Diagnosis of Hypersensitivity Pneumonitis

Review and Summary of American College of Chest Physicians Statement

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Abstract: Assessment of lung biopsies for the diagnosis of hypersensitivity pneumonitis (HP) is one of the most difficult diagnostic problems for surgical pathologists. It is a form of interstitial lung disease resulting from an immune reaction provoked by an inhaled antigen in susceptible individuals. Although this definition sounds simple, in practice, the diagnosis of HP can be challenging. To address these issues, the American College of Chest Physicians (CHEST) has recently published a guideline for the diagnosis of HP. In this review, we will explore the multidisciplinary diagnostic evaluation of HP with a focus on the pathologic features as outlined in the CHEST guidelines. The histologic criteria are divided into 4 diagnostic categories: (1) *Typical* nonfibrotic HP or fibrotic HP; (2) *Compatible with* nonfibrotic HP or fibrotic HP; (3) *Indeterminate* for nonfibrotic or fibrotic HP; and (4) *Alternative Diagnosis.* It is important to emphasize that patterns 1 to 3 do not represent discrete histologic entities or pathologic diagnoses. Rather, these categories are meant to serve as a practical guide for organizing a complex set of overlapping histologic patterns into an integrated diagnostic framework for facilitating multidisciplinary discussion. High-resolution computed tomography features are also summarized, emphasizing how the correlation of lung biopsies with computed tomography findings can help to favor the diagnosis, particularly in cases where biopsies are not typical for HP. This review highlights details of the histologic spectrum of HP as well as the utility of different types of biopsies and bronchoalveolar lavage. We also emphasize the importance of multidisciplinary discussion and the complex differential diagnosis.

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DEFINITION AND CLASSIFICATION

Assessment of lung biopsies for the diagnosis of hypersensitivity pneumonitis (HP) is one of the most challenging diagnostic problems for surgical pathologists. HP is a form of interstitial lung disease (ILD) resulting from an immune reaction provoked by an inhaled antigen in susceptible individuals. Although this definition sounds simple, in practice, the diagnosis of HP can be challenging. In part, this problem arises from the fact that in a given case, it may be difficult or impossible to pinpoint the offending antigen, even with an extremely detailed history, and the approaches employed to confirm the antigen, for example, detection of specific serum IgG or inhalation challenge, are poorly standardized and controversial. In part, this problem also reflects a lack of consensus about the clinical, radiologic, and pathologic features of HP. For example, Walsh et al[1] asked 7 experienced multidisciplinary discussion (MDD) groups to review 70 ILD cases. Across groups, there was good agreement on other ILDs including idiopathic pulmonary fibrosis (IPF; weighted $\kappa = 0.71$) and connective tissue disease (CTD)-associated ILD (weighted $\kappa = 0.73$), but only fair agreement on a diagnosis of HP (weighted $\kappa = 0.29$). Morell et al[2] reexamined 43 patients initially thought to have IPF according to the 2011 American Thoracic Society (ATS) guidelines; by looking for specific serum antibodies, performing inhalation challenge, or obtaining a lung biopsy, 20 of the 43 patients were reclassified to chronic HP.

This issue is confounded by a lack of agreement on the classification of HP. The traditional classification divides HP into acute, subacute, and chronic forms. Acute HP in this context is an acute febrile self-limited illness believed to be caused by very high-level exposure to the antigen in question. Such cases appear to be infrequent and are rarely biopsied so that the pathologic features of acute HP are poorly defined. Subacute HP is the form that is most often encountered clinically and pathologically and is an ILD that develops slowly over weeks or months;

most important, by definition, subacute HP does not show fibrosis on imaging or biopsy.

The major issue with this classification scheme is the definition of chronic HP. Some authors use the term "chronic" for a disease that has been present for some arbitrary length of time, for example, 4 months, 6 months, or 1 year.[3] Other authors reserve the term chronic HP for disease with a fibrotic component on imaging or biopsy and do not take disease duration into account. Because fibrotic forms of ILD generally have a worse prognosis than nonfibrotic forms, and fibrotic HP has a worse prognosis than nonfibrotic HP, "chronic HP" becomes a term that means completely different things to different clinicians in terms of treatment and prognosis.

To address these issues, the ATS and the American College of Chest Physicians (CHEST) have recently published HP guidelines.[4–6] Both propose that HP be simply classified as fibrotic or nonfibrotic, and both provide a set of pathology guidelines for clinical practice. CHEST also suggests stratifying HP according to the inciting antigen (IA) exposure likelihood. In this review, we will explore the multidisciplinary diagnostic evaluation of HP with a focus on the pathologic features as outlined in the most recent CHEST guidelines.

IMPORTANCE OF MULTIDISCIPLINARY DIAGNOSIS

MDD aims to enhance the accuracy and confidence of diagnosis through consensus and provide recommendations on the need for additional testing such as lung biopsy.[4–6] A common challenge when diagnosing HP is the multifaceted clinical presentation and the interobserver variability in the imaging and biopsy interpretation. Therefore, integrating the radiologic and histologic findings with the exposure history by a multidisciplinary team underscores that higher confidence of HP diagnosis relies on the meticulous evaluation and integration of all available data rather than any single test results.[7] For example, although some fibrotic HP cases are morphologically indistinguishable from usual interstitial pneumonia (UIP) or fibrotic nonspecific interstitial pneumonia (NSIP), the distinction is evident in many cases when a multidisciplinary team consensus makes the diagnosis.

CLINICAL FEATURES

The clinical presentation and disease course of patients with HP are variable. They are influenced by the intensity and duration of exposure to an IA, the presence and extent of lung fibrosis, and individual susceptibility. Early on, in nonfibrotic HP cases, a temporal relation of dry cough, dyspnea, and systemic symptoms such as fever, chills, and malaise to exposure is frequently recognized. In this context, removing the IA may lead to disease resolution or clinical, radiologic, and functional stability. Recurring reexposure to the IA can contribute to disease progression. In a subgroup of patients with HP, the IA exposure may have ceased before the recognition of disease progression to pulmonary fibrosis. Patients with fibrotic HP commonly present with an insidious onset of progressive exertional dyspnea and dry cough.

PATHOLOGIC FEATURES

Pathologically, HP can present with a wide range of histologic patterns depending on the clinical course and disease progression when the lung tissue, most commonly biopsy, is obtained.[8] In general, the biopsy findings are divided into "Nonfibrotic HP" (cellular HP) and "Fibrotic HP" patterns, with the latter being associated with an interstitial fibrosing pattern and worse survival.[6] In the CHEST guideline, the histologic criteria are divided into 4 diagnostic categories: (1) *Typical* nonfibrotic HP or fibrotic HP; (2) *Compatible with* nonfibrotic HP or fibrotic HP; (3) *Indeterminate* for nonfibrotic or fibrotic HP; and (4) *Alternative Diagnosis* (Tables 2, 3).[6]

Nonfibrotic HP Patterns

Classification of *Typical Nonfibrotic HP Pattern* requires the presence of 4 *Major Features* in at least 1 lobe and the lack of features suggesting an alternative diagnosis (Table 1).[9–12] The 4 *Major Features* include: (1) distribution centered on small airways involving bronchioles and/or alveolar ducts (Figs. 1A, B). This is frequently described as "bronchiolocentricity"; (2) cellular interstitial inflammation of alveolar walls and bronchioles (cellular bronchiolitis) that is relatively diffuse and uniform (Fig. 1B), including a cellular NSIP pattern[12,13]; (3) inflammation composed primarily of lymphocytes with only few plasma cells (Figs. 1C, D); and (4) poorly formed, usually single, nonnecrotizing granulomas and/or multinucleated giant cells (Figs. 1C, D) that are interstitial and often situated in a peribronchiolar location. In addition, *Minor Features* represent nonspecific findings that can be seen in HP but are not part of the diagnostic criteria, including small foci of organizing pneumonia (Fig. 1C), foamy macrophages (Fig. 2A), cholesterol clefts (Fig. 2B), Schaumann bodies (Fig. 2C) and calcium oxalate crystals (Fig. 2D) with the latter 2 features being more common in sarcoidosis.[14]

The granulomas that are present in HP are typically small and non-necrotizing and consist of poorly formed loose clusters of epithelioid cells and multinucleated histiocytes (Figs. 1C, D). While they are usually found in the interstitium with peribronchiolar distribution, they can be seen in air spaces as well.[15–17] The inflammation of HP is predominantly lymphocytic, with relatively few plasma cells and minimal-to-absent eosinophils.[18] In some cases, the bronchiolocentric inflammation and cellular bronchiolitis can cause local airway obstruction, leading to extensive accumulation of foamy alveolar macrophages.

Compatible with Nonfibrotic HP Pattern is a category for biopsies that fulfill the first 3 *Major Features* but lack both granulomas and features of an alternative diagnosis (Figs. 3A, B). Here, the term "compatible with" may be preferable over the term "probable" since these histologic features are fairly nonspecific and can also be associated with other conditions including collagen vascular disease,[18,19] inhalational injury,[20] other environmental exposures,[21,22] and drug toxicity.[23,24]

TABLE 1. Nonfibrotic HP: Diagnostic Pathologic Criteria*

Typical for Nonfibrotic HP	Compatible With Nonfibrotic HP	Indeterminate for Nonfibrotic HP	Alternative Diagnosis (See More Detail in Table 4)
Major features Presence of all 4 major features in at least 1 of the sampled lobes of lung: (1) Small airway distribution (bronchioles and/or alveolar ducts) (2) Relatively diffuse and uniform cellular interstitial inflammation of alveolar walls and bronchioles (cellular bronchiolitis); may include regions with a cellular NSIP pattern (3) Inflammation consisting of mostly lymphocytes (4) Interstitial scattered, usually single, poorly formed non-necrotizing granulomas and/or multinucleated giant cells **Minor features** (a) Organizing pneumonia, small foci (b) Foamy macrophages (c) Cholesterol clefts, Schaumann bodies, calcium oxalate crystals And *Lack of* Features suggesting an alternative diagnosis (see column 4)	**Major features** Presence of these 3 major features: (1) Small airway distribution (2) Cellular interstitial inflammation causing cellular bronchiolitis and/or interstitial pneumonia (including a cellular NSIP pattern) (3) Inflammation consisting mostly of lymphocytes **Minor features** (a) Organizing pneumonia, small foci (b) Foamy macrophages (c) Cholesterol clefts, Schaumann bodies, calcium oxalate crystals And *Lack of* (a) Poorly formed non-necrotizing granulomas (b) Features of an alternative diagnosis (see column 4)	Biopsies that show an ILD pattern that does not meet criteria for *Nonfibrotic HP, Compatible with Nonfibrotic HP*, or an *Alternative Diagnosis* **Comment**: There is uncertainty about the histologic features in these cases that raise the consideration of nonfibrotic HP as well as other differential diagnoses that become part of the MDD whether the case is HP or not *Note*: Cellular NSIP pattern is in this category	A biopsy favoring other processes such as: Primary small airway disease (ie, bronchiolitis from a variety of causes) is usually distinguishable since the findings are restricted to the small airways and there is a lack of appreciable involvement of the surrounding alveoli **Other ILDs** *Sarcoidosis* *Aspiration* *Connective tissue disease, drug-induced lung disease, immunodeficiency* (increased plasma cells, prominent lymphoid hyperplasia and/or cellular interstitial lymphoid infiltrates, pleuritis, granulomas) *RB or other smoking-related lesions* (bronchiolocentric pigmented alveolar macrophages) *Granulomatous infection*, (robust, frequent necrotizing granulomas, especially mycobacterial, and fungal infections) *Pneumoconiosis/occupational exposures* (flock workers-lymphocytic bronchiolitis and lymphoid hyperplasia; berylliosis—well-formed granulomas, BADE†) *Langerhans cell histiocytosis* (peribronchiolar cellular infiltrates of Langerhans cells with or without cavitation and/or fibrosis

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†Lymphocytic bronchiolitis, alveolar ductitis, and emphysema in industrial machine manufacturing workers.

RB indicates respiratory bronchiolitis.

The *Indeterminate for Nonfibrotic HP Pattern* category is reserved for ILD pattern that does not meet the histologic criteria for *Typical nonfibrotic HP*, *Compatible with nonfibrotic HP*, or an *Alternative Diagnosis*, but is associated with radiologic and/or clinical features that suggest HP. In these cases, there is uncertainty about the histologic features that raise the consideration of nonfibrotic HP, as well as, other differential diagnoses that are explored during the MDD. Examples include biopsies that show a pure cellular NSIP pattern or cellular interstitial pneumonia without prominent or definitive bronchiolocentricity. Another scenario includes cases where the biopsy findings are classified as indeterminate for the HP pattern on the initial review (Figs. 3C, D). However, during MDD, the radiologic assessment reveals findings that favor HP, and subsequent rereview of the biopsy shows subtle findings that are reinterpreted to be *Typical for nonfibrotic* HP (eg, granulomas [Fig. 3D, inset] or bronchiolocentricity).

