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Review Article

Hypersensitivity Pneumonitis

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Introduction

Hypersensitivity pneumonitis (HP), also called extrinsic allergic alveolitis, is a respiratory syndrome which contributes a spectrum of granulomatous, interstitial, bronchiolar and alveolar-filling lung diseases[1-2]. HP was first described by Bernadino Ramazzini, an Italian researcher, who researched in subjects with 52 different professions. He proposed that a repeated exposure to particles with diameter less than 5 μm can reach the alveoli and trigger an immune response. The most at risk professional categories are farmers and breeders[1, 3]. HP was first described in 1932. There was an outbreak of illness in 10 employees of a sleepers company in Michigan. These people developed dyspnea, productive cough, night sweats, and weight loss after resuming of work. Their labor barked stripes from maple logs and about 30% of workers developed these symptoms. Their chest radiographs showed increased opacities at peribronchial and perihilar areas and poorly defined nodules in the lower lungs[2].

There was another similar outbreak in 36 of 800 employees at a nearby sawmill, which most of its logs were maple. Investigators noticed that there was black dust lying beneath the bark. It was isolated a fungus called *Cryptostroma corticale*. They supposed that this disease was an allergic reaction to its aerosolized spores [2].

Epidemiology and Etiology of HP

Prevalence of HP is difficult to evaluate because of uncertainty in detection and lack of widely accepted diagnostic criteria. Prevalence of HP varies between countries and depends on climatic, seasonal, and geographical conditions. Prevalence of HP is more common in males than females and overrepresents in middle-aged individuals[1, 3, 4].

In Thailand, Bagassosis is characterized as HP. It is caused by *Thermophilic actinomycetes* which are grown in bagasse. People who repeated inhaled dust from waste sugar cane fiber, called bagasse, developed

dyspnea and cough. Risk factors of bagassosis are workers in sugar and paper factories. The first report of bagassosis was described in 1974 by Kamtorn P. It occurred in a paper factory in Ratchaburi province. People developed dyspnea, cough, chest pain, and fever. Onset of these symptoms was peak at 3 to 8 hours after exposure. Six patients were autopsied to confirm cause of the disease[5-6.]

HP can be caused by multiple agents in work places and homes, such as, microbes, animal and plant proteins, organic and inorganic chemicals as in table 1[3].

Farmer's lung disease (FLD) was first described in 1932[2, 7]. It was a prototype of acute HP, which is an immunological reaction to bacterial and/or fungal products found in hay handled during the indoor feeding season, especially in cold and rainy area[8]. The antigen itself can be moldy grains, moldy hay, or moldy straw. The microbial agent classically said to induce FLD is *Saccharopolyspora rectivirgula*, which is a thermophilic actinomycete[8].

Table 1. Causative agents of HP [1, 3, 4]

Disease	Antigen Source	Putative Antigen
Fungal and bacterial		
Farmer's lung	Moldy hay	*Saccharopolyspora rectivirgula*
Ventilation pneumonitis; humidifier lung; air conditioner lung	Contaminated forced-air systems; water reservoirs	*Thermoactinomyces vulgaris, Thermoactinomyces sacchari, Thermoactinomyces candidus, Klebsiella oxytoca*
Bagassosis	Moldy sugarcane (i.e., bagasse)	*Thermoactinomyces vulgaris*
Maple bark stripper's lung	Moldy maple bark	*Cryptostroma corticale*
Summer-type pneumonitis	Contaminated old Japanese houses	*Trichosporon cutaneum*
Cheese worker's lung	Moldy cheese	*Penicillium casei, Aspergillus clavatus*
Hot tub lung	Hot tub mists, mold on ceiling	*Mycobacterium avium complex*
Machine worker's lung	Aerosolized metalworking fluid	*Mycobacterium immunogenum, Pseudomonas fluorescens*
Sauna taker's lung	Contaminated sauna water	*Aureobasidium spp.*
Animal proteins		
Bird fancier's disease	Various birds	Avian droppings, serum, feathers
Fish meal worker's lung	Fish meal dust	Fish meal
Bat lung	Bat droppings	Bat serum protein
Furrier's lung	Animal fur	Animal fur protein

