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An Official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias

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An Official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias

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This official statement of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) was approved by the ATS Board of Directors, June 2013, and by the ERS Steering Committee, March 2013

CONTENTS

Background: **In 2002 the American Thoracic Society/European Respiratory Society (ATS/ERS) classification of idiopathic interstitial pneumonias (IIPs) defined seven specific entities, and provided standardized terminology and diagnostic criteria. In addition, the historical "gold standard" of histologic diagnosis was replaced by a multidisciplinary approach. Since 2002 many publications have provided new information about IIPs.**

Purpose: **The objective of this statement is to update the 2002 ATS/ERS classification of IIPs.**

Methods: **An international multidisciplinary panel was formed and developed key questions that were addressed through a review of the literature published between 2000 and 2011.**

Results: **Substantial progress has been made in IIPs since the previous classification. Nonspecific interstitial pneumonia is now better defined. Respiratory bronchiolitis–interstitial lung disease is now commonly diagnosed without surgical biopsy. The clinical course of idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia is recognized to be heterogeneous. Acute exacerbation of IIPs is now well defined. A substantial percentage of patients with IIP are difficult to classify, often due to mixed patterns of lung injury. A classification based on observed disease behavior is proposed for patients who are difficult to classify or for entities with heterogeneity in clinical course. A group of rare entities, including pleuroparenchymal fibroelastosis and rare histologic patterns, is introduced. The rapidly evolving field of molecular markers is reviewed with the intent of promoting additional investigations that may help in determining diagnosis, and potentially prognosis and treatment.**

Conclusions: **This update is a supplement to the previous 2002 IIP classification document. It outlines advances in the past decade and potential areas for future investigation.**

Keywords: idiopathic interstitial pneumonia; usual interstitial pneumonia; nonspecific interstitial pneumonia; respiratory bronchiolitis; desquamative interstitial pneumonia; cryptogenic organizing pneumonia; acute interstitial pneumonia; lymphoid interstitial pneumonia; pleuroparenchymal fibroelastosis; acute fibrinous and organizing pneumonia

EXECUTIVE SUMMARY

There are several specific areas that are given special attention in this revision of the 2002 American Thoracic Society/European Respiratory Society idiopathic interstitial pneumonia (IIP) statement.

1. Idiopathic nonspecific interstitial pneumonia (NSIP) is now accepted as a specific clinicopathologic entity. It has become evident that clinical progression is highly heterogeneous, with several studies suggesting that a subset of patients demonstrate progression to end-stage fibrosis; criteria to define this group at the time of diagnosis would be helpful.

This document has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

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2. New information has accumulated on smoking-related interstitial lung disease, including patients with combined emphysema and interstitial fibrosis. In clinical practice, respiratory bronchiolitis–interstitial lung disease is increasingly diagnosed without surgical lung biopsy in smokers on the basis of clinical and imaging features (ground-glass opacities and centrilobular nodules) and bronchoalveolar lavage (smoker's macrophages and absence of lymphocytosis).
3. The natural progression of idiopathic pulmonary fibrosis (IPF) is acknowledged to be heterogeneous with some patients remaining stable for prolonged periods, others showing more rapid steady progression, and still others succumbing to acute exacerbation.
4. Acute exacerbation is better defined and recognized to occur in chronic fibrosing IIPs (IPF and NSIP).
5. Some patients with IIP are difficult to classify, often because of mixed patterns of lung injury.
6. It is recognized that there is a need to provide a clinical algorithm for classifying and managing IIP cases. This is particularly applicable when no biopsy is available and high-resolution computed tomography is not diagnostic.
7. Pleuroparenchymal fibroelastosis is recognized as a specific rare entity, usually idiopathic. Other less well-defined histologic patterns, such as bronchiolocentric inflammation and fibrosis, are also included.
8. A rapidly emerging field of molecular markers holds promise for improving diagnostic approaches. These markers may also be useful in predicting prognosis and response to different therapies. Incorporation of genetic and molecular studies may revolutionize the approach to diagnosis and classification of the IIPs.

INTRODUCTION

The objective of this statement is to update the 2002 American Thoracic Society/European Respiratory Society (ATS/ERS) classification of idiopathic interstitial pneumonias (IIPs) (1). Focus is placed on describing changes to previously described clinical entities, describing new clinical entities, and describing new histologic patterns. This update is not intended as a stand-alone document and should be used as a supplement to the original 2002 IIP classification. In 2002, the ATS/ERS IIP classification (1) defined seven disease categories, and proposed standardized terminology and diagnostic criteria. In addition, the historical "gold standard" of histologic diagnosis was replaced by a "dynamic integrated approach" using multidisciplinary discussion (MDD). The 2002 IIP classification was used in 75% (157 of 208) of all clinical publications on the topic of IIPs between 2004 and 2011. The new information from these publications is incorporated in this update.

METHODS

This project was performed under supervision by the ATS Documents Development and Implementation Committee in collaboration with the ERS (Table E1 in the online supplement). An international multidisciplinary panel was assembled. The panel consisted of 34 experts in interstitial lung diseases (19 pulmonologists, 4 radiologists, 5 pathologists, 2 experts in evidence-based medicine, and 4 molecular biologists). Several meetings were held by members of the international multidisciplinary panel (Table E2), who disclosed conflicts of interest, which were vetted according to ATS and ERS policies.

Key questions were developed that the committee believed important for the classification of IIPs (*see* APPENDIX 1 in the online supplement). A literature search was performed to identify new publications that pertained to these key questions, assisted by two librarians experienced in literature searches for pulmonary diseases. Literature retrieved from Medline searches between 2000 and 2011 was used to produce this statement.

The committee was divided into subgroups assigned to specific sections of the document. These subgroups reviewed the relevant literature and produced the first draft of their respective sections. These sections were compiled by the committee chair and a complete first draft was edited by the writing subcommittee. This document was reviewed and edited by all committee members before final review by the writing subcommittee. The revised document was approved by all authors.

SUMMARY OF MAJOR REVISIONS OF THE IIP CLASSIFICATION

In the revision of the IIP classification, the main entities are preserved (Table 1). However, there are several important changes. First, cryptogenic fibrosing alveolitis is removed, leaving idiopathic pulmonary fibrosis (IPF) as the sole clinical term for this diagnosis. Second, idiopathic nonspecific interstitial pneumonia (NSIP) is now accepted as a distinct clinical entity with removal of the term "provisional" (2). Third, major IIPs are distinguished from rare IIPs and unclassifiable cases. Fourth, rare histologic patterns of acute fibrinous and organizing pneumonia (AFOP) and interstitial pneumonias with a bronchiolocentric distribution are recognized. Fifth, the major IIPs are grouped into chronic fibrosing (IPF and NSIP; Figures 1 and 2), smoking-related (respiratory bronchiolitis–interstitial lung disease [RB-ILD] and desquamative interstitial pneumonia [DIP]; Figure 3), and acute/subacute IIPs (cryptogenic organizing pneumonia [COP] and acute interstitial pneumonia [AIP]; Figure 4 and Table 2). Sixth, a clinical disease behavior classification is proposed. Last, molecular and genetic features are reviewed.

