Hypersensitivity pneumonitis

A multifaceted, challenging disorder

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More than 300 microbes, proteins and other chemicals have been implicated in hypersensitivity pneumonitis, which involves an exaggerated immune response to inhaled allergens. A high index of suspicion is the key to early diagnosis while the disease is potentially reversible.

Hypersensitivity pneumonitis (HP), also called extrinsic allergic alveolitis, is an immune-mediated inflammatory disorder of the lung involving alveolar walls and terminal airways. It is caused by repeated inhalation of organic dusts that trigger an immunological reaction within the pulmonary parenchyma of a susceptible host. It is a complex syndrome with varying clinical presentations, intensity and disease course. A typical case history appears in the Box and Figures 1 and 2.

A recent review of HP included an extensive historical description.[1] In 1713, an Italian medical professor described the health hazards associated with 52 occupations and provided the first account of what is now termed HP. The first detailed clinical descriptions of HP appeared in 1932, with multiple cases reported in the USA and England.

Epidemiology

The prevalence and incidence of HP are thought to be low, with only a small proportion of exposed individuals developing clinically significant HP. Many people with mild disease are misdiagnosed with a viral illness or asthma. Common types of HP include farmer's lung, bird fancier's lung and chemical worker's lung. Other types include bagassosis, hot tub lung and mushroom worker's lung. The prevalence of HP varies considerably around the world, depending on disease definition, diagnostic methods, type and intensity of exposure, geographical conditions, local agricultural and industrial practices and host risk factors. High attack rates may be found among exposed individuals during sporadic outbreaks and in occupational settings.[2] The epidemiology of HP in Australia remains largely unknown.

Aetiology

More than 300 agents have been implicated as causes of HP, with exposure occurring as a result of occupation, hobby, recreation or contaminated air systems (Table).[3] The reported triggers include animal and plant proteins, microbes (especially fungi) and low molecular weight chemicals. HP has been described in relation to farming, bird and poultry handling, veterinary work, grain and flour processing, milling and construction, chemical and textile industries, and ventilation and water-related contamination.

Pathogenesis

HP is caused by an exaggerated immune response to organic particles small enough to reach the alveoli (less than 5 μm) or hapten-forming low molecular weight chemicals. (A hapten is a small molecule that can elicit an immune response only when attached to a larger carrier such as a protein.) The very early (acute) reaction is characterised by an increase in polymorphonuclear leucocytes in the alveoli and small airways. This is followed by an influx of mononuclear cells into the lung and granuloma formation, a result of a delayed hypersensitivity reaction mediated by T cells.

The pathogenesis of HP is complex and not yet fully understood. Initially thought to be an immune complex-mediated disease, current evidence supports the role of T cell-mediated, delayed-type hypersensitivity. HP is defined as a T helper type 1 (Th1) disease with overproduction of Th1 cytokines.[4]

Individual susceptibility is a characteristic feature of HP with only a small percentage of exposed individuals developing the disease. Many exposed asymptomatic individuals develop a mild

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CASE HISTORY: HYPERSENSITIVITY PNEUMONITIS IN A TEXTILE WORKER

Mr W, a 46-year-old previously healthy textile mill worker, presented with recurrent lower respiratory tract symptoms, worsening dyspnoea and hypoxia. A recent episode of lower respiratory tract symptoms had resolved with antibiotic treatment and time away from work. However, after the first day back at work, his symptoms recurred and worsened rapidly.

He had quit smoking 15 years previously (7.5 pack years) and he was not taking any medications. He had worked with textiles for 26 years before the illness.

There were diffuse crackles on chest auscultation and bilateral upper and mid-zone infiltrates on chest x-ray (Figure 1) and CT scan (Figures 2a and b). Spirometry revealed lung restriction. Bronchoalveolar lavage showed a very high lymphocyte count (72% of white blood cells) with a CD4/CD8 lymphocyte ratio of 1.6. No bacterial or fungal pathogens were cultured. The patient had normal serum levels of angiotensin-converting enzyme (ACE), total IgE and specific IgE against common allergens. *Aspergillus* serological results were positive, with one precipitin band. A subsequent workplace visit revealed a regulated high temperature (22 to 24°C) and humidity (85 to 87%) inside the weaving area, with mould visible on the ceiling and extending down the walls.

