Hypersensitivity Pneumonitis

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INTRODUCTION

Hypersensitivity pneumonitis (HP), synonymous with extrinsic allergic alveolitis (EAA), is a complex syndrome resulting from repeated exposure to a variety of antigenic particles found in the environment.1 Because the resulting inflammatory response involves not only the alveoli but the terminal bronchioli and the interstitium, the term HP may be more correct.

The prevalence of HP is difficult to determine, because the disease is often unrecognized or misdiagnosed. The estimated prevalence of farmer’s lung ranges from 1% to 19% of exposed farmers,2–4 the prevalence of pigeon breeder’s lung is from 6% to 20% of exposed individuals,5 and the prevalence of budgerigar’s lung is from 1% to 8% of

KEY POINTS

- Clinical manifestations of hypersensitivity pneumonitis may closely mimic other interstitial lung diseases, and the disease onset is usually insidious.
- High-resolution computed tomography and bronchoalveolar lavage are the sensitive and characteristic diagnostic tests for hypersensitivity pneumonitis.
- The relevant antigen to hypersensitivity pneumonitis cannot be identified in up to 20% to 30% of patients.
- Clinicians should be aware that hypersensitivity pneumonitis must be considered in all cases of interstitial lung disease, and a detailed environmental exposure history is mandatory.

KEYWORDS

- Extrinsic allergic alveolitis
- Farmer’s lung
- Bird fancier’s disease
- HRCT
- Bronchoalveolar lavage
- Prognosis

INTRODUCTION

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The prevalence of HP is difficult to determine, because the disease is often unrecognized or misdiagnosed. The estimated prevalence of farmer’s lung ranges from 1% to 19% of exposed farmers,2–4 the prevalence of pigeon breeder’s lung is from 6% to 20% of exposed individuals,5 and the prevalence of budgerigar’s lung is from 1% to 8% of
exposed individuals. The disease may also arise in children. Clinical behavior in children is similar to adult cases.

The clinical manifestations have regional characteristics. Farmer’s lung and pigeon breeder’s lung are more common in cold and wet regions, mainly in Europe, whereas summer-type HP is limited to Japan.

A wide variety of particles sized less than 5 μm can reach the alveoli and may be the pathogens of HP. The causative particles include fungal (ie, Aspergillus and Penicillium species), bacterial, protozoal, animal (mostly bird) and insect proteins, and low-molecular-weight chemical compounds (ie, isocyanates, zinc, inks, and dyes) (Table 1). More recent studies have suggested that mist from a domestic ultrasonic humidifier, steam iron, dry sausage dust, wind instruments including saxophone and trombone, colistin, catechin (green tea extract), and methylmethacrylate (in dental technicians) can be the cause of HP. Feather duvet lung has been reported as a rare subgroup of bird fancier’s lung.

HP may present as acute, subacute, or chronic clinical forms, but these forms frequently overlap. The clinical presentation of HP is influenced by several factors including the nature and the amount of inhaled antigen, the intensity and frequency of exposure, and the host immune response, which is likely determined by a genetic background (Table 2).

It is not known why HP develops only in a minority of exposed individuals, or why some cases of chronic HP show progression without further antigen exposure.

CLINICAL FEATURES

The spectrum of clinical features varies and has been conventionally classified into acute, subacute, and chronic forms. The interval between sensitization by antigen inhalation and the symptomatic onset of HP is unknown. It seems to be variable and may range from several months to several years after the antigen exposure.

**Acute Form**

Acute HP is characterized by an influenzalike syndrome (fever, chills, malaise, myalgia, headache) and respiratory symptoms (dry cough, dyspnea, tachypnea, chest tightness). However, respiratory symptoms in acute HP are sometimes absent. The disease onset is abrupt and usually occurs 4 to 12 hours after antigen exposure. In general, acute HP is nonprogressive and spontaneously improves within a few days after antigen avoidance. The disease often recurs after the reexposure of antigen. The clinical examination shows bibasilar crackles and occasional cyanosis, whereas finger clubbing is rare. Patients with recurrent acute farmer’s lung may sometimes develop an obstructive lung disease with centrilobular emphysema instead of fibrosis.

**Subacute Form**

Subacute HP may be associated with repeated low-level exposure to inhaled antigens. After recurrent acute episodes, this form may also become chronic, resulting in fibrosis. It is characterized by an insidious onset of dyspnea, fatigue, and cough. Because the respiratory symptoms are usually mild or absent in subacute HP, infectious pneumonia or noninfectious interstitial lung disease (ILD) is the important differential diagnosis.