GENERAL PROGRESS IN IIPS SINCE 2002

Multidisciplinary Approach

The process of achieving a multidisciplinary diagnosis in a patient with IIP is dynamic, requiring close communication between clinician, radiologist, and when appropriate, pathologist (1). Clinical data (presentation, exposures, smoking status, associated

TABLE 1. REVISED AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS: MULTIDISCIPLINARY DIAGNOSES

Major idiopathic interstitial pneumonias
Idiopathic pulmonary fibrosis
Idiopathic nonspecific interstitial pneumonia
Respiratory bronchiolitis–interstitial lung disease
Desquamative interstitial pneumonia
Cryptogenic organizing pneumonia
Acute interstitial pneumonia
Rare idiopathic interstitial pneumonias
Idiopathic lymphoid interstitial pneumonia
Idiopathic pleuroparenchymal fibroelastosis
Unclassifiable idiopathic interstitial pneumonias*

*Causes of unclassifiable idiopathic interstitial pneumonia include (*1*) inadequate clinical, radiologic, or pathologic data and (*2*) major discordance between clinical, radiologic, and pathologic findings that may occur in the following situations: (*a*) previous therapy resulting in substantial alteration of radiologic or histologic findings (e.g., biopsy of desquamative interstitial pneumonia after steroid therapy, which shows only residual nonspecific interstitial pneumonia [153]); (*b*) new entity, or unusual variant of recognized entity, not adequately characterized by the current American Thoracic Society/European Respiratory Society classification (e.g., variant of organizing pneumonia with supervening fibrosis) (79); and (*c*) multiple high-resolution computed tomography and/or pathologic patterns that may be encountered in patients with idiopathic interstitial pneumonia.

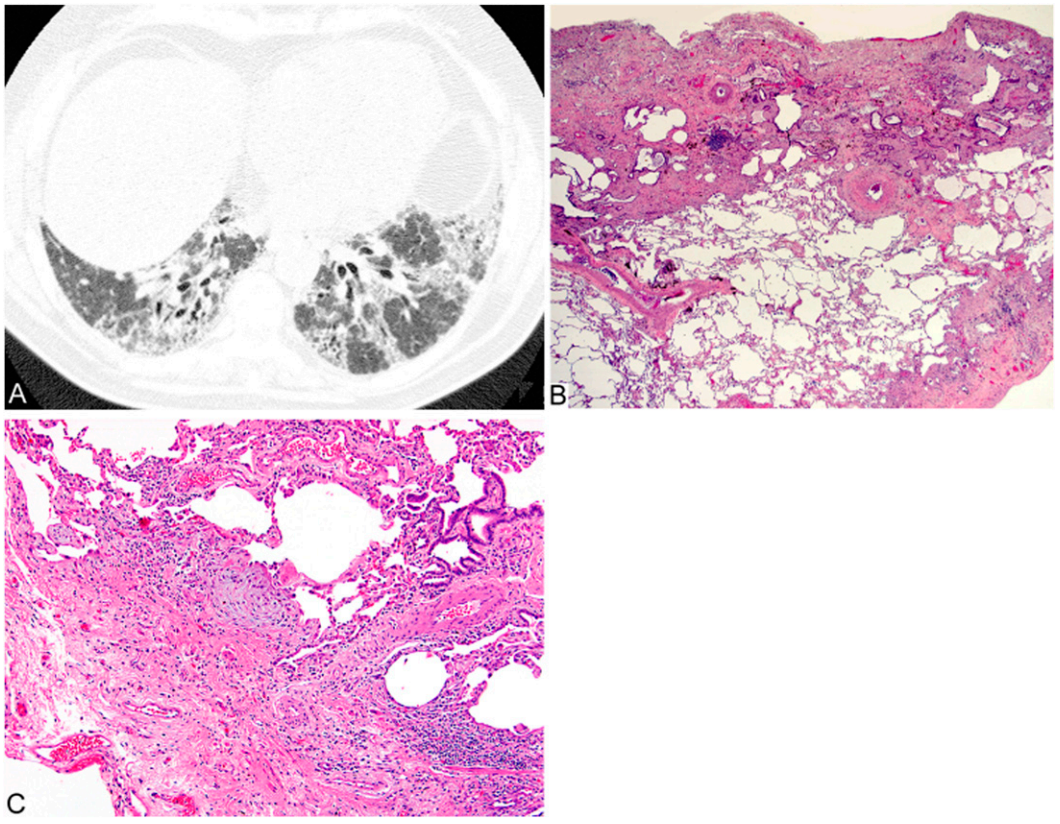

Figure 1. Atypical usual interstitial pneumonia/idiopathic pulmonary fibrosis. Computed tomography (CT) features: (*A*) CT image of atypical usual interstitial pneumonia (UIP). Prone axial CT through the lung bases in a patient with histologically proven UIP shows predominantly peribronchovascular ground-glass/reticular opacities with traction bronchiectasis. Under the ATS/ERS/JRS/ALAT Statement (8), this would be classified as inconsistent with UIP. Histologic features: (*B*) The biopsy shows patchy subpleural dense fibrosis with honeycomb change adjacent to preserved lung. (*C*) Dense scarring fibrosis is present with a small nodular fibroblastic focus.

diseases, lung function, laboratory findings) and radiologic findings are essential for multidisciplinary diagnosis.

The multidisciplinary approach does not lessen the importance of lung biopsy in the diagnosis of IIPs; rather, it defines the settings where biopsy is more informative than high-resolution computed tomography (HRCT) and those where biopsy is not needed. Also, once a pathologist has recognized a histologic pattern (e.g., NSIP or organizing pneumonia [OP]), the clinician should reconsider potential causes (e.g., hypersensitivity pneumonitis [HP], collagen vascular disease [CVD], and drug exposure).

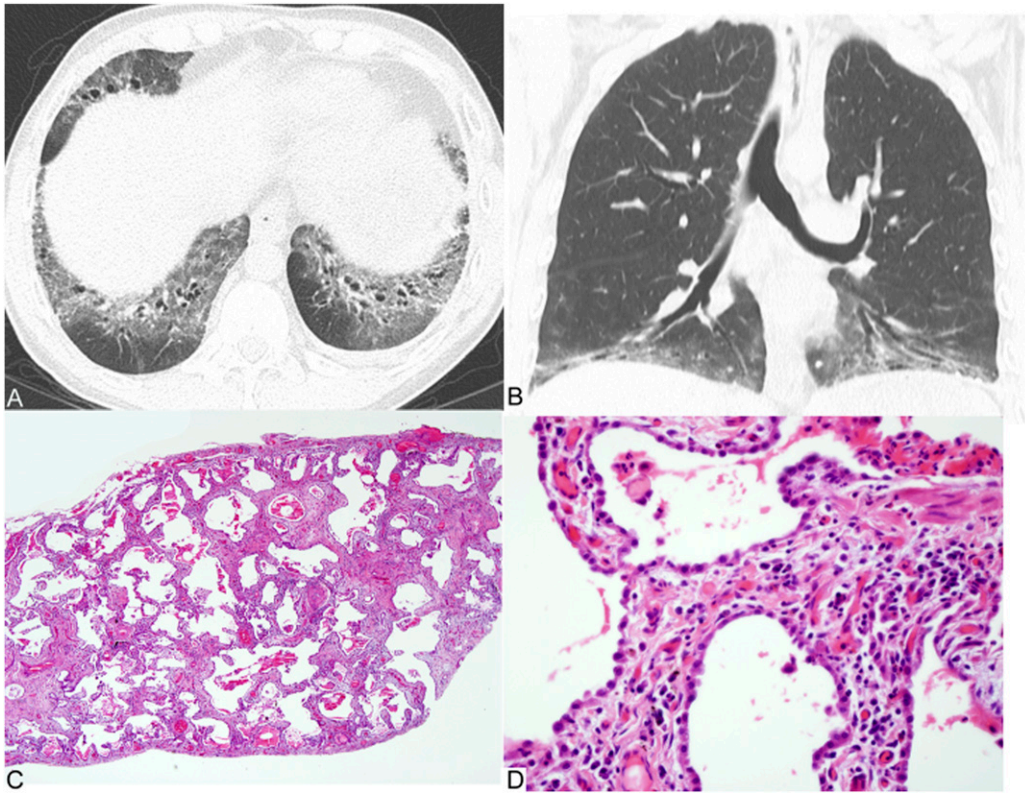

Figure 2. Nonspecific interstitial pneumonia. Computed tomography (CT) features: (*A*) Axial and (*B*) coronal CT reconstructions show confluent bilateral lower lobe ground-glass opacities with marked traction bronchiectasis and lower lobe volume loss. The peribronchovascular predominance with subpleural sparing is well shown on the axial image. (*C* and *D*) Histologic features: Lung biopsy shows diffuse alveolar wall thickening by uniform fibrosis. The alveolar architecture is preserved and no honeycombing or fibroblastic foci are seen. Interstitial inflammation is mild.

