Chronic hypersensitivity pneumonitis: important considerations in the work-up of this fibrotic lung disease

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Purpose of review
Chronic hypersensitivity pneumonitis is increasingly recognized as an important mimic of other fibrotic lung diseases. This review will summarize recent data regarding the importance and difficulty of determining causative exposures both for accurate diagnosis and prognosis, and describe the expanded pathologic spectrum of the disease, the effects of fibrosis on prognosis and challenges in the diagnostic evaluation.

Recent findings
Several recent publications show the potential pathologic patterns induced by chronic hypersensitivity pneumonitis are broader than the classic triad of bronchiolitis, interstitial infiltrates and granulomas. Other pathologic patterns include nonspecific interstitial pneumonia, usual interstitial pneumonia, organizing pneumonia, bronchiolitis and airway centric fibrosis. Detecting a causative antigen in fibrotic hypersensitivity pneumonitis is challenging but critically important both for accurate diagnosis and improved prognosis. The prognosis in hypersensitivity pneumonitis worsens in the presence of fibrosis, but it remains significantly better than idiopathic pulmonary fibrosis.

Summary
Hypersensitivity pneumonitis is increasingly recognized as an important cause of fibrotic interstitial lung disease. Hypersensitivity pneumonitis demonstrates a remarkable tendency to mimic other idiopathic interstitial pneumonias. A detailed exposure history remains a cornerstone of diagnosis and management.

Keywords
extrinsic allergic alveolitis, hypersensitivity pneumonitis, interstitial lung disease, usual interstitial pneumonia

INTRODUCTION

Hypersensitivity pneumonitis is a diffused parenchymal lung disease caused by repeated exposure and sensitization to a variety of organic and chemical antigens. Despite the efforts of two recent collaborations of international experts, including an National Heart Lung and Blood Institute (NHLBI)/Organization for Rare Diseases (ORD) workshop, a unifying definition or set of diagnostic criteria remains elusive. The NHLBI/ORD workshop stated: 'hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, is a complex health syndrome of varying intensity, clinical presentation and natural history. Hypersensitivity pneumonitis is the result of an immunologically induced inflammation of the lung parenchyma in response to inhalation exposure to a large variety of antigens' [1]. Establishing a diagnosis is challenging as no gold standard exists. Diagnosis relies on integration of a variety of factors including history, laboratory, radiologic and pathologic abnormalities.

Although the clinical phenotype of classic hypersensitivity pneumonitis is well described [2], the importance of hypersensitivity pneumonitis as a mimic of other diffused parenchymal lung diseases, especially fibrotic interstitial lung diseases (ILDs), is becoming increasingly apparent. Hypersensitivity pneumonitis is now recognized as one of the most common ILDs along with nonspecific interstitial pneumonia (NSIP), autoimmune disease-related ILD and idiopathic pulmonary fibrosis (IPF) [3▪,4▪]. A recent cohort study from Denmark found

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KEY POINTS

- The pathologic spectrum of chronic hypersensitivity pneumonitis is broader than previously appreciated and as a result it frequently mimics other interstitial lung diseases.
- A detailed exposure history including a search for seemingly minor exposures like feather bedding is essential for accurate diagnosis and is important for the prognosis of chronic hypersensitivity pneumonitis.
- Fibrosis is a negative prognostic indicator in hypersensitivity pneumonitis, but fibrotic chronic hypersensitivity pneumonitis still has a significantly better prognosis than idiopathic pulmonary fibrosis, especially if the causative exposure is identified and avoided.

hypersensitivity pneumonitis was the third most common ILD [5▪]. In a recent American Thoracic Society (ATS) project on NSIP, the diagnosis was changed from idiopathic NSIP to hypersensitivity pneumonitis by multidisciplinary review in 59 of the 193 cases reviewed [6]. Another study on the value of multidisciplinary review in the diagnoses of ILD showed hypersensitivity pneumonitis was the third most common disease after IPF and NSIP [7]. Sarcoid patients were not included in that trial. Others report multidisciplinary review changes the initial pathologic diagnosis between 20 and 40% of the time and the most common change is from an idiopathic interstitial pneumonia (IIP) to hypersensitivity pneumonitis [8▪]. The latest IPF guidelines state that 'it is of particular importance to evaluate patients thoroughly for possible chronic hypersensitivity pneumonitis, since such patients may mimic IPF' [9]. Finally, the latest international consensus classification of IIPs states that hypersensitivity pneumonitis and IIP are frequently confused [10▪]. This review will thus focus on chronic fibrotic hypersensitivity pneumonitis with particular attention to new data regarding exposure, the importance of fibrosis to prognosis, the expanded pathologic spectrum of the disease and the limitations of some common diagnostic tests.