**Chronic Form**

Chronic HP may result from continuous, low-level exposure to inhaled antigens. Bird antigen exposure is the most common in this form of disease. The onset of chronic HP is insidious with slowly increasing dyspnea, dry cough, fatigue, and weight loss. Digital
<table>
<thead>
<tr>
<th>Disease</th>
<th>Exposure</th>
<th>Antigen</th>
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<tbody>
<tr>
<td>Farmer's lung</td>
<td>Moldy hay, grain</td>
<td>Saccharospora rectivirgula, Thermoactinomyces vulgaris, Aspergillus spp</td>
</tr>
<tr>
<td>Humidifier lung; air conditioner lung</td>
<td>Contaminated humidifiers and air conditioners</td>
<td>Amoebae, nematodes, yeasts, bacteria</td>
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<tr>
<td>Misting fountain HP</td>
<td>Contaminated water</td>
<td>Bacteria, molds, yeasts</td>
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<tr>
<td>Steam iron HP</td>
<td>Contaminated water reservoir</td>
<td>Sphingobacterium spiritivorum</td>
</tr>
<tr>
<td>Suberosis</td>
<td>Moldy cork</td>
<td>Penicillium spp</td>
</tr>
<tr>
<td>Sequoiosis</td>
<td>Moldy redwood dust</td>
<td>Graphium spp, Pullularia spp, Trichoderma spp</td>
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<tr>
<td>Woodworker's lung</td>
<td>Contaminated wood pulp or dust</td>
<td>Alternaria spp</td>
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<td>Wood-trimmer's lung</td>
<td>Contaminated wood trimmings</td>
<td>Rhizopus spp, Mucor spp</td>
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<tr>
<td>Maple-bark stripper's lung</td>
<td>Contaminated maple logs</td>
<td>Cryptostroma corticale</td>
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<tr>
<td>Domestic allergic alveolitis</td>
<td>Decayed wood</td>
<td>Molds</td>
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<td>Sauna-taker's lung</td>
<td>Contaminated sauna water</td>
<td>Aureobasidium spp</td>
</tr>
<tr>
<td>Basement lung</td>
<td>Contaminated basements</td>
<td>Cephalosporium spp, Penicillium spp</td>
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<tr>
<td>Hot-tub lung</td>
<td>Mold on ceiling, tub water</td>
<td>Mycobacterium avium complex</td>
</tr>
<tr>
<td>Swimming pool lung</td>
<td>Mist from pool water, sprays and fountains</td>
<td>M avium complex</td>
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<tr>
<td>Thatched roof lung</td>
<td>Dried grasses and leaves</td>
<td>Saccharomonospora viridis, T vulgaris, Aspergillus spp</td>
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<tr>
<td>Bagassosis</td>
<td>Moldy pressed sugar cane (bagasse)</td>
<td>Thermoactinomyces sacchari, T vulgaris</td>
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<td>Mushroom-worker's lung</td>
<td>Moldy compost and mushrooms</td>
<td>S rectivirgula, T vulgaris, Aspergillus spp</td>
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<tr>
<td>Malt-worker's lung</td>
<td>Contaminated barley</td>
<td>Aspergillus clavatus</td>
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<tr>
<td>Cheese-washer's lung</td>
<td>Moldy cheese or cheese casings</td>
<td>Penicillium casei</td>
</tr>
<tr>
<td>Dry sausage worker's lung</td>
<td>Moldy sausage dust</td>
<td>Penicillium spp</td>
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<td>Paprika slicer's lung</td>
<td>Moldy paprika pods</td>
<td>Mucor stolonifer</td>
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<tr>
<td>Compost lung</td>
<td>Compost</td>
<td>Aspergillus spp, T vulgaris</td>
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<tr>
<td>Wine-maker's lung</td>
<td>Mold on grapes</td>
<td>Botrytis cinerea</td>
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<tr>
<td>Tobacco-grower's lung</td>
<td>Mold on tobacco</td>
<td>Aspergillus spp</td>
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<tr>
<td>Potato-riddler's lung</td>
<td>Moldy hay around potatoes</td>
<td>Thermophilic actinomycetes, Aspergillus spp</td>
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<td>Summer-type HP</td>
<td>Contaminated houses</td>
<td>Trychosporon cutaneum</td>
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<td>Detergent lung, washing powder lung</td>
<td>Detergents (during processing or use)</td>
<td>Bacillus subtilis enzymes</td>
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Clubbing may be present in 20% to 50% of patients\textsuperscript{1,23} and predicts clinical deterioration.\textsuperscript{24} Chronic HP often develops progressive fibrosis with cor pulmonale and mimics idiopathic pulmonary fibrosis (IPF) or fibrotic nonspecific interstitial pneumonia (NSIP) in the advanced stage.\textsuperscript{25} This form of disease, therefore, often leads the

