Chapter 8
Hypersensitivity Pneumonitis

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Introduction

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is a complex syndrome of varying intensity, clinical presentation, and natural history [1, 2]. Numerous provocative agents have been described around the world, including, mammalian and avian proteins, fungi, thermophilic bacteria, and certain small molecular weight chemical compounds (Table 8.1). Importantly, new HP antigens are being constantly described. For example, in the last 15 years evidence accumulate supporting that *Mycobacterium avium complex* (MAC), often from hot tub exposure, may provoke the disease [3, 4]. Therefore, in the presence of acute respiratory illness or a patient with a clinical behavior of an interstitial lung disease, clinicians should always consider HP in the spectrum of the differential diagnosis and should carefully search for any potential source of HP-related antigens.

The incidence and prevalence of HP remains largely unknown. Much of the epidemiological information has been derived from studies of farmers and bird fanciers and primary from acute cases. Both, prevalence and incidence of HP vary considerably around the world, depending upon disease definitions and diagnosis, intensity of exposure to offensive antigens, geographical and local conditions, cultural practices, and genetic risk factors. Farmer's lung disease is one of the most common forms of HP, affecting variable percentages of the farming population. For example, the mean annual incidence of farmer's lung among the entire farming population (standardized for age and sex to the total population in Finland in 1975) was 44 per 100,000 persons in farming [5]. However, more recent studies indicate that the incidence of farmer's lung is now in decline [6].

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R.P. Baughman et al. (eds.), *Pulmonary Hypertension and Interstitial Lung Disease*, DOI 10.1007/978-3-319-49918-5_8

Table 8.1 Identified agents that cause hypersensitivity pneumonitis

Disease	Antigen	Source
Fungal and bacterial		
Farmer's lung	*Saccharopolyspora rectivirgula, Thermoactinomyces vulgaris, Absidia corymbifera*	Moldy hay, grain, silage
Mushroom worker's lung	*Thermoactinomyces sacchari*	Moldy mushroom compost
Malt worker's lung	*Aspergillus fumigatus, Aspergillus clavus*	Moldy barley
Woodworker's lung	*Alternaria* sp., wood dust	Oak, cedar, and mahogany dust, pine and spruce pulp
Maple bark strippers' lung	*Cryptostroma corticale*	Moldy maple bark
Cheese washers' lung	*Penicillium casei*	Moldy cheese
Sewage worker's lung	*Cephalosporium*	Sewer
Sequiosis	*Pullularia*	Moldy sawdust
Stipatosis	*Aspergillus fumigatus*	Esparto fibers
Suberosis	*Penicillium frequentans, Aspergillus fumigatus*	Cork dust
Harwood lung	*Paecilomyces*	Hardwood processing plant
Bagassosis	*Thermoactinomyces sacchari*	Moldy sugarcane
Sauna taker's lung	*Aureobasidium* sp., *Pullularia*	Contaminated sauna water
Ventilation/humidifier lung	*Thermoactinomyces vulgaris, Thermoactinomyces sacchari, Thermoactinomyces candidus*	Contaminated forced-air systems; water reservoirs
Metal working fluid-associated HP	*Mycobacterium immunogenum*	Metal working fluids
Sax lung	*Candida albicans*	Saxophone
Hot tub lung	*Mycobacterium avium complex*	Hot tubs; swimming pools, whirlpools
Summer-type pneumonitis	*Trichosporon cutaneum*	Contaminated old houses
HP in peat moss processing plant workers	*Monocillium* sp. *Penicillium citreonigrum*	Peat moss processing plants
Animal proteins		
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, pelts proteins
Pituitary snuff taker's lung	Pork	Pituitary snuff
Chemical compounds		
Pauli's reagent alveolitis	Sodium diazobenzene sulfate	Laboratory reagent
Chemical worker's lung	Isocyanates; trimellitic anhydride	Polyurethane foams, spray paints, special glues
Epoxy resin lung	Phthalic anhydride	heated epoxy resin
Pyrethrum pneumonitis	Pyrethrum	Insecticide

A study estimating the incidence of HP in the UK showed that between 1991 and 2003 the incident rate for this disorder was stable at approximately 0.9 cases per 100,000 person-years [7]. Data from a European survey suggest that HP constitutes 4–13% of all interstitial lung diseases [8]. In general, the prevalence of HP is difficult to estimate accurately because it represents a group of syndromes with different causative agents, and because epidemiologic studies lack uniform diagnostic criteria. Overall, the prevalence and incidence of HP are low, in part because a number of individuals with mild HP are not detected and patients with subacute and chronic disease are misdiagnosed as suffering other type of interstitial lung disease.

It is well known that HP occurs more frequently in nonsmokers than in cigarette smokers under similar risk exposure [9–11]. However, when the disease occurs in smokers it seems to be characterized by an insidious and chronic presentation with a worst clinical outcome [12].

