Chronic Hypersensitivity Pneumonitis

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KEYWORDS

• Hypersensitivity pneumonitis • Farmer's lung
• Bird fancier's disease • HRCT • Histopathology • Prognosis

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is a syndrome caused by an exaggerated immune response to the inhalation of a variety of antigenic particles found in the environment. Because the resulting inflammatory response is not confined to the alveoli, which the term extrinsic allergic alveolitis implies, but also involves the terminal bronchiole, the term HP pneumonitis may be more correct.

The development of disease and the clinical presentation is influenced by several factors, such as the nature and the amount of the inhaled antigen; the intensity and frequency of exposure; and the host immune response, which is likely determined by a genetic background. Genetic susceptibility may explain why one individual develops disease, another individual with exactly the same exposure is only sensitized but remains healthy, and still another one will not even become sensitized.[1]

CAUSATIVE AGENTS

Farmer's lung, a term coined by Pepys and colleagues,[2] is the prototype of HP. In 1962, Pepys and coworkers were the first to associate HP with the development of serum precipitins to hay and mold extracts.[2] Since then, many agents have been identified as potential causes and the number is ever increasing. The antigens may be fungal, bacterial, protozoal, and animal (mostly bird) proteins, or low-molecular-weight chemical compounds (**Table 1**). HP may potentially arise in any work or home environment where bacteria and fungi grow or birds are kept. Moreover, the intake of certain drugs may cause HP as a noninhalational variant.

New Environments and Causes

A new type of domestic ultrasonic humidifier (misting fountain) has been described as the cause of cases of humidifier pneumonitis.[3] The patients were exposed to mist from fountain water contaminated with bacteria, molds, and yeasts. The contaminated water reservoir of a steam iron was the cause of HP in a woman who developed symptoms strictly associated with the use of the steam iron.[4] Several cases caused by exposure to dry sausage molds have been reported.[5–8] Wind instruments, saxophone and trombone, contaminated with mycobacterial or fungal species have caused disease.[9–11] A chiropodist developed HP caused by inhalational exposure to fungi in the foot skin and nails of her clients.[12] A larger series of patients with feather duvet lung, a rare subgroup of bird fancier's lung, has recently been published.[13]

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Table 1
Environmental exposure and antigens in various types of hypersensitivity pneumonitis

Disease	Exposure	Antigen
		Microorganisms
Farmer's lung	Moldy hay, grain	*Saccharospora rectivirgula*, *Thermoactinomyces vulgaris*, *Aspergillus* spp
Humidifier lung; air conditioner lung	Contaminated humidifiers and air conditioners	Amoebae, nematodes, yeasts, bacteria
Misting fountain HP	Contaminated water	Bacteria, molds, yeasts
Steam iron HP	Contaminated water reservoir	*Sphingobacterium spiritivorum*
Suberosis	Moldy cork	*Penicillium* spp
Sequoiosis	Moldy redwood dust	*Graphium* spp, *Pullularia* spp, *Trichoderma* spp
Woodworker's lung	Contaminated wood pulp or dust	*Alternaria* spp
Wood trimmer's lung	Contaminated wood trimmings	*Rhizopus* spp, *Mucor* spp
Maple-bark stripper's lung	Contaminated maple logs	*Cryptostroma corticale*
Domestic allergic alveolitis	Decayed wood	Molds
Sauna taker's lung	Contaminated sauna water	*Aureobasidium* spp
Basement lung	Contaminated basements	*Cephalosporium* spp, *Penicillium* spp
Hot tub lung	Mold on ceiling, tub water	Mycobacterium avium complex
Swimming pool lung	Mist from pool water, sprays, and fountains	Mycobacterium avium complex
Thatched roof lung	Dried grasses and leaves	*Saccharomonospora viridis, T vulgaris, Aspergillus* spp
Bagassosis	Moldy pressed sugar cane (bagasse)	*Thermoactinomyces sacchari*, *T vulgaris*
Mushroom worker's lung	Moldy compost and mushrooms	*Saccharospora rectivirgula, T vulgaris, Aspergillus* spp
Malt worker's lung	Contaminated barley	*Aspergillus clavatus*
Cheese washer's lung	Moldy cheese or cheese casings	*Penicillium casei*
Dry sausage worker's lung	Moldy sausage dust	*Penicillium* spp
Paprika slicer's lung	Moldy paprika pods	*Mucor stolonifer*
Compost lung	Compost	*Aspergillus* spp, *T vulgaris*
Wine maker's lung	Mold on grapes	*Botrytis cinerea*