Last, the category of *Alternative Diagnosis* encompasses a wide array of other conditions that can affect the lung interstitium and/or small airways in a manner that may overlap with HP and therefore can be considered as differential diagnoses. In some cases, the radiologic changes before biopsy may suggest HP although the histology is quite different. Examples include sarcoidosis,[25] aspiration,[26,27] CTD,[18,28] drug toxicity,[29] immunodeficiency,[30,31] smoking-related lesions such as respiratory bronchiolitis,[32] infection,[33] environmental exposure or pneumoconiosis[34,35] and Langerhans cell histiocytosis.[36] The histopathologic features of these disorders and their distinction with HP are discussed in greater detail under the Differential Diagnosis section (Table 4).

Fibrotic HP Pattern

Classification of the *Typical Fibrotic HP pattern* requires the presence of 3 *Major Features* in at least 1 of the sampled lobe(s) and the lack of features suggesting an alternative diagnosis (Table 2, Figs. 4A–F). The 3 *Major Features* include: (1) small airway-centered fibrosis (Figs. 4B, D) with or without widespread peribronchiolar metaplasia involving > 50% of the bronchioles (Figs. 4E, F)[18]; (2) a chronic fibrosing interstitial pneumonia (Figs. 4A–D) affecting at least 1 sampled area/lobe showing at least 1 of the following patterns: (a) NSIP-fibrosing pattern,[13] (b) UIP-pattern (Figs. 4A–D),[13] (c) a fibrosing pattern that is difficult to classify, and (d) fibrosis that is solely peribronchiolar[13,21]; and (3) poorly formed interstitial non-

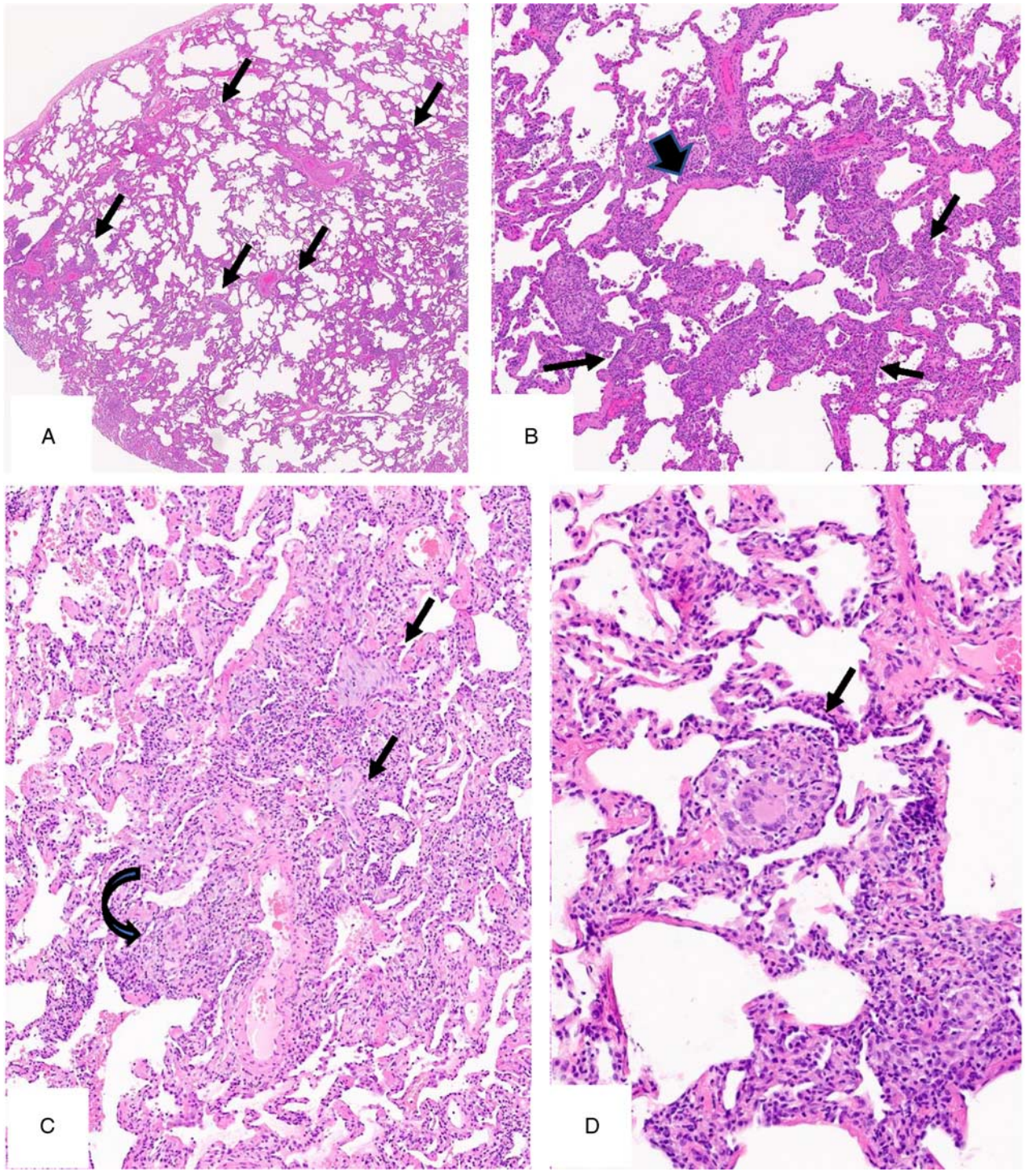

FIGURE 1. *Typical nonfibrotic HP pathologic pattern*. A, A bronchiolocentric distribution is demonstrated by patchy nodules of chronic inflammation centered on bronchioles (arrows). B, This alveolar duct (arrowhead) is infiltrated by chronic inflammation. The inflammation extends into the surrounding interstitium (arrows). C, The interstitium shows a chronic inflammatory infiltrate with a poorly formed granuloma (curved arrow) and small foci of organizing pneumonia (arrows). D, A loose cluster of epithelioid histiocytes and a multinucleated giant cell (arrow) represent a poorly formed granuloma.

necrotizing granulomas and/or multinucleated giant cells (Figs. 4B, D insets).[9,13,18,19,42–51] Alternatively, biopsies can be classified as *Typical Fibrotic HP pattern* in cases that only show *Major Feature #2*: a fibrosing interstitial pneumonia pattern in at least 1 lobe but fulfill the criteria for *Typical Nonfibrotic HP* in a separate or same lobe. In cases with UIP-

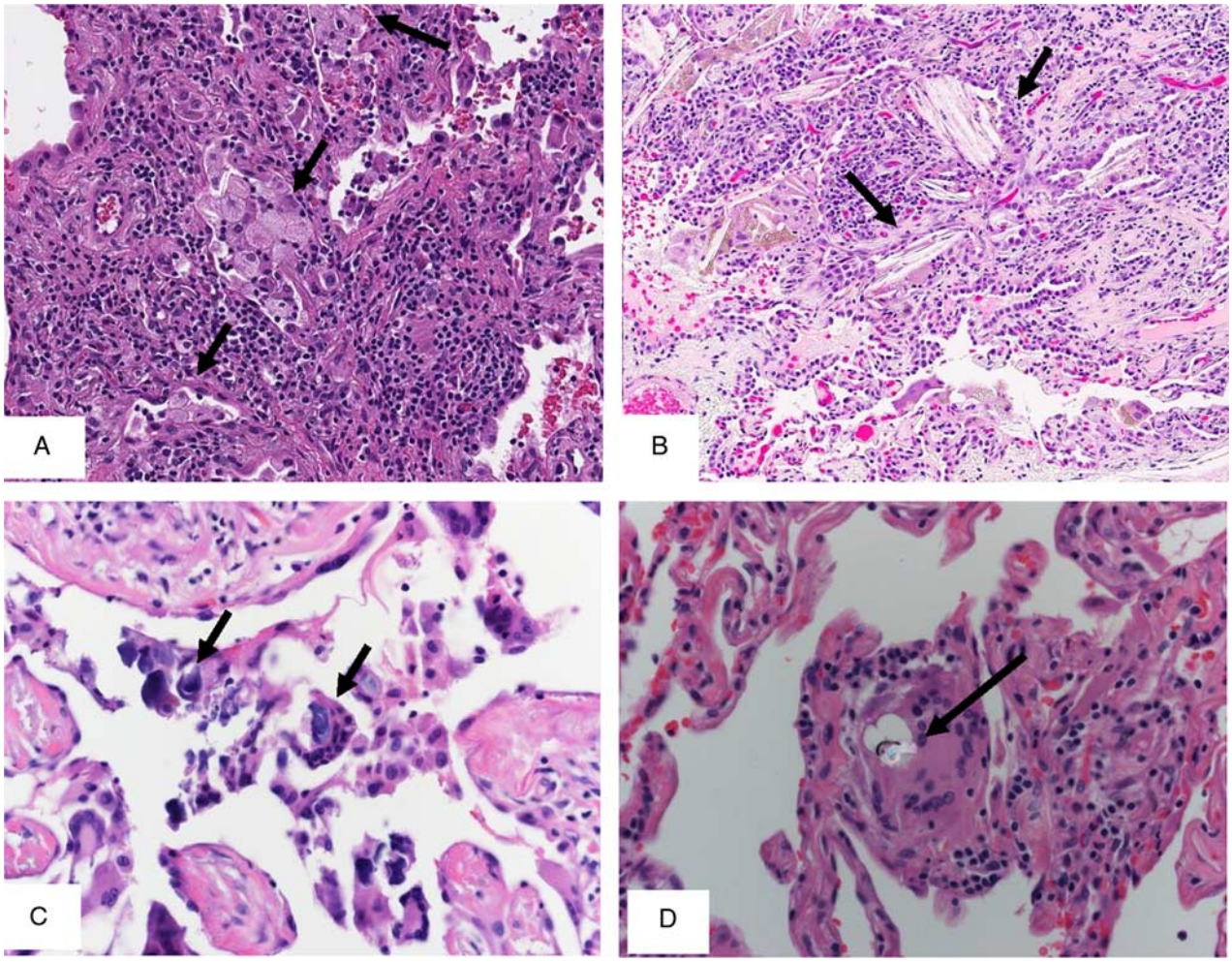

FIGURE 2. *Nonspecific inclusions*. A, Alveolar spaces are filled with foamy macrophages (arrows) and the interstitium is markedly infiltrated by chronic inflammation. B, Interstitial chronic inflammation and epithelioid histiocytes surround cholesterol clefts (arrows). C, Schaumann bodies consist of laminated calcifications (arrows). D, This calcium oxalate crystal within a giant cell shows birefringence under polarized light (arrow).

pattern, fibroblast foci can be seen in subpleural, paraseptal, or peribronchiolar locations (Figs. 4A, C insets).[9,12,43,51] While peribronchiolar metaplasia is a nonspecific reaction to bronchiolar and peribronchiolar injury, widespread involvement affecting >50% of bronchioles should raise the consideration for fibrotic HP (Figs. 4E, F).[19,51,52]

Compatible with Fibrotic HP is a category for biopsies that show *Major Features* #1 and #2 in at least 1 of the sampled lobes (Figs. 5A, B) but lack both poorly formed nonnecrotizing granulomas and features of an alternative diagnosis. Similar to *Typical Fibrotic HP,* biopsies can be classified as *Compatible with Fibrotic HP* in cases that show only *Major Feature* #2 such as UIP in at least 1 lobe but also meet criteria for *Compatible with Nonfibrotic HP*, such as bronchiolocentric fibrosis, in a separate or same lobe. Cases with pure bronchiolar fibrosis with little peribronchiolar interstitial involvement can be classified in this category (Figs. 5C, D).

Similar to nonfibrotic HP, the category of *Indeterminate for Fibrotic HP* pattern defines a pattern of fibrosing ILD that by itself does not meet the pathologic criteria for *Typical fibrotic HP*, *Compatible with fibrotic HP*, or an *Alternative Diagnosis* but is associated with clinical and radiologic findings that suggest fibrotic HP. Biopsies that show a pure UIP (Figs. 6A–D) or fibrosing NSIP (Figs. 6E, F) pattern without bronchiolocentricity or granulomas can be classified in this category.[2,42,50,53] In such cases, radiologic correlation can favor HP over UIP/IPF (Figs. 6C, D) or idiopathic fibrosing NSIP (Fig. 6F), respectively.

Lastly, the category of *Alternative Diagnosis* is limited to biopsies that show definitive features of other ILDs. The histopathologic features of these disorders and their distinction with HP are discussed in greater detail under the Differential Diagnosis section (Table 4).