Pathogenic Mechanisms

The pathogenesis of HP is complex and probably involves the coexistence of genetic and/or environmental risk factors with the exposure to the offending HP antigen. The nature of the genetic predisposition is unknown, but susceptibility associated to the major histocompatibility complex (MHC) class II alleles has been reported [13]. More recently, it was shown that HP patients had a significant increase in the frequency of the immunoproteasome catalytic subunit (PSMB8) KQ genotype as well as of the allele Gly-637 and the genotypes Asp-637/Gly-637 and Pro-661/Pro-661 of the subunit of the transporter associated with antigen processing TAP1 compared to matched controls [14, 15]. PSMB8 participates in the degradation of ubiquitinated proteins generating peptides presented by MHC class I molecules while TAP transports peptides for loading on to class I MHC molecules that present them to cytotoxic T lymphocytes.

Some other host processes may also contribute as a risk factor. In this context, it has been recently reported that female HP patients show increased frequency of microchimerism, that is, the presence of circulating cells transferred from one genetically distinct individual to another [16]. In this study, fetal microchimeric cells was also revealed in bronchoalveolar lavage and lung tissues of HP patients demonstrating that these cells traffic to and home the lungs. However, the putative role of these microchimeric fetal cells in the HP lungs is presently unknown, although they seem to increase the severity of the disease.

Viral infections involving common respiratory viruses, primarily Influenza A, and the exposure to a second inhalatory injury (i.e., pesticides) may also have a promoting effect enhancing the development of HP [17, 18].

The mechanisms of hypersensitivity lung damage involve both humoral and cellular processes depending on the clinical presentation. Inflammation in the acute episodes seems to be provoked by immune-complexes deposit, which may explain the 4–8 h late onset of symptoms after massive antigen inhalation. Supporting this

concept are the findings of activated complement components, activated blood neutrophils, and bronchoalveolar lavage neutrophilia in patients with acute HP and in those studied few hours/days after antigen inhalation challenge [19–21].

By contrast, subacute and chronic HP appears to be mediated by an exaggerated T-cell-mediated response and actually, a striking increase of T-lymphocytes characterizes this disorder. The mechanisms implicated in the T-cell alveolitis are not completely understood but appear to include increased T-cell recruitment and migration, increased proliferation in the local microenvironment, and decreased programmed cell death [1, 22–26]. A recent global gene expression study identified a variety of genes typically associated with inflammation, T cell activation, and immune responses in the lungs of patients with subacute/chronic disease [27]. Genes related to T-lymphocyte activation included Src-like-adaptor 2, CD2, components of the T cell receptor complex (CD3-D, and -E), and the alpha chain of CD8. Likewise, MHC class II transactivator, the master regulator of MHC class II expression, and several genes encoding MHC class I and II molecules were also overexpressed. Several chemokines such as CXCL9 and CXCL10 which are involved in the recruitment of activated T cells and NK cells were upregulated. CXCR4 and CCR5 and their ligands CCL5 and CCL4 were overexpressed as well suggesting that the recruiting/homing program for lung lymphocytes involves multiple chemokines.

Clinical Behavior

The clinical features of the disease are usually similar, regardless of the type of the inhaled dust. In general, three overlapping clinical forms are recognized: acute, subacute, and chronic [1]. The nature of the antigen, as well as the intensity and frequency of antigen exposure influences the clinical presentation.

Acute HP

This form of HP usually follows a heavy exposure to an offending agent. Acute presentation is characterized by an abrupt onset of symptoms few hours after intermittent and intense antigen exposure. Patients present fever, chills, dyspnea, chest tightness, and dry or mildly productive cough. Removal from exposure to the provoking antigen results in improvement of symptoms within hours to days and complete resolution of clinical and radiographic findings within several weeks. However, the disease often recurs after the next inhalation of the causative antigen. Occasionally, respiratory failure mimicking adult respiratory distress syndrome may occur requiring intensive unit care management [28]. Acute HP behaves similar to an acute respiratory infection provoked by virus or mycoplasma [1]. In farmers, the differential diagnosis must include the organic dust toxic syndrome (ODTS) provoked by exposure to bacterial endotoxins and fungal toxins of moldy hay [29].

In contrast to patients with acute HP, ODTS patients have no precipitins to antigens of molds and usually present with normal clinical findings upon respiratory examination and chest radiographs. ODTS is usually self-limiting, with symptoms rarely exceeding 36 h.

Subacute HP

Subacute HP is characterized by progressive dyspnea and cough occurring during weeks or few months after continued exposure. Patients often display fever, fatigue, anorexia, and weight loss. Some improvement of symptoms is noticed if patients avoid further exposure, but takes longer than with the acute form of the disease (weeks to months), and usually pharmacological treatment is necessary.