Pathogenesis of HP

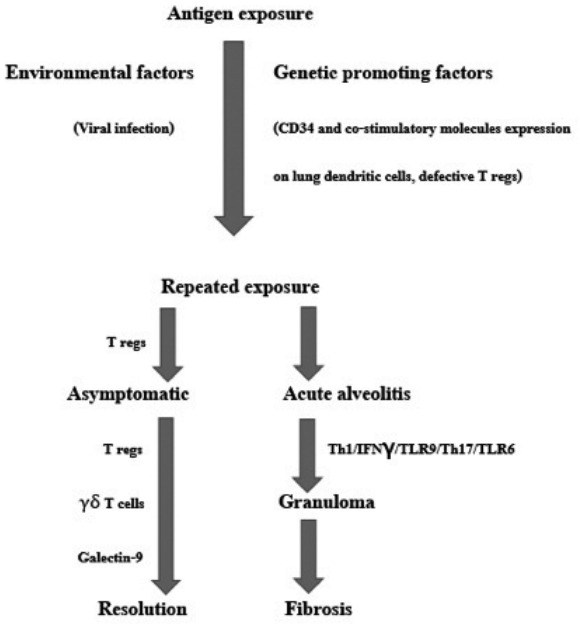

Figure 1. Proposed pathogenesis of HP (Adapted from Bourke SJ, Dalphin JC, Boyd G, McSharry C, Baldwinz CI, Calvert JE. Hypersensitivity pneumonitis: current concepts. Eur Respir J 2001; 18 Suppl 32, 81S–92S., Glazer CS, Martyny JW, Lee B, Sanchez TL, Sells TM, Newman LS, et al. Nontuberculous mycobacteria in aerosol droplets and bulk water samples from therapy pools and hot tubs. J Occup Environ Hyg 2007; 4: 831–40.)

Bird fancier's lung, also called Pigeon-breeder's lung, was first described in 1960. It can be presented with acute, subacute or chronic HP. It is an allergic reaction to organic protein compounds that come from the droppings of birds, immunoglobulins, intestinal mucin, or the substance that coats the birds' feathers. We can perform specific antibody levels, and the results are high in late summer. People who work with cleaning out bird cages have chance of the highest exposures to respirable avian antigen. The common birds which are

well known to be the cause of the pigeon breeder's disease are parakeets, shell parakeets, turtle doves, chickens, pigeons, cockatiels, parrots, and turkeys [2].

Hot tub lung is one of HP which occurs by inhalation of non-tuberculous mycobacterium, especially, *Mycobacterium avium* complex colonized in heated water [4]. NTM are slowly growing, hydrophobic bacteria that can adhere to surfaces and produce a biofilm in water pipes[9]. The concentrations of NTM were significantly higher in pools disinfected with hydrogen peroxide and ultraviolet light than in chlorine- and bromide-disinfected pools[10].

Antigens less than 5 μm in diameter may be inhaled to the lung parenchyma and distributed to the lymphatic vessels and deposited at respiratory bronchioles. Inflammatory response was mediated by lymphocytic reactions. The main role in the development of HP is Th1-cytokine system where as the chronic form a Th2-like immune response[1-2]. Inflammatory response of alveolar mucosa is a hypersensitivity reaction of type 3 (immune-complex mediated) or type 4 (T lymphocytes mediated).

Genetic basis of HP is still unclear. Some studies suggest that class II Major Histocompatibility Complex molecules are primary susceptibility locus in HP. If they exposed to antigens which can induce to develop HP, most individuals develop immune tolerance, and antigen may result in a mild increase in local lymphocytes, without clinical significance. According to a two hit hypothesis, the coexistence of genetic or environmental promoting factors and these antigens provokes the development of an exaggerated immune reaction. It results to develop alveolitis, granulomatous inflammation, and finally turn to lung fibrosis[2, 7].

