

## Hypersensitivity pneumonitis: a multifaceted deceiving disorder

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Hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, represents a heterogeneous group of diseases that result from inhalational exposure to various organic particles. In a susceptible host, it provokes a diffuse immunopathologic reaction of the small airways and pulmonary parenchyma [1]. HP may occur in several clinical forms (ie, acute, subacute, chronic), any of which may mimic multiple other diseases. A high degree of clinical suspicion and a meticulous occupational and environmental history are indispensable for accurate diagnosis. Recurrent subacute episodes and insidious chronic HP may lead to lung fibrosis or emphysema depending on several factors, including the nature of the inhaled particles, the amount and duration of exposure, and the host response. HP can be a serious and potentially life-threatening disorder.

### Antigens sources

There is a wide spectrum of causative antigens, such as mammalian and avian proteins, fungi, bacteria, and even certain small-molecular-weight chemical compounds, and new sources of airborne organic particles are continually being recognized (Table 1). A broad range of occupations increases the risk of developing HP. Outbreaks of HP have been observed in residential and office buildings [2–5]. Various water sources can act as reservoirs for microorganisms associated with HP, including heated water reservoirs, humidifiers, cool-mist vaporizers, wooden water buckets, water flume slides, water-damaged carpeting, and other sources in which water provides

a reservoir for fungi or bacteria growth. Cases of HP also have been reported among people exposed to contaminated water in swimming pools and hot tubs [6,7].

A contaminated home environment also is an important source of cases. Examples of home exposure include bird-keeping, use of ultrasonic humidifiers, and summer-type HP, an allergic alveolitis described in Japan that is caused by seasonal mold contamination (*Trichosporon asahii* or *Trichosporon mucoides*) [1,8–11].

### Some examples of classic or emergent types of hypersensitivity pneumonitis

#### *Bird-related hypersensitivity pneumonitis*

Probably the most common form of avian-related hypersensitivity develops among individuals exposed to pigeons, parakeets (budgerigars), and other small caged birds, such as finches and canaries, in the home environment [1,12]. The disease is induced by exposure to excreta and proteinaceous material on dried, finely dispersed dust from these birds [13]. Exposure also may occur from aerosol spread of droppings by the vent of a clothes dryer, contamination of heating vents from a garage in which the birds were housed, and exposure to feather duvets and pillows, wreaths, and down comforters [1,14].

The so-called avian antigens represent a complex mixture of proteins, and patients usually become sensitized to a wide range of these antigens [15]. Mucin and IgA are found in secretions from birds' gastrointestinal and respiratory epithelia, and they seem to be the main antigenic components.

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Table 1  
Some etiologic agents of hypersensitivity pneumonitis

Disease	Antigen	Source
<b>Fungal and bacterial</b>		
Farmer's lung	<i>Saccharopolyspora rectivirgula</i> , <i>Thermoactinomyces vulgaris</i> , <i>Absidia corymbifera</i>	Moldy hay, grain, silage
Ventilation pneumonitis; humidifier lung	<i>Thermoactinomyces vulgaris</i> , <i>Thermoactinomyces sacchari</i> , <i>Thermoactinomyces candidus</i>	Contaminated forced-air systems; water reservoirs
Metal-working fluid-associated HP	<i>Mycobacterium immunogenum</i>	Metal-working fluids
Mushroom worker's lung	<i>Thermoactinomyces sacchari</i>	Moldy mushroom compost
Malt worker's lung	<i>Aspergillus fumigatus</i> , <i>Aspergillus clavus</i>	Moldy barley
Woodworker's lung	<i>Alternaria</i> sp, wood dust	Oak, cedar, and mahogany dust, pine and spruce pulp
Sauna taker's lung	<i>Aureobasidium</i> sp, <i>pullularia</i>	Contaminated sauna water
Maple bark stripper's lung	<i>Cryptosporium corticale</i>	Mouldy maple bark
Cheese washer's lung	<i>Penicillium caseii</i>	Mouldy cheese
Sequiosis	<i>Pullularia</i>	Mouldy sawdust
Stipatosis	<i>Aspergillus fumigatus</i>	Esparto fibers
Suberosis	<i>Penicillium frequentans</i> , <i>Aspergillus fumigatus</i>	Cork dust
Hot tub lung	<i>Mycobacterium avium</i> complex; <i>Cladosporium</i> sp	Hot tub mists, mold on ceiling
Summer-type pneumonitis	<i>Trichosporon cutaneum</i>	Contaminated old houses
HP in peat moss processing plant workers	<i>Monocillium</i> sp, <i>Penicillium citreonigrum</i>	Peat moss processing plants
<b>Animal proteins</b>		
Pigeon breeder's disease	Avian droppings, feathers, serum	Parakeets, budgerigars, pigeons, chickens, turkeys
Furrier's lung	Animal fur dust	Animal pelts
Animal handler's lung; laboratory worker's lung	Rats, gerbils	Urine, serum, pelt proteins
<b>Chemical</b>		
Pauli's reagent alveolitis	Sodium diazobenzene sulfatate	Laboratory reagent
Chemical worker's lung	Isocyanates; trimellitic anhydride	Polyurethane foams, spray paints, elastomers, special glues
Epoxy resin luna	Phthalic anhydride	Heated epoxy resin
Pyrethrum pneumonitis	Pyrethrum	Insecticide

### Farmer's lung

Farmer's lung is one of the most studied forms of HP that results from repeated exposure to high concentrations or prolonged exposure to low concentrations of inhaled antigens from moldy hay or straw. Exposure to microorganisms varies widely according to farms and periods but reaches a peak when harvesting conditions favor excessive humidity in hay. The most common species implicated have been *Saccharopolyspora rectivirgula* and *Thermoactinomyces vulgaris* [16]. Recent studies in France and Finland have shown that *Absidia corymbifera* and, to

a lesser degree, *Eurotium amstelodami* are major etiologic agents, however [17,18].

