Hypersensitivity Pneumonitis and Related Conditions in the Work Environment

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KEYWORDS

• Hypersensitivity pneumonitis • Extrinsic allergic alveolitis
• Occupational

Hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, is an uncommon non–immunoglobulin E (IgE), T-helper cell type 1 (Th1)–mediated inflammatory pulmonary disease with systemic symptoms resulting from repeated inhalation and subsequent sensitization to a large variety of aerosolized antigenic organic dust particles. The exaggerated immune response to repeated inhalation of these particles leads to infiltration and proliferation of activated pulmonary macrophages and lymphocytes, resulting in lymphocytic alveolitis and bronchiolitis with noncaseating granulomas. Fibrosis may occur with chronic exposure. Recurrent or chronic cough and/or dyspnea with or without systemic symptoms should alert the physician to the diagnosis. The earliest forms of hypersensitivity pneumonitis were related to farming and, each year, new antigens causing occupational disease are described.

Hypersensitivity pneumonitis was originally described in 1713 as an occupational lung disease in grain workers and later, in 1932, in farmers inhaling moldy hay contaminated with thermophilic actinomyces, hence the term farmer's lung.[1] With this recognition, modernization of farming methods has resulted in the reduction in farmer's lung prevalence estimated at 0.5% to 3% of exposed farmers in studies spanning from 1980 to 2003. Definite conclusions on prevalence and incidence of farmers lung are elusive because of methodological issues in study design and definitions of disease, fewer farmers in general, and erroneous diagnoses.[2] However, farming continues to represent a major source of exposure to antigens capable of causing occupational

Funding support: None.
The authors have nothing to disclose.
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Immunol Allergy Clin N Am 31 (2011) 769–786
doi:10.1016/j.iac.2011.07.004 **immunology.theclinics.com**
0889-8561/11/$ – see front matter

hypersensitivity pneumonitis. National surveillance screening in the United Kingdom from 1992 to 2001 estimated 50 cases of hypersensitivity pneumonitis annually, representing 1.8% of all cases of work-related respiratory disease seen by chest physicians. For occupational physicians, the average annual rate of hypersensitivity pneumonitis was 1 per million employees, representing about 4 cases per year or 0.7% of all work-related respiratory disease.[3]

SPECIFIC OCCUPATIONS AND WORK-RELATED ANTIGENS

Many diverse occupations in which workers are exposed to antigens small enough to reach the distal airway (<5 μm) have been implicated as inducing hypersensitivity pneumonitis (**Table 1**). These antigens include organic dusts containing bacteria, fungi,[4] animal or plant proteins, or low-molecular-weight chemicals.

Farming

Farmer's lung is the prototype occupational hypersensitivity pneumonitis. The antigens of farmer's lung vary between countries and within countries depending on the climate and the methods of farming and hay production used. Many forms of farmer's lung are now fungal induced and include a worker sorting onions and potatoes[5]; workers in large and small commercial indoor mushroom farms[6]; and workers exposed to moldy crops of grapes, tobacco,[7] sugarcane,[8] and peat moss.[9] Agricultural exposures were the most common occupation for hypersensitivity pneumonitis in the Czech Republic, with 69% of cases of farmer's lung (cattleman and dairyman), followed by malt workers and chemical workers.[10] A report of coffee-worker's lung was reconsidered after a patient developed additional laboratory and clinical findings consistent with cryptogenic fibrosing alveolitis associated with rheumatoid arthritis.[11]

Animal and Bird Raising Industry

A quality control worker in a feed factory developed acute disease after taking samples of cattle feed treated with phytase, a fungal-derived enzyme used to treat cattle feed to strengthen bone.[12] Historically, feather bloom and droppings from pigeons or indoor pet birds have been implicated in triggering pigeon breeder's lung or bird fancier's disease. Occupations with bird antigen exposure include keeping domesticated fowl (chicken, turkey) and game farms raising pheasants.[13]

Machinists

More than a dozen outbreaks of hypersensitivity pneumonitis affecting hundreds of workers exposed to contaminated airborne synthetic metalworking fluids (MWF) have been reported since the mid-1990s.[14] This disorder is presumed to be related to the increased use of water-based fluids and automation of high-speed machining processes resulting in the generation of airborne aerosols. MWF are used during grinding, drilling, cutting, and shaping metal to cool, lubricate, and remove metal particles thus prolonging the life of the machinery. Although MWFs contain biocides, they are prone to contamination of rapidly growing *Mycobacterium immunogenum* and *Pseudomonas* species that form biofilms that line the pipes, pumps, and containers and are resistant to treatment.[15] The current Occupational Safety and Health Administration (OSHA) standard for allowable oil mist exposure of 5 mg/m^3 does not prevent hypersensitivity pneumonitis. Despite multiple publications on the health effects of MWF, legal action from union groups, and recommendations from the National Institute for Occupational Safety and Health (NIOSH) to lower the exposure limit to 0.5 mg/m^3, no further action has been taken and court challenges have been denied.[16]