\begin{table}
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\begin{tabular}{|l|l|l|}
\hline
Disease & Exposure & Antigen \\
\hline
Machine-operator's lung & Contaminated metalworking fluid & \textit{Pseudomonas} spp, nontuberculous mycobacteria \textit{Aspergillus fumigatus} \\
\hline
Stipatosis & Esparto dust & Thermophilic actinomycetes \\
\hline
Peat moss HP & Contaminated peat moss & \textit{Monocillium} spp; \textit{Penicillium citreonigum} \\
\hline
Wind-instrument lung & Contaminated saxophones, trombone & Molds, bacteria \\
\hline
Chiropodist's lung & Foot skin and nail dust & Fungi \\
\hline
Animal proteins & & \\
\hline
Bird fancier's lung; pigeon breeder's lung & Parakeets, budgerigars, pigeons, parrots, cockatiels, chickens, turkeys, geese, ducks, lovebirds & Proteins in avian droppings, in serum, and on feathers \\
\hline
Feather duvet lung & Feather beds, pillows, duvets & Avian proteins \\
\hline
Pituitary snuff-taker's lung & Bovine and porcine pituitary powder & Pituitary proteins \\
\hline
Furrier's lung & Animal pelts & Animal fur dust \\
\hline
Animal handler's lung, laboratory worker's lung & Rats, gerbils & Proteins from urine, serum, pelts \\
\hline
Pearl oyster shell HP & Dust of shells & Pearl oyster proteins \\
\hline
Mollusk shell HP & Sea snail shell dust & Sea snail shell protein \\
\hline
Silk production HP & Dust from silkworm larvae and cocoons & Silkworm proteins \\
\hline
Miller's lung & Contaminated grain & \textit{Sitophilus granarius} (wheat weevil) \\
\hline
Chemicals & & \\
\hline
Chemical worker's lung & Polyurethane foams, spray paints, elastomers, glues & Diisocyanates, trimellitic anhydride \\
\hline
Epoxy resin lung & Heated epoxy resin & Phthalic anhydride \\
\hline
Unknown & & \\
\hline
Mummy-handler's lung & Cloth wrappings of mummies & — \\
\hline
Coffee-worker's lung & Coffee-bean dust & — \\
\hline
Tap water lung & Contaminated tap water & — \\
\hline
Tea-grower's lung & Tea plants & — \\
\hline
\end{tabular}
\caption{Continued}
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physician to mistake the disease for other chronic ILDs. The auscultatory findings include bibasilar crackles and characteristically inspiratory squeaks resulting from the coexisting bronchiolitis.

**Acute Exacerbation**

Acute exacerbation of chronic HP is an emerging concept showing an accelerated respiratory deterioration with the presence of new bilateral ground-glass opacities on high-resolution computed tomography (HRCT).\textsuperscript{26,27} The pathogenesis of acute exacerbations in chronic HP is unknown.

It is likely to occur without further exposure to the inhaled antigens. Low total lung capacity (TLC) and diffusing capacity of the lung for carbon monoxide (DL\textsubscript{CO}), fewer lymphocytes and increased neutrophils in bronchoalveolar lavage (BAL) fluids, and a UIP-like pattern in histology at the time of diagnosis seem to be the risk factors for acute exacerbation.\textsuperscript{26} Pathologic findings include organizing pneumonia (OP) or diffuse alveolar damage.

The definitions of acute exacerbations in chronic HP have been proposed as shown in \textbf{Box 1}.\textsuperscript{26,27} As in IPF, acute exacerbations predict poor outcome. The 2-year frequency of an acute exacerbation is 11.5%.\textsuperscript{26}

**IMAGING FINDINGS: CHEST RADIOGRAPHY**

On the chest radiograph, combined findings of transient diffuse ground-glass attenuation, airspace consolidation, micronodules, reticular shadows, and honeycombing are

<table>
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<th>Table 2</th>
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<tr>
<td>Symptoms and signs in 116 patients with HP</td>
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<tr>
<td><strong>Feature</strong></td>
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<tr>
<td>Dyspnea</td>
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<td>Cough</td>
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<td>Chills</td>
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<td>Fever</td>
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<td>Chest tightness</td>
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<td>Weight loss</td>
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<td>Body aches</td>
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<td>Wheezing</td>
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<tr>
<td>Inspiratory crackles</td>
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<tr>
<td>Cyanosis</td>
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<tr>
<td>Clubbing</td>
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prominent according to the clinical subforms of HP. In acute HP, diffuse ground-glass attenuation (GGA) and/or airspace consolidation, associated with some micronodules, may be seen. In subacute HP, micronodules, GGA, and reticular shadows are prominent. In chronic HP, reticular shadows and honeycombing are more predominant. In contrast with IPF, the changes are diffuse or may show upper zone predominance.