There are numerous hypothesis about HP.

a. Role of antigen presenting cells

Antigen presentation dendritic cells are key cells in the development of T cell-dependent adaptive immune responses. In an animal model of HP, expression of stem cell antigen CD 34 by lung mucosal dendritic cells was essential for dendritic cells migration from the lung to the lymph nodes. Loss of expression CD34 is a protective factor from development of HP. Viral infection can also promote dendritic cells maturation [12.]

b. Role of T cells

CD 4 Helper T cell can be differentiated to Th1, Th2 and Th17 cells. Th1 cells secrete IFN-γ, which is an important role in granuloma formation of HP. Th17 cells produce IL-17A, IL-17F and IL-22, which stimulate neutrophil mobilization and recruitment. TLR6 and TLR9 are essential for developing of Th 17-mediated granulomatous inflammation [1, 4, 7.]

T regulatory-cells, which are one type of effector CD4+ T cells, may be resulted in an antigen tolerance in asymptomatic subjects. Defect of regulatory T-cells function, potentially caused by increased IL-17 production, results to exaggerate immune response and develop HP [13].

γδT cells are a unique subset of lymphocytes whose function is poorly understood. These cells are located in the subepithelium of alveolar and non-alveolar regions of the lung. In a mouse model, γδ cells are the predominant source of the Th17 cytokine IL-22. Blockade of expression of IL-22 results to accelerate pulmonary fibrosis[14].

Galectin-9 is a ligand for T-cell immunoglobulin and mucin domain-containing molecule 3 (Tim-3). It is an important roles in both innate and adaptive immunity. Galectin-9 induces apoptosis of activated Th1 and Th17 cells and expands the immunosuppressive macrophages and ameliorates experimental Th1/Th17 cell-mediated HP[11, 14].

c. Role of inflammation and apoptosis

Macrophages and neutrophils are activated via Fc-γ receptors and accumulate in tissues. Activated neutrophils loaded with matrix metalloproteinase 9 and collagenase-2 were found to develop lung damage and fibrosis in chronic HP[15]. Angiostatic and angiogenic chemokines also promote the development of fibrosis[16].

Increased apoptosis in non-hematopoietic cells enhances maturation and chemokine production of CD11c + DC to develop HP. Surgical lung specimens from HP patients showed up-regulation on epithelial cells of Fas, Fas ligand, p53 and p21 expression in usual interstitial pneumonia-like lesions compared with nonspecific interstitial pneumonia-like lesions. p53 and p21 expression was also increased in fibrotic NSIP-like lesions compared with normal lung tissues [17].

Smoking is less prevalent in patients with HP than non-smoking. The protective effect of smoking is poorly understood. Nicotine is thought to inhibit macrophage activation and lymphocyte proliferation and function. Mice challenged with *Saccharopolyspora rectivirgula*, which is an antigen capable to develop Farmer's lung disease, treated with nicotine showed a significant decrease of lung inflammation. However, HP in smokers may develop a chronic clinical course with more recurrent episodes and a significantly poorer survival rate compared with non-smokers [2-4].

Clinical course of HP

The division of HP into acute, subacute and chronic categories is outdated and little prognostic value. Recently, it was proposed two main categories based on clinical-radiologic-pathologic correlation into acute/ inflammatory HP and chronic/ fibrotic HP[18].

Acute HP usually occurs within 6 months with history of intermittent high level of exposure. Its onset is 2 to 9 hours after exposure. It may gradually increase symptoms over days to weeks. Its symptoms are fever, cough and dyspnea, but predominantly influenza-liked symptoms. Its symptom recur on re-exposure and may progress to severe dyspnea [1-2].

Chronic HP usually occurs after 6 months with history of continuous low level of exposure and insidious onset. Many patients with chronic HP were unrecognized acute episodes and present as a progressive chronic respiratory disease. Its symptom are progressive dyspnea, cough and weight loss. Physical examination showed inspiratory crackles, digital clubbing or cor pulmonale. Exacerbation may occur despite avoidance of exposure [1-2].

