

Hypersensitivity Pneumonitis: A Historical, Clinical, and Radiologic Review¹

CME FEATURE

See accompanying test at http://www.rsna.org/education/rg_cme.html

LEARNING OBJECTIVES FOR TEST 2

After reading this article and taking the test, the reader will be able to:

- Describe the most common clinical manifestations of hypersensitivity pneumonitis.
- Correlate the histologic features of hypersensitivity pneumonitis with the radiologic findings.
- Identify the most important abnormalities indicative of hypersensitivity pneumonitis at chest radiography and CT.

TEACHING POINTS

See last page

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Most cases of hypersensitivity pneumonitis develop only after many years of inhaling allergens, which include microbes, animal or plant proteins, and certain chemicals that form haptens. The initial clinical presentation is either episodes of acute illness with dyspnea and prominent constitutional symptoms, such as fever, or an insidious onset of dyspnea, coughing, and weight loss, sometimes with superimposed acute episodes. The histopathologic process consists of chronic inflammation of the bronchi and peribronchiolar tissue, often with poorly defined granulomas and giant cells in the interstitium or alveoli. Fibrosis and emphysema may develop. The radiologic findings include diffuse ground-glass opacification, centrilobular ground-glass opacities, air trapping, fibrosis, lung cysts, and emphysema. The histologic and radiologic features in some cases may resemble those of usual interstitial pneumonia or nonspecific interstitial pneumonia. The diagnosis usually rests on a variable combination of findings from history, serology, radiography, lung biopsy, and bronchoalveolar lavage, which characteristically reveals a lymphocyte content of more than 30%, often with an increased CD4-to-CD8 ratio of T cells. Treatment includes avoiding the allergen, if possible, and, in severe cases, systemic corticosteroids. The long-term prognosis is usually good, but some patients develop severe respiratory insufficiency, and a few die of the disease.

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Abbreviations: BAL = bronchoalveolar lavage, IPF = idiopathic pulmonary fibrosis, NSIP = nonspecific interstitial pneumonia, UIP = usual interstitial pneumonia

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Introduction

In 1713, Bernardino Ramazzini (1633–1714), an Italian medical professor, described the health hazards associated with 52 occupations. About grain workers, he stated, “Almost all who make a living by sifting or measuring grain are short of breath and cachectic and rarely reach old age; in fact, they are very liable to lapse into orthopnea and finally dropsy” (*dropsy* being edema) (1). With that observation, Ramazzini provided the first account of what is now called hypersensitivity pneumonitis (or extrinsic allergic alveolitis), an inflammatory reaction caused by the repeated inhalation of particles small enough (less than 5 μm) to reach the lung parenchyma and evoke an immune response. As Ramazzini recognized, chronic exposure can lead to respiratory failure and cor pulmonale.

The first detailed clinical descriptions of hypersensitivity pneumonitis appeared in 1932, and with remarkable detail and insight, these reports delineated the major features of the disorder. The initial paper described an outbreak of illness the previous year in 10 employees of an upper Michigan company that made railroad ties (2). Their symptoms—which included dyspnea, coughing, night sweats, weight loss, and sputum production—began 2–3 months after they resumed work following a plant closure during the winter months. Their labor entailed stripping bark from maple logs or shoveling it, and about 30% of those working directly with it developed the disease. Chest radiographs disclosed increased peribronchial and perihilar opacities and, in severe cases, 3–5-mm, irregular, poorly defined nodules in the lower portions of both lungs. A similar disorder occurred in 36 (4.5%) of 800 employees at a nearby sawmill, which was operating only 2–3 days per week and where about 75% of the logs were maple. The symptoms abated during the laborers’ days off and recurred when they resumed work. In both locales, investigators noticed that lying beneath the bark was black dust, from which they isolated a fungus, now called *Cryptostroma corticale*. They hypothesized that the disease was an allergic reaction to its aerosolized spores.

In December 1932, 4 months after that first published description, J. Munro Campbell, a county health officer, reported an outbreak of respiratory disease among five agricultural workers in northern England (3). Tuberculosis was suspected, but Campbell believed the disease had a different cause. An unusually rainy summer in 1931 had forced farmers to store hay that was still damp, causing a substantial growth of mold. Later, work with the hay led to the dispersion of dense clouds of dust, and in the spring of 1932, after months of such exposure, the laborers developed progressive weight loss and dyspnea to the point of severe breathlessness, cyanosis, and seemingly imminent death. Once their contact with the hay ended, however, the symptoms slowly dissipated over several weeks. Chest radiographs initially disclosed a generalized fine granular stippling. As the patients improved clinically, the radiographic abnormalities generally resolved, except for apparent fibrosis that had developed in some cases. Twelve years later, a Yorkshire clinician, W. N. Pickles, recognized cases of a similar condition, which he referred to as farmer’s lung (4).

In the sections that follow, the clinical, pathologic, and radiologic aspects of hypersensitivity pneumonitis are described on the basis of a thorough review of the published English-language literature as well as chest radiographs and computed tomographic (CT) scans compiled by the authors over the past 30 years.

Etiology

Since these observations, publications have delineated numerous types of hypersensitivity pneumonitis, particularly from occupational exposures, but sometimes from hobbies, recreational activities, or contaminated air systems (Table 1). The reported culprits have included microbes, animal and plant proteins, and low-molecular-weight chemicals that combine with host proteins to form haptens.

The responsible microorganisms are bacteria, fungi, or protozoa, including amoebae contaminating water in ventilation systems. The most commonly implicated bacterial causes are thermophilic (heat-loving) actinomycetes, which are Gram-positive filamentous bacilli that flourish in

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Table 1
Examples of Hypersensitivity Pneumonitis

Disease	Antigen Source	Putative Antigen
Bird fancier's disease	Various birds	Protein in avian feces, feathers
Cheese worker's lung	Moldy cheese	<i>Penicillium</i> species
Coffee worker's lung	Coffee bean	Unknown
Farmer's lung	Moldy hay	Thermophilic actinomycetes
Furrier's lung	Animal fur	Protein in animal fur
Hot tub lung	Warm water	<i>Mycobacterium avium</i> complex
Humidifier lung	Warm water	Thermophilic actinomycetes
Japanese summer disease	Moldy houses	Various fungi
Machine worker's lung	Metal-cutting fluid	<i>Mycobacterium</i> species, Gram-negative bacilli
Malt worker's lung	Moldy malt	<i>Aspergillus</i> species
Mushroom worker's lung	Mushrooms	Mushroom spores, various other fungi
Peat moss worker's lung	Moldy peat moss	Various fungi
Sauna bather's lung	Sauna water	Various fungi
Sequoiosis	Moldy redwood dust	Various fungi
Suberosis	Cork	<i>Aspergillus</i> species, cork dust

warm (50°–60°C) and moist conditions like those produced by decaying vegetation. Most cases of farmer's lung develop from inhalation of thermophilic actinomycetes that proliferate in damp hay (5). These bacteria may also grow in the stagnant warm water present in forced-air heating, cooling, and humidification equipment, which disperses them into the ambient air. In confined spaces, such as office buildings, simultaneous and widespread illness can occur.

Colonization of heated water by *Mycobacterium avium* has led to hypersensitivity pneumonitis in hot tub users (6). *Mycobacterium* species also may contaminate the fluids used to cool and lubricate metalworking machinery, causing disease when they become aerosolized (7). In some cases involving metalworking fluids, Gram-negative bacilli, instead, may be the culprits, as they are in other settings: in a study of grain workers, for example, they were the most common allergens (8) and, indeed, may have been the source of disease in the cases described by Ramazzini in the 18th century.

Fungi that produce hypersensitivity pneumonitis include *Aspergillus* species, which are ubiquitous in nature and have provoked disease among corn (9) and malt (10) workers. The

fungus *Penicillium* has caused hypersensitivity pneumonitis in workers with repeated exposure to cheese (11), cork (12), and peat moss (13). *Candida* species on a mouthpiece apparently provoked hypersensitivity pneumonitis in a saxophone player (14). In some environments, the same clinical disease may result from different allergens. For example, mushroom worker's lung may be caused either by inhalation of thermophilic actinomycetes from compost or inhalation of mushroom spores (15). Furthermore, hypersensitivity pneumonitis may result from exposure to multiple agents present in the same environment, as is suggested by the simultaneous presence of antibodies to several organisms in some patients (16,17).