Tobacco grower's lung	Mold on tobacco	*Aspergillus* spp
Potato riddler's lung	Moldy hay around potatoes	Thermophilic actinomycetes, *Aspergillus* spp
Summer-type HP	Contaminated houses	*Trychosporon cutaneum*
Detergent lung, washing powder lung	Detergents (during processing or use)	Bacillus subtilis enzymes
Machine operator's lung	Contaminated metal-working fluid	*Pseudomonas* spp, nontuberculous mycobacteria, *Aspergillus fumigatus*
Stipatosis	Esparto dust	T actinomycetes
Peat moss HP	Contaminated peat moss	*Monocillium* spp, *Penicillium citreonigum*
Wind instrument lung	Contaminated saxophones, trombone	Molds, bacteria
Chiropodist's lung	Foot skin and nail dust	Fungi
		Animal proteins
Bird fancier's lung; pigeon breeder's lung	Parakeets, budgerigars, pigeons, parrots, cockatiels, chickens, turkeys, geese, ducks, love birds	Proteins in avian droppings, in serum and on feathers
Feather duvet lung	Feather beds, pillows, duvets	Avian proteins
Pituitary snuff taker's lung	Bovine and porcine pituitary powder	Pituitary proteins
Furrier's lung	Animal pelts	Animal fur dust
Animal handler's lung, laboratory worker's lung	Rats, gerbils	Proteins from urine, serum, pelts
Pearl oyster shell HP	Dust of shells	Pearl oyster proteins
Mollusk shell HP	Sea snail shell dust	Sea snail shell protein
Silk production HP	Dust from silkworm larvae and cocoons	Silkworm proteins
Miller's lung	Contaminated grain	*Sitophilus granarius* (ie, wheat weevil)
		Chemicals
Chemical worker's lung	Polyurethane foams, spray paints, elastomers, glues	Diisocyanates, trimellitic anhydride
Epoxy resin lung	Heated epoxy resin	Phthalic anhydride
		Unknown
Mummy handler's lung	Cloth wrappings of mummies	
Coffee worker's lung	Coffee-bean dust	
Tap water lung	Contaminated tap water	
Tea grower's lung	Tea plants	

EPIDEMIOLOGY

The more common forms of HP are farmer's lung, budgerigar (parakeet) keeper's lung (keeping of domestic birds), and pigeon breeder's lung in Europe, whereas summer-type HP is a disease limited to Japan. However, the prevalence of HP is difficult to determine, given that the disease is often unrecognized or misdiagnosed. Further, exposure conditions vary from country to country; even within a country, the climate, local customs, and local working conditions depend on the geographic areas. Farmer's lung is more prevalent in cold and wet regions. The introduction of modern techniques of haymaking and silage making has reduced the incidence of farmer's lung.

The estimates for the prevalence of farmer's lung range from 1% to 19% of exposed farmers[14–16]; from 6% to 20% of exposed pigeon breeders[17]; and for budgerigar's lung, from 0.5% to 7.5% of the at-risk population, which is 10% to 12% of the UK population who keep these birds in their homes.[18] The disease may arise in all age groups, including children. Clinical behavior in childhood is similar to adult disease.[19,20]

Smoking is less prevalent in patients with HP than in control populations.[16] Cigarette smoking seems to be protective against the development of HP. Nonsmokers exposed to antigens have significantly higher levels of specific immunoglobulin G (IgG) antibodies than smokers.[21] Cigarette smoking suppresses lymphocyte and macrophage function, thus, it may interfere with the alveolar macrophage capacity to take up, process, and present the inhaled antigen to lymphocytes. This activity may dampen the cellular immune response that is necessary to develop HP.

PATHOGENESIS

The pathogenesis of HP is complex, and many of the mechanisms involved are poorly understood. Particulate matters with an aerodynamic diameter smaller than 5 μm can reach the periphery of the lung and are capable of inducing HP. Most of the antigens are home or workplace related.

Several immune reactions seem to be involved. Early observations, especially the presence of circulating precipitins to the relevant sensitizing antigens,[2] supported the concept that the disease is mediated by the deposition of antigen/antibody complexes within the alveolar walls, which is compatible with a humoral, immune-complex–mediated reaction (type III hypersensitivity). However, several findings are not consistent with this hypothesis: (1) patients may develop disease but may lack serum precipitins[22]; (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.[23]

