

7. Immunologic lung disease

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The lung is an extremely complex organ and participates in initial responses to inhaled antigens, infectious agents, and irritants or as a response to exposure through the oral, parenteral, or transdermal routes. There can be constriction of the airways or involvement or even destruction of the lung parenchyma, depending on the condition. This review focuses on selected aspects of the pulmonary innate and adaptive immune responses; the new condition World Trade Center cough, which can cause an asthma-like presentation and resemble reactive airways dysfunction syndrome; and the diagnosis and treatment of various immunologic lung conditions. Innate immune responses occur in the acute respiratory distress syndrome and in transfusion-related acute lung injury. Adaptive immune responses involve specialized mucosal and systemic immune responses, lymphocytes, and antibodies and can result in CD4⁺ T_H1 and T_H2 phenotypes, such as T_H1 for tuberculosis and T_H2 for asthma. (J Allergy Clin Immunol 2008;121:S393-7.)

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Immunologic lung diseases include many different conditions that can be classified according to major patterns of pulmonary immune responses. The categories include those characterized by innate immune responses, including complement activation or polymorphonuclear leukocyte (PMN) presence and adaptive pulmonary inflammatory responses (T_H1 or T_H2 lymphocytes, eosinophils, granuloma formation, and antibody mediated).¹ Immunologic lung conditions typically comprise more than a single predominant pattern or have aspects of bronchial hyperreactivity without the airway inflammation of asthma. This review will highlight some of the conditions that serve as examples of the remarkable complexity of the pulmonary and systemic immune responses.

INNATE IMMUNE RESPONSES

Transfusion-related acute lung injury

Transfusion-related acute lung injury produces acute severe dyspnea, cyanosis, noncardiogenic pulmonary edema, arterial

Abbreviations used

ABPA: Allergic bronchopulmonary aspergillosis
ANCA: Anti-neutrophil cytoplasmic antibody
ARDS: Acute respiratory distress syndrome
COPD: Chronic obstructive pulmonary disease
CT: Computed tomography
FVC: Forced vital capacity
HDAC: Histone deacetylase
LT: Leukotriene
PMN: Polymorphonuclear leukocyte
RADS: Reactive airway dysfunction syndrome

hypoxemia, and respiratory failure during the early minutes to 6 hours after transfusions.² Donor plasma contains detectable allorreactive anti-PMN antibodies with specificity often for the recipient's HLA class I or II antigens.² The pathogenesis involves infusion of anti-PMN antibodies in any blood product containing plasma, which results in pulmonary sequestration of PMNs, production of IL-8, IL-13, and TGF- β , and complement activation, which severely damages the endothelium. In a few cases the recipient also has anti-donor PMN antibodies. The patient will require mechanical ventilation, and there is a fatality rate of 5% to 20%.² Some patients become cyanotic within 10 minutes of receiving fresh frozen plasma, whole blood, or platelets (suspended in plasma). This presentation resembles anaphylaxis. Acute management includes stopping the infusion, oxygenation, mechanical ventilation, and vasopressors for reversal of hypotension. The donor should be deferred from future donations.

Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is characterized by acute dyspnea, tachypnea, tachycardia, and profound arterial desaturation. The chest roentgenogram demonstrates a "white-out" pattern of alveolar consolidation from fluid-filled alveoli. Chest computed tomographic (CT) analysis reveals infiltrates from airspace collapse or filling of alveoli. The mortality remains high at 20% to 40%.³ Bronchoalveolar lavage demonstrates PMNs; IL-8, which is chemotactic for PMNs; TGF- β ; IL-2; and IL-6.¹ The proinflammatory transcription factor nuclear factor κ B is upregulated in alveolar macrophages. TGF- β is considered a major mediator in that it participates in the development of fibrosis, chemoattraction of macrophages, lung hyperpermeability, and impairment of fibrinolysis.³ ARDS comprises the responses of the innate immune system and acute intense inflammation.