Chronic HP

Chronic HP may exhibit different clinical behaviors [30–34]. One subgroup of patients evolves to interstitial lung fibrosis after recurrent acute episodes (chronic recurrent HP); other subgroup of patients presents slowly progressive chronic fibrotic disease with no history of acute/subacute episodes (chronic insidious HP), and finally a third subgroup may progress to a chronic obstructive lung disease. The reasons for these different outcomes (fibrosis versus emphysema) are unknown but it may be related with the characteristics of the inhaled antigen, the type of exposure, cigarette smoking status, and the genetic background. Pulmonary fibrosis is the general outcome of chronic HP induced by avian antigens while emphysematous lung lesions are observed in farmers exposed to thermophilic bacteria and fungi.

Subacute HP as well as chronic recurrent and insidious HP may mimic virtually any interstitial lung disease and the diagnosis may be extremely difficult. Differential diagnosis of subacute HP includes some lung infections such as miliary tuberculosis or histoplasmosis, as well as noninfectious granulomatous lung disorders like sarcoidosis. Also, several idiopathic interstitial pneumonias such as lymphoid interstitial pneumonia, cryptogenic organizing pneumonia, and idiopathic nonspecific interstitial pneumonia should be considered. Chronic HP (primarily the insidious form) may be misdiagnosed as idiopathic pulmonary fibrosis (IPF) or other advanced fibrotic lung disorder if a careful history and specific studies are not carried out [30, 31]. In this context, a recent study has shown that almost half of the patients previously diagnosed as IPF were subsequently diagnosed with chronic hypersensitivity pneumonitis, and most of these cases were attributed to exposure of occult avian antigens from commonly used feather bedding [32]. The authors conclude that chronic HP can be diagnosed in patients with clinical and HRCT findings of usual interstitial pneumonia meeting any one of the following three criteria: (1) Positive bronchial challenge testing (this criterion is reinforced by often coinciding with

positivity of specific IgG). (2) Specific IgG positivity and surgical lung biopsy sample compatible with HP or greater than 20% lymphocytes in BAL fluids. (3) Surgical lung biopsy sample or explanted lung showing histopathological features or characteristics of subacute HP [32].

Tachypnea and bibasilar dry crackles are common findings in any clinical presentation of HP. Patients with chronic insidious or recurrent HP may develop digital clubbing, pulmonary arterial hypertension, and even Cor pulmonale [1, 35].

Chest Imaging

The chest radiograph is useful to know that the patient has some kind of interstitial lung disease. However, it is generally nonspecific. Also, the sensitivity of chest radiographs for detecting HP seems to have steadily declined over the last decades [36], and patients with acute and occasionally mild subacute HP may exhibit normal chest x-ray. When abnormal, chest radiographs show nodular opacities with ground-glass attenuation in acute/subacute presentations while the chronic stages are characterized by a predominantly reticular pattern which may evolve to honeycombing changes.

Findings on High-Resolution Computed Tomography (HRCT)

Acute HP is characterized by a diffuse and hazy increase of parenchymal density (ground-glass attenuation) and occasionally by patchy or widespread air space consolidation [33]. Patients with subacute HP show areas of ground-glass opacities, small poorly defined centrilobular nodules, and mosaic attenuation (Fig. 8.1a, b; [37–39]). A CT scan obtained at the end of expiration is useful to detect patchy air trapping images. The micronodular pattern consists of poorly defined micronodules, usually of less than 5 mm in diameter, with a centrilobular distribution that affect both the central and peripheral portions of the lung. Chronic fibrotic HP is characterized by the presence of reticular opacities superimposed on findings of subacute HP. Reticulation may evolve to honeycombing, mainly in chronic patients that show slowly progressive (insidious) disease [Fig. 8.2, [30, 40]]. In these cases, the disease may mimic idiopathic pulmonary fibrosis. Patients with chronic farmer's lung show more frequently emphysematous changes than interstitial fibrosis [33, 34]. HRCT features that best differentiate chronic HP from NSIP included evidence of secondary lobular areas of decreased attenuation and vascularity, extensive upper lobe involvement, and the presence of centrilobular nodules. In contrast, findings that best differentiated NSIP includes relative subpleural sparing, absence of centrilobular ground-glass nodules, absence of honeycombing, and lack of air trapping. Finally, findings that best distinguish IPF from chronic HP include honeycombing without subpleural sparing or centrilobular nodules [41].

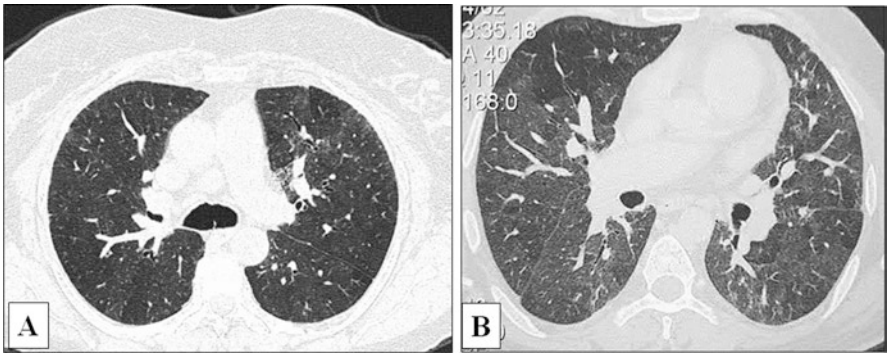

Fig. 8.1 (**a**) High-resolution computed tomography image showing bilateral poorly defined centrilobular nodules and ground-glass opacities in a HP patient with subacute presentation. (**b**) HRCT illustrates ground-glass opacities and areas of decreased attenuation (mosaic pattern) that are typical findings in subacute disease