A type of hypersensitivity pneumonitis associated with animal exposure is bird fancier's lung, in which the major antigens are proteins in avian serum, feces, and feathers, including bloom, the waxy powder coating them (18). Pigeons and parakeets, including budgerigars (a type of parakeet), are the birds most commonly implicated,

but poultry, finches, doves, canaries, and other birds also have caused the disease. Exposure to live birds is not necessary to produce hypersensitivity pneumonitis: the illness has resulted from using feather pillows and duvets (19), being exposed to a wreath made from the feathers of a dead pet bird (20), and laundering a pigeon keeper's overalls (21). Other examples of animal proteins that are known to have caused the disease when inhaled include proteins from the dust of mollusk shells used to make buttons (22) and from animal fur used in garment manufacture (23). Plant proteins that have provoked hypersensitivity pneumonitis include proteins found in a jellylike Japanese food that contains flour from a tuberous root and a powder derived from a brown alga (24).

Some low-molecular-weight chemicals that by themselves are not antigenic may combine with the host's proteins to form haptens, which then may provoke hypersensitivity pneumonitis. For example, the agents implicated in chemical worker's lung are isocyanates found in such products as foam, glue, and spray paint (25).

Clinical Features

Inhalation of the etiologic agent may occur in the home, at work, or at places of recreation. In general, among those exposed to an allergen, approximately 5%–15% develop hypersensitivity pneumonitis (26). However, the frequency of disease may be much higher. In the original report of maple bark disease, for example, 30% of those working directly with the material were affected (2). The disease frequency probably relates to several issues, including the amount of allergen inhaled, the duration of exposure, the nature of the antigen, and host factors. Heredity may be important; some families seem to have a greater predisposition to illness than others (27). Tobacco use is also significant: Most patients (80%–95%) with hypersensitivity pneumonitis are nonsmokers, a substantially higher proportion than that in unaffected populations with similar antigen contact (26). In smokers, however, the disease is associated with higher mortality (28).

Although symptoms occasionally develop after just a few weeks of contact with the allergen (25), most cases of hypersensitivity pneumonitis occur following months or years of continuous or intermittent inhalation of the inciting agent. For example, the average duration of exposure before symptom onset is approximately 9 years among those with bird fancier's disease (18), 5 years among those with mushroom worker's lung (29), 11 years among those with mollusk shell hypersensitivity pneumonitis (22), and 2 years among those with hot tub lung (6).

Experts generally have divided symptomatic disease into acute, subacute, and chronic types, but often with unclear or conflicting definitions. The term *acute* usually refers to an episode of illness with an abrupt onset, but it sometimes indicates any type of hypersensitivity pneumonitis with symptoms lasting less than 1 month. Differentiation between *subacute* and *chronic* disease also is variable. Some have considered *chronic* to indicate irreversible lung damage in general (30) or fibrosis specifically (31), whereas others define both *subacute* and *chronic* as having an insidious onset, with *subacute* including superimposed acute episodes (32). In one scheme, several features are combined to differentiate the two: Subacute disease develops over weeks to 4 months and includes episodic flare-ups; chronic disease takes 4 months to years to develop and consists of fibrosis, emphysema, or both (33). This use of *subacute* defies its common meaning in medical discourse, in which it usually refers to a duration of a few days to a few weeks. Furthermore, the radiographic findings labeled *subacute* often are seen in patients who have had the disease for many years. No classification system seems entirely satisfactory, but one that avoids these inconsistencies and contradictions and provides a more accurate terminology for symptomatic disease is as follows: (a) acute (or episodic), with improvement between attacks; (b) insidious (gradual onset and progressive course) with superimposed acute episodes; and (c) insidious without acute attacks. Which pattern of illness occurs presumably depends upon the intensity and duration of contact, the nature of the antigen, and host factors, but not in a currently predictable manner.

In acute hypersensitivity pneumonitis, fever, chills, myalgia, headache, coughing, chest tightness, dyspnea, and leukocytosis in various combinations typically occur 4–12 hours after exposure.

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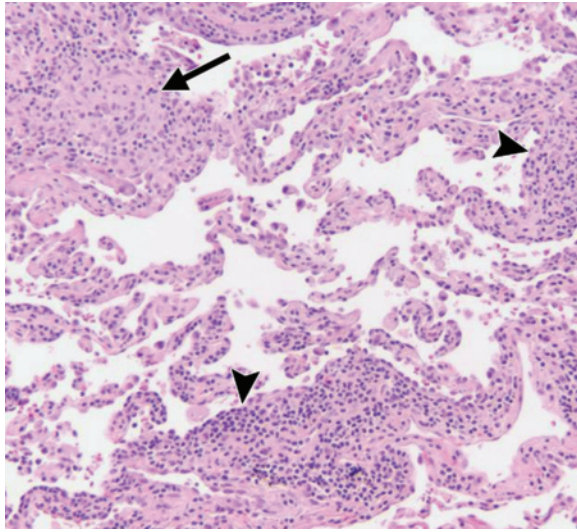


Figure 1. Photomicrograph shows the two most common and most characteristic histopathologic features of hypersensitivity pneumonitis: lymphocytic infiltrates within the interstitium, sometimes referred to as cellular interstitial pneumonitis (arrowheads), and a poorly formed granuloma (arrow). (Image courtesy of Rodney A. Schmidt, MD, Department of Pathology, University of Washington Medical Center, Seattle, Wash.)

These symptoms may begin after patients return to an environment from which they have been absent for a while (eg, resuming work following weekends or holidays) but sometimes do not develop with uninterrupted, daily contact with the same antigen. Attacks often follow exposure to the allergen within enclosed spaces with poor ventilation. In patients with farmer's lung, for example, symptoms typically occur after feeding livestock in barns during the winter. Sometimes respiratory symptoms in acute episodes are mild or absent and the illness is primarily a nonspecific febrile disorder. In fact, hypersensitivity pneumonitis can be a rare cause of episodic fever of unknown origin, defined as recurrent, unexplained bouts of pyrexia interrupted by afebrile periods with apparent disease remission of at least 2 weeks' duration (34). The fevers may be as high as 104°–106°F (40°–40.1°C) (35). The symptoms of an acute attack of hypersensitivity pneumonitis generally peak after 12–24 hours and resolve within 48 hours, but they may per-

sist for several days or even weeks, mimicking a pulmonary infection rather than a short-lived immunologic reaction to an inhaled allergen (36). Tachypnea, tachycardia, and bibasilar inspiratory crackles are typically present, and hypoxemia and respiratory failure may occur. White blood cell counts commonly reveal neutrophilic leukocytosis without eosinophilia, and the immunoglobulin E level is normal. Pulmonary function tests during episodes characteristically demonstrate a restrictive defect and diminished diffusing capacity, which usually resolve within 4–6 weeks in the absence of further exposure. A reversible airflow obstruction may occur alone or in combination with a restrictive defect in some patients.

With insidious patterns of disease, there is a gradual onset of exertional dyspnea, fatigue, coughing, sputum production, anorexia, and weight loss, which may be substantial. Bibasilar crackles are typically audible at lung examination, and finger clubbing may be present. Pulmonary function tests characteristically demonstrate restriction, often with decreased diffusing capacity. Airflow obstruction also may occur alone or in combination with restriction. Patients may experience discrete episodes of fever, dyspnea, and coughing within a few hours after exposure that typically resolve within 24 hours after inhalation of the allergen ceases. These episodes may become more severe and protracted over time.