Table 1
Antigens of occupational hypersensitivity pneumonitis

Occupation	Source	Antigen	Disease
Farming	Hay/silage	Thermophilic actinomycetes *Saccharopolyspora rectivirgula* *Lichtheimia corymbifera* (France) *Eurotia amstelodami* *Wallemia sebi* (Finland)	Farmer's lung
	Grain[a]	*Aspergillus fumigatus*	
	Moldy sugar cane	*Thermoactinomyces sacchari*	Bagassosis
	Tobacco	*Aspergillus*	Tobacco workers' disease
	Moldy grapes	*Botrytis cinerea*	Wine grower's lung
	Peat moss	*Penicillium* sp, *Monocillium*	Peat moss processor's lung
	Moldy onions or potatoes	*Fusarium*, *Penicillium* sp	
	Mushrooms	*Penicillium citrinum*	Mushroom picker's lung
Animal/bird industry	Cattle feed	Phytase enzyme[a]	
	Veterinary feed	Soybean hulls	
	Feather bloom, droppings	Pheasant	Pheasant rearer's lung
Food Industry			
Sausage/salami makers	Dry sausage molds	*Penicillium camembertii*	
Cheese makers	Moldy cheese	*Penicillium roqueforti*	Cheese worker's lung
Mill workers	Wheat flour (contaminated)	*Sitophilus* (wheat weevil)	Wheat weevil disease
Malt workers	Moldy brewing malt[a]		Malt worker's lung
Soy sauce brewer	Soy sauce production	*Aspergillus oryzae*	
Laboratory workers	Laboratory reagent	Pauli reagent	Pauli HP
	Rodents[a]	Rat or gerbil urinary proteins	Gerbil keeper's lung
Textile/clothing industry	Nylon plant air-conditioning	*Cytophaga* producing endotoxin	
	Silk production	Silkworm larvae cocoon fluff	Sericulturist's lung disease
	Hair and fur from pelts	Proteins in animal fur dust[a]	Furrier's lung
	Button making	Mollusk/oyster shell dust	
Machine operators	Metal working fluids[a]	*Mycobacterium immunogenum*, *Pseudomonas*	Machine operator's lung
Detergent industry	Enzyme dust[a]	*Bacillus subtilis*	Enzyme worker's lung

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Table 1
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Occupation	Source	Antigen	Disease
Professional musician	Trombone	*Mycobacterium chelonae* or *Fusarium*	Trombone player's lung
Medical/dental	Dental prosthesis production	Methylmethacrylate	
Stucco workers	Plaster for stucco	Thermophilic or *Aspergillus*	Stipatosis
Polyurethane industry	Foam production	Isocyanates[a]	
	Yacht making	Dimethylphthalate or styrene	Yacht-maker's lung
	Epoxy resin	Phthalic anhydrides	
Wood processing plants	Wood dust	Cabreuva, pine sawdust	Wood worker's lung
	Moldy wood planks	*Paecilomyces*	Woodman's disease
	Cork dust	Cork proteins or mold (*Penicillium glabrum*)	Suberosis
	Moldy maple bark	*Cryptosroma corticale*	Maple bark strippers disease
	Moldy wood dust	*Alternaria*, *Rhizopus*, *Mucor*	Wood trimmer's disease
	Moldy redwood dust	*Pullaria*	Sequoiosis

[a] Antigens also implicated in occupational asthma.

The number of new cases of MWF-induced hypersensitivity pneumonitis is difficult to determine because of the sporadic nature of the outbreaks and the possibility of underreporting. The last major outbreak, published in 2007, reported on 19 workers diagnosed between 2003 and 2004 in a car engine manufacturing plant in the United Kingdom.[17] The number of published reports on outbreaks has decreased from 4 in 2003 to 1 report annually from 2005 to 2007 and none in the last 3 years.

Food Industry

Food-related occupations have been associated with fungus-induced occupational hypersensitivity pneumonitis in cheese (blue and Gruyere),[18] malt,[19,20] and sausage[21] workers and even in a soy sauce brewer.[22]

Textile/Clothing Industry

Workers developed disease after sawing nacre (mother-of-pearl) used to make buttons.[23] The inhalation of hair and dust by furriers working with fox and other pelts led to disease with hair shafts found in the granulomas on lung biopsy.[24] In the process of collecting silk for making garments, inhalational exposure to the cocoon fluff containing larval proteins can trigger disease termed sericulturist's lung.[25]

Industrial Exposures of Low-Molecular-Weight Chemicals

Workers exposed to isocyanates during the production of polyurethane foam, elastomers, adhesives, and paints have developed hypersensitivity pneumonitis. In 2008, a secretary in a car body repair shop exposed to low amounts of diisocyanates developed the subacute form.[26] Phthalates or styrene was implicated in a woman rolling panels in making yacht hulls[27] or phthalic anhydrides in epoxy resin workers.[28]