Mr W was diagnosed with hypersensitivity pneumonitis secondary to airborne mould. He was treated with prednisolone (weaned over four weeks) and time off work. He improved quickly, and his lung infiltrates cleared on x-ray. A trial of a return to work resulted in recurrence of symptoms and deterioration of lung function, which confirmed the diagnosis. Subsequent workplace rehabilitation led to Mr W working full-time in other parts of the factory, avoiding work in the weaving area, where the heat and humidity promoted mould growth. He has had no recurrence.

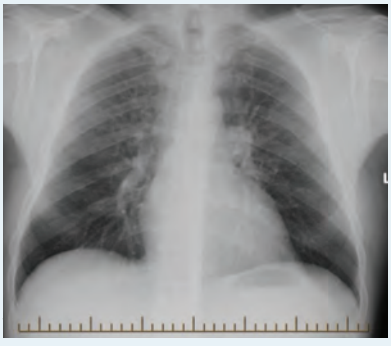
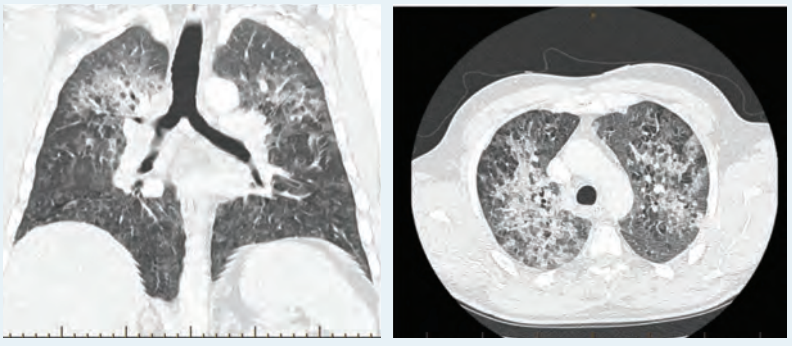


Figure 1. Chest x-ray showing bilateral upper and mid-zone infiltrates in a patient with acute hypersensitivity pneumonitis.



Figures 2a and b. CT images of the lungs showing areas of patchy airspace shadowing with areas of air trapping.

lymphocytic alveolitis, suggesting the development of an immune-tolerance response (which may be mediated by regulatory T cells [Treg]). A 'two-hit' hypothesis has been suggested, wherein pre-existing genetic susceptibility or environmental factors (the first hit) increase the risk for the development of HP after antigen exposure (the second hit). Antigen exposure acts as the inducing factor, and genetic or environmental factors act as promoting risk factors (Figure 3).[2]

HP is less frequent in smokers than in nonsmokers. However, HP occurring in smokers may follow a chronic clinical course with poorer survival compared with nonsmokers.[5]

Clinical features

The clinical picture of HP is variable and depends on the frequency and intensity of antigen exposure and the duration of subsequent illness. Classically, clinical manifestations of HP have been categorised as acute, subacute or chronic.

Acute hypersensitivity pneumonitis

Acute HP is the most classic form and closely resembles an influenza-like illness. It is characterised by cough, fever, chills, malaise and dyspnoea, occurring four to eight hours after exposure to the inciting antigen. Physical examination reveals tachypnoea and diffuse fine crackles.

Laboratory tests may show an elevated erythrocyte sedimentation rate and elevated levels of C-reactive protein, immunoglobulins, rheumatoid factor and lactate dehydrogenase. Precipitating IgG antibodies to the antigen may be found. Chest x-ray may show poorly defined, patchy or diffuse infiltrates, micronodular infiltrates or air-space consolidation. Lung function tests may show a restrictive defect and mild hypoxaemia.