Mild enlargement of the mediastinal lymph nodes is occasionally found. Pleural involvement is rare. Clinicians should be aware that the chest radiograph may be normal in up to 30% of patients with HP.

**IMAGING FINDINGS: HRCT**

HRCT is useful in detecting HP and in separating the clinical subforms of HP. In acute HP, HRCT may be normal.\(^2^8\) When abnormal, the characteristic findings on HRCT are patchy or diffuse GGA and/or centrilobular poorly defined small nodules; consolidation is rarely seen.\(^2^9\)–\(^3^4\) Mosaic perfusion (air trapping) caused by concomitant bronchiolitis is also observed. This finding represents indirect signs of small airway obstruction. These small nodules are the common characteristics in not only acute but subacute or chronic HP (Fig. 1).

In subacute HP, patchy air-trapping areas on expiratory scans become more prominent, often in a lobular distribution.\(^3^0\),\(^3^5\) Because of the considerable overlap in subacute and chronic HP, the findings in chronic HP may be observed in subacute HP to varying degrees.

In chronic HP, the prominent findings on HRCT are the signs of lung fibrosis combined with GGA and centrilobular small nodules. The signs of lung fibrosis include interlobular septal thickening, lobar volume loss, linear-reticular opacities, traction bronchiectasis, and honeycombing (Fig. 2).\(^2^9\),\(^3^6\)

The reticulation is often distributed in the peribronchovascular area and lacks lower zone or subpleural predominance as in IPF. HRCT seems to be useful to distinguish IPF and NSIP from HP in many cases.\(^3^6\),\(^3^7\) In 1 study, the most characteristic findings in NSIP compared with chronic HP were the subpleural sparing, absence of lobular areas with GGA, and lack of honeycombing.\(^3^7\) The most characteristic findings in IPF compared with chronic HP were the basal predominance of honeycombing, absence of relative subpleural sparing, and absence of centrilobular nodules. Honeycombing was seen in 64% of patients with chronic HP, which was as high a frequency as in IPF.\(^3^6\)

Additional emphysema can be seen in 20% of nonsmoking patients with chronic HP.\(^3^2\)–\(^3^4\) Patients with chronic farmer’s lung are more likely to develop emphysema than fibrosis.\(^2^2\)

Subacute and chronic HP sometimes show thin-walled cysts in areas of ground-glass attenuation, which mimic those observed in lymphocytic interstitial pneumonia.\(^3^6\),\(^3^8\)

**PULMONARY FUNCTION TESTS**

Although lung function may be normal in acute HP,\(^2^8\) abnormal lung function is common in most patients with chronic HP. The most frequent functional abnormalities are a restrictive impairment and/or an impaired gas exchange (decreased diffusing capacity or increased alveolar/arterial oxygen gradient). Only few patients with farmer’s lung show obstructive impairment resulting from emphysema.\(^3^9\) However, these changes are not characteristic for chronic HP but are also found in any type of ILDs. Therefore, these abnormalities are not diagnostic for HP. Although hypoxemia is common in HP, patients with mild to moderate disease may lack this symptom and only present hypoxemia with exercise.
The functional impairment is not well correlated with the severity of radiological abnormalities. The importance of pulmonary function tests is to evaluate the severity of the physiologic impairment at diagnosis and during follow-up.24

**Fig. 1.** HRCT of a patient with acute HP showing bilateral ground-glass densities with centrilobular micronodular accentuation and minor consolidation. (A) Upper lobes, (B) middle lobes, (C) lower lobes.