Patients require mechanical ventilation and small-volume respiration (tidal volume, 6 mL/kg) with positive end-expiratory pressures of 5 to 10 cm H₂O. Use of much higher positive end-expiratory pressures (initially to 25 cm H₂O) has been attempted to open up "degassed atelectasis" and fully shunted areas of the lung affected by ARDS.⁴ Pharmacologic interventions, such as corticosteroids, nitric oxide, and surfactants, have not been effective.⁵

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MISCELLANEOUS, NONINFECTIOUS PULMONARY CONDITIONS

Organic toxic dust syndrome is a toxic alveolitis that occurs within 12 hours after the inhalation of organic dusts. Symptoms resemble those of influenza because there is abrupt onset of fever, chills, headache, dyspnea, nonproductive cough, and myalgias. The physical examination can reveal fine crackles in the lungs. When there is massive inhalation of microbial products and endotoxins from moldy silage, there can be onset of severe dyspnea, cough, and fever associated with an ARDS presentation.⁶ Such cases are designated as pulmonary mycotoxicosis or referred to as the organic dust toxic syndrome (see chapter 10 on occupational asthma in this supplement).⁶ It should be emphasized that this condition is not hypersensitivity pneumonitis and is related to direct occupational exposure to mycotoxins.⁷ In contrast, silo-unloader's disease occurs after inhalation of nitric oxide, NO₂, and N₂O₄. Inhalation of nitrogen oxides generates nitric and nitrous acids and causes acute pulmonary edema and even methemoglobinemia. Survivors can have bronchiolitis obliterans.

Byssinosis results from inhalation of dusts from cotton, flax, hemp, and sisal.⁸ These dusts produce bronchoconstriction on the first day of the workweek,⁸ but tachyphylaxis can develop, so that there is less bronchoconstriction during the week. Because of exposure to endotoxin, at-risk workers are those involved in carding (processing of raw cotton) as opposed to workers who spin the cotton and are not exposed to endotoxin.⁹ Byssinosis and the organic toxic dust syndromes are not forms of hypersensitivity pneumonitis or asthma, although both conditions have features that overlap.

Reactive airways dysfunction syndrome

Reactive airways dysfunction syndrome (RADS) is a condition associated with a single inhalation of high concentrations of irritant vapors, fumes, fog, or smoke.¹⁰ Within 24 hours, the patient experiences cough, dyspnea, and wheezing. Bronchial hyperreactivity is present, but the patient has normal or reduced FEV₁, forced vital capacity (FVC), and FEV₁/FVC ratio. Symptoms and pulmonary function abnormalities can last for years after exposure or remain normal. Bronchial biopsy specimens might demonstrate desquamation of the epithelium, lymphocytic infiltrates, and subepithelial fibrosis. Eosinophils (characteristic of asthma) are not present. Sensitization to the inhaled irritant does not occur because the symptoms begin in proximity to the exposure. An asthma-like picture then occurs, which can last for years or resolve over months. Compared with patients with occupational asthma, which develops after a latency period, patients with RADS might have less reversible responses to β -adrenergic agonists (see chapter 10). Irritant-induced vocal cord dysfunction can be confused with RADS.¹¹

World Trade Center cough

World Trade Center cough is a cough that began within 24 hours of the collapse of the World Trade Center buildings.¹² Exposures include asbestos, glass fibers, lead, and aromatic compounds. Most subjects have normal spirometric results. However, there is methacholine hyperreactivity (24% of patients), an FEV₁/FVC ratio of less than 0.75 (16% of patients), and bronchodilator responsiveness (63% of patients).¹² Half of the group of firefighters with high exposure have been considered to have RADS when assessed over a 6-month period.¹³