Diagnosis of HP

Diagnosis of HP needs information about occupational and environmental history. We should explore about a chronology of current and previous occupations, description of job processes and specific work practices, symptom improvement away from work or worsening with specific workplace exposures, presence of persistent respiratory symptoms in exposed coworkers, pets and other domestic animals (esp. birds), use of hot tubs or saunas, visible fungal growth, similar symptoms in other family members, etc. Physical examination in patients may be completely normal. In fibrotic phase, it showed coarse inspiratory rales or inspiratory squeaks [19].

There are six clinical predictors for the diagnosis of HP.

1. Exposure to a known offending antigen (odd ratio, OR 38.8)

2. Positive precipitating antibodies (OR 5.3)

3. Recurrent episodes of symptoms (OR 3.3)
4. Inspiratory crackles (OR 4.5)
5. Symptoms 4-8 hours after exposure (OR 7.2)
6. Weight loss (OR 2)

If all 6 predictors are present, probability of having HP is 98% [2].

Serum precipitins

Serum precipitins is an assay for precipitating IgG antibodies against various potential antigens. They are only a marker of exposure. About forty percent of farmers have positive serum precipitins to common causes of HP without clinically significant disease. Absence of serum precipitins does not rule out HP. Many routine precipitin panel are virtually useless because of the high rate of falsely negative results and antigen preparation is not highly standardized [2]. There is often misunderstanding that skin test reactivity has the same implication as the finding of serum precipitins. However, skin tests are not helpful in the diagnosis of HP [20].

Specific Inhalation challenge

A positive test is characterized by a decrease in forced vital capacity (FVC) of more than 15% or of more than 10% in combination with a recurrence of clinical symptoms (desaturation, hyperthermia, cough, dyspnea) and radiological signs (appearance of radiological infiltrates). Sensitivity and specificity of test were 72.7% and 84%, respectively. A negative test does not rule out the diagnosis (negative predictive value of 47%). Having HP caused by an antigen other than birds or fungi predicted a false-negative result (p=0.001). However, it also lacks of standardization [2].

Chest radiography

Sensitivity of chest radiography for detection of this disease is relatively low. Many patients may have normal radiographs [1]. Chest radiograph in acute HP showed diffuse ground glass opacities. Chest radiograph in chronic HP showed fibrotic changes (such as reticular opacities and honeycombing) which are predominant at upper lobes [2]. Volume loss may occur and cardiomegaly may develop as a result of cor pulmonale [3].

High Resolution Computerized Tomography Chest

HRCT chest is an important tool for diagnosis of HP. The accuracy of HRCT-based diagnosis of HP is 88-92%. The sensitivity of HRCT-based diagnosis of HP is 44-61% [18]. HRCT chest in acute HP showed centrilobular diffuse micronodular pattern (usually less than 5 mm in diameter), ground-glass opacification (GGO) and mosaic attenuation, predominantly in upper and middle lobes. Ground-glass opacities usually distribute along bronchovascular area [3, 18]. Head-cheese sign, which is characteristic of HRCT chest that showed a combination of patchy ground glass opacity, normal and air trapping, is a specific sign of acute HP [21].

HRCT chest in chronic HP showed signs of fibrosis, such as reticulation, architectural distortion and traction bronchiectasis with or without honeycomb change [2]. Imaging features that favor HP over IPF and idiopathic NSIP include an upper or mid zone predominance, extensive GGO, centrilobular nodules, and conspicuous air trapping [21].

Pulmonary function tests

The most sensitive parameter in pulmonary function tests in all HP is reduction of DLco. Pulmonary

function tests results of most patients are restriction. However, obstruction and mixed deficits may be seen. HP should be considered in non-smokers presenting with either fixed or reversible obstruction. An exercise-induced desaturation is an early sign of functional impairment in patients with mild disease. In farmer's lung, the most frequent profile is an obstructive defect resulting from emphysema [19, 23].