### Mycobacterial-induced hypersensitivity pneumonitis

Exposure to aerosols of environmental opportunistic nontuberculous mycobacteria, including *Mycobacterium avium* complex (MAC), *M. terrae*, *M. komossense*, and *M. immunogenum*, have been implicated in outbreaks of HP in various settings, including metal-working fluid of machining and grinding operations, hot tubs, swimming pools, whirlpools, and water-damaged buildings [19]. Mycobac-

teria may be responsible for many outbreaks of HP in the workplace and home [19].

Although pulmonary disease caused by nontuberculous mycobacteria usually occurs in immunocompromised patients, this HP-like disorder arises in otherwise healthy, immunocompetent individuals. Exposure to metal-working fluid aerosols among industrial metal-grinding machinists can lead to HP, and mycobacteria, including the rapidly growing mycobacterial species *M immunogenum*, have been recovered from the metal-working fluid in several studies [20–23]. Metal-working fluids are used in the manufacturing process to cool and lubricate machined parts and remove metal waste, and they are contaminated easily by bacteria or fungi [20]. Research has shown that the use of hexahydrotriazine bactericides increases the likelihood of elevated mycobacterial growth in metal removal fluids [24].

MAC has received much attention because it likely has been responsible for several HP cases related mainly to exposure to hot tubs. MAC is thermophilic, resistant to chemical germicides, and readily aerosolized [25]. Association between hot tub lung and MAC has been proposed based on the identity of patient specimens and hot tub mycobacterial isolates by matching fingerprints with either restriction fragment length polymorphism analysis or multilocus enzyme electrophoresis [7,25–27]. Exposure to hot tubs also has been related temporally to onset of symptoms, and many patients improve or heal after avoiding hot tubs, even without pharmacologic treatment. Because it can be difficult to differentiate hypersensitivity reaction to MAC from a true infection, antimycobacterial therapy (in addition to corticosteroids) may be indicated.

#### *Chemical-induced hypersensitivity pneumonitis*

Although HP is classically associated with antigen (protein/micro-organism) exposure, inhalation of some low molecular weight chemical compounds also may provoke the disease. Workers exposed to toluene diisocyanate and diphenylmethane diisocyanate in the plastic manufacturing process, painting, and electronics industry may develop HP [28,29]. Diisocyanates contain the highly reactive isocyanate; various products, especially urethane resin, are made from these chemicals. A wide spectrum of respiratory disorders has been described as a result of exposure to diisocyanates, including bronchitis, asthma, and HP. The mechanisms involved in chemical-induced HP are still unclear, but it seems that diisocyanates may conjugate with some human proteins, such as serum albumins, and then elicit a humoral and cellular

immune response. IgG and IgA antibodies to diisocyanates have been detected in patients with diisocyanate-induced HP, and circulating lymphocytes proliferate and express various proinflammatory cytokines in the presence of diisocyanates [30].

#### *Clinical presentation*

Clinical manifestations of HP are classically divided into three forms: acute, subacute, and chronic [1,31]. Several situations influence clinical presentation, including the nature of the organic particle and the intensity and frequency of antigen exposure.

#### *Acute and subacute hypersensitivity pneumonitis*

Acute HP typically occurs 4 to 8 hours after intermittent and intense antigen exposure. Symptoms and signs begin abruptly and include fever, chills, severe dyspnea, chest tightness, and dry or mildly productive cough, which mimic a flu-like syndrome or atypical pneumonia. Symptoms gradually decrease over the next days but often recur after the next inhalation of the causative antigen.

Subacute HP is characterized by the gradual development of similar—although less severe—symptoms that occur during weeks or months after continued exposure. Patients consult with a physician primarily because of progressive dyspnea and cough, often accompanied by fever. Patients also complain of fatigue, anorexia, and weight loss.

#### *Chronic hypersensitivity pneumonitis*

The chronic form of HP may develop in two different settings [32]. One setting involves continuous, long-term, low-level antigen exposure. In this case, patients show few, if any, symptoms during the early stages. As a consequence, they may delay getting medical care for several months or even years after the onset of illness. The pivotal symptom in this insidious chronic form of HP is slowly progressive dyspnea on exertion. The disease may be misdiagnosed as idiopathic pulmonary fibrosis or other advanced fibrotic lung disorder if a careful history is not performed and specific studies are not conducted. Associated symptoms include cough, fatigue, malaise, and weight loss. The second way to develop chronic HP is through recurrent undiagnosed acute or subacute episodes [32]. Type of exposure seems to be a critical determinant of each chronic form. For example, patients with recurrent acute bird breeder's lung tend to breed dozens of pigeons in a loft,

whereas patients with insidious disease are likely to be exposed to smaller birds kept indoors [32,33].

Chronic HP may progress to pulmonary fibrosis or emphysema, although the reasons for this opposite outcome remain unclear. Interstitial fibrosis is a frequent consequence of chronic pigeon breeder's disease [32–35]. By contrast, although fibrosis also occurs in patients with farmer's lung, airway obstruction and emphysema seem to be more frequent chronic complications [36–38]. Whereas in some studies smoking seems to increase the risk for emphysema in patients with farmer's lung, in other studies it seems to be associated with a fibrotic response [37,39].

Upon examination of the thorax, tachypnea and bibasilar inspiratory crackles can be found in any clinical presentation of HP. Wheezing provoked by small airway obstruction may be found in some patients and may lead to an erroneous diagnosis (ie, asthma). Digital clubbing may be seen in advanced disease, and it seems to predict clinical deterioration [35]. In chronic cases, an increased pulmonic component of the second heart sound and peripheral edema are manifestations of pulmonary hypertension and cor pulmonale.

### **Cigarette smoking and its paradoxical effect on hypersensitivity pneumonitis**

Research has demonstrated that HP occurs more frequently in nonsmokers than smokers [9,40,41]. The putative protective mechanisms of tobacco smoke are unclear but seem to be related to its immunosuppressive effect, primarily on alveolar macrophages [42,43]. A marked decrease in macrophage expression of the B7 costimulatory molecules (CD80 and CD86) has been observed in smokers compared with patients with active HP [44]. Likewise, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and nicotine inhibit alveolar macrophage expression or release of several cytokines, including tumor necrosis factor alpha (TNF- $\alpha$ ), macrophage inflammatory protein-1 alpha, interleukin (IL)-12, nitric oxide, IL-10, and interferon-gamma [45,46]. The inhibitory effect has been observed even after specific in vitro stimulation with *Saccharopolyspora rectivirgula*. Acute exposure to cigarette smoke also may provoke apoptosis of alveolar macrophages [47].

