical Features

AIP occurs over a wide age range, with a mean age of approximately 50 yr, and there is no sex predominance, nor association with smoking (19, 39, 40, 119, 120). Most case series fail to distinguish between those patients with a putative cause and idiopathic cases.

Patients often have a prior illness suggestive of a viral upper respiratory infection with constitutional symptoms such as myalgias, arthralgias, fever, chills, and malaise (39). Severe exertional dyspnea develops over a few days and at presentation for medical attention (median time from first symptom to presentation is less than 3 wk) is associated with signs of widespread pneumonic consolidation with prominent diffuse crackles (19, 39).

TABLE 10. HISTOLOGIC FEATURES OF ORGANIZING PNEUMONIA PATTERN

Key Histologic Features
Organizing pneumonia: intralumenal organizing fibrosis in distal airspaces (bronchioles, alveolar ducts, and alveoli)
Patchy distribution
Preservation of lung architecture
Uniform temporal appearance
Mild interstitial chronic inflammation
Pertinent Negative Findings
Lack of interstitial fibrosis (except for incidental scars or apical fibrosis)
Absence of granulomas
Lack of neutrophils or abscesses
Absence of necrosis
Lack of hyaline membranes or prominent airspace fibrin
Lack of prominent infiltration of eosinophils
Absence of vasculitis

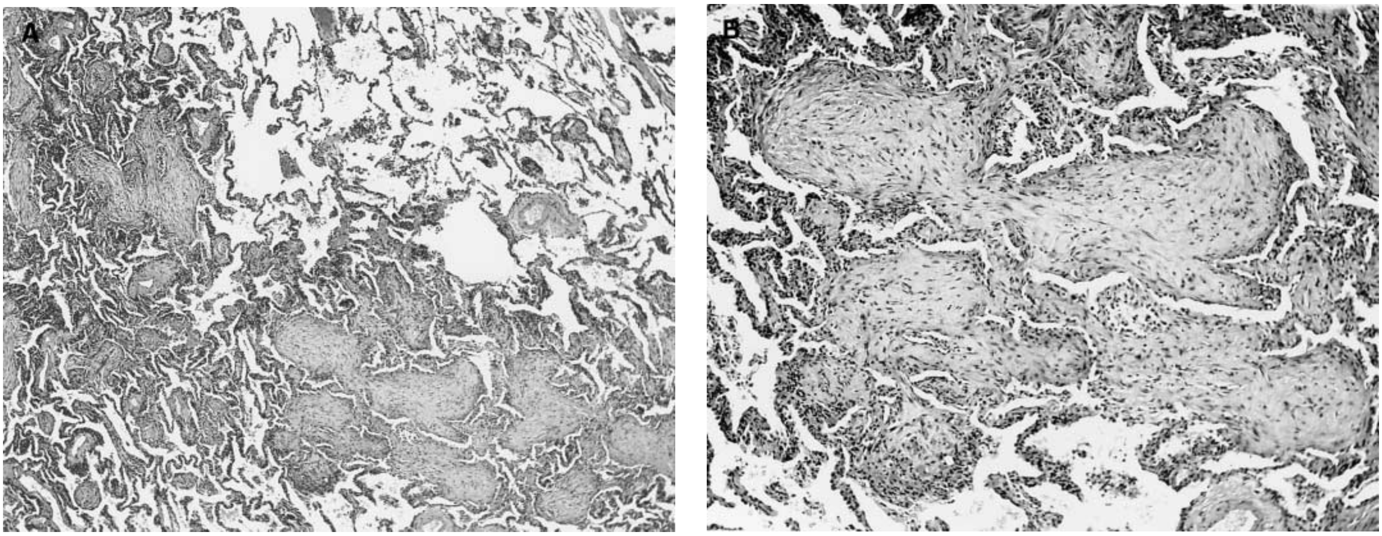

Figure 10. Organizing pneumonia pattern in patient with cryptogenic organizing pneumonia. (*A*) There is patchy lung involvement by loose plugs of connective tissue within a bronchiole and the adjacent alveolar ducts and alveolar spaces. The architecture of the lung is preserved and the connective tissue is all the same age. (*B*) The organizing pneumonia consists of polypoid plugs of loose organizing connective tissue within an alveolar duct and the adjacent alveolar spaces.

Pulmonary function tests show a restrictive pattern with reduced diffusing capacity. Hypoxemia develops early and progresses rapidly to respiratory failure, which may be refractory to supplemental oxygen (19). Mechanical ventilation is usually required. The majority of patients fulfill the diagnostic clinical criteria for ARDS: acute onset, a Pa_{O_2}/FI_{O_2} (fraction of inspired oxygen) ratio equal to or less than 200 mm Hg, diffuse bilateral opacities on chest radiograph, and a pulmonary capillary wedge pressure of less than 18 mm Hg when measured or no clinical evidence of left atrial hypertension (121).

AIP needs to be distinguished from DAD superimposed on UIP (accelerated decline of UIP) (70), DAD in patients with collagen vascular diseases, ARDS (DAD of known cause), infection (especially due to *Pneumocystis carinii* pneumonia and cytomegalovirus), drug-induced pneumonitis, hypersensitivity pneumonitis, and acute eosinophilic pneumonia (73, 122).

Clinical course. There is no proven treatment and mortality rates are high (50% or more), most deaths occurring between 1 and 2 mo of illness onset (39). Survivors of AIP may experience recurrences and chronic, progressive interstitial lung disease (123, 124).

Bronchoalveolar lavage features. Bronchoalveolar lavage fluid (BALF) contains increased total cells, hemorrhage (red blood cells and/or hemosiderin), neutrophils, and occasionally increased lymphocytes (98). Atypical reactive pneumocytes and fragments of hyaline membranes may be seen.

Radiologic Features

Chest radiographic features. The chest radiograph reveals bilateral airspace opacification with air bronchograms in essentially all patients (Table 3) (125). The distribution is often patchy, with sparing of the costophrenic angles. The cardiac silhouette and vascular pedicle are normal and interstitial abnormalities such as septal lines and peribronchial cuffing are usually absent. Pleural effusions are uncommon. The lung volumes are usually low but may be near normal. As the disease progresses the lungs tend to become diffusely consolidated. As AIP moves from the exudative to the organizing stage the radiograph shows less consolidation and presents a ground glass appearance with irregular linear opacities.