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**BAL AND INDUCED SPUTUM**

BAL is a highly sensitive method to detect HP. An increase in the total cell count (usually more than 20 million in a total of 100 mL of BAL fluid) with a large increment
of lymphocytes (usually more than 50%) is characteristic for HP, but not specific. BAL lymphocytes show the highest count in HP of all ILDs. This increase is unusual in other differential diagnoses, including IPF. However, in patients with chronic HP or smokers, the increase in BAL lymphocytes may be less prominent. In contrast, even asymptomatic sensitized individuals may show increased lymphocytes in BAL fluid.
The evaluation of CD4+ and CD8+ T-cell subsets usually shows a relative predominance of CD8+ T cells resulting in a low CD4/CD8 ratio with mean values ranging between 0.5 and 1.0. However, the routine evaluation of the CD4/CD8 ratio is not recommended for clinical practice, because the various studies showed no consistent findings in CD4/CD8 ratio. The reasons for this discrepancy are unclear. The possible confounding factors may include the different disease manifestations (eg, the mean value of the CD4/CD8 ratio is higher in chronic HP than in subacute HP46), the timing of BAL investigations, the type of inhaled antigen, the intensity of exposure, the smoking habit, and the clinical stage.24,42,46–48 CD4/CD8 ratios are increased within 24 hours after the last antigen exposure, and become lowest between 7 and 30 days.49 Persistent BAL abnormalities during the follow-up may indicate incomplete antigen avoidance.

Small numbers of neutrophils, eosinophils, mast cells, and, more characteristically, plasma cells are also found in BAL fluid.32,49–52 The number of plasma cells in BAL fluid and immunoglobulin levels revealed a positive correlation, suggesting that the local production of immunoglobulins by plasma cells may play a pathogenetic role in susceptible individuals.51 Other morphologic features include signs of T-cell and macrophage activation.53 Activated T cells show folded nuclei and/or broad cytoplasm, and have increased expression of counterligand CD28. Activated macrophages show foamy macrophages, and have increased expression of CD80/CD86.54

The proteomic analysis of BAL fluids in HP seems to be useful for differentiating usual interstitial pneumonia (UIP) pattern from NSIP pattern.55 Surfactant protein A, immunoglobulin heavy chain, heat shock glycoprotein, haptoglobin, and immunoglobulin J chain were increased in patients with UIP pattern, whereas glutathione S-transferase, vitamin D–binding protein, and β-actin were increased in patients with NSIP pattern.56

In induced sputum from patients with HP, total cells and lymphocytes are also increased.56 Differential cell counts showed that induced sputum and BAL reflected different compartments of inflammation.56 A recent study showed that the CD4/CD8 ratio recovered from induced sputum is as useful as that recovered from BAL fluid.57 Therefore, induced sputum may be complementary, but not an alternative, to BAL. The usefulness of induced sputum in the clinical practice or research use for HP is currently unclear.

LABORATORY TESTS

The presence of specific immunoglobulin (Ig) G antibodies (serum precipitins) to the exposed antigen is evidence of sensitization but not of disease. However, a positive test can be complementary for the diagnosis of HP and give the clinician useful additional information.58 Approximately 10% of asymptomatic farmers and 40% of asymptomatic pigeon breeders show positive precipitating antibodies to the exposed antigens.59–61 Negative precipitating antibodies do not exclude the diagnosis of HP.62–64 Various serologic/imunologic techniques including immune-electrophoresis enzyme immunoassay, fluoroenzyme immunoassay, peptide nucleic acid–fluorescence in situ hybridization, and DNA–fluorescence in situ hybridization assays were found to be useful for detecting HP antigens.65–67 Enzyme-linked immunosorbent assay is usually the preferred method. Increasing IgG antibody titers are correlated with the likelihood of HP, and decreasing titers reflect antigen avoidance.58 A recent study enrolling a total of 122 patients with a suspected HP (including 31 cases of true HP) evaluated the diagnostic value of serum precipitins to mold antigens in HP, and showed that negative predictive values varied from 81% to 88% and
positive predictive values varied from 71% to 75%. The selection of antigens to be tested needs to be determined based on the local predominant antigens. In acute HP, the neutrophil fraction of the white blood cell count and the levels of C-reactive protein are increased. In chronic HP, polyclonal hypergammaglobulinemia is frequent. The rheumatoid factor may be positive in 50% of patients with pigeon HP.

PROVOCATION TESTS

Inhalative provocation tests with the suspected antigen should only be performed in selected patients, because of the risk of a severe attack and the lack of standard procedure. A natural exposure to the workplace or home seems to be a safer and more reasonable way to provoke symptoms. Positive provocation findings typically include cough, dyspnea, fever, decrease in forced vital capacity and oxygen desaturation 8 to 12 hours after exposure. Because of the severity of the attack, patients should be monitored closely for at least 24 hours.

