Multidisciplinary Approach to Hypersensitivity Pneumonitis

Brett M. Elicker, MD, Kirk D. Jones, MD,†*
Travis S. Henry, MD,‡ and Harold R. Collard, MD§

Abstract: Hypersensitivity pneumonitis (HP) may be a challenging diagnosis given the wide variability of its clinical, radiographic, and pathologic manifestations. A multidisciplinary approach to diagnosis is critical in maintaining a high specificity for HP. An in-depth knowledge of all 3 arms of the multidisciplinary approach helps clinicians, radiologists, and pathologists interpret their own findings in the context of the entire presentation. In some cases, the combination of clinical findings (ie, an identifiable exposure) and typical findings on high-resolution computed tomography is considered diagnostic of HP, and pathologic confirmation is not necessary. As many as 50% of patients do not have a clear exposure, however. These patients may be difficult to distinguish from idiopathic disorders. In these cases, high-resolution computed tomography and pathology are the primary data points that may suggest the correct diagnosis. The goal of this paper is to discuss recent advances in HP and to present the spectrum of clinical, radiographic, and pathologic findings.

Key Words: hypersensitivity pneumonitis, diffuse lung disease, interstitial lung disease, idiopathic pulmonary fibrosis

(*J Thorac Imaging* 2016;31:92–103)

Hypersensitivity pneumonitis (HP) represents a significant diagnostic challenge given the wide variability of its clinical, radiographic, and pathologic manifestations. It may closely resemble a variety of other diffuse lung diseases and may be indistinguishable from several of the idiopathic interstitial pneumonias.[1] HP is a common cause of diffuse lung disease, in some series accounting for a quarter or more of patients.[2] A multidisciplinary approach to diagnosis that integrates clinical history, high-resolution computed tomography (HRCT) findings, and pathologic features is critical in maximizing diagnostic accuracy given the wide variety of presentations and appearances. Clinicians, radiologists, and pathologists must not only have an in-depth knowledge of their own discipline, but also must understand the other arms of the multidisciplinary approach so they can interpret their findings in the context of all of the information available. The goal of this paper is to provide an update on recent advances in the diagnosis of HP and to discuss its varying clinical, radiographic, and pathologic features.

From the Departments of *Radiology and Biomedical Imaging; †Pathology; §Internal Medicine, University of California San Francisco, San Francisco, CA; and ‡Department of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, GA.

Conflicts of Interest and Source of Funding: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Correspondence to: Brett M. Elicker, MD, Department of Radiology and Biomedical Imaging, University of California San Francisco, 505 Parnassus Avenue, Box 0628, San Francisco, CA 94143 (e-mail: brett.elicker@ucsf.edu).

DOI: 10.1097/RTI.0000000000000186

CLINICAL

Classically, the clinical presentation of HP has been divided into 3 categories: acute, subacute, and chronic.[3] In reality, many patients present with clinical, radiographic, and pathologic findings that do not fit solely into only 1 of these categories. For instance, a patient may have dyspnea that is slowly progressive over years, with periodic subacute exacerbations. Moreover, there are no universally agreed-upon definitions for these terms. The distinction between acute, subacute, and chronic HP may be based upon the clinical time course, the presence of inflammation or fibrosis on imaging or pathology, or reversibility of changes after the administration of immunosuppressive medications. Alternative classification systems have been described. A recent analysis divided patients into 2 clusters, each with maximally differing clinical and radiographic features.[4]

(1) Cluster 1: recurrent systemic systems (chills and body aches), symptoms developing within 4 to 8 hours after exposure, less likely to have diffuse chest radiograph abnormalities.
(2) Cluster 2: clubbing, hypoxemia, restrictive pattern on pulmonary function tests, fibrosis on HRCT.

Although it would appear that Cluster 1 would correspond to the acute/subacute forms of HP and Cluster 2 would correspond to chronic forms of HP, these associations were not confirmed.

Despite the limitations of the traditional classification scheme of acute, subacute, and chronic HP, this system still provides a framework in which to understand the spectrum and diversity of clinical presentations. Acute HP, at one end of the spectrum, is seen several hours after an acute exposure to a large volume of antigen. This exposure induces a prominent inflammatory reaction that is thought to be predominantly antibody mediated. Patients present with a rapid onset of pronounced fever, chills, dyspnea, and cough. The classic example of acute HP is farmer's lung characterized by exposure to agricultural mold antigens, typically from hay. Acute HP is usually self-limited with symptoms resolving over a 24- to 48-hour period after removal of the exposure.

At the other end of the spectrum is chronic HP. This is characterized by the slow onset of cough and dyspnea, typically over years. Presumably the antigen exposure is less than that with acute HP, and the inflammatory reaction is milder and more insidious. As opposed to acute HP, the immune reaction in chronic HP is thought to be predominantly cell mediated. Given the insidious nature of the disease, chronic HP is often associated with fibrosis on HRCT and pathology. Subacute HP represents an intermediate presentation between the acute and chronic forms,

although it probably more closely resembles the acute form, albeit with less severe symptoms.

Acute Exacerbation of HP

There is growing evidence that acute exacerbations may occur in patients with HP, similar to those seen in patients with idiopathic pulmonary fibrosis (IPF). Criteria have been developed for exacerbations in IPF patients.[5] These same criteria have been adapted for HP patients and include:

(1) Acute worsening of symptoms over 30 days or less.
(2) New bilateral radiographic abnormalities.
(3) Absence of infection or other identifiable abnormality.

Most cases of exacerbation of chronic HP have been described in case reports; however a recent study that analyzed 100 patients with chronic HP over a 13-year period found that 14% of patients met criteria for acute exacerbation at some point.[6] The pathology in these patients showed diffuse alveolar damage and organizing pneumonia superimposed on preexisting lung fibrosis. The lung fibrosis in all cases resembled usual interstitial pneumonia (UIP), drawing parallels with IPF. Radiographic features include new ground-glass opacity (GGO) or consolidation superimposed on fibrosis (Fig. 1). As with IPF, acute exacerbation in chronic HP has a poor prognosis.

Antigen Identification

One vital component in the diagnosis of HP is the identification of an offending antigen. The most common offending antigens are those derived from bird and mold sources. Direct exposure to birds has the clearest risk; however, products derived from bird feathers, such as down pillows, also put patients at risk. Other potential exposures include nonfungal microorganisms (eg, bacteria), other animal-derived antigens (eg, rat urine), plant materials (eg, soybeans), a variety of chemicals (eg, toluene), and others. Hot tub lung, a form of HP related to exposure to atypical mycobacterial organisms that colonize warm, moist conditions, is another well-described form of HP and in one cohort comprised >20% of all HP cases.[7]

It is important to note that in as many as 50% of patients or more with pathologically proven HP, no antigen can be identified. Patients in whom an exposure cannot be identified tend to have a poorer prognosis. In a recent study by Fernández Pérez et al,[8] it was shown that patients without an identifiable exposure had a median mortality of 4.88 years compared with 8.75 years in those patients in whom an exposure was found. Chronic HP patients without an exposure are clinically difficult to distinguish from idiopathic diseases. This particular conundrum is often encountered in older patients with fibrotic lung disease and a suspicion for IPF. Given that clinical information may not be helpful in this distinction, radiology and pathology are critical in suggesting chronic HP as an alternative to IPF.

The incidence of HP shows significant variation depending upon geography and other factors. In certain clinical practices, HP may comprise a relatively high percentage of cases of diffuse lung disease, whereas in others it may be seen infrequently. As an example, HP is common in Japan, and nearly 75% of cases are due to seasonal mold, termed "summer-type" HP.[9] Occupations also have a significant impact on the likelihood of HP. In an older study, 21% of pigeon fanciers had evidence of HP.[10]

Familial HP

There are some data suggesting the presence of familial clustering of HP cases. Familial HP may occur because of a shared genetic susceptibility to an abnormal immune reaction to one or more antigens. In a study by Okamoto et al[11] 17.5% of cases of chronic HP had a family history of pulmonary fibrosis. All affected individuals within each family had all lived apart for several decades, suggesting that the clustering was more than just a common environment. There was also a tendency toward a younger age at presentation.