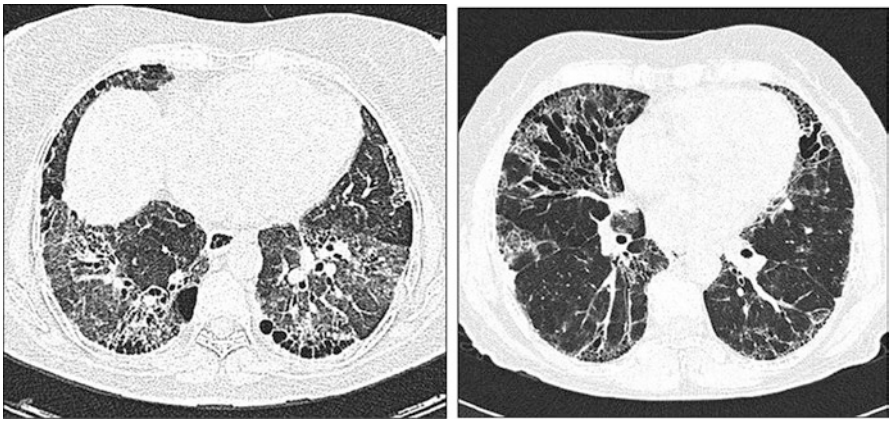

Fig. 8.2 HRCT scan of a patient with chronic HP. It can be observed bilateral reticular opacities, traction bronchiectasis, and subpleural microcysts. Idiopathic pulmonary fibrosis is the usual differential diagnosis

Physiologic Abnormalities

The main purpose of the pulmonary function tests is to determine the severity of the lung impairment. HP is characterized by a restrictive ventilatory defect with a reduction of forced vital capacity and total lung capacity [42]. The static expiratory pressure–volume curve is downward and rightward shifted of the normal curve, showing a decrease in lung compliance over the entire range of the reduced inspiratory capacity [43]. However, these changes are neither specific nor diagnostic for HP because similar abnormalities are revealed in most interstitial lung diseases.

Patients display impaired gas exchange characterized by hypoxemia which usually worsens with exercise and increased alveolar-arterial oxygen gradient [P(A-a) O2]. Patients with mild disease or in the early stages may present normoxemia at rest, but exercise always reveals hypoxemia. Diffusing capacity of carbon monoxide (DL_{CO}) is typically reduced being a good predictor of arterial oxygen desaturation during exercise.

Some degree of obstruction of the peripheral airways, as suggested by a decrease in the maximum to mid-flow rates and in the ratio of dynamic to static lung compliance, may be present due to bronchiolitis [44]. However, small airways obstruction is usually not detected by functional tests [45]. Nevertheless, in chronic farmer's lung, functional defects reflecting airways obstruction and emphysematous lesions can be noticed [34].

The correlation between pulmonary functional abnormality and the severity or prognosis of HP is poor. Patients with a severe decrease in lung volume and DL_{CO} may recover fully, whereas others with relatively mild functional abnormalities at the onset of disease may develop progressive pulmonary fibrosis or airway obstruction and emphysematous changes [1].

Hemodynamic Measurements

Several studies dealing with the effect of lung inflammation/fibrosis on pulmonary arterial vessels, hemodynamic, and cardiac function in HP have been recently reported. Previously (mostly from case reports), a marked pulmonary arterial hypertension (PAH) has been found in acute/subacute patients, where pulmonary embolism was suspected [46–50]. In an old study dealing with ten HP patients and performed with right heart catheterization, it was found that all patients had PAH and increased pulmonary arterial resistance [51]. Abnormal pulmonary artery diastolic pressure/pulmonary wedge pressure difference was noticed in most of the patients. Hemodynamic abnormalities correlated with arterial oxygen saturation and furthermore, a significant improvement was observed after oxygen breathing. Interestingly, all patients showed vascular abnormalities on samples of lung tissues. Most of them displayed medial hypertrophy in arteries and arterioles while in some of them cellular intimal proliferation in the smallest muscular arteries and intimal fibrosis were also seen. The study was performed in Mexico City at 2240 m altitude, and the authors concluded that alveolar hypoxia produced by HP, presumably enhanced by living at a high altitude, provoke pulmonary hypertension.

Other studies dealing with the histopathologic changes in HP have also reported vascular abnormalities including intimal hyperplasia and some muscle hypertrophy in chronic cases [52].