Histopathologic Features

Most cases of hypersensitivity pneumonitis, whether acute or insidious, include the following four histologic features in variable amounts and combinations (26,37–40):

1. Cellular bronchiolitis, which is the presence of chronic inflammatory cells lining the small airways, sometimes with resultant epithelial ulceration.
2. Diffuse chronic interstitial inflammatory infiltrates, primarily consisting of lymphocytes and plasma cells but often including eosinophils, neutrophils, and mast cells.
3. Poorly circumscribed interstitial nonnecrotizing (noncaseating) granulomas consisting of lymphocytes, plasma cells, and epithelioid histiocytes, with or without giant cells (Fig 1). Both the interstitial mononuclear and the granulomatous inflammation tend to form around bronchioles, and obliterative bronchiolitis may occur. Scattered areas of organizing pneumonia with intraluminal bronchiolar polyps also are common.
4. Individual giant cells in the alveoli or interstitium. These cells may contain inclusions of en-

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ogenous metabolic products, such as cholesterol clefts, Schaumann bodies (blue, concentrically laminated, calcified particles), and lucent birefringent oxalate crystals.

Another feature frequently seen in the peribronchiolar alveoli is an accumulation of foamy macrophages. Occasionally, the source of the antigen is visible, such as hairs in a furrier's lung (23) or organisms in patients with maple bark disease or hot-tub lung whose pulmonary biopsy specimens may also grow the microbe on culture (6,41). The observation of granulomas in the spleen, liver, and mediastinal lymph nodes in several patients with farmer's lung indicates that extrapulmonary inflammatory reactions may occur, particularly early in the course of illness (in the first 3 months) (42,43).

In some patients with insidious-onset disease, emphysema is a prominent component. Fibrosis also may develop, generally in one of three patterns: irregular peribronchiolar fibrosis; resembling usual interstitial pneumonia (UIP), the histologic pattern of idiopathic pulmonary fibrosis (IPF)—subpleural patchy fibrosis obliterating the underlying structure and distorting the architecture, with few accompanying inflammatory cells; or resembling fibrotic nonspecific interstitial pneumonia (NSIP)—homogeneous fibrosis without architectural distortion (44). In patients in whom the pattern of fibrosis is consistent with UIP or NSIP, the presence of Schaumann bodies, giant cells, granulomas, areas of interstitial granulomatous inflammation, or peribronchiolar fibrosis should suggest the diagnosis of hypersensitivity pneumonitis.

NSIP may occur in a cellular form in which temporally homogeneous interstitial inflammation with lymphocytes and plasma cells is present, often with a peribronchiolar distribution. In some patients with hypersensitivity pneumonitis, this pattern may be seen alone or with fibrosis, and these cases can be difficult to distinguish from NSIP that is idiopathic or due to other causes (eg, rheumatologic disorders), except with a clinical evaluation that includes a careful history (45,46).



Figure 2. Hypersensitivity pneumonitis. Anteroposterior radiograph demonstrates patchy airspace disease and multiple ill-defined lung nodules with minimal upper lung volume loss.

Imaging Features

Chest radiographs obtained in many patients with hypersensitivity pneumonitis are normal (47). Abnormal radiographic findings observed in some patients include numerous poorly defined small (less than 5-mm) opacities throughout both lungs, sometimes with sparing of the apices and bases. Airspace disease is represented often as ground-glass opacity (which can be patchy or diffuse, resembling pulmonary edema) or, more rarely, as consolidation (Fig 2) (48). A pattern of fine reticulation also may occur. The zonal distribution varies from patient to patient and may vary over time in the same patient (49). When fibrosis develops, chest radiographs show a reticular pattern and honeycombing, which sometimes are more severe in the upper lobes than in the lower ones. Volume loss may occur, particularly in the upper lungs, and peribronchial thickening may be visible (47). Cardiomegaly may develop as a result of cor pulmonale (47).

High-resolution CT has greatly improved the radiologic diagnosis of hypersensitivity pneumonitis: abnormalities are seen in more than 90% of patients (50). Several features may appear at any stage of the disease. One is homogeneous ground-glass opacity, which is usually bilateral and symmetric but sometimes patchy and concentrated in the middle part and base of the lungs (51) or

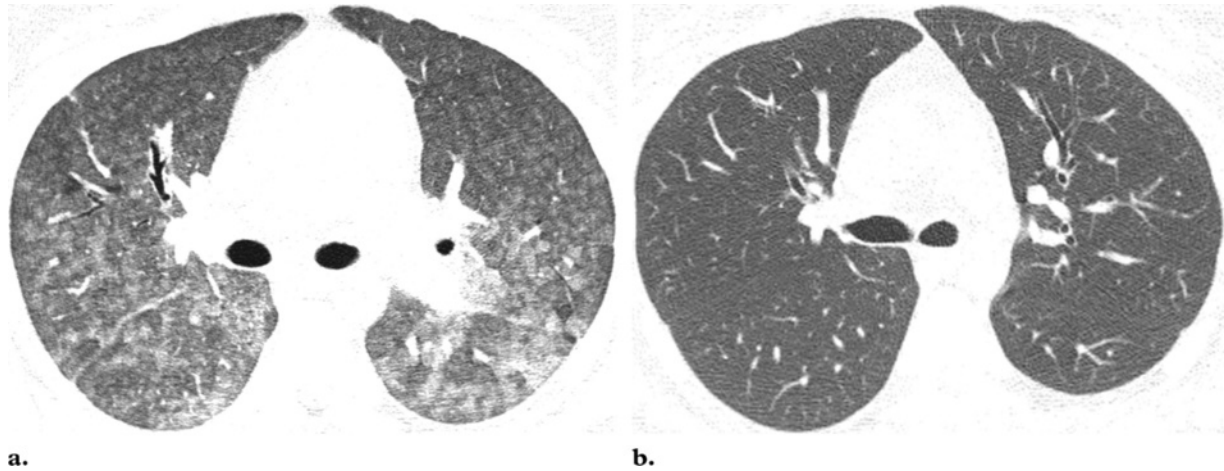


Figure 3. Insidious hypersensitivity pneumonitis in a 39-year-old woman with a history of exposure to parakeets and cockatiels. (a) Axial high-resolution CT image demonstrates extensive ground-glass opacity with a centrilobular concentration. (b) Axial CT image obtained after therapy and removal from exposure shows complete resolution.

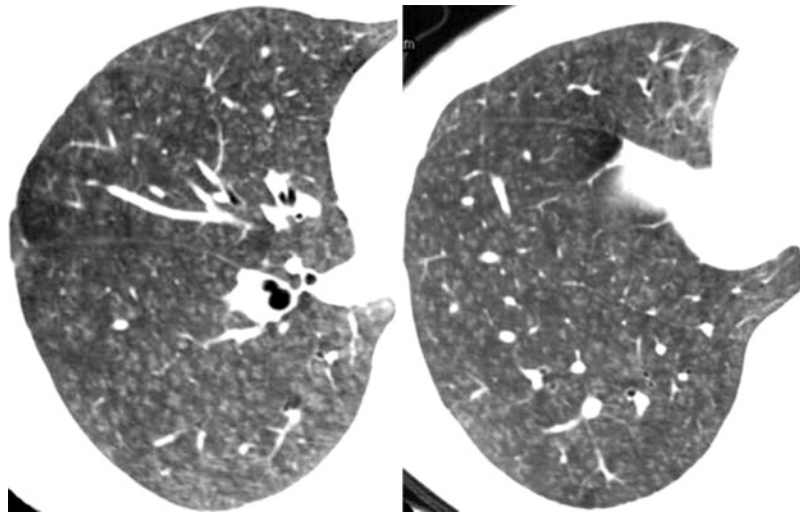


Figure 4. Insidious hypersensitivity pneumonitis. Axial high-resolution CT images depict ill-defined centrilobular ground-glass opacities. (Case courtesy of Cris Meyer, MD, Madigan Army Medical Center, Fort Lewis, Wash.)