COMPARISON WITH ATS HP GUIDELINE

Recently, a multidisciplinary clinical practice guideline was established and adopted by the ATS, European Respiratory Society, Japanese Respiratory Society,

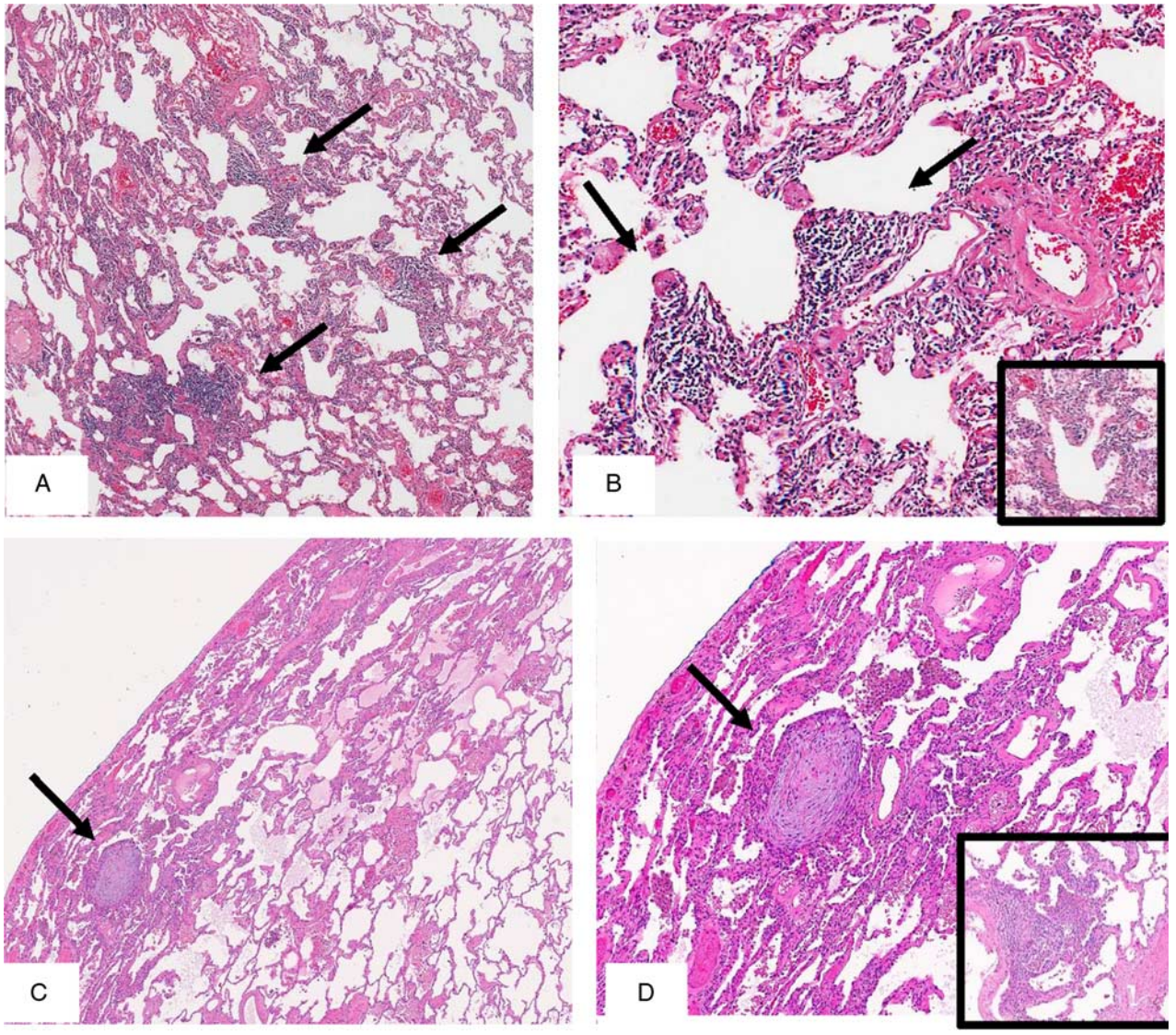

FIGURE 3. *Compatible with nonfibrotic HP.* A, This biopsy shows chronic inflammatory infiltrates in a bronchiolocentric distribution (arrows). B, This alveolar duct (arrows and inset) is infiltrated by chronic inflammation. No granulomas were seen. *Indeterminate for nonfibrotic HP*. C, This biopsy showed very focal organizing pneumonia (arrow) and interstitial chronic inflammation. But otherwise there were minimal histologic changes. D, Higher power shows a polypoid plug of loose organizing connective tissue within an alveolar space. The surrounding interstitium shows minimal chronic inflammation. After review of the CT which showed features of typical nonfibrotic HP, the biopsy was rereviewed and vague collections of epithelioid histiocytes were reinterpreted as a poorly formed granuloma (inset).

and Latin American Thoracic Society to standardize the diagnosis of HP. Similar to the new CHEST guideline, the ATS recommendation provides a set of histologic criteria for pathologic classification of HP.[4–6] In the ATS guideline, the histopathologic criteria are organized into 3 diagnostic categories (definite HP, probable HP, and indeterminate for HP) that are analogous to those in the CHEST guideline (typical for HP, compatible with HP, and indeterminate for HP) and include separate features for fibrotic and nonfibrotic HP. While both histopathologic criteria from the ATS and the CHEST share many similarities, there are a few conceptual and organizational differences that are important for discussion.

Here, conceptual differences reflect important diagnostic distinctions that may have potential clinical impact. For instance, in the CHEST guideline, the term "compatible with HP" is used for the second-tier histologic category rather than "probable HP" as proposed by the ATS guideline. The phrase "compatible with HP" was chosen because the constellation of histologic findings in this category are nonspecific and outside of a clinical and radiologic picture favoring HP, this pattern by itself does not indicate that the diagnosis is probably HP. Secondly, although both guidelines share the "indeterminate for HP" category, the ATS classification is based on inclusionary criteria and requires the presence of select histologic features that are characteristic for HP

TABLE 2. Fibrotic HP: Diagnostic Pathologic Criteria*

Typical for Fibrotic HP	Compatible With Fibrotic HP	Indeterminate for Fibrotic HP	Alternative Diagnosis (See More Detail in Table 4)
Major features Presence of all 3 major features in at least 1 of the sampled lobe(s) of lung: (1) Regions where small airway-centered fibrosis is clearly present with or without peribronchiolar metaplasia (2) Fibrosing interstitial pneumonia affecting at least 1 sampled area/lobe of lung parenchyma with regions showing 1 or more of the following patterns (a) NSIP-fibrosing pattern (b) UIP-pattern (c) Fibrosing pattern that is difficult to classify (d) Fibrosis that is solely peribronchiolar (3) Poorly formed noncaseating granulomas *Or* Fibrosing interstitial pneumonia showing only Major Feature #2 in at least 1 lobe), as well as all criteria for *Typical Nonfibrotic HP* in a separate/same lobe(s) **Minor features** (a) Organizing pneumonia, small foci (b) Focal peribronchiolar metaplasia (c) Foamy macrophages (d) Cholesterol clefts *Lack of* Features of an alternative diagnosis (see column 4)	**Major features** Presence of these 2 major features in at least 1 of the sampled lobe(s) of lung: (1) Regions where small airway-centered fibrosis is clearly present with or without widespread peribronchiolar metaplasia† (2) Fibrosing interstitial pneumonia affecting at least 1 sampled area of lung parenchyma with 1 or more of the following patterns (a) NSIP-fibrosing pattern (b) UIP-pattern (c) Fibrosing pattern that is difficult to classify (d) Fibrosis that is solely peribronchiolar (e) Depending on the morphology this category could include some bronchiolocentric interstitial pneumonias. See Table 4 *Or* Fibrosing interstitial pneumonia meeting only Major Feature #2 in at least 1 lobe, as well as criteria for *Compatible with Nonfibrotic HP* in a separate/same lobe(s) **Minor features** (a) Organizing pneumonia, small foci (b) Focal peribronchiolar metaplasia (c) Foamy macrophages (d) Cholesterol clefts, Schaumann or calcium oxalate crystals *Lack of* (a) Poorly formed non-necrotizing granulomas (b) Features of an alternative diagnosis (see column 4)	Cases that show a pattern of fibrosing ILD that does not meet the criteria for the pattern of *Fibrotic HP, Compatible with Fibrotic HP* or an *Alternative Diagnosis* **Comment**: There is uncertainty about the histologic features in these cases that raise the consideration of *Fibrotic HP* as well as other differential diagnoses that become part of the MDD whether the case is HP or not *Note*: Fibrotic NSIP and UIP-patterns are in this category. Depending on the morphology, this category could include some bronchiolocentric interstitial pneumonias, See Table 4	A biopsy that shows definitive features of other ILDs such as: *Idiopathic pulmonary fibrosis* *Fibrosing sarcoidosis* *Aspiration with fibrosis* *Fibrosing interstitial pneumonia in CTD*,[18,28] *drug-induced lung disease*, *immunodeficiency*[30] (prominent lymphoid hyperplasia and/or cellular interstitial lymphoid infiltrates, marked pleuritis, with or without granulomas) *Smoking-related patterns* (airspace enlargement with fibrosis−which overlaps with smoking-related interstitial fibrosis−which is usually accompanied by RB and emphysema[37,38]) *Pneumoconiosis/occupational exposures* (asbestos, hard metal, BADE‡)[39–41] *Fibrotic pulmonary Langerhans cell histiocytosis*

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†Widespread means peribronchiolar metaplasia affecting > 50% of the bronchioles.[18]

‡Lymphocytic bronchiolitis, alveolar ductitis and emphysema in industrial machine manufacturing workers.

RB indicates respiratory bronchiolitis.

(eg, bronchiolocentric cellular interstitial pneumonia or cellular bronchiolitis). In contrast, the CHEST criteria do not require specific features other than an ILD pattern that does not meet the criteria for "typical for HP," "compatible with HP," or an alternative diagnosis. In doing so, the latter approach leads to a broader and more open-ended indeterminate category, which could be more clinically applicable given that this inconclusive category essentially represents a "wastebasket" category rather than a specific disease entity with well-defined histologic features. Last, in contrast to the CHEST guideline, the ATS criteria include bridging fibrosis as a diagnostic feature under airway-centered fibrosis for fibrotic HP. In short, bridging fibrosis represents a pattern of fibrosis that spans bronchioles to the pleura or interlobular septa. While this feature has been historically associated with fibrotic HP, more recent studies show that bridging fibrosis can be seen in UIP/IPF and, therefore, may not be a specific feature for fibrotic HP.[19,51] In the light of these new findings, bridging fibrosis is not included as a supportive feature for fibrotic HP in the CHEST criteria, given its uncertain diagnostic utility.

In addition, there are variations in the organization of the histologic criteria, particularly in the summary tables, that may lead to a different emphasis on the interpretation of the guidelines. For example, the CHEST guideline separates the diagnostic criteria into major and minor features to emphasize the critical histologic findings supporting HP. Furthermore, the CHEST guideline