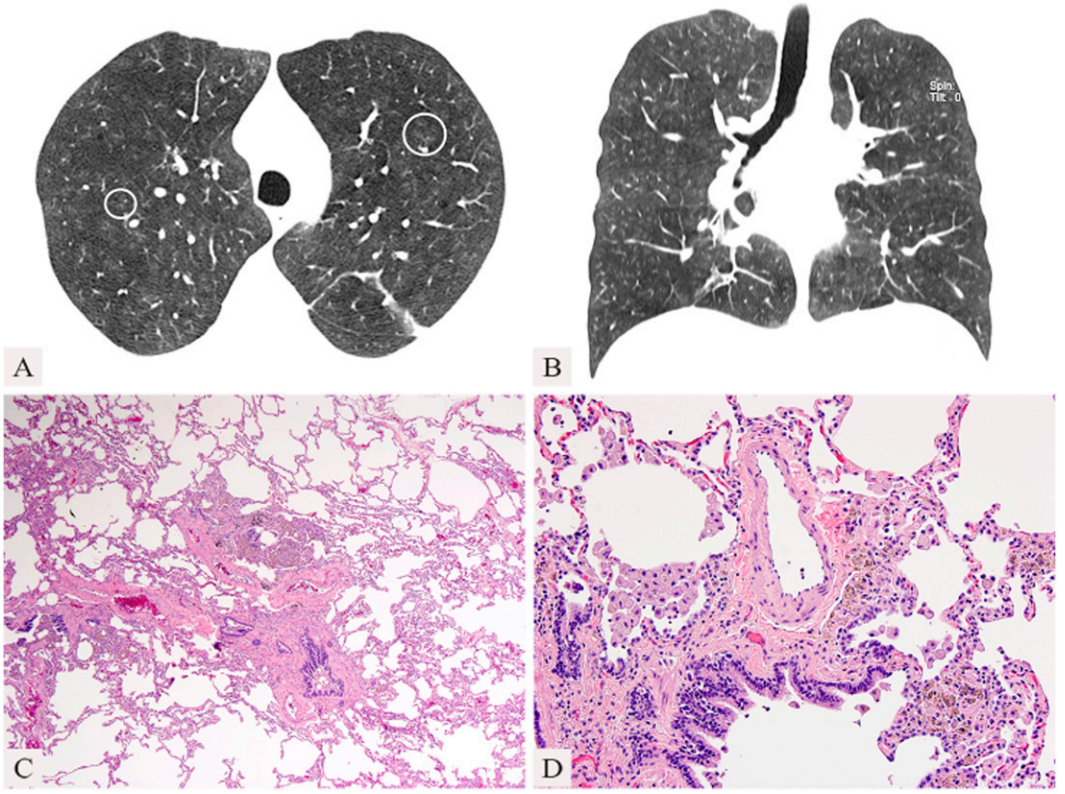

Figure 3. Respiratory bronchiolitis–interstitial lung disease. (*A*) Axial and (*B*) coronal computed tomography (CT) reconstructions in a 47-year-old heavy cigarette smoker show moderately extensive ground-glass opacities and centrilobular nodules (*circles*). The bronchi are markedly thick-walled and there is minimal emphysema. Bronchoalveolar lavage yielded 91% macrophages. (*C*) Histologic features: lung biopsy shows peribronchiolar pigmented macrophage accumulation and emphysema. (*D*) There is mild bronchiolar fibrosis and pigmented macrophages within airspaces.

The diagnosis of IIPs requires exclusion of known causes of interstitial lung disease such as drug or inhalational exposure and CVD. Despite the known association of smoking with RB-ILD and DIP, these disorders were included in the classification in 2002 and they are maintained in this revision.

Observer Agreement in Diagnosis of IIP

Observer agreement is dependent on observer experience and the integration of data from all modalities. In early series, observer agreement was marginal among clinicians, radiologists, and pathologists (3–5). However, agreement between radiologists and pathologists has improved substantially with accumulated experience (6) and, especially, with integration of clinical data in a multidisciplinary conference (4, 7). Academic physicians in a multidisciplinary setting have better diagnostic agreement than community physicians, who are more likely to assign the diagnosis of IPF (7). These data underline the need for patient evaluation in regional centers using multidisciplinary evaluation (7, 8).

IMPORTANT DIFFERENTIAL DIAGNOSTIC CONSIDERATIONS

Hypersensitivity Pneumonitis

IIPs are frequently confused with HP, and vice versa, except when the exposure is readily apparent. The ATS workshop on NSIP showed that MDD is particularly important in distinguishing HP from NSIP (2). In the past 10 years, the clinical (9), HRCT (10–12), and pathologic (13–15) features of chronic HP have been more sharply defined, helping to separate these cases from the IIPs, particularly IPF and NSIP (9, 11–16). HRCT findings suggesting HP include centrilobular nodules, mosaic air-trapping, and upper lobe distribution (Figures 5A and 5B) (11, 12). Biopsy findings suggesting HP include bronchiolocentric distribution and poorly formed granulomas (Figures 5C and 5D) (13–15). A detailed search for potential exposure in patients with these findings is essential, including consideration of specific circulating IgG antibodies, but up to 30% of subjects with histologic HP have no identifiable exposure (17, 18).

Collagen Vascular Disease

CVD is a frequent cause of interstitial pneumonia patterns, especially NSIP. Clinical, serologic, HRCT, and histologic findings may be helpful in distinguishing IIPs from ILD associated with CVD (19–22). The extent of serologic evaluation to be performed in the evaluation of suspected IPF has been suggested previously (8). A substantial percentage of patients with NSIP have findings suggesting, but not meeting, criteria for a defined CVD (23–25). However, these cases are still accepted as IIPs.

Familial Interstitial Pneumonia

IIPs have been reported in closely related family members in 2–20% of cases (26–29). These cases remain classified as IIPs despite the genetic predisposition. Heterozygous mutations in *SFTPC* (~1%), *SFTPA2* (~1%), *TERT* (~15%), and *TERC* (~1%) are responsible for about 20% of all familial interstitial pneumonias (FIPs) (29–32). Sporadic IPF, in the absence of telomerase mutations, is often associated with telomere shortening, suggesting that pathways involved in familial disease may contribute to sporadic disease (33–35). Most FIP families (80%) have evidence of vertical transmission suggesting single autosomal dominant mechanisms, but most responsible genes have not yet been identified. A recent genome-wide linkage scan showed that a common variant in the promoter of the *MUCB* gene is associated with the development of both familial and sporadic IPF. This result was confirmed in an independent cohort (36, 37).

Familial IIPs can be indistinguishable from nonfamilial cases on HRCT and lung biopsy. All patients with suspected IIP should therefore be questioned about relevant family history as this may guide gene mutation search, and management or evaluation of other family members (38).

