Hypersensitivity pneumonitis (HP), also called "extrinsic allergic alveolitis," is an immunologically-induced inflammatory disease affecting the alveoli and terminal airways (bronchioles), caused by repeated inhalation of a variety of inciting agents in a susceptible host. A wide range of organic antigens have been identified from different occupations. The clinical presentations of hypersensitivity pneumonitis vary depending upon the frequency, length, and intensity of exposure to the inciting agent. Surprisingly, cigarette smoking reduces the risk of developing the disease due to decreased antibody reaction to the antigen.

Etiology of Hypersensitivity Pneumonitis

The most common types of Hypersensitivity pneumonitis in the United States are farmer’s lung, bird fancier’s lung, and Chemical worker’s lung.

Farmer’s lung

It's one of the most common forms of Hypersensitivity pneumonitis, where inhalation of proteins, such as thermophilic bacteria in moldy hay are commonly responsible for the development of HP.

Bird Fancier’s Lung

Exposure to excreta and proteinaceous material on dust from pigeons and other birds may induce Hypersensitivity pneumonitis.
Chemical Worker’s Lung

Different organic chemicals, such as isocyanates may induce immune-mediated disease.

Some causes of Hypersensitivity pneumonitis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Situation</th>
<th>Antigens</th>
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| Farmer’s lung            | Forking mouldy hay or any other mouldy vegetable material | • Thermophilic actinomycetes, e.g. *Micropolyspora faeni*  
• Fungi, e.g. *Aspergillus umbratus* |
| Bird fancier’s lung      | Handling pigeons, cleaning lofts or budgerigar cages | Proteins present in the ‘bloom’ on the feathers and in excreta          |
| Maltworker’s lung        | Turning germinating barley                      | *Aspergillus clavatus*                                                    |
| Humidifier fever         | Contaminated humidifying systems in air conditioners or humidifiers in factories (especially in printing works) | Possibly a variety of bacteria or amoeba (e.g. *Naegleria gruberi*)  
Thermoactinomycetes |
| Mushroom workers         | Turning mushroom compost                        | Thermophilic actinomycetes                                                |
| Cheese washer’s lung     | Mouldy cheese                                   | • *Penicillin casei*  
• *Aspergillus clavatus* |
| Winemaker’s lung         | Mould on grapes                                 | Botrytis                                                                  |

Pathogenesis of Hypersensitivity Pneumonitis

Two mechanisms have been demonstrated in the pathogenesis of hypersensitivity pneumonitis after inhalation of an allergic antigen:

- Cell-mediated hypersensitivity reaction
- Immune complex-mediated reaction

The early stage of the disease is characterized by polymorphonuclear leukocytes infiltration in the alveoli and bronchioles, followed by infiltration of T-lymphocytes and macrophages leading to formation of non-caseating granulomas as a result of delayed cell-mediated hypersensitivity reaction. Antibodies are formed against the allergic antigen followed by immune-complex deposition causing inflammation of the alveoli and small airways (bronchioles) through activation of complement via the classical pathway.

Continual exposure to the eliciting antigen may result in further polymorphonuclear leukocytes infiltration, granuloma formation and eventually progressive development of lung fibrosis.
Clinical Features of Hypersensitivity Pneumonitis

The clinical presentations of hypersensitivity pneumonitis vary from patient to patient depending upon the frequency, length, and intensity of exposure to the inciting agent. They have been categorized into acute, sub-acute and chronic hypersensitivity pneumonitis.

Acute hypersensitivity pneumonitis

Acute hypersensitivity pneumonitis usually follows massive exposure to an inciting agent.

Symptoms
The patient presents with an abrupt onset of a cough, fever, chills, malaise, and dyspnea without wheezes, usually 6 to 8 h after inhalation of the eliciting antigen, and resolves within days if no further exposure occurs. The patient can be misdiagnosed as having a viral or bacterial infection and is frequently treated with antibiotics.