There is more evidence for a cell-mediated immune reaction (type IV hypersensitivity), such as the histology of lymphocytic interstitial infiltrates with granuloma formation and the bronchoalveolar lavage (BAL) findings with a significant lymphocytosis and signs of macrophage and lymphocyte activation.[24] Further, HP can be passively transferred with sensitized lymphocytes of the Th1-type followed by inhalational challenge.[25] There is evidence for overproduction of interferon-γ (Th1 cytokine) and amelioration by interleukin (IL)-10 of the severity of the disease from animal models and from BAL studies of patients with HP.[26] Overproduction of the Th1 cytokines, IL-12 and IL-18, by BAL macrophages from patients with HP has been reported.[27–29] Altered expression of tumor necrosis factor (TNF) superfamily receptors by alveolar macrophages is also seen.[30] Alveolar macrophages from patients with HP produce increased levels of soluble TNF receptors that may act as counter regulators of TNF.[31]

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. In this regard, BAL T cells from patients with chronic HP display a Th2 phenotype with an increase in CXCR4 (a Th2 chemokine receptor) and a decrease in CXCR3 (a Th1 chemokine receptor) expression.[32] Antigen-specific-stimulated cells from chronic HP produce higher levels of IL-4 and lower levels of interferon-γ compared with those from subacute HP.[32] Patients with chronic HP with a fibrotic histopathology showed a predominant Th2 response as evidenced by a higher ratio of TARC (a Th2 chemokine) to IP-10 (a Th1 chemokine) in comparison with those who had organizing pneumonia (OP) or nonspecific interstitial pneumonia (NSIP)–like histopathology.[33] A murine model of chronic HP confirmed that Th2-biased immune responses are important in the development of lung fibrosis in chronic HP.[34]

Although these studies have helped to understand the disease mechanisms, it is unknown why the disease develops only in a minority of exposed individuals. To explain this, it was postulated that for disease to occur, the presence of an inducing factor (inhaled antigen) and a promoting factor is necessary. An intrinsic promoting factor can be a genetic predisposition linked to the major histocompatibility complex. Differences in the TNF-α polymorphism were found in patients with pigeon breeder's disease and farmer's lung.[35,36] More recently, polymorphisms in the transporter

associated with antigen processing (TAP) genes and in the low-molecular-weight proteasome LMP7 gene have been shown to be involved in the susceptibility to pigeon breeder's disease,[37,38] whereas polymorphisms in the TIMP-3 promoter region may protect against the development of HP.[39,40] Extrinsic promoting factors may be inhalation of insecticides, weed killers, or superimposed viral infections. In an animal model of farmer's lung with mice exposed to both the offending antigen and the parainfluenza 1 virus, the pulmonary inflammatory response was more enhanced and prolonged compared with antigen exposure only.[41] Despite all this progress, we still do not understand why some patients show resolution of disease and others progress to fibrosis even without further antigen exposure.

PATHOLOGY

The acute response within a few days is a nonspecific diffuse pneumonitis with infiltration of mononuclear cells and neutrophils of the bronchioles, alveoli, and the interstitium. With further continued or intermittent exposure, the subacute stage is characterized by a lymphocytic infiltration centered on the bronchioles. Within several weeks, noncaseating epithelioid cell granulomas may be formed and are seen in about 70% of histopathologic specimens. The characteristic histopathologic lesions of typical subacute HP are (1) cellular interstitial pneumonia (cellular NSIP), (2) cellular bronchiolitis, and (3) granulomatous inflammation. This histologic triad is seen in no more than 75% of patients with HP. Characteristically, the central regions of the secondary lobule are predominantly involved.[42]

With long-term exposure, chronic HP with progressive fibrosis and bronchiolitis obliterans may develop. Fibrosis may become extensive with honeycombing, so that in late chronic stages, histopathology may be similar to usual interstitial pneumonia (UIP). In general, histologic changes in chronic HP may not be different from the patterns found in other fibrotic lung disease. Several investigators have reported isolated UIP-like or fibrotic NSIP-like patterns.[43–48] A review of 13 cases of chronic HP identified 3 patterns of fibrosis: (1) predominantly peripheral fibrosis in a patchy pattern with architectural distortion and fibroblastic foci resembling UIP in 9 cases; (2) relatively homogeneous linear fibrosis resembling fibrotic NSIP in 4 cases; and (3) irregular predominantly peribronchiolar fibrosis in 3 cases, all of which also had UIP-like fibrosis. In all cases, granulomas or giant cells or areas of typical subacute HP were also present and helpful to arrive at the correct diagnosis.[49] Another study of 16 autopsy cases of chronic HP found that the fibrotic pattern closely resembled that in lungs with idiopathic pulmonary fibrosis (IPF)/UIP. Granulomas were not detected in any chronic HP case. Centrilobular fibrosis was the outstanding feature in all cases, often connecting to the perilobular areas in the appearance of bridging fibrosis, although considerable overlap with IPF/UIP was found.[50]

CLINICAL FEATURES

The spectrum of clinical presentation varies and is determined by the frequency and intensity of antigen exposure (**Table 2**). Acute, subacute, and chronic forms have been described. The term subclinical alveolitis has been coined for individuals being exposed to antigens and with a lymphocytic alveolitis on BAL but without clinical evidence of disease (no symptoms, normal chest radiographs and lung function test). These individuals are obviously sensitized to the offending antigen. Long-term follow-up studies of Canadian dairy farmers show that the BAL lymphocytosis persisted in these individuals and that no subject developed manifest farmer's lung disease.[51] The interval between sensitization by antigen inhalation and the clinical appearance of HP is unknown. It seems to be extremely variable and may range from many months to several years after the beginning of exposure.