CT features. The most common findings on CT in patients with AIP are areas of ground glass attenuation, bronchial dilatation, and architectural distortion (Table 3 and Figure 11) (67). The extent of the areas of ground glass attenuation correlates with disease duration. In the early exudative phase the lung shows areas of ground glass attenuation that are most often bilateral and patchy, with areas of focal sparing of lung lobules giving a geographic appearance (125). The ground glass opacities are neither distinctly subpleural nor central. Consolidation is seen in the majority of cases but is not as common as ground glass attenuation. The distribution is most often basilar but can occasionally be diffuse or rarely have an upper lobe predominance. In patients with classic AIP the areas of consolidation are most often in the dependent area of lung, suggesting alveolar closure from the weight and hydrostatic pressure of the more superior lung tissue. Intralobular linear opacities and subpleural honeycombing are seen in a minority of cases.

The later, organizing stage of AIP is associated with distortion of bronchovascular bundles and traction bronchiectasis. The areas of consolidation tend to be replaced by ground glass opacities. Cysts and other lucent areas of lung become more common in the late stages of AIP.

The few patients who survive show progressive clearing of the ground glass attenuation and consolidation. The most common residual HRCT findings are areas of hypoattenuation, lung cysts, reticular abnormality, and associated parenchymal distortion occurring mainly in the nondependent lung (126).

Radiologic differential diagnosis. Although the CT features of AIP are similar to those of ARDS, patients with AIP are more likely to have a symmetric bilateral distribution with lower lung predominance, when compared with patients with ARDS (127). The radiologic differential diagnosis of AIP depends on the stage but can include the following: widespread infection (particularly *P. carinii* pneumonia), hydrostatic edema, hemorrhage, alveolar proteinosis, bronchioloalveolar cell carcinoma, and DIP.

CT–pathologic correlation. Consolidation and ground glass attenuation, when not associated with traction bronchiectasis, correlate with the exudative or early proliferative phase of DAD (128). Ground glass attenuation or consolidation associated with traction bronchiectasis correlates with the proliferative and fibrotic phases of DAD. The focal areas of apparent sparing usually show mild exudative changes. Interlobular septal thickening usually correlates with juxtaseptal alveolar collapse and organization during the proliferative and fibrotic phases.

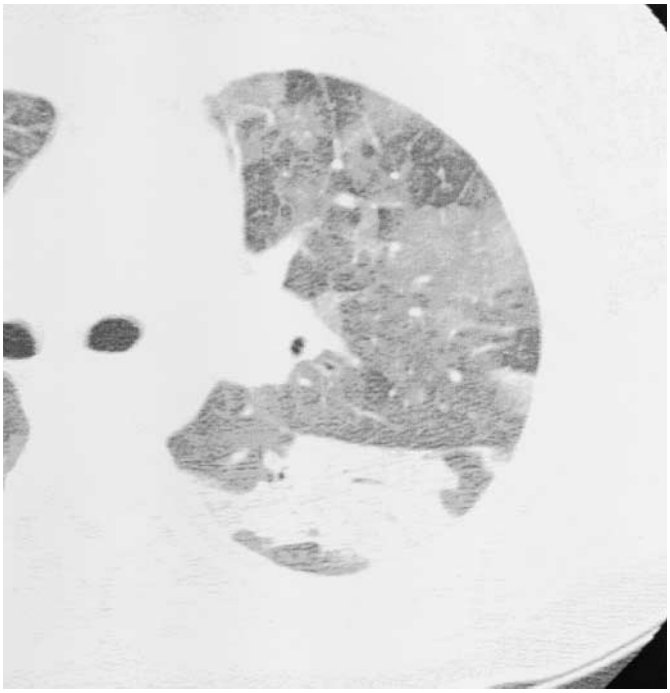

Figure 11. Acute interstitial pneumonia. HRCT shows a geographic distribution of ground glass abnormality with consolidation in the more dependent lung.

Pathologic Features

Lung biopsies from patients with AIP show histologic features of the acute and/or organizing phases of DAD (Table 11) (19, 39, 129). The lung biopsy typically shows diffuse involvement (Figure 12), although there may be variation in the severity of the changes among different histologic fields. The exudative phase shows edema, hyaline membranes, and interstitial acute inflammation (Figure 12A). The organizing phase shows loose organizing fibrosis, mostly within alveolar septa and Type II pneumocyte hyperplasia (Figure 12B) (19). Thrombi are common in small to medium-sized pulmonary arterioles (19, 39). If the patient survives, the lungs may resolve to normal. The lungs may also progress to end-stage honeycomb fibrosis.

Histologic differential diagnosis. The major histologic differential diagnostic considerations are listed in Table 11. In most cases the histologic pattern of DAD is readily apparent. Hyaline membranes are a histologic hallmark of DAD and their presence is helpful in the distinction from the UIP, NSIP, or organizing pneumonia patterns (89). They will be seen in most cases of AIP, but because these patients are often biopsied during the organizing phase, they may be inconspicuous (36). The presence of granulomas, viral inclusions, foci of necrosis, or neutrophilic abscesses suggest infection. Special stains for microorganisms should be performed routinely to exclude an infection. Exclusion of the variety of conditions that can be associated with the DAD pattern requires careful clinical correlation (Table 12).

AIP: Areas of Uncertainty

- What are the incidence and prevalence of the disease?
- What is the relationship of AIP to other forms of acute lung injury?
- Do corticosteroids alter the natural history of the disease?
- What are the mechanisms of lung injury and fibrosis?
- What are mechanisms that result in persistent/progressive or recurrent disease?
- What role does AIP play in acute exacerbations in patients with other patterns of interstitial pneumonia?