Table 2. Accuracy of thin-section CT in distinguishing chronic HP from IPF and NSIP [22]

Characteristics	Chronic HP (%)	IPF (%)	NSIP (%)
Lobular areas of mosaic attenuation	80	43	34
Centrilobular nodules	56	15	14
Thin-walled cyst	39	0	12

Diagnostic role of bronchoscopic techniques

Bronchoalveolar lavage is the most sensitive tool to detect alveolitis in patients suspected of HP 2. Typical pattern is a marked lymphocytic alveolitis (more than 20%). Lymphocyte count is usually higher than 50% in subacute HP, and increase of CD8+ T cells (CD4:CD8 < 1). Mast cells, plasma cells and foamy macrophages can be seen in the BAL and support a diagnosis of HP [2].

In acute HP, neutrophils was influxed with peak level at 48 hours after exposure. BAL showed acute alveolitis then increase in lymphocytes is observed between 48-72 hours. In subacute HP, BAL showed lymphocytosis, composed of CD4+ and CD8+ cells. In chronic HP, there is a shift toward a profibrotic Th2 lymphocyte profile and it showed a higher CD4+/CD8+ ratio[19]. Although a low CD4+: CD8+ ratio is suggestive of HP, it is non-specific and insensitive. CD4+/CD8+ ratio may not be significantly increased in a substantial number of patients with sarcoidosis or significantly decreased in a substantial proportion of patients with hypersensitivity pneumonitis, and can change during the course often disease process [18]. So 2012 American Thoracic Society Clinical Practice Guidelines do not support the use of the T cell subsets in BAL fluid as a routine test for patients undergoing evaluation for diagnosis of interstitial lung disease [18].

Transbronchial biopsy

In acute HP, it is not necessary for diagnosis. In the few reported cases, the main abnormalities were fibrin deposition and neutrophils (mostly interstitial and sometimes with features of capillaritis). The variable combination of fibrin, neutrophils, cellular infiltrates, and tiny granulomas can lead to get a suspicion of acute HP with a compatible clinical scenario [2, 19].

In subacute HP, classic histologic triad is composed of interstitial infiltrate, cellular bronchiolitis and poorly formed granuloma. Granuloma can be found in about 75% of cases with cholesterol cleft. The characteristic of granuloma in HP is centered upon the peribronchiolar interstitium rather than the lumens of airways and peribronchiolar air spaces. It is poorly formed, subtle and small cluster of loosely organized epithelioid histiocytes [2, 9, 19].

In chronic HP, histology may have a combination of findings characteristic of UIP, including patchy fibrosis with subpleural/ paraseptal distribution, fibroblastic foci, and honeycombing. The main ancillary features for differentiating chronic HP from IPF are centrilobular fibrosis/inflammation (sometimes with "bridging" fibrosis, consisting of a fibrotic net connecting bronchioles with each other and with pleural/septal regions), a significant lymphoid/ plasmacytic infiltrate (particularly outside the fibrotic areas), and small granulomas/giant cells [2, 19].

Multidisciplinary discussion is very important thing in diagnosis of HP. Figure 2 showed diagnostic algorithm for HP [14]. If there is no diagnostic samples from transbronchial biopsy, transbronchial cryobiopsy or surgical lung biopsy should be considered. Meta-analysis by Sharp and colleagues showed diagnostic yield of transbronchial cryobiopsy is better than forceps transbronchial biopsy, as table 3. However, transbronchial cryobiopsy is currently only available in a few experienced centers [18, 25].

There are many factors associated with worse prognosis, such as, male sex, older age, longer and higher intensity of exposure, cigarette smoking, unidentified source of exposure, digital clubbing and crackles on lung examination, histologic pattern of either fibrotic nonspecific interstitial pneumonia or usual interstitial pneumonia, baseline low total lung capacity and low DLCO, absence of lymphocytosis in BAL fluid [1,14].

