

Occupational immunologic lung disease

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ABSTRACT

Occupational immunologic lung disease is characterized by an immunologic response in the lung to an airborne agent inhaled in the work environment and can be subdivided into immunologically mediated occupational asthma (OA) and hypersensitivity pneumonitis (HP). Irritant-induced OA, a separate nonimmunologic entity, can be due to chronic exposure to inhaled irritants or reactive airways dysfunction syndrome (RADS). RADS is defined as an asthma-like syndrome that persists for >3 months and occurs within minutes to hours after a single exposure to a high concentration of a respiratory irritant. Workers in high-risk fields for OA include farmers, printers, wood workers, painters, plastics workers, cleaners, spray painters, electrical workers, and health-care workers. OA can be triggered by high-molecular-weight (HMW) proteins that act as complete allergens or by low-molecular-weight (LMW) sensitizers that act as haptens. HMW proteins (>10 kDa) are generally derived from microorganisms (such as molds and bacteria, including thermophilic actinomycetes), plants (such as latex antigens and flour proteins), or animals (such as animal dander, avian proteins, and insect scales) and are not specifically regulated by the Occupational Safety and Health Administration. LMW haptens that bind to proteins in the respiratory mucosa include some Occupational Safety and Health Administration regulated substances, such as isocyanates, anhydrides, and platinum. HP can present in an acute, chronic, or subacute form. The acute, subacute, and early chronic form is characterized by a CD4⁺ T-helper type 1 and CD8⁺ lymphocyte alveolitis. Classically, the bronchoalveolar lavage in HP will show a CD4/CD8 ratio of <1.

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Occupational immunologic lung disease (OILD) is characterized by an immunologic response in the lung to an airborne agent inhaled in the work environment and can be subdivided into immunologically mediated occupational asthma (OA) and hypersensitivity pneumonitis (HP).^{1,2} Irritant-induced OA, a separate nonimmunologic entity, can be due to chronic exposure to inhaled irritants or reactive airways dysfunction syndrome (RADS). RADS is defined as an asthma-like syndrome that persists for > 3 months and occurs within minutes to hours after a single exposure to a high concentration of a respiratory irritant. Diagnostic criteria for RADS have been published elsewhere.^{3,4} OILD must also be differentiated from “work exacerbated asthma” in which preexisting or concurrent asthma is worsened by workplace conditions, such as cold air or dust exposure, rather than caused by an immune response to a workplace sensitizer.⁴

The incidence and prevalence of OILD have remained difficult to estimate. Affected workers may avoid or leave a profession before coming to the attention of medical personnel (the healthy worker effect, which leads to underestimation). Two percent of all

asthma cases in industrialized nations and 9 to 15% of all U.S. adult asthma cases have been estimated to be occupational in origin.⁴ Workers in high-risk fields for OA include farmers, printers, wood workers, painters, plastics workers, cleaners, spray painters, electrical workers, and health-care workers. Information that details professions and the specific associated sensitizer have been described elsewhere.^{3,4} More than 400 substances have been implicated in OA, including isocyanates, flour and grain dust, airborne particles from food, colophony, latex, animal dander, aldehydes, and wood dust.⁴ The incidence of OA varies by the level, duration of exposure, and specific agent implicated. Genetic risk has also been identified through positive associations with various human leukocyte antigens (HLA) alleles and glutathione S-transferase polymorphisms, but this has not been shown to be helpful in the diagnosis.³

OA can be triggered by high-molecular-weight (HMW) proteins that act as complete allergens or by low-molecular-weight (LMW) sensitizers that act as haptens.⁵ HMW proteins (>10 kDa) are generally derived from microorganisms (such as molds and bacteria, including thermophilic actinomycetes), plants (such as latex antigens and flour proteins), or animals (such as animal dander, avian proteins, and insect scales) and are not specifically regulated by the Occupational Safety and Health Administration. LMW haptens that bind to proteins in the respiratory mucosa include some Occupational Safety and Health Administration regulated substances, such as isocyanates, anhydrides, and platinum.⁴

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HMW sensitizers and some LMW sensitizers, such as trimellitic anhydride, phthalic anhydride, platinum, chromium, nickel, epoxy amines, and penicillin, act through an immunoglobulin E (IgE) mediated mechanism.³ Further arguing for an IgE-mediated mechanism in select LMW agents is the recent effective use of an anti-IgE monoclonal antibody (omalizumab) in the treatment of mouse models,⁶ and in some patients,⁷ with OA due to LMW agents. In type I hypersensitivity reactions,⁸ allergen cross-links IgE on sensitized mast cells or basophils in the airway mucosa, which leads to the release mediators, including histamine and leukotrienes, as well as cytokines (e.g., interleukin [IL] 4, IL-5, IL-13, and chemokines). The bioactive mediators contribute to immediate-type asthma *via* the development of allergic inflammation, which involves the large airways. Wheezing is the predominant symptom during the acute stage.