When the disease does occur in current or recent ex-smokers, however, the clinical course seems to be more severe, and most patients experience recurrent episodes or an insidious type of onset with a worse survival rate compared with nonsmokers [39]. The reason is unknown, but it can be associated with an

increase in CD4<sup>+</sup> T-cells and in the CD4<sup>+</sup>/CD8<sup>+</sup> ratio [48]. Cigarette smoke also is a source of free radicals that may increase injury by damaging lung structural proteins [49]. Similarly, the expression and activity of matrix metalloproteinases, which are altered in chronic HP, are regulated by redox status [50].

### **Laboratory abnormalities and specific tests for diagnosis**

In acute and subacute episodes, slight to moderate neutrophilic leukocytosis with lymphopenia may occur. Elevated levels of C-reactive protein, erythrocyte sedimentation rate, and immunoglobulin IgG and IgM are usual but nonspecific findings. Rheumatoid factor and immune complexes also may be detected [1]. Plasma lactate dehydrogenase is elevated and decreases with improvement, which suggests that it may be useful in assessing the disease activity [51].

Serum-precipitating IgG antibodies against the offending antigens are usually detectable in patients with HP. Although these specific antibodies also may be found in some exposed but asymptomatic individuals, their presence is still one of the major diagnostic criteria for the disease. It is important to consider that the traditional precipitation techniques are unreliable, difficult to reproduce, insensitive, and impractical in daily laboratory work [52]. Commercially available (or laboratory prepared) enzyme-linked immunosorbent assay (ELISA) systems are generally recommended and mostly used.

Recently, the diagnostic and prognostic value of presumed disease-associated antibodies precipitating pigeon antigens (immunoglobulin A and P2 component) was determined in 90 patients with HP and 315 bird-exposed subjects by using co-immunoelectrodifusion [53]. Results showed a high specificity and sensitivity and an appropriate percentage of positive and negative predictive values.

Conversely, the advent of DNA-based technology offers new alternatives for reliable detection of microorganisms in contaminated fluids and patients. Polymerase chain reaction in combination with amplicon DNA, genome fingerprinting by pulsed-field gel electrophoresis, and quantitative competitive polymerase chain reaction have been applied successfully for identification and quantification of mycobacteria and pseudomonas [54]. Likewise, these molecular methods also are recommended for other bacteria. For example, it is difficult to distinguish phenotypically the eight species of the genus *Thermoactinomyces* spp. By means of partial 16S rDNA polymerase chain reaction amplification and direct

sequencing, all four isolates associated with mushroom worker's lung were successfully identified [55].

## Imaging

### *Chest radiograph*

Conventional radiology shows low sensitivity, mainly in patients with mild acute and subacute forms of HP [56]. In the acute form, transient diffuse or patchy ground-glass attenuation or some areas with air space consolidation can be observed. In the subacute form, the chest radiograph reveals a fine nodular or reticulonodular shadowing with some degree of ground-glass attenuation (Fig. 1). The chronic stages are characterized by a predominantly reticular pattern, which may evolve to honeycombing changes.

### *High-resolution computed tomography*

The sensitivity of high-resolution computed tomography (HRCT) for the detection of HP in individual cases and in population-based studies is greater than that of chest radiography [57]. HRCT shows low sensitivity in individuals with relatively mild disease, however, which limits its usefulness in screening of HP [57]. Ground-glass attenuation, which predominates in the lower lobes, is the most frequent feature in acute HP [36]. HRCT features in the subacute presentation include small, poorly defined nodules, patchy ground-glass opacities, and air trapping (mosaic pattern consistent with small airways disease) (Fig. 2A, B) [58]. A HRCT scan obtained at the end of expiration is useful for im-



Fig. 1. Chest radiograph of a patient with subacute HP shows a bilateral reticulonodular pattern. The abnormalities are more severe in the middle and lower lung zones.

proving visualization of the patchy air trapping images (Fig. 2C). Although areas of decreased attenuation are observed in many patients on inspiratory scans, additional areas of air trapping can be demonstrated on expiratory scans [59]. Findings of lung infiltration on inspiratory HRCT scans and air trapping on expiratory CT correlate with functional measures of restrictive and obstructive lung disease, respectively [60]. Thin-walled cysts, which resemble those seen in lymphocytic interstitial pneumonia, can be noticed occasionally in patients with subacute HP [61]. The combination of centrilobular nodules with air trapping and ground-glass attenuation particularly indicates the diagnosis [62]. In general, patients with subacute HP exhibit a return to normal or improvement of HRCT changes after cessation of exposure and treatment.

Patients with chronic disease also may exhibit centrilobular nodules and ground-glass opacities, but they usually show a reticular infiltrate (which suggests fibrosis) that may evolve to honeycombing (Fig. 2D). Air space consolidation may be observed in chronic HP that arises from recurrent subacute episodes, whereas honeycombing is observed more frequently in insidious chronic cases [32]. The presence of irregular fibrotic opacities, traction bronchiectasis, and honeycombing may mimic idiopathic pulmonary fibrosis [63]. The absence of air trapping and nodules and the characteristic basal and subpleural localization of the idiopathic pulmonary fibrosis lesions may help with the differential diagnosis. In farmer's lung, emphysematous changes frequently are seen and seem to be even more common than interstitial fibrosis [36]. Airway obstruction and emphysema also may be relevant in pigeon breeder's disease, and they may vary from areas of focal air trapping to diffuse emphysematous changes [56]. Occasionally, patients with chronic HP may show radiologic evidence of emphysema and interstitial fibrosis [36].