Serum Precipitating Antigens and Inhalational Challenge

The use of serum precipitating antigens in antigen identification is controversial. The goal of this test is to identify an occult causative antigen. The significance of a positive serum precipitating antigen in the absence of a clear exposure, however, is unclear. Some studies have shown a significant correlation between a positive precipitin test and the likelihood of a diagnosis of HP.[12] However, the

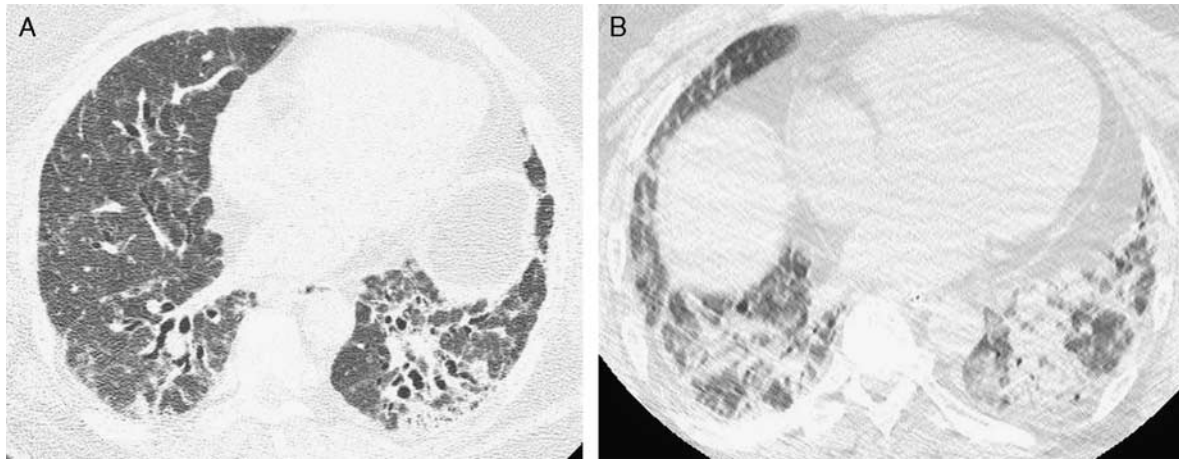

FIGURE 1. A and B, Acute exacerbation. Baseline HRCT (A) shows reticulation and traction bronchiectasis in a patient with chronic HP. After the development of acute symptoms (B), a repeat HRCT shows new extensive bilateral GGO and consolidation compatible with an acute exacerbation.

sensitivity and specificity of this test are poor. In one study, 31% of control patients had a positive precipitin test.[2] Although this test usually indicates an exposure to a specific antigen, it does not necessarily indicate that the antigen is causing clinically relevant disease.

Inhalation challenge has also been suggested as a method of antigen identification. This is performed by monitoring changes in pulmonary function test parameters after the administration of the inhaled antigen. The utility of this test is also controversial; however, a recent study by Muñoz et al[13] found a positive and negative predictive value of 94% and 47%, respectively. The authors suggested that a positive test is highly suggestive of the diagnosis, but a negative test cannot confidently exclude HP, particularly with antigens that were not of avian or fungal origin.

Pulmonary Function Tests

Pulmonary function tests are limited in their ability to distinguish HP from other diffuse lung diseases. A restrictive defect is most common, but an isolated obstructive defect also may be seen.[7] The main role of pulmonary function tests is in the detection and quantification of the severity of lung disease. In addition, pulmonary function tests are useful in quantifying serial changes over time after treatment for HP. These may be more sensitive in detecting a serial changes compared with HRCT.

PATHOLOGY

Bronchoalveolar Lavage (BAL)

BAL may be obtained in suspected HP to provide additional supportive evidence of the diagnosis. The characteristic result on BAL is a lymphocytosis. According to the American Thoracic Society (ATS) guidelines on the clinical utility of BAL analysis, a lymphocytosis of $>50\%$ is highly suggestive of HP.[14] Using a threshold of 50% essentially rules out IPF as a diagnosis, a common diagnostic consideration. Unfortunately, a significant lymphocytosis in chronic HP is much less common compared with subacute HP. In a study by Espoladore et al,[15] 40% of all cases of HP showed a lymphocytosis of $<25\%$, and patients with fibrosis on CT had a significantly lower lymphocyte count. Thus, when chronic HP is a consideration, BAL is much less likely to be clinically helpful. A decreased CD4/CD8 ratio (<1) has also previously been described as suggestive of HP; however, more recent investigations have questioned its accuracy.[16,17]

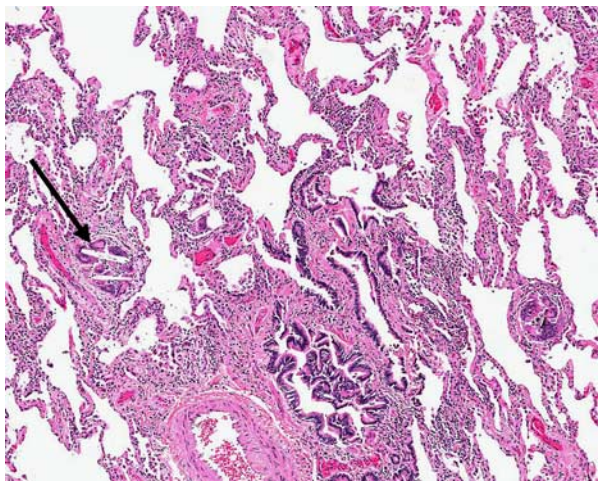

FIGURE 2. Surgical lung biopsy of subacute HP. Video-assisted thoracoscopic surgical lung biopsy sample shows diffuse alveolar septal thickening centered on bronchovascular bundles associated with several granulomas, many of which contain cholesterol clefts (arrow).

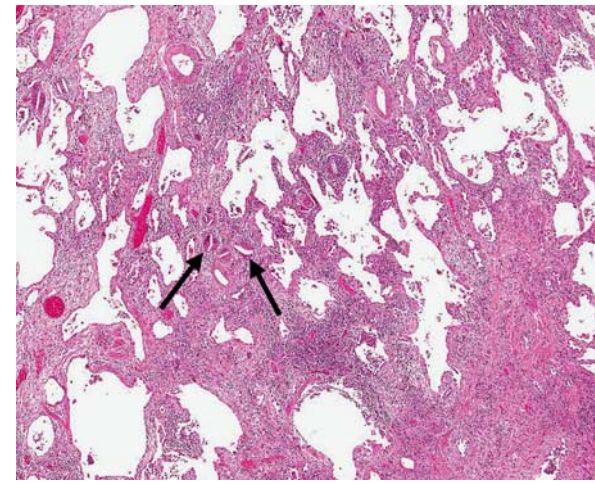

FIGURE 3. Surgical lung biopsy of chronic HP. Video-assisted thoracoscopic surgical lung biopsy sample shows significant peribronchiolar fibrosis, moderate chronic inflammation, and several poorly formed granulomas (arrows).

Bronchoscopic-guided Biopsy

Bronchoscopic-guided biopsies have been proposed as an alternative to video-assisted thoracoscopic lung biopsy in selected patients with diffuse lung disease. Several studies have investigated their use; however, there are little data available specifically in patients with suspected HP. For instance, in a retrospective analysis of 21 patients with UIP, transbronchial biopsy obtained adequate tissue for diagnosis in 32%.[18] In a large study of 603 patients with diffuse lung abnormalities, transbronchial biopsy was clinically helpful in 76%; however, none of these patients had a diagnosis of HP.[19]

Performing biopsies using cryoprobes has recently been investigated as an alternative to traditional bronchoscopic-guided biopsies given their ability to obtain larger amounts of tissue. In a randomized trial comparing conventional forceps biopsy with cryoprobes, the overall yield of diagnostic tissue was 34% versus 74%, respectively.[20] Nearly 8% of the cryoprobe cohort had tissue considered confirmatory of HP, compared with 0% in the forceps group. Although cryobiopsy is an exciting new technique, its utility in patients with suspected HP is unclear and probably should be reserved only for cases in which there is a high pretest probability of disease based upon clinical and HRCT data.