EXPOSURE

Agents capable of inducing hypersensitivity pneumonitis are found in a variety of settings including the workplace, home and in recreational activities. Although the list of causative environments continues to expand [11], the antigens reported are similar to prior publications (see below).

Causes of hypersensitivity pneumonitis:

(1) Microbial agents
(2) Fungi, for example, *Aspergillus*, *Penicillium*, *Cladosporium*, *Trichosporon*, *Aureobasidium*
(3) Bacteria, for example, thermophilic actinomyces, *Bacillus subtilis*, *Klebsiella*, *Epicoccum nigrum*
(4) Mycobacteria, for example, *Mycobacterium avium*, *M. immunogen*
(5) Amoebae
(6) Animal proteins
  (a) Common – avian
  (b) Rare – fish meal, rat urine, silkworm larvae
(7) Chemical sensitizers
(8) Isocyanates, anhydrides, pyrethrum, sodium diazobenzene sulfate, copper sulfate

The most common causes remain exposure to avian antigen and moldy environments [2,12▪▪,13]. Over the past 5–10 years, mycobacterial antigens, typically encountered in hot tubs, pools or metal working fluids, have also become an accepted cause of hypersensitivity pneumonitis [13–15,16▪]. The latency between the onset of the exposure and the onset of disease is variable, ranging from months to decades. A recent population-based study from the Czech Republic reported a range of 1 month to 49 years and a median latency of 12.5 years [17]. Other series report a similar range with median latency of 8.7 years [18].

Recent publications have expanded our knowledge regarding several features of exposure in chronic hypersensitivity pneumonitis including: the importance of finding the relevant exposure, the importance of occult or low level exposure as a cause of disease and the difficulty in detecting the exposure in the setting of fibrotic hypersensitivity pneumonitis. Identification and removal of exposure is a cornerstone of management and is important for prognosis in subacute hypersensitivity pneumonitis. However, in chronic hypersensitivity pneumonitis, progression even after removal from exposure is well described and data regarding the importance of exposure removal were lacking. A recent study by Fernandez Perez *et al.* [12▪▪] addressed this important issue. They identified 142 cases with surgical lung biopsies where a multidisciplinary review found a diagnosis of chronic hypersensitivity pneumonitis. Antigen avoidance and abatement procedures were recommended for all patients with a detected causative exposure. They found improved mortality in those with an identifiable exposure and this benefit remained statistically significant after multivariate analysis [12▪▪]. The average survival for the cohort declined from 18.2 to 9.3 years when a causative exposure was not discovered.

Another study highlights the importance of occult exposure as a cause of disease and the ability of hypersensitivity pneumonitis to mimic IPF. Morrell *et al.* [19▪▪] performed a case-cohort study on 46 consecutive patients diagnosed with IPF according to 2011 guidelines. A standardized questionnaire designed to look for occult exposure was then administered at follow-up visits. They found previously undetected avian antigen in 19 patients, usually in bedding, mold in 4 patients and isocyanates in 1 patient. This led to additional testing including inhalational challenge to the putative antigen, precipitin testing, bronchoalveolar lavage (BAL) and additional surgical biopsies. In the end, the diagnosis was changed from IPF to hypersensitivity pneumonitis in 20 of the 46 (46%) patients [19▪▪].