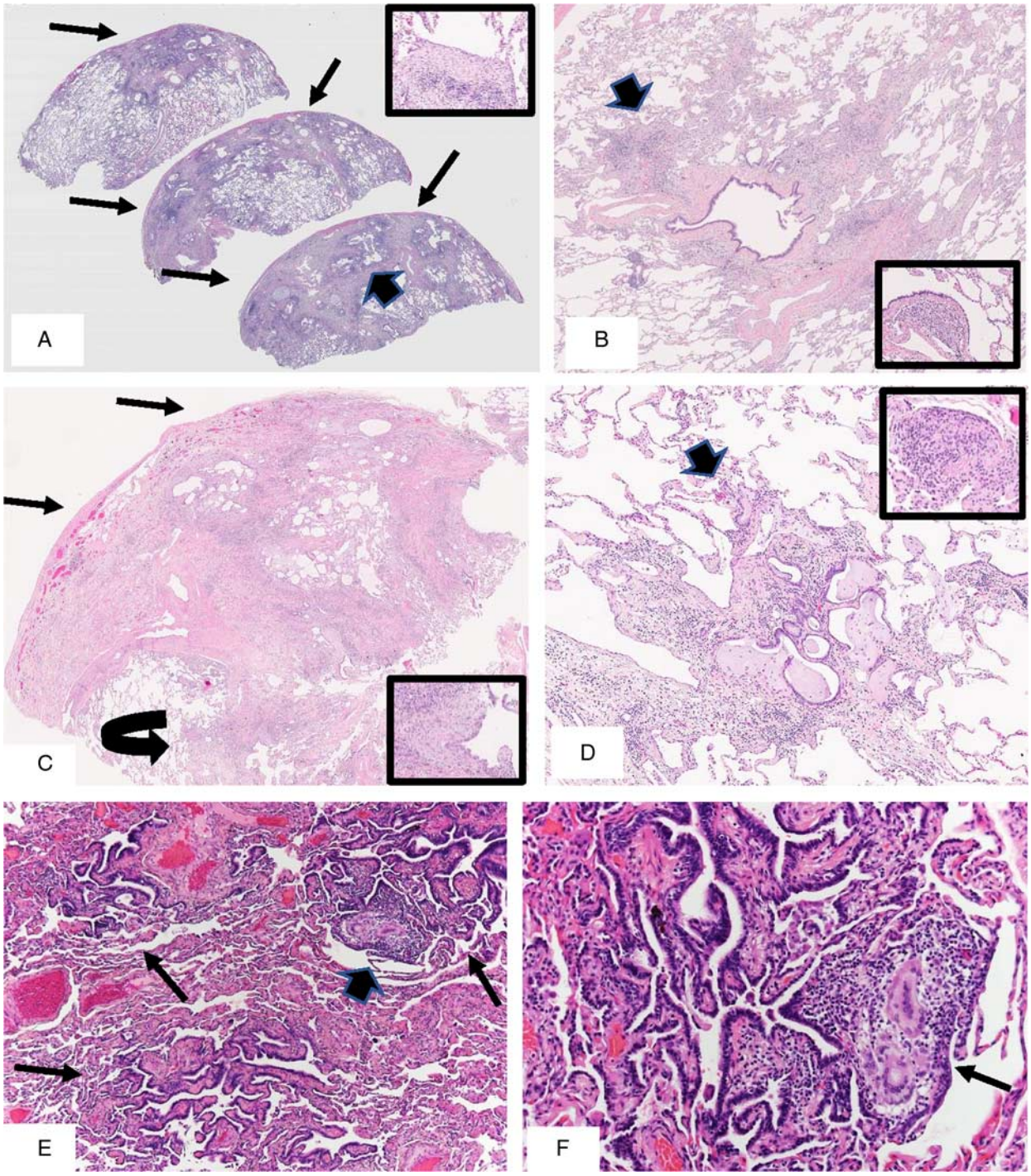

FIGURE 4. *Typical fibrotic HP*. A, This fibrotic HP case shows patchy subpleural fibrosis with extensive remodeling of the lung architecture (arrows). Bands of fibrosis show bridging patterns between bronchioles (arrowhead). Multiple fibroblastic foci were present (inset). B, Fibrosis and mild chronic inflammation surround this bronchiole (arrowhead). Poorly formed granulomas were also present (inset). C, Extensive patchy dense interstitial fibrosis is present with a subpleural distribution (arrows) in a pattern that is difficult to classify with some bronchiolocentricity (curved arrow and part D). Fibroblastic foci were also present (inset). D, Dense fibrosis and mild chronic interstitial inflammation surround this bronchiole (arrowhead). The inset shows a poorly formed granuloma which was difficult to find. E, Peribronchiolar metaplasia, consisting of bronchiolar fibrosis causing remodeling of the bronchiole with extension of the fibrosis into the surrounding interstitium, was widespread in this case, affecting each of the bronchioles in this image (arrows). One of the bronchioles shows a poorly formed noncaseating granuloma (arrowhead). F, There is proliferation of bronchiolar epithelium along the surface of the fibrotically thickened alveolar walls. Within the bronchiole is a poorly formed noncaseating granuloma (arrow).

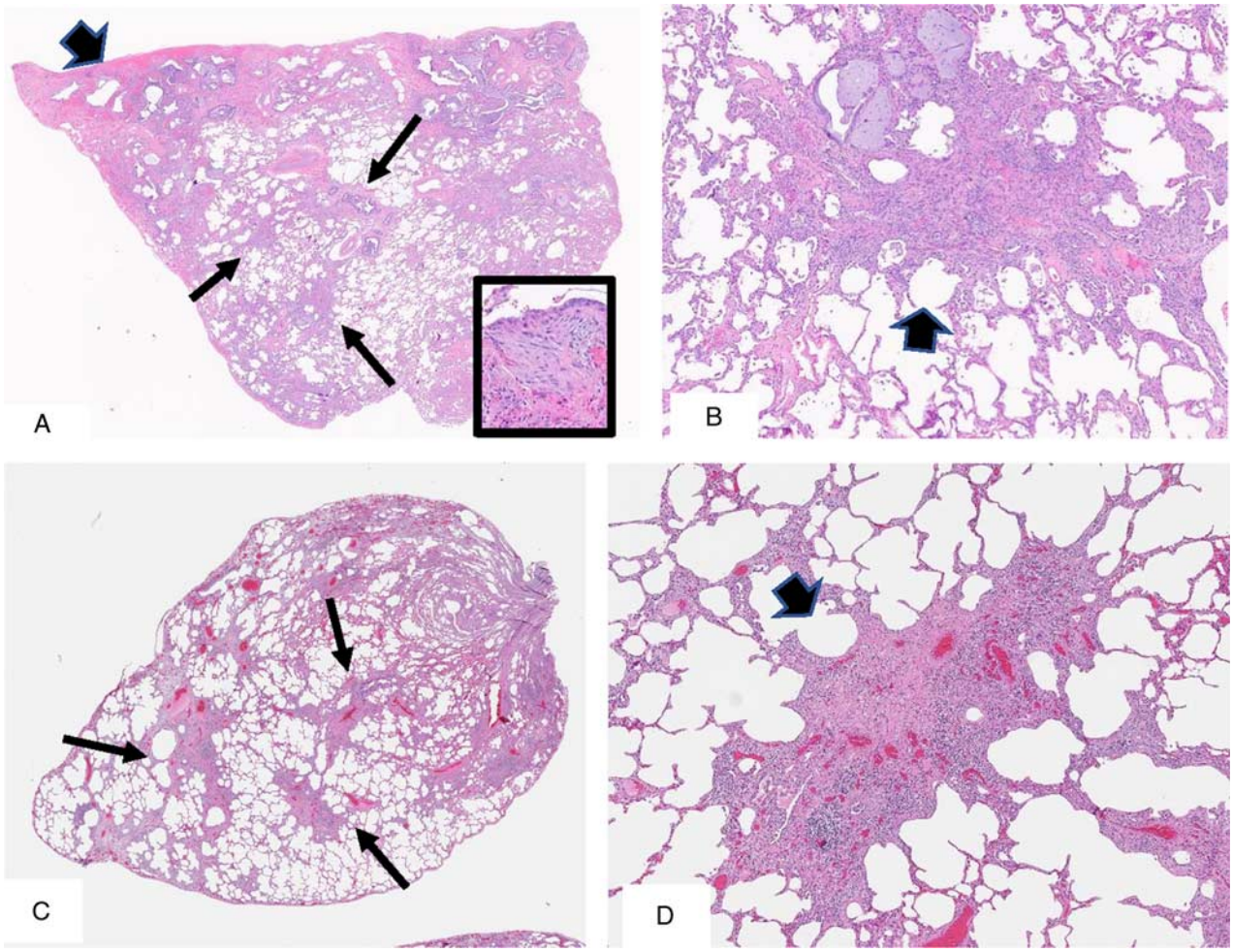

FIGURE 5. *Compatible with fibrotic HP*. A, A UIP pattern present in this biopsy is characterized by patchy subpleural fibrosis with remodeling of the lung architecture showing focal honeycombing (arrowhead). At the edges of fibrotic scars, fibroblastic foci were seen (inset). Bronchiolocentric fibrosis is also present (arrows). B, A bronchiolocentric pattern (arrowhead) of fibrosis, was present in this separate lobe biopsy specimen from the same case as in part A. However, no granulomas were seen. The CT showed features of typical HP. Idiopathic pulmonary fibrosis is excluded by the bronchiolocentricity and CT features. C, In this second case, the bronchiolar fibrosis is the dominant histologic feature. The fibrosis of the bronchioles in this biopsy is evident by the low power view showing evenly distributed nodules of fibrosis (arrows). D, This bronchiole is replaced by a nodular fibrotic scar accompanied by mild chronic inflammation (arrowhead). There is little extension of the fibrosis and inflammation into the surrounding interstitium. No granulomas were seen. CT features showed a typical HP pattern.

creates a fourth column in the main table that lists the alternative diagnoses for nonfibrotic and fibrotic HP in greater detail.

In addition, despite the similarity of the main histologic features for nonfibrotic HP between the 2 criteria, the CHEST guideline leads with the small airway distribution of the cellular interstitial inflammation, and in doing so, highlights the importance of the chronic inflammation that is seen around alveolar ducts and not just bronchioles (cellular bronchiolitis) for the diagnosis of HP.

While both guidelines include UIP-pattern as an example of diffuse fibrosing interstitial pneumonia that can be seen in fibrotic HP, the ATS guideline refrains from the "UIP" terminology and includes a descriptive statement instead: "architectural distortion, fibroblast foci, ± subpleural honeycombing," whereas the CHEST criteria uses the term "UIP-pattern" to describe these features. Clearly, it is important to be judicious in the usage of "UIP" and provide a distinction between UIP and IPF. However, in the context of these diagnostic criteria, it is evident that UIP encompasses a pattern of injury that can be seen in a variety of clinical settings rather solely in the context of a clinical diagnosis of IPF. Therefore, the usage of the "UIP-pattern" terminology may be appropriate in the setting of HP.

HIGH-RESOLUTION COMPUTED TOMOGRAPHY EVALUATION

High-resolution computed tomography (HRCT) consists of thin-section computed tomography (CT) images

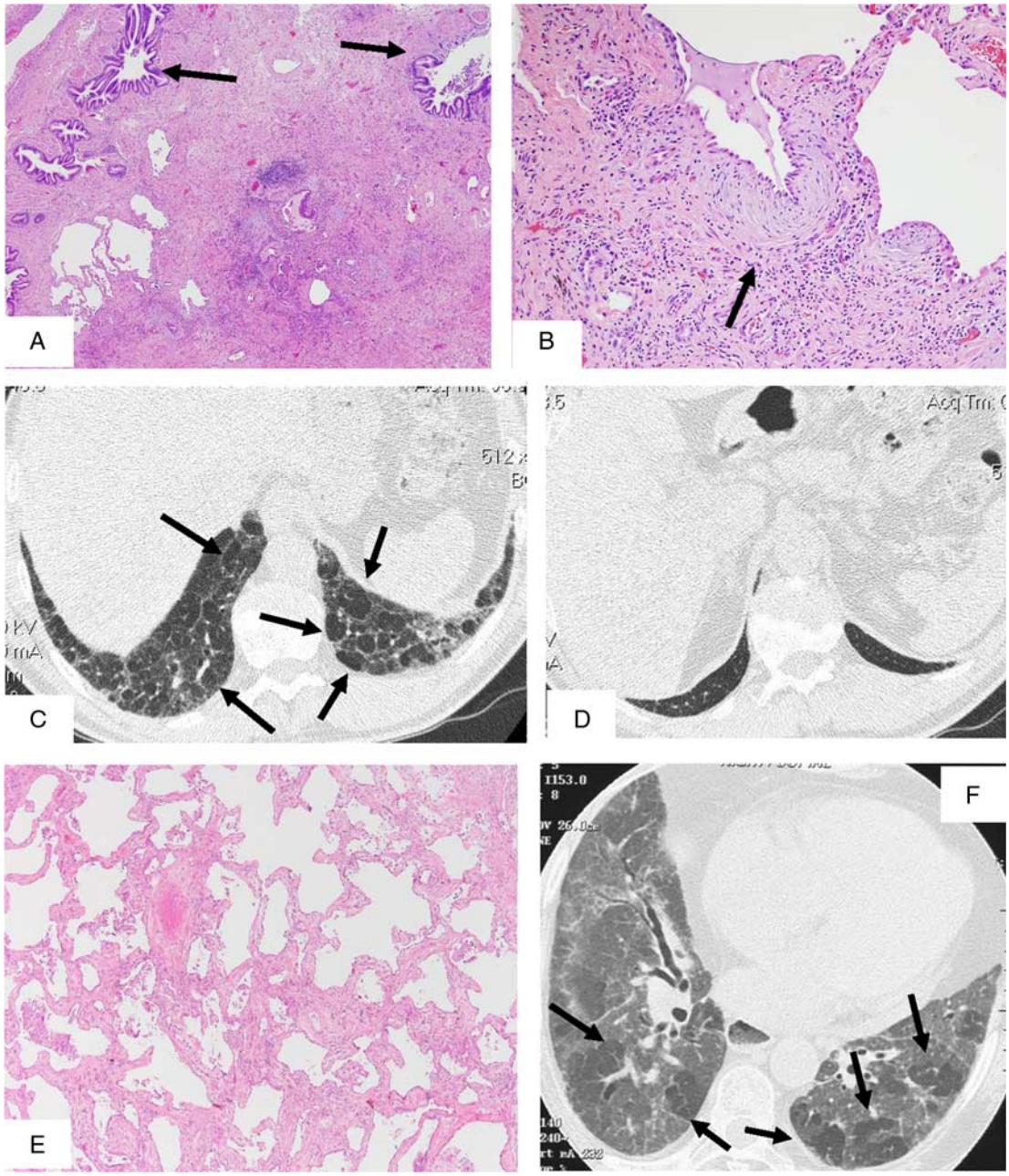

FIGURE 6. *Indeterminate for fibrotic HP*. A, A UIP-pattern is present in this biopsy with extensive fibrosis causing remodeling of the lung parenchyma and areas of honeycombing (arrows). However, bronchiolocentricity and granulomas were absent. B, Fibroblastic foci with nodular collections of myxoid connective tissue adjacent to dense eosinophilic collagen were present at the edges of the dense fibrotic scars (arrow). *Typical HP by CT*. Radiologic pathologic correlation was performed and revealed the CT from this patient whose biopsy showed a UIP-pattern in (A) and (B). C, The CT shows bilateral ground glass, mild reticulation, traction bronchiectasis and the 3 density sign (scattered areas of ground-glass attenuation, interspersed with normal lung attenuation, and mosaic attenuation, [arrows]) typical of HP. D, The lung bases show relative sparing, a feature against the possibility of IPF and in favor of HP. *Indeterminate for fibrotic HP by SLB but typical fibrotic HP by CT*. E, This biopsy shows diffuse involvement by uniform fibrotic thickening of alveolar walls with mild chronic inflammation lacking any bronchiolocentric distribution in a pattern of fibrotic NSIP. No honeycombing or granulomas are seen. *Typical HP by CT*. F, Radiologic pathologic correlation showed the CT from the patient whose biopsy in (E) reveals compatible with typical fibrotic HP rather than NSIP. The findings consist of the three-density sign (predominant ground-glass attenuation with lobules of normal attenuation and lobules with decreased attenuation and vascularity, [arrows]) with mild reticulation and traction bronchiectasis.