RESPIRATORY BRONCHIOLITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE

Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) is the clinical manifestation of interstitial lung disease associated with the pathologic lesion of respiratory bronchiolitis. RB-ILD has been linked to DIP and any discussion of DIP must also include RB and RB-ILD. Respiratory bronchiolitis is a histopathologic lesion found in cigarette smokers and is characterized by the presence of pigmented intraluminal macrophages within first- and second-order respiratory bronchioles. It is rarely symptomatic and is usually associated with no more than minor small airway dysfunction (130). However, in rare cases the condition presents as a form of interstitial lung disease with significant pulmonary symptoms, abnormal pulmonary function, and imaging abnormalities. It is then described as respiratory bronchiolitis-associated interstitial lung disease (RB-ILD).

The invariable relationship of RB-ILD to smoking means that it is also frequently associated with the presence of centrilobular emphysema and not uncommonly encountered as an incidental finding in the context of other forms of lung disease. DIP is considered to be a more extensive form of RB-ILD in which the pigmented macrophages fill alveolar spaces diffusely throughout larger areas of the lung. RB-ILD may be regarded as a spectrum with DIP, depending on the extensiveness of the alveolar macrophage accumulation, although there are differences in the clinical presentation, imaging findings, and prognosis between the two patterns and as such they are described separately in this document (16, 40, 131, 132).

Clinical Features

Most patients with RB-ILD have mild symptoms that are not disabling. However, the lung disease in some patients is associated with significant dyspnea and hypoxemia. Nearly all patients present with nonspecific respiratory complaints including gradual onset of dyspnea and the presence of a new or changed cough. It usually affects current smokers in the fourth and fifth decades of life with average exposures of more than 30 pack-years of cigarette smoking. When the disease occurs at a younger age, it is usually in the setting of a history of smoking 2–3 packs of cigarettes for at least 10 yr. Men are more often affected than women, by a ratio of almost 2:1 (16, 131). Finger clubbing is usually absent (132–134).

Clinical course. Many patients improve after cessation of smoking (131, 132). Progression to dense pulmonary fibrosis

TABLE 11. HISTOLOGIC FEATURES OF DIFFUSE ALVEOLAR DAMAGE

Key Histologic Features
Diffuse distribution
Uniform temporal appearance
Alveolar septal thickening due to organizing fibrosis, usually diffuse
Airspace organization (may be patchy or diffuse)
Hyaline membranes (may be focal or diffuse)
Pertinent Negative Findings
Lack of granulomas, necrosis, or abscesses
Lack of infectious agents (no viral inclusions and negative results with special stains for organisms)
Lack of prominent eosinophils and neutrophils
Negative cultures

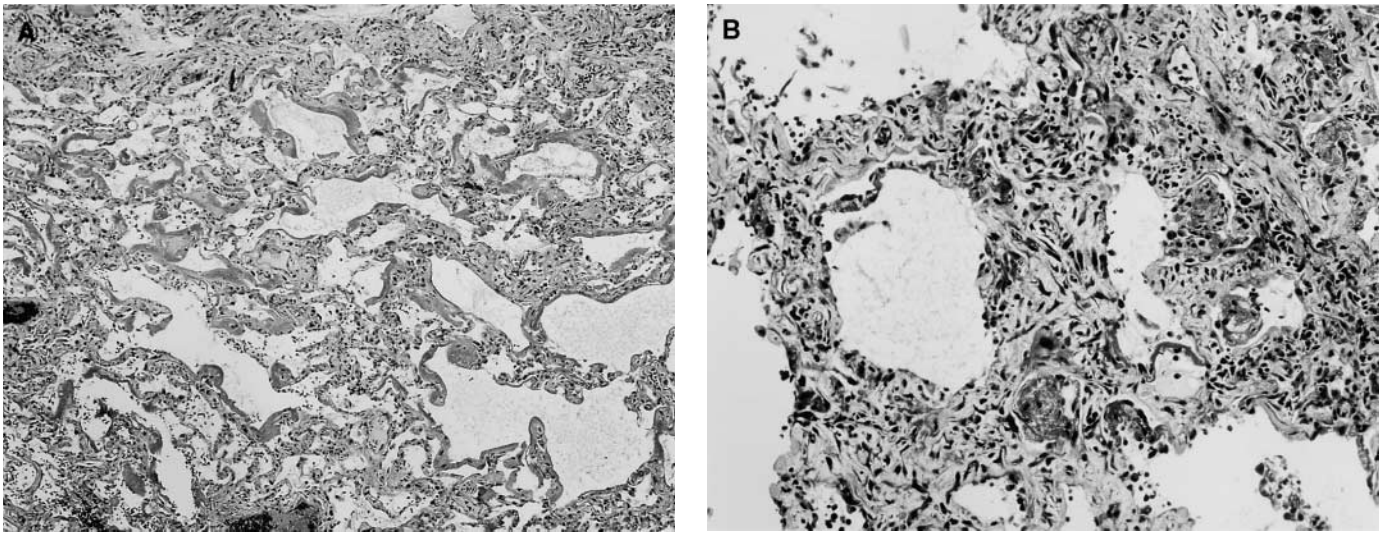

Figure 12. Diffuse alveolar damage in a patient with acute interstitial pneumonia. (*A*) The lung shows diffuse alveolar wall thickening by proliferating connective tissue and inflammation. (*B*) The lung shows diffuse alveolar wall thickening by proliferating connective tissue, Type II pneumocytes, and hyaline membranes.

has not been reported. As the number of patients studied to date is small, definitive reports of its natural history are not available (16, 132, 134).

In patients with minimal symptoms, testing typically reveals a mild to moderate reduction in carbon monoxide transfer factor. In more established cases features of both airway obstruction and restriction, or occasionally an isolated increase in residual volume, may be found (16). These features are explained by the variable combination of RB-ILD and centrilobular emphysema in different cases. Patients with severe symptoms may have more significant reductions in carbon monoxide transfer factor (133).

Bronchoalveolar lavage findings. Bronchoalveolar lavage fluid contains alveolar macrophages with varying (but usually numerous yellow) golden, brown, or black pigmented inclusions characteristic and indistinguishable from those observed in normal smokers (98, 133, 135). Absence of these cells should alert to an alternative diagnosis. A modest increase in neutrophils may also be present (133, 135, 136).