In our center we reviewed the clinical records of 87 patients with chronic HP in which an echocardiography was performed as part of their clinical evaluation. One-third of the patients exhibited increased pulmonary artery systolic pressure (Fig. 8.3). Higher defect in gas exchange was the only parameter that correlated with the

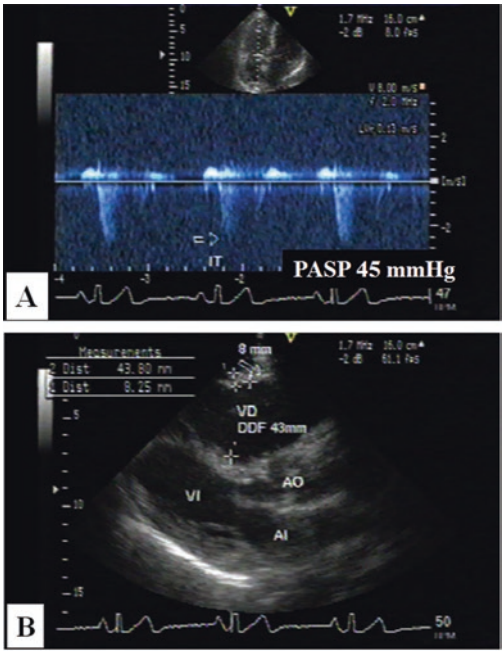

Fig. 8.3 Echocardiography in HP patients showing tricuspid insufficiency and increased pulmonary artery systolic pressure (**a**) and dilatation and hypertrophy of right ventricle (**b**)

Table 8.2 Oxygen saturation in patients with and without pulmonary arterial hypertension

	Without PAH ($n = 57$)	With PAH ($n = 30$)	P
PaO_2 (mmHg)	50 ± 10	45 ± 9	0.03
Rest SpO_2%	85 ± 7	80 ± 9	0.01
PASP	25 ± 4.7	51 ± 18.3	0.0001

PaO_2 arterial pressure of oxygen, *SpO_2* pulse oximetry, *PASP* pulmonary artery systolic pressure

presence of PAH (Table 8.2). Alveolar hypoxia may lead to vasoconstriction of small pulmonary arteries (hypoxic pulmonary hypertension) and right heart failure. Hypoxic pulmonary vasoconstriction contributes to ventilation–perfusion matching in the lung by diverting blood flow to oxygen-rich areas. With prolonged hypoxia, small pulmonary arteries suffer a process described as pulmonary vascular remodeling characterized primarily by thickening of the smooth vascular layer with neointima formation, medial thickening, inflammatory cell recruitment, and endothelial dysfunction. Both hypoxic vasoconstriction and architectural remodeling contribute to the development of progressive pulmonary hypertension.

It is important to take into account, however, that our study was performed with echocardiography that compared with right heart catheterism may give inaccurate measurement of systolic pulmonary artery pressure, mainly in patients with advanced lung disease leading to considerable overdiagnosis of pulmonary hypertension [53].

In a similar study, 73 patients with chronic HP and available Doppler echocardiography data were evaluated. Pulmonary hypertension (sPAP ≥ 50 mmHg) was detected in 14 patients (19%) and was associated with a greater risk of death. Patients with pulmonary hypertension were older and had a significantly decreased PaO_2. There was a weak correlation between pulmonary function parameters and the underlying sPAP, for FVC, FEV_1, and PaO_2 and inversely with $PaCO_2$ [54].

A more recent study assessed the hemodynamic changes in chronic HP by right heart catheterization. A prevalence of 44% of precapillary pulmonary hypertension was observed and the correlation with the pulmonary function tests suggested that the severity of pulmonary hypertension is proportional to the severity of lung alterations because it was more frequent among patients with lower lung function and hypoxemia [54]. Moreover, the dynamic exercise evaluation using cardiopulmonary exercise testing showed that patients with precapillary PAH had lower values than did the patients without PAH for FVC, DLCO, and PaO_2 [55].

Diagnostic Appraisal and Additional Tools for Difficult Cases

In general, the criteria for HP diagnosis should include a high index of suspicion by the clinician when dealing with an interstitial lung disease. In any case of an acute respiratory illness, or a subacute/chronic ILD, clinicians should always consider HP in the spectrum of the differential diagnosis and should carefully search for any potential source of HP-related antigens. Although the disease seems to be less frequent in children, it should be considered in any child with recurrent or unexplained respiratory symptoms [56, 57].

A key consideration in acute HP is the important improvement of a flu-like syndrome after removing the patient from the suspected environment and worsening after reexposure. Similar improvement although less dramatic can be also observed in the subacute form.

In a multicenter study that included a cohort of 400 patients (116 with HP and 284 with other interstitial lung disease), six significant clinical predictors of HP were identified [58]: (1) exposure to a known offending antigen, (2) positive precipitating antibodies to the offending antigen, (3) recurrent episodes of symptoms, (4) inspiratory crackles on physical examination, (5) symptoms occurring 4–8 h after exposure, and (6) and weight loss.