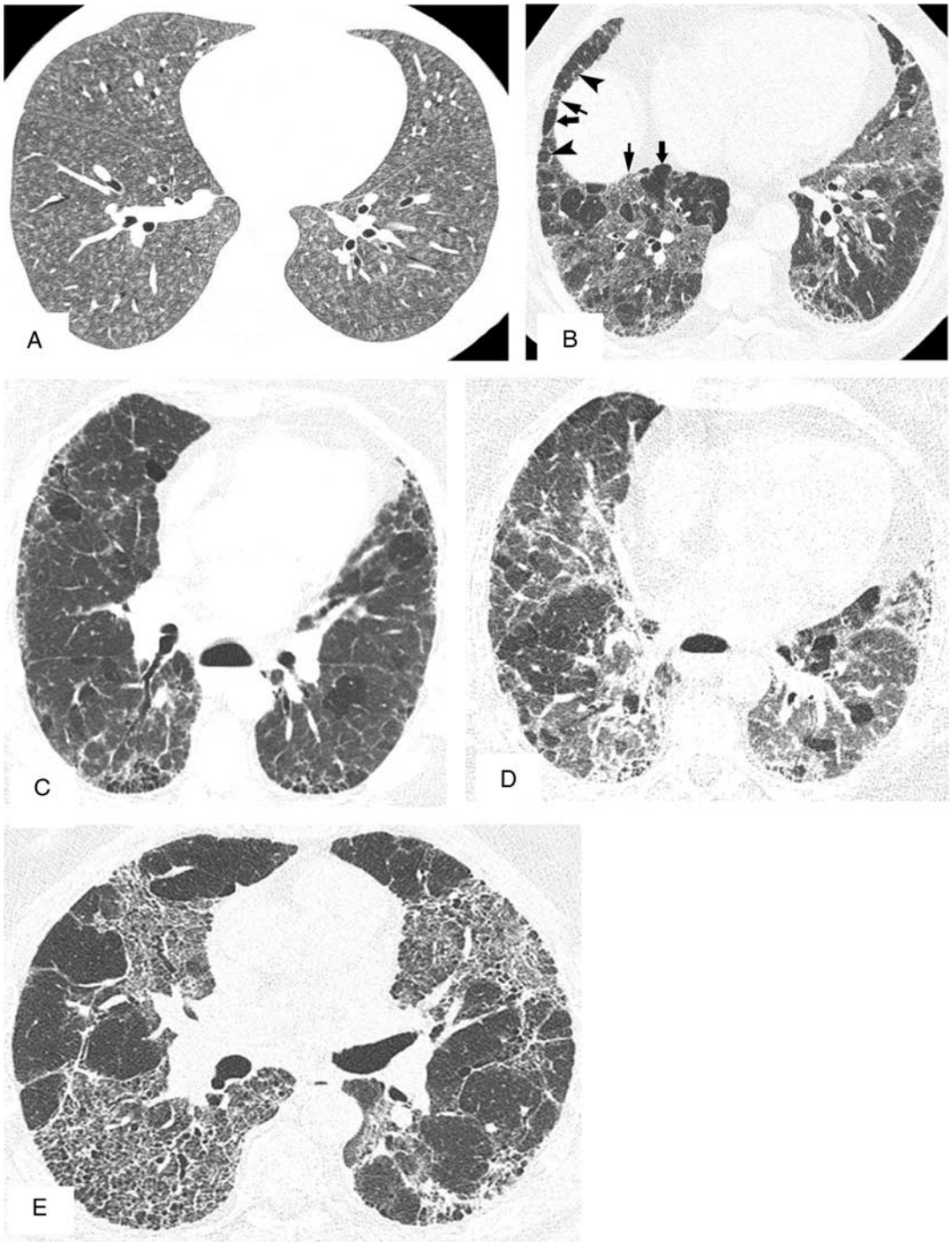

FIGURE 7. A, *Centrilobular nodules*. HRCT in a patient with nonfibrotic HP shows poorly defined centrilobular nodules of ground-glass attenuation throughout both lungs. Note that the nodules are centered a few mm away from the pleura, a feature which characterizes them as centrilobular. B, *Three-density sign*. HRCT in a patient with fibrotic HP demonstrates pulmonary lobules with 3 different density patterns within the same lobe, that is, lobules of decreased attenuation and decreased vascularity (broad arrows), lobules with ground-glass opacity (thin arrows), and lobules with normal attenuation (arrowheads). C, *Mosaic attenuation*. HRCT in a patient with fibrotic HP demonstrates moderately extensive reticular abnormality with honeycombing, as well as multiple areas of decreased attenuation and vascularity resulting in a mosaic pattern. The areas of decreased attenuation are sharply marginated and have a polygonal contour consistent with involvement of 1 or more adjacent pulmonary lobules. D, *Mosaic attenuation*. Expiratory image at a slightly lower level confirms multilobular air trapping. E, *Typical fibrotic HP pattern*. HRCT demonstrates extensive bilateral reticulation with associated dilatation and distortion of the bronchi (traction bronchiectasis) characteristic of fibrosis. Also noted are multiple sharply marginated areas of decreased attenuation and vascularity (mosaic attenuation) that have a polygonal contour consistent with involvement of 1 or more adjacent pulmonary lobules.

TABLE 3. Diagnostic CT Categories of Nonfibrotic and Fibrotic HP Based on CT Patterns*

HRCT	Features
Typical for *Nonfibrotic* HP	Any of the following: Profuse poorly defined centrilobular nodules of ground-glass opacity affecting all lung zones Inspiratory mosaic attenuation with 3-density sign Inspiratory mosaic attenuation and air trapping associated with centrilobular nodules *And* Lack of features suggesting an alternative diagnosis
Compatible with *Nonfibrotic* HP	Any of the following: Centrilobular nodules of ground-glass attenuation that are not profuse or diffuse, and not associated with mosaic attenuation or lobular air trapping Patchy or diffuse ground-glass opacity Mosaic attenuation and lobular air trapping without centrilobular nodules or ground-glass abnormality *And* Lack of features suggesting an alternative diagnosis
Typical for *Fibrotic* HP	CT signs of fibrosis with either of the following: Profuse poorly defined centrilobular nodules of ground-glass opacity affecting all lung zones Inspiratory mosaic attenuation with 3-density sign and multilobar lobular air trapping *And* Lack of features suggesting an alternative diagnosis
Compatible with *Fibrotic* HP	CT signs of fibrosis with any of the following: Patchy or diffuse ground-glass opacity Patchy, nonprofuse centrilobular nodules of ground-glass attenuation Mosaic attenuation and air trapping that do not meet criteria for typical fibrotic HP *And* Lack of features suggesting an alternative diagnosis
Indeterminate for *Fibrotic* HP	CT signs of fibrosis without other features suggestive of HP

In a nonsmoker, the presence of diffuse, profuse, poorly defined ground-glass centrilobular nodules is highly suggestive of the diagnosis of HP; similar findings may occasionally occur for example in infections, pulmonary hemorrhage, metastatic pulmonary calcification, or severe group 1 pulmonary hypertension, but the clinical context will usually identify these rare causes. Fibrosis is identified on CT by the presence of any or all of the following: reticulation or GGO with traction bronchiectasis or bronchiolectasis; honeycombing; or lobar volume loss.

*From Fernández Pérez et al.[6] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

($\leq$1.5 mm) optimized for assessment of fine parenchymal detail by using a high-spatial-frequency reconstruction algorithm. It should be obtained at full inspiration and at maximal expiration using standardized techniques (www.acr.org/-/media/ACR/Files/Practice-Parameters/HRCT-Lungs.pdf). Characteristic CT features of HP include centrilobular nodules, bilateral ground-glass opacities, mosaic attenuation, and multilobar air trapping. The centrilobular nodules measure < 5 mm, are of ground-glass attenuation (ie, poorly defined) and reflect the typical bronchiolocentric distribution of HP (Fig. 7A). Ground-glass opacification (GGO) is hazy increased lung attenuation that does not obscure the underlying vessels and airway walls. The GGO in HP is typically widespread but ranges from patchy to diffuse. Mosaic attenuation is defined as a sharply defined geographic patchwork of regions of differing attenuation on inspiratory images. The type of mosaic attenuation that is most specific for HP is the three-density sign (previously referred to as the headcheese sign) (Fig. 7B).[4,54,55] This sign is characterized by a combination of lung lobules of normal attenuation, surrounded by patchy or lobular GGO, and interspersed with lobules of decreased attenuation and decreased vascularity occurring within the same lobe. A second category of mosaic attenuation common in HP is lobular decreased attenuation interspersed with normal lung and associated with lobular air trapping on expiratory images (Figs. 7C, D). Air trapping is considered present on HRCT in areas of the lung parenchyma that remain lucent or show less than normally increased attenuation at maximal expiration. To be suggestive of HP, it needs to involve multiple lobes and preferably to be lobular, that is, to be sharply demarcated. Both the lobular areas of decreased attenuation and vascularity on inspiratory CT and the expiratory air trapping reflect the presence of bronchiolar obstruction (Fig. 7D). Fibrosis is identified by the presence of reticulation or GGO with traction bronchiectasis or bronchiolectasis with or without honeycombing or lobular volume loss (Fig. 7E).

The distribution of findings on HRCT is variable and often not diagnostically helpful, particularly in fibrotic HP. One exception is a mid-lung predominance of fibrosis which is highly suggestive of HP because it is seldom found in other fibrotic lung diseases.[56,57] In fibrotic HP, predominance occurs in the upper lobe versus lower lobe in 10% to 20% and 30% of patients, respectively.[58–60] Upper or mid-lung predominance, when present, help distinguish fibrotic HP from IPF.[61]

Based on the HRCT findings, HP is classified into nonfibrotic or fibrotic (Table 3).[4] Nonfibrotic patterns are