GRANULOMATOUS T_H1 INFLAMMATORY CONDITIONS

Granulomatous T_H1 conditions include tuberculosis, sarcoidosis and berylliosis, and hypersensitivity pneumonitis, which will be considered later in the discussion of T_H1 inflammatory conditions.¹ Tuberculosis and sarcoidosis require CD4⁺ T_H1 cells for formation of granulomas and the proinflammatory cytokines IL-2, IL-12, and IFN- γ . Low numbers of CD4⁺ T lymphocytes in HIV/AIDS are associated with impaired delayed hypersensitivity responses and the recognized high prevalence and severity of tuberculosis.^{14,15} IFN- γ generation by CD4⁺ T_H1 cells (and CD8⁺ suppressor lymphocytes) comprises a significant part of the response in tuberculosis, and its detection has provided the basis of a newly approved *in vitro* assay by the US Food and Drug Administration.¹⁴⁻¹⁶ There are some data for class I MHC-restricted CD8⁺ lymphocytes serving as memory cells in response to *Mycobacterium tuberculosis* infections.¹⁶ Patients with more severe pulmonary tuberculosis have higher percentages of CD4⁺ lymphocytes and increased CD4⁺/CD8⁺ ratios in bronchoalveolar lavage fluid but lower percentages of CD4⁺ lymphocytes in peripheral blood.¹⁷ The peripheral blood CD4⁺/CD8⁺ ratio is decreased also because of increased CD8⁺ lymphocytes. These results are consistent with sequestration or compartmentalization of the CD4⁺ lymphocytes in the lungs.¹⁷

The CD4⁺ T_H1 effector cells help limit the replication of mycobacteria but at a price of the effects of granuloma formation. CD4⁺CD25^{high} regulatory T cells are thought to modify this process and are increased in number.^{16,18} The transcription factor FoxP3 helps to upregulate the numbers of CD25 and cytotoxic T lymphocyte-associated antigen 4 receptors on T regulatory cells. It has been reported that FoxP3 mRNA expression is increased, which is consistent with T regulatory cell suppression or modification of the T_H1 response in tuberculosis.^{16,18}

GRANULOMATOUS T_H2 INFLAMMATORY CONDITIONS

The Churg-Strauss syndrome is a systemic, necrotizing, eosinophilic vasculitis with granuloma formation.^{1,19} The key part of the presentation might be that of asthma with pulmonary infiltrates, purpura, peripheral neuropathy, or peripheral blood eosinophilia. Sinusitis often is present. The presence of palpable purpura or mononeuritis multiplex in a patient with asthma should suggest Churg-Strauss syndrome. Laboratory findings include CD4⁺ T_H2 lymphocytes in peripheral blood, increased total serum IgE concentrations, peripheral blood (and tissue) eosinophilia, and the presence of anti-cytoplasmic nuclear antibodies (ANCA). About 60% of patients will have a perinuclear ANCA specific for myeloperoxidase, and 10% of patients will have positive results for a cytoplasmic ANCA specific for proteinase 3. The titers of ANCA do not correlate strongly with disease activity.¹⁹ During exacerbations of Churg-Strauss syndrome, urinary concentrations of leukotriene (LT) E₄, a major metabolite of LTC₄ and LTD₄ produced by eosinophils, eosinophil-derived neurotoxin, and 3-bromotyrosine, the latter a marker of eosinophil oxidation, are increased sharply.²⁰

The 6-year survival rate for treated patients is 70%,¹⁹ but survival for 26 years has been described.²¹ Initial treatment consists of oral corticosteroids.^{19,21} Additional therapies have included cyclophosphamide, which carries its own side effects, such as hemorrhagic cystitis, cytopenias, and malignancy potential, and azathioprine, which is considered less toxic.¹⁹ Therapy with