Acute Form

This presentation is the most characteristic and specific presentation and is associated with intermittent, high-level exposure to the offending

Table 2
Symptoms and signs in 116 patients with HP

Feature	Frequency (%)
Dyspnea	98
Cough	91
Chills	34
Fever	19
Chest tightness	35
Weight loss	42
Body aches	24
Wheezing	31
Inspiratory crackles	87
Cyanosis	32
Clubbing	21

Data from Lacasse Y, Selman M, Costabel U, et al. Clinical diagnosis of hypersensitivity pneumonitis. Am J Respir Crit Care Med 2003;168:952–8.

antigen, typically in farmers working with moldy hay or in pigeon breeders when cleaning the pigeon loft. Symptoms occur approximately 4 to 12 hours after exposure. The disease onset is abrupt. Patients suffer a flulike syndrome (fever, chills, malaise, myalgia, headache) and respiratory symptoms (dry cough, dyspnea, tachypnea, chest tightness). The symptoms may occur at night once patients have gone to bed after a day with exposure. The clinical examination reveals bibasilar crackles and occasional cyanosis; finger clubbing is very unusual. These signs and symptoms peak between 6 and 24 hours and usually resolve spontaneously within a few days.[1]

Subacute Form

Occasionally, mild, acute episodes with fever may be seen in patients with a background of more chronic, progressive disease. This form would represent the subacute form, which may also become chronic and progress to fibrosis, after recurrent acute episodes. The patients with recurrent chronic bird fancier's lung tend to breed dozens of pigeons in a loft, whereas the patients with insidious chronic bird fancier's lung are exposed to smaller birds, usually budgerigars kept indoors.[52]

Chronic Form

The chronic form results from continuous, low-level exposure, usually to birds in the domestic environment (budgerigar/parakeet keepers). The onset of disease is insidious with slowly increasing dyspnea on exertion, usually dry cough, fatigue, and weight loss. The patients never relate their symptoms to the exposure to the birds. The insidious onset of symptoms and lack of acute episodes lead the physician often to mistake the disease for other chronic interstitial lung diseases (ILD), such as IPF.

The clinical examination reveals bibasilar crackles. Digital clubbing may be seen in 20% to 50% of patients[1,52] as well as the manifestation of cor pulmonale. A rather unique clinical finding in chronic HP, in contrast to other chronic fibrotic lung disease, is the presence of inspiratory squeaks, which are caused by coexisting bronchiolitis in some patients. The frequency of important clinical and investigational characteristics seems to be determined by the histologic pattern in chronic HP (**Table 3**).[47]

INVESTIGATIONS

Chest Radiography

In acute HP, a transient, diffuse, ground-glass or airspace consolidation, associated with some micronodules, may be seen. The subacute forms may show micronodular and reticular shadowing. The chronic forms show a predominantly reticular pattern, with associated honeycombing. In contrast to IPF, the changes are diffuse and may show upper-zone predominance. Mild enlargement of the mediastinal lymph nodes can be observed occasionally. Pleural involvement is usually absent. The chest radiograph may be normal in up to 30% of patients and also in some patients with physiologically significant disease.

High-Resolution Computed Tomography

In acute and subacute HP, the characteristic findings on high-resolution computed tomography (HRCT) are patchy or diffuse ground-glass densities.

Table 3
Histologic pattern in chronic pigeon breeder's disease: correlation with clinical findings

	Typical HP Pattern $n = 58$	NSIP Pattern $n = 22$	UIP-like Pattern $n = 10$	*P*
Finger clubbing (%)	30/56 (53)	10/21 (48)	8/10 (80)	.26
BAL				
Lymphocytes (%)	65 ± 21	52 ± 23	36 ± 23	.0011
Macrophages (%)	34 ± 20	45 ± 23	59 ± 18	.0028
Eosinophils (%)	1 (0–9)	0 (0–13)	2 (0–13)	.11
Neutrophils (%)	0 (0–10)	1 (0–10)	1 (0–4)	.61
HRCT				
Inflammation (%)	30/40 (75)	11/16 (69)	1/7 (14)	<.007
Fibrosis (%)	10/40 (25)	5/16 (31)	6/7 (86)	<.007

Abbreviation: HRCT, high-resolution computed tomography.