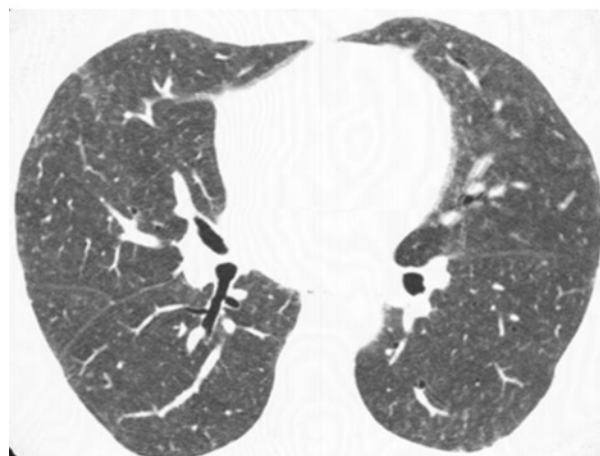
in a bronchovascular distribution. Ground-glass opacity usually represents chronic interstitial inflammation but occasionally may be caused by fine fibrosis or organizing pneumonia. Another characteristic feature is numerous round centrilobular opacities, usually less than 5 mm in diameter (Figs 3–5). Occasionally these opacities have well-defined borders and soft-tissue attenuation, as the term *nodule* usually connotes; however, they more often have indistinct borders and ground-glass attenuation, and, instead of being solid, they contain a small central lucency caused by air in a patent bronchiole (Fig 6). Although some have described these lesions as nodules, we prefer to

reserve the latter term to denote well-defined solid lesions and, instead, use the phrase *centrilobular ground-glass opacities* to describe these characteristic findings of hypersensitivity pneumonitis. These abnormalities probably represent cellular bronchiolitis, peribronchiolar interstitial inflammation, or, less frequently, focal organizing pneumonia (52). Respiratory bronchiolitis–interstitial lung disease is a smoking-related lung disease that has similar imaging features. Another finding is hypoattenuation and hypovascularity of scattered secondary lobules (Fig 7). Hypoattenuating regions that

Figure 5. Hypersensitivity pneumonitis attributed to use of a down pillow. **(a)** Anteroposterior radiograph shows subtle ground-glass opacity in the mid and lower portions of both lungs. **(b)** Axial high-resolution CT images show ill-defined centrilobular opacities, ground-glass opacities, and early reticulation.



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b.

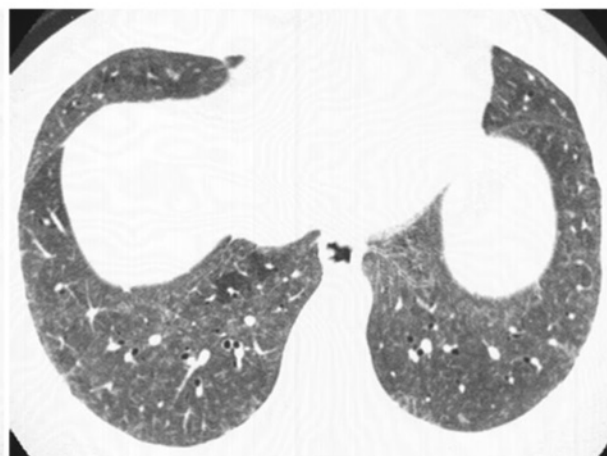
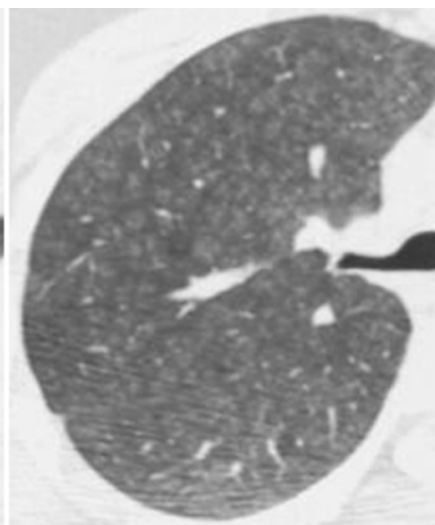
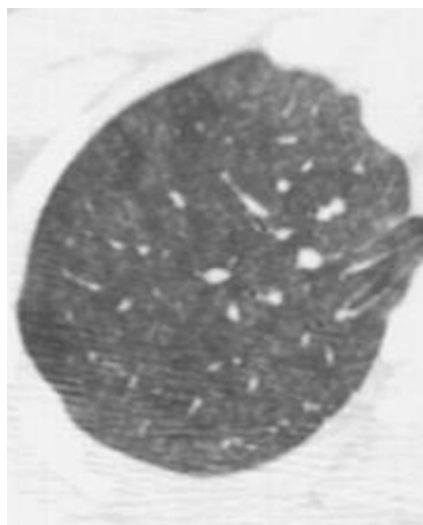


Figure 6. Hypersensitivity pneumonitis from residential exposure to mold. Axial high-resolution CT images of the right lung demonstrate centrilobular ground-glass opacities in a uniform distribution. (Case courtesy of Matthew Gilman, MD, Madigan Army Medical Center, Fort Lewis, Wash.)

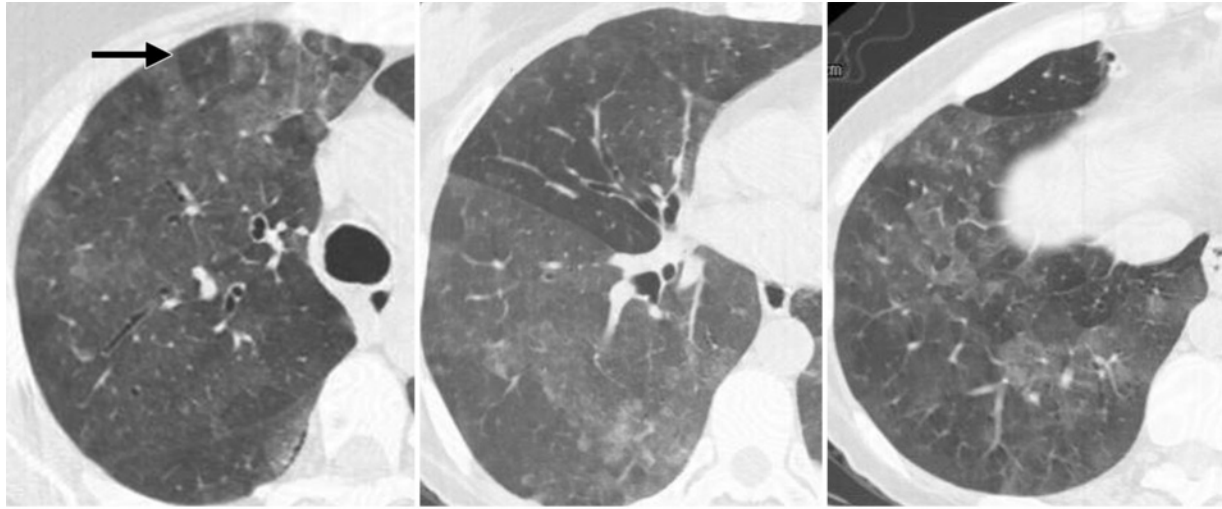


persist on expiratory CT scans are indicative of air trapping, which is caused by bronchiolar inflammation and obstruction. Air trapping is also reflected in pulmonary function tests as an

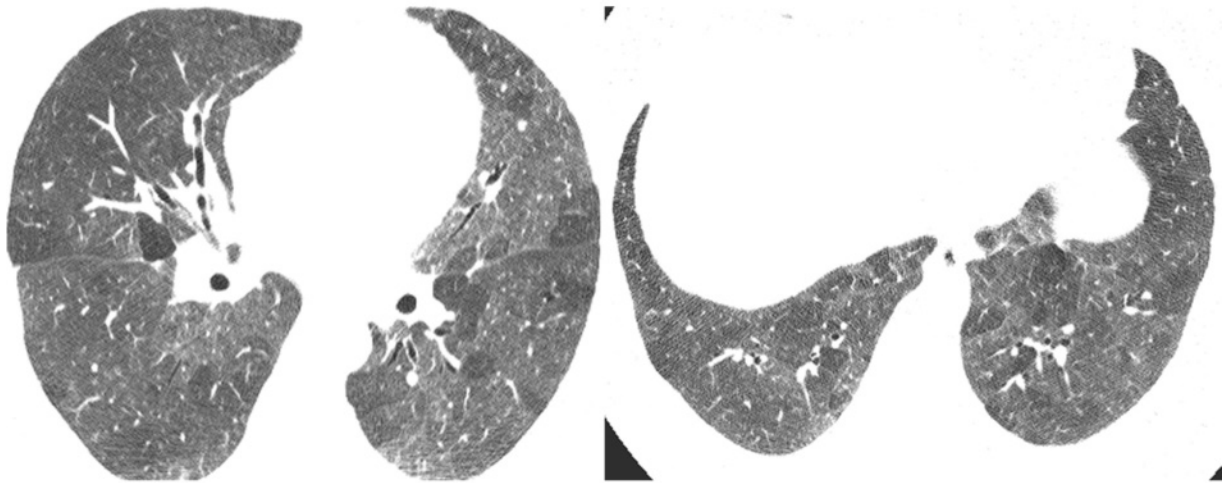
increased ratio of the residual volume to the total lung capacity (53).