TABLE 4. Differential Diagnosis of HP for the Pathologist

Entity	Key Pathologic Features	Key Clinical/Laboratory Features*	Key Radiologic Features*	Comments
Nonfibrotic and fibrotic HP (for comparison with entities below)	Airway-centered process; relatively diffuse inflammatory infiltrate; scattered small single poorly formed granulomas; Schaumann bodies and birefringent oxalate crystal seen in some cases; paucity of plasma cells and germinal centers; ± organizing pneumonia; ± scarring; prominent PBM[4–6]	Causative exposure not always identified	Three density pattern/lobular air trapping; ground-glass centrilobular nodules; ± findings of fibrosis	Discussion with clinician and radiologist helpful in putting the histologic findings identified into context
IPF (idiopathic UIP)	Absence of granulomas/ interstitial giant cells; PBM/ airway centering less prominent; prominent fibroblast foci; increased subpleural scarring[93]	Absence of causative exposure	Usually lower lobe predominant without 3 density pattern or lobular air trapping. May be indistinguishable from fibrotic HP	Some cases of fibrotic HP can be pathologically and radiologically indistinguishable from IPF
Idiopathic NSIP	Absence of granulomas; minimal/absent airway centering[7,91]	Absence of causative exposure	Usually lower lobe predominant without 3-density pattern or lobular air trapping. May be indistinguishable from HP	Some cases of nonfibrotic HP and fibrotic HP can be pathologically and radiologically indistinguishable from cellular and fibrotic idiopathic NSIP, respectively
Airway-centered ILDs (ILD centered on airways has been reported as: airway-centered interstitial fibrosis, centrilobular fibrosis, idiopathic bronchiolocentric interstitial pneumonia, and peribronchiolar metaplasia; see comments)	Absence of granulomas; airway-centered process that may include inflammation, fibrosis, and/or peribronchiolar metaplasia; see comments[37,38,52]	See comments	See comments. Indistinguishable from HP	It has been documented that this pattern can be a pathologic manifestation in cases of confirmed diagnosis of fibrosing HP. These cases include a spectrum of lesions some of which after MDD may fall into the category of *Compatible with Fibrotic HP* and others that belong in the category of *Indeterminate for Fibrotic HP*
CTD-ILD	Lymphoid hyperplasia with germinal centers; prominent plasma cells; tend not to be airway centered unless a bronchiolitis component with the CTD is present; PBM tends to be less than in fibrotic HP; granulomas less often (except in Sjögren's)[18]	Known history of CTD; positive serologies	Lung findings often indistinguishable from HP. May have esophageal dilatation, enlarged mediastinal or axillary nodes, pleural or pericardial effusion	Prominence of T lymphocytes in the infiltrate in HP in contrast to the B cell (with germinal centers) and plasma cell proliferation in CTD-ILD
Drug toxicity	Lacks airway centering; ± granulomas depending on the drug; interstitial cellular lymphoid infiltrates and/or fibrosis; ± pleuritis[94,95]	Drug history and correlation with patterns associated with the drugs[94,95]	Some cases may be indistinguishable from HP	Some drug toxicities are associated with a cellular or fibrotic NSIP and as such indistinguishable from some cases of HP
Aspiration	Presence of foreign material/ degenerate food (± birefringent material) in granulomas or giant cells; often more of a pure bronchiolitis; relative sparing of some lobules compared with others; neutrophils often present if acute/subacute[26,27]	Risk factors for, or known history of, GERD/aspiration often present	May be more localized or multifocal in contrast to HP which tends to be diffuse; Lower lobe and dependent lung predilection	Aspiration with peribronchiolar interstitial lymphocytic infiltrates and/ or fibrosis can closely resemble fibrotic HP, particularly when food or other particulate matter is not present[26,27]

TABLE 4. (*continued*)

Entity	Key Pathologic Features	Key Clinical/Laboratory Features*	Key Radiologic Features*	Comments
Hot tub lung	Granulomas are larger and more "sarcoid-like"; granulomas tend to be in airways or alveoli and overshadow interstitial infiltrate; granulomas may have necrosis; AFB rarely identified[96,97]	History of exposure; MAI cultured from hot tub and/or lung	Usually indistinguishable from HP due to causes other than mycobacterial antigens	Hot tub lung is likely a distinct variant of HP due to exposure to mycobacterial antigens in which MAI can be cultured from the lung and the hot tub
Sarcoidosis	Coalescing well-formed non-necrotizing granulomas (often with hyaline fibrosis) along lymphatic routes with minimal/no associated interstitial inflammatory infiltrate[25]	Known history of sarcoid at other site(s)	Micronodular/nodular opacities in a perilymphatic distribution. Usually associated bilateral hilar and mediastinal lymphadenopathy	With the exception of hot tub lung the granulomas in HP are *very different* from those in sarcoid: they tend to be "poorly formed", small, single, scattered, and nonlymphangitic
Infection				
Granulomatous	Large well-formed granulomas often with necrosis; granulomas overshadow interstitial inflammation and may follow airways; positive special stains[14,98]	Positive cultures; MAI infection may have "middle lobe syndrome" with involvement of middle lobe and/or lingula	Tends to be patchy unilateral or bilateral asymmetric. Nodules better defined; tree-in-bud pattern may be seen	Like sarcoid above, granulomatous infections usually have granulomas that are very different from those in HP
Nongranulomatous	Acute injury with, neutrophils, fibrin, and/or hyaline membranes may be present; bronchiolitis and interstitial inflammation similar to HP can be seen	Exposure history; cultures; serologies	Diverse findings some of which can overlap with HP	Uncommon for nongranulomatous infections to be biopsied
Pneumoconiosis:				
Asbestosis	Asbestos bodies, some in giant cells; paucity of inflammation; lack of granulomas[99]	Exposure/occupational history	Tends to be lower lobe with pleural plaques or diffuse pleural thickening	Rarely a problem in the differential of HP
Silicosis	Dust macules; histiocytes with birefringent particles; lack of granulomas; little if any interstitial lymphocytic inflammation[99]	Exposure history	Simple silicosis can mimic HP; complicated silicosis has large nodules distinct from HP	Rarely a differential problem with HP; the sheets of dust filled macrophages should not be confused with epithelioid histiocytes
Cobalt/hard metal	Absence of granulomas BUT intra-alveolar giant cells typical; is typically bronchiolocentric[99]	Exposure history; analysis for hard metal	Diverse findings that can overlap with HP	Formerly known as giant cell interstitial pneumonia
Berylliosis	As for sarcoidosis above[99]	Exposure history; positive lymphocyte transformation test to beryllium	As for sarcoidosis above except that lymphadenopathy is less common	Berylliosis is very similar to sarcoidosis and comments for sarcoidosis above apply
Smoking-related ILD: RB-ILD; airspace enlargement with fibrosis	Absence of granulomas; RB present with "smokers' macrophages"; airspace enlargement with fibrosis—which is usually accompanied by RB and emphysema[37,38]	Smoking history; BAL findings	Considerable overlap with HP	HP uncommon in smokers; RB-ILD often in the radiologic differential of HP but not in the pathologic differential
Pulmonary Langerhans cell histiocytosis (PLCH)	Absence of granulomas; centrilobular nodules with variable numbers of Langerhans cells, eosinophils and variable fibrosis; "late" lesions less cellular and with centrilobular scarring that is distinctly more stellate than in HP; associated with RB[36]	Smoking history; BAL findings	Some overlap with HP but classic cases of PLCH with upper lobe nodular and cystic changes are quite different from HP	PLCH is smoking-related and may have other coexisting smoking-related changes (see above). HP uncommon in smokers
Bronchiolitis	Inflammatory process primarily restricted to bronchioles; necrosis, acute inflammation, granulomas and/or lymphoid hyperplasia (follicular bronchiolitis) may be present[100,101]	See comments	Variable findings depending on the type of bronchiolitis, some of which overlap with HP	"Bronchiolitis" encompasses numerous conditions that primarily affect airways (eg, infections, CTD-associated, etc.) many of which can share clinical and radiologic features with HP

TABLE 4. (*continued*)

Entity	Key Pathologic Features	Key Clinical/Laboratory Features*	Key Radiologic Features*	Comments
IgG4-RD	Marked plasma cell infiltrate with increased proportion $IgG4^+$ cells; fibrosis; vascular/airway infiltration; absence of granulomas[102]	IgG4-RD at other sites; elevated serum IgG4 levels	Often mediastinal lymphadenopathy. Presence of more nodular/localized disease; diffuse disease can be seen which can overlap with HP	Rarely a problem in the differential of HP
Immunodeficiency (esp. common variable/CVID)	Granulomas well-formed if present; lymphoid hyperplasia with germinal centers; nodular infiltrates; some cases show features of granulomatous lymphocytic interstitial lung disease or lymphoid interstitial pneumonia[30]	Clinical history; serum Ig levels; extrapulmonary disease	Majority have bronchiectasis and findings related to recurrent infections. Little overlap with HP	Not common in the differential of HP
Bronchiolitis, alveolar ductitis, and emphysema (BADE)	Absence of granulomas; prominence of B-cell follicles with occasional germinal centers especially along alveolar ducts; emphysema[41]	Rare with only one cluster reported from a machine manufacturing facility; nonsmokers with emphysema and airflow obstruction	Emphysema and evidence of airway disease; interstitial changes not a feature	Clinically and radiologically not a lot of overlap with HP but the airway-centered inflammatory process could resemble HP without granulomas

*As these features relate to pathologic differential diagnosis.

AFB indicates acid-fast bacillus; GERD, gastroesophageal reflux disease; Ig, immunonoglobulin; IgG4-RD, immunonoglobulin G4–related disease; MAI, Mycobacterium avium-intracellulare; PBM, peribronchiolar metaplasia; RB, respiratory bronchiolitis.

classified as typical for HP or compatible with HP and fibrotic abnormalities as typical for HP, compatible with HP (Fig. 7E), or indeterminate. An indeterminate fibrotic pattern for HP is one that is neither suggestive nor compatible with HP. They include patterns characteristic of UIP, fibrotic NSIP, and organizing pneumonia because, although these patterns are most suggestive of other diagnoses, they do not exclude the possibility of fibrotic HP.

Although HRCT features typical for HP are highly suggestive, they should not be used in isolation to make a clinical diagnosis of HP.[6] Assessment of the overall probability of HP needs to consider not only the HRCT findings but also the prevalence of the disease in the particular setting (eg, referral center or primary care clinic, farming region), the clinical context, laboratory findings, and the exposure history.[55,56,62,63]

SPECIAL TOPICS

Specimen Type

The recently published CHEST guidelines and expert panel report suggest considering histologic lung biopsy "when all available data … do not yield a confident diagnosis and results may help guide management" and further suggest "integrating biopsy findings with clinical and radiologic findings to support the diagnosis of HP in the context of the MDD."[6] Both recommendations were qualified as "weak" recommendations with "very low-quality evidence."[6] Limitations of lung biopsy for HP diagnosis include interobserver variation in pathologic interpretation, biopsy size, and number of specimens affecting diagnostic yield, sampling error, and the presence of atypical findings such as NSIP or UIP-like patterns.[6]

Surgical lung biopsy (SLB) has a higher diagnostic yield than more limited sampling techniques such as transbronchial forceps biopsy (TBBX) or transbronchial cryobiopsy (TBLC), particularly when multiple lobes are sampled.[4–6,50,64–68] It is generally accepted that the majority of ILD cannot be reliably diagnosed by standard TBBX.[69] Occasionally, nonfibrotic HP may be diagnosed if the findings of peribronchial chronic inflammation and giant cells/poorly formed granulomas are present in the correct clinical and radiologic setting, but this is generally not the case with fibrotic HP.[65,70,71]

TBLC has emerged as a potential alternative to SLB and TBBX due to the decreased risk of complications relative to the former and the larger amount of tissue obtainable compared with the latter. Various studies and meta-analyses have generally shown a fairly high concordance rate between TBLC and SLB and added value in the setting of MDD,[72–75] with a lower diagnostic yield for TBLC than SLB in other studies[76,77] The recent COLDICE Study incorporates data from multiple centers in Australia and shows fairly good concordance between TBLC and SLB for a variety of ILD diagnoses including HP.[78,79] Conversely, the bicenter CryoPID Study from Italy found poor diagnostic concordance between TBLC and SLB from the same patient.[80] Differences between the 2 studies were attributed at least in part to differences in sample size and study methodology,[81] which illustrates the challenges in determining the value of TBLC in the context of ILD. A systematic review reported very low-quality evidence that TBLC had a higher diagnostic yield of 82%

(95% confidence interval, 78%-86%) compared with 37% (95% confidence interval, 32%-42%) for TBBX but[82] also complication rates for severe bleeding, bleeding and pneumothorax were similar for both.

While efforts are ongoing, standardized methods for obtaining TBLC are currently lacking, and the amount of material obtained is variable, with reported mean sizes ranging from 10 to 64.2 mm^2, which impacts diagnostic yield.[77,83] As expected, a greater amount of tissue typically improves diagnostic yield.[79,82,84] Recently, Churg and Wright[85] aimed to specifically determine the ability of cryobiopsy specimens to detect features supporting a diagnosis of fibrotic HP by using an "in silico" method of creating 20 mm^2 "cryobiopsies." This study found that the sensitivity to detect giant cells/granulomas was poor. In contrast, peribronchiolar metaplasia in >50% of bronchioles was detected with a higher frequency, when at least 4 "cryobiopsies" were examined. This suggested sufficient sensitivity for detecting features of fibrotic HP when at least 4 "cryobiopsies" with an area of 20 mm^2 each were evaluated.