PATHOGENESIS

The pathogenesis of HP is complex, and the mechanisms involved are poorly understood. The presence of circulating precipitins to the relevant exposed antigens supported the concept that the disease is mediated by the deposition of antigen/antibody complexes within the alveolar walls (type III hypersensitivity).

However, several findings are not consistent with this hypothesis: (1) patients may develop disease but may lack serum precipitins, (2) histopathology does not show vasculitis or prominent neutrophil infiltration, and (3) in animal models passive serum transfer followed by aerosol exposure is not able to induce histologic changes of HP. Histology of lymphocytic interstitial infiltrates with granuloma formation and signs of macrophage and lymphocyte activation in BAL may suggest a cell-mediated immune reaction (type IV hypersensitivity).

There is evidence for overproduction of Th1 cytokines (interferon-γ, interleukin [IL]-12, and IL-18) along with tumor necrosis factor (TNF) receptors, counterregulators of TNF, by alveolar macrophages from patients with HP.

Although HP is typically defined as Th1 disease, chronic HP evolving to fibrosis seems to be characterized by a switch to a Th2-biased immune response. The BAL fluid analyses from patients with chronic HP show overproduction of a Th2 chemokine family (CXC chemokine receptor [CXCR] 4, thymus and activation-regulated chemokine [TARC]/C-C motif ligand [CCL] 17), and downregulation of a Th1 chemokine family (CXCR3, interferon γ–induced protein [IP]-10, interferon-γ). Although the mechanisms of HP have been partially clarified, it is still unclear why the disease develops only in a minority of exposed individuals. A 2-hit hypothesis suggested that the presence of an inducing factor (inhaled antigen) and a promoting factor (genetic susceptibility) may be essential for the development of HP. Several gene polymorphisms including TNF-α, transporter associated with antigen processing (TAP) genes, and the low-molecular-weight proteasome (LMP) 7 gene have been shown to be involved in the susceptibility HP. By contrast, polymorphisms in the tissue inhibitor of metalloproteinase (TIMP)-3 promoter gene may protect against the development of HP.

Toll-like receptors (TLRs) are expressed on immune cells and recognize various antigens. When specific TLRs are activated, many proinflammatory cytokines and mediators are released through an intracellular pathway (MyD88 pathway). In experimental models of HP, the expression of TLR-9 and CD34 are essential for the development of a Th1 granulomatous inflammatory response.
Despite this progress, it is still not known why some patients show resolution of disease and others progress to fibrosis even without further antigen exposure.

PATHOLOGY

The difficulty in the interpretation of pathology results from the lack of a gold standard defining HP. Pathologic analyses in acute HP are rare. A retrospective study of selected cases of acute HP showed nonspecific diffuse pneumonitis and interstitial inflammation in a peribronchiolar pattern with mononuclear cell and neutrophil infiltration and fibrin deposition. Intra-alveolar fibrin accumulation may be prominent in some selected cases with acute fibrinous and organizing pneumonia (AFOP).

Subacute HP is characterized by a lymphocytic, bronchiolocentric interstitial pneumonitis. The central regions of the secondary lobule are the predominant site to be involved. It is independent of the presence or absence of further antigen exposure. Lymphocytes with fewer plasma cells and histiocytes are the main cells associated with inflammation. The granulomas are typically small, loose, poorly formed, and non-necrotizing, with the exception of hot-tub lung. Granulomatous changes may be absent in approximately 30% of patients with HP. The staining with cathepsin K, a cysteine protease expressed in activated macrophages and epithelioid cells, may be useful for detecting microgranulomas in HP. Cathepsin K staining is negative in patients with desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis-ILD (RB-ILD), in which accumulation of alveolar macrophages is prominent. These findings suggest that cathepsin K may be a sensitive and specific marker to detect granulomas in chronic HP.

Chronic HP is characterized by progressive fibrosis, bronchiolitis obliterans, and architectural distortion in addition to the subacute changes. However, chronic HP may lack typical subacute changes. The pathologic patterns may mimic UIP, NSIP, OP, or peribronchiolar interstitial fibrosis. In late chronic stages, the pathologic findings may become more similar to IPF/UIP.

The characteristic pathologic findings supporting HP includes bronchiolocentric inflammation, peribronchiolar fibrosis, bronchiolar epithelial hyperplasia, and the presence of granulomas or multinucleated giant cells. Peribronchiolar metaplasia is frequently observed in HP, but is rare in IPF/UIP. Peribronchiolar (centrilobular) fibrosis often extends to the perilobular areas, and forms the appearance of bridging fibrosis. This pathologic finding can distinguish chronic HP from IPF.