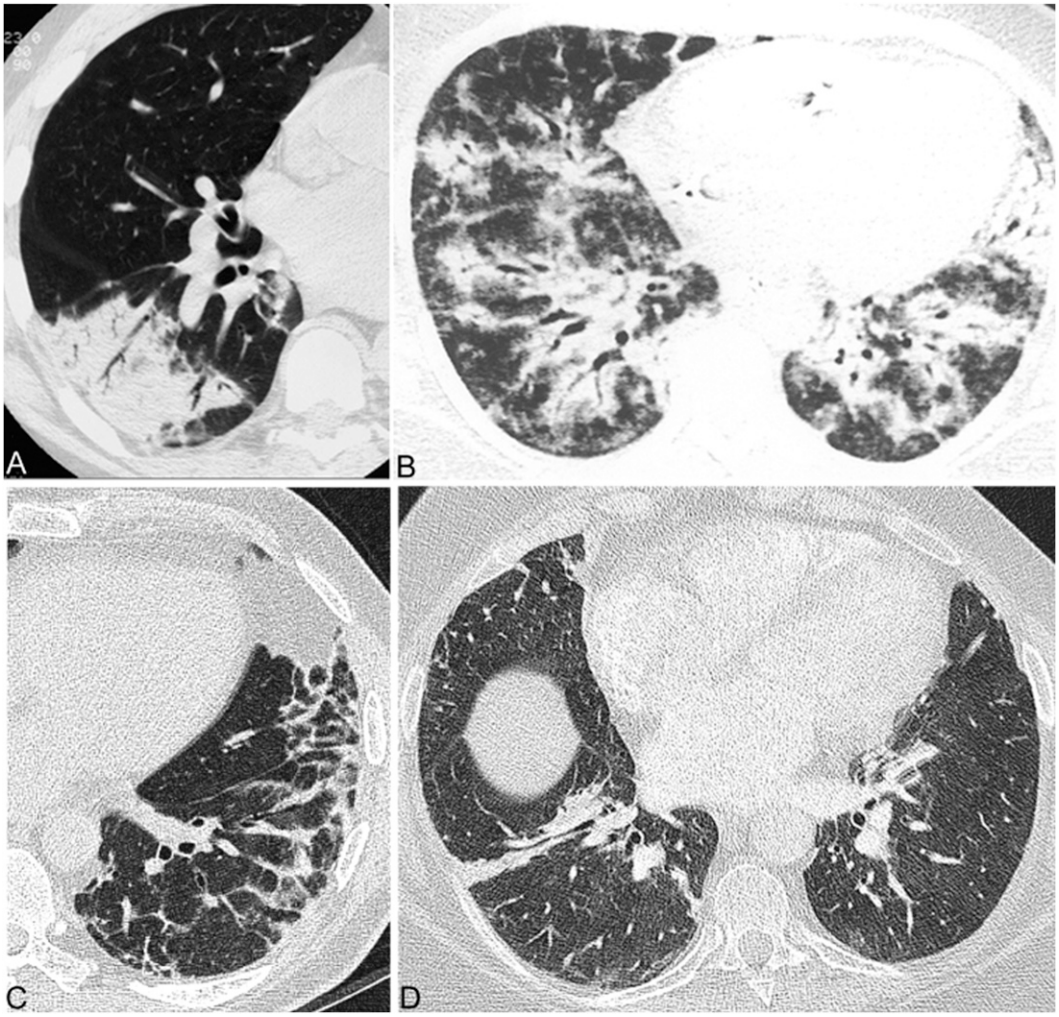

Figure 4. Cryptogenic organizing pneumonia. Computed tomography (CT) features with (*A*) peripheral consolidation and air bronchograms, (*B*) bronchocentric distribution, (*C*) perilobular pattern showing focal right lower lobe consolidation, with more central ground-glass opacity, corresponding to the reversed halo sign, and (*D*) bandlike consolidation.

Coexisting Patterns

Most patients with a chronic IIP can be given a single clinical–radiologic–pathologic diagnosis. However, multiple pathologic and/or HRCT patterns may be found in the same patient. Different patterns may be seen in a single biopsy or in biopsies from multiple sites (e.g., usual interstitial pneumonia [UIP] in one lobe and NSIP in another) (39), or when pathologic and HRCT patterns differ. In smokers, multiple HRCT and histologic features may coexist including Langerhans' cell histiocytosis, respiratory bronchiolitis (RB), desquamative interstitial pneumonia (DIP), pulmonary fibrosis (UIP or NSIP), and emphysema (40–42). Combined pulmonary fibrosis and emphysema (CPFE) is an example of coexisting patterns. CPFE comprises a heterogeneous population of patients, not believed to represent a distinctive IIP. Patients with CPFE have increased risk of developing pulmonary hypertension, which portends poor prognosis (43–46). When coexisting patterns occur, MDD may determine the clinical significance of individual patterns (4, 47, 48).

PROGRESS IN SPECIFIC IIPS SINCE 2002

Chronic Fibrosing IIPs

Idiopathic pulmonary fibrosis. An updated evidence-based guideline for the diagnosis and management of IPF was recently published (8). A new diagnostic algorithm and schema for correlating histologic and radiologic findings in patients with suspected IPF was provided in this guideline (8). New aspects of this algorithm included criteria for three levels of certainty for patterns of UIP based on HRCT findings (UIP, possible UIP, and inconsistent with UIP) and four levels of certainty for pathologic diagnosis (UIP,

TABLE 2. CATEGORIZATION OF MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIAS

Category	Clinical–Radiologic–Pathologic Diagnoses	Associated Radiologic and/or Pathologic–Morphologic Patterns
Chronic fibrosing IP	Idiopathic pulmonary fibrosis	Usual interstitial pneumonia
	Idiopathic nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia
Smoking-related IP*	Respiratory bronchiolitis-interstitial lung disease	Respiratory bronchiolitis
	Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Acute/subacute IP	Cryptogenic organizing pneumonia	Organizing pneumonia
	Acute interstitial pneumonia	Diffuse alveolar damage

Definition of abbreviation: IP = interstitial pneumonia.
*Desquamative interstitial pneumonia can occasionally occur in nonsmokers.