Radiologic Features

Chest radiographic features. The commonest chest radiographic abnormality in RB-ILD is thickening of the walls of central or peripheral bronchi (131), seen in about 75% of patients (Table 3). Ground glass opacity is seen in about 60%. The chest radiograph is normal in 14% of patients.

CT features. The CT findings of RB-ILD include centrilobular nodules, patchy ground glass attenuation, and thickening of the walls of central and peripheral airways (Table 3 and Figure 13) (2, 137). Upper lobe centrilobular emphysema is common but not severe (131, 134). Patchy areas of hypoattenuation are thought to be due to air trapping. Similar findings are seen in many asymptomatic smokers, but the findings in patients with RB-ILD are usually more extensive. The CT findings of RB-ILD may be reversible in some patients who stop smoking and/or are treated with corticosteroids.

CT–pathologic correlation. The extent of centrilobular nodules on CT correlates with the degree of macrophage accumulation and chronic inflammation in respiratory bronchioles (131, 134). Ground glass attenuation correlates with macrophage accumulation in the alveolar spaces and alveolar ducts.

Radiologic differential diagnosis. The CT features of RB-ILD overlap with those of hypersensitivity pneumonitis, DIP, and NSIP. RB-ILD differs from DIP in that the ground glass attenuation of RB-ILD is usually less extensive, patchier, and more poorly defined than in DIP. Centrilobular nodules are uncommon in DIP. However, RB-ILD may be indistinguishable from DIP (131).

Histologic Features

In respiratory bronchiolitis the changes are patchy at low magnification and have a bronchiolocentric distribution. Respiratory bronchioles, alveolar ducts, and peribronchiolar alveolar spaces contain clusters of dusty brown macrophages (Table 13 and Figure 14) (16, 89, 132). The lightly pigmented cells have abundant cytoplasm, which contains finely granular golden brown particles. Intralumenal macrophages are accompanied by a patchy submucosal and peribronchiolar infiltrate of lymphocytes and histiocytes. Mild peribronchiolar fibrosis is also seen and expands contiguous alveolar septa, which are lined by hyperplastic Type II cells and cuboidal bronchiolar-type epithelium. Centrilobular emphysema is common.

Histologic differential diagnosis. The histologic differential diagnosis of the RB pattern includes DIP, bronchiolitis, and NSIP. DIP and RB represent the ends of a spectrum and overlap is common as one views multiple fields in a single specimen.

RB-ILD: Areas of Uncertainty

- Does RB-ILD progress to DIP?
- What are potential causes of RB-ILD other than cigarette smoking?

DESQUAMATIVE INTERSTITIAL PNEUMONIA

The term DIP is retained in this document but it presents several problems. The name originated from the belief that the

TABLE 12. CLINICAL CONDITIONS ASSOCIATED WITH DIFFUSE ALVEOLAR DAMAGE PATTERN

Idiopathic (acute interstitial pneumonia)	Uremia
Infection	Sepsis
Collagen vascular disease	Transfusion-related acute lung injury
Drug toxicity	Shock
Toxic inhalation	Trauma

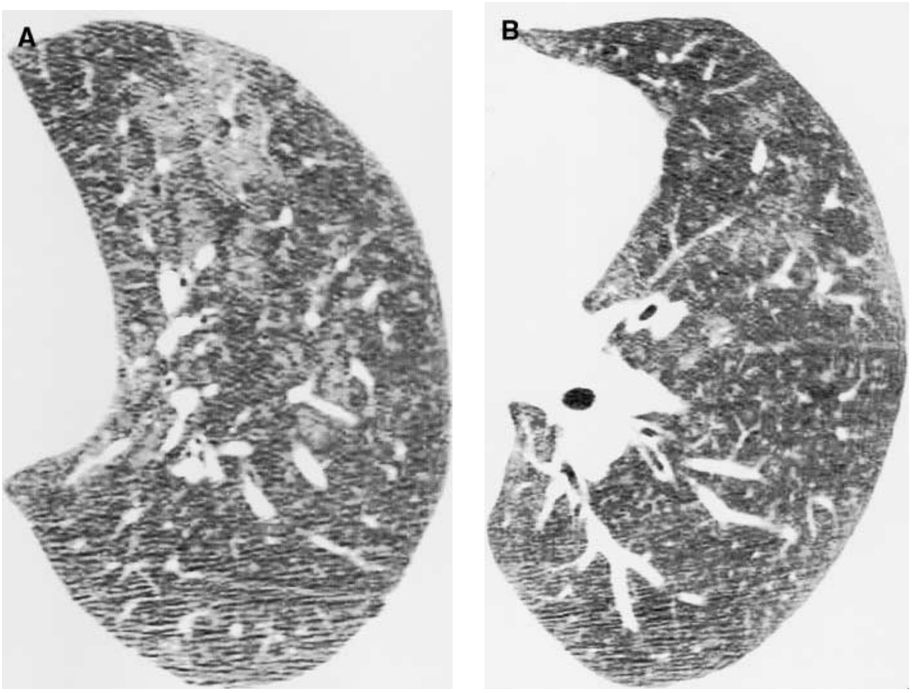

Figure 13. Respiratory bronchiolitis-associated interstitial lung disease. HRCT shows centrilobular nodules and patchy ground glass abnormality.

dominant histologic feature was desquamation of epithelial cells (34, 138). However, this is now recognized to be intra-alveolar macrophage accumulation (139) rather than desquamation of epithelial cells as originally thought by Liebow and Carrington. Second, the condition is considered by many to represent the end of a spectrum of RB-ILD in view of its similar pathology and almost invariable association with cigarette smoke (16, 40, 132, 140). However, rare cases occur in nonsmokers, some of whom have had exposure to environmental inhalation exposures including passive exposure to cigarette smoke (140). The panel seriously considered changing this term to *alveolar macrophage pneumonia*, which is a more accurately descriptive term. After considerable discussion, particularly in light of the rarity of this entity, it was decided to retain the term DIP.