SLB has traditionally been the gold standard for the histologic diagnosis of ILD, including HP. Although the frequency of SLB has decreased in patients with "definite UIP" radiologically as defined by the ATS guidelines for IPF, HP was the most frequent clinical diagnosis for radiologic cases of "Probable UIP" in at least one study.[86] For several reasons; however, SLB has its limitations in regard to the diagnosis of HP, and a final diagnosis should always involve MDD despite studies showing variable diagnostic agreement.[1,2]

While "typical" features of nonfibrotic HP may occasionally be present in cases of fibrotic HP, particularly if >1 site is sampled, 25% to 30% of cases will lack identifiable granulomas or giant cells.[16,50] Peribronchiolar metaplasia, particularly when present in over 50% of airways or greater, is a helpful diagnostic clue generally favoring HP when present.[51] While useful, occasional foci of peribronchiolar metaplasia are not pathognomonic and may also be encountered in pulmonary fibrosis due to other causes, including IPF.[19] In one study, 33% of patients with clinical IPF were found to have significant bronchiolocentric fibrosis.[49] In spite of these challenges, the ATS clinical guidelines suggest SLB be performed in both the setting of nonfibrotic and fibrotic HP when all other diagnostic testing has failed to yield a diagnosis.[4]

Diagnostic Terminology

Given that the histologic features of both fibrotic and nonfibrotic HP may overlap with other entities, the pathologic categories recommended by the ATS and CHEST guidelines should be used in the context of MDD as opposed to being used as diagnostic terminology for pathology reports. As such, a descriptive diagnosis (ie, chronic, bronchiolocentric inflammation and fibrosis with associated poorly formed granulomas) is generally warranted, with a comment that HP should be considered in the clinical differential diagnosis or "consistent with" if there is a known clinical suspicion of HP. In the context of MDD, the provided example could be described as being "typical HP"; however, a final clinical diagnosis of HP rests on evaluation of all clinical and radiologic information.

Use of Bronchoalveolar Lavage

HP is associated with a T-cell–mediated immune response, and lymphocytes comprise the majority of infiltrating immune cells. In HP, the bronchoscopy and the timing of histologic findings influence the degree of bronchoalveolar lavage (BAL) lymphocytosis. For instance, the BAL fluid lymphocyte level appears to vary inversely according to fibrosis burden in the lung.[6] Indeed, while the lack of BAL lymphocytosis may help exclude nonfibrotic HP in the appropriate clinical context, it does not rule out fibrotic HP.

Marked BAL lymphocytosis with 40% to 60% lymphocytes, although not specific, is highly suggestive of HP in the appropriate clinical and radiology context and can help exclude competing causes such as IPF, particularly when combined with supportive findings on TBBX.[6,65,70,87–90]

CHALLENGES IN MULTIDISCIPLINARY DIAGNOSIS OF HP

A confident multidisciplinary diagnosis of HP may be made when the patient has a history of exposure to a recognized antigenic cause of HP, along with typical HRCT features of nonfibrotic or fibrotic HP; biopsy is unnecessary in such cases.[6] When typical exposure and typical CT features of HP are not present, the diagnosis is more challenging, and biopsy may be required. In interpreting the biopsy of a patient with suspected HP, it is important to correlate with the CT appearances. For example, some patients with typical features of fibrotic HP on CT may show only NSIP or UIP pattern on biopsy[50,91]; conversely, some patients with typical NSIP or UIP pattern on CT may have histologic findings of HP. For this reason, it is always important to review the CT findings when interpreting a biopsy of a patient with suspected HP. A study of 142 patients with chronic HP (predominantly fibrotic) on biopsy showed that 75 (53%) did not have an identifiable antigenic exposure.[92] Lack of an identifiable antigen was an independent predictor of poorer survival compared with those who had an identifiable antigen. While this proportion may be elevated because of selection bias at a referral center for ILD, it indicates that the pathologist should not be surprised if no antigen is identified even in an individual with typical histologic features of HP.

DIFFERENTIAL DIAGNOSIS

The differential diagnostic considerations for fibrotic and nonfibrotic HP are included in Table 4. The most important conditions include the idiopathic interstitial pneumonias, ILD in the setting of CTD (Figs. 8A–F),[18,28] drug reactions, aspiration (Figs. 9A, B), immunodeficiency (Figs. 9C, D), and other conditions in the lung associated with granulomas such as infections (Figs. 9E, F).

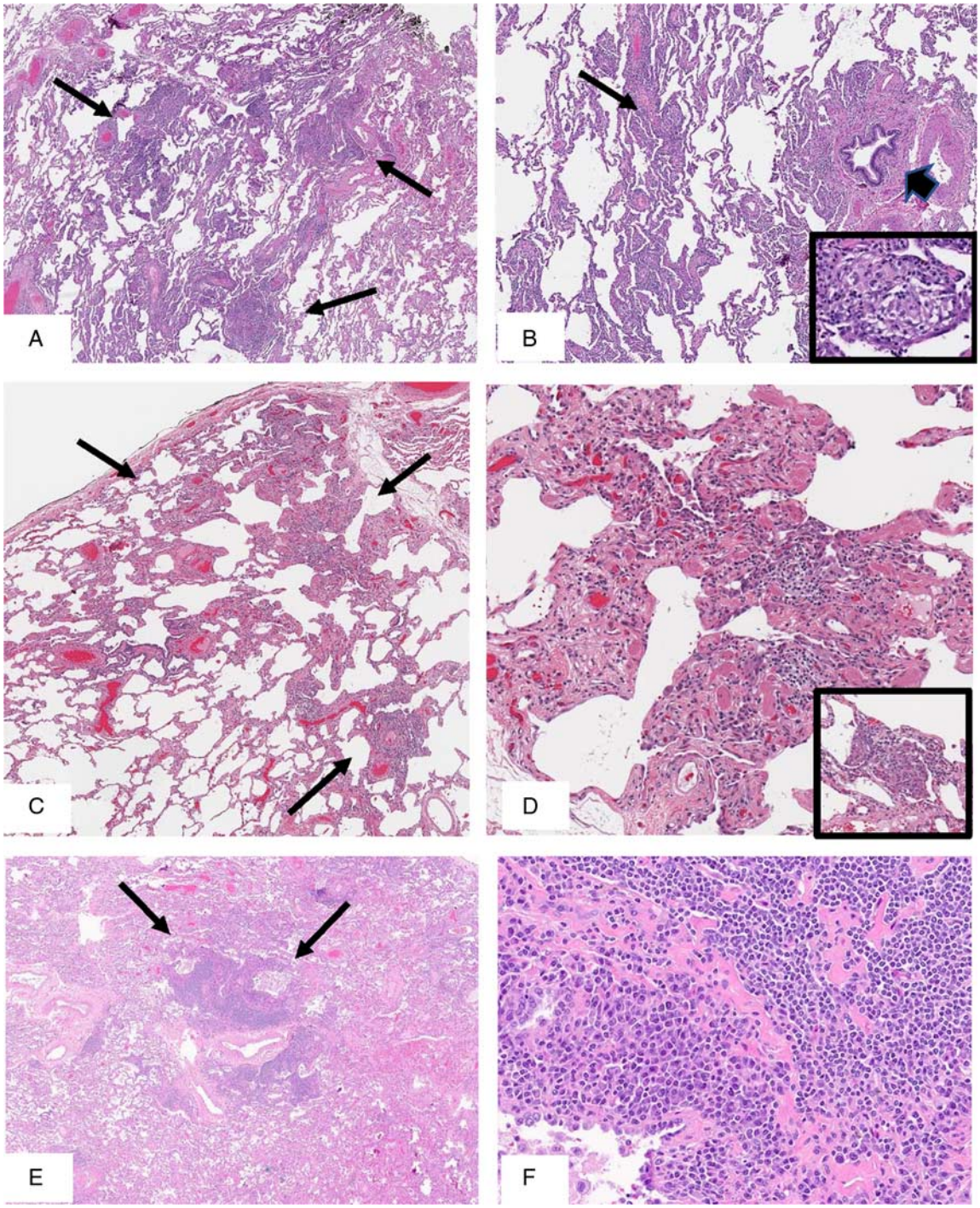

FIGURE 8. *Collagen vascular disease: scleroderma patient with CREST syndrome and esophageal dysmotility*. A, The bronchioles in this biopsy show a nodular thickening by a cellular chronic inflammatory infiltrate (arrows). B, Marked chronic inflammation surrounds this bronchiole (arrowhead). The surrounding alveolar walls are infiltrated by chronic inflammation with a poorly formed granuloma (arrow and inset). *Systemic lupus eythematosus*. C, Marked interstitial chronic inflammation surrounds these bronchioles, (arrows) forming a bronchiolocentric cellular interstitial pneumonia. D, Numerous lymphocytes and prominent plasma cells infiltrate this bronchiole. The inset shows a poorly formed granuloma. *Mixed CTD with overlap of systemic lupus erythematosus and rheumatoid arthritis*. E, Bronchiolocentric cellular chronic inflammation is present (arrows). F, The interstitium is markedly infiltrated by chronic inflammation consisting of lymphocytes with numerous plasma cells. CTD indicates connective tissue disease.

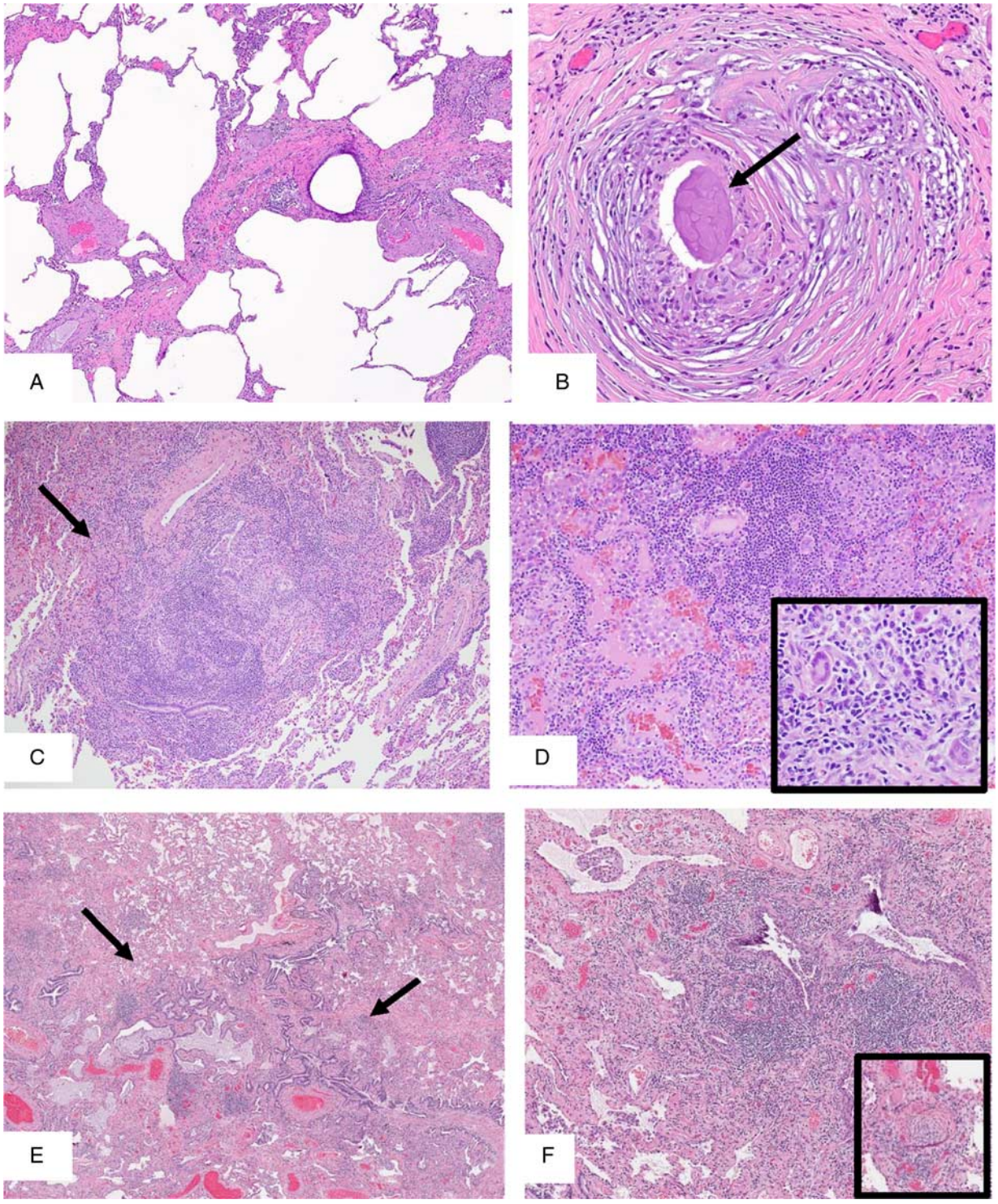

FIGURE 9. *Chronic aspiration*. A, Dense fibrosis and chronic inflammation surrounds this bronchiole. B, An aspirated vegetable particle (arrow) is associated with granulomatous inflammation. *Common variable immunodeficiency*. C, This biopsy shows bronchiolocentric cellular interstitial chronic inflammation (arrow) with lymphoid aggregates. D, A closer view shows marked chronic inflammation surrounding this bronchiole with a lymphoid aggregate. Within the inflammatory infiltrate there were a few poorly formed granulomas consisting of loose aggregates of multinucleated giant cells (inset). *Atypical mycobacterial infection*. E, This biopsy showed bronchiolocentric inflammation (arrows) and fibrosis. Cultures were positive for atypical mycobacterial infection. F, The peribronchiolar interstitium showed marked chronic inflammation. Focal small noncaseating granulomas were present (inset).