Detecting relevant exposures is thus critically important in the evaluation of patients with fibrosing lung disease for an accurate diagnosis and in the management of patients when hypersensitivity pneumonitis is diagnosed. Unfortunately, finding the inciting antigen is extremely difficult in fibrotic hypersensitivity pneumonitis. When computed tomography (CT) findings typical of subacute or acute hypersensitivity pneumonitis are present (ground glass and/or diffuse centrilobular nodules), the exposure is detectable by an experienced clinician over 90% of the time [2]. However, when the high-resolution computed tomography (HRCT) is more typical of a fibrotic IIP, it becomes much more challenging. In a series of 85 consecutive cases seen at the Mayo clinic, an antigen was not found in 25% [13]. In the series by Fernandez Perez *et al.* [12▪▪] discussed above, an inciting antigen was not discovered in 53% of the patients. Likewise, an exposure was not detected in 60% of the 206 patients from the University of California San Francisco cohort [20▪]. In this trial, the study cohort was enrolled in their database from 2001 to 2012. Patients had ILD of at least 3 months duration and both initial and follow-up pulmonary function tests. Hypersensitivity pneumonitis was diagnosed by multidisciplinary conference, and in only 40% of the 207 cases was an inciting exposure identified [20▪]. Taken together, these studies illustrate the challenge and importance of determining the relevant exposure, not just for the management of hypersensitivity pneumonitis, but also in the evaluation of fibrotic lung diseases. A thorough exposure history looking for exposures associated with hypersensitivity pneumonitis, including attention to seemingly minor exposures, is thus an essential part of the evaluation of patients presenting with diffuse parenchymal lung disease (see below).

The exposure history for chronic hypersensitivity pneumonitis:

(1) Part 1: search for the antigen
   (a) Avian antigen – birds at work or in the home, feather pillows, feather duvets or mattress covers, feather decorations
   (b) Microbial products
      (i) A – visible contamination with mold or mildew on walls, floors, furniture, air conditioning vents or filters, the presence of musty odors in the home or workplace
      (ii) B – liquid sources that could allow growth – humidifiers, vaporizers, hot tubs, pools, swamp coolers, indoor fountains, metal working fluids, including questions regarding clarity, slime and odors
      (iii) C – potential for water contamination – known water damage from floods, leaks, broken pipes in the home or workplace. High-humidity environments or products from th ose environments including greenhouses, compost, mushroom farming, other food production where mold growth can occur, use of water-damaged materials including wood or wood with bark in place, moldy hay or animal feed.
   (c) Chemical sources: use of isocyanates (two part paint use, furniture manufacture, spray foam use), anhydrides, Pauli's reagent (in chromatography), use of pyrethrum insecticide or copper sulfate
(2) Part 2: timing – exposure must precede disease onset but still be present at disease onset to be causative. These antigens do not persist in tissue.
(3) Part 3: latency – widely variable ranging from a few weeks to decades
(4) Part 4: symptoms – association of constitutional and/or increased respiratory symptoms within 12 h of any of the above exposures (less likely in chronic than subacute or acute disease) [2].

THE EXPANDED PATHOLOGIC SPECTRUM OF HYPERSENSITIVITY PNEUMONITIS

The classic pathology of hypersensitivity pneumonitis includes the triad of cellular bronchiolitis, a lymphoplasmacytic interstitial infiltrate and poorly formed non-necrotizing granulomas. Small patches of organizing pneumonia are also commonly seen [21]. However, it is becoming increasingly clear that hypersensitivity pneumonitis manifests with other

pathologic patterns. First, any of the above components may occur in isolation and the full triad is present in less than half the cases [22]. When the bronchiolitis occurs in isolation, cases mimic obliterative bronchiolitis [23▪,24]. Pathologists interpret NSIP if only the lymphoplasmacytic interstitial infiltrate is present [25]. Other studies show that fibrotic NSIP, organizing pneumonia, usual interstitial pneumonia (UIP) and airway centric fibrosis are all potential pathologic patterns (see below) [22,26–28].