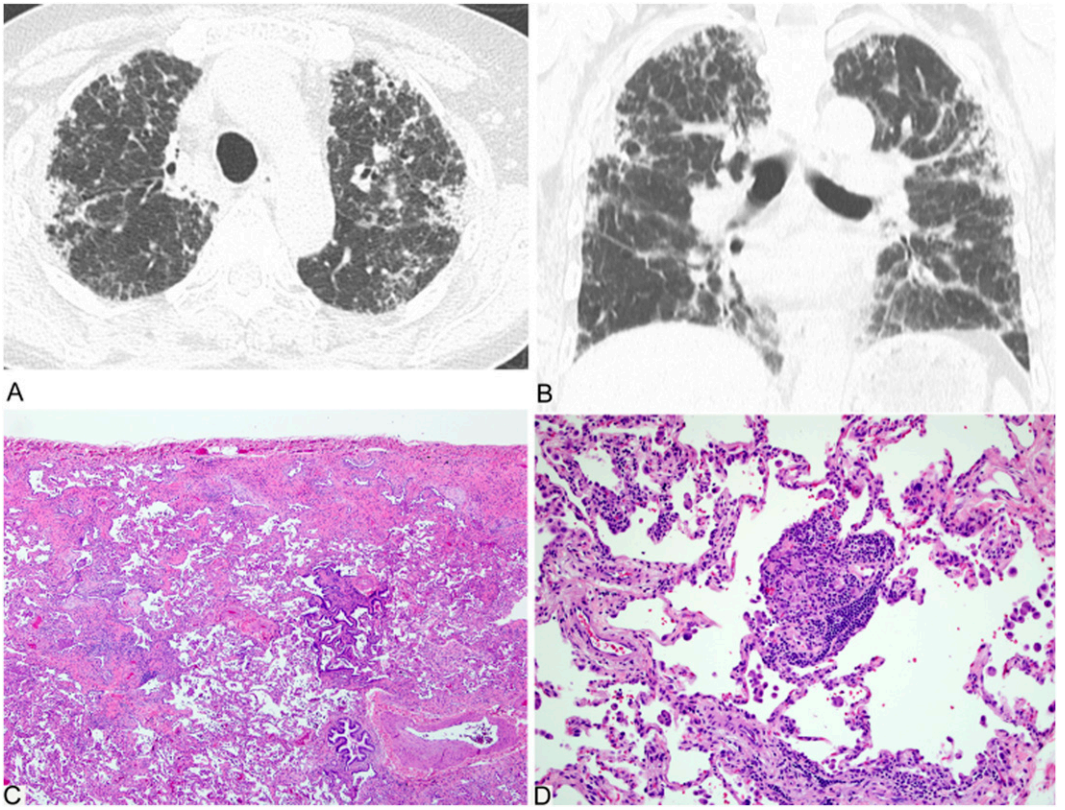

Figure 5. Fibrotic hypersensitivity pneumonitis. (*A*) Axial and (*B*) coronal computed tomography (CT) reconstructions in a 76-year-old bird-keeper with progressive shortness of breath over 6 years show upper lung–predominant subpleural reticulation with some confluent areas of dense opacification, traction bronchiectasis, and patchy ground-glass opacities. Honeycombing is not identified. (*C*) Histology shows a bronchiolocentric cellular and fibrosing interstitial pneumonia. (*D*) There is a patchy cellular interstitial infiltrate and poorly formed granulomas.

probable, possible, and not UIP) (8). The diagnosis of IPF requires (*1*) exclusion of other known causes of ILD, (*2*) the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy (SLB), and (*3*) specific combinations of HRCT and SLB patterns in patients subjected to SLB (Figures 1A–1C).

Histologic UIP may be associated with atypical HRCT patterns (Figures 1A–1C) (8), including extensive ground-glass opacity, nodules, or mosaic attenuation, and after MDD some of these patients will be diagnosed with IPF (49–52). Typical UIP HRCT pattern is illustrated elsewhere (1, 8). Patients with IPF and definite UIP by HRCT have shorter survival than those with indeterminate HRCT findings (49, 51, 53).

Idiopathic nonspecific interstitial pneumonia. The diagnostic criteria for NSIP were summarized in a recent ATS workshop (2). On the basis of the analysis of cases and the available literature, this workshop recommended that NSIP be accepted as a distinct entity among the IIPs, with removal of the term "provisional." Importantly, the NSIP pattern occurs not only as an idiopathic condition, but also in a variety of settings including CVD, HP, and drug toxicity, and in some patients with familial pulmonary fibrosis. MDD is especially important to establish the diagnosis of idiopathic NSIP (2).

The most common HRCT abnormality in NSIP is bilateral ground-glass opacity (Figures 2A and 2B) (26, 54–62). Irregular reticular opacities with traction bronchiectasis and bronchiolectasis occur in approximately 75% of cases (2, 54–62). Subpleural sparing may be helpful in distinguishing NSIP from UIP (2, 12, 52). Consolidation, if present, reflects an OP component and may suggest CVD. Honeycombing is sparse or absent at presentation but may increase in prevalence and extent during follow-up (63).

The histologic features include varying amounts of interstitial inflammation and fibrosis with a uniform appearance (Figures 2C and 2D) (2, 64, 65). Most cases of NSIP have a predominantly fibrotic pattern of injury with rare cases of isolated cellular NSIP (59, 62, 66). OP and honeycomb fibrosis should be inconspicuous or absent.

The prognosis is variable. Some patients improve, others remain stable or improve on treatment, but some evolve to end-stage fibrosis and eventually die of the disease (2, 63, 67).

Smoking-related IIPs

RB-ILD and desquamative interstitial pneumonia (DIP) represent a histologic spectrum of macrophage accumulation, with the distinction dependent on the extent and distribution of this process (and also reflected by the pattern of disease on HRCT). However, clinical presentation, imaging findings, and response to therapy differ and they remain classified separately. In the last decade, the term "smoking-related interstitial lung disease" has increasingly been used, encompassing most cases of DIP, and nearly all cases of RB-ILD and Langerhans' cell histiocytosis (68, 69).

Respiratory bronchiolitis–interstitial lung disease. Histologic RB is always present in current smokers (70) and can be viewed as a physiological response to smoking, which in a few individuals becomes extensive enough to result in an interstitial lung disease (RB-ILD). Characteristic HRCT features are ground-glass opacity and centrilobular nodules (Figures 3A and 3B). In clinical practice, RB-ILD is increasingly diagnosed without surgical lung biopsy in smokers with these HRCT findings and where bronchoalveolar lavage demonstrates smokers' macrophages and the absence of lymphocytosis (potentially suggestive of HP in this setting, although HP is uncommon in smokers) (68, 71). The disease course is heterogeneous, with a significant minority having progression despite smoking cessation (72).

Desquamative interstitial pneumonia. DIP has been recognized in nonsmokers (69), perhaps reflecting extension of childhood DIP into adult life (with the latter often due to surfactant protein [SP] gene mutations) (73, 74). Ten-year survival remains approximately 70%, with resistance to treatment in a significant minority.

Airspace enlargement with fibrosis. DIP and RB-ILD need to be distinguished from the smoking-related changes including

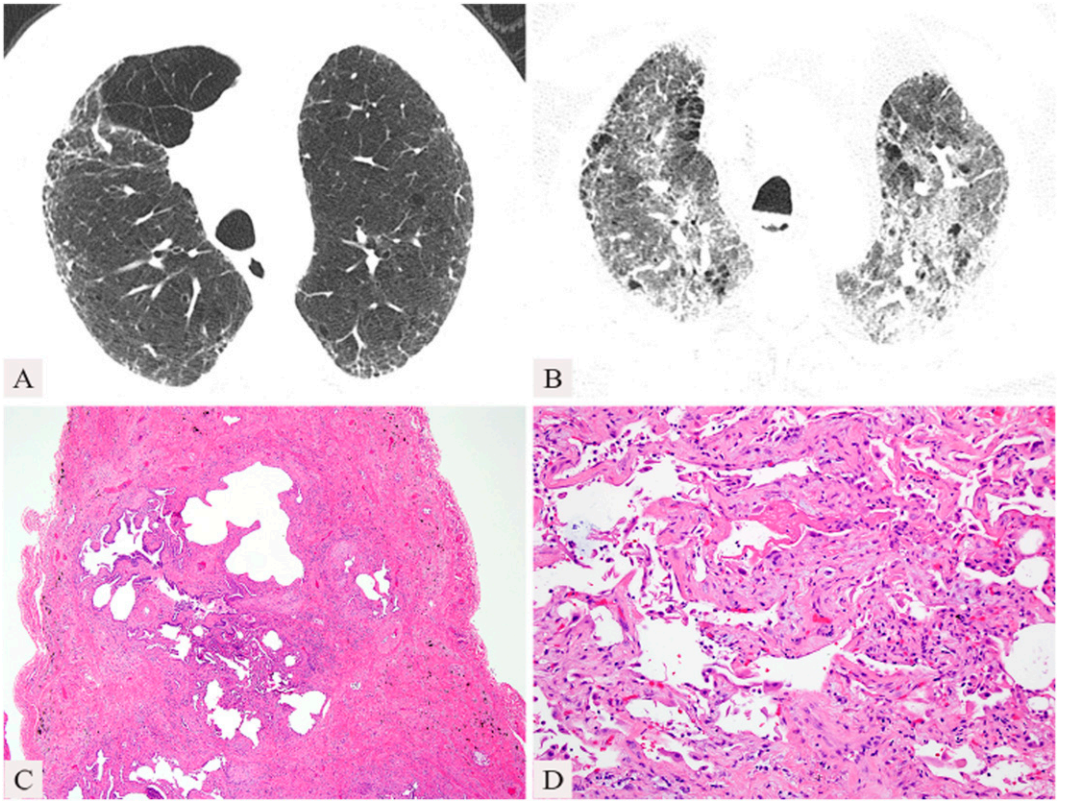

Figure 6. Acute exacerbation of idiopathic pulmonary fibrosis (IPF). Computed tomography (CT) features: (*A*) Axial image through the upper lungs at baseline shows mild peripheral, basal predominant reticular abnormality without honeycombing and mild emphysema. (*B*) Axial image during an acute exacerbation 4 months later shows extensive new bilateral ground-glass opacities, with some superimposed reticular abnormality. (*C* and *D*) Histologic features: (*C*) Usual interstitial pneumonia pattern with honeycomb fibrosis and fibroblastic foci. (*D*) Focally, features of diffuse alveolar damage are present with uniform thickening of alveolar walls and hyaline membranes.