Thus, the typical high-resolution CT abnormalities in hypersensitivity pneumonitis of acute onset and insidious onset without fibrosis include ground-glass opacity, air trapping, and centrilobular ground-glass opacities (Figs 7–10).

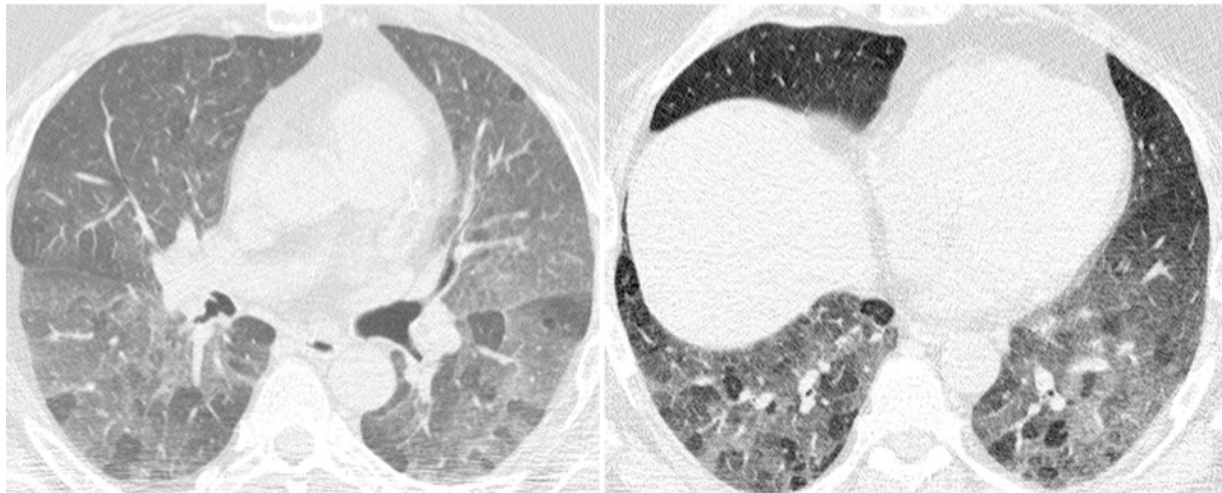
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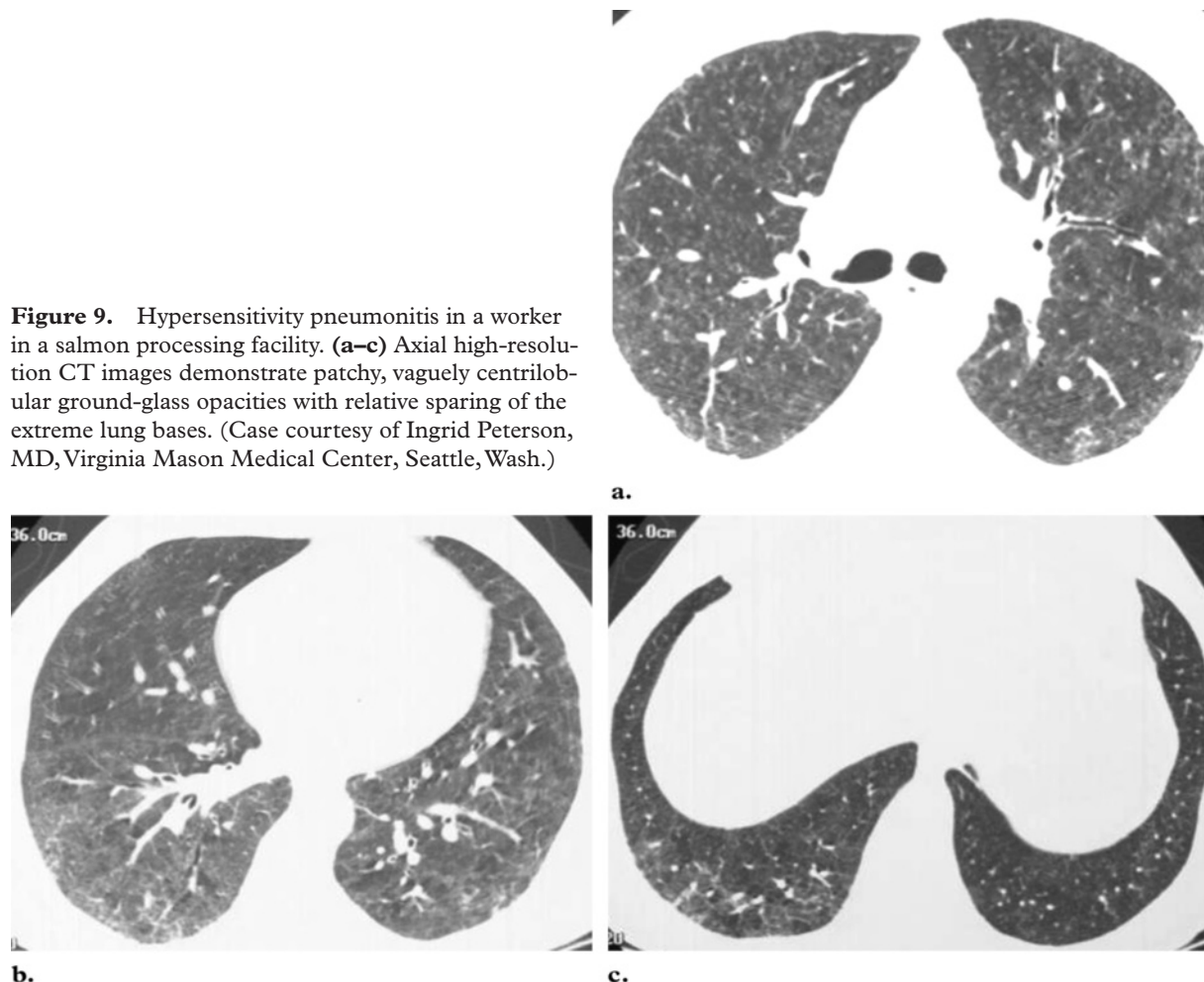
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8b.

Figures 7, 8. (7) Bird fancier's disease. Axial high-resolution CT images show multifocal ground-glass opacities in the right lung. Spared lobules (arrow) probably represent air trapping, but expiratory high-resolution CT images were not available for confirmation. (8) Insidious onset of hypersensitivity pneumonitis in a 63-year-old man with repeated exposure to birds and mold. The results of serum testing were positive for mold precipitins, and lymphocyte predominance was found in bronchoalveolar lavage (BAL) fluid. Axial high-resolution inspiratory (a) and expiratory (b) CT images demonstrate patchy ground-glass opacities, normal regions, and air trapping. This combination of findings, known as the headcheese sign, is indicative of hypersensitivity pneumonitis. The accentuation of the attenuation difference between lobules with low or normal attenuation and those with high attenuation on expiratory images helps confirm the presence of air trapping.