TABLE I. Some features of hypersensitivity pneumonitis

Radiographic	Ground-glass opacifications (active alveolitis or fine fibrosis), centrinodular infiltrates, air trapping, pulmonary fibrosis
Histology	Lymphocytic infiltrates; CD20 ⁺ B cells in aggregates; CD8 ⁺ , IFN- γ ⁺ , and CXCR3 ⁺ lymphocytes; thickened or fibrotic alveoli; noncaseating granulomas; fine-to-diffuse pulmonary fibrosis
Bronchoalveolar lavage	Lymphocytosis of 30% to 90%, CD8 ⁺ and CD25 ⁺ (activated) lymphocytes, CD4/CD8 ratio <1, CD56 ⁺ natural killer cells, mast cells, CD80/CD86 ⁺ macrophages (increased costimulation), IL-18 and TNF- α values increased, reduced annexin-positive cells (reduced apoptosis), decreased mitogen responsiveness (reduced suppressor function despite increased numbers of lymphocytes)
Peripheral blood	Precipitating antibodies to causative antigen

Data were obtained from references 23 to 32.

IFN- α decreases the production of eosinophils¹⁹ but has been associated with depression and progressive multifocal leukoencephalopathy.¹⁹ It remains to be established whether treatment with mepolizumab (anti-IL-5), omalizumab (anti-IgE), or anti-sialic acid-binding immunoglobulin-like lectin 8 (which, when ligated, causes eosinophil apoptosis)²² antibodies might prove beneficial in the Churg-Strauss syndrome.

T_H1-RELATED INFLAMMATORY CONDITIONS **Hypersensitivity pneumonitis**

Hypersensitivity pneumonitis is characterized by a lymphocyte and macrophage alveolitis with granuloma formation and pulmonary fibrosis. There are small nodules (<5 mm) present in high-resolution CT scans of the lung that represent active alveolitis or fibrosis of the lung parenchyma. Repeated exposure to various inhaled antigens results in a T_H1 and CD8⁺ T lymphocyte–predominant inflammatory pulmonary condition with striking levels of bronchoalveolar lavage lymphocytosis to as high as 60% to 80%.^{1,23–25} The CD4⁺/CD8⁺ ratio is less than 1 compared with 8 in sarcoidosis, which, conversely, is characterized by a CD4⁺ alveolitis.²⁶ IFN- γ participates in granuloma formation, and IL-12, IL-18, and TNF- α are just some of the cytokines involved in the pathogenesis.²⁷

Hypersensitivity pneumonitis can be classified into acute, subacute, and chronic stages.^{28–30} In the acute and subacute stages patients experience cough, shortness of breath, and systemic symptoms, such as fever and myalgias, that occur within 4 to 6 hours after exposure. The physical examination can reveal diffuse crackles, which might suggest a viral pneumonia. In the patient with subacute hypersensitivity pneumonitis, such as that associated with birds in the home, continued exposure results in cough, dyspnea, and even weight loss over a period of months or years. Alternatively, it has been suggested that hypersensitivity pneumonitis be categorized into either active or residual states because most patients present in subacute or chronic states.³¹ Pulmonary function testing results most often have restrictive findings and reductions in diffusing capacity for carbon monoxide. A pattern of airway obstruction can occur, especially in cases of hypersensitivity pneumonitis from avian exposure.²⁸ Patients with chronic hypersensitivity pneumonitis have chronic dyspnea and restrictive pulmonary function measurements, and deaths can occur from fatal pulmonary fibrosis. Some key features of hypersensitivity pneumonitis are summarized in Table I.^{25–32} Avoidance of the antigen and a short course of oral corticosteroids remain the initial approach. Bird lovers might refuse to give up their birds, so that continued exposure occurs with progressive dyspnea and loss of lung function.

Chronic obstructive pulmonary disease

In addition to the very important roles of PMNs and macrophages in chronic obstructive pulmonary disease (COPD), there is

the presence of CD4⁺ T_H1 and CD8⁺ T lymphocytes.^{33–35} IL-4 can be expressed by CD8⁺ T lymphocytes.³³ The pathogenesis of COPD includes multiple effects of cigarette smoking, infection (bacterial, viral, and combined viral/bacterial)³⁶ or no apparent infection,³⁶ immune responses, oxidative stress, genetics, and steroid resistance. Sputum neutrophilia is typical during exacerbations of COPD from any cause, but sputum eosinophilia is associated with both viral and combined viral/bacterial exacerbations.³⁶ In other words sputum eosinophilia appears to be a marker of viral infection–related exacerbations that are independent of bacteria in sputum.