Clinical examination
- It usually shows tachycardia and coarse diffuse end-inspiratory crackles. Wheezing is rare.
- Patient maybe cyanotic.

Subacute or intermittent hypersensitivity pneumonitis

Subacute hypersensitivity pneumonitis may occur after an acute presentation of the
disease due to repeated and continued exposure to the eliciting antigen.

**Symptoms**

The patient usually presents with an insidious onset of a cough and dyspnea that may progress to cyanosis requiring hospitalization. The symptoms develop gradually over a period of weeks. Progression of the disease into the chronic form may occur.

**Clinical examination**

- It also shows tachycardia and diffuses fine crackles.
- The patient can be severely cyanotic and may require hospitalization.

**Chronic hypersensitivity pneumonitis**

Repeated and continuous low exposure to the antigenic agent over a long period can lead to the chronic form of the disease. The patient may lack a history of acute or subacute manifestations. At this stage, avoiding exposure to the eliciting agent usually results in only partial resolution of symptoms, and the patient usually requires prednisone therapy.

**Symptoms**

- Patient presents with insidious onset of a cough, dyspnea, fatigue, and weight loss, the patient may be clinically indistinguishable from idiopathic pulmonary fibrosis (IPF).
- Progression of the disease may lead to pulmonary hypertension, and respiratory failure and the patient may become dependent on supplemental oxygen.

**Clinical examination**

- It usually shows fine diffuse crackles, and digital clubbing in the advanced disease stage.
- The patient can be cyanotic.

**Diagnosis of Hypersensitivity Pneumonitis**

**Laboratory findings in hypersensitivity pneumonitis**

- Erythrocyte sedimentation rate (ESR), C-reactive protein and serum immunoglobulins are usually elevated.
- The positive rheumatoid factor may be found.
- Serum LDH may be high in the acute phase.
- Bronchoalveolar lavage shows (BAL) lymphocytosis.
- Neutrophilia and lymphopenia may occur following acute exposure. Eosinophilia is not a feature.
- Examination of the precipitating antibodies against suspected antigen is important. These precipitating antibodies are evidence of exposure, not the disease.
- Arterial blood gas (ABG) may show mild hypoxemia.

**Pulmonary function tests may show:**

- Restrictive ventilator defects during symptomatic episodes.
The obstructive pattern may also be found.
- Impaired diffusing capacity.
- Decreased compliance.

Pulmonary function tests may reverse to normal in acute and subacute forms if there is no further exposure to the eliciting agent.

Radiographic findings in hypersensitivity pneumonitis

**Chest X-ray:**

**In acute and sub-acute forms:**
Poorly defined, patchy micronodular or reticular opacities in the lower and middle lung zones with apical sparing.

**In chronic form:**
- Diffuse reticulonodular infiltrates with progressive fibrotic changes.
- In very advanced cases, honeycomb lung may occur.
- **Emphysema** without a history of smoking has been found in up to 15% of patients.

**High-resolution chest CT (HRCT):**

**In acute form:**
It may appear as diffuse “ground-glass” infiltrates, confluent alveolar opacification.

**In subacute form:**
Diffuse micronodules, ground-glass changes become more prominent, focal air trapping or emphysema and mild fibrotic changes. These findings often resolve with antigen avoidance and treatment with glucocorticoids.

**In chronic form:**
Diffuse changes may appear as parenchymal micronodules and interstitial fibrosis, accompanied by honeycombing and/or emphysema.

Biopsy in hypersensitivity pneumonitis
A lung biopsy obtained through flexible bronchoscopy, open-lung procedures, or thoracoscopy may be used for diagnosis.

The histopathology differs according to the form of the disease. Although the findings are distinctive, they may not be pathognomonic of hypersensitivity pneumonitis.

The histopathologic findings in HP include:

- Poorly formed granulomata located near respiratory or terminal bronchioles
- Patchy mononuclear cell infiltration of the alveolar walls.