Clinical Features

DIP affects primarily cigarette smokers in their fourth or fifth decades of life. DIP is more common in men than in women by a ratio of 2:1. Insidious onset of dyspnea and dry cough over weeks or months is usual and patients may progress to respiratory failure. Digital clubbing develops in about half (140, 141). Lung physiology confirms normal lung volumes or a mild restrictive abnormality, and the $D_{L_{CO}}$ is moderately decreased (40).

Clinical course. The prognosis of DIP is generally good. Most patients improve with smoking cessation and corticosteroids (140). The overall survival is about 70% after 10 yr (40, 140, 141).

Bronchoalveolar lavage findings. Bronchoalveolar lavage fluid invariably contains increased numbers of alveolar macrophages, a large proportion of which have granules of "smoker's pigment" consisting of intracellular yellow, golden, brown, or black smoke particulates (133). Increases in neutrophils, eosinophils, and lymphocytes may also be found (98).

Radiologic Features

Chest radiographic features. The chest radiograph is relatively insensitive for detection of DIP, and has been reported to be normal in 3–22% of biopsy-proven cases (Table 3) (138, 140, 142). Reported radiographic signs of DIP include widespread

TABLE 13. HISTOLOGIC FEATURES OF RESPIRATORY BRONCHIOLITIS PATTERN

Key Histologic Features
Bronchiolocentric alveolar macrophage accumulation
Mild bronchiolar fibrosis and chronic inflammation
Macrophages have dusty brown cytoplasm (may be positive for iron stains)
Pertinent Negative Findings
Lack of diffuse macrophage accumulation
Lack of interstitial fibrosis and/or honeycomb fibrosis

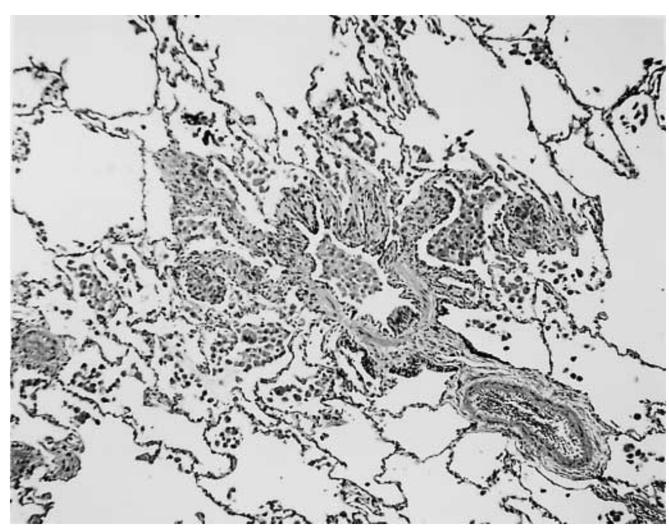

Figure 14. Respiratory bronchiolitis in patient with respiratory bronchiolitis-associated interstitial lung disease. Faintly pigmented alveolar macrophages fill the lumen of this respiratory bronchiole and the surrounding airspaces. There is mild thickening of the wall of the respiratory bronchiole.

patchy ground glass opacification, with a lower zone predilection and sometimes a peripheral predominance (Table 3). A granular or nodular texture to ground glass opacification has been reported (143).

CT features. Ground glass opacification is present on CT in all cases of DIP (Figure 15) (144). This has a lower zone distribution in the majority (73%) of cases, a peripheral distribution in 59% of cases, and is patchy in 23%. The distribution is diffuse and uniform in 18%. Irregular linear opacities and reticular pattern are frequent (59%) but limited in extent and usually confined to the lung bases. Honeycombing is seen in less than one-third of cases, and is usually peripheral and limited in extent (144).

On follow-up HRCT, patients receiving treatment can be expected to show partial or near complete resolution of areas of ground glass opacification (83). Progression of ground glass opacification to a reticular pattern occurs infrequently (less than 20%).

CT–pathologic correlation. There have been no formal studies of CT–pathologic correlation in DIP. The ground glass attenuation, which is the hallmark of this disease, is presumed to be due to a combination of diffuse intra-alveolar cells and diffuse mild septal fibrosis. Irregular linear opacities and honeycombing are presumed to correlate with evidence of lung fibrosis.

Radiologic differential diagnosis. Conditions that may be indistinguishable from DIP include RB-ILD, acute or subacute hypersensitivity pneumonitis, sarcoidosis, and infections such as *Pneumocystis carinii* pneumonia.

Histologic Features

The DIP pattern is characterized by diffuse involvement of the lung by numerous macrophage accumulations within most of the distal airspaces (Figure 16) (89, 132, 145). The alveolar septa are thickened by a sparse inflammatory infiltrate that often includes plasma cells and occasional eosinophils, and they are lined by plump cuboidal pneumocytes (Table 14 and Figure 16). Lymphoid aggregates may be present. The main feature that distinguishes DIP from RB is that DIP affects the lung in a uniform diffuse manner and lacks the bronchiolocentric distribution seen in RB. The intralumenal macrophages in DIP frequently contain dusty brown pigment identical to that seen in RB. Finely granular iron may be seen in the macrophage cytoplasm (146). Emphysema is often present.

Histologic differential diagnosis. The histologic differential diagnosis of the DIP pattern includes a number of interstitial lung diseases because intra-alveolar macrophage accumulation or a focal nonspecific "DIP-like" reaction is an expected consequence of cigarette smoking. Because many patients with other IIPs are frequently current or former smokers, this pattern often overlies the histologic patterns of UIP, RB, NSIP, eosinophilic pneumonia, chronic hemorrhage or hemosiderosis, and veno-occlusive disease (89). Peribronchiolar fibrosis coupled with hyperplasia of peribronchiolar epithelium may mimic the appearance of the UIP pattern. The DIP pattern differs from that of UIP in that the interstitial changes are more diffusely distributed, and the fibrotic reaction has a more uniform temporal appearance without dense widespread fibrosis, fibroblastic foci architectural remodeling, or honeycomb change.