respiratory bronchiolitis and airspace enlargement with fibrosis (AEF) that have been described in the nonneoplastic lung parenchyma in lung cancer resection specimens (75, 76). These incidental HRCT and histologic findings in smokers are not regarded as a distinct form of IIP, but AEF shows more interstitial fibrosis than described in the classic definition of emphysema (77). AEF is an incidental histologic or HRCT finding, whereas patients with CPFE have clinically manifestations reflecting coexisting patterns of interstitial fibrosing and emphysema.

Acute or Subacute IIPs

IIPs may have an acute or subacute presentation, or an acute exacerbation may occur in a previously subclinical or unrecognized chronic IIP.

Cryptogenic organizing pneumonia. COP continues to be included in the classification of IIP because of its idiopathic nature and the tendency on occasions to be confused with other forms of IIP, especially when there is progression to fibrosis. Because many cases are secondary, use of the generic term "OP" for this reaction pattern is suggested with modifiers as appropriate, for example, OP associated with rheumatoid arthritis.

Patients with COP typically present with a subacute illness of relatively short duration (median, less than 3 mo) with variable degrees of cough and dyspnea (78–81). HRCT characteristically demonstrates patchy and often migratory consolidation in a subpleural, peribronchial, or bandlike pattern (Figures 4A–4D) (82–84), commonly associated with ground-glass opacity (79, 83). Perilobular opacities and reversed halo (or atoll) sign (Figure 4C) may be helpful in suggesting the diagnosis (85, 86). Small unilateral or bilateral pleural effusion may occur in 10–30% of patients (83, 84, 86). The OP pattern is a patchy process characterized primarily by organizing pneumonia involving alveolar ducts and alveoli with or without bronchiolar intraluminal polyps. Some cases show more marked interstitial inflammation such that there is overlap with cellular NSIP.

The majority of patients recover completely with oral corticosteroids, but relapse is common (2, 78, 87). Sporadic reports have identified a subgroup of patients with OP that does not completely resolve despite prolonged treatment. Some of these cases are characterized by residual or progressive interstitial fibrosis, with or without recurrent episodes of OP (79, 88, 89). It is likely that some patients reported with fibrotic NSIP fall into this

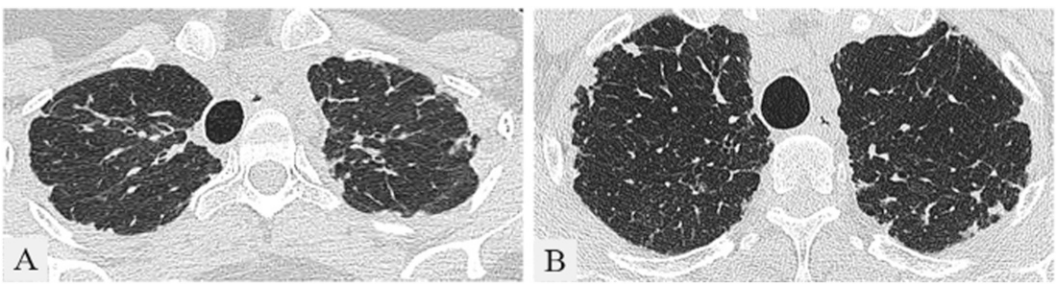

Figure 7. Pleuroparenchymal fibroelastosis. Computed tomography (CT) features: (*A*) High-resolution computed tomography (HRCT) through the upper lobes shows irregular pleural-based opacities and a reticular pattern associated with parenchymal distortion. The pleura and lungs in the lower lobes appeared normal. (*B*) Section through the upper lobes shows scattered pleuroparenchymal opacities and some distortion of the underlying lung parenchyma. In the lower lobes there was no pleural irregularity, but there was a subtle subpleural reticular pattern.

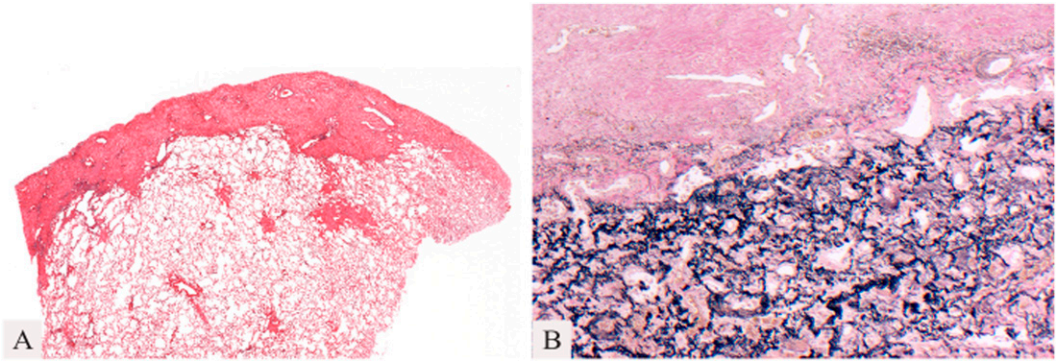

Figure 8. Pleuroparenchymal fibroelastosis. (*A*) Low power shows pleural thickening and subpleural fibrosis. (*B*) Dense masses of elastic fibers are highlighted beneath the fibrotically thickened pleura (elastic stain).

subgroup of patients with a fibrosing variant of OP. In such patients consolidation is prominent on HRCT, variably associated with reticular abnormalities. Some patients with this pattern of mixed fibrosis and organizing pneumonia are found to have underlying polymyositis or antisynthetase syndrome (90).

Acute interstitial pneumonia. AIP is a distinct IIP characterized by rapidly progressive hypoxemia, mortality of 50% or more, and no proven treatment. Survivors usually have a good long-term prognosis (similar to adult respiratory distress syndrome [ARDS] survivors) but some experience recurrences or chronic, progressive interstitial lung disease (91–93). AIP is idiopathic and should be distinguished from ARDS with known cause.

In the early, exudative phase of AIP, HRCT shows bilateral patchy ground-glass opacities, often with consolidation of the dependent lung (94–96). The later, organizing stage of AIP is associated with distortion of bronchovascular bundles and traction bronchiectasis. HRCT scoring of extent of abnormality is independently associated with mortality (93, 97). Biopsy shows an acute and/or organizing form of diffuse alveolar damage (DAD) that is indistinguishable from the histologic pattern found in ARDS (1). In the organizing phase, when most patients undergo biopsy, hyaline membranes may be inconspicuous or absent and the key findings include diffuse distribution, loose organizing connective tissue causing alveolar wall thickening and prominent pneumocyte hyperplasia. Occult background fibrosis may be present and if this shows features of UIP, acute exacerbation of underlying IPF should be considered (98). AIP can progress to a pattern similar to fibrotic NSIP (64) or to severe fibrosis resembling honeycombing (99).