### Differential Diagnosis of Hypersensitivity Pneumonitis

There are several clinical syndromes that mimic hypersensitivity pneumonitis, and it is important to recognize and differentiate them since they are also induced by inhalation of organic agents.

<table>
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<tr>
<th>Condition</th>
<th>Description</th>
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| **Inhalation fever**                   | - It’s characterized by fevers, chills, malaise, headaches, and myalgias without prominent pulmonary findings.  
   - Symptoms usually start 4 - 12 hours after exposure. |
| **Organic dust toxic syndrome**        | - It is also known as pulmonary mycotoxicosis, which occurs after exposure to bioaerosols contaminated with toxin-producing fungi.  
   - It’s characterized by fever, chills, dyspnea, and myalgias with or without dyspnea and a cough, which occurs 4 to 6 hours after exposure to contaminated dust.  
   - Antibody precipitins are absent, and the chest x-ray is usually normal.  
   - It’s a self-limited disease, in contrast to hypersensitivity pneumonitis which can result in permanent disability. |
| **Chronic bronchitis**                 | **Chronic obstructive pulmonary disease (COPD)** is the most common cause of lung disease in agricultural workers, and can occur in 10% of farm workers without a previous history of cigarette smoking. |
Airway-centered interstitial fibrosis

It’s characterized by bronchiolitis and fibrosis and with epithelial hyperplasia of the adjacent alveolar septa.

Management of Hypersensitivity Pneumonitis

There are both environmental and host factors involved in the development of hypersensitivity pneumonitis. Management of the disease is based mainly on modification of the environment since the pathogenesis of the disease is not completely understood to help modify the host’s response.

Prevention of hypersensitivity pneumonitis

The most effective treatment of hypersensitivity pneumonitis is to identify the causative antigen and completely avoid (preferred) or minimize ongoing exposure to the agent. The simplest method to avoid the antigen is either to remove the patient from the environment where the antigen exists, or remove the antigen from the patient’s environment.

The source of exposure (birds, humidifiers, molds) can be removed. Purifying the air inhaled through pollen masks, airstream helmets and supplying fresh air can decrease the risk of exposure. It’s advisable to avoid contact with the eliciting agent completely if the patient has chronic hypersensitivity pneumonitis since lung fibrosis may already be partially or completely irreversible.

Treatment of hypersensitivity pneumonitis

Acute form:

It’s not recommendable to give glucocorticoids to a patient with acute hypersensitivity pneumonitis because the acute form usually recovers with antigen avoidance and without the need for glucocorticoids.

Subacute form:

Patient with subacute HP present with severe respiratory distress and cyanosis that may progress into frank respiratory failure despite hospitalization. Therefore, immediate diagnosis and administration of glucocorticoids are indicated for this patient. Prednisone 1 mg/kg/day continued for 7 to 14 days has been shown to accelerate recovery, but
doesn’t affect the long-term prognosis.

**Chronic form:**
A patient with chronic form hypersensitivity pneumonitis usually benefits from environmental control without the need for glucocorticoids because the lungs have already been damaged from repeated exposure to the allergic agent.

A trial of glucocorticoids can be given to obtain maximal reversibility of the lung disease.

**Eosinophilic Pneumonia**

Eosinophilic pneumonia, also known as pulmonary infiltrates with eosinophilia, includes distinct syndromes of different etiology characterized by eosinophilic pulmonary infiltrates and an increase in the number of eosinophils in the peripheral blood (eosinophilia). These diseases are also considered immunologically-mediated, but shouldn’t be confused with hypersensitivity pneumonitis in which there is no associated eosinophilia.

Eosinophilic pneumonia involves a large group of diseases which are classified according to the etiology into either disease with known or unknown etiologies.