DIP: Areas of Uncertainty

- What are the incidence and prevalence of the disease?
- What is the relationship of DIP to the fibrosing pattern of NSIP?
- What is the relationship of DIP to UIP?
- What is the relationship of RB-ILD/DIP to pulmonary Langerhans' cell histiocytosis?
- What is the role of passive cigarette smoke exposure in the development of RB-ILD/DIP? Does the disease occur in the absence of cigarette smoke exposure (direct or indirect)?
- Do corticosteroids alter the natural history of the disease?
- Do genetic factors affect susceptibility to the disease? How do genetic factors alter expression of the disease?
- What are the mechanisms of lung injury and fibrosis?
- What are the mechanisms that result in persistent or recurrent disease?

LYMPHOID INTERSTITIAL PNEUMONIA

The term *lymphoid interstitial pneumonitis* (LIP) was introduced by Liebow and Carrington in 1969 to describe a diffuse lymphocytic interstitial infiltrate that was distinct from other patterns of interstitial pneumonitis, namely UIP, DIP, BIP, and GIP (34). However, the position of LIP within classification systems has changed with advances in understanding the

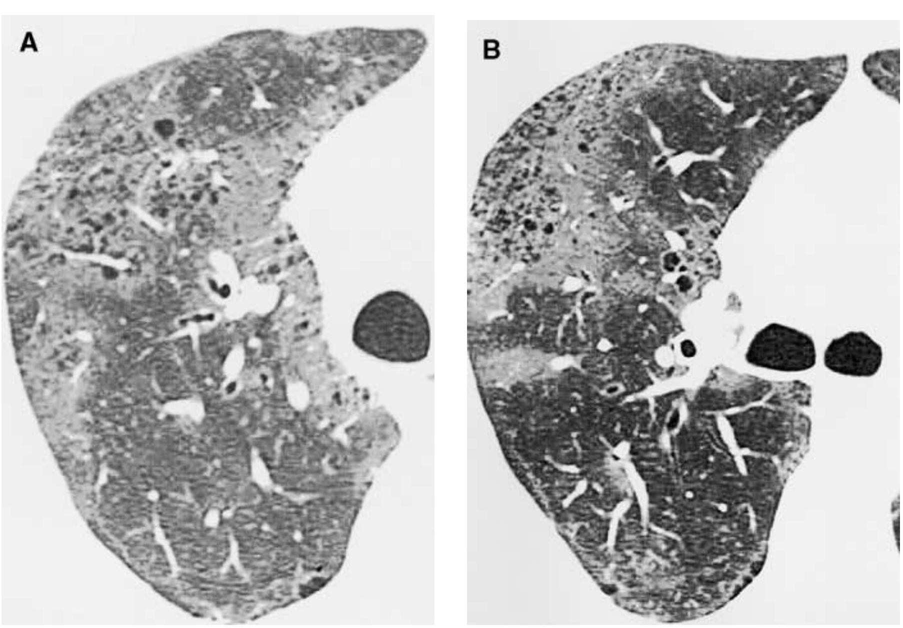

Figure 15. Desquamative interstitial pneumonia. (*A* and *B*) HRCT shows peripheral-predominant ground glass abnormality, with some associated cystic changes.

TABLE 14. HISTOLOGIC FEATURES OF DESQUAMATIVE INTERSTITIAL PNEUMONIA*

Key Histologic Features
Uniform involvement of lung parenchyma
Prominent accumulation of alveolar macrophages (may show fine granular positivity with iron stains)
Mild to moderate fibrotic thickening of alveolar septa
Mild interstitial chronic inflammation (lymphoid aggregates)
Pertinent Negative Findings
Dense and extensive fibrosis: inconspicuous or absent
Smooth muscle proliferation: inconspicuous or absent
Honeycomb fibrosis absent
Fibroblastic foci and organizing pneumonia: inconspicuous or absent
Eosinophils: inconspicuous, absent, or only focal

* Adapted from Reference 23.

nature of pulmonary lymphoid infiltrates, and many groups prefer to classify LIP under the heading of pulmonary lymphoproliferative disorders. This is because many cases were thought to develop into lymphoma, and LIP was therefore considered to be preneoplastic. In fact, many putative cases of LIP were probably non-Hodgkin's low-grade B cell MALT (mucosa-associated lymphoid tissue) lymphomas from the outset. This distinction between idiopathic LIP and lymphoma may be difficult to define on routine histologic sections (147). However, with the advent of immunohistochemistry and molecular analysis, reactive and neoplastic infiltrates are usually separable, with only a small number of cases of LIP found to actually undergo malignant transformation (148, 149). With regard to histogenesis, LIP is perhaps best regarded as a histologic variant of diffuse pulmonary lymphoid hyperplasia with predominantly interstitial changes. A related condition, follicular bronchiolitis, is predominantly a peribronchial (or peribronchiolar) lymphocytic infiltrate with germinal centers (147, 150–154).

The incidence of idiopathic LIP is low and its existence is doubted by some. It is also argued that LIP should be taken out of the classification of interstitial pneumonias and assigned to a separate group of lymphoid hyperplasia among the pulmonary lymphoproliferative diseases. However, given that its clinical and radiological presentation enters the differential diagnosis of diffuse lung disease, and histologically its pattern is unequivocally that of an interstitial pneumonia, it seems more logical to maintain its position within such a classification system. However, it should be noted that many cases that previously might have been called LIP are now being classified as cellular NSIP.

Clinical Features

The clinical presentation of idiopathic LIP remains poorly defined. LIP is more common in women, and although it may present at any age, is most typically diagnosed in the fifth decade (154–156). Onset is often slow with gradually increasing cough and breathlessness over 3 or more years. Fever, weight loss, chest pain, and arthralgia are occasionally found. Crackles may be detected as the disease progresses and lymphadenopathy is present in some cases, but is more common in the presence of Sjögren's syndrome (154). Clinically, cases of LIP must be thoroughly investigated for any known cause or associations, such as collagen vascular diseases and immunodeficiency. This is because of the rarity of idiopathic LIP. Mild anemia may be present, and dysproteinemia in the form of a polyclonal increase in gammaglobulin or a monoclonal increase in IgG or IgM is found in more than 75% of cases (157). The presence of a monoclonal gammopathy or hypogammaglobulimemia raises the possibility of a lymphoproliferative malignancy.