Patients with COPD experience fewer exacerbations if treated with a combination regimen of fluticasone and salmeterol.³⁷ Nevertheless, there was no reduction in the number of deaths in treated patients.³⁷ In another study of COPD treatment, the addition of salmeterol/fluticasone or salmeterol to the anticholinergic tiotropium did not reduce the rate of exacerbations of COPD. However, there was an increase in FEV₁ and quality of life measures, along with reduced numbers of hospitalizations in patients who received salmeterol/fluticasone.³⁸ Glucocorticoids must reach the nucleus and interact with glucocorticoid response elements of the DNA.³⁹ This process is important so that proinflammatory transcription factors, such as nuclear factor κ B and activator protein 1, which might have been activated by a viral upper respiratory tract infection, can be suppressed. These transcription factors are generated after the DNA-histone complex is acetylated by histone acetyltransferase. Acetylation opens up (unwinds) the DNA-histone complex so that there is “switched on” transcription and gene expression. Glucocorticoids can switch on anti-inflammatory genes and switch off proinflammatory genes. Histone acetylation is increased in asthma but not always in COPD.³⁹ When the DNA is deacetylated by histone deacetylases (HDACs), it is compacted, and gene repression occurs. Histone deacetylation is reduced in both COPD and asthma, but corticosteroids are able to increase HDACs in asthma, although not in COPD.³⁹ It is suspected that the lack of deacetylation of the DNA in COPD permits continued proinflammatory processes to occur. This finding might help explain the steroid insensitivity in COPD. In experimental systems theophylline increases HDACs, which might suggest that this phosphodiesterase inhibitor is anti-inflammatory.³⁹

T_H2-RELATED INFLAMMATORY CONDITIONS

Eosinophils differentiate and proliferate in the bone marrow from CD34⁺ progenitor cells under the influence of IL-5, IL-3, and GM-CSF.^{40,41} Eosinophils have a half-life in peripheral blood of 8 to 18 hours and in tissue of 2 to 5 days or longer.⁴² Some of the chemoattractants for eosinophils include CCL11 (eotaxin-1), RANTES, platelet-activating factor, and LTB₄.^{39,40} Firm adhesion results from the interaction of very late antigen 4 on eosinophils with vascular cell adhesion molecule 1 on endothelial

TABLE II. Pulmonary eosinophilia syndromes/conditions

Asthma (allergic and nonallergic)
Asthma with atelectasis from mucus plugging
Allergic bronchopulmonary aspergillosis
Allergic bronchopulmonary mycosis
Churg-Strauss syndrome
Collagen vascular disease (rare)
Drug allergy
Eosinophilic pneumonia
Acute (bronchoalveolar lavage fluid eosinophilia, 25% to 60%; little or no peripheral blood eosinophilia)
Chronic
Simple eosinophilia (Löffler syndrome)
Tropical pulmonary eosinophilia
Hypereosinophilic syndromes (interstitial infiltrates and pleural effusions)
Neoplasms
Parasitism (helminthic)
Sarcoidosis (rare)

cells.⁴⁰ IL-4, IL-13, and TNF- α upregulate the expression of vascular cell adhesion molecule 1 on endothelial cells.^{40,41} Most of the conditions that are associated with pulmonary eosinophilia have some demonstrated evidence for these cytokines, chemokines, adhesion molecules, or mediators. It is worth emphasizing that the ratio of tissue/blood eosinophils is at least 100,⁴² so as not to underestimate the deleterious effects of eosinophil activation in the lung.