### *Physiologic features*

Lung functional abnormalities are neither specific nor diagnostic because similar changes are found in most interstitial lung diseases. Pulmonary function tests are characterized by a predominantly restrictive ventilatory pattern, with reduction of static lung volumes represented by decreased forced vital capacity and total lung capacity [1]. The static expiratory pressure-volume curve of lung compliance shifts down and to the right of the normal curve, whereas lung recoil increases over the entire range of the reduced inspiratory capacity. Because the disease also affects the peripheral airways, a decrease in the

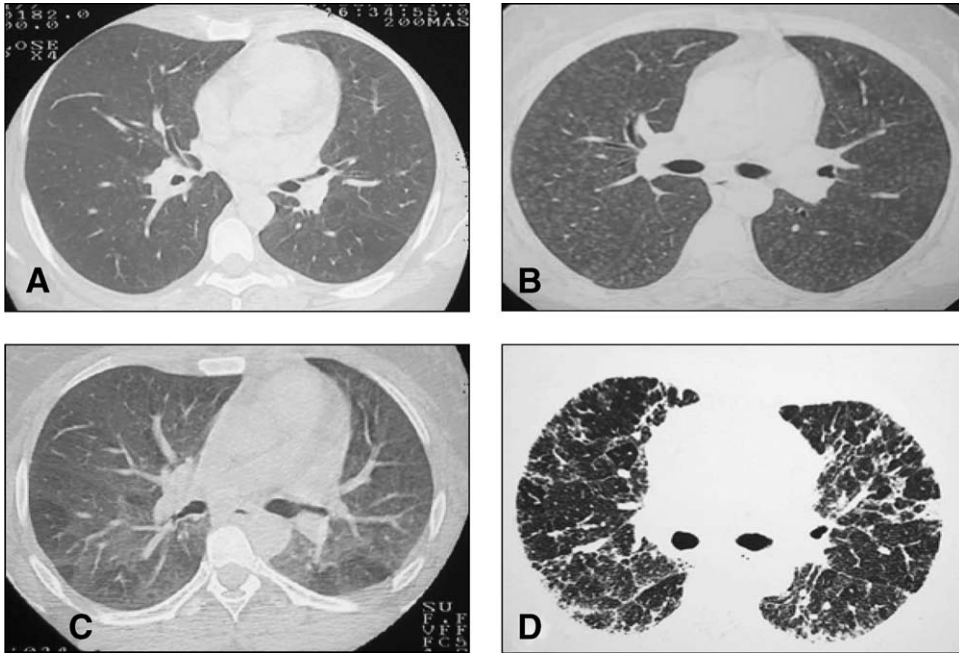


Fig. 2. (A) High-resolution CT (HRCT) scan of a patient with subacute HP shows ground-glass attenuation and bronchiolocentric micronodules. (B) HRCT demonstrates diffuse, small, poorly defined nodules. (C) HRCT at expiration of the same patient in (A) reveals patchy air trapping images (mosaic pattern). (D) HRCT scan in a patient with chronic HP exhibits reticular fibrotic opacities with few areas of ground-glass attenuation.

maximum to mid-flow rates and the ratio of dynamic to static lung compliance may be detected [64]. Correlations of CT abnormalities and functional patterns suggest that areas of decreased attenuation correlate with severity of air trapping (bronchiolitis) indicated by residual volume, whereas ground-glass opacification and reticulation correlate independently with restrictive lung function [60,65].

In the gas exchange analysis, patients exhibit resting hypoxemia, which usually worsens with exercise, normal or slightly reduced arterial carbon dioxide tension ( $\text{PaCO}_2$ ), and increased alveolar-arterial oxygen gradient ( $\text{P}[A-a]\text{O}_2$ ). In mild to moderate disease, patients may present with normoxemia at rest, but exercise reveals hypoxemia. Arterial pH is typically normal.

A variable decrease in the diffusing capacity of the lung for carbon monoxide ( $\text{DL}_{\text{CO}}$ ) is usually revealed. Research recently demonstrated that an extended method of measuring exhaled nitric oxide (NO) at several exhalation flow rates may determine alveolar nitric oxide concentrations and distinguish alveolitis from airway hyperreactivity and normal lungs [66]. The study, which was performed in patients with HP and idiopathic pulmonary fibrosis, also showed that the alveolar nitric oxide concentra-

tion correlated negatively with  $\text{DL}_{\text{CO}}$ , vital capacity, and alveolar volume, which suggests that it may be a marker of disease severity.

A few hours after antigen exposure, patients with HP show an increase of  $\text{P}(A-a)\text{O}_2$  and functional dead space ventilation during exercise, with a reduction of the breathing reserve [67]. Some patients, primarily those with farmer's lung, may show an obstructive pattern with decreased forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio and increased residual volume [68]. Functional long-term sequelae of these patients can be restrictive (fibrosis), obstructive (emphysema), or mixed [68,69].

### Bronchoalveolar lavage

HP is a lymphocytic alveolitis characterized by a remarkable increase in bronchoalveolar lavage (BAL) lymphocytes, typically T cells, often more than 50% (Fig. 3) [70–74]. BAL lymphocytosis (which takes place to expend alveolar macrophages that significantly decrease) occurs regardless of the clinical form and type of inhaled antigen. In this context, evaluation of BAL cell pattern may be useful to distinguish HP from other forms of interstitial lung diseases.

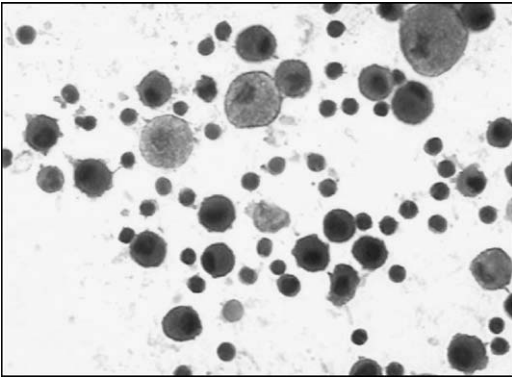


Fig. 3. BAL cell profile in a patient with subacute HP. The predominant cells are lymphocytes.

Patients with chronic HP exhibit a smaller increase of BAL lymphocytes compared with the acute or subacute presentation [32,72,75]; however, a value of less than 30% makes diagnosis of HP uncertain.