Acute exacerbation of IIP. Acute exacerbation occurs mostly in IPF, but is also found in other fibrosing interstitial pneumonias (100–106). Diagnostic criteria have been published for acute exacerbation of IPF (107). In acute exacerbations of IPF, HRCT shows new bilateral ground-glass opacities and/or consolidation superimposed on a reticular pattern or honeycombing (Figures 6A and 6B) (108–110). The pathology most often shows a mixed pattern of UIP and DAD (Figures 6C and 6D), but OP and prominent fibroblastic foci are also described as the acute component (103). It is important to exclude infection, left heart failure, and other identifiable causes of acute lung injury before diagnosing an acute exacerbation of an underlying IIP (107).

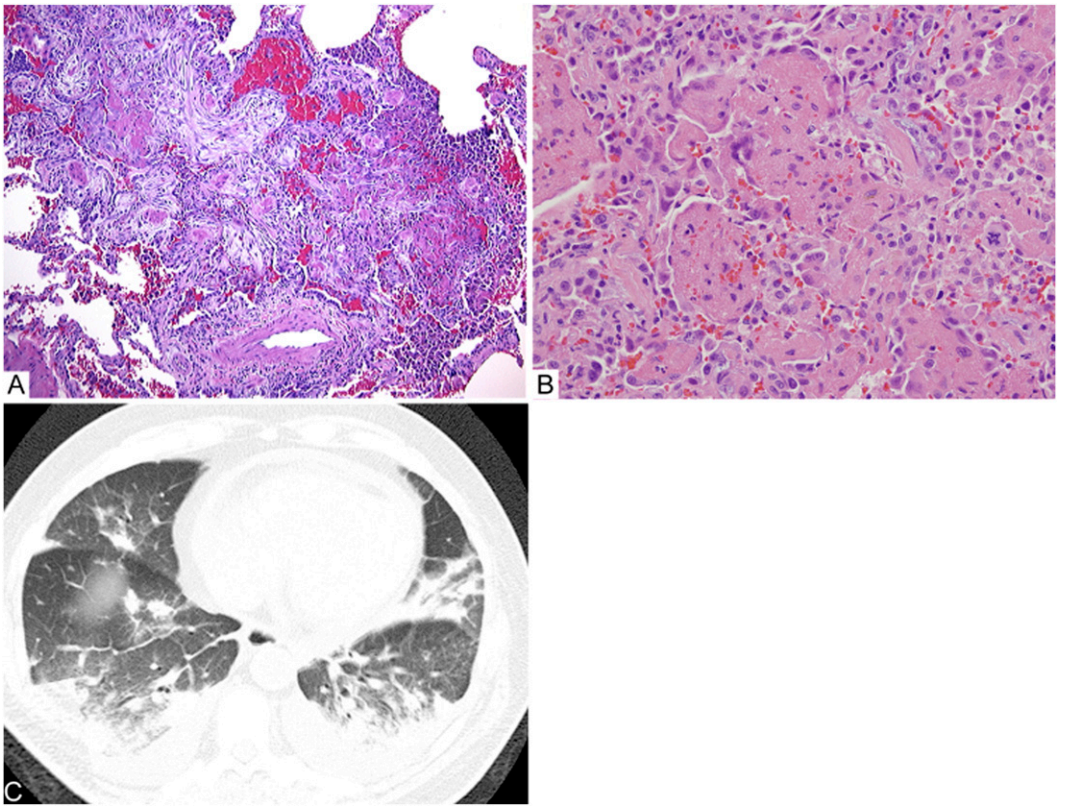

Figure 9. Acute fibrinous and organizing pneumonia. Computed tomography (CT) features. (*A*) Axial CT through the lung bases shows multiple poorly defined nodules and areas of consolidation, with peribronchovascular and basal predominance. Pleural and pericardial effusions are present. Histologic features: (*B*) Biopsy shows nodules of alveolar fibrin and organizing pneumonia. (*C*) The histology is dominated by intraalveolar plugs of alveolar fibrin.

RARE IIPS

The category of rare IIPs has been created to include idiopathic lymphoid interstitial pneumonia (LIP) and idiopathic pleuroparenchymal fibroelastosis (PPFE). In addition, several rare histologic patterns of ILD have been described including AFOP and a group of bronchiolocentric patterns, although current data do not support these as distinct IIPs.

Idiopathic Lymphoid Interstitial Pneumonia

Most cases of LIP are associated with other conditions, although idiopathic cases still rarely occur (111). Idiopathic LIP has therefore been moved to the category of rare IIPs. The clinical, imaging, and histopathologic criteria for LIP proposed in 2002 remain unchanged, apart from recognition that some cases show striking cyst formation on HRCT (111, 112). Both the 2002 IIP classification and the ATS NSIP project demonstrated that many of the cases previously diagnosed as LIP are now considered cellular NSIP (1, 2). Consequently, few cases of idiopathic LIP have been published since 2002 (111).

Idiopathic Pleuroparenchymal Fibroelastosis

PPFE is a rare condition that consists of fibrosis involving the pleura and subpleural lung parenchyma, predominantly in the upper lobes. HRCT shows dense subpleural consolidation with traction bronchiectasis, architectural distortion, and upper lobe volume loss (Figures 7A and 7B) (113). The fibrosis is elastotic, and intraalveolar fibrosis is present (Figures 8A and 8B) (113–117). It presents in adults with a median age of 57 years and has no sex predilection (113). Approximately half of patients have experienced recurrent infections. Pneumothorax is common. A minority has familial interstitial lung disease and nonspecific autoantibodies. Histologically, biopsies may show mild changes of PPFE or other patterns such as UIP. Disease progression occurs in 60% of patients with death from disease in 40% (113, 118).

RARE HISTOLOGIC PATTERNS

Rare histologic interstitial pneumonia patterns have been described and these were not included as new IIP entities because of questions concerning whether they are variants of existing IIPs or exist only in association with other conditions such as HP or CVD. When encountered histologically, these terms may be of value in provisionally classifying biopsy features before MDD.

Acute Fibrinous and Organizing Pneumonia

AFOP was first reported in 17 patients with acute respiratory failure and initially regarded to represent a possible new IIP (119). The principal HRCT findings are bilateral basal opacities and areas of consolidation (Figure 9A). The dominant histologic pattern is intraalveolar fibrin deposition and associated organizing pneumonia (Figures 9C and 9D). Classical hyaline membranes of DAD are absent. AFOP may represent a histologic pattern that can occur in the clinical spectrum of DAD and OP or it may reflect a tissue sampling issue. AFOP may be idiopathic or associated with CVD (120), hypersensitivity pneumonitis (121), or drug reaction (122). As this pattern can be seen in eosinophilic pneumonia, this diagnosis should be excluded by absence of tissue and peripheral eosinophilia.

Bronchiolocentric Patterns of Interstitial Pneumonia

Several small retrospective series have recently described bronchiolocentric fibroinflammatory changes (123–126). Of these, two studies in particular suggest these cases may be an IIP centered on airways (123, 125), although imaging findings were not well characterized and in one series there were environmental or occupational exposures in most cases (123). One study described cases of peribronchiolar metaplasia-ILD, which probably represent a form of small airway disease. The HRCTs in these cases were either normal or showed air trapping (124).

UNCLASSIFIABLE IIP

The 2002 ATS/ERS classification proposed an "unclassifiable" category of IIP, acknowledging that a final diagnosis may not be achieved, even after lengthy MDD (1). Examples of circumstances in which a case cannot be satisfactorily classified are summarized in Table 1 (127). Cases that are "unclassifiable" in terms of overlap of histologic patterns often prove to be related to CVD (e.g., interstitial pneumonia and follicular bronchiolitis in a patient with rheumatoid arthritis) or drug induced, rather than being idiopathic on MDD. If ILD is difficult, or impossible, to classify, management should be based on the most probable diagnosis after MDD and consideration of the expected disease behavior (as described below).

