CHEST Recent Advances in Chest Medicine

Recent Advances in Hypersensitivity Pneumonitis

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Hypersensitivity pneumonitis (HP) is a pulmonary disease with symptoms of dyspnea and cough resulting from the inhalation of an allergen to which the subject has been previously sensitized. The diagnosis of HP most often relies on an array of nonspecific clinical symptoms and signs developed in an appropriate setting, with the demonstration of interstitial markings on chest radiographs, serum precipitating antibodies against offending antigens, a lymphocytic alveolitis on BAL, and/or a granulomatous reaction on lung biopsies. The current classification of HP in acute, subacute, and chronic phases is now challenged, and a set of clinical predictors has been proposed. Nonspecific interstitial pneumonitis, usual interstitial pneumonia, and bronchiolitis obliterans organizing pneumonia may be the sole histologic expression of the disease. Presumably, like in idiopathic interstitial pneumonia, acute exacerbations of chronic HP may occur without further exposure to the offending antigen. New offending antigens, such as mycobacteria causing hot tub lung and metalworking fluid HP, have recently been identified and have stimulated further research in HP. ***CHEST 2012; 142(1):208–217***

Abbreviations: AE = acute exacerbation; DLCO = diffusing capacity of the lung for carbon monoxide; ELISA = enzyme-linked immunosorbent assay; HP = hypersensitivity pneumonitis; HRCT = high-resolution CT; IPF = idiopathic pulmonary fibrosis; MWF = metalworking fluid; NHLBI/ORD = National Heart, Lung, and Blood Institute/Office of Rare Diseases; NSIP = nonspecific interstitial pneumonitis; SR = *Saccharopolyspora rectivirgula*; Th = T helper; TLR = toll-like receptor

Hypersensitivity pneumonitis (HP) has long been considered as an orphan disease. Over the last 10 to 15 years, continued interest in HP has been stimulated by the development of experimental models of HP, the identification of new antigens causing specific forms of the disease, the creation of the HP Study Group, and the publication of an important summary of a National Heart, Lung, and Blood Institute in collaboration with the Office of Rare Diseases (NHLBI/ORD) of the National Institutes of Health of the United States.[1] This review summarizes the most recent advances in our understanding of HP. It updates and supplements our previous in-depth reviews of the clinical and pathophysiologic aspects of the disease.[2,3]

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Definition

Two major groups of international experts have failed to arrive at a consensual definition of HP. The report of the NHLBI/ORD workshop stated that "hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, is a complex health syndrome of varying intensity, clinical presentation, and natural history. HP is the result of an immunologically induced inflammation of the lung parenchyma in response to inhalation exposure to a large variety of antigens."[1] The HP Study Group defined HP as "a pulmonary disease with symptoms of dyspnea and cough resulting from the inhalation of an antigen to which the patient has been previously sensitized."[4] Notwithstanding these differences, one must retain: (1) HP is a pulmonary disease with or without systemic manifestations (such as fever and weight loss); (2) it is

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caused by the inhalation of an antigen to which the subject is sensitized and hyperresponsive; (3) sensitization and exposure alone in the absence of symptoms do not define the disease, as many exposed subjects develop an immune response manifested by the presence of serum IGg antibodies to the antigen and often by the presence of large number of lymphocytes in their lungs[5] but never develop lung disease.[6]

Etiology

Antigens responsible for HP mostly originate from bacteria (eg, *Saccharopolyspora rectivirgula* [SR]), molds (eg, *Penicillium* species), yeasts, or fowl (eg, pigeon proteins). Some chemicals, such as isocyanates, zinc, inks, and dyes, can act as haptens to induce HP (Table 1). Spores of macroscopic fungi can also induce HP.[7] The list of environments associated with HP is ever increasing, but most cases are caused by similar antigens in a different setting. Other antigens have recently been described. These include colistin,[8] catechin (green tea extract),[9] and methylmethacrylate (in dental technicians).[10] Any environment containing sufficient quantities of any of these antigens can cause HP. There is increasing evidence that although HP is caused by specific antigens, a trigger factor may be needed to induce the disease. Potential triggers are viruses,[11,12] endotoxins,[13] β-glucan,[14] and anthrax vaccination.[15] The challenge to the clinician is to suspect HP as a cause of all interstitial lung diseases and, if the initial investigation fits the diagnosis of HP, a frequent challenge is to find the type and source of the antigen.