Removal of the individual from exposure results in symptom improvement within hours to days and resolution of radiological findings within weeks. The disease generally is intermittent and nonprogressive. It can recur with re-exposure.

Subacute hypersensitivity pneumonitis

Subacute HP may develop from repeated low-level exposure. It is characterised by a gradual development, over weeks to months, of cough, dyspnoea, fatigue, anorexia and weight loss. Physical examination reveals tachypnoea and diffuse crackles. Chest x-ray may show micronodular or reticular opacities. Lung

TABLE. EXAMPLES OF HYPERSENSITIVITY PNEUMONITIS*

Disease	Antigen	Antigen source
Farmer's lung	Thermophilic actinomycetes	Mouldy hay, grain, silage
Bird fancier's lung	Parakeet, chicken, pigeon, turkey proteins	Avian droppings or feathers
Chemical worker's lung	Isocyanates	Foam, varnishes, paints
Bagassosis	Thermophilic actinomycetes	Mouldy bagasse (sugarcane)
Compost lung	*Aspergillus* spp.	Compost
Hot tub lung	*Cladosporium* spp., *Mycobacterium avium* complex	Mould on ceiling, contaminated water
Humidifier or air conditioner lung	Thermophilic actinomycetes, *Aureobasidium* spp.	Contaminated water in humidification or air conditioning systems
Mushroom worker's lung	Thermophilic actinomycetes, mushroom spores	Mushrooms, mushroom compost
Cheese washer's lung	*Penicillium* spp.	Mouldy cheese
Laboratory worker's lung	Urine, serum, pelts, proteins	Rats
Miller's lung	*Sitophilus granarius* (wheat weevil)	Infested wheat flour
Woodworker's lung	Wood dust, *Alternaria* spp.	Oak, cedar, pine and mahogany dusts

* More complete lists of environmental exposure and antigens have been published recently.[3]

function tests reveal a restrictive or a mixed obstructive–restrictive pattern with reduced diffusion capacity and mild hypoxaemia.

Removal from exposure may lead to resolution, with improvement taking longer than in patients with acute HP. The subacute form of HP can be progressive, with cough and dyspnoea becoming persistent.[2]

Chronic hypersensitivity pneumonitis

Chronic HP may occur with or without recognisable episodes of acute HP and usually results from continuous low-level antigen exposure. It presents as an insidious respiratory disease with progressive dyspnoea, cough, fatigue, malaise and weight loss. Physical examination reveals inspiratory crackles. The presence of digital clubbing may indicate advanced disease and predict clinical deterioration.[6]

Chest x-ray may show progressive fibrotic changes with loss of lung volume (similar to idiopathic pulmonary fibrosis). Lung function tests usually show a moderate to severe restrictive defect (although an obstructive or a mixed obstructive–restrictive defect may be seen). Progressive worsening may result in pulmonary fibrosis, pulmonary hypertension, respiratory failure, supplemental oxygen dependence and increased mortality.[7]

Diagnosis

There is no gold standard for the diagnosis of HP. A high index of suspicion remains the key to establish the diagnosis. A prompt diagnosis is important because of the reversible nature of the disease early in its course. A thorough detailed history is essential to make a diagnosis. In the absence of any single pathognomonic clinical feature or laboratory test result, the diagnosis relies on a combination of exposure history, clinical features and results of serology, radiography, lung function tests and bronchoalveolar lavage (BAL). The diagnosis is further supported by spontaneous resolution within weeks of avoiding the allergen.

Prediction rule

A prediction rule for the clinical diagnosis of HP was developed by the International HP Study Group.[8] Six clinical predictors of HP were identified:

- exposure to a known offending antigen
- positive precipitating antibodies to the offending antigen
- recurrent episodes of symptoms
- inspiratory crackles on physical examination
- symptoms occurring four to eight hours after exposure
- weight loss.

The probability of having HP is proportional to the number of criteria fulfilled. If all six predictors are present, the probability of having HP is 98%. If none of the six predictors is present, the probability is 0.