Figure 9. Hypersensitivity pneumonitis in a worker in a salmon processing facility. (a–c) Axial high-resolution CT images demonstrate patchy, vaguely centrilobular ground-glass opacities with relative sparing of the extreme lung bases. (Case courtesy of Ingrid Peterson, MD, Virginia Mason Medical Center, Seattle, Wash.)



The combination of patchy ground-glass opacities, normal regions, and air trapping at CT is often referred to as the headcheese sign (54) (Fig 8). Bronchiolar wall thickening also may occur. Lung cysts have been found occasionally (55) and probably are caused by partial obstruction of bronchioles. Occasionally in patients with an insidious onset of disease, focal consolidation is present, presumably representing organizing

pneumonia or a superimposed unrelated process such as aspiration pneumonia or infectious pneumonia. Mediastinal lymph node enlargement (generally 10–20 mm in short-axis diameter) was found in approximately 30% of patients with farmer's lung in one series (51). Pulmonary arteries are occasionally enlarged, presumably reflecting pulmonary arterial hypertension (50). In some patients, particularly those with farmer's lung or bird fancier's disease, widespread centrilobular emphysema develops, even in those who are lifelong nonsmokers (50,51).

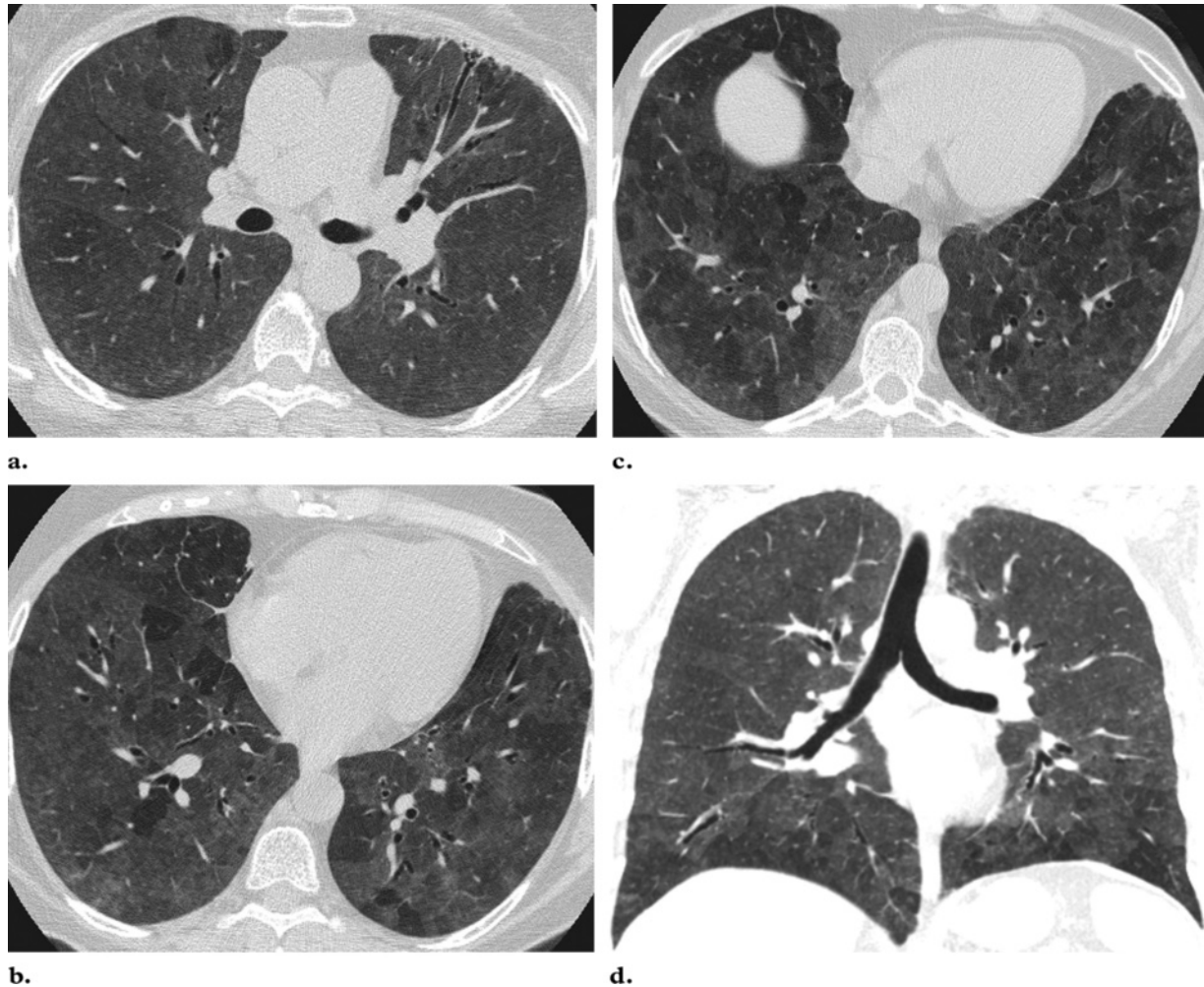
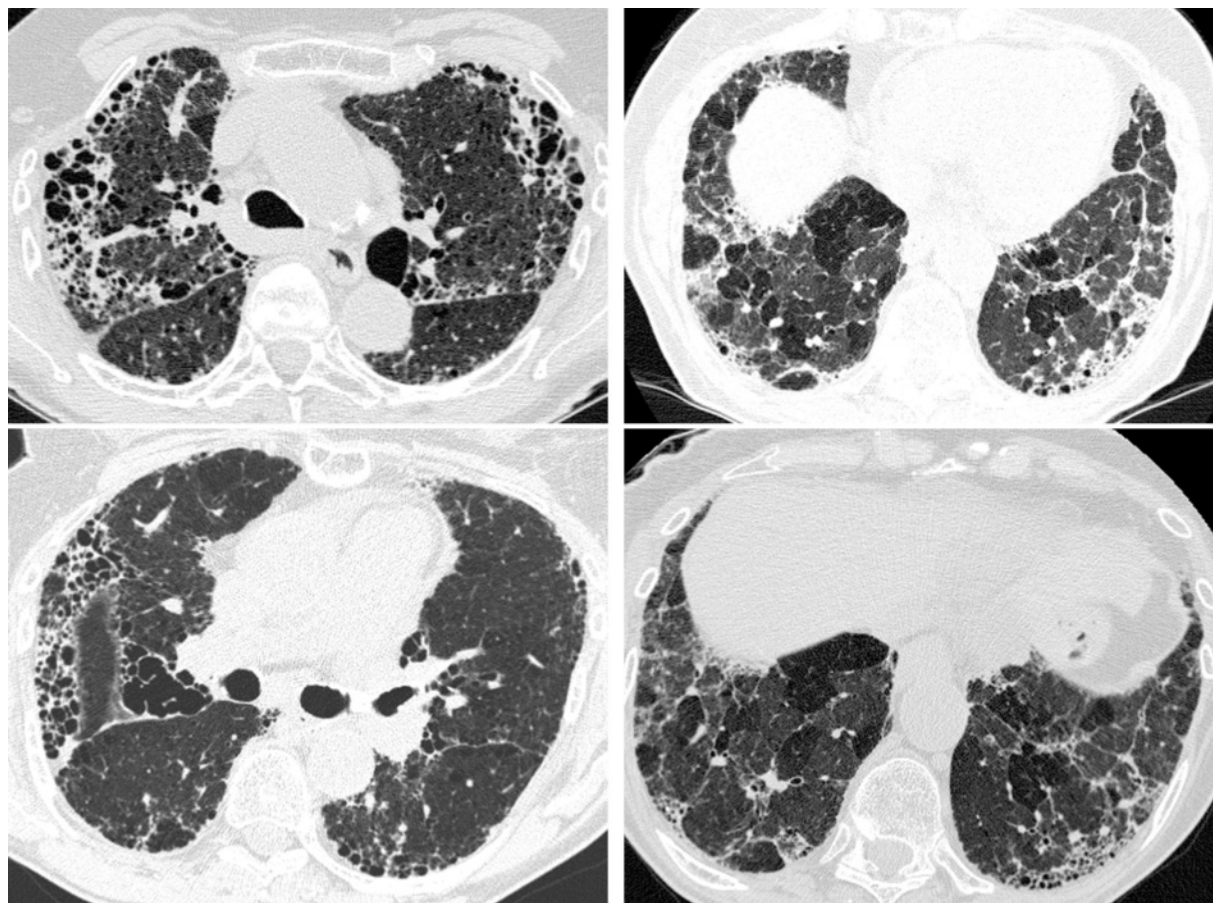


Figure 10. Insidious hypersensitivity pneumonitis in a 61-year-old woman with a history of exposure to cockatiels (*Nymphicus hollandicus*). Axial high-resolution (**a–c**) and coronal reformatted (**d**) CT images demonstrate ground-glass opacities with a somewhat centrilobular concentration in the upper part of the lungs, with combined ground-glass opacities and air trapping in the lower part. The distribution of these findings is best appreciated in **d**.