CLINICAL CLASSIFICATION OF DISEASE BEHAVIOR

Patterns of disease behavior in diffuse lung disorders and related treatment approaches can be broadly subdivided as shown in Table 3. This approach is most useful in unclassifiable cases and for some IIPs, such as NSIP, that can be associated with all five patterns of disease behavior. This disease behavior classification is complementary to the IIP classification and should not be used as a justification for delaying SLB. Such delays increase the risk of surgical complications and may result in

TABLE 3. IDIOPATHIC INTERSTITIAL PNEUMONIAS: CLASSIFICATION ACCORDING TO DISEASE BEHAVIOR*

Clinical Behavior	Treatment Goal	Monitoring Strategy
Reversible and self-limited (e.g., many cases of RB-ILD)	Remove possible cause	Short-term (3- to 6-mo) observation to confirm disease regression
Reversible disease with risk of progression (e.g., cellular NSIP and some fibrotic NSIP, DIP, COP)	Initially achieve response and then rationalize longer term therapy	Short-term observation to confirm treatment response. Long-term observation to ensure that gains are preserved
Stable with residual disease (e.g., some fibrotic NSIP)	Maintain status	Long-term observation to assess disease course
Progressive, irreversible disease with potential for stabilization (e.g., some fibrotic NSIP)	Stabilize	Long-term observation to assess disease course
Progressive, irreversible disease despite therapy (e.g., IPF, some fibrotic NSIP)	Slow progression	Long-term observation to assess disease course and need for transplant or effective palliation

Definition of abbreviations: COP = cryptogenic organizing pneumonia; DIP = desquamative interstitial pneumonia; HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia; RB-ILD = respiratory bronchiolitis–interstitial pneumonia.

*The distinctions in Table 3 are made by assimilating several factors: (*1*) A confident multidisciplinary diagnosis that often identifies the expected pattern of disease behavior (e.g., IPF). However, in other idiopathic interstitial pneumonias (e.g., NSIP) more than one pattern of behavior is possible; (*2*) disease severity, based on lung function and/or HRCT. In severe NSIP (154) a progressive irreversible course is frequent; (*3*) evaluation of potentially reversible and irreversible features based on review of the HRCT and biopsy if available; and (*4*) short-term disease behavior. Disease behavior classification must be refined over time in individual patients considering longitudinal changes in disease severity.

TABLE 4. BIOMARKERS FOR OUTCOME IN BLOOD AND BRONCHOALVEOLAR LAVAGE (HIGHER LEVELS PREDICTING POOR SURVIVAL)

Biomarker	Patients	HR (95% CI)	*P* Value	Reference
SP-A	52 IPF (survivors vs. nonsurvivors)		0.0125	Takahashi *et al.* (155)
SP-D			0.0032	
SP-A	142 IPF	1.73	0.031	Greene *et al.* (156)
SP-D		2.04	0.003	
KL-6 (>1,000 U/ml)	27 IPF	12.56 (1.195–131.90)	0.035	Yokoyama *et al.* (157)
KL-6 (⩾1,000 U/ml)	152 IIP and 67 CVD	2.95 (1.71–5.08)	0.0001	Satoh *et al.* (129)
SP-D (⩾253)	82 IPF		0.0013	Takahashi *et al.* (158)
SP-A			NS	
KL-6 (>1.014)			0.0087	
Oxidative stress levels	21 IPF	FVC $r = -0.79$	<0.01	Daniil *et al.* (159)
		D_{LCO} $r = -0.75$	<0.01	
MMP-7	74 IPF	Higher decline of D_{LCO} ($r = -0.53$) and FVC ($r = -0.51$)	0.002	Rosas *et al.* (160)
MMP-1			0.002	
SP-A	82 IPF	3.27 (1.49–7.17)	0.003	Kinder *et al.* (128)
SP-D (>460 ng/ml)	72 IPF	3.22 (1.33– 7.81)	0.01	Barlo *et al.* (29)
CCL18 above 150 ng/ml	72 IPF	7.98 (2.49–25.51)	0.0005	Prasse *et al.* (131)
$CD4^+CD28^{null}$ > 18% of total CD4	89 IPF	13.0 (1.6–111.1)	0.0004	Gilani *et al.* (161)
MMP-7, ICAM-1, IL-8, VCAM-1, S100-A12	241 IPF (140, derivation; 101, validation)	In the derivation cohort, high concentration predicted poor survival, poor transplant-free survival and poor progression-free survival. In the validation cohort high concentrations of all five were predictive of poor transplant-free survival; MMP-7, ICAM-1, and IL-8 of overall survival; and ICAM-1 of poor progression-free survival	Overall survival derivation cohort MMP-7: 0.0021 ICAM-1: 0.0015 IL-8: 0.029 VCAM-1: 0.00030 S100-A12: 0.0013	Richards *et al.* (162)
BAL	20 IPF	Higher in rapid progressors	0.028	McKeown *et al.** (163)
MMP-8, MMP-9			0.015	
BAL	39 IPF	Higher in nonsurvivors	<0.02	Shinoda *et al.** (164)
CCL2				
BAL	20 IPF	Negative correlation with PFT		Richter *et al.** (165)
Endostatin		FVC ($r = -0.604$)	0.006	
		T_{LCO} ($r = -0.612$)	0.005	

Definition of abbreviations: BAL = bronchoalveolar lavage; CI = confidence interval; CCL = chemokine ligand; CVD = collagen vascular disease; D_{LCO} = diffusing capacity or transfer factor of the lung for carbon monoxide; HR = hazard ratio; ICAM = intercellular adhesion molecule; IPF = idiopathic pulmonary fibrosis; KL-6 = Krebs von den Lungen-6; MMP = matrix metalloproteinase; NS = not significant; PFT = pulmonary function test; S100-A12 = protein encoded by S100-A12 gene; SP = surfactant protein; T_{LCO} = carbon monoxide diffusion factor; VCAM = vascular cell adhesion protein.

inappropriate management. This classification system needs to be validated for practicality and clinical relevance (127).

BIOMARKERS

Identification of biomarkers has been focused on IPF and usually in small cohorts and without independent validation. However, some interesting findings have emerged that may have implications for diagnosis, management, or prognostication of other IIPs (Table 4). For example, rapidly declining lung function and/or reduced survival have been associated with high serum levels of some epithelial or macrophage-related proteins such as SP-A, SP-D, KL-6 (Krebs von den Lungen-6), CCL18 (chemokine ligand-18), and MMP-7 (matrix metalloproteinase-7) (29, 128–131). These associations require validation, but suggest that biomarkers may be clinically useful to identify patients at high risk of progression.

Regarding biomarkers for differential diagnosis, serum SP-A and SP-D were found significantly higher in IPF compared with NSIP/COP or CVD-IP, respectively (132, 133). Likewise, higher levels of serum DNA seem to distinguish patients with IPF from non-IPF patients (134). Studies in lungs and bronchoalveolar lavage fluid indicate that NSIP is characterized by a helper T-cell type 1–like pattern whereas a helper T-cell type 2–like response with increased expression of chemokine receptor-7 (CCR7) and CCL7 is observed in IPF (135–138). Last, gene expression profiling has given contradictory results. Whereas one study found that most NSIP lungs did not resemble IPF, another identified only minor gene expression differences between UIP and NSIP (139).

Many association studies have failed to identify genetic polymorphisms that may confer increased risk of developing IPF (140, 141), whereas those showing association have not been validated in independent cohorts (140–152).

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