Data from Gaxiola M, Buendia-Roldan I, Mejia M, et al. Morphologic diversity of chronic pigeon breeder's disease: clinical features and survival. Respir Med 2011;105:608–14.

Usually, there are small, centrilobular, ill-defined nodules of ground-glass densities, and evidence of mosaic perfusion (trapped air) caused by concomitant bronchiolitis. These micronodules may be found in those with acute, subacute, or chronic disease in decreasing frequency (**Fig. 1**). In the correct clinical context, they are strongly suggestive of HP.[53–57]

In chronic HP, there are signs of lung fibrosis, such as lobar volume loss, linear-reticular opacities, or honeycombing (**Fig. 2**). The distribution may be more prominent in the upper lobes or in the lower lobes. Usually, there is not the predominant subpleural involvement as in IPF. CT can be used to distinguish IPF from HP in many cases.[58] In most chronic cases, the presence of poorly defined centrilobular micronodules is suggestive of HP. In addition, emphysema can be seen in 20% of nonsmoking patients with chronic HP, particularly in farmer's lung.[54–56]

A study evaluated the role of HRCT in the differential diagnosis of chronic HP with IPF and idiopathic NSIP. In this study, a confident first-choice diagnosis at HRCT was made in 70 (53%) of 132 readings in patients with chronic HP, IPF, and NSIP and was correct in 94% of these readings.[59] These results are similar to those obtained in another study that included patients with IPF and HP. In that study, a first-choice diagnosis with a high level of confidence was made in 62% of the cases, and this diagnosis was correct in 90% of the observations.[58] The features that best differentiated chronic HP from IPF and NSIP at thin-section CT were the presence of lobular areas with decreased attenuation, centrilobular nodules, and a lack of lower-zone predominance of the abnormalities. NSIP can be differentiated from chronic HP mainly by the presence of relative subpleural sparing, absence of lobular areas with decreased attenuation, and lack of honeycombing.

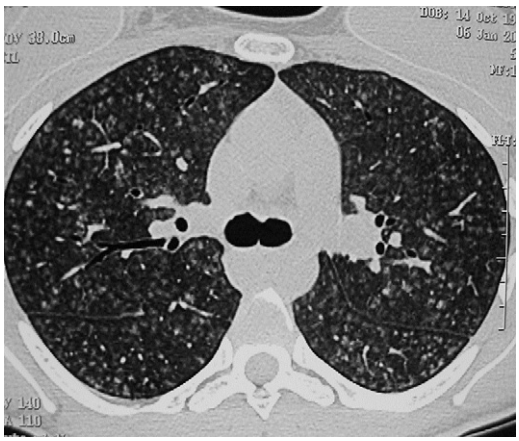

Fig. 1. HRCT of a patient with acute hypersensitivity pneumonitis.

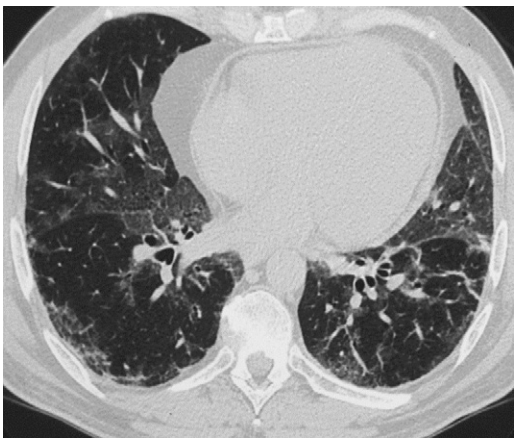

Fig. 2. HRCT of a patient with chronic hypersensitivity pneumonitis.

IPF can be differentiated from chronic HP by the basal predominance of honeycombing and the absence of relative subpleural sparing and centrilobular nodules. Cysts were also seen more commonly in patients with chronic HP than in those with IPF or NSIP and were only noticed in areas of ground-glass opacities. Importantly, honeycombing was seen in 64% of patients with chronic HP, which was similar to the frequency observed in the patients with IPF.[59]

Lung Function

The most frequent lung-function abnormalities are a restrictive ventilatory impairment or an impaired gas exchange (decreased diffusing capacity or increasing hypoxemia during exercise). In fact, these changes are consistent with the functional pattern of any ILD and are not specific for HP. During acute episodes and late in chronic progressive patients, hypoxemia at rest is observed. The most frequent functional abnormality is hypoxemia during exercise, with an elevated alveolar/arterial oxygen gradient greater than 10 mm Hg; the next frequent is a restrictive pattern. Only a few patients show obstruction of the peripheral airways. Some patients may develop bronchial hyperreactivity. The pulmonary function changes do not correlate with the magnitude of changes seen on the chest radiograph or HRCT scan.