Although pathologic changes in HP are uniform in distribution, lung biopsy specimens sometimes show discordant findings. This observation suggests that biopsy should be taken from at least 2 different lobes, as in IPF.

A recent study reported the coexistence of HP and pulmonary alveolar proteinosis (PAP). Although all patients had typical HRCT findings of PAP to a varying degree, typical HRCT findings of HP were sometimes absent. The linkage between HP and PAP is still unclear.

DIAGNOSTIC CRITERIA

Several diagnostic criteria for HP have been recommended. However, none of these criteria has been validated. The diagnosis of HP relies on a high level of clinical suspicion; the recognition of antecedent antigen exposure; and a constellation of clinical, radiologic, laboratory, and pathologic findings.

A large prospective multicenter cohort study (116 patients with HP, 284 control subjects with other ILD) showed that the diagnosis of HP could be made with 6
significant predictors (Box 2). If all of the 6 predictors are present, the probability of having HP is 98%. If none of the 6 predictors are present, the probability is 0%. Careful history taking is mandatory. Clinicians should have specific expertise concerning the relevant antigens to HP. Important factors are hay feeding, bird keeping, feather duvet and pillows in the home, air conditioning or ventilators in the buildings, and formation of mold on room walls or in the cellars. Indirect contact with birds should also be asked for, such as visits to friends or relatives who keep birds in their homes. Improvement on vacation or during hospitalization may also be a clue to the diagnosis.

HRCT is a useful diagnostic test. Although it may be normal in some patients, the sensitivity is more than 95%, and the finding of a centrilobular micronodular ground-glass pattern and evidence of mosaic perfusion (trapped air) is characteristic of HP. The major differential diagnosis in this setting is respiratory bronchiolitis/ILD or Pneumocystis carinii infection.

The most sensitive diagnostic test is BAL. In the author’s experience and based on literature review, a normal BAL widely excludes the diagnosis of HP. The characteristic finding is a lymphocytosis in the subacute and chronic forms. In asymptomatic sensitized individuals (subclinical alveolitis), BAL lymphocytosis is also apparent. BAL lymphocytosis greater than 30% is recommended as a discriminative factor of chronic HP showing UIP pattern on HRCT from IPF.

BAL analyses have complementary information on HRCT. Lymphocytosis is characteristic for HP, a predominance of smoker’s macrophages is characteristic for RB-ILD, and the presence of microorganisms is characteristic for Pneumocystis carinii pneumonia.

Pathologic evaluation of lung tissue is usually unnecessary for the diagnosis of HP. If needed, the preferred approach is surgical biopsy rather than transbronchial biopsy.

An important problem in the diagnosis of HP is that the relevant antigen cannot be identified in up to 20% to 30% of patients. In these patients the diagnosis must be suspected based on histopathology, BAL findings, and HRCT characteristics.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses include the wide spectrum of ILD, mainly idiopathic interstitial pneumonias (IIPs) and sarcoidosis. Frequent misdiagnosis is pneumonia in acute forms and chronic bronchitis in chronic forms with normal chest radiograph, which may occur in 20%. Chronic HP, especially the insidious form of bird fancier’s lung, may closely mimic IPF or idiopathic fibrotic NSIP.

Clinicians should be aware that HP must be considered in all cases of ILD, and a detailed environmental exposure history is mandatory. Fig. 3 shows the diagnostic algorithm for HP.

### Box 2

**Diagnosis of HP**

1. Exposure to a known offending antigen
2. Positive precipitating antibodies
3. Recurrent episodes of symptoms
4. Inspiratory crackles
5. Symptoms 4 to 8 hours after exposure
6. Weight loss
PITFALLS: EFFECT OF CIGARETTE SMOKING

HP is less frequent in smokers than in nonsmokers under the same exposure.24 Cigarette smoking seems to protect against the development of HP. When exposed to high levels of antigens, smokers have lower levels of specific antibodies to the causative antigen compared with nonsmokers.

Although the mechanisms of the protective effect of smoking against HP are unclear, nicotine seems to be one of the key factors.95 Nicotine inhibits macrophage activation, decreases lymphocyte proliferation, and impairs T-cell function.95,96

Although HP develops more frequently in nonsmokers, when HP occurs in smokers, the patients may develop a chronic clinical course with more recurrent episodes and a significantly poorer survival compared with nonsmoker patients.97

Fig. 3. Flow chart of diagnostic algorithm for HP. BAL, bronchoalveolar lavage; COP, cryptogenic organizing pneumonia; CT, computed tomography; NSIP, nonspecific interstitial pneumonia; RB-ILD, respiratory bronchiolitis-interstitial lung disease.
MANAGEMENT

Early diagnosis and antigen avoidance are key factors in the management of HP. Although complete avoidance of antigen exposure is difficult in some patients with HP, sustained antigen inhalation is associated with a poorer outcome.