The pathologic patterns associated with hypersensitivity pneumonitis:

1. Typical
   (a) The triad of lymphoplasmacytic interstitial infiltrates, cellular bronchiolitis, poorly formed granulomas
2. Other potential pathologic patterns associated with hypersensitivity pneumonitis
   (a) Usual interstitial pneumonia
   (b) Cellular nonspecific interstitial pneumonia
   (c) Fibrotic nonspecific interstitial pneumonia
   (d) Bronchiolitis
   (e) Airway centric fibrosis
   (f) Organizing pneumonia

This morphologic diversity is reflected in the imaging as well and likely explains the ability of hypersensitivity pneumonitis to mimic other ILDs. In addition, the granulomatous inflammation that is the hallmark of typical hypersensitivity pneumonitis becomes less prominent, the more fibrotic the disease [27,28]. Differentiating IIP, especially IPF, from chronic hypersensitivity pneumonitis on pathology is thus challenging. However, distinguishing features have been reported (Table 1) and an experienced pulmonary pathologist can differentiate the two conditions the vast majority of the time [26,29]. HRCT clues that suggest hypersensitivity pneumonitis is more likely than IPF include the absence of lower lobe predominance, the presence of lobular areas of air-trapping and the presence of centrilobular nodules (Fig. 1) [31].

THE PROGNOSTIC IMPLICATIONS OF FIBROSIS IN HYPERSENSITIVITY PNEUMONITIS

The presence of fibrosis on biopsy or HRCT dramatically affects the prognosis in hypersensitivity pneumonitis. In the absence of pathologic fibrosis, the average survival is approximately 20 years; however, when fibrosis is present, this falls to 5–8 years [12▪▪,22,27,32]. In addition, when the responsible antigen is not discovered and removed, the average survival falls even further. In the study by Fernandez Perez *et al.* reviewed above, the median survival of fibrotic hypersensitivity pneumonitis with an identifiable antigen was 8.75 years compared to only 4.88 years when the exposure was not discovered [12▪▪]. Very similar mortality estimates are derived from HRCT studies when the mortality of patients with and without HRCT signs of fibrosis (traction bronchiectasis and honeycombing) is compared [33,34▪,35]. In addition, HRCT, unlike pathologic specimens, allow quantification of whole lung fibrosis. The mortality increases with increasing fibrosis scores on HRCT, demonstrating a dose–response effect of fibrosis on mortality [33,34▪,35].

Although fibrosis has a significant affect on mortality, differentiating hypersensitivity pneumonitis from other fibrotic ILDs, especially IPF, remains critically important for several reasons. As discussed above, finding and removing the responsible antigen is associated with significantly better survival. In addition, exposure removal is important to prevent disease in other individuals who share the exposure. Exposure identification, removal and abatement are thus important therapeutic interventions in chronic hypersensitivity pneumonitis and are unlikely to occur without the correct diagnosis.

Table 1. Differentiating idiopathic pulmonary fibrosis from hypersensitivity pneumonitis–usual interstitial pneumonia [4▪,26,29,30▪]

Finding	IPF	HP–UIP
Fibrosis	Predominantly subpleural	Predominantly bronchiolocentric and centrilobular
Fibroblastic foci	Frequent and at the leading edge of fibrosis	Infrequent and inconsistent in location
Granulomas	Absent/rare	Present in small numbers
Giant cells	Rare	Frequent
Mononuclear chronic interstitial inflammation	Mild (fibrosis > inflammation)	Moderate to severe (fibrosis = inflammation)
Organizing pneumonia	Absent	May be present
Chronic bronchiolitis	Absent	May be present

HP, hypersensitivity pneumonitis; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