Laboratory Tests

The presence of specific IgG antibodies (serum precipitins) to the inducing antigen is evidence of sensitization but not of disease. Between 30% and 60% of healthy farmers produce precipitating antibodies to the antigens they are exposed to. In budgerigar fanciers, only 3% of healthy exposed individuals produce precipitating antibodies, so

that in this form of HP, the demonstration of precipitins against bird serum or droppings is much more specific for disease than findings of the precipitins in farmers. On the other hand, between 10% and 15% of patients do not develop serum precipitins, so a negative finding does not exclude the presence of the disease.[22,60,61] Despite these limitations, the precipitin assay is a useful additional laboratory test in the diagnostic assessment of HP, in particular to suggest a potential exposure that has not been recognized. Precipitins are usually assessed by radial diffusion (Ouchterlony) or by enzyme-linked immunosorbent assay techniques. Fenoglio and coworkers[62] assessed the diagnostic value of a relevant panel of antigens to detect serum precipitins in mold-induced HP. The predictive negative values varied from 81% to 88% and the predictive positive values from 71% to 75%. This finding was considered of help to diagnose mold-induced HP in a specific geographic region.[62]

In acute episodes, the white blood cell count shows increased leukocytes with a predominance of neutrophils. The C-reactive protein levels may also be elevated. In chronic forms, polyclonal increase of gamma globulins is a frequent finding. The rheumatoid factor may be positive in 50% of patients with pigeon HP.[63]

Bronchoalveolar Lavage

HP shows, by far, the most marked increase in BAL lymphocytes of all the interstitial diseases, usually with a relative predominance of CD8 T cells resulting in a low CD4/CD8 ratio. The total cell yield is very high, usually more than 20 million from a BAL of 100 mL total instillation. The lymphocyte count is usually greater than 50% of the total cells but may be less in the chronic fibrotic forms.[47,52,54] In addition, neutrophils, eosinophils, and mast cells may be mildly elevated.[24,64] A more specific finding is the increase in plasma cells. This cell type was found in a low percentage in 18 of 30 patients with bird keeper's disease; values ranged from 0.1% to 3.9% in this study.[65] Other morphologic features include signs of T-cell activation (folded nuclei, broad cytoplasm) and foamy macrophages.[66] A normal BAL cytology probably excludes acute or subacute extrinsic allergic alveolitis. On the other hand, BAL cannot differentiate between patients with overt disease and healthy subjects who have been exposed and sensitized.

In regard to the CD4/CD8 ratio, the different series reported in the literature show no consistent findings. Most studies show a significant decrease in the CD4/CD8 ratio, with mean values ranging between 0.5 and 1.0. Two studies found that CD4/CD8 ratios were borderline (1.3 and 1.5, respectively). In Japan, a normal ratio of 2.0 has been reported for ventilation HP and even an increased mean ratio of 4.4 for farmer's lung.[67] The reasons for this discrepancy in reported CD4/CD8 ratios are unclear. Several explanations are possible and include different disease manifestations (acute vs chronic form), the timing of BAL investigations in relation to the last antigen exposure, and the type of antigen causing the disease. CD4/CD8 ratios are higher shortly after the last antigen exposure (within 24 hours) and lowest between 7 and 30 days after the last exposure.[68] In chronic HP, among patients exposed to avian antigens, the CD4/CD8 ratio is frequently increased, with a higher mean value relative to that found in subacute HP.[32]

Acute episodes of extrinsic allergic alveolitis are associated with an influx of neutrophils into the lungs, lasting for up to 1 week. After this period, the cellular profile of the BAL fluid returns to the significant increase in lymphocytes that was previously seen. In the follow-up, persistent BAL abnormalities may indicate that complete avoidance has not been achieved.

Provocation Tests

Inhalation provocation tests with the suspected antigen have been performed, but these tests are not standardized and are usually not needed. Natural workplace or home exposure seems a more reasonable way to provoke symptoms or deterioration of functional parameters in unclear cases.

DIAGNOSIS

Diagnosis should be suspected in every patient with unexplained cough and dyspnea on exertion, functional impairment (restriction or diffusion defect), and unclear fever, especially if exposure to potential antigens is known (workplace, domestic bird keeping, moldy walls in the home).