Surgical Lung Biopsy

In patients lacking diagnostic clinical and radiologic findings for HP, a surgical biopsy may be performed to establish a diagnosis. The histologic appearance of HP has been well characterized and consists of a chronic granulomatous interstitial pneumonitis (Fig. 2).[21–23] A generous surgical biopsy obtained from video-assisted thoracoscopic surgery is significantly more likely than a transbronchial

TABLE 1. Radiographic Manifestations of HP and Their Differential Diagnosis

	HRCT Finding	
Pattern	**Notes**	**Differential Diagnosis**
Ground glass opacity (GGO)	Nonspecific when seen in isolation, but often seen in association with other findings such as nodules, mosaic perfusion, or air trapping	*Acute symptoms:* Infection (eg, viral) Edema Diffuse alveolar damage Diffuse alveolar hemorrhage Acute eosinophilic pneumonia *Chronic symptoms:* Connective tissue disease (CTD) Idiopathic NSIP Smoking-related lung disease Drug toxicity IPF (rare to present with ground glass as the primary finding)
Centrilobular nodules	Usually diffuse and ground-glass density	Respiratory bronchiolitis Follicular bronchiolitis Viral infection Pneumoconioses (eg, siderosis) Vascular etiologies (eg, pulmonary hypertension)
Mosaic perfusion and/or air trapping	May be seen in isolation or associated with other findings such as GGO, nodules, or fibrosis	*When seen in isolation:* Constrictive bronchiolitis Asthma Vascular etiologies (eg, chronic thromboembolic disease)
Headcheese sign	Combination of significant GGO and mosaic perfusion or air trapping	Smoking-related lung disease Lymphoid interstitial pneumonia Viral infection Sarcoidosis
Organizing pneumonia (OP) pattern	Patchy, focal bilateral areas of subpleural and peribronchovascular consolidation; rare as the predominant manifestation of HP	*Other causes of organizing pneumonia:* Cryptogenic OP Drugs CTD Toxic inhalations Chronic eosinophilic pneumonia
Fibrosis	Classically NOT subpleural or basilar predominant; may be associated with nodules, GGO, mosaic perfusion, or air trapping	Sarcoidosis Drugs Pneumoconioses Atypical distribution of IPF
NSIP pattern	Peripheral, basilar GGO or fibrosis; subpleural sparing is quite suggestive of NSIP	CTD Drugs Idiopathic NSIP
UIP pattern	Peripheral, basilar fibrosis with honeycombing; rare manifestation of HP	IPF CTD Drug toxicity Asbestosis

biopsy to show all the features of this disease. The most consistent histologic feature is interstitial inflammation. The biopsy shows alveolar septal thickening by lymphocytes and plasma cells. This inflammation is often accentuated around bronchioles and is observed in nearly all cases. The granulomas in HP have been described as poorly formed. This is due to the fact that they often consist only of a few loosely aggregated histiocytes and multinucleate giant cells. These histiocytes may show cytoplasmic cholesterol clefts. Granulomas are observed in around 70% of

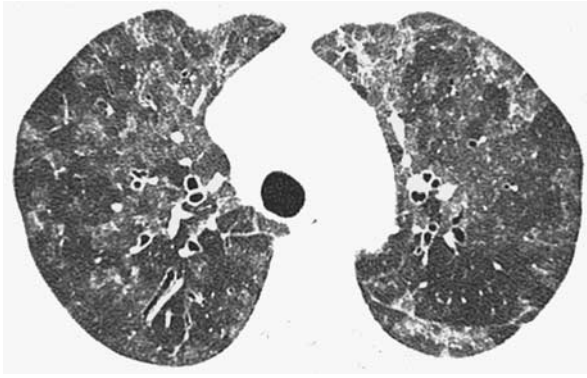

FIGURE 4. GGO. Nonspecific patchy bilateral GGO is present on this axial HRCT image in a patient with subacute HP. HP is the most common interstitial lung disease to show this finding.

cases. Other features include foci of organizing pneumonia characterized by polypoid plugs of granulation tissue within airspaces. This finding is almost always observed in conjunction with accumulation of macrophages with foamy cytoplasm within airspaces. When granulomas are not observed, the histologic appearance is identical to nonspecific interstitial pneumonia (NSIP)[24]; therefore, the histologic differential diagnosis of NSIP pattern includes HP. Fibrosis is variable in many subacute cases. In chronic disease, fibrosis becomes more prominent and may mimic UIP in its subpleural accentuation and basilar distribution. In these difficult cases, careful examination for peribronchiolar fibrosis and loosely formed granulomas can be helpful in distinguishing chronic HP from UIP (Fig. 3).[1,25,26]

RADIOLOGY

HRCT findings in HP vary widely depending on several factors including the degree of fibrosis or inflammation present and the predominant pathologic manifestations. Certain patterns are highly suggestive of HP, whereas others are nonspecific. In some cases, a combination of clinical information (eg, exposures) and HRCT findings may be diagnostic of HP, and pathologic confirmation is not necessary. In the absence of an exposure, pathology is usually considered necessary for confirmation of diagnosis. The main radiographic findings and patterns are summarized in Table 1 and listed in more detail below:

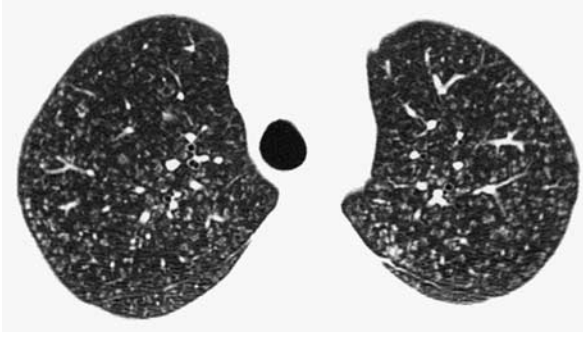

FIGURE 5. Centrilobular nodules. Diffuse ground-glass centrilobular nodules are seen on this axial HRCT image of a patient with subacute HP. Pathologically this corresponds to interstitial inflammation that is bronchiolocentric.

Ground Glass Opacity (GGO)

GGO may be seen in isolation (Fig. 4) or in association with other findings (see the headcheese sign and fibrosis). In isolation it is a nonspecific finding that represents changes below the resolution of HRCT; however, HP is one of the most common diffuse lung diseases to show GGO as the predominant abnormality. A recent study by Hewitt et al[27] showed that the most common chronic interstitial lung diseases to produce widespread GGO were HP (46% of cases), connective tissue disease (CTD) (27% of cases), and idiopathic NSIP (12% of cases). GGO is also a common finding in smoking-related lung disease (desquamative interstitial pneumonia and respiratory bronchiolitis).

Pathologically GGO in HP corresponds to interstitial inflammation or fibrosis, although inflammation is more common in the absence of HRCT signs of fibrosis. The bronchiolocentric distribution of findings in HP may not be evident on HRCT unless it is associated with centrilobular nodules (see below). Pathology is often necessary for confirmation of diagnosis to distinguish HP from other diffuse lung diseases characterized predominantly by GGO. Although isolated GGO is a nonspecific finding, it may motivate more aggressive immunosuppressive treatment given its closer association with inflammation as opposed to fibrosis. In a study by Tateishi et al,[28] all patients with GGO and/or centrilobular nodules showed improvement of radiographic findings after treatment.