Woodworkers

Either wood itself or fungal-contaminated wood can induce hypersensitivity pneumonitis in sensitized workers. Mold-contaminated wood dust has been reported to cause hypersensitivity pneumonitis in tree trimmers, sawmill workers, lumberjacks, and wood pulp workers.[29] A worker installing parquet floors made of cabreuva wood developed acute disease caused by the wood dust itself.[30] Cork dust containing suberin cork protein and fungal-colonized cork (*Penicillium*, *Aspergillus*, *Mucor*, *Rhizopus*) led to hypersensitivity pneumonitis in cork workers termed suberosis and first identified in 1955.[31]

Rare Causes

Case reports of hypersensitivity pneumonitis have included a worker that inhaled 1,1,1,2-tetrafluoroethane (HFC134a) coolant as part of laser hair removal.[32] In Spain, stucco workers were exposed to either esparto grass (*Stipa tenacissima*) termed stipatosis or to grass contaminated with thermophilic actinomycetes or *Aspergillus*.[33] Workers using enzymes may develop occupational asthma or hypersensitivity pneumonitis from *Bacillus subtilis* exposure.[34]

IMMUNOPATHOPHYSIOLOGY

The pathogenesis of hypersensitivity pneumonitis is complex and still not fully understood.[35] The duration and degree of antigen exposure necessary to sensitize and induce symptoms is also not known.

Although many workers are exposed to potentially sensitizing organic dusts, few develop hypersensitivity pneumonitis, which suggests a genetic susceptibility. Genetic susceptibility is associated with polymorphisms in (1) the promoter region in the tumor necrosis factor (TNF)-α gene on chromosome 6[36]; (2) the low-molecular-weight proteosome genes that affect the enzymatic function of protein degradation into peptides for presentation in the major histocompatibility complex (MHC) class 1 pathway[37]; and (3) in transporters associated with antigen processing (TAP) genes for MHC class I molecules.[38]

Environmental factors associated with an increased risk of developing disease include high insecticide exposures[39] and influenza viral infections.[40] Nicotine in cigarette smoke affects alveolar function, thus downregulating the inflammatory effect, resulting in less-acute hypersensitivity pneumonitis in smokers but a worse prognosis for those who develop the chronic form. Other factors that may contribute to hypersensitivity pneumonitis are abnormal surfactant and low levels of antioxidant enzymes in alveoli.[41]

A Th1 immune response with Gell and Coombs type III immune complex and type IV cell-mediated mechanisms seems to be involved. After inhalation of small organic antigens into the alveoli, alveolar macrophages become activated and release Th1-associated inflammatory cytokines including TNF-α, interleukin (IL)-1, IL-8, and IL-12. The antigen can have direct nonspecific actions including complement activation via the alternate pathway leading to vascular permeability related to C3a and chemoattraction of neutrophils and macrophages via C5a. The antigen can also interact with toll-like receptor 2 (TLR2) and MyD88 for neutrophil recruitment.[42] After interaction with CD8+ T cells, IL-2, IL-8, IL-12, IL-16, IL-18, and interferon γ (IFN-γ) are released and IL-10 is reduced.[43] IFN-γ is responsible for granuloma formation. Chemokines such as IL-8 in the acute phase attract neutrophils into the airway that release potent mediators such as hydroxyl anions and toxic oxygen species. An influx of CD8+ lymphocytes and eosinophils releasing inflammatory factors promotes airway

inflammation, activates endothelium, and leads to collagen synthesis by secreting glycoproteins capable of leading to airways fibrosis. T regulatory cells in patients with hypersensitivity pneumonitis are nonfunctional and unable to suppress the uncontrolled inflammation, possibly through increased IL-17 production.[44] Decreased lymphocyte apoptosis leads to airways lymphocytosis possibly through antiapoptotic cytokines.

In mouse models, the enhanced maturation of antigen-presenting CD11c+ cells explains the virus-induced enhanced immune response to farmer's lung antigens.[45] The overexpression of GATA binding protein 3 transcription factor, which participates in Th2 differentiation, attenuates the development of hypersensitivity pneumonitis by correcting the Th1-polarizing condition.[46] Mice models may not simulate human disease in all cases.

CLASSIFICATIONS

Despite the wide variety of antigens responsible, the clinical features of hypersensitivity pneumonitis are essentially the same with recurrent respiratory and systemic features or insidious respiratory and systemic symptoms depending on frequency and intensity of exposure of the organic dust. There is overlap of the various forms. Traditionally, the classifications have been clinically divided into acute, subacute, and chronic forms.[47] Other approaches suggested are to view the disease as active versus sequelae or as recurrent systemic with normal chest radiographs versus those with features of advanced interstitial disease on high-resolution computed tomography (HRCT), resting hypoxemia, and a restrictive pattern on lung function.[48]

Acute Form

In a sensitized worker, within 4 to 6 hours (up to 22 hours) of significant antigen exposure, flulike symptoms with high fever, chills, sweating, body aches, nonproductive cough, chest tightness, dyspnea, and malaise occur, with spontaneous resolution within 24 hours of avoidance of the inciting antigen. Subsequent antigen exposures result in similar symptoms with variable intensity depending on the antigen load. Recurrent acute episodes may lead to chronic symptoms and lung function changes even after antigen exposure ceases.