By contrast, the evaluation of cell phenotypes, primarily  $CD4^+/CD8^+$  T-cell subsets, has given inconsistent results. Several studies have reported an increase of  $CD8^+$  T cells with a decrease in the  $CD4^+/CD8^+$  ratio [1,71,72,76–78]. Some studies have shown that both subpopulations accumulate without changes in the ratio, however, whereas other studies have reported a clear predominance of  $CD4^+$  T cells with the consequent increased  $CD4^+/CD8^+$  ratio [48,73,79,80]. Several reasons may account for this variability, including the type of HP, the clinical presentation, and the time elapsed between last antigen exposure and the attainment of BAL [11]. For example, significant differences between summer-type HP (decreased  $CD4^+/CD8^+$  ratio) and pigeon breeder's disease (increased  $CD4^+/CD8^+$  ratio) with intermediate values in humidifier lung have been reported [79]. HP caused by MAC also displayed increased  $CD4^+$  subset and  $CD4^+/CD8^+$  ratio [27,81]. Likewise, smokers and patients with chronic HP exhibit higher levels of  $CD4^+$  [11,48]. In summary,  $CD4^+/CD8^+$  ratio varies, and currently there is no rule to distinguish when one or the other subset increases. A predominant accumulation of  $CD8^+$  seems to be a feature primarily in nonsmokers with acute or subacute HP, whereas a prevalent elevation of  $CD4^+$  frequently is found in smokers or individuals with chronic or fibrotic forms of the disease.

Based on the nature and proportion of cytokines that T cells release, diseases can be characterized (putatively) as either T-cell helper (Th) 1 or Th2-type disorders. In HP, a predominance of interferon gamma that produced BAL T cells was identified in patients

with HP, which suggested a polarized type 1 cytokine profile [82]. Increased natural killer cells, non-major histocompatibility complex-restricted cytotoxic lymphocytes, and lymphokine-activated killer cells have been detected in BAL from patients with HP [1].

Patients with acute HP or individuals in the early stages (hours/days) after antigen exposure or challenge also display an increase of BAL neutrophils and a modest increase in plasma cells and mast cells [1,34,83–88].

### Histopathologic features

Experience on acute HP is scant, but morphology is characterized by interstitial infiltration of neutrophils, lymphocytes, plasma cells, and macrophages. The alveolar spaces may contain amorphous proteinaceous exudates, edema, or hemorrhage [31].

The histologic hallmark of subacute and chronic HP is a bronchiolocentric interstitial granulomatous pneumonitis (Fig. 4A) [89]. The interstitial pneumonitis is mostly mononuclear and composed predominantly of lymphocytes, plasma cells, and macrophages. Differences are present in the granulomas depending on the type of HP. For example, in bird breeder's lung, granulomas are usually small, poorly differentiated, and loosely arranged [33]. By contrast, histologic examination of hot tub lung usually reveals exuberant non-necrotizing, frequently bronchiolocentric granulomas [90]. Bronchiolar changes also seem to vary according to the type of HP. Whereas proliferative bronchiolitis obliterans has been described in farmer's lung [91], peribronchiolar inflammation and fibrosis with smooth muscle hypertrophy and extrinsic narrowing of the small airways lumen have been reported in chronic pigeon breeder's disease [92]. Several patients presented with areas of organizing pneumonia with typical intra-alveolar buds composed of loose collagen-embedding fibroblasts and myofibroblasts.

The chronic stage is characterized by variable degrees of interstitial fibrosis (Fig. 4B). When present, the association of mild or moderate infiltration with lymphocytes, some giant cells, and the occasional observation of poorly formed granulomas may indicate that the pulmonary fibrosis may be secondary to HP. Destruction of the normal architecture may result in extensive honeycombing [33,93].

Researchers recently demonstrated that some patients with HP may present with a pattern of nonspecific interstitial pneumonitis (NSIP) as the sole histopathologic finding [94]. The most important difference is that NSIP exhibits a temporally and geo-

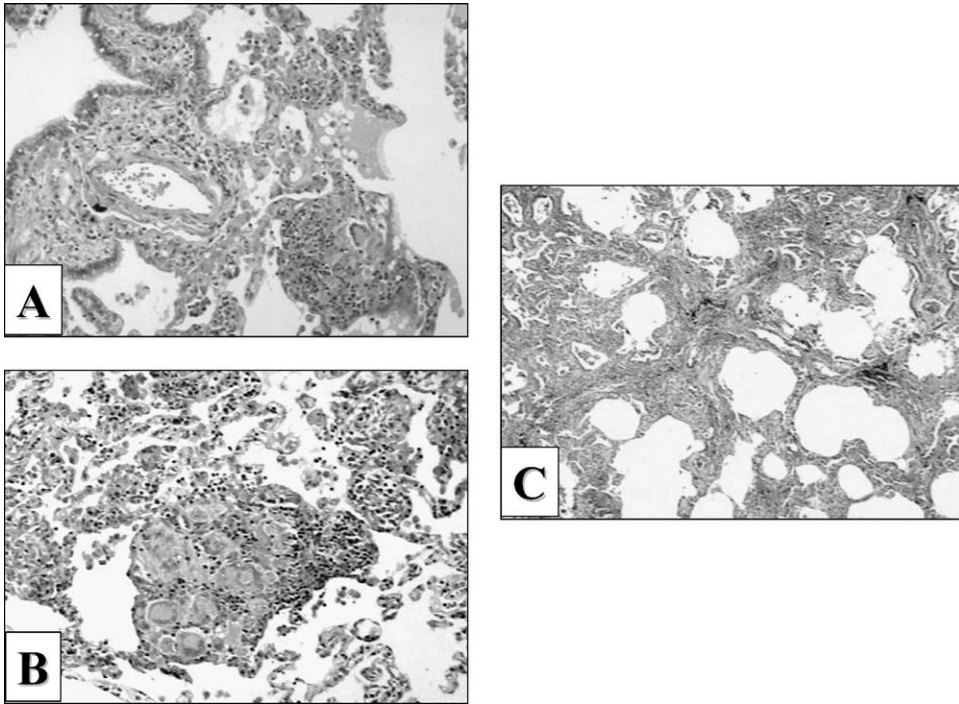


Fig. 4. (A, B) Granulomatous lesions in patients with subacute HP consist mostly of a cluster of giant cells and lymphocytes. There is also moderate interstitial lymphocytic infiltrate. (C) Lung biopsy of an insidious chronic case shows an area of fibrosis with cystic remodeling and loss of architecture.

graphically uniform inflammatory or fibrotic lesion without the characteristic bronchiolocentricity of HP. This NSIP pattern also has been found in approximately 5% to 10% of cases of bird breeder's lung (unpublished observations). The lesson is that the pathologic diagnosis of NSIP requires a clinician to be vigilant in questioning patients as to potential home or workplace antigen exposures.