Centrilobular Nodules

HP is one of the most common diffuse lung diseases to produce centrilobular nodules.[29] The nodules are typically ground glass in density and diffuse or symmetric in distribution (Fig. 5). This finding is characteristic of subacute HP but can also be seen in association with fibrosis with the chronic form. The centrilobular distribution on HRCT reflects the bronchiolocentric nature of the interstitial inflammation pathologically. Averaging of thickening of the interstitium with air in the alveolar spaces produces nodules that are intermediate in density between normal lung and soft tissue attenuation. Other patterns or diseases that may produce diffuse centrilobular ground-glass nodules include: respiratory bronchiolitis, follicular bronchiolitis, acute viral infection, and occasionally pneumoconioses such as siderosis. This finding may also be seen in association with pulmonary hypertension and other vascular diseases.

Mosaic Perfusion, Air Trapping, and Cysts

Geographic areas of decreased lung density on inspiratory CT (mosaic perfusion or mosaic attenuation) may reflect airways obstruction and reflex vasoconstriction. This is a common finding seen in both subacute and chronic HP. In one study, 86% of patients with HP had mosaic perfusion on HRCT.[30] These lucent lung regions are typically lobular, reflecting the bronchiolocentric nature of the disease. On expiratory CT, air trapping should be seen in the same regions. Mosaic perfusion and air trapping may be seen in isolation (Fig. 6) or in combination with other findings (eg, GGO, nodules, fibrosis). Other airways diseases that produce isolated mosaic perfusion or air trapping include asthma and bronchiolitis obliterans.

Cysts are another finding that may be seen in HP and may relate to small airways obstruction as hypothesized in cystic lung diseases such as lymphangioleiomyomatosis. Franquet et al[31] found cysts in 13% of patients with the

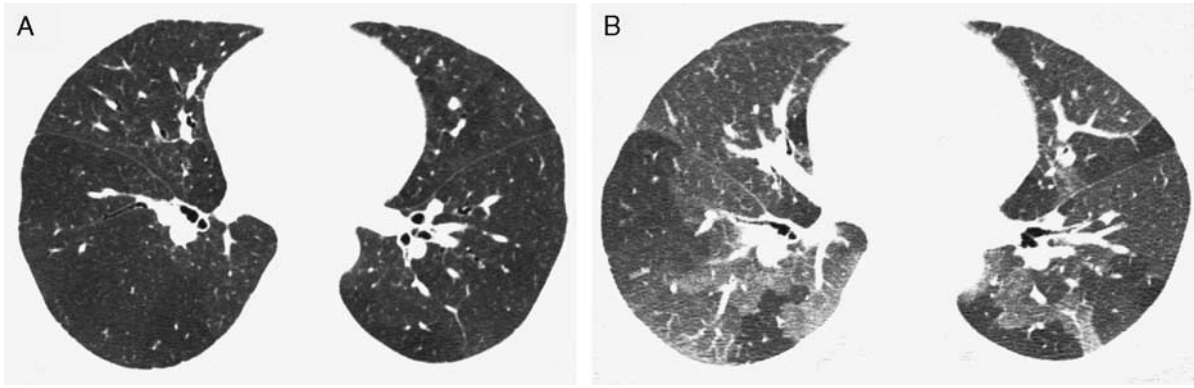

FIGURE 6. A and B, Air trapping in HP. Inspiratory HRCT (A) shows slight heterogeneity of lung attenuation, but is otherwise normal. Dynamic expiratory HRCT (B) shows bilateral air trapping, a finding that may be seen in isolation or associated with other findings such as GGO.

subacute form of HP. The cysts were few in number, averaging only 4 per patient (range, 1 to 15).

The Headcheese Sign

A combination of GGO and mosaic perfusion or air trapping on HRCT may resemble the deli meat headcheese (Fig. 7). This meat is created by taking small bits of the head of a calf or pig, placing them in a gelatinous mold, and slicing the mold into pieces. This resembles the HRCT appearance of geographic areas of varying lung density.

Three densities of lung must be seen on HRCT, all in significant amounts, to confidently describe the headcheese sign:

(1) Lung that is too opaque (GGO).
(2) Lung that is too lucent (mosaic perfusion or air trapping).
(3) Normal lung.

This sign reflects a process with both infiltrative and obstructive components.[32] In HP, the infiltrative component is due to interstitial inflammation, and the obstructive component is due to small airway obstruction. HP is the most common disease to produce this pattern. Rarely, the headcheese sign may be seen with other diseases including respiratory bronchiolitis, follicular bronchiolitis, acute viral infection, and sarcoidosis.

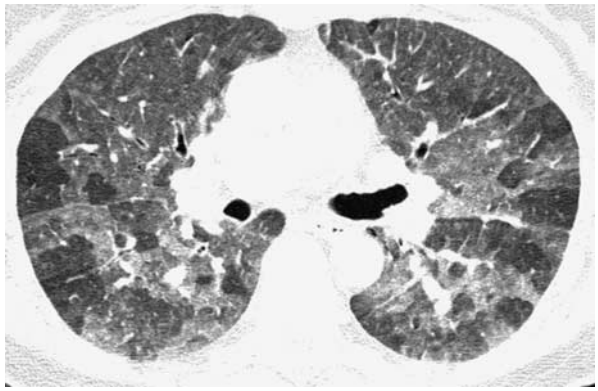

FIGURE 7. The headcheese sign. Geographic areas of GGO, mosaic perfusion, and relatively normal lung resembling the deli meat headcheese are present on this axial HRCT image. This finding is most commonly seen in patients with HP.

Organizing Pneumonia Pattern

Organizing pneumonia is a characteristic pathologic feature of HP; however, it is not usually the major abnormality on HRCT. Patients with HP may have small focal areas of consolidation on imaging that pathologically correspond to areas of organizing pneumonia; however, other findings usually predominate. Rarely, HP may closely mimic cryptogenic organizing pneumonia. In these cases, the HRCT will show patchy, bilateral, peripheral, and peribronchovascular areas of consolidation (Fig. 8).

Fibrosis

Fibrosis is the HRCT finding most commonly associated with chronic HP. The presence and severity of fibrosis on imaging correlates with a worse prognosis.[33] In at least one study, the severity of traction bronchiectasis and honeycombing on HRCT was more predictive of mortality compared with pulmonary function tests.[34] Typical signs of fibrosis are irregular reticulation and traction bronchiectasis. Honeycombing may be seen in $>50\%$ of patients with chronic HP.[35] These findings closely correlate with the presence of fibrosis pathologically.[36]

The distribution of fibrosis in chronic HP is also important, particularly in distinguishing it from IPF and other interstitial pneumonias (Fig. 9). Classically, HP spares the lung bases in the craniocaudal plane, and a mid-upper-lung predominance may be a clue to the diagnosis. However, it is important to note that a lower-lobe predominance can be seen in a minority of cases of chronic HP, and in such cases the distinction of HP from other interstitial pneumonias is difficult. Silva et al[35] reported that 31% of cases of chronic HP had a lower-lung predominance, which was much less than UIP and NSIP (83% and 94%, respectively) but still represents a significant number of cases. Fibrosis may be associated with mosaic perfusion and/or air trapping, a combination that is quite suggestive of HP (Fig. 10). In addition, fibrosis may be associated with GGO or centrilobular nodules. Rarely, chronic HP may have HRCT features that are indistinguishable from IPF.