Subacute Form

In the sensitized worker, repeated low-level antigen exposures during weeks to months can result in an indolent and subtle presentation with progressive cough and dyspnea on exertion. Although high fever is lacking, nonspecific systemic symptoms of anorexia and malaise may occur. This classification is more difficult to define.

Chronic Form

The chronic form is subdivided into chronic insidious and chronic recurrent. Continuous low-level exposure results in a slowly progressive course with insidious exertional dyspnea during months to years with anorexia, weight loss, weakness, and fatigue. In contrast, recurrent acute episodes can progress to chronic disease.

DIAGNOSIS

Like other occupational disorders, the clinician must first confirm the diagnosis of hypersensitivity pneumonitis and then identify the relationship to workplace exposures. At the current time, there is no single diagnostic study or biomarker to confirm hypersensitivity pneumonitis. Instead, an assemblage of signs, symptoms, and

laboratory, radiologic, and lung function studies can support the diagnosis (**Box 1**).[49] To assess for an antigen that is of occupational origin, a detailed, targeted, and extended occupational history is required. Frequently, a team approach including industrial hygienist, allergist, pulmonologist, and occupational physician is necessary. A sentinel case should prompt additional inquiries into the worksite processes and exposures and seek to identify other exposed workers with disease.

History and Physical Examination

A detailed history of symptoms and exposures is critical to determining the correct diagnosis. Work history should include details on current and previous occupations with attention to work processes and exposures to chemicals, dusts, and aerosols. This history should include use of personal respiratory protective equipment, workplace ventilation, shifts worked, and whether symptoms occur away from work. Review of material safety data sheets and a personal worksite assessment may be necessary. The collection of dust, fumes, and water/fluid samples for staining and culture may assist in identifying the causative antigen. Information on maintenance records and sick days can be reviewed. Improvement of symptoms away from work and/or a rapid response to oral steroids should heighten the awareness of occupational hypersensitivity pneumonitis.

The physical examination can be completely normal between acute episodes. With acute symptoms, the worker appears extremely ill, tachypneic and dyspneic without rhinitis, pharyngitis, or conjunctivitis. Lung auscultation reveals fine, bibasilar, end-inspiratory rales and, occasionally, diffuse wheezing. Rash, adenopathy, cardiac, joint, and abdominal symptoms are absent. In the chronic form, the worker may appear well at rest, but may be dyspneic with minor activity, show clubbing of the digits, and exhibit rales or wheezing on lung auscultation.

Box 1
Occupational hypersensitivity pneumonitis: diagnosis

Major Criteria (requires at least 2):

1. Symptoms compatible with hypersensitivity pneumonitis
2. Exposure to an antigen by history or detection of antibody in serum or bronchoalveolar lavage (BAL) fluid
3. Chest radiograph or HRCT with compatible findings
4. Lymphocytosis in lung lavage fluid if BAL is performed
5. Compatible histopathologic changes on lung biopsy, if biopsy is performed
6. Reproduction of symptoms and laboratory and lung function abnormalities after exposure to the suspect workplace

Minor Criteria:

1. Dyspnea on exertion
2. Bibasilar dry inspiratory crackles
3. Recurrent febrile episodes
4. Decreased lung diffusion capacity (DLCO)
5. Arterial hypoxemia at rest or with exercise

Pulmonary Function Testing

Spirometry, lung volumes, and diffusing capacity should be obtained to assess impairment and guide therapy. Between attacks, pulmonary function may be normal. In acute disease, a restrictive pattern with declines in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) is usually observed with normal peak expiratory flows within 6 hours of antigen exposure. The diffusing capacity as measured by DLCO is reduced, consistent with impaired alveolar function. Arterial blood gas measurement reveals hypoxemia with exercise and, in some cases, at rest. A biphasic response with reductions in FVC and FEV_1 1 to 2 hours after antigen exposure, and again 4 to 6 hours after exposure, has been described. In the chronic form, workers may have a mixture of restrictive and obstructive lung disease patterns with an inconsistent response to bronchodilator. Methacholine challenge tests are frequently normal but, in chronic disease, can be positive. Exhaled nitric oxide was increased in 1 case.[50]

Chest Radiography

Findings suggestive of acute hypersensitivity pneumonitis include bilateral diffuse ground-glass infiltrate, patchy opacifications in lower lung fields, and interstitial infiltrates or a fine nodular or reticulonodular pattern (**Fig. 1**). These findings are completely reversible. Up to 30% of patients may have a normal radiograph. In the subacute form, fine nodular opacities reflecting granulomas may be observed. The chronic form is characterized by reticular opacities, fibrosis, honeycombing, and volume loss.[51] Notably absent are single nodular lesions, hilar adenopathy, consolidations, and pleural effusions.