A study that included 22 patients with chronic bird breeder's lung who underwent biopsy showed that patients with recurrent subacute episodes displayed mostly a NSIP pattern, whereas most of the insidious chronic cases exhibited interstitial fibrosis indistinguishable from usual interstitial pneumonia. Lymphoid hyperplasia, intraluminal organizing processes, and diffuse interstitial infiltration of inflammatory cells were the outstanding histologic features. Granulomas were found only in 18% of the cases [32].

A provocative study suggested that several patients with otherwise idiopathic interstitial pneumonia diagnosed by biopsy may have had an organic particles-induced lung disease [95]. Morphologic diagnosis included chronic eosinophilic pneumonia, NSIP, usual interstitial pneumonia, bronchiolitis oblit-

erans organizing pneumonia, and nonclassifiable morphologic patterns. Most of the patients were free of active disease after remediation of the environmental contamination, with a mean survival of 8.2 years. This report, if confirmed, suggests that in some settings a spectrum of interstitial lung diseases also may be caused by inhalation of organic dusts in the home or workplace, as described with HP.

### Differential diagnosis

#### *Acute hypersensitivity pneumonitis*

Acute HP closely mimics a respiratory tract infection. Without a history of illness occurring within hours of exposure to an identifiable antigen, the clinical syndrome is indistinguishable from an acute respiratory infection, such as an episode of flu, or from an atypical pneumonia caused by viral or mycoplasma agents [96].

In some types of HP, particularly in farmers, the differential diagnosis must include organic dust toxic syndrome provoked by exposure to bacterial endotoxins and fungal toxins of moldy hay [97,98].



Important for the differential diagnosis, no specific antibodies against usual offending antigens are found in patients with organic dust toxic syndrome. They usually present with normal clinical findings upon respiratory examination and chest radiographs. The syndrome is characterized by a flu-like symptomatology and may include mild dyspnea, chest tightness, and wheezing.

#### *Subacute and chronic forms*

Subacute and chronic HP may mimic virtually any interstitial lung disease. Differential diagnosis of the subacute form of the disease includes some granulomatous lung infections, such as tuberculosis or histoplasmosis, and noninfectious granulomatous lung disorders, mainly sarcoidosis [1,99]. Many nongranulomatous lung disorders, such as lymphoid interstitial pneumonia, cryptogenic organizing pneumonia, and idiopathic NSIP, may mimic HP. Chronic HP may be confused with idiopathic pulmonary fibrosis, and lung biopsy often is required for a precise diagnosis [32,33,100].

#### **Basic diagnostic criteria**

Criteria for HP diagnosis include a high index of suspicion by the clinician. A detailed history of occupational and home (direct and indirect) exposures is critical. The starting points for the diagnosis of acute HP are (1) evidence of exposure, documented by history and specific antibodies (when the test is available); (2) flu-like syndrome, (3) increased BAL lymphocytes and neutrophils, and (4) partial but significant improvement after removing the patient from the suspected environment and worsening after re-exposure.

Diagnostic criteria for subacute HP include (1) evidence of exposure with cause-effect relationship and precipitins against the offending antigen, (2) BAL lymphocytosis (usually more than 50%), (3) diffuse micronodular pattern with air trapping and ground-glass attenuation on HRCT.

In a recent collaborative study designed to identify diagnostic criteria and develop a clinical prediction rule for this disease, six significant predictors were identified: (1) exposure to a known offending antigen, (2) positive specific precipitating antibodies, (3) recurrent episodes of symptoms, (4) inspiratory crackles on physical examination, (5) symptoms occurring 4 to 8 hours after exposure, (6) and weight loss [101]. These predictors may facilitate diagnosis

of HP, primarily acute or subacute presentation, especially in areas of high prevalence.

For occupational outbreaks, an HP diagnostic index recently was developed to help reduce the uncertainties in case identification [102]. The index was based on (1) work-related symptoms, (2) dry crackles on auscultation, (3) restrictive spirometry, (4) decreased diffusion capacity or increased A-a oxygen gradient, (5) elevated erythrocyte sedimentation rate, (6) abnormal radiographic images, and (7) abnormal gallium scans. It was demonstrated to be useful in identifying patients with HP.

Insidious chronic HP may mimic idiopathic pulmonary fibrosis or advanced fibrotic stage of any interstitial lung disease [32,33]. In these cases, a precise diagnosis may be difficult to achieve. In addition to the criteria mentioned for subacute HP, at least two additional tools can be used: (1) environmental or laboratory-controlled challenge test with the suspected antigen [34,103] and (2) lung biopsy. Fever and significant reduction in lung function are common a few hours after inhalation challenge in patients with chronic HP. These factors may facilitate the diagnosis. Cardiopulmonary exercise testing also may help to identify individuals with possible subclinical HP [67].

#### **Management and outcome**

Early diagnosis and prevention of recurrent antigen exposure are critical, and these steps are enough to improve or heal most patients while continued antigen inhalation is one of the identified causes of progression. A combination of interventions, including fluid management, improved fresh air ventilation, and medical surveillance or restriction, is important to decrease the incidence of occupational risk. Preventive maintenance checks should be performed routinely to ensure that all water systems and heating, ventilation, and air conditioning equipment are properly maintained and that the indoor environment is clean. The use of dust masks may significantly reduce acute episodes of farmer's lung [104], but they are usually uncomfortable.