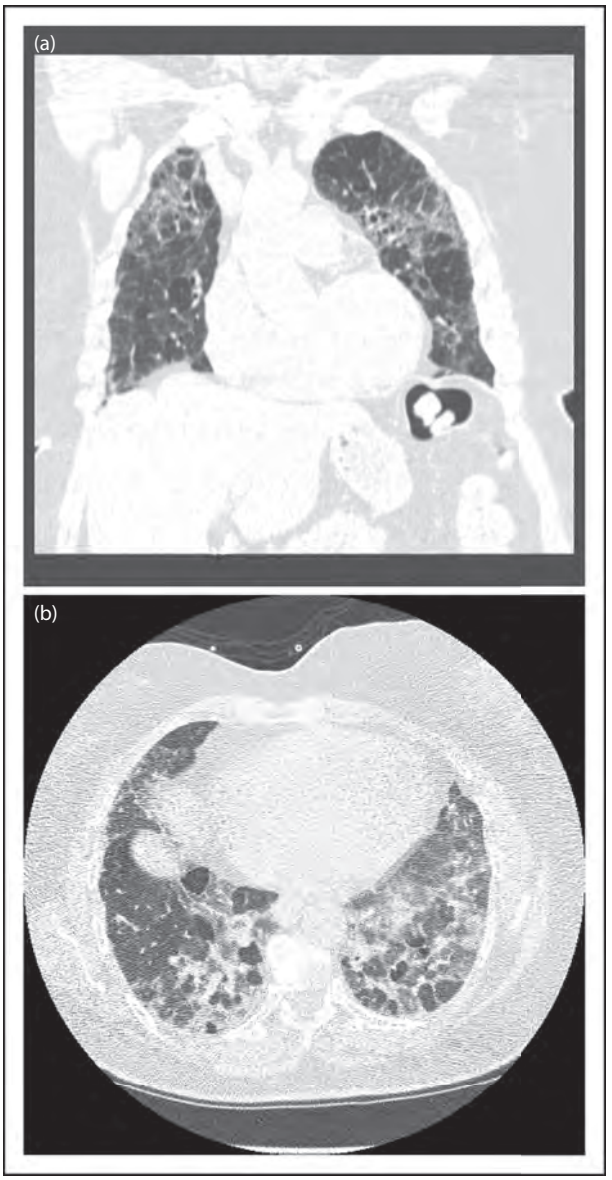

FIGURE 1. (a) Coronal image from an HRCT of a patient with chronic hypersensitivity pneumonitis demonstrating the absence of lower lobe predominance and some scattered centrilobular nodules. (b) HRCT cross-sectional image from the same patient demonstrating lobular areas of air-trapping.

There are other potential therapeutic implications as well. Gene expression profiles in IPF are vastly different than in hypersensitivity pneumonitis [36]. The genes activated in hypersensitivity pneumonitis are associated with inflammation and cellular immune activation. In IPF, the gene activation signature is characterized by genes for tissue remodeling accompanied by epithelial and myofibroblast genes instead of inflammatory genes [36]. Therefore, although the phenotype of chronic fibrotic hypersensitivity pneumonitis and IPF may be similar, the available evidence suggests the underlying pathogenesis is quite different. The absence of inflammation in IPF led to the recent PANTHER trial that showed an increased mortality in IPF patients treated with prednisone and immunosuppressants [37]. Similar randomized controlled trials of these agents in fibrotic hypersensitivity pneumonitis have not been performed. However, steroids and, if necessary, steroid-sparing agents are indicated in patients with fibrotic hypersensitivity pneumonitis which progresses despite exposure avoidance [12▪▪,38,39].

Even if an antigen is not discovered, the prognosis of fibrotic hypersensitivity pneumonitis remains better than IPF. The average survival for fibrotic hypersensitivity pneumonitis without an identifiable exposure is approximately 5 years [12▪▪]. This compares favorably to the 2–3-year average survival in IPF patients [9]. The difference in prognosis was highlighted by a recent study that attempted to expand the gender, age physiology (GAP) risk prediction score from IPF to other causes of ILD. The GAP index and calculator is a multidimensional tool that utilizes easily accessible clinical information (gender, age, forced vital capacity and diffusing capacity for carbon monoxide) to better define prognosis in patients with IPF [40]. In the subsequent trial that tried to expand the GAP index to other causes of ILD, the prognosis of hypersensitivity pneumonitis was significantly better than IPF and the model required a correction to achieve accurate risk prediction in chronic hypersensitivity pneumonitis [20▪].

LIMITATIONS OF BRONCHOALVEOLAR LAVAGE AND PRECIPITINS FOR THE DIAGNOSIS OF CHRONIC HYPERSENSITIVITY PNEUMONITIS

The above discussion illustrates the importance of distinguishing chronic hypersensitivity pneumonitis from other fibrotic ILDs. However, there are limitations of the available diagnostic tests in the setting of chronic hypersensitivity pneumonitis. Detection of a potential causative exposure on history is by far the most powerful predictor for hypersensitivity pneumonitis, emphasizing the importance of a thorough exposure history (see list given under the heading 'EXPOSURE' as 'The exposure history for chronic hypersensitivity pneumonitis') [2]. BAL provides useful supportive information when hypersensitivity pneumonitis is considered. Measuring the CD4/CD8 ratio is no longer recommended as it varies significantly according to exposure and disease stage, so that a normal or elevated ratio does not exclude hypersensitivity pneumonitis [39,41]. Typical or subacute hypersensitivity pneumonitis features a marked