In Australia, many respiratory physicians would also perform a bronchoscopy and BAL for additional diagnostic information (see below) and to exclude alternative diagnoses, including unusual respiratory infections.

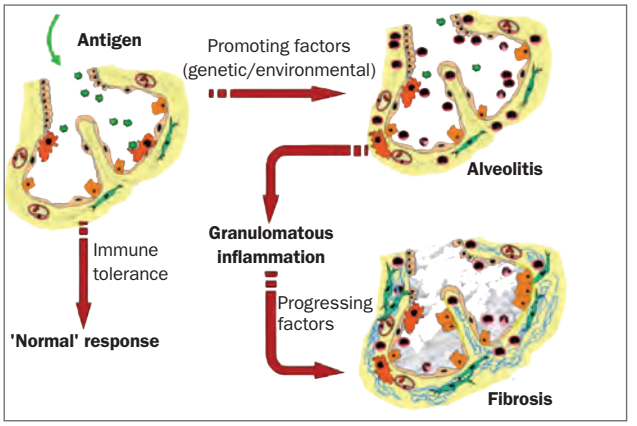


Figure 3. Proposed mechanisms in the pathogenesis of hypersensitivity pneumonitis.[2]

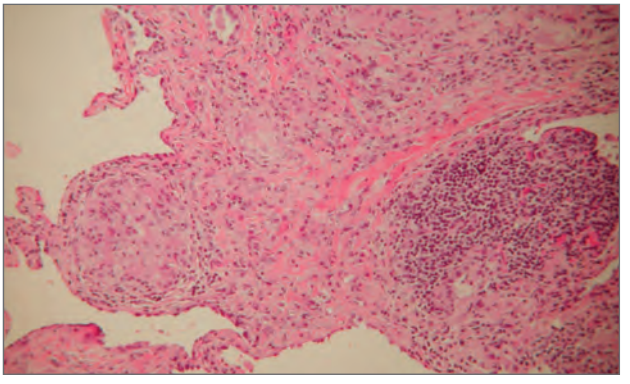


Figure 4. Thoracoscopic lung biopsy specimen showing extensive lymphocytic interstitial infiltrate and noncaseating granulomas (in a different patient to the patient reported in the case history [Box])

Antibody testing

Serum precipitins are precipitating IgG antibodies against antigens such as moulds, fungi, grain dust or body fluids from animal sources. The presence of serum precipitins confirms a sufficient level of exposure to the antigen. However, these antibodies can also be found in the sera of many individuals exposed to the appropriate antigens who have no other evidence of disease. Hence, these antibodies are not sufficient on their own to establish the diagnosis.

Inhalation challenge

Inhalation challenge by re-exposure of the individual to the antigen may assist diagnosis. The patient should be monitored closely or have ready access to medical care following the challenge. The recurrence of symptoms within 12 hours of exposure along with laboratory and functional abnormalities supports the diagnosis of hypersensitivity pneumonitis.

High resolution CT

Characteristic findings of HP on a high-resolution CT scan include mid to upper lobe predominance of centrilobular ground-glass or nodular opacities with signs of air trapping. The pattern varies depending on the stage of the disease, as follows.[9]

- In acute HP, the typical finding is ground-glass opacification. Diffuse areas of dense air-space consolidation may be associated with ground-glass opacities (Figures 2a and b).
- In subacute HP, diffuse micronodules, ground-glass attenuation, air trapping and mild fibrotic changes are seen.
- In chronic HP, parenchymal micronodules, ground-glass attenuation and honeycombing and/or emphysema are seen.

Bronchoalveolar lavage

BAL findings of marked lymphocytosis (more than 50% of white blood cells recovered) and a CD4/CD8 lymphocyte ratio less than 1.0 (normal range, 0.9 to 2.5[10]) may be helpful in supporting the diagnosis of HP. The BAL neutrophil count may also be elevated after recent antigen exposure.