The presentation of LIP is usually that of the underlying systemic or autoimmune disorder such as rheumatoid arthritis, Sjögren's syndrome (155, 156), Hashimoto's disease (158), pernicious anemia (158), chronic active hepatitis (160), systemic lupus erythematosus (161), autoimmune hemolytic anemia (155, 157), primary biliary cirrhosis (150), myasthenia gravis (155), hypogammaglobulinemia, and severe combined immunodeficiency, particularly in children with AIDS (162–164). Detection of pulmonary involvement in these diseases may be incidental or prompted by the development of dyspnea and nonproductive cough. Constitutional symptoms are rare. As idiopathic LIP rarely progresses to fibrosis, digital clubbing, crackles, and physiologic features of IIP are absent or mild (165).

Clinical course. Corticosteroids are the most widely used treatment, and are thought to arrest or improve symptoms in a

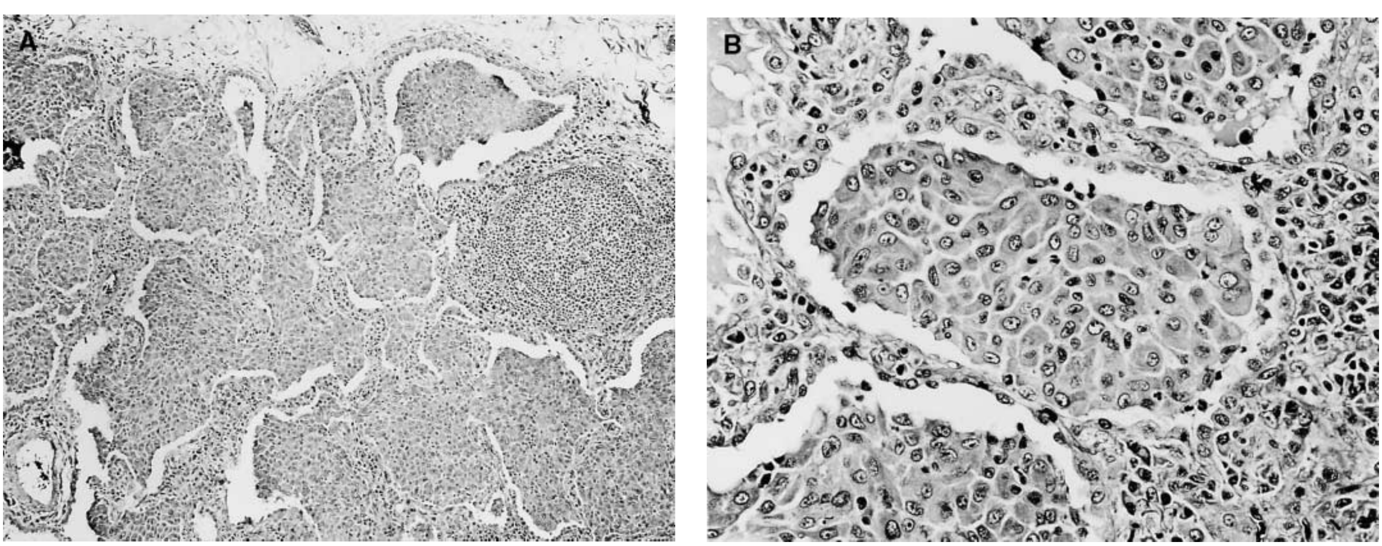

Figure 16. Desquamative interstitial pneumonia pattern. (*A*) The alveolar spaces are diffusely involved by marked alveolar macrophage accumulation and there is mild interstitial thickening. (*B*) The alveolar walls are mildly thickened by fibrous connective tissue and a few chronic inflammatory cells. The alveolar spaces are filled with macrophages.

large proportion of patients. More than one-third progress to diffuse fibrosis, and it is unclear whether treatment influences the course of the disease or has a significant effect on lung physiology (154, 166). Occasional cases resolve or improve substantially.

Bronchoalveolar lavage findings. The BAL fluid shows many lymphocytes. Immunophenotyping of these cells should not reveal any clonality (167).

Radiologic Features

Chest radiographic features. Two chest radiographic patterns for lymphocytic interstitial pneumonia have been described: basilar with an alveolar component and diffuse with associated honeycombing (158).

CT features. The dominant CT finding is usually ground glass opacity (Figure 17). Curious perivascular cysts or perivascular honeycombing can also be seen (168). Reticular abnormality is seen in about 50% of patients. Lung nodules and widespread consolidation may occur. In LIP related to multicentric Castleman's disease, thin-walled cysts, thickening of the bronchovascular bundles, and interlobular septal thickening are the commonest findings (166).

Histologic Features

LIP is defined as a dense interstitial lymphoid infiltrate, including lymphocytes, plasma cells, and histiocytes with associated Type II cell hyperplasia and a mild increase in alveolar macrophages (Table 15 and Figure 18). The alveolar septa should be extensively infiltrated. Lymphoid follicles, including follicles with germinal centers, are often present, usually in the distribution of pulmonary lymphatics. Some architectural derangement (including honeycombing) and nonnecrotizing granulomas may be seen. Intra-alveolar organization and macrophage accumulation may also be present, but only as minor components.

Histologic differential diagnosis. The differential diagnosis for LIP includes diffuse lymphoid hyperplasia (hyperplasia of bronchial mucosa-associated lymphoid tissue [MALT]), nodular lymphoid hyperplasia, lymphoma (of mucosal-associated lymphoid tissue or small lymphocytic types), and the patterns of OP, NSIP, hypersensitivity pneumonitis, and UIP (89). Diffuse lymphoid hyperplasia without alveolar septal infiltration has been included under the category of LIP in previous studies (151). Although there may be some overlap in these patterns, for the purposes of this classification the term LIP is limited to those cases with extensive alveolar septal infiltration (147).