The late asthmatic response occurs several hours later and may result from a type IVa2 hypersensitivity reaction in which T-helper (Th) type 2 cells are involved.⁸ The late response presents as small-airway obstruction and lasts several hours. Patients frequently have a cough and dyspnea but less commonly have wheezing. Other responses have been described, including the repetitive asthmatic responses in which patients have recurrent bronchospastic events over several days after a single inhalation challenge. This may be mediated by a type IVb hypersensitivity reaction that involves CD8⁺ T cells.⁸ A latent period of asymptomatic inhalation exposure of months to years usually occurs before the onset of any respiratory symptoms. Occupational rhinitis or conjunctivitis often predates the development of OA.⁹ Removal of the worker from the offending environment typically results in improvement or termination of symptoms.⁴

Occupational HP results from various occupational agents, including bacteria, fungi, animal or plant protein, chemicals, and metals.¹⁰ HP can present in an acute, chronic, or subacute form. The acute, subacute, and early chronic forms are characterized by a CD4⁺ Th1 and CD8⁺ lymphocyte alveolitis.¹¹ Classically, the bronchoalveolar lavage will show a CD4/CD8 ratio of <1. Later in the course of the disease, there may be a skewing toward Th2 lymphocytes and IL-4 production.¹¹ The acute form results from short-term, high-level exposure to a workplace antigen. Symptoms occur 4–8 hours after inhalation exposure; resolve within 24 hours; and include fever, chills, nonproductive cough, and dyspnea without wheezing.⁴ The chronic form results from persistent low-level exposure to an antigen. Patients present with cough, dyspnea, weight loss, and fatigue.⁴ In the subacute form, patients usually have an insidious onset of symptoms after several days to weeks of exposure. Symptoms in the subacute form include dyspnea, productive cough, and mal-

aise.⁴ All three forms can progress to irreversible lung disease with severe pulmonary fibrosis. Early recognition of HP and avoidance of further exposure to the causative antigen are instrumental in preventing the progression to irreversible disease.¹⁰

Tools for the diagnosis of OILD include the medical history and examination, immunologic testing, pulmonary function studies, and bronchial provocation challenge. The history should include the clinical features of airway disease, temporal relationships between symptoms and workplace exposure, a detailed job history, a review of work processes, and the presence of concomitant rhinitis and conjunctivitis.^{3,12} Review of the materials safety data sheets may be helpful for workplace exposure, but they may be incomplete and lack information about potential for respiratory sensitization.³ Validated skin tests for HMW antigens have a high negative predictive value and thus can rule out a specific antigen as the culprit.¹² Conjugated extracts for LMW antigens are not commercially available, and *in vitro* IgE assays are of low sensitivity.³ Double gel immunodiffusion techniques can detect the presence of precipitating antibodies against antigens present in the workplace and suggest a causal relationship in HP.⁴

Serial measurements of spirometry or peak expiratory flow at least 4 times daily during a 1-week period of work absenteeism, followed by a 3–4-week period of work attendance can demonstrate a relationship to a workplace antigen.³ Generally, patients demonstrate a trans-shift decrement in expiratory flow that either worsens or stabilizes during the workweek and improves on the weekend.³ Specific allergen inhalation challenges are regarded as the criterion standard for the diagnosis of OILD; however, these studies require specialized equipment and are only available in select centers.¹² Natural challenges can be performed by exposure of the patient to the work environment, with measurement of pulmonary functions before and after exposure. Nonspecific bronchoprovocation with methacholine is highly sensitive but not specific for OA. A threefold improvement in provocation concentration causing a 20% fall in FEV1 (PC₂₀) after 10–14 days of absenteeism compared with the end of a workweek suggests OA.¹² The prognosis of OILD can be favorable if the disease is detected early and additional exposure is avoided.³ However, many patients do not recover completely, despite further exposure avoidance. Poor prognosis of occupational asthma is associated with the duration of symptoms for >1 to 2 years, abnormal pulmonary function test results, persistently elevated specific IgE levels, and a high degree of bronchial hyperreactivity.⁴

The first step in the management of OILD involves preventing further exposure to the causative antigen. Complete avoidance of the antigen is ideal; however, environmental measures can be instituted at the work-

place to control the worker's exposure. These measures include transferring the worker to another department, providing respiratory protection devices, or improving the ventilation of the workplace. However, even levels of exposure below the established legal limits of toxicity may still result in immunologic reactions.⁴ Inhaled bronchodilators, cromolyn, and corticosteroids are useful in the treatment of occupational asthma but are not efficacious in the setting of ongoing exposure and should not be used as a substitute for complete avoidance. A short course of oral corticosteroids may be useful in acute HP. Immunotherapy with allergens that cause occupational asthma has reportedly been used in oyster gatherers, bakers, and laboratory animal workers with some success.⁴ However, the prevention of OILD through education, safe work practices, and adherence to established limits of exposure is the primary objective.⁴ The success of prevention has been seen in the significant decline of farmer's lung with the improvement of animal feed storage techniques on farms.¹⁰

IMMUNOLOGY

- HMW sensitizers are complete allergens, whereas LMW sensitizers behave as haptens.
- The immediate immunologic response occurs in the large airways through classic IgE cross-linking and release of histamine; leukotrienes; cytokines, such as IL-3, IL-4, and IL-5; and chemokines.
- The late asthmatic response in occupational asthma occurs in the small airways and may result from a type IVa2 hypersensitivity reaction in which Th2 cells are involved.
- The bronchoalveolar lavage in HP shows a CD4/CD8 ratio of <1.

CLINICAL PEARLS

- The earlier OILD is diagnosed and the sooner the worker is removed from the environment, the better the prognosis.

- The most common sensitizers include isocyanates; flour and grain dust; and airborne particles from food, colophony, latex, animal dander, aldehydes, and wood dust.
- Occupational rhinitis or conjunctivitis often precedes asthma and may provide a warning for at-risk workers.
- The primary goal should be in the prevention of the disease rather than in management.
- Pharmacologic treatment of occupational lung disease should not be used as a substitute for complete avoidance of the causative agent.

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