In HP, lymphocytes typically make up more than 20% and often more than 50% of white blood cells recovered by BAL. Raised lymphocyte proportions can also be seen in other conditions but are rarely as high as 50%. For example, in sarcoidosis, the lymphocyte proportion is usually in the range 25 to 50%, and the CD4/CD8 ratio is usually over 2.0. An exception to the low CD4/CD8 ratio typical of HP has been reported in hot tub lung, where the ratio is often over 2.0.[11]

Lung biopsy

Histopathological confirmation by lung biopsy may be needed for diagnosis of HP in some patients. Findings vary with the stage of the disease, as follows.

- In acute HP, features include a lymphocytic interstitial inflammatory infiltrate, poorly formed noncaseating granulomas and cellular bronchiolitis (Figure 4).
- Chronic HP is characterised by interstitial fibrosis and giant cells, often with minimal granulomatous inflammation.

Differential diagnosis

The acute form of HP can resemble acute bacterial and viral pulmonary infections, asthma exacerbations, inhalation fever and organic dust toxic syndrome.

Inhalation fever ('Monday morning miseries') is characterised by fever, chills, malaise, headaches, myalgias, mild dyspnoea and cough, without prominent pulmonary findings, developing four to 12 hours after exposure. There are no long-term sequelae.

Organic dust toxic syndrome results from exposure to bioaerosols contaminated with toxin-producing fungi (*Fusarium* and aflatoxin-producing fungi). Although this syndrome can

present similarly to acute HP, it is not associated with previous sensitisation of the host and a serological response to common fungal antigens is not present.

The differential diagnosis of chronic HP includes the wide spectrum of interstitial lung diseases, and HP must be considered as a differential diagnosis in all patients with suspected interstitial lung disease.

Management of hypersensitivity pneumonitis

Antigen avoidance

An accelerated decline in lung function may occur with continued antigen exposure, making early diagnosis and avoidance of antigen exposure the cornerstone of treatment. Antigen exposure can be minimised by using protective equipment (e.g. personal respirators), altered handling and storage of potential sources (e.g. wetting compost before handling) or preventive maintenance (ventilation and air conditioning equipment). Sometimes, allergen exposure cannot be eliminated without complete removal of the patient from the responsible environment.

Therapy

Antigen avoidance generally results in disease regression, but glucocorticoids may be required in patients with severe HP. Glucocorticoids appear to accelerate initial recovery in severely ill patients with farmer's or bird fancier's lung but do not alter the long-term outcome.

Treatment is usually prescribed for patients with:[12]

- subacute or chronic disease
- persistent symptoms (e.g. dyspnoea, cough, fatigue, weight loss)
- abnormal lung function on testing (e.g. lung restriction and reduced diffusing capacity)
- hypoxaemia or
- radiographic evidence of extensive lung involvement.

Therapy is started with prednisone, typically beginning at a dose of 60 mg daily, plus supplemental oxygen for hypoxaemia and other appropriate supportive measures. Prednisone is usually continued until there is significant symptomatic and functional improvement, followed by tapering off. Given the paucity of treatment studies and the known side effects of systemic corticosteroids, clinical judgement and careful medical follow up are needed to guide individual patient management.[13]

Prognosis

Most patients with acute disease who are diagnosed and treated in a timely fashion improve and have a good prognosis. Some patients with subacute or chronic disease (particularly bird fancier's lung) may progress to irreversible pulmonary fibrosis and may die within a few years after diagnosis. Poor prognostic features include the development of pulmonary hypertension or fibrosis seen at lung biopsy or high-resolution CT.[14,15]

Conclusion

HP is a complex syndrome that requires a high index of suspicion for early diagnosis. Only a small proportion of exposed individuals develop the disease. Diagnosis is based on a combination of exposure history, clinical features, serology, radiography, lung function tests and BAL. Avoidance of antigen exposure remains the cornerstone of treatment and is necessary to prevent accelerated decline in lung function. MT

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