As mentioned, HRCT plays a central role for diagnosis. The acute form is characterized by ground-glass attenuation and confluent opacities. The subacute form is distinguished by centrilobular nodules, areas of ground-glass attenuation, a mosaic perfusion pattern, and air trapping on expiratory imaging. The chronic phase is characterized by irregular reticular opacities superimposed to some subacute changes and with associated architectural distortion.

Following are other important tests to evaluate patients with suspected HP:

Specific antibodies: Precipitating IgG antibodies against the offending antigens can be identified in the patient's serum. However, a percent of exposed but asymptomatic

individuals (mostly with a high degree of exposure) may also have positive serum precipitins [59–62]. Perhaps more important from the clinical point of view is that in a number of patients with chronic insidious HP circulating specific antibodies are not detected [30]. Therefore, the absence of serum precipitins does not rule out HP while the presence of them does not rule in. Ideally, it will be better to obtain a sample of the suspected causative agent from the original source and test it against the patient's blood.

Bronchoalveolar lavage (BAL): BAL may give important supportive evidence for diagnosis of HP because it is a highly sensitive tool to detect the alveolitis [1, 27, 63, 64]. The disease (in any of its clinical presentations) is characterized by a remarkable increment of lymphocytes, usually greater than 30% and often exceeding 50% of the inflammatory cells recovered (Fig. 8.4). However, as mentioned for the presence of specific antibodies, the presence of an alveolar lymphocytosis by itself does not establish the diagnosis because asymptomatic, exposed individuals can also have increased numbers of lymphocytes in their BAL [65]. Also, similar levels can be found in infectious and noninfectious granulomatous diseases such as sarcoidosis, berylliosis, or miliary tuberculosis.

It is the general belief that the main lymphocyte subset that increases is the $CD8^+$ with the subsequent decrease of BAL $CD4^+/CD8^+$ ratio to less than 1.0 [66]. However, a number of studies have found that CD4+ T-cells are increased with the consequent increased CD4+/CD8+ ratio [67, 68]. Several circumstances seem to explain this variability including the clinical form (acute, subacute, or chronic), cigarette smoking habit, type/dose of inhaled antigen, and the time elapsed since antigen exposure. A predominant increase of CD8+ seems to occur in nonsmokers

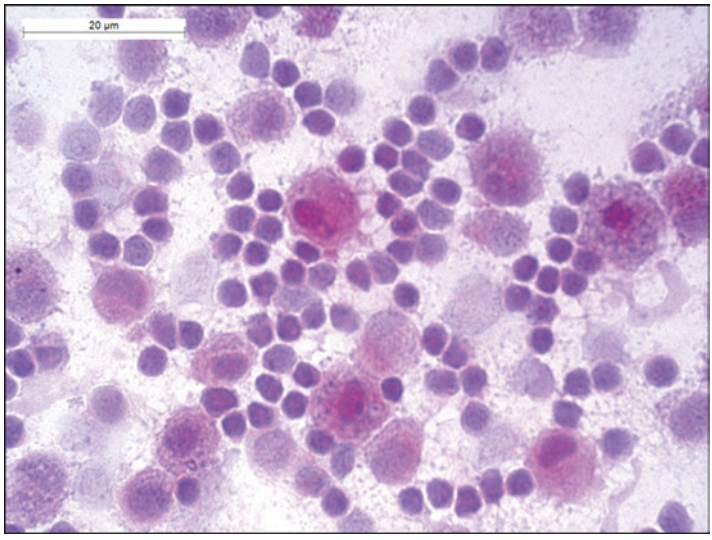

Fig. 8.4 Bronchoalveolar lavage from a patient with subacute HP. Most of the obtained cells are lymphocytes (hematoxylin & eosin, original magnification 20×)

with acute/subacute HP, while an increase of CD4+ is frequently found in smokers or those with chronic/fibrotic forms of the disease.

BAL neutrophils are usually elevated in acute cases and after recent antigen exposure [69]. Therefore, an increase in BAL lymphocytes and neutrophils in a patient with an acute respiratory syndrome is strongly indicative of HP. Also, a modest but significant increase of neutrophils is detected in advanced disease [70].

As well, several studies have reported slight but considerable increase of plasma cells mainly after recent exposure [71]. This finding together with the increase in T-lymphocytes may help to distinguish HP from others ILD [72]. Also, a small but significant increase of mast cells has been reported in HP [73, 74].

Antigen-induced lymphocyte proliferation: In vitro proliferation of peripheral and bronchoalveolar lymphocytes to avian antigens has been assayed for diagnostic and research purposes [30, 75]. Importantly, this test resulted to be positive in more than 90% of the recurrent and insidious cases of chronic pigeon breeder's disease where the presence of circulating antibodies may be negative [30]. Experiments also demonstrated that a positive stimulation index was usually 2.0 or higher. In a more recent study, it was found that antigen-induced lymphocyte proliferation in peripheral blood or bronchoalveolar lavage cells was positive in all the studied patients with chronic HP presumably caused by feather duvets [76].