Diagnosis is based on 3 criteria:

- Proven or suspected exposure associated with exposure-related symptoms
- Proof of sensitization, which is possible by demonstration of serum precipitins or of lymphocytosis in the BAL fluid
- Demonstration of the consistent pattern of an ILD on chest radiography/HRCT or with pulmonary function test (restriction or diffusion defect)

A large, prospective, multicenter cohort study (116 patients with HP, 284 control subjects with other ILD) designed to develop a clinical prediction rule for the diagnosis of HP was able to determine simple clinical predictors. In this study, a logistic

regression identified 6 significant predictors of HP: exposure to the known offending antigen, positive precipitating antibodies, recurrent episodes of symptoms, inspiratory crackles, symptoms 4 to 8 hours after exposure, and weight loss. If all 6 are present, the probability of having HP is 98%.[69]

Careful history taking is obligatory. The physician should have a specific expertise in the knowledge of exposure conditions and of the occupational and domestic environment, to be able to ask the relevant questions to detect potential sources of exposure. 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 sought, for example, visits to friends or relatives who keep birds in their home or cleaning the clothing of someone who is a bird keeper. Improvement on vacation or during hospitalization may also be a hint toward the diagnosis.

The most sensitive diagnostic test is BAL. In the authors' experience and based on literature review, a normal BAL excludes the diagnosis of HP. The characteristic finding is a lymphocytosis in the subacute and chronic forms and also in those cases without symptoms being sensitized only (subclinical alveolitis). It has been proposed that BAL lymphocytosis greater than 30% discriminates chronic HP showing UIP pattern on HRCT from IPF.[70]

HRCT is an extremely 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 (RB-ILD) respiratory bronchiolitis/ILD or pneumocystis carinii infection. Here, BAL can then facilitate the differentiation: lymphocytosis in HP, a predominance of smoker's macrophages in RB-ILD, and the demonstration of the organisms in pneumocystis carinii pneumonia.

Histopathologic evaluation of lung tissue is usually not necessary for the diagnosis of HP. If a biopsy is needed in unclear cases with low pretest probability of HP, the preferred approach is surgical because transbronchial biopsy specimens are of limited diagnostic accuracy.

An important problem in the diagnosis of HP is the fact that in up to 20% to 30% of the patients in some series, the inciting antigen cannot be identified by exposure history or serologic testing. In these patients, the diagnosis is suspected based on histopathology, BAL findings, and HRCT characteristics.[71,72]

The differential diagnosis includes the wide spectrum of ILD. 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.[44]

NATURAL HISTORY AND PROGNOSIS

The prognosis of HP varies greatly and depends on the type and duration of antigen exposure, the dose of the inhaled antigen, and the clinical form of disease. Some patients may experience progression, even despite avoiding exposure and undergoing treatment. There is no good explanation for the mechanism behind this.

In general, acute HP seems to have a favorable prognosis. After acute attacks, complete remission is usually seen. Patients with recurrent attacks of farmer's lung tend to have emphysema more often than patients who experienced only a single attack and also have a significantly lower diffusing capacity.[73] No differences were observed in relation to fibrosis.[73]

In pigeon breeders, a long-term follow-up study of almost 20 years compared symptomatic with asymptomatic pigeon breeders. Symptomatic pigeon breeders had a 3- to 4-fold increase in the expected proportional decrease of FEV_1 and FVC with increasing age, whereas the group of asymptomatic pigeon breeders showed no difference compared with a healthy control population.[74] In bird breeder's lung, the prognosis was found to be excellent. If the duration of symptoms was less than 6 months, complete recovery and normalization of lung function was seen in every such patient.[75] Similar findings were reported in another study.[76] If, on the other hand, recognition of disease occurs late, in the chronic stage, with end-stage fibrosis and cor pulmonale, the prognosis is less favorable. These patients may experience a fatal outcome.[52]

In a Finish study, the estimated mortality rate of farmer's lung was 0.7% between 1980 and 1990.[77] Other earlier studies on farmer's lung showed a mortality rate between 9% and 17%, with a mean survival from onset of symptoms to death of 17 years.[77–80] In acute pigeon breeder's disease, mortality is low and was reported to be less than 1%.[81] In one study of a selective population of pigeon breeders from Mexico, who kept their birds as pets in their homes and had chronic disease, mortality was higher with approximately 25% within 5 years after the initial diagnosis.[82]

Acute exacerbations can occur not only in IPF but also in chronic HP.[83,84] A review of 100 consecutive patients with chronic bird farmer's lung showed that 14 patients developed an acute exacerbation,

defined according to the criteria used in IPF, and 12 of them died of this episode. The 2-year frequency of an acute exacerbation was 11.5%.[84]