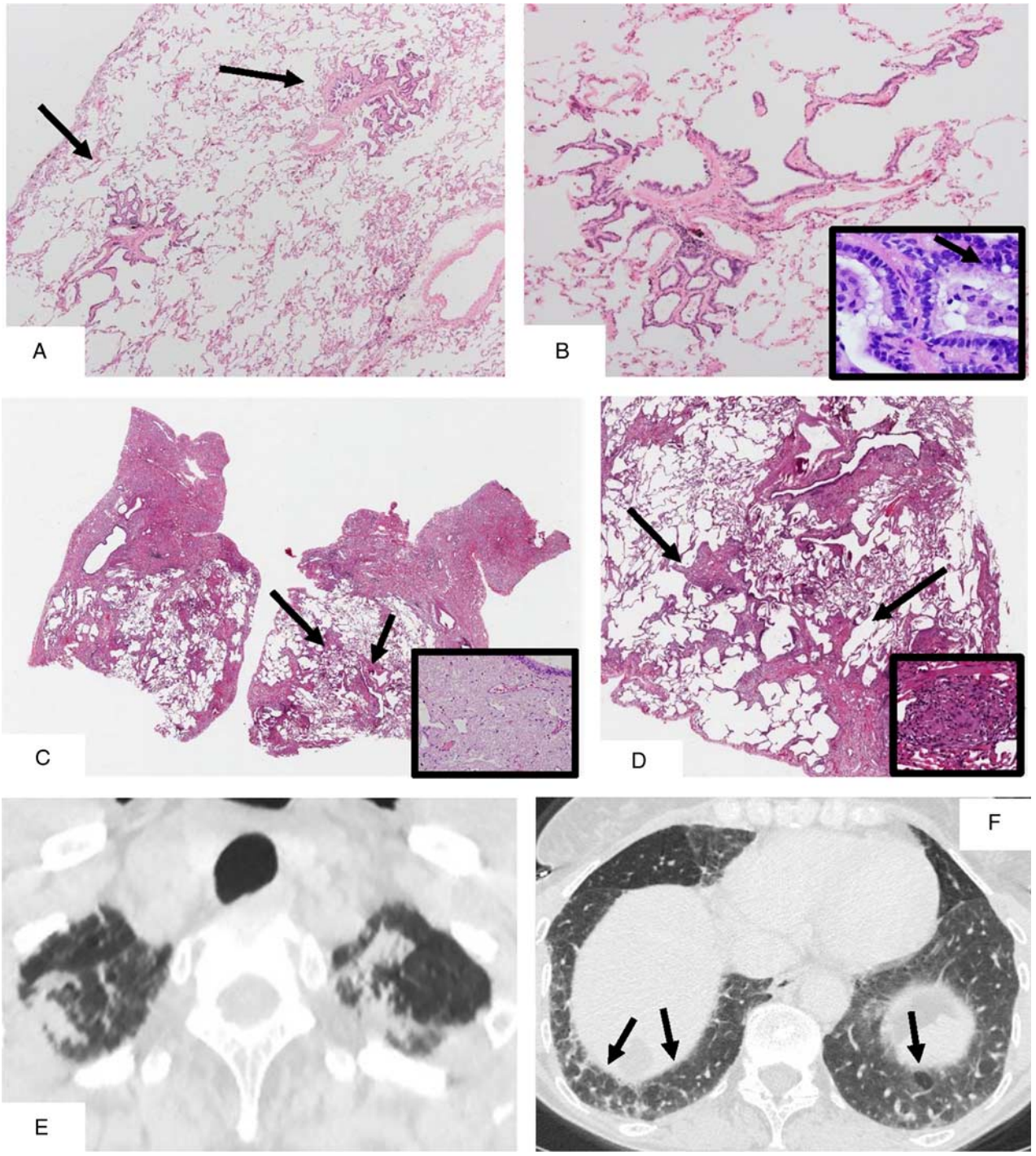

FIGURE 10. *Airway-centered fibrosis: peribronchiolar metaplasia ILD*. A, The primary finding in this biopsy is that of bronchiolar fibrosis consisting of multiple small nodules (arrows). B, Peribronchiolar metaplasia is made up of bronchiolar wall fibrotic thickening with extension of the fibrosis into the adjacent alveolar walls causing mild thickening. The surrounding alveolar parenchyma is relatively normal. The inset shows bronchiolar epithelium with ciliated (arrow) and nonciliated columnar and cuboidal epithelial cells. *Pleuroparenchymal fibroelastosis*. (PPFE) C, This upper lobe biopsy shows extensive subpleural fibroelastotic fibrosis extending into the underlying lung parenchyma. The underlying lung parenchyma shows a bronchiolocentric cellular and fibrosing process (arrows). High power of the fibroelastotic connective tissue shows numerous elastic fibers (inset). D, This intermediate magnification shows the bronchiolocentric cellular inflammation and fibrosis (arrows). Poorly formed granulomas were present on high power (inset). E, The HRCT of the upper lobes shows bilateral dense parenchymal opacities corresponding to the subpleural fibroelastotic scars of PPFE. F, This expiratory HRCT shows patchy ground-glass opacities with multilobular air trapping (arrows).

Airway-centered ILD such as peribronchiolar metaplasia ILD (Figs. 10A, B) show considerable overlap with HP and some cases in fact may represent examples of HP without granulomas.

CTD-ILD and HP may be histologically indistinguishable (Figs. 8A–F). Nevertheless, clues in favor of CTD-ILD are often present, and these include prominent lymphoid follicles with germinal centers (especially follicular bronchiolitis), as well as an inflammatory infiltrate that includes a much greater proportion of plasma cells than lymphocytes.[18,28]

Some cases of fibrotic HP lack distinguishing features and are histologically indistinguishable from IPF or idiopathic NSIP, and are ultimately diagnosed based on clinical and radiologic features (Figs. 6A–F). Nevertheless, the majority of cases of fibrotic HP do provide clues histologically. The presence of bronchiolocentricity (Figs. 4B, D), particularly if peribronchiolar metaplasia involves >50% of the small airways (Figs. 4E, F), and/or the presence of scattered non-necrotizing granulomas and/or giant cells (Figs. 4B, D insets) are good clues for fibrotic HP. Fibrotic HP with a pure UIP-pattern tends to have fewer fibroblast foci than IPF. ILD with features of HP can also occur in up to 10% of patients with pleuroparenchymal fibroelastosis (PPFE) characterized by fibroelastosis primarily in the subpleural region but also extending into the underlying lung parenchyma (Fig. 10C). It typically affects the upper lobes but can extend into the lower lobes. Biopsies show features of nonfibrotic HP or fibrotic HP (Fig. 10D) in addition to PPFE, and CT also shows characteristic findings of PPFE (Fig. 10E) and HP (Fig. 10F).

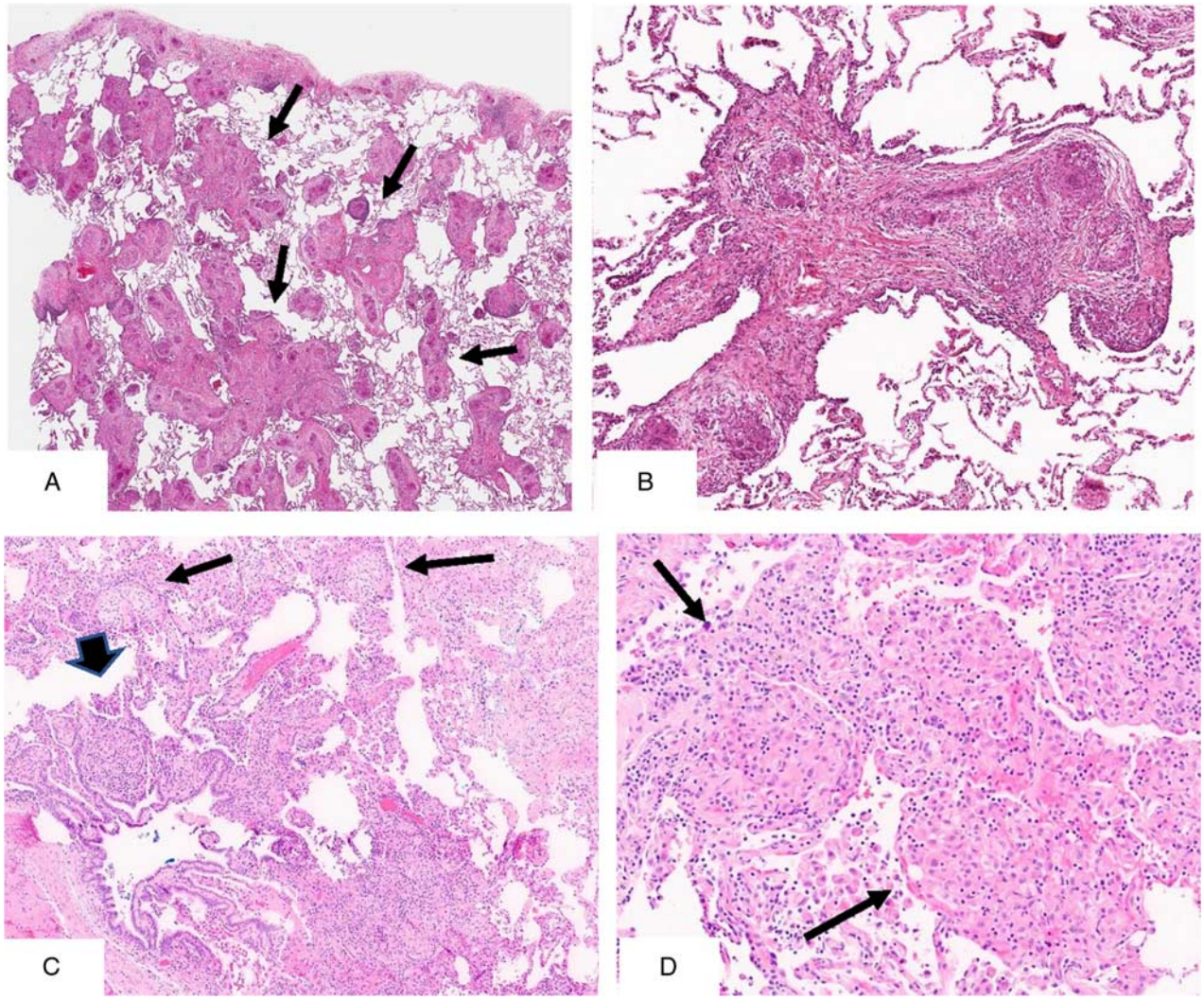

FIGURE 11. *Sarcoidosis*. A, Extensive noncaseating granulomas are distributed along lymphatic routes involving the pleura and bronchovascular bundles (arrows). B, Multinucleated giant cells and epithelioid histiocytes make up the well-formed granulomas many of which are surrounded by fibrosis. *Hot tub lung*. C, In the wall of this bronchiole (arrowhead) and surrounding air spaces (arrows) there are granulomas. Rounded collections of epithelioid histiocytes compose the granulomas. D, These rounded collections of epithelioid cells form noncaseating granulomas that are surrounded by a cuff of chronic inflammation. The granulomas are situated within the alveolar spaces (bottom arrow) as well as the alveolar wall interstitium (top arrow).

A large number of drugs may be associated with ILD and an appreciable portion of these may have associated granulomas that are scattered similar to those identified in HP. Distinguishing features between drug reactions with granulomas and HP have not been formally identified but bronchiolocentricity would likely favor HP and any history of administration of a drug that may be associated with ILD and granulomas would obviously be important.

Aspiration primarily presents as a bronchiolitis but peribronchiolar changes including peribronchiolar metaplasia are also encountered along with granulomas as in HP (Figs. 9A, B). Sparing of some lobules, foreign material (which may or may not be birefringent), and neutrophils as well as the mononuclear infiltrate all favor aspiration. Nevertheless, not all cases of aspiration pneumonia have these features, and knowing the history, risk factors, and radiologic features are helpful.

A number of other granulomatous conditions are in the differential diagnosis of HP including sarcoidosis (Figs. 11A, B), granulomatous infections, and hot tub lung (Figs. 11C, D). These conditions all tend to show more prominent granulomatous features including a greater number of granulomas, larger and better-formed granulomas, and coalescence of granulomas, or in the case of infections, necrosis. While sarcoid granulomas can also be found in bronchial walls and near bronchioles, they are more well-formed and tightly packed (Figs. 11A, B), often show characteristic concentric lamellar fibrosis (Fig. 11B), and typically lack the chronic inflammatory infiltrate seen in HP granulomas (Table 4). Hot tub lung is likely a special form of HP in which the granulomas are larger and more prominent relative to classic HP, and they tend to overshadow the inflammatory infiltrate (Figs. 11C, D). Hot tub lung cases occasionally will show acid-fast bacilli with special stains.

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