Recommended interventions in metal-working facilities include improving metal-working fluid management practices, enclosing selected metal-working fluid machining operations, eliminating mist cooling, increasing general dilution ventilation, and providing worker training [105]. Cleaning one's home also is important in home-related HP. Eliminating *Trichosporon cutaneum* from the colonizing places or birds prevents summer-type or bird-related HP relapses. It is important to consider that high levels of bird

antigen may persist for prolonged periods of time despite removal of the birds and a complete environmental clean-up [106].

Corticosteroids can be used as a pharmacologic approach, but they do not replace the need to keep patients away from antigen exposure. Although long-term efficacy of corticosteroid therapy remains to be established definitively, oral corticosteroids are often used. In a controlled study in farmer's lung, researchers demonstrated that on the basis of lung function, a relatively short course of corticosteroids accelerated the recovery from the acute stage, but they had no beneficial effect on long-term prognosis [107]. There are no prospective, randomized, placebo-controlled trials for other types of HP or subacute or chronic stages.

Patients with hot tub lung (MAC-related HP) have been treated with corticosteroids alone, antimycobacterial therapy, or both, with significant improvement at the time of follow-up [81,90]. Inhaled corticosteroids theoretically could be used to reduce the severe side effects of long-term systemic steroid therapy. There is little experience with this approach, however [108,109]. The potential of TNF- $\alpha$  inhibitors, such as infliximab and etanercept, as remission-inducing agents in subacute and chronic HP could be (with the exception of MAC-induced HP) tried, but currently there is no clinical experience in this disorder. As with any other fibrotic lung disorder, there is no antifibrotic treatment for chronic advanced patients, and lung transplantation should be considered.

### Prognosis and survival

Patients with acute bird-related HP usually have a favorable outcome [110]. By contrast, patients with the chronic form may develop diffuse lung fibrosis and eventually may die from the disease [33,35,111]. Patients with acute farmer's lung who stayed on the farm have subnormal values for pulmonary function but comparable values to individuals who left their farms [112]. In a 14-year follow-up of patients with farmer's lung, impairment of the pulmonary transfer factor and airway obstruction were the most important long-term consequences [113]. Lung emphysema seems to be a major long-term risk in farmer's lung [37,38].

### Pathogenic mechanisms

HP is associated with various occupational and residential antigens, but only a small percentage of

exposed people develop the disease. This observation strongly suggests that HP is probably the result of a double-strike process, but an unambiguous promoting cofactor has not been identified. How antigen exposure, environment, and genetics interact to induce or prevent HP is not known.

### Promoting factors

#### *The genetic connection*

The role of host genetic factors in determining susceptibility to complex polygenic diseases has become evident but difficult to evaluate. In HP, several genes are likely to be involved, but studies are scant and have focused on the major histocompatibility complex. Initial research using serologic techniques did not consistently identify major histocompatibility complex alleles or haplotypes associated to HP [1]. By using polymerase chain reaction–based major histocompatibility complex class II typing, we have demonstrated that several alleles and haplotypes of major histocompatibility complex class II alleles are implicated in conferring HP susceptibility (HLA-DRB1\*1305/HLA-DQB1\*0501) or resistance (HLA-DRB1\*0802) in bird-related HP in Mexican patients [114]. Analysis of polymorphisms of the 5' promoter region of the TNF- $\alpha$  gene showed that patients who exhibited the TNF-2-(308) allele were younger, presented the disease after less time of bird exposure, and displayed a more active inflammatory process [114]. TNF- $\alpha$  promoter polymorphisms also have been examined in farmer's lung together with the TNF- $\beta$  intron 1 gene polymorphism [115]. The frequency of the TNF- $\alpha$ 2 allele, a genotype associated with increased TNF- $\alpha$  expression, was higher in patients with farmer's lung than in controls or patients with pigeon breeder's disease.

Preferential usage of several V beta regions of T-cell receptor genes was observed in three familial cases with summer-type HP, but no correlation between the HLA type and the TCR V gene usage was found [116].

As in humans, strains of HP-resistant and HP-sensitive mice exist, and research has suggested that Th1/Th2 polarization of the immune response after antigen exposure determines susceptibility to the disease [117]. Specifically, the Th1-biased C57BL/6 mice are susceptible to experimental HP, whereas Th2-biased mice are resistant to developing HP [118]. Susceptibility was associated to decreased IL-4 mRNA stability with lower IL-4 expression by CD4<sup>+</sup> T cells, without differences in the expression

of the Th1 cytokines IL-2 and IFN- $\gamma$  [117]. The possible relationship of this finding with the human disease is currently unknown.

#### *The viral connection*

A viral infection may be an environmental promoting cofactor for triggering the development of HP. There is the clinical belief that in some patients, prior viral infections may enhance the clinical expression of HP. An old study suggested that patients with farmer's lung were exposed to a wider variety of pathogens and showed higher frequency of complement-fixing antibodies against *Mycoplasma pneumoniae* and parainfluenza virus types 1, 2, and 3 [119]. More recently, research showed that common respiratory viruses, primarily influenza A, are often present in the lower airways of patients with HP [120]. A positive correlation between proportion of influenza A-positive macrophages and total number of BAL cells was observed [120].

Mice challenged with respiratory syncytial virus or Sendai virus infection augment the inflammatory response to subsequent *Saccharopolyspora rectivirgula* exposure that may persist long after the viral infection has declined [121,122]. Prior viral replication was necessary for this to occur, and the amplification of the pathologic process was likely mediated through the release of IL-8 with a greater early neutrophil-type response to the antigen and by the upregulation of Th1 immune response [121]. Potential theoretical mechanisms by which viral infection may promote HP include virus-induced mucociliary dysfunction, alteration of alveolar macrophage phagocytic functions, and increased secretion of chemokines that enhance the recruitment of lymphocytes to the lungs [120].