NSIP Pattern

Occasionally, HP will show pathologic or radiographic findings that are indistinguishable from NSIP[1] due to CTD, drugs, and idiopathic NSIP (Fig. 11). These findings include subpleural and basilar-predominant GGO and/or fibrosis. Subpleural sparing is particularly suggestive of NSIP.[35] In the absence of a known CTD or drug exposure, many patients with NSIP will undergo lung biopsy. Pathology in these cases may

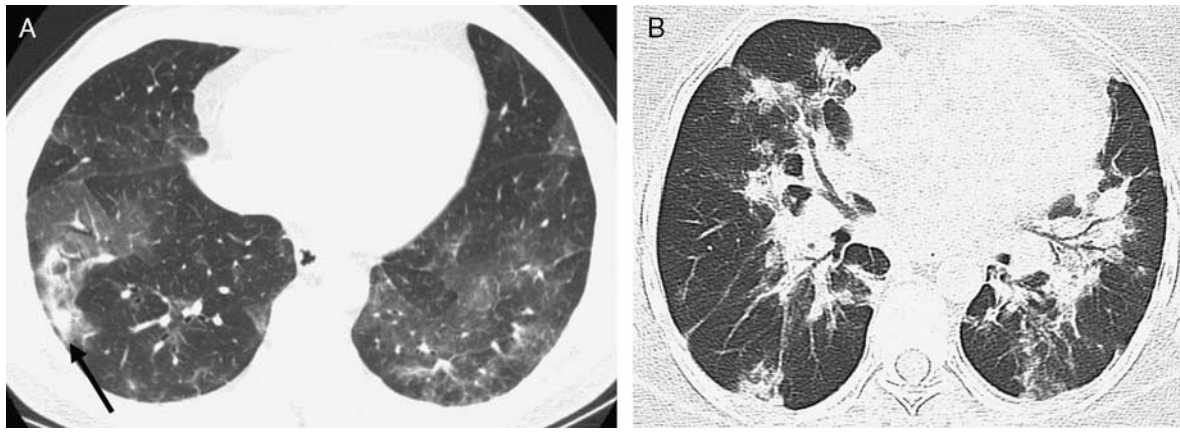

FIGURE 8. A and B, Organizing pneumonia pattern. Axial HRCT (A) demonstrates patchy bilateral GGO and small regions of consolidation (arrow). Pathologically the ground glass corresponded to interstitial inflammation and the consolidation to areas of organizing pneumonia. Rarely HP may closely mimic cryptogenic organizing pneumonia (B) in which case the consolidation is the predominant feature.

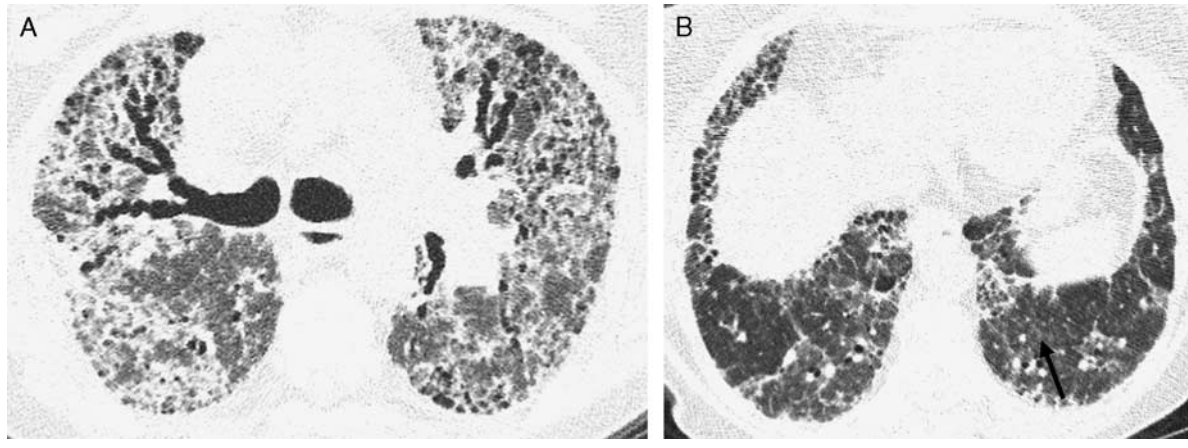

FIGURE 9. A and B, Distribution of fibrosis in HP. HRCT in a patient with chronic HP shows honeycombing, reticulation, and traction bronchiectasis. Note the lack of a subpleural distribution of findings (A). Also, the fibrosis shows relative sparing of the lung bases and is associated with ground-glass centrilobular nodules (arrow) and mosaic perfusion (B).

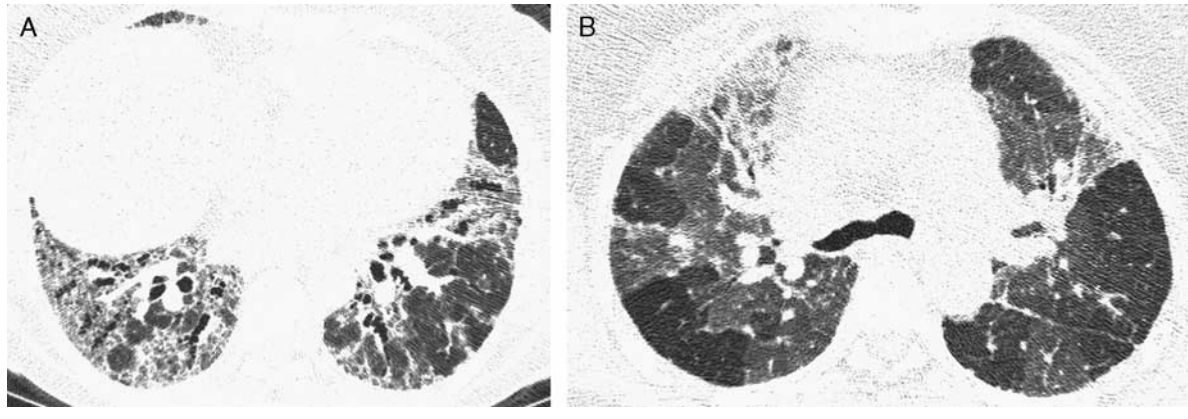

FIGURE 10. A and B, Combination of fibrosis and air trapping in HP. A basilar distribution of irregular reticulation and traction bronchiectasis is present on this axial HRCT image (A). Expiratory HRCT through the upper lobes shows significant air trapping (B). The combination of fibrosis and air trapping is suggestive of HP.

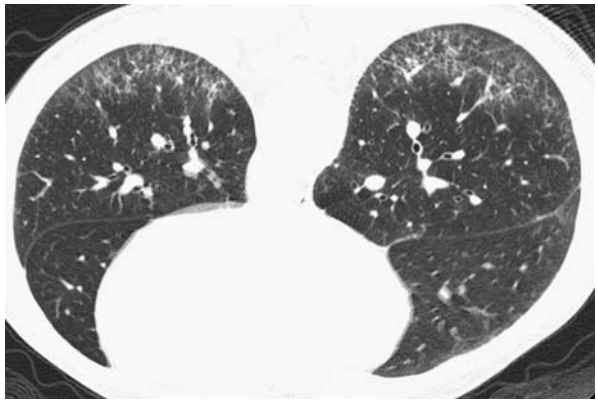

FIGURE 11. NSIP pattern in HP. Prone HRCT demonstrates a basilar predominance of irregular reticulation and GGO. The findings have a peripheral predominance, but show sparing of the immediate subpleural lung. Occasionally, HP shows findings characteristic of NSIP.

reveal characteristic findings of HP that are below the resolution of CT. Of note, patients with chronic HP presenting with an NSIP pattern have a significantly poorer prognosis compared with idiopathic NSIP or NSIP related to CTD.[37]

UIP Pattern

In rare cases, HP may show a "definite UIP pattern" on HRCT as classified by Raghu et al[38] (Fig. 12). The features of this pattern include:

(1) Honeycombing.
(2) Irregular reticulation.
(3) Subpleural and basilar distribution.
(4) Absence of features inconsistent with UIP.

A close inspection of the HRCT should be undertaken to search for subtle radiographic clues to the diagnosis of HP such as centrilobular ground-glass nodules, mosaic perfusion, air trapping, or more central disease than would be expected for UIP. When these are lacking, HP without an identifiable exposure may be indistinguishable from IPF.