Lung biopsy: Histopathological confirmation of the diagnosis is required in a number of subacute and chronic cases. It is critical that the pathologist is informed when HP is being considered; the findings are often subtle and must be interpreted with knowledge of the clinical presentation. This is particularly important because we now know that a relatively large number of patients with subacute or chronic HP may exhibit a different histological pattern, including nonspecific interstitial pneumonia [NSIP, [77]], cryptogenic organizing pneumonia (COP), or even usual interstitial pneumonia (UIP)-like changes.

Classical histopathologic findings include small, poorly formed noncaseating bronchiolocentric granulomas (Fig. 8.5a, b; [78]). These poorly defined aggregates of epithelioid macrophages are often associated with multinucleated giant cells. There is also a patchy mononuclear cell infiltration (predominantly lymphocytes and plasma cells) of the alveolar walls, typically in a bronchiolocentric distribution. Bronchiolar abnormalities are usually present although they may differ according to the type of HP. Thus, in farmer's lung it has been described proliferative bronchiolitis obliterans [79], while in pigeon breeder's disease peribronchiolar inflammation/fibrosis with smooth muscle hypertrophy and extrinsic narrowing of the small airways are usually found [45]. Occasionally, classic BOOP-like lesions are described [80, 81].

Chronic stage is characterized by variable degrees of interstitial fibrosis (Fig. 8.6a, b). In these cases, the presence of giant cells, poorly formed granulomas, or inflammatory features of subacute HP may corroborate the diagnosis of HP [30, 31, 82]. It has been proposed that three different patterns of fibrosis may occur: (a) predominantly peripheral fibrosis in a patchy pattern with architectural distortion and fibroblast foci resembling usual interstitial pneumonia, (b) temporal and geographic homogeneous interstitial fibrosis resembling fibrotic NSIP, and (c) irregular

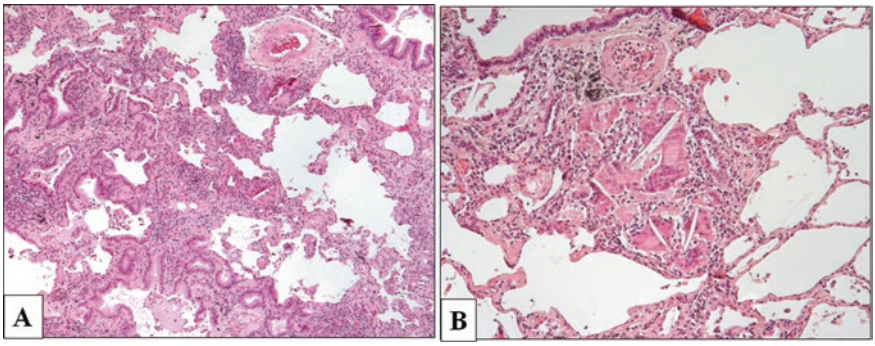

Fig. 8.5 (**a**) Photomicrograph of histopathologic specimen of a patient with subacute hypersensitivity pneumonitis showing diffuse, chronic lymphocytic inflammatory infiltrate (H&E 10×). (**b**) Another patient with subacute disease showing a granulomatous lesion with several multinucleated giant cells (H & E, 40×)

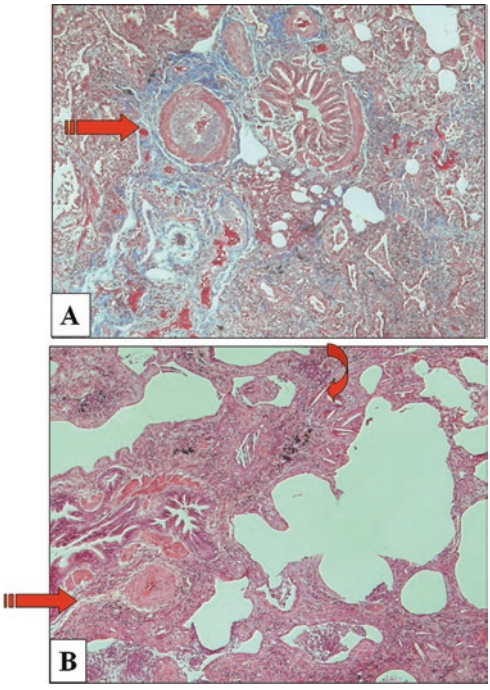

Fig. 8.6 (**a**, **b**) Photomicrographs of histopathologic samples from two patients with chronic HP showing collagen deposit [(**a**) Masson's trichrome, 10×] and honeycomb changes [(**b**) H & E, 10×]. It can be noticed the vascular remodeling (arrows). There is moderate inflammatory infiltrate and a small granuloma [(**b**) curved arrow]

peribronchiolar fibrosis [83]. Other features of chronic HP are alveolar epithelial cell hyperplasia and thickened arterioles [84]. Recently, our group reported that chronic HP may display seven morphological patterns including the "typical" one (characteristics already discussed), nonspecific interstitial pneumonia (NSIP-pattern), usual interstitial pneumonia (UIP-like pattern), mixed pattern, organizing pneumonia (OP-like pattern), airway-centered interstitial fibrosis (ACIF-pattern),

and nonclassified. UIP-like patients exhibited the worst survival rate while NSIP-like pattern showed the best survival [85].