Epidemiology

Data from registries of interstitial lung diseases in three European countries indicated that HP represents 4% to 15% of all interstitial diseases.[16] In a population-based study conducted in New Mexico, the estimated annual incidence of interstitial lung disease was 30 per 100,000.[17] HP accounted for < 2% of the incident cases. The study was done in a dry environment that is not propitious to the development of many forms of HP. Nevertheless, this figure is consistent with that obtained from a more recent British population-based study that found an incident rate of 0.9 cases per 100,000 person-years.[18] A more interesting statistic is the proportion of individuals exposed to a potential antigen who will develop HP. For most antigens, this proportion is unknown. It is estimated that 0.5% to 3% of farmers will develop HP.[19] In a 23-year surveillance study of occupational HP in the United States, mortality rates were higher among farmers and in agricultural production industries.[20]

Table 1—*Major Antigens Causing HP*

Type of Antigen	Examples of Sources
Mushrooms, fungi, yeasts	Contaminated wood, humidifiers, central hot air heating ducts, peat moss plants
Bacteria	Dairy barns (farmer's lung)
Mycobacteria	Metalworking fluids, sauna, hot tub
Bird proteins	Pigeons, dove feathers, ducks, parakeets
Chemicals	Isocyanates (auto painters), zinc, dyes

HP = hypersensitivity pneumonitis.

Genetics of HP

There is no evidence of a clear genetic susceptibility to develop HP. However, recent studies have described cytokine gene polymorphisms in patients with HP. Compared with gene expression in the lung of patients with idiopathic pulmonary fibrosis (IPF), there is a different genetic signature that could help in the differential diagnosis of these two diseases. In IPF, there is an increased expression of CCL24 and genes encoding for IL-1 receptor antagonist, tumor necrosis factor, and complement receptor 1.[21] In contrast, the expression of genes associated with inflammatory cytokines and chemokines is observed in HP.[22] Cytokines and chemokines are important players in the induction of the inflammatory environment. Previous studies related genetic susceptibility to develop HP to the major histocompatibility complex class 2 genes and tumor necrosis factor promoter polymorphisms. A study reported that Mexican patients with HP have increased frequencies of the alleles Gly-637 and the genotypes Asp-637/Gly-637 and Pro661/Pro661 on the *TAP1* (transporters associated with antigen processing 1) gene.[23] Polymorphisms in this gene may lead to exacerbated immune response and interruption of antigen tolerance, which may explain susceptibility of patients with HP to the disease. Others also found a polymorphism in the *PSMB8* gene among Mexican patients with HP.[24] This gene is involved in the antigenic presentation by the degradation of proteins and the generation of antigenic peptides. This genetic variation may affect peptide cleavage specificity, which may be important to determine susceptibility in immune disease, such as HP. Vasakova et al[25] correlated gene polymorphisms with BAL fluid cytokine and chemokine levels in BAL from patients with HP. They demonstrated the influence of polymorphisms of the IL-6 gene from patients with HP.

Pathophysiology

Cell Activation Signals

Lung cellular influx and inflammatory responses characteristic of HP are initiated by causing agents via immune cell receptors called toll-like receptors

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(TLRs). TLRs are expressed on immune cells and recognize most antigens, be they viral, bacterial, or other. In HP, when specific TLRs are activated, they react through an intracellular pathway, known as the MyD88 pathway, to release many proinflammatory cytokines and mediators. Nance et al[26] have demonstrated that in mice, exposure to SR, the main antigen for farmer's lung, activates MyD88, through TLR2, to initiate a cytokine and chemokine cascade resulting in neutrophil recruitment. Moreover, less lung inflammation and cytokine production are observed in $TLR6^{-/-}$ mice compared with wild-type mice exposed to SR.[27] Identifying the TLRs involved in the recognition of SR antigens will help in determining if TLR polymorphisms contribute to HP susceptibility. Kim et al[28] observed that SR antigen induces activation of another signal (PKD1) that also uses MyD88. Hence, activation of PKD1 through MyD88 is probably involved in the generation of the inflammatory environment, necessary for the development of SR-induced HP. This has also been observed with *Mycobacterium avium*-induced allergic response similar to the reaction found in hot tub lung.[29] Taken together, these studies suggest that TLRs and the MyD88 pathway could be attractive targets for future therapy of HP.