The hypersensitivity pneumonitis pattern usually has less inflammation than LIP, tends to have a peribronchiolar distribution, and also characteristically shows poorly formed granulomas and organizing intralumenal fibrosis (169). The cellular NSIP pattern also shows an interstitial lymphocytic and/or plasma cell infiltrate; however, compared with LIP the extent is generally less severe and some alveolar walls are spared. Pure follicular bronchiolitis or diffuse lymphoid hyperplasia of the bronchus-associated lymphoid tissue differs from LIP in that it lacks extensive alveolar septal infiltration. Malignant lymphomas are more likely to show a monomorphous and dense population of lymphoid cells with destruction of alveolar architecture, Dutcher bodies, pleural infiltration, and tracking along lymphatic routes (169). Immunohistochemistry and/or gene rearrangement studies may be necessary to exclude a lymphoproliferative disorder (167).

Once a histologic diagnosis of LIP pattern has been established the clinician should re-evaluate the patient to see if they have any of the clinical conditions that potentially may be associated with LIP (Table 16).

TABLE 15. HISTOLOGIC FEATURES OF LYMPHOID INTERSTITIAL PNEUMONIA

Key Histologic Features
Diffuse interstitial infiltration of involved areas
Predominantly alveolar septal distribution
Infiltrates comprise mostly T lymphocytes, plasma cells, and macrophages
Lymphoid hyperplasia (MALT hyperplasia)—frequent
Pertinent Negative Findings
Lack of tracking along lymphatic routes (bronchovascular bundles, pleura, and interlobular septa), characteristic of lymphomas
Organizing pneumonia, inconspicuous or absent
Lack of Dutcher bodies
Lack of monoclonal light chain staining pattern of plasma cells (polyclonal pattern present)
Lack of extensive pleural involvement or lymph node involvement
Lack of necrotizing granulomas

Definition of abbreviation: MALT = bronchial mucosa-associated lymphoid tissue.

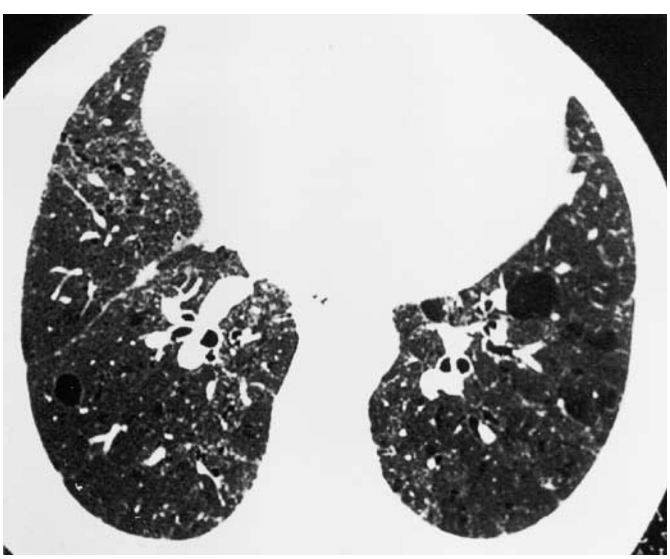

Figure 17. Lymphocytic interstitial pneumonia. Prone HRCT shows diffuse ground glass attenuation with multiple lung cysts.

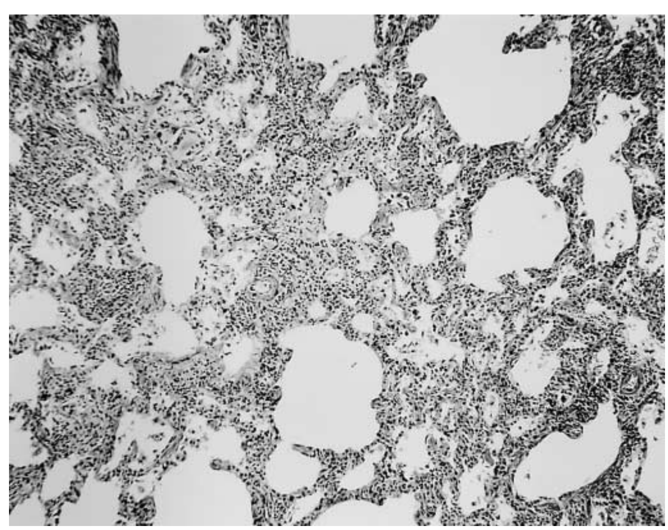

Figure 18. Lymphocytic interstitial pneumonia pattern. There is diffuse thickening of alveolar walls by a moderately severe infiltrate of lymphocytes and plasma cells.

TABLE 16. CLINICAL CONDITIONS ASSOCIATED WITH LYMPHOID INTERSTITIAL PNEUMONIA PATTERN

Idiopathic
Infection (especially *Pneumocystis carinii*, hepatitis B, Epstein–Barr virus)
Collagen vascular disease, especially Sjögren's syndrome, rheumatoid arthritis, or systemic lupus erythematosus
Immunodeficiency (HIV, SCID)
Other immunologic disorders
Autoimmune hemolytic anemia, myasthenia gravis, pernicious anemia, Hashimoto's thyroiditis, chronic active hepatitis, primary biliary cirrhosis
Drug-induced/toxic exposure

Definition of abbreviation: SCID = severely compromised immune deficiency.

LIP: Areas of Uncertainty

- What are the incidence and prevalence of disease? How common are idiopathic cases of LIP?
- What is the relationship of LIP to lymphoma? What is the malignant potential of LIP?
- What is the relationship of pseudolymphoma to LIP?
- What is the relationship between LIP and follicular bronchitis/bronchiolitis (pulmonary lymphoid hyperplasia), nodular lymphoid hyperplasia of lung, angioimmunoblastic lymphadenopathy, and Castelman's disease?
- Do corticosteroids alter the natural history of the disease?
- Do genetic factors affect susceptibility to the disease?

APPENDIX

This official statement was prepared by an ad hoc multidisciplinary core panel of the Assembly on Clinical Problems.

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