lymphocytic alveolitis on BAL, oftentimes more than 50% lymphocytes [27,28,41,42]. This led to recommendations that one should use 30–40% lymphocytes on BAL as a diagnostic cut-off for chronic hypersensitivity pneumonitis [9,38,39]. Others have stated a normal BAL lymphocyte percentage excludes active disease [38,43]. However, as noted above, the granulomatous inflammation that is the hallmark of typical hypersensitivity pneumonitis becomes less prominent the more fibrotic the disease becomes [27,28]. This is reflected in the degree of lymphocytic alveolitis seen on BAL, especially if the underlying pathology is UIP. Ohtani *et al.* [28] confirmed hypersensitivity pneumonitis in their series with exposure challenge and positive lymphocyte proliferation testing and showed a mean lymphocyte percentage of only 19% when UIP was present. Akashi *et al.* [44] also found a lymphocyte percentage below 30 in more than half of the UIP cases in their series. In the series by Gaxiola *et al.* [27], the mean lymphocyte percentage in patients with hypersensitivity pneumonitis-induced UIP was 36 + 22.9. The percentage of lymphocytes was significantly lower in UIP than in typical hypersensitivity pneumonitis or hypersensitivity pneumonitis–NSIP in all these studies. All also showed increased mortality in UIP even though many patients had lymphocyte percentages in the normal range, suggesting BAL alone should not be used to define quiescent disease. Others have shown more than 80% of chronic hypersensitivity pneumonitis patients have at least 20% lymphocytes on BAL [18,41]. In contrast, the mean lymphocyte percentage in IPF is 11% and the vast majority of IPF patients have less than 20% lymphocytes [42]. This suggests that if a fibrotic ILD patient has an exposure and an elevated BAL lymphocyte percentage, one should consider further testing (including surgical biopsy) to exclude or confirm chronic hypersensitivity pneumonitis even if the HRCT shows definite UIP. Surgical biopsy is efficacious in this setting and leads to therapeutic change with subsequent positive responses in the majority of patients [19▪▪,45▪]. Whether or not BAL should be used routinely in the setting of a definite scan without a known exposure is unclear, but the results of the study by Morrell *et al.* [19▪▪] suggest that further research is indicated.

There are significant limitations to both the sensitivity and specificity of precipitins [38,39,43]. In addition, the sensitivity likely declines when the underlying pathologic pattern is UIP [28]. In a trial of avian hypersensitivity pneumonitis, the sensitivity of precipitins was 85% when the biopsy was inflammatory, 62% when fibrotic NSIP was present, but only 18% with a UIP pattern [28]. Positive precipitins do provide supportive information [2]. For example, a surgical biopsy is not required in a patient with fibrotic ILD, a known exposure, positive precipitins to that exposure and a lymphocytic alveolitis on bronchoscopy [18,19▪▪]. However, hypersensitivity pneumonitis should not be diagnosed solely on the basis of positive precipitins and hypersensitivity pneumonitis cannot be excluded because precipitins are negative.

CONCLUSION

Hypersensitivity pneumonitis is a diffuse parenchymal lung disease with protean manifestations, resulting in a remarkable degree of clinic overlap with other ILDs. It is now clear that the pathologic spectrum is much broader than the classic triad of inflammatory interstitial infiltrates, cellular bronchiolitis and poorly formed noncaseating granulomas. A high degree of suspicion of hypersensitivity pneumonitis must be maintained when evaluating patients for ILD. A thorough exposure history looking for potential causative exposures, even seemingly low level exposures such as down pillows, is essential. Finding and removing exposures has important prognostic implications. In addition, if exposures are found, clinicians should have a low threshold for further testing including immunologic tests for sensitization, bronchoscopy including BAL looking for a lymphocytic alveolitis and possibly surgical lung biopsy. Most importantly, hypersensitivity pneumonitis should always be considered and excluded prior to diagnosing an idiopathic ILD.

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