Regulation of the Immune Response

Although traditionally classified as a T helper (Th) cell type 1 (Th1) disease characterized by the production and release of tumor necrosis factor, interferon-α, IL-12, and IL-18, recent studies support that IL-17- and IL-22-secreting Th17 cells are also involved in HP.[30,31] The importance of this Th17-polarized immune response is not well understood in the pathophysiology of HP, but IL-17 seems to be associated with the disease severity.[32] Th1 and Th17 cells, via their cytokine production, promote lung inflammation in HP, whereas another lymphocyte subset, known as regulatory T cells, help downregulate the disease[33] by suppressing the proliferative response of activated T cells.[34] These cells could explain why many individuals exposed to HP antigen do not develop the disease.

Pathology

Several reports have first emphasized that fibrotic or cellular nonspecific interstitial pneumonitis (NSIP), usual interstitial pneumonia, and bronchiolitis obliterans organizing pneumonia may be the sole histologic expression of the disease.[35-39] We agree that all these reports rightly emphasize that HP must be considered in all cases of diffuse lung disease, and a detailed environmental exposure history is mandatory. The difficulty in the interpretation of these reports is in the lack of gold standard defining the presence or absence of HP, especially in the absence of supporting BAL findings (ie, BAL lymphocytosis) or other evidence of immunologic activation. In this regard, it is noteworthy that in the HP Study, 33% of the 284 control subjects (ie, patients classified as not having HP) were exposed to potential offending antigens.[4] Among these 284 control subjects, 132 were finally classified as having either of the idiopathic interstitial pneumonias. We submit that there must be evidence of an immune response to an inhaled antigen (ie, lymphocytic activation or production of specific serum antibodies) before the diagnosis of HP can be confirmed. Exposure to a potential offending antigen and interstitial lung disease do not equate as a proof of HP.[40] This is certainly an area for further discussion and research.

Clinical Presentation

Two large cohorts of consecutive patients with HP provide the best clinical picture of the disease (Table 2).[4,41] Overall, the two cohorts had remarkably similar presenting features. The main difference is in the offending antigens. In the Mayo Clinic

Table 2—*Presenting Features and Causes of HP in Two Large Cohorts of Consecutive Patients*

Characteristics	HP Study[4] (N = 199)	Mayo Clinic[41] (N = 85)
Sex, % women	56	62
Age, mean ± SD, y	55 ± 14	53 ± 14
Current smokers	6	2
Symptoms		
Dyspnea	98	93
Cough	91	65
Flulike symptoms	34	33
Chest discomfort	35	24
Signs		
Crackles	87	56
Wheezes	16	13
Digital clubbing	21	5
Causes		
Not identified	1.5	25
Avian antigens	66	34
Farmer's lung	19	11
Hot tub lung	0	21
Molds	13	9
Pulmonary function		
Obstructive pattern	1	16
Restrictive pattern	64	53
Mixed pattern (both obstructive and restrictive)	1	Not reported
Nonspecific abnormalities	1	12
Normal	34	10

Data are given as % unless otherwise indicated. See Table 1 legend for expansion of abbreviation.

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series, 25% had HP from unknown origin, whereas in the HP Study, this situation occurred in only 1.5% of patients. Referral bias at the Mayo Clinic may account for this difference.

Diagnostic Criteria

A number of diagnostic criteria recommendations for HP have been published.[42-45] None of these sets of criteria has been validated. Their diagnostic accuracy is, therefore, unknown. They correspond in effect to definitions of the disease. The results of the HP Study, a multicenter cohort study, are often presented as new "diagnostic criteria" for HP, but they are not.[4] The objective of this study was rather to develop a clinical prediction rule for the diagnosis of active HP. Such a rule aims at helping clinicians to arrive at a more accurate estimate of probability of HP and decide whether further investigation is needed to either rule in or rule out HP. We identified six significant predictors of HP (Table 3). The clinical prediction model produced an equation expressing the probability of HP, from which we constructed a table of probability for combinations of predictors. The probability of HP ranged from 98% when all six predictors were present to 0% when none of the predictors was identified. The HP Study emphasized that a thorough clinical history is of outmost importance in the diagnosis of HP.