Thin-section computed tomography (CT) or HRCT using 0.5-mm to 1-mm slice thickness provides a highly detailed image that is fundamental in identifying and quantifying severity in diffuse parenchymal and interstitial lung diseases as well as identifying coexisting or alternative diagnoses.[52] In acute/subacute disease, ground-glass attenuation is seen in the bilateral middle lung zones and fine, centrilobular micronodules are found primarily in the midlung to lower lung zones. In the chronic forms, irregular linear opacities, volume loss, traction bronchiectasis, and honeycombing suggest fibrosis. Other findings include emphysema and mosaic patterns from combinations of

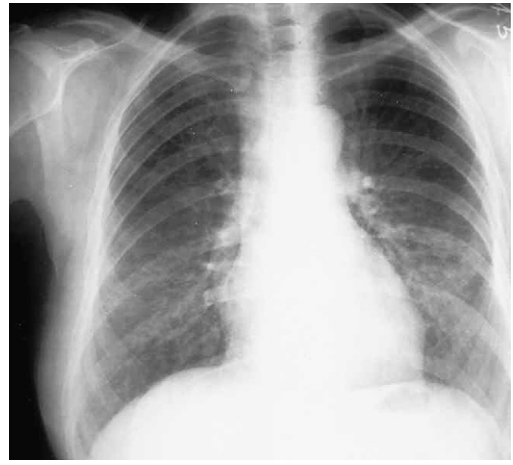

Fig. 1. Chest radiograph of acute hypersensitivity pneumonitis.

ground-glass attenuation and air trapping.[53] Mediastinal adenopathy less than 20 mm in diameter are seen with HRCT in more than 25% of cases.

Laboratory Studies

Symptomatic workers with the acute form typically have leukocytosis with a left shift and occasionally eosinophilia up to 20%. Serum complement, erythrocyte sedimentation rate (ESR), C-reactive protein (CR-P), and lactate dehydrogenase (LDH) may be increased, but are not necessarily useful in monitoring disease activity. Quantitative serum immunoglobulins (Ig; IgA, IgG, IgM) may be increased, except IgE. Although antinuclear antibodies are negative, rheumatoid factor (RF) may be positive. Serum precipitating antibody to antigen as identified by Ouchterlony gel technique or other IgG immunoassays is the classic immunologic finding confirming exposure to the putative offending antigen. (**Fig. 2**) Serum precipitins may wane with time if antigen exposure ends. Up to 50% of similarly exposed asymptomatic workers may have detectable antibodies without apparent disease. Negative commercial antibody panels in a confirmed clinical case may result from using incorrect antigens, low serum concentrations of antibody, or from nonstandardized antigens. Newer serologic techniques such as electrosyneresis on cellulose acetate may be more discriminating for patients compared with healthy exposed workers.[54] In vitro lymphocyte transformation studies using specific antigen are positive in symptomatic patients but also in up to 15% of asymptomatic, similarly exposed individuals. Skin-prick testing is unnecessary because the pathogenesis is not IgE mediated and intradermal skin testing can result in both false-positive and false-negative reactions.

BAL

BAL can assist in excluding other interstitial lung disorders and reveal consistent findings in cell types.[55] In nonexposed, asymptomatic individuals, low numbers of CD4+ lymphocytes and alveolar macrophages predominate. The results are dependent on the timing of the last antigen exposure. Neutrophils are increased within 48 hours

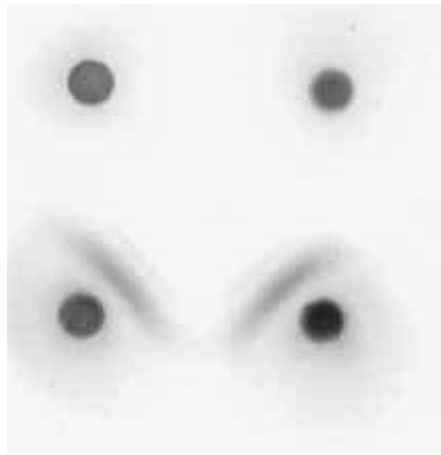

Fig. 2. Serum precipitins as shown by the Ouchterlony double immunodiffusion gel system. The intensity of the stained bands between the central well (barely visible) containing antigen and the 2 lower wells containing patient serum indicates the presence of precipitating antigen-antibody complexes. The upper 2 wells contain serum that does not have antibody against the antigen being tested.

and return to normal levels within 1 week. In symptomatic or exposed and nonsymptomatic nonsmoking workers, BAL reveals high numbers (>50% lymphocytes) of both CD4+ and CD8+ lymphocytes. These levels may remain increased for years and wane in time if further antigen exposure is avoided. Current smokers may have lower percentages of alveolar lymphocytes. The symptomatic worker with acute disease who is a nonsmoker, exhibits a predominately CD8+ response resulting in a low CD4+/CD8+ ratio whereas a worker with the chronic/fibrotic form or in those who smoke is likely to have a predominance of CD4+ T cells thus increasing the CD4+/CD8+ ratio. Compared with other interstitial lung diseases, there are increased mast cells and plasma cells. A normal BAL excludes hypersensitivity pneumonitis.[56] In nonsmokers, BAL lymphocytes less than 30% make the diagnosis unlikely. Pulmonary sarcoidosis classically presents with a predominance of CD4+ T cells and high CD4+/CD8+ ratio. Cultures are typically negative.