Lung cancer has been recognized with increased frequency in IPF. A recent study of 104 cases of chronic HP identified a similar prevalence of lung cancer (10.6%) as seen in IPF.[85]

Histopathologic Patterns and Survival

Recently, surgical lung biopsies from a cohort of Japanese patients with chronic bird fancier's lung were analyzed. The inflammatory and fibrotic lesions showed significant variation, with changes suggestive of OP, NSIP, or UIP. Patients with OP-like or cellular NSIP-like lesions tended to have presented with acute episodes, whereas patients with UIP-like lesions had an insidious onset. Patients with OP–like or cellular NSIP-like lesions had a more favorable outcome than those with fibrotic NSIP-like and UIP-like lesions.[44]

In another study, the median survival in patients with fibrotic HP was 7.1 years, which was significantly less than the survival in those without fibrosis. In an age-adjusted regression analysis, antigen class, symptom duration, and lung function had no effect on survival. Only the presence of pathologic fibrosis was predictive of increased mortality (hazard ratio 6.01).[86] A study of chronic pigeon breeder's disease showed that patients with UIP-like histology had the worst survival rate (hazard ratio 4.19), whereas those with an NSIP-like pattern showed the best survival (hazard ratio 0.18).[47] Similar results were reported by Churg and colleagues,[45] who found that 16 of the 18 patients with a UIP-like pattern died of the disease. Thus, the presence of histologic fibrosis, especially a UIP-like pattern, is associated with decreased survival.

HRCT Patterns and Survival

In chronic HP, CT findings of extensive reticular pattern, traction bronchiectasis, and honeycombing are closely related to the presence of histologic fibrosis.[46,72] CT findings of fibrosis are associated with reduced survival in patients with chronic HP and may serve as useful prognostic indicator.[44,46,57,71] One HRCT study compared 26 fibrotic and 43 nonfibrotic consecutive patients with HP and found that fibrotic patients had a markedly increased mortality (hazard ratio 4.6).[71]

MANAGEMENT

Avoidance of further antigen exposure is the first essential measure. This avoidance may be difficult in some patients who fear loss of employment or hesitate to remove a pet bird or give up a beloved hobby. Antigens may persist in rooms where birds have been kept for a long time. One patient suffered a relapse from the disease after taking off the curtains from a room 3 months after the bird had been given away. Indirect and occasional exposure in home of friends or relatives where birds are kept should also be avoided. Feather pillows and blankets should be removed. Outbreak of the disease has been observed in patients who have moved into a new home where birds were formerly kept.[87]

In farmers, dust masks with filters, appropriate ventilation, mechanization of the feeding process on farms, and alterations in forced-air ventilatory systems may be useful precautionary measures. Also, for farmers, it is prudent to recommend complete avoidance of further antigen exposure.

Corticosteroid therapy is usually recommended in patients who show functional impairment. Treatment continues until no further improvement in physiologic abnormalities is observed. The treatment schedule is similar to that in sarcoidosis and other ILD, 40 to 50 mg/d for 1 month, followed by a period of tapering during the next 2 to 3 months and a maintenance dose between 7.5 and 15.0 mg/d. There are no controlled treatment trials in subacute and chronic forms of the disease. There is one placebo-controlled study in acute farmer's lung from Finland.[88] Steroids were given over a period of 2 months, which induced a more rapid improvement in lung function. Five years later, no functional differences were observed, an outcome that is not surprising for acute HP. In chronic, progressive HP, immunosuppressants may be added as corticosteroid sparing agents, as done in other fibrotic ILD.[44]

Routine follow-up investigations should be narrower initially 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 (ie, complete remission after avoidance of further exposure or corticosteroid treatment), then routine follow-up can be stopped after 2 to 3 years.

SUMMARY

HP is a complex syndrome caused by repeated inhalation of environmental and occupational antigens. The major exposures are against bird proteins and fungi. Although the acute and subacute forms have a favorable prognosis, usually with complete remission, chronic HP may become a relentlessly progressive fibrotic lung disorder with an increased mortality rate, even when avoiding exposure and undergoing treatment. There is no good explanation for the mechanism behind this. Chronic HP, especially the insidious form of bird fancier's lung, may

closely mimic IPF or idiopathic fibrotic NSIP. Diagnosis may be difficult. Prompt recognition of the antigen is critical for diagnosis. Removal of antigen exposure is important for treatment. Histologic changes in chronic HP may not be different from the patterns found in other fibrotic lung diseases. The UIP-like or fibrotic NSIP-like pattern of histopathology can been seen in isolation. Fibrotic changes on the biopsy specimen or HRCT are markers of a poor prognosis.

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