Acute Exacerbations of Chronic HP

An emerging concept is that of "acute exacerbations of chronic HP."[46] Presumably, like in idiopathic interstitial pneumonia, acute exacerbation (AE) may occur without further exposure to the offending antigen. Such clinical events must be distinguished from bouts of acute HP related to continued exposure to antigen. Case definitions for AEs of fibrotic HP, with minor variations, have been proposed and are not different from AEs in IPF: (1) prior diagnosis of chronic HP; (2) worsening of dyspnea within 1 to 2 months; (3) new radiographic opacities; (4) absence of apparent infection, heart disease, and/or other identifiable cause.[46,47] As in IPF, the pathogenesis of AEs in chronic HP is unknown. Organizing pneumonia or diffuse alveolar damage were observed when surgical lung biopsy or autopsy were performed in the course of an AE.[47] As in IPF, AEs predict very poor outcome. In the case series by Miyazaki et al,[47] all 14 patients with AEs were treated with high-dose systemic corticosteroids, with or without cyclosporine or cyclophosphamide; 12 died of respiratory failure, 11 within 1 month after the onset of AE. We remain unsure, however, whether AEs of chronic HP truly exist. In the study by Miyazaki et al,[47] low lymphocyte count in BAL fluid at diagnosis (13.7% ± 7.5%, which makes the diagnosis of HP uncertain in our opinion) predicted AEs in HP.[47]

Table 3—*Significant Predictors of HP in the HP Study*

Variables	OR	95% CI
Exposure to a known offending antigen	38.8	11.6-129.6
Positive precipitating antibodies	5.3	2.7-10.4
Recurrent episodes of symptoms	3.3	1.5-7.5
Inspiratory crackles	4.5	1.8-11.7
Symptoms 4-8 h after exposure	7.2	1.8-28.6
Weight loss	2.0	1.8-28.6

See Table 1 legend for expansion of abbreviation.

Classification of HP

Confusion still surrounds the classification of HP. Its clinical presentations have classically been defined as acute, subacute and chronic.[43] We recently took advantage of the HP Study to determine whether this classification of HP truly reflects categories of patients with distinct clinical features.[48] Data were used to divide a cohort of patients with HP into a limited number of categories ("clusters") with maximally differing clinical patterns, without prejudgment. The variables included in this cluster analysis were obtained from clinical history (smoking status, wheezing, cough, tightness of chest, chills, body aches, weight loss, recurrent symptoms after exposure), physical examination (cyanosis, clubbing, inspiratory crackles, wheezing), blood work (positive serum precipitins, Po_2), chest radiograph (normal chest radiograph vs upper-zone predominance vs lower-zone predominance vs diffuse infiltrates), high-resolution CT (HRCT) scan (ground-glass infiltrates, nodular opacities, fibrosis), and BAL (lymphocyte count). One hundred sixty-eight patients were included in the analysis. A two-cluster solution best fitted the data. Patients in cluster 1 (41 patients) had more recurrent systemic symptoms (chills, body aches) and normal chest radiographs than those in cluster 2 (127 patients), who showed significantly more clubbing, hypoxemia, restrictive patterns on pulmonary function tests, and fibrosis on HRCT scan. Nodular opacities were seen on HRCT scan as often in cluster 1 as in cluster 2. There was considerable disagreement between the current classification of HP and the results of this analysis, and subacute HP was particularly difficult to define. Our new classification scheme needs to be prospectively validated, however.

Investigation

High-Resolution CT Scan

Several pictorial assays illustrating the spectrum of HRCT scan in HP are available.[49,50] Normal HRCT

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scans may be seen in acute HP. This should be the exception rather than the rule, however. The time interval between the removal from the offending antigen and HRCT scan may be an explanation for normal HRCT scan in HP.[51] In the HP study, among the 199 patients with HP who contributed to the analysis, only eight patients (4%) had a normal HRCT scan.[4] All were submitted to additional diagnostic procedures for confirmation of diagnosis.