A list of the major pulmonary eosinophilia syndromes/conditions is presented in Table II. One prototypic pulmonary eosinophilia condition is allergic bronchopulmonary aspergillosis (ABPA), which complicates asthma and cystic fibrosis.^{1,43,44} Although ABPA can convert asthma from mild to severe persistent states, it is not proved that ABPA alters the course of cystic fibrosis.⁴⁴ ABPA also has been described in patients with chronic granulomatous disease and hyper-IgE syndrome.⁴⁵ ABPA can cause central (proximal) bronchiectasis (inner two thirds of the high-resolution CT field), which distinguishes it from distal bronchiectasis that occurs with chronic infection and cystic fibrosis, in which bronchiectasis is both central and distal. In susceptible patients the immune phenotype is that of CD4⁺ T_H2 lymphocytosis; increased total IgE concentration; increased anti-*Aspergillus* species IgE, IgG, and IgA antibodies; and precipitating antibodies to *Aspergillus fumigatus*, along with many other immunologic findings.

The initial treatment of ABPA has been with oral corticosteroids to clear the pulmonary infiltrates. Not all patients require long-term systemic corticosteroids, even if the total serum IgE concentration remains increased. For example, if the initial total IgE concentration is 16,000 kU/L (normal, <417 kU/L) and it decreases to 5000 after 3 months of prednisone administration, there should be clearing of mucus plugging and pulmonary infiltrates on the high-resolution CT examination. Prednisone can be discontinued unless it is required for control of asthma. Continued treatment of asthma is required, but the total IgE concentration can remain increased sharply in the absence of additional pulmonary infiltrates. A doubling of the total IgE concentration suggests a possible new ABPA exacerbation. The role of antifungal therapy remains adjunctive; itraconazole has been associated with reduced sputum eosinophilia.⁴⁶ Whether the more potent antifungal agent voriconazole will prove a safe and effective modality remains to be established as.⁴⁷ Omalizumab has been administered in some cases,⁴⁸ but its role is not established.

Summary

The new information about immunologic lung diseases increases the opportunities for effective interventions, although it remains to be established that a single, targeted, novel treatment will be safe and effective for such complex conditions. Immunologic determinations are available to assist in diagnosis and treatment. The future holds hope for primary prevention or early diagnosis of many immunologic lung conditions based on continued discoveries. Even in COPD, immunologic intervention might offer the chance for improved outcomes in the future.

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Immunologic lung disease

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Test ID no.: mai00141

Contact hours: 1.0

Expiration date: January 31, 2010

Category 1 credit can be earned by reading the text material and taking this CME examination online. For complete instructions, visit the Journal's Web site at www.jacionline.org.

Learning objectives: "Immunologic lung disease"

1. To review the differences between the CD4⁺ T_H1 and CD4⁺ T_H2 granulomatous pulmonary diseases.
 2. To understand the clinical and immunologic findings of hypersensitivity pneumonitis.
 3. To consider the differential diagnosis of pulmonary eosinophilic conditions.
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CME items

Question 1. In chronic obstructive pulmonary disease, the activity of histone deacetylases is best described as —

- A. decreased.
- B. increased.
- C. responsive to oral corticosteroids.
- D. similar to asthma.

Question 2. A positive result in Churg-Strauss syndrome for antineutrophil cytoplasmic antibody would be expected to be specific for —

- A. myeloperoxidase.
- B. double-stranded DNA.
- C. proteinase 3.
- D. lysozyme.

Question 3. In association with the formation of granulomas in pulmonary tuberculosis, the most characteristic immunologic finding is the presence of —

- A. CD8⁺ lymphocytes.
- B. CD4⁺ T_H1 lymphocytes.
- C. CD4⁺ T_H2 lymphocytes.
- D. reduced numbers of Treg (CD4CD25⁺) lymphocytes.

Question 4. The ratio of tissue/blood eosinophils is estimated to be —

- A. 1 to 1.
- B. 10 to 1.
- C. 100 to 1.
- D. 1000 to 1.