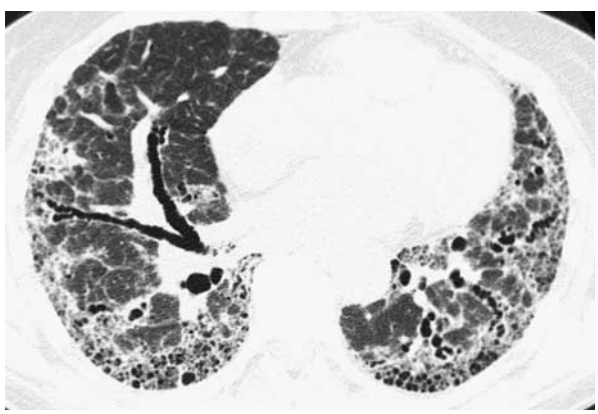

FIGURE 12. UIP pattern in HP. Axial HRCT image through the lung bases shows honeycombing, reticulation, and traction bronchiectasis with a subpleural predominance. This would be considered "definite UIP" and is indistinguishable from IPF.

DIFFERENTIAL DIAGNOSIS AND THE MULTIDISCIPLINARY APPROACH

Multiple diseases may mimic HP from a clinical, radiographic, or pathologic perspective (Fig. 13). The multidisciplinary approach is most effective when information from all three arms is combined in an integrated and interactive manner. Although HP can closely resemble other diseases, usually at least one arm of the multidisciplinary approach will have features suggestive of the correct diagnosis. The most common diseases to resemble HP radiographically are listed in Table 2 and discussed below with an emphasis on distinguishing features.

IPF

Chronic HP and IPF are both common diagnoses in patients with lung fibrosis over the age of 50. As discussed previously, as many as 50% of patients with HP will have no identifiable exposure. When no exposure history is present, HRCT and pathologic findings are the primary data points that make the distinction between these two diseases. A "definite UIP pattern" on HRCT, as defined by the ATS/ERS/JRS/ALAT criteria, is considered diagnostic of IPF assuming there is no clinical information to suggest an alternative.[38] The majority of patients with chronic HP, in distinction, will show HRCT findings considered "inconsistent with UIP" including a mid-upper-lung distribution, a central-lung predominance in the axial plane, centrilobular ground-glass nodules, or the presence of significant mosaic perfusion or air trapping. This later finding must be present bilaterally and in at least 3 lobes to be considered significant. According to the study by Silva et al[35] the primary features helpful in distinguishing HP from UIP were: lobular areas of decreased attenuation, centrilobular nodules, cysts, and lack of basilar distribution of findings.

Pathology is usually obtained in patients with an HRCT that is considered "inconsistent with UIP" in order to obtain a definite diagnosis. Histologic features that have been shown to aid in differentiation of chronic HP from IPF include bronchiolocentric fibrosis and poorly formed granuloma.[1,25,26] Of note, pathology limited by inadequate sampling may be indistinguishable from IPF.

In one study, 43% of patients diagnosed with IPF could be reclassified as HP upon expert review and clinical follow-up.[39] In terms of prognosis, this distinction may not be important, as IPF and HP presenting with a UIP pattern have a similar mortality.[40]

Smoking-related Lung Disease

Both respiratory bronchiolitis and desquamative interstitial pneumonia show significant radiographic overlap with HP, primarily subacute HP. Overlapping findings include patchy bilateral GGO, centrilobular ground-glass nodules, and/or mosaic perfusion or air trapping.[41] In cases of desquamative interstitial pneumonia, extensive cystic lucencies may be present associated with areas of ground glass. These cystic lucencies resemble emphysema and may be more numerous than seen in HP. Clearly, history is critical in making this distinction. It has recently been suggested that a combination of an appropriate exposure to cigarette smoke, typical HRCT findings, and a lack of lymphocytosis on BAL is adequate to make a confident diagnosis of smoking-related lung disease.[42]

Conversely, typical HRCT findings in combination with an identifiable exposure are highly suggestive of HP, particularly when a lymphocytosis is present on BAL. In

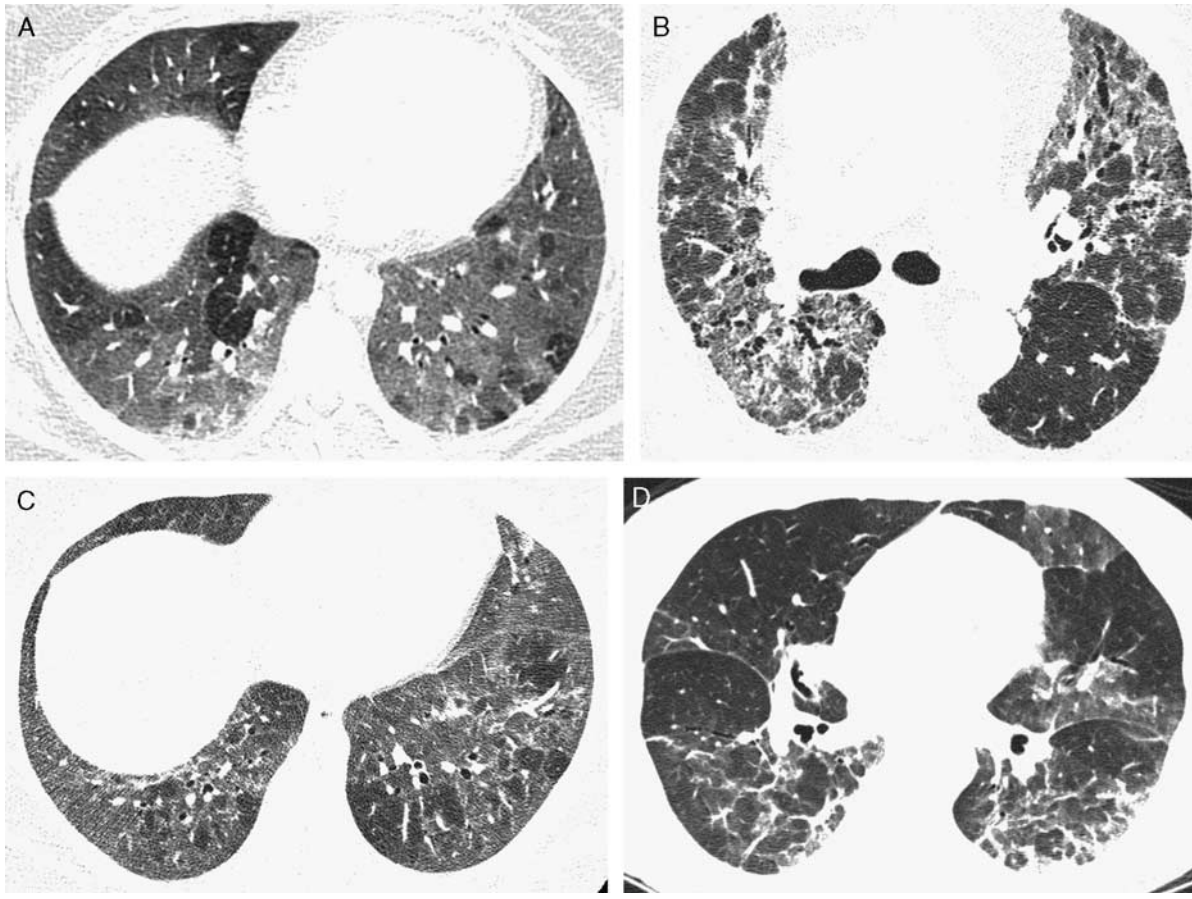

FIGURE 13. Mimics of HP. Axial CT through the lung bases in a patient with desquamative interstitial pneumonia due to smoking (A) demonstrates a combination of GGO and mosaic perfusion, the headcheese sign. Reticulation and traction bronchiectasis without a subpleural predominance is seen on this axial HRCT image (B) in a patient with sarcoidosis. Axial CT through the lung bases (C) shows patchy, bilateral GGO and lobular areas of sparing that corresponded to air trapping on expiratory images (not shown) in a patient with dermatomyositis-related NSIP. Axial CT in a patient with an HP-like drug reaction due to infliximab (D) shows patchy bilateral GGO and irregular reticulation.