Several studies trying to differentiate chronic HP from IPF or NSIP by using HRCT scanning have been conducted. Prior to the publication of the American Thoracic Society/European Thoracic Society consensus classification of interstitial idiopathic pneumonias, HRCT scan proved moderately adequate to distinguish HP from IPF.[51] In this study, desquamative interstitial pneumonia could not reliably be distinguished from acute or subacute HP, whereas chronic HP had images identical to those of usual interstitial pneumonia. This study did not include any case of NSIP that had only been described the year before its publication.[52] More recently, the CT scan features that best differentiated chronic HP were lower areas with decreased attenuation and vascularity, centrilobular nodules, and absence of lower-zone predominance of abnormalities.[53] Another study emphasized again that the performance of HRCT scan is increased by adding clinical data to the diagnostic reasoning.[54]

Pulmonary Function Tests

Pulmonary function tests have no discriminative properties in differentiating HP from other interstitial lung diseases.[4] Their usefulness is primarily to describe the physiologic abnormalities and the associated impairment. The results of pulmonary function tests may also guide therapy by helping the clinician in selecting those for whom corticosteroids may be justified. The typical physiologic profile of acute HP is a restrictive pattern with low diffusing capacity of the lung for carbon monoxide (DLCO).[55] In chronic disease, the pattern can be restrictive, but at least in farmer's lung, the most frequent profile is an obstructive defect resulting from emphysema.[56] A currently held belief is that a decreased DLCO is always present in HP. Nevertheless, in the HP Study, 39 of the 177 patients in whom DLCO could be measured (22%; 95% CI, 16%-29%) had normal results (defined as a DLCO $\geq$ 80% predicted) at the time of diagnosis (HP Study Group, unpublished data, 2003).

Specific Antibodies

HP cannot be ruled in solely on the basis of positive antibodies or ruled out on the basis of negative antibodies. Many asymptomatic farmers (10%) and pigeon breeders (40%) have positive results,[57-59] and many cases of HP have negative specific antibodies. In addition, a study showed fluctuations over 4 years in the precipitin status of dairy farmers who had repeated measurements of serum antibodies against SR, *Thermoactinomyces vulgaris*, and *Aspergillus fumigatus*.[60] It is currently unclear if the false negatives result from inappropriate antigens tested or if HP can occur in the absence of specific antibodies to the responsible allergen. However, specific antibodies analysis can be useful as supportive evidence.[61] The results of the HP Study demonstrate that positive serum antibodies are a significant predictor of HP (Table 3).[4] The selection of antigens to be tested often needs to be determined locally according to the prevalent antigens.[4,62]

Several methods for determination of precipitins or total IgG antibodies (immunodiffusion, immunoelectrophoresis, enzyme-linked immunosorbent assays [ELISAs], electrosyneresis) and different antigen preparations have been described.[63] ELISA is usually the preferred method. Unfortunately, even the ELISA technique lacks standardization.[64] The importance of the proper determination of reference values for serum antibodies against pigeon serum antigen has also been emphasized.[65]

Inhalation Challenge

Inhalation challenges to suspected environments, usually at the workplace, as well as specific provocation tests in controlled conditions have been described.[66,67] These tests lack standardization both in the inhalation protocols and the criteria defining a positive response. Further studies are needed before recommending inhalation challenges in the diagnosis of HP.

BAL and Induced Sputum

BAL can provide useful, supportive elements in the diagnosis of HP. Unfortunately, BAL technique also lacks standardization. The usual threshold values used to define BAL lymphocytosis ($\geq$30% for nonsmokers and ex-smokers, and $\geq$20% for current smokers) are from the BAL Cooperative Group report[68] and represent the 95th percentile of expected percent lymphocyte in healthy individuals (healthy never smokers, 34.3%; healthy ex-smokers, 29.3%; healthy current smokers, 18.6%). BAL lymphocytosis is mandatory for the diagnosis of HP; a normal number of lymphocytes rules out all but residual disease.[69] Asymptomatic, exposed individuals can also have increased numbers of lymphocytes in their BAL,[70] and BAL lymphocytosis is not specific for HP, as many other diseases are also characterized by an

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alveolar lymphocytosis.[71] Lymphocyte subsets, especially the CD4/CD8 ratio and activation, were previously believed to be helpful in differentiating HP from sarcoidosis. This is now challenged, since the CD4/CD8 ratio can be increased in HP to levels as high as those seen in sarcoidosis.[72,73]

Induced sputum from patients with acute HP contains increased total cells and lymphocytes. Differential cell counts suggest that induced sputum and BAL reflected different compartments of inflammation.[74] The usefulness of induced sputum in the investigation of interstitial lung diseases, including HP, is currently unclear.[75]