Inhalation challenge test: Reexposure of the patients to the environment of the suspected agent may be recommended. Inhalation challenge in the hospital is not generally performed because lack of standardized antigens and limited access to a specialized setting to conduct the study. A positive challenge is characterized by fever, malaise, headache, peripheral and BAL neutrophilia, and decrease of FVC and/or oxygen saturation 8–12 h after exposure [75, 86, 87]. Inhalation challenge must be rigorously controlled to avoid an exaggerated reaction. In addition, the patient should be monitored closely for at least 24 h. Occasionally, the patient may present a two-stage reaction with an immediate, transient wheezing and a decrease in the FEV1 which is followed in 4–6 h by decrease in FVC, fever, and leukocytosis.

In our experience, false-positive results are obtained in approximately 15% of patients with other ILD but not in avian antigen exposed subjects, suggesting that provocation test can identify patients with HP in the majority of the cases [86]. In another more recent study, specific provocation test was performed in 59 patients with HP induced by avian antigens, and in 20 healthy pigeon keepers and 20 patients with diffuse interstitial lung disease other than HP as controls. The test was positive in 54 of the 59 patients with bird breeder's lung and negative in all controls; the authors concluded that the test had a sensitivity of 92% and a specificity of 100% [88].

Treatment and Prognosis

Early diagnosis, and identification and avoidance of the inciting antigen exposure are vital in the management of HP. In acute form avoidance alone may be sufficient intervention. In a study, no recurrence of summer-type HP was noticed when the colonization by *T. cutaneum*, the causative agent, was eliminated from the domestic environment. By contrast, recurrence was observed in all patients who resided in homes that were not cleaned or in homes where cleaning was not adequate [89]. In occupationally exposed individuals, the risk of HP can be reduced by adapting modern practices and conditions that reduce the content of causative antigens. Nevertheless, in chronic fibrotic HP patients subsequent antigen avoidance may not reverse the disease and some of them show progressive worsening and eventually die from the disease.

Prednisone is indicated in subacute/chronic presentations, although long-term efficacy of these agents has yet to be determined. An optional approach consists of 0.5 mg per kg per day of prednisone for a month, followed by a gradual reduction until a maintenance dose of 10–15 mg per day is reached. Prednisone is discontinued when the patient is considered to be healed (or after a substantial improvement of symptoms and functional abnormalities) or when there is no clinical and/or functional response. Inhaled corticosteroids have been suggested for acute/subacute cases but long-term experience is insufficient.

Reports in pediatric HP are scanty. In one study, monthly courses of high dose of intravenous methylprednisolone were used [90]. Additionally, oral prednisolone was employed in most cases, and according to severity, other immunosuppressive drugs such as azathioprine or cyclosporine were added. Most children improved, and no mortality was observed. In chronic advanced HP in adults, we also have explored the combination of prednisone plus azathioprine with some encouraging results. However, there is no solid published experience so far.

Since pulmonary hypertension may negatively influence the outcome, treatment with antihypertensive drugs such as sildenafil or iloprost may be considered on individual basis.

Progressive lung scarring that characterizes chronic advanced HP has no effective therapy, and lung transplantation should be recommended [1]. In a recent study, the survival posttransplant was evaluated in chronic HP and compared with IPF [91]. Survival at 1, 3, and 5 years after lung transplant was significantly better in HP (96%, 89%, and 89% versus 86%, 67%, and 49% in IPF). HP subjects manifested a reduced adjusted risk of death compared to IPF subjects. Interestingly, the diagnosis of hypersensitivity pneumonitis was made at explant in 16% of the patients emphasizing the diagnostic complexity of this disease when clinicians face a patient with chronic advanced interstitial lung disorder.

The prognosis of this disease for patients displaying the acute and subacute presentations is favorable (in the absence of further exposure) and most patients heal or display a significant improvement with some residual respiratory functional abnormalities remaining.

By contrast, patients with chronic HP, primarily pigeon breeder's disease, may evolve to interstitial fibrosis showing a high rate of mortality with median survivals of 5 and 7 years, respectively [31, 92].

Patients with farmer's lung, mainly those that experience recurrent acute attacks, develop more often a syndrome similar to chronic obstructive pulmonary diseases with airflow obstruction and emphysema, but survival data are unavailable [34, 93].

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