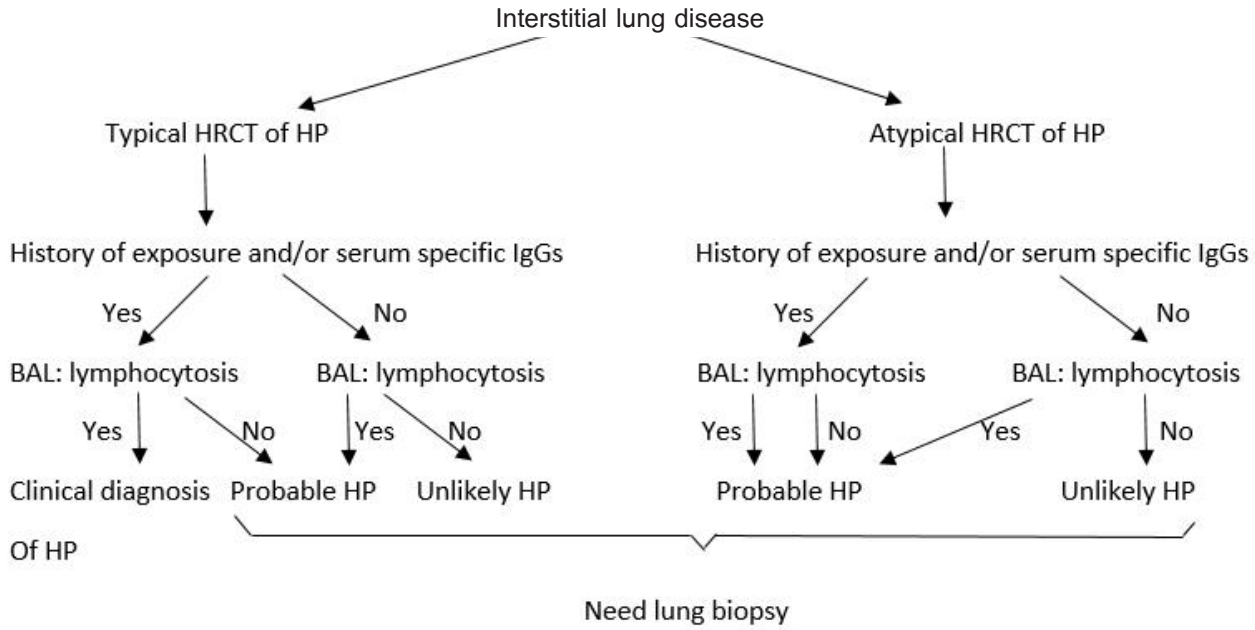

Figure 2. Diagnostic algorithm for hypersensitivity pneumonitis (HP) (Adapted from Vasakova M, Morell F, Walsh S, Leslie K, Raghu G. Hypersensitivity pneumonitis: perspectives in diagnosis and management. Am J Respir Crit Care Med 2017; 196: 680-9.)

Table 3. Diagnostic yield, mortality and morbidity in various procedures in meta-analysis by Sharp and colleagues[25]

Procedure	Forceps transbronchial biopsy	Transbronchial cryobiopsy	VATS-biopsy
Studies	11	11	24
Total patients	1214	704	2665
Diagnostic yield % (95%CI)	64.3 (52.6-75.1)	84.4 (75.9-91.4)	91.1 (86.9-93.2)
Mortality	No deaths reported	0.5% (3 deaths)	2.3% (1.3-3.6%)
Morbidity	Pneumothorax 6.0% Bleeding 10.1%	Pneumothorax 10.0% Bleeding 20.9%	Surgical morbidity 12.9%

Serum biomarkers

The serum biomarkers were found potential of minimally invasive diagnosis and prediction of prognosis of HP [18].

Serum Krebs von den Lungen-6 (KL-6) is a mucin-like glycoprotein. Surfactant protein D (SP-D) is a member of C-type lectin superfamily. Both markers are produced by regenerating type II pneumocytes [26]. Retrospective study by Okamoto and colleagues revealed that serum KL-6 and SP-D levels in acute HP (2,710 U/ml and 338 ng/ml, median) and chronic HP (1,500 U/ml and 264 ng/ml, median) were significantly higher than those in IPF (744 U/ml and 140 ng/ml), collagen vascular disease-associated interstitial pneumonia (959 U/ml and 140 ng/ml) and sarcoidosis (362 U/ml and 44 ng/ml). High levels of serum KL-6 and CCL17 were associated with current or future exacerbation of HP [26].