Antigens may persist in rooms where birds have been kept for a long time. Feather pillows and blankets should be removed. Indirect and occasional exposure in the homes of friends or relatives where birds are kept should also be avoided. It is important to minimize microbial or avian antigen exposure by having a clean environment at home. The use of air-purifying respirators may be useful in some cases. Farmers should wear dust masks with filters, and ensure appropriate ventilation. Mechanization of the feeding process on farms and alterations in forced-air ventilatory systems may also be useful.

Corticosteroid therapy is usually recommended in patients who show functional impairment, although its long-term efficacy has not been evaluated in prospective clinical trials. Treatment continues until no further improvement in physiologic abnormalities is observed. An empiric therapy schedule may consist of 40 to 50 mg per day of prednisone for a month, followed by a gradual tapering during the next 2 to 3 months and a maintenance dose between 7.5 and 15 mg per day.

In chronic progressive HP, immunosuppressants may be added as corticosteroid sparing agents, as is done in other fibrotic ILDs.94

Routine follow-up investigations should be more narrow immediately after diagnosis and during treatment (1–3 months is appropriate); later the interval can be extended to every 6 to 12 months. If the course is favorable, with complete remission after avoidance of further exposure and/or corticosteroid treatment, routine follow-up can be stopped after 2 to 3 years.

Inhaled steroids or pentoxifylline may be other options of treatment98; however, their efficiency has not yet been validated.

In chronic progressive HP not responding to corticosteroid and/or immunosuppressant therapy, lung transplantation should be recommended.

PROGNOSIS

The prognosis of HP is variable and depends on the type, duration, and intensity of antigen exposure; the type of pathologic changes (UIP, NSIP, OP-like fibrosis, or emphysema); and possibly genetic background.9 The findings of fibrosis at lung biopsy or HRCT are associated with poor prognosis in patients with chronic HP and may serve as a useful prognostic indicator.93

Patients with OP-like or cellular NSIP-like fibrosis have a more favorable outcome than those with fibrotic NSIP-like and UIP-like fibrosis.94 The UIP-like and fibrotic NSIP-like fibrosis are associated with decreased survival.99

Some patients may experience progression, despite avoiding exposure and undergoing treatment. There is no good explanation for the mechanism. Acute exacerbation of chronic HP is associated with a poor prognosis.26 In a previous study enrolling 100 consecutive patients with chronic bird farmer’s lung, 14 patients developed an acute exacerbation, and 12 of them died of this episode.26

A previous surveillance in the United States showed that overall age-adjusted death rates in HP increased significantly ($P<.0001$) between 1980 and 2002, from 0.09 to 0.29 per million, although it is unclear what factors were associated with this increase.100 By contrast, another surveillance in England and Wales showed that the mortality in HP was almost stable between 1968 and 2008, from 0.04 to 0.08 per million.101
In general, acute HP seems to have a favorable prognosis. After acute attacks, if correctly and timely diagnosed and treated, patients usually have a complete remission. If acute attacks occur frequently, such as in some patients with farmer’s lung, the outcome may be the development of emphysema.

Patients with farmer’s lung who experienced recurrent attacks tend to have emphysema more frequently and lower diffusing capacity than patients who experienced only a single attack.102

Complications of lung cancer may affect the prognosis in HP. A recent retrospective review on 104 patients with chronic HP showed that the prevalence of lung cancer in chronic HP seems to be increased (10.6%), as seen in IPF.103

Pulmonary hypertension occurs in approximately 20% of patients with chronic HP, and is associated with a greater risk of death (see Box 2).104

SUMMARY

HP is a complex syndrome caused by repeated inhalation of environmental and occupational antigens. Clinical manifestations of HP may closely mimic other ILDs, including IPF or NSIP, and the disease onset is usually insidious; diagnosis of HP is therefore sometimes difficult. An appropriate removal of antigen exposure is essential for treatment of HP, otherwise the disease results in poor outcomes. Therefore, clinicians should be aware that HP must be considered in all cases of ILD, and should start the appropriate management as soon as possible.

REFERENCES


89. Akashi T, Takemura T, Ando N, et al. Histopathologic analysis of sixteen autopsy cases of chronic hypersensitivity pneumonitis and comparison with idiopathic