Histopathology

Although a tissue diagnosis is not required, it may eliminate other diseases in the differential diagnosis. Video-assisted thoracoscopic surgery (VATS) for biopsy is becoming the procedure of choice for lung biopsy because of its lower morbidity and mortality, shorter hospital stay, and good diagnostic yield.[57] Transbronchial biopsies may not obtain adequate samples for representative pathology. The classic triad of findings is lymphoplasmocytic interstitial infiltrate, poorly formed nonnecrotizing granulomas, and cellular bronchiolitis (**Fig. 3**). Depending on the stage of disease and intensity of antigen exposure, the findings may range from the acute form with neutrophils, activated foamy macrophages, prominent lymphocytic alveolitis, plasma cells, and granulomas in up to 70% compared with the subacute and chronic forms having a nonspecific interstitial pneumonia (NSIP) pattern or usual interstitial pneumonia (UIP) pattern without granulomas.[58,59] A difficult problem is prognosis and therapeutic decisions for the patient with irrefutable idiopathic pulmonary fibrosis IPF/UIP with relevant antigen exposure and positive serum precipitins . Antigen avoidance and corticosteroid therapy may occasionally delay or prevent progression of fibrotic hypersensitivity pneumonitis. Similarly, if the CT scan shows findings of fibrotic end-stage UIP, the value of a biopsy should be weighed against the risks of the procedure. Even in the chronic form, with a UIP-like pattern, centrilobular and bridging fibrosis are important hallmarks of chronic hypersensitivity pneumonitis with less than half showing granulomas. These patterns can also be seen in connective tissue disorders

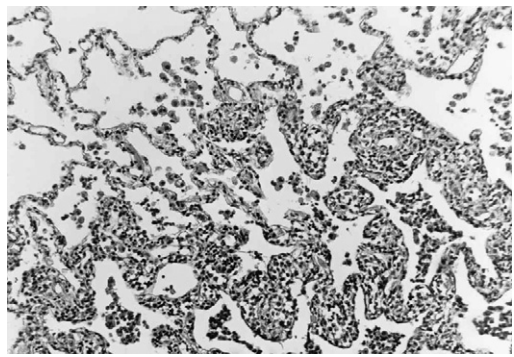

Fig. 3. Low-power view of a lung biopsy revealing noncaseating granulomas and lymphocytic interstitial infiltrate.

and pneumotoxic drug reactions.[60] Recently, a subgroup of patients have been identified that have both hypersensitivity pneumonitis and a rare condition termed pulmonary alveolar proteinosis. The link between these distinct disorders is unclear.[61] Vasculitis and connective tissue destruction should prompt an evaluation for other causes.

Inhalation Challenge

A natural challenge at the workplace after a period of avoidance can precipitate symptoms and show laboratory and lung function changes, but not necessarily confirm the specific causative antigen. A purposeful challenge to a suspect antigen using a nebulizer is typically reserved for unique cases or clinical research when a new antigen is being investigated. Because of a lack of standardized antigens (imprecise mixtures of antigen and nonspecific irritants) and techniques and the risk of significant symptoms, the challenge should be performed by qualified personnel in specialized centers with experience. A positive challenge is represented by cough and dyspnea, increased body temperature, peripheral leukocytosis, and decrements in FVC and oxygen saturation usually occurring 4 to 6 hours after exposure. As an example, in Montreal, Canada, in 2009, an inhalation challenge was performed for malt dust. Lactose inhaled by a particle generator was used as the control with FVC and FEV_1 measurements. For the next 2 days, aerosolized malt dust via a particle generator was administered for 30 minutes with similar spirometric measurements and oral temperatures. Methacholine challenge was performed after the second day of malt dust inhalation. The next day, 120 minutes of malt dust exposure were followed by serial spirometric measurements at 10, 40, 60, 90, 120, 180, 240, 300, 360, and 420 minutes as well as serial oral temperature measurements. After symptoms occurred, diffusion capacity, blood gas measurement for oxygen tension, chest radiograph, and blood counts for leukocytes and neutrophils were obtained.[20] The diagnosis of malt-induced hypersensitivity pneumonitis was confirmed.

DIFFERENTIAL DIAGNOSIS

Many disorders may mimic occupational hypersensitivity pneumonitis and should be considered in the evaluation of individual workers (**Table 2**).

Berylliosis

Although acute berylliosis resembling a chemical pneumonitis is rare, chronic beryllium disease (CBD) or berylliosis from exposure in industries such as nuclear reactors and weapons, aerospace, ceramics, dental supplies, and others results in a granulomatous lung response identical to sarcoidosis.[62] The lymphocyte transformation test that quantifies the proliferation of lymphocytes incubated with beryllium is always positive in patients with CBD if BAL lymphocytes are used, but in only 50% of cases if peripheral blood cells are used.[63] Findings on CT not seen in hypersensitivity pneumonitis include hilar or mediastinal lymph nodes with amorphous or eggshell calcification.