addition, it has been suggested that cigarette smoke is protective against the development of HP. In one of the largest cohorts of HP patients studied only 6% of patients were smokers, compared with 20% in other diffuse lung diseases.[2] Histologic clues suggesting smoking-related lung disease include accumulation of lightly pigmented "smoker's" macrophages, airspace enlargement with fibrosis, and diffuse hyaline-like acellular fibrotic thickening of alveolar septa.[43]

CTD

One unifying feature that CTD and HP share is a great variability in their HRCT and pathologic findings. CTD is associated with multiple different patterns of injury,[44] many of which overlap with those of HP. Also, patients with CTD may demonstrate the coexistence of more than one pattern in the same patient, adding to the diagnostic uncertainty. The most common patterns seen in CTD that overlap with HP include:

(1) Follicular bronchiolitis: GGO, centrilobular ground-glass nodules, and/or mosaic perfusion or air trapping.
(2) Bronchiolitis obliterans: mosaic perfusion and/or air trapping.
(3) Organizing pneumonia: patchy bilateral subpleural and peribronchovascular consolidation.
(4) NSIP: subpleural and basilar-predominant GGO and/or fibrosis with subpleural sparing.
(5) UIP: subpleural and basilar-predominant irregular reticulation and honeycombing.

The diagnosis of CTD is made by a combination of typical clinical findings and serologies; however, there has been an increased recognition of patients with interstitial lung disease and features suggestive but not diagnostic of CTD. This has been named interstitial pneumonia with autoimmune features. Thus, in some cases the clinical history may not be able to differentiate CTD and HP when no exposure is evident.

Screening serologies are often obtained in many of these patients and may be helpful in identifying those with diffuse lung disease due to CTD. Radiographically, NSIP is more commonly due to CTD compared with HP. Evidence of serositis is common with CTD but rare with HP. Lung biopsy may be required when there is a lack of clinical clues and when serologies are negative. Histologic clues for CTD include prominent lymphoid aggregates with germinal center formation, chronic pleuritis, and pulmonary artery myointimal thickening out of proportion to the surrounding fibrosis.[45]

TABLE 2. Common Diseases That May Resemble HP on HRCT and Their Distinguishing Clinical, Radiographic, and Pathologic Features

Disease	HRCT Features That Overlap With HP	Features That Suggest This Diagnosis (ie, It Is Not HP)
IPF	Irregular reticulation Traction bronchiectasis Honeycombing	*Clinical*: lack of an exposure (although exposure only present in 50% of HP patients) *Imaging*: subpleural and basilar distribution; lack of centrilobular nodules, mosaic perfusion, and air trapping *Pathology*: lack of bronchiolocentric fibrosis and poorly formed granulomas
Smoking-related lung disease	Centrilobular nodules GGO Mosaic perfusion or air trapping	*Clinical*: history of cigarette smoke *Imaging*: may be indistinguishable, cystic lucencies resembling emphysema in desquamative interstitial pneumonia *Pathology*: smoker's macrophages, airspace enlargement with fibrosis, and diffuse hyaline-like acellular fibrotic thickening of alveolar septa
CTD	Centrilobular nodules GGO Mosaic perfusion or air trapping Organizing pneumonia pattern NSIP pattern UIP pattern	*Clinical*: joint symptoms, muscle weakness, esophageal dysmotility, positive serologies, etc. *Imaging*: CTD is a more common cause of NSIP on HRCT than HP, serositis *Pathology*: prominent lymphoid aggregates with germinal center formation, chronic pleuritis, and pulmonary artery myointimal thickening out of proportion to the surrounding fibrosis
Sarcoidosis	GGO Mosaic perfusion or air trapping Fibrosis that is NOT subpleural and basilar predominant	*Clinical*: other systemic manifestations of sarcoidosis such as eye and skin findings *Imaging*: perilymphatic nodules, strong peribronchovascular distribution of fibrosis *Pathology*: well-formed rounded coalescing granulomas in a lymphatic distribution
Drugs and pneumoconioses (eg, hard metal)	GGO Mosaic perfusion or air trapping Fibrosis that is NOT subpleural and basilar predominance	*Clinical*: exposure to drug or dust *Imaging*: often indistinguishable *Pathology*: whereas drug toxicity may have pathologic features identical to HP, hard metal pneumoconiosis has characteristic features

Sarcoidosis

Similar to IPF, clinical history may not be able to distinguish between sarcoidosis and HP without an exposure, although patients with sarcoidosis may have other systemic findings such as those involving the eye and skin. Although many cases of sarcoidosis have characteristic HRCT findings, there is some overlap between these two diseases. Sarcoidosis rarely may show GGO as the predominant finding on HRCT. Mosaic perfusion and air trapping are relatively common findings seen in both diseases. The headcheese sign has been described in patients with sarcoidosis. In a recent analysis of patients with both interstitial lung disease and moderate to severe air trapping, 29% of patients had sarcoidosis, and 10% had HP.[46] Both sarcoidosis and HP may show fibrosis that spares the lung bases and involves the central lung. The main distinguishing radiographic features that specifically suggest sarcoidosis as opposed to HP are a perilymphatic distribution of nodules and a strongly peribronchovascular distribution of fibrosis.

The histologic findings in sarcoidosis correlate with the radiologic findings and show well-formed rounded coalescing granulomas composed of epithelioid histiocytes with tight, almost undetectable cell borders. This is in distinction to the poorly formed granulomas of HP. These granulomas course along lymphatic routes and are observed in bronchovascular bundles, subpleurally, and along interlobular septa. In cases of fibrotic sarcoidosis where granulomas are sparse, differentiation from chronic HP can be difficult. HP often shows more prominent interstitial inflammation and organizing pneumonia, but there can be significant overlap, often necessitating keeping both diseases in the differential diagnosis.

Drug Toxicity and Other Exposures

Similar to CTD, drugs may induce a myriad of different patterns of lung injury and findings on HRCT.[47] In fact, drug toxicity may present with imaging and pathologic findings identical to subacute or chronic HP. Some of the common drugs to present with an HP pattern include chemotherapeutic drugs (eg, bleomycin), methotrexate, and nitrofurantoin.

Rarely pneumoconioses may also closely mimic HP. The findings of hard metal pneumoconiosis, for example, are very similar to those of HP and include GGO, fibrosis, and air trapping.[48] A clear exposure history is usually present in pneumoconioses.

CONCLUSIONS

HP has a myriad of clinical presentations, HRCT findings, and pathologic features. The most challenging cases are those in patients without a clear exposure in which case HP is easily confused with idiopathic disorders such as IPF. In these cases, an in-depth knowledge of the imaging and pathologic findings is vital in making an appropriate diagnosis.

REFERENCES

1. Ohtani Y, Saiki S, Kitaichi M, et al. Chronic bird fancier's lung: histopathological and clinical correlation. An application of the 2002 ATS/ERS consensus classification of the idiopathic interstitial pneumonias. *Thorax*. 2005;60:665–671.