YKL-40 is a chitinase-like protein. It mainly secreted by macrophages, neutrophils and epithelial cells, which is involved in the inflammatory response to tissue injury [27]. Retrospective study by Long and colleagues showed that serum YKL-40 levels were significant higher in HP patients (127 + 9 ng/ml) than in healthy controls (39 + 4 ng/ml), but lower than other ILD. Using ROC analysis, at a cut-off level of >119 ng/ml, serum YKL-40 levels showed the best sensitivity (81%), specificity (77%) and accuracy (79%) to predict disease progression (AUC 0.797; $p<0.001$). At a cut-off of 119 ng/ml, the baseline serum YKL-40 level predicted disease progression (hazard ratio 6.567; $p<0.001$), and at a cut-off of 150 ng/ml was associated with mortality (hazard ratio 9.989; $p<0.001$) [27].

C-C chemokine ligand (CCL) 17 is a Th2 chemokine produced by epithelial cells. C-C chemokine receptor (CCR) 4 is a CCL17 receptor preferentially expressed on Th2 cells. Miyazaki Y and colleagues found that serum CCL17 levels and CCR4-positive cells were both increased during acute exacerbation in HP. CCL17 recruit CCR4-positive cells into the lesions. This process promotes fibrogenesis and leads to acute exacerbation of HP. Higher serum concentrations of baseline CCL17 may be a promising predictive marker of acute exacerbation in patients with chronic HP [28].

In the future, we need prospective studies to determine whether these serum biomarkers measurements should be routinely used in HP.

Management of HP

The cornerstone of management is avoidance of exposure. Education of "at risk" populations is helpful in the early recognition of symptoms and in encouraging them to perform preventative strategies. Bird fancier's disease can be prevented by bird removal and effort to eliminate residual feathers and droppings. Farmer's lung disease can be prevented by drying of hay before storage and using mechanical feeding systems. Indoor microbial contamination can be prevented by control of moisture and temperature with high efficiency filters [2,18,20].

Systemic corticosteroids can be used in acute attack of HP with dose of prednisolone 0.5-1 mg/kg/day (up to a maximum daily dose of 60mg). Duration of steroid in acute HP is 1-2 weeks. Duration of subacute HP is 4-8 weeks, and followed by a gradual taper to off or a maintenance dose of 10 mg/day. The efficacy of corticosteroid treatment lasting 12 weeks is not significantly superior to that of 4 weeks' duration [2, 20]. Although, there is no randomized-controlled trial on pharmacological treatment in chronic HP, steroid in adults with farmer's lung disease improves quickly lung function compared to placebo. In adults with chronic HP, prednisolone was effective in only 58% of cases. For progressive chronic HP immunosuppressive drugs may therefore be necessary [11].

In a retrospective study by Morisset and colleagues, treatment with azathioprine and mycophenolate mofetil was associated with an improvement of gas exchange and reduction of prednisolone. There is very low quality evidence suggested the use of rituximab and leflunamide in HP [18]. Antifibrotic treatment in HP is off-label and cost concerning. Randomized-controlled trial with either nintedanib or pirfenidone will be conducted soon for these patients [18].

Early lung transplant should be considered in patients with progressive disease, as they have excellent post-transplant medium-term survival and a reduced risk for death [18]. From a retrospective cohort study of all patients undergoing lung transplantation between January 1, 2000, and July 1, 2013, at the University of California San Francisco, lung transplantation in HP showed better outcome than in idiopathic pulmonary fibrosis. The rate of acute rejection in HP was approximately 10%. Factors associated with better survival are patients with HP were younger and more likely to undergo bilateral lung transplantation [29].

Conclusion

HP is a complex syndrome caused by an immunologic reaction to a variety of inhaled antigens. Clinical findings, disease severity and natural history are heterogeneous. Diagnosis of HP needs clinical suspicion and multidisciplinary discussion between pulmonologists, radiologists and pathologists. Avoidance of exposure is the cornerstone of treatment of HP.

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