#### *Other exposures*

Cigarette smoking protects from HP, whereas exposure to other contaminants may increase susceptibility to HP. In an old study of two families with several members affected by the disease, researchers noticed that both families used a gamma isomer of hexachlorobenzene to eradicate mite infestations in their birds [123].

#### **Disturbed lung hypersensitivity**

Exaggerated local response to the offending antigen involves humoral and cellular processes [1,124]. It has been suggested that tissue damage in acute

episodes may have an immune-complex basis, which may explain the 4- to 8-hour late onset of symptoms after antigen inhalation that resembles the Arthus-type skin reaction after intradermal skin tests [1,125]. Formation of immune complexes in the lung parenchyma can activate the complement system with the generation of C3a and C5a, C3b, which covalently associates with immune complexes, and the C5b-9 membrane attack complex. Supporting an immune complexes-mediated injury are the findings of activated complement components: activated blood neutrophils and bronchoalveolar lavage neutrophilia in patients with acute HP and in patients studied a few hours or days after antigen inhalation challenge [34,126–128].

By contrast, a strong body of experimental and clinical evidence demonstrates that an exaggerated T-cell-mediated response plays a critical role in the inflammatory response of subacute and chronic forms of the disease [129]. Evidence includes the histopathologic features (T-cell lymphocytic alveolitis), the noteworthy increase of BAL T lymphocytes, and the cytokine production by antigen-stimulated lung T cells [71,130]. Likewise, cultured murine CD4<sup>+</sup> T cells from antigen-sensitized donors can transfer murine experimental HP adoptively, whereas B cells and antibodies fail to provoke the disease in response to the sensitizing antigen [131–133].

The mechanisms that account for the lymphocytic alveolitis in subacute and chronic HP are not completely understood but seem to include increased T-cell recruitment and migration, increased proliferation in the local microenvironment, in part caused by a defect in the ability of lung macrophages to suppress the proliferation of lymphocytes, and decreased programmed cell death [134–138]. A recent report suggested oligoclonal expansion of T cells that express homologous or identical complementary-determining region 3. T-cell clones isolated from blood and lung expressed similar, sometimes identical, junctional regions, which indicated that the immune reaction that occurred at lung level gives rise to a systemic reaction [139].

Recent experimental and clinical evidence suggests that a Th1-type cytokine network plays an important role in HP [82,131,140]. These findings should be viewed cautiously, however. First, the Th1/Th2 hypothesis rises from data obtained in animal models, primarily in mice, rather than in humans. Th1 and Th2 cells can be found in human disease but without the clear-cut polarization observed in mice [141]. There is a growing recognition that in many diseases clear distinctions cannot be made, and Th1 and Th2 cells often can be generated simultaneously.

Second, and perhaps more important, HP is not a homogeneous disease, and immunologic mechanisms involved in one subacute episode, in recurrent subacute episodes, or in insidious chronic disease can be substantially different. Third, it is possible that under certain circumstances, Th1 cell activity may decline while Th2 activity increases (Th1/Th2 switch hypothesis). To increase uncertainty, researchers demonstrated recently that mushroom workers, most of whom have specific serum precipitins and may develop HP, exhibited an increase in Th2 type cells, Th2/Th1 ratio, and serum IL-13 with decreased IFN- $\gamma$ , which indicated a Th2-biased status [142]. Follow-up showed that CD4<sup>+</sup> T and Th2 cells increased gradually as employment time lengthened, which indicated that mushroom antigens contain immunogenic substances that stimulate a Th2-like immune response.

#### *The fibrosis connection*

It is well known that many patients with repeated subacute episodes or insidious chronic HP develop interstitial fibrosis and eventually end-stage lung with similar features of usual interstitial pneumonia [1,32,33,48,100]. The sequence of the molecular mechanisms implicated in the resolution of the lymphocytic alveolitis and healing or in the abnormal extracellular remodeling and progression to fibrosis remains incompletely understood. Infiltrating mononuclear cells from unsolved inflammation may activate fibroblasts to proliferate and secrete extracellular matrix components. The observation that increased BAL CD4<sup>+</sup> T cells may be related with development of fibrosis is intriguing [48]. Mice depleted of CD4<sup>+</sup> T lymphocytes exhibited markedly diminished subepithelial fibrosis in the airways [143]. Endothelin-1 upregulation in the lungs resulted in development of progressive pulmonary fibrosis and recruitment of inflammatory cells, predominantly CD4<sup>+</sup> positive cells [144]. Because of the complex heterogeneity of T cells and the multiple regulatory functions of CD4<sup>+</sup> during antigen stimulation, many questions remain regarding its possible connection with the fibrotic response. Understanding the T cell–driven mechanisms of fibrosis may be important for identifying potential therapeutic molecular targets.

#### **Summary**

Hypersensitivity pneumonitis represents a group of immunologically mediated lung disorders provoked by recurrent exposure to various environmen-

tal agents. HP is multifaceted and may mimic almost any interstitial lung disease, some infectious diseases, and even bronchiolar disorders. In the absence of a diagnostic gold standard, diagnosis of HP requires a combination of clinical, environmental, radiologic, physiologic, and pathologic findings that represent a diagnostic challenge for clinicians and—in the chronic form—even for experienced pathologists. Therapeutic approach includes avoiding further exposure and, depending on the clinical form, the administration of a course of prednisone. New anti-inflammatory, immunoregulatory, and antifibrotic drugs are urgently needed for this and other interstitial lung diseases.

The precise cellular and molecular mechanisms involved in the pathogenesis of the disease are incompletely understood. Host susceptibility factors that may determine the occurrence, development, and severity of HP have not been elucidated, and studies have focused primarily on the major histocompatibility complex. Likewise, environmental promoting factors that may be critical for the pathogenesis of the disease are largely unknown. Several questions remain unanswered. For example, what is the explanation for the variability in the time of exposure (from days to years) and the beginning of symptoms in susceptible individuals? We ignore why some patients with subacute or chronic disease improve or heal, whereas others develop fibrosis. Vigorous research is necessary to reveal the relationships among gene polymorphisms, gene expression, gene products, and environmental agents putatively implicated in the development of HP and in the different disease phenotypes.

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