Endotoxin-induced Disease

Monday morning fever refers to flulike symptoms that occur on the first day of the work week without radiologic abnormalities or long-term changes in lung function and is likely caused by inhalation of endotoxin. Humidifier fever refers to contaminated humidification or cooling equipment used during a manufacturing process. The gram-negative bacteria *Cytophaga* was identified in a nylon plant, leading to workers

Table 2
Differential diagnosis of occupational hypersensitivity pneumonitis

Acute Form	Disorder	Trigger
Farming	Silo unloader's disease	Nitrogen dioxide
Organic dust toxic syndrome	Humidifier fever, animal house fever, grain fever, pulmonary mycotoxicosis	Endotoxin, mycotoxin
Inorganic dust toxic syndrome	Acute berrylliosis	Beryllium dust: aerospace, nuclear, ceramics, dental
Textile dust	Byssinosis	Cotton dust and endotoxin
	Mill fever	Tannins in cotton mill dust, kapok
	Weaver's cough	Tamarind seed powder
Bird raising	Psittacosis	*Chlamydia psittaci* infection
Chronic Form		
Inorganic respiratory dust syndromes	Silicosis and siderosis	Silica in mining, quarrying, drilling, foundry working, ceramics manufacturing, sandblasting
	Chronic berylliosis	Beryllium dust -aerospace, nuclear, ceramics, dental
	Asbestosis	Fibrous silicate minerals (eg, chrysotile)
	Coal worker's pneumoconiosis	Mixed dust consisting of coal, kaolin, mica
	Talcosis and calcicosis	Leather, ceramic, paper, plastics, rubber, building, paint, or cosmetic industries; limestone dust
Food industry	Flavor-worker's lung	Diacetyl butter flavor ketone in microwave popcorn
	Rice-miller's syndrome	Rice husk dust containing silica
Textile dust	Byssinosis	Cotton, hemp, flax, jute, sisal
	Nylon flock	Pulverized fibers applied to fabrics
	Ardystil syndrome	Acramin-FWN (a polyamidoamine)
Lifeguards	Lifeguard lung	Trichloramine and/or endotoxin
Office buildings	Sick building syndrome	VOC, smoke, poor ventilation, dampness

Abbreviation: VOC, volatile organic compound.

with symptoms.[64] Lung function is either normal or shows mild airway obstruction with normal DLCO. Lifeguard lung is a condition of workers at indoor swimming pools contaminated with gram-negative bacteria and high levels of endotoxin. Although features include lymphocytic alveolitis and noncaseating granulomas, as seen in hypersensitivity pneumonitis, the high attack rate after a short duration of exposure suggests a toxic response.[65] Alternatively, when the disinfectant chlorine combines with nitrogen-containing compounds like sweat and urine, indoor airborne concentrations of trichloramine can increase in pool water to levels causing eye and lung irritation.[66] The levels correlate with the number of occupants in the pool.

Diacetyl Flavoring–induced Bronchiolitis Obliterans

In 2000, workers in microwave popcorn plants exposed to diacetyl flavorings experienced rapid progression to obliterative bronchiolitis and severe airway obstruction without reversibility.[67,68] Clinical findings include chronic nonproductive cough, wheezing, and progressive dyspnea.

Siderosis and Silicosis

Inhalation of fine iron particles by welders using electric arc or oxyacetylene may result in the accumulation of iron oxide in pulmonary macrophages leading to siderosis. Functional impairment and fibrosis are uncommon and the radiological abnormalities resolve with avoidance. In the iron ore mining and processing industry, if silica is involved, silicosiderosis can develop. Silicosis may develop after a latency period of 10 to 30 years after inhaling silica dust during work in mining, quarrying, drilling, foundry work, ceramics manufacturing, and sandblasting. Multiple small nodules are often seen on HRCT in both disorders.

Talcosis and Calcicosis

Hydrated magnesium silicate, known as talc, may be inhaled during processing in the leather, ceramic, paper, plastics, rubber, building, paint, or cosmetic industries, leading to nonnecrotizing pulmonary inflammation. Recreational intravenous drug use has been associated with talcosis. Inhaling limestone dust containing calcium carbonate, magnesium oxide, silica dioxide, and aluminum oxide may result in calcicosis. Widespread nodules are seen on HRCT and histology reveals numerous birefringent crystals consistent with limestone.

Ardystil Syndrome

Inhalation of Acramin-FWN (polyamidoamine) by employees in the textile industry during its application with a brush or sponge for printing resulted in organizing pneumonia.[69] Progressive interstitial fibrosis could evolve into respiratory failure with a poor prognosis.