Differential Diagnosis

Lung infection is by far the most frequent differential diagnosis for patients with acute HP. In the chronic form of the disease, the differential diagnosis of HP is particularly wide. In the HP Study, the control group (462 patients without HP) covered the whole spectrum of diffuse parenchymal diseases, with either of the idiopathic interstitial pneumonias (n = 226) and sarcoidosis (n = 52) representing the top two differential diagnoses.[4] As granulomatous lung diseases, HP and sarcoidosis must be distinguished. In addition to granulomatous inflammation, chronic interstitial pneumonia away from the granulomas is a dominant characteristic of HP. On the contrary, in sarcoidosis, mild inflammation is usually found in the vicinity of the granulomas. Another distinctive feature is that granulomas have a lymphangitic distribution in sarcoidosis, whereas they are seen along the airways in HP.[76] In the HP Study, several clinical characteristics distinguished HP from sarcoidosis.[4] The two main distinctive features were from physical examination and chest radiograph (HP Study Group, unpublished data, 2003). Compared with patients with sarcoidosis, those with HP presented more often with inspiratory crackles (87% vs 15%). As expected, hilar and/or mediastinal lymphadenopathies were seen more often in sarcoidosis than in HP (46% vs 2%). Of note, mediastinal lymphadenopathy on HRCT scan is not a rare occurrence in HP and has no negative diagnostic value.[77]

Prevention and Treatment

The obvious best treatment of HP is contact avoidance. When this is possible and rapidly done, the patient will be cured. If, however, the disease has progressed to a point of leaving significant permanent lung damage, such as fibrosis and/or emphysema, it is likely that the disease can progress even after all contacts with the antigen have been eliminated.[78] The only current accepted medical treatment is oral or systemic corticosteroids. These are only needed in severe cases or when the offending antigen cannot be completely removed. Steroids hasten the initial recovery but do not seem to alter the long-term course of the disease.[79] One study suggested that inhaled steroids could be effective,[80] and pentoxifylline may also be of some benefit.[81] There is currently no specific drug targeting the different cytokines, chemokines, inflammatory cell subtypes, surfactant proteins, and ecosanoids involved in the development of the disease.

Prognosis and Outcome

The long-term outcome of subjects with HP is highly variable. Factors that are important in determining the outcome include duration, type, and intensity of exposure, lung pathologic changes (fibrosis[82,83] and emphysema[56]), and possibly genetic background. CT scan findings of parenchymal fibrosis[84] as well as pathologic pulmonary fibrosis[83] are associated with diminished survival in HP. With appropriate treatment, most cases of HP have a favorable outcome, with improvement or normalization of lung function.[85,86] Farmers with chronic HP more often develop emphysema,[56] whereas pigeon breeders usually evolve toward lung fibrosis, with a poor 5-year prognosis as subjects with IPF.[87] As mentioned previously, AEs of chronic HP bear a very poor prognosis.[47] Overall, there is an increased mortality in patients with HP compared with the general population (hazard ratio, 2.98), even though these individuals are less likely to smoke.[18]

New Offending Agents of Special Interest

Two specific forms of HP related to exposure to environmental mycobacteria have recently raised special interest. Hot tub lung and metalworking fluid (MWF) HP illustrate some of the most recent efforts and advances in HP-related research.

Hot Tub Lung

Microorganisms from the *Mycobacterium* genus (most often *M avium*) were identified as the offending antigens in sputum, lung biopsy, and/or water cultures in patients with HP-like reaction from hot tub exposure.[88] Although most cases have been from indoor hot tub exposure, outdoor pool exposure has been reported.[89] Hot tub lung may present as acute or chronic disease.[88,90,91] There has been some debate as to whether hot tub lung represents HP, another type of granulomatous lung reaction or infection.[88,92]

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On clinical grounds, arguments favoring the HP hypothesis are numerous: (1) mycobacterial cell wall antigen can induce hypersensitivity reaction; (2) clinical and HRCT scan features are those of HP (Fig 1); (3) full functional, radiologic, and lung function recovery following exposure withdrawal or corticosteroid therapy is the rule[88,90,92,93]; and (4) antimicrobial therapy is not required in the management of the disease, which occurs mostly in immunocompetent patients.[90] Others have suggested that the findings of well-formed granulomas in hot tub lung (as opposed to loosely formed granulomas in HP) and increased CD4/CD8 lymphocyte ratio on BAL indicate that hot tub lung represents a different entity from HP. As counterargument, we would submit that well-formed granulomas are seen in HP.[94] Also, we have already indicated that the CD4/CD8 ratio is highly variable in HP.