2. Lacasse Y, Selman M, Costabel U, et al. Clinical diagnosis of hypersensitivity pneumonitis. *Am J Respir Crit Care Med*. 2003;168:952–958.
3. Richerson HB, Bernstein IL, Fink JN, et al. Guidelines for the clinical evaluation of hypersensitivity pneumonitis. Report of the Subcommittee on Hypersensitivity Pneumonitis. *J Allergy Clin Immunol*. 1989;84:839–844.
4. Lacasse Y, Selman M, Costabel U, et al. Classification of hypersensitivity pneumonitis: a hypothesis. *Int Arch Allergy Immunol*. 2009;149:161–166.
5. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2007;176:636–643.
6. Miyazaki Y, Tateishi T, Akashi T, et al. Clinical predictors and histologic appearance of acute exacerbations in chronic hypersensitivity pneumonitis. *Chest*. 2008;134:1265–1270.
7. Hanak V, Golbin JM, Ryu JH. Causes and presenting features in 85 consecutive patients with hypersensitivity pneumonitis. *Mayo Clin Proc*. 2007;82:812–816.
8. Fernández Pérez ER, Swigris JJ, Forssen AV, et al. Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. *Chest*. 2013;144:1644–1651.
9. Ando M, Arima K, Yoneda R, et al. Japanese summer-type hypersensitivity pneumonitis. Geographic distribution, home environment, and clinical characteristics of 621 cases. *Am Rev Respir Dis*. 1991;144:765–769.
10. Christensen LT, Schmidt CD, Robbins L. Pigeon breeders' disease—a prevalence study and review. *Clin Allergy*. 1975;5: 417–430.
11. Okamoto T, Miyazaki Y, Tomita M, et al. A familial history of pulmonary fibrosis in patients with chronic hypersensitivity pneumonitis. *Respiration*. 2013;85:384–390.
12. Fenoglio C-M, Reboux G, Sudre B, et al. Diagnostic value of serum precipitins to mould antigens in active hypersensitivity pneumonitis. *Eur Respir J*. 2007;29:706–712.
13. Muñoz X, Sánchez-Ortiz M, Torres F, et al. Diagnostic yield of specific inhalation challenge in hypersensitivity pneumonitis. *Eur Respir J*. 2014;44:1658–1665.
14. Meyer KC, Raghu G, Baughman RP, et al. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med*. 2012;185: 1004–1014.
15. Espoladore LMW, Gregório BB, Lima MS, et al. Cytological analysis of bronchoalveolar lavage in patients with interstitial lung diseases and the relation of cytological analysis to fibrosis in high-resolution computed tomography. *Anal Quant Cytopathol Histpathol*. 2014;36:206–212.
16. Barrera L, Mendoza F, Zuñiga J, et al. Functional diversity of T-cell subpopulations in subacute and chronic hypersensitivity pneumonitis. *Am J Respir Crit Care Med*. 2008;177: 44–55.
17. Caillaud DM, Vergnon JM, Madroszyk A, et al. Bronchoalveolar lavage in hypersensitivity pneumonitis: a series of 139 patients. *Inflamm Allergy Drug Targets*. 2012;11:15–19.
18. Berbescu EA, Katzenstein A-LA, Snow JL, et al. Transbronchial biopsy in usual interstitial pneumonia. *Chest*. 2006; 129:1126–1131.
19. Ensminger SA, Prakash UBS. Is bronchoscopic lung biopsy helpful in the management of patients with diffuse lung disease? *Eur Respir J*. 2006;28:1081–1084.
20. Pajares V, Puzo C, Castillo D, et al. Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: a randomized trial. *Respirology*. 2014;19:900–906.
21. Kawanami O, Basset F, Barrios R, et al. Hypersensitivity pneumonitis in man. Light- and electron-microscopic studies of 18 lung biopsies. *Am J Pathol*. 1983;110:275–289.
22. Reyes CN, Wenzel FJ, Lawton BR, et al. The pulmonary pathology of farmer's lung disease. *Chest*. 1982;81:142–146.
23. Coleman A, Colby TV. Histologic diagnosis of extrinsic allergic alveolitis. *Am J Surg Pathol*. 1988;12:514–518.
24. Vourlekis JS, Schwarz MI, Cool CD, et al. Nonspecific interstitial pneumonitis as the sole histologic expression of hypersensitivity pneumonitis. *Am J Med*. 2002;112:490–493.
25. Takemura T, Akashi T, Kamiya H, et al. Pathological differentiation of chronic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis/usual interstitial pneumonia. *Histopathology*. 2012;61:1026–1035.
26. Trahan S, Hanak V, Ryu JH, et al. Role of surgical lung biopsy in separating chronic hypersensitivity pneumonia from usual interstitial pneumonia/idiopathic pulmonary fibrosis: analysis of 31 biopsies from 15 patients. *Chest*. 2008;134:126–132.
27. Hewitt MG, Miller WT, Reilly TJ, et al. The relative frequencies of causes of widespread ground-glass opacity: a retrospective cohort. *Eur J Radiol*. 2014;83:1970–1976.
28. Tateishi T, Ohtani Y, Takemura T, et al. Serial high-resolution computed tomography findings of acute and chronic hypersensitivity pneumonitis induced by avian antigen. *J Comput Assist Tomogr*. 2011;35:272–279.
29. Okada F, Ando Y, Yoshitake S, et al. Clinical/pathologic correlations in 553 patients with primary centrilobular findings on high-resolution CT scan of the thorax. *Chest*. 2007;132: 1939–1948.
30. Hansell DM, Wells AU, Padley SP, et al. Hypersensitivity pneumonitis: correlation of individual CT patterns with functional abnormalities. *Radiology*. 1996;199:123–128.
31. Franquet T, Hansell DM, Senbanjo T, et al. Lung cysts in subacute hypersensitivity pneumonitis. *J Comput Assist Tomogr*. 2003;27:475–478.
32. Chung MH, Edinburgh KJ, Webb EM, et al. Mixed infiltrative and obstructive disease on high-resolution CT: differential diagnosis and functional correlates in a consecutive series. *J Thorac Imaging*. 2001;16:69–75.
33. Mooney JJ, Elicker BM, Urbania TH, et al. Radiographic fibrosis score predicts survival in hypersensitivity pneumonitis. *Chest*. 2013;144:586–592.
34. Walsh SLF, Sverzellati N, Devaraj A, et al. Chronic hypersensitivity pneumonitis: high resolution computed tomography patterns and pulmonary function indices as prognostic determinants. *Eur Radiol*. 2012;22:1672–1679.
35. Silva CIS, Müller NL, Lynch DA, et al. Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. *Radiology*. 2008;246:288–297.
36. Sahin H, Brown KK, Curran-Everett D, et al. Chronic hypersensitivity pneumonitis: CT features comparison with pathologic evidence of fibrosis and survival. *Radiology*. 2007; 244:591–598.
37. Nunes H, Schubel K, Piver D, et al. Nonspecific interstitial pneumonia: survival is influenced by the underlying cause. *Eur Respir J*. 2015;45:746–755.
38. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183:788–824.
39. Morell F, Villar A, Montero M-Á, et al. Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. *Lancet Respir Med*. 2013;1:685–694.
40. Churg A, Sin DD, Everett D, et al. Pathologic patterns and survival in chronic hypersensitivity pneumonitis. *Am J Surg Pathol*. 2009;33:1765–1770.
41. Heyneman LE, Ward S, Lynch DA, et al. Respiratory bronchiolitis, respiratory bronchiolitis-associated interstitial lung disease, and desquamative interstitial pneumonia: different entities or part of the spectrum of the same disease process? *Am J Roentgenol*. 1999;173:1617–1622.
42. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2013;188:733–748.

43. Kawabata Y, Hoshi E, Murai K, et al. Smoking-related changes in the background lung of specimens resected for lung cancer: a semiquantitative study with correlation to postoperative course. *Histopathology*. 2008;53:707–714.
44. Capobianco J, Grimberg A, Thompson BM, et al. Thoracic manifestations of collagen vascular diseases. *Radiographics*. 2012;32:33–50.
45. Cipriani NA, Strek M, Noth I, et al. Pathologic quantification of connective tissue disease-associated versus idiopathic usual interstitial pneumonia. *Arch Pathol Lab Med*. 2012;136:1253–1258.
46. Miller WT, Chatzkel J, Hewitt MG. Expiratory air trapping on thoracic computed tomography. A diagnostic subclassification. *Ann Am Thorac Soc*. 2014;11:874–881.
47. Rossi SE, Erasmus JJ, McAdams HP, et al. Pulmonary drug toxicity: radiologic and pathologic manifestations. *Radiographics*. 2000;20:1245–1259.
48. Choi JW, Lee KS, Chung MP, et al. Giant cell interstitial pneumonia: high-resolution CT and pathologic findings in four adult patients. *Am J Roentgenol*. 2005;184:268–272.