When fibrosis develops, high-resolution CT usually demonstrates reticulation, mainly in the middle portion of the lungs or fairly evenly throughout the lungs but with relative sparing of the extreme apices and bases (Fig 11) (56). Other findings include traction bronchiectasis

and bronchiolectasis (57). Honeycombing may occur, usually with a subpleural and middle-lung distribution but sometimes in the bases, resembling that in patients with IPF (58).

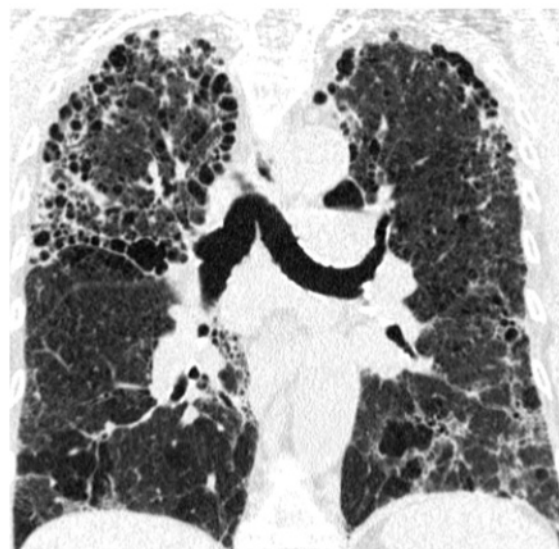


a.

b.

Figure 11. Insidious hypersensitivity pneumonitis with fibrosis. (a) Axial high-resolution CT images of the upper part of the lungs show predominant reticulation with honeycombing, traction bronchiectasis, and architectural distortion. (b) Axial high-resolution CT images of the lower part of the lungs demonstrate ground-glass opacity, reticulation, and lobular air trapping. (c) Coronal reformatting CT image allows a better evaluation of the distribution of these abnormalities.

In some patients with fibrosis, generalized or centrilobular ground-glass opacities are seen. These are suggestive of active inflammation. Air trapping also may be present. When combined with fine reticulation and traction bronchiectasis, these findings may resemble those of NSIP (Fig 12). When fibrotic hypersensitivity pneumonitis is compared with IPF or NSIP, the CT features favoring a diagnosis of hypersensitivity pneumonitis are lobular air trapping, centrilobular ground-glass opacities, and absence of lower lobe predominance (Figs 11, 13) (58). Upper lung predominance of fibrosis (most extensive above the level of the tracheal carina) sometimes



c.

occurs in hypersensitivity pneumonitis, but it is uncommon in IPF and NSIP. The features suggestive of NSIP are relative subpleural sparing, absence of air trapping, and absence of honeycombing. Table 2 outlines the diagnostic imaging features of hypersensitivity pneumonitis.

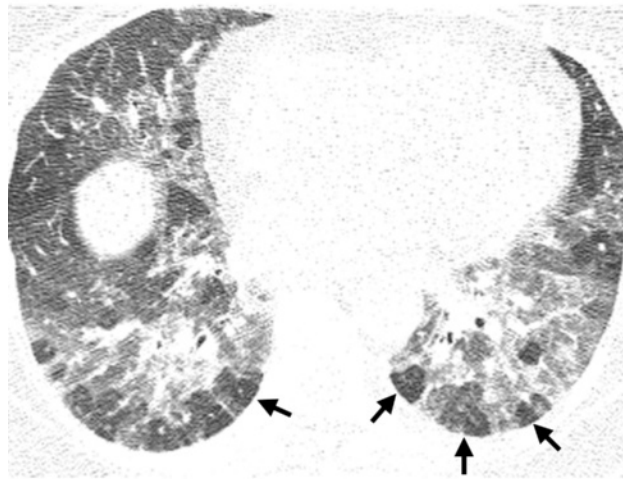
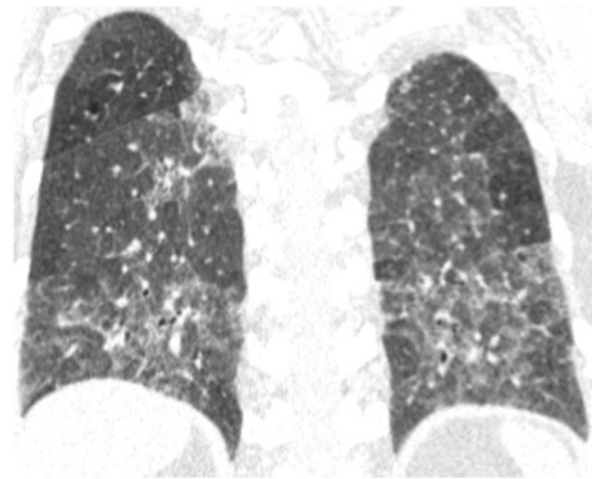
**a.****b.****c.**

Figure 12. Hypersensitivity pneumonitis with imaging features similar to those of NSIP. (**a, b**) Axial CT images of the lower part of the lungs (**a** obtained during inspiration; **b**, during expiration) demonstrate mild reticulation with ground-glass opacity and air trapping (arrows in **b**). (**c**) Coronal reformatted CT image better demonstrates the distribution of these abnormalities.

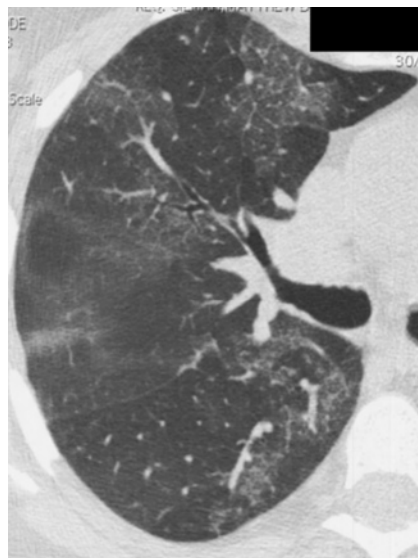
**a.****b.**

Figure 13. Progression of insidious hypersensitivity pneumonitis to fibrosis. (**a**) Axial high-resolution CT image of the right lung at the takeoff of the right middle lobe bronchus shows patchy ground-glass opacity. (**b**) Axial high-resolution CT image obtained at a similar level 3 years later demonstrates a predominantly reticular abnormality with associated traction bronchiectasis, findings suggestive of fibrosis.

Table 2
Imaging-based Diagnosis of Hypersensitivity Pneumonitis

Type of Disease	Diagnostic Imaging Features
Acute or insidious onset without fibrosis*	Diffuse GGO, centrilobular GGO, air trapping, headcheese sign
Insidious onset with fibrosis	Reticulation, peribronchovascular interstitial thickening, architectural distortion, honeycombing, air trapping, sparing of extreme basal lung, ill-defined centrilobular GGO†

Note.—GGO = ground-glass opacities.