MWF Hypersensitivity Pneumonitis

MWFs are used in several industries, mainly to decrease heat from the machine tools and the object in production. MWFs may be pure petroleum oils, emulsion of petroleum in a water base (semisynthetic fluids), or emulsion of synthetic oils in water (synthetic fluids).[95] Although biocides are added to MWFs, resistant microorganisms survive, leading to selection of organisms such as mycobacteria. MWFs are almost always contaminated with microorganisms originating from environmental sources (such as water used for their dilution) or from workers' flora.[96] As in hot tub lung, microorganisms of the *Mycobacterium* genus (most often *Mycobacterium immunogenum*) have been implicated in MWF HP.[97] MWFs containing mycobacteria have induced granulomatous lung lesions, peribronchiolar lymphocytosis, increased cell concentration in BAL, and up-regulation of several cytokines in mice.[98] These findings are consistent with HP and represent, in our opinion, a clear demonstration that mycobacteria can definitely induce HP. Detection of *M immunogenum* in MWF is difficult and requires specialized techniques. Unlike hot tub lung, mycobacteria are not cultured from BAL fluid, and measurement of *M immunogenum*-specific cell-mediated immunity has been investigated as an aid to diagnosis.[99] Detection of specific antibodies against recombinant *M immunogenum* antigens by ELISA has recently been described[100] and looks promising. Prevention strategies in the industry include improving MWF management practices, enclosing selected MWF machining operations, eliminating mist cooling, exhausting additional water-based industrial processes, increasing general dilution ventilation, and worker training.[101]

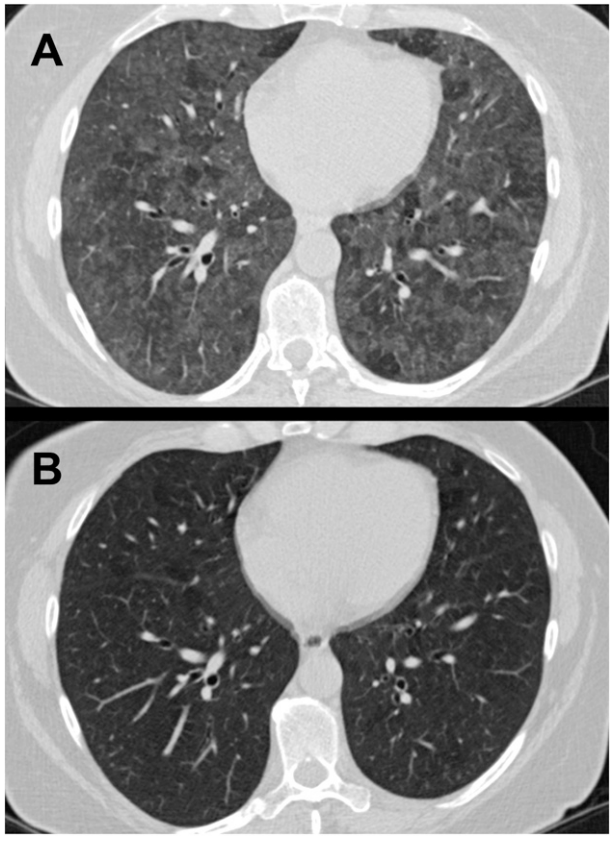

FIGURE 1. A, High-resolution CT scan of a patient with hot tub lung: patchy bilateral ground-glass opacities with poorly defined small centrilobular nodules. B, Same patient, 6 weeks following exposure withdrawal, showing full radiologic recovery.

CONCLUSION

In the past decade, we have witnessed the publication of several studies that improved our understanding of HP. As in most of the diffuse parenchymal lung diseases, however, much remains to be learned. The workshop of the NHLBI/ORD identified several areas for future clinical research in HP.[1] These include, among others, (1) the need for a better documentation of its incidence and prevalence; (2) the identification of genetic and environmental risk factors that affect its occurrence and natural history; (3) the validation of biomarkers of both exposure and disease; (4) the definition of its natural history; and (5) the development of a battery of standardized antigens known to cause HP, which should be available to clinicians and researchers for use in both the diagnosis and investigations of pathogenesis.

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