Organic Dust Toxic Syndrome

Farmers may develop cough and chest tightness after exposure to inhaling dense clouds of dust when working with swine, poultry, or grains. Multiple workers are usually affected. Fungal spores and increases of total cells are found in BAL. The exact trigger is unclear, but may include endotoxin, ammonia, and/or hydrogen sulfide gases. Symptoms resolve quickly and spontaneously with complete recovery. In a population-based survey, California farmers exposed to agricultural dust self-reported a high incidence of persistent wheeze and other respiratory symptoms, asthma, and bronchitis.[70] Personal respiratory protection was rarely used. Malaysian workers inhaling rice husk dust during milling developed acute and chronic irritant effects of the eyes and skin, rhinitis, asthma, eosinophilia, or interstitial lung disease without restriction, postulated to be related to deposition of the elongated spikes on the rice husks shown on electron microscopy.[71]

Sick Building Syndrome

The working population spends about 20% of its time at work. Since the 1970s, in buildings designed and manufactured for maximum efficiency, groups of workers have presented with nonspecific complaints affecting their eyes, skin, and upper airways, as well as headache and fatigue without objective findings, radiologic abnormalities, or lung function changes. Several factors associated with sick building syndrome (SBS) include relative air humidity, temperature, building dampness, air ventilation, tobacco smoke, chemical indoor exposures (volatile organic compounds, ozone, formaldehyde), and video display terminal work. Workers with certain personality characteristics such as anxiety, depression, and neuroticism are more likely to experience SBS. Furthermore, a psychosocial work environment where workers

have high demands but lack control and lack support from superiors and colleagues was more common in SBS.[72]

TREATMENT

Avoidance

As with other occupational lung diseases, the obvious and most important treatment is avoidance of the triggering antigen. Frequently, this is sufficient intervention and can be accomplished by removing and replacing the antigen with a nonsensitizing alternative, altering the process to prevent antigen from becoming airborne, or moving the worker away from the exposure. On occasion, the specific antigen is elusive despite establishing the worksite as causative. Wearing well-fitted, appropriate respiratory protection with filters can be effective when complete avoidance is not possible.

Examples of successful avoidance measures for MWF include changes in engineering such as enclosing machines, improving ventilation, and wearing personal respiratory protection as well as treatment and replacement of metalworking fluids to decrease the bacterial contamination. Effective concentrations of biocides containing methyloxazolidine can reduce the growth and proliferation of *Mycobacterium* species in water-based machining coolants. Simple dipslides can monitor the effectiveness of this approach.[73]

For farmer's lung, changes in storing process or treating hay with buffered proprionic acid significantly reduced the concentration of thermophilic bacteria and fungi without affecting the machinery or cattle. Job retraining and changing professions are usually reserved for when avoidance measures are insufficient because this extracts a financial and emotional toll on both workers and employers.

Pharmacologic Therapy

In acutely ill workers with abnormal lung function and chest radiograph changes, supplemental oxygen and parenteral corticosteroids are recommended. Prednisone at 40 to 80 mg daily for 1 to 2 weeks may be sufficient for acute disease, whereas a gradual taper lasting weeks to months may be necessary for those with subacute or chronic disease, depending on their response to treatment. Case reports have shown improvement with inhaled beclomethasone 400 μg daily in hydrofluoroalkane propellant or inhaled budesonide after either oral or pulse intravenous infusions of corticosteroids, respectively. If reversible airway obstruction is shown, short-acting β bronchodilators and inhaled corticosteroids can be used. In vitro studies have shown promise for thalidomide, pentoxifylline, low-dose, long-term macrolide antibiotics, and cyclosporine, but controlled clinical trials have not been performed.

PROGNOSIS

For acute or subacute disease, early recognition and treatment results in complete recovery unless permanent damage has occurred. Unrecognized hypersensitivity pneumonitis with ongoing antigen exposure may result in permanent sequelae. The clinical course is variable, as shown by progression of symptoms despite avoidance measures in some individuals, whereas other workers remain stable despite continued exposure. Fibrosis, as seen in the chronic form or a UIP-like pattern, portends a generally poor prognosis with median survival of 2 years compared with 22 years in the subacute form in which no fibrosis is present.[58] Oral steroids may improve symptoms, but have not been shown to affect the long-term prognosis. Although tobacco smokers are less likely to develop acute hypersensitivity pneumonitis, they may experience a worse outcome from progression of the chronic form.

SUMMARY OF IMPORTANT POINTS

Hypersensitivity pneumonitis can occur from a wide variety of occupational exposures in which workers inhale fungi, bacteria, animal emanations, or low-molecular-weight chemicals. Although uncommon and difficult to recognize, through a detailed work exposure history, physical examination, radiography, pulmonary function studies, and selected laboratory studies using sera and BAL fluid, workers can be identified early to effect avoidance of the antigen and institute pharmacologic therapy if necessary. A lung biopsy may be necessary to rule out other interstitial lung diseases. Despite the varied organic antigen triggers, the presentation is similar with acute, subacute, or chronic forms. Systemic corticosteroids are the only reliable pharmacologic treatment but do not alter the long-term outcome.

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