*Diseases that may have features similar to those of acute and insidious-onset hypersensitivity pneumonitis without fibrosis include respiratory bronchiolitis–interstitial lung disease, NSIP, desquamative interstitial pneumonitis, infectious bronchiolitis, acute eosinophilic pneumonia, viral infection, and *Pneumocystis jiroveci* infection.

†This finding is rare and may be seen also in chronic interstitial pneumonias, IPF, NSIP, and sarcoidosis.

Diagnosis

Most patients with hypersensitivity pneumonitis have precipitating antibodies to the offending agent in their serum—usually immunoglobulin G, but sometimes immunoglobulin M or A—but these are often present in exposed asymptomatic people as well, limiting their diagnostic value (59). Furthermore, the antigen preparations used in testing are not highly standardized. Therefore, the absence of these antibodies does not exclude hypersensitivity pneumonitis.

Another diagnostic approach is an antigen challenge, in which the patient inhales the putative allergen through a nebulizer or is placed in an environment, such as the workplace, where the agent is present. The criteria defining a positive response vary among studies but generally include the appearance of respiratory or systemic findings, especially fever, 4–10 hours after exposure; leukocytosis; diminished diffusing capacity, diminished vital capacity, or both; increased radiographic abnormalities; worsening alveolar-arterial oxygen pressure difference; and elevation of C-reactive protein levels (60,61). Unfortunately, no standardized antigen preparations for such testing exist.

In BAL, a widely performed diagnostic procedure, saline solution is injected into a lung subsegment during fiberoptic bronchoscopy. The

fluid is then retrieved and examined at microscopy. Normally, about 90% of the cells recovered in the BAL fluid are alveolar macrophages, 10% are lymphocytes, less than 3% are neutrophils, and less than 1% are eosinophils (62). In one study of 10 patients with bird fancier's disease, BAL samples obtained 24 hours after inhalation exposure to the responsible antigen demonstrated a significant increase in white cells, primarily neutrophils, in comparison with the baseline level (63). The leukocytosis persisted at repeat BAL performed 1 week later, but lymphocytes were predominant. **This latter finding is the most common BAL feature in hypersensitivity pneumonitis: The white blood cell count is increased, with lymphocytes accounting for at least 20%–30% of white blood cells, but commonly more than 50%.** Most of these are T cells, and a frequent but highly variable finding is a ratio of CD4 to CD8 lymphocyte subsets that is less than 1 (the normal ratio is 1.8). This feature is particularly helpful in distinguishing hypersensitivity pneumonitis from sarcoidosis, in which the CD4-to-CD8 ratio is usually elevated, often to more than 3.5. Several diseases can cause BAL lymphocytosis (62)—including sarcoidosis, infections, rheumatologic disorders, inflammatory bowel disease, radiation pneumonitis, drug-induced pulmonary reactions, cryptogenic organizing pneumonia, and NSIP—but in the appropriate clinical setting

Teaching Point

this finding is strongly suggestive of hypersensitivity pneumonitis. Indeed, in one scheme, the diagnosis of hypersensitivity pneumonitis relies on the characteristic features of bilateral ground-glass opacities or poorly defined centrilobular nodular opacities on high-resolution chest CT images and lymphocytosis in BAL fluid ($\geq 30\%$ lymphocytes in nonsmokers, $\geq 20\%$ in smokers), with a supplemental role played by typical histologic findings at lung biopsy in confusing or ambiguous cases (64). The numbers of mast cells and plasma cells also are elevated at BAL in patients with hypersensitivity pneumonitis (62).

Asymptomatic people exposed to agents that can cause hypersensitivity pneumonitis may have abnormal BAL findings, sometimes in the absence of serum precipitins, suggesting that mild pulmonary inflammation is present even in clinically normal subjects. In one study of 43 asymptomatic dairy farmers, a lymphocyte content of more than 20% was found in BAL fluid from more than one-half of the study subjects (65). Lymphocytosis also was seen in BAL fluid from patients with a history of hypersensitivity pneumonitis but with no recent acute episodes, including some who had no recognized exposure to the antigen for years (66).

In a series of 400 patients (116 with hypersensitivity pneumonitis and 284 control patients, primarily with another interstitial lung disease), significant clinical predictors of the diagnosis of hypersensitivity pneumonitis were exposure to a known etiologic agent, serum precipitating antibody to the putative antigen, recurrent symptomatic episodes, inspiratory crackles at lung auscultation, symptom onset within 4–8 hours after exposure, and weight loss (64). In the same study, the diagnostic criteria for hypersensitivity pneumonitis were lymphocytosis at BAL ($\geq 30\%$ lymphocytes in nonsmokers, $\geq 20\%$ in smokers) and high-resolution CT findings of bilateral ground-glass opacification or poorly defined centrilobular nodular opacities.

The distribution of causes of hypersensitivity pneumonitis depends on the patient population and locale. In Mexico City, for example, the most common disorder is bird fancier's disease (67), usually caused by pigeons kept as pets and allowed to roam freely throughout the house,

whereas in Japan it is "summer-type" hypersensitivity pneumonitis arising from the inhalation of seasonal molds that contaminate homes during the hot, humid summers (68). Among 85 patients at the Mayo Clinic, the most frequent causes of hypersensitivity pneumonitis were bird exposure, hot tub lung, and farmer's lung (69). In a substantial number of cases, the provoking allergen is not apparent, despite a thorough evaluation. In the Mayo Clinic series, for example, the cause was unidentified in 25% of patients (69).

Treatment and Prognosis

The most important recommended therapy is curtailing exposure to the causal agent by eliminating it from the environment, avoiding settings where it is present, or using a respirator in those settings. Systemic corticosteroids at doses equivalent to 40–60 mg of prednisone daily for a few days to weeks may improve symptoms of all forms of the disease (70), although substantial fibrosis and emphysema are less likely to respond. Indications for the use of such drugs include acute, severe, or progressive disease. The effectiveness of corticosteroid therapy lasting 12 weeks is not evidently superior to that of 4 weeks' duration (71), and corticosteroid therapy apparently confers no long-term benefits (70,71).

Most of the information about prognosis derives from studies of farmer's lung or bird fancier's disease, but whether these observations apply to other causes is uncertain. It appears, however, that patients with hypersensitivity pneumonitis generally improve. About 50% with farmer's lung are left with chronic lung impairment, usually just mild airflow obstruction; only occasionally are the abnormalities severe (72,73). Even most patients with continuing exposure to the putative antigen—at least, those with farmer's lung—improve, and the outcome for them is equivalent to that for patients with no further exposure (71,72), although high-resolution CT abnormalities resolve more frequently and more completely in the latter (50). The minimal risk with continued exposure is important because abandoning farming and finding further employment or obtaining education and training for a new vocation may be financially and emotionally arduous.

The information about prognosis in bird fancier's lung is disparate, with most patients improving or remaining stable (74). However, in a series of patients from Mexico City, the 5-year survival was only about 70%, with the risk of death most strongly related to the presence of fibrosis and honeycombing at lung biopsy (67). Other studies have shown that a finding of fibrosis at lung biopsy (75) or high-resolution CT (76) in patients with hypersensitivity pneumonitis portends a worse prognosis. The risk of mortality also increases with evidence of more severe respiratory impairment as indicated by oxygen desaturation ($\leq 88\%$) at the end of exercise and pulmonary function tests demonstrating worse restrictive defects and diminished diffusing capacity (76,77). Thus, a few patients die of the disease, sometimes with cor pulmonale, as Ramazzini first observed in 1713.

Summary

Hypersensitivity pneumonitis occurs from repetitive inhalation of certain microbes, plant or animal proteins, or low-molecular-weight chemicals that combine with host proteins to form haptens. Symptomatic disease usually develops only after years of exposure and may be acute or episodic, with symptoms including fever and dyspnea, or insidious, with a gradual onset of dyspnea, coughing, anorexia, and weight loss. Some patients with an insidious onset experience repeated acute episodes.

The major histologic findings are cellular bronchiolitis, interstitial chronic inflammation (typically in a peribronchiolar pattern), poorly defined granulomas, and isolated giant cells in the