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<tr>
<th>Pulmonary Infiltrates with Eosinophilia</th>
<th>Idiopathic</th>
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<td>Loeffler’s syndrome</td>
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<td>Parasitic infestations</td>
<td>Acute eosinophilic pneumonia</td>
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<tr>
<td>Drug reactions</td>
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<td>Eosinophilia-myalgia syndrome</td>
<td>Allergic granulomatosis of Churg and Strauss</td>
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<tr>
<td></td>
<td>Hypereosinophilic syndrome</td>
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**Idiopathic Syndromes**

**Loeffler’s Syndrome**

This syndrome consists of acute eosinophilic pneumonia of unknown cause characterized by migrating pulmonary infiltrates and minimal clinical features.

**Acute Eosinophilic Pneumonia**

It’s an idiopathic acute febrile illness that occurs in a span of less than seven day’s characterized with severe hypoxemia; pulmonary infiltrates, and no history of asthma.

**Chronic Eosinophilic Pneumonia**

It presents with significant systemic symptoms including fever, chills, night sweats, cough, anorexia and weight loss over a duration of several weeks to months. The chest x-ray classically shows peripheral infiltrates resembling a photographic negative of pulmonary edema. Dramatic clearing of symptoms and chest x-ray peripherals infiltrates is often noted within 48 hours after initiation of corticosteroids therapy.

**Churg-Strauss Syndrome**

It is a vasculitis disorder that affects different body organs. It frequently involves the skin, kidney and central nervous system in addition to the lungs. Any age can be affected by the disease, especially patients with bronchial asthma.
A patient with Churg-Strauss typically presents with pulmonary infiltrates, chronic bronchial asthma, vasculitis, and eosinophilia. The disease is progressive, but it responds well to glucocorticoids which may regress the progression of the disease.

**Hypereosinophilic Syndrome**

This syndrome is characterized by the presence of over 1500 eosinophils per microliter of peripheral blood over a period of six months or longer, and absence of parasitic, allergic, or other known causes of eosinophilia. The heart can be affected by tricuspid valve abnormalities or endomyocardial fibrosis and a restrictive cardiomyopathy.

Other organs may also be involved including the liver, spleen, skin and central nervous system. Corticosteroids are the treatment of choice.

**Disorders with known causes**

**Allergic bronchopulmonary mycosis**

Allergic bronchopulmonary mycosis should be suspected if a patient with eosinophilic pneumonia has bronchial asthma and wheal-and-flare skin reaction due to Aspergillus or other fungal antigens. A. fumigatus is the most common cause.

This disease should be distinguished from Churg-Strauss Syndrome, which is also associated with bronchial asthma.

**Parasitic infestations**

Different parasitic infestations can result in pulmonary eosinophilia, such as Ascaris spp., Ancyclostoma spp., Toxocara spp., and Strongyloides stercoralis.

Suspect parasitic-induced eosinophilia in patients with a recent travel history.

**Drug-induced eosinophilia pneumonias**

These are the most common cause of eosinophilic pulmonary infiltrates in the United States (US). It can be treated simply by withdrawing the drug and the use of glucocorticoids.

**Review Questions**

The answers are below the references.

1. **The main pathophysiological mechanism involved in the pathogenesis of hypersensitivity pneumonitis is:**
   
   A. Cell-mediated hypersensitive reaction.  
   B. Ig-E medicated hypersensitivity reaction.  
   C. Toxic-mediated inflammation of the alveoli.  
   D. Autoimmune destruction of the alveoli.

2. **A patient was suspected to have hypersensitivity pneumonitis, the most probable finding in his bronchoalveolar lavage was:**
   
   A. Neutrophilia.  
   B. Eosinophilia  
   C. Basophilia.  
   D. Lymphocytosis.
3. The most effective treatment of hypersensitivity pneumonitis is:

A. Methotrexate.
B. Strong antibiotics.
C. Glucocorticoids.
D. Non-Steroidal Anti-inflammatory Drugs.

References


Correct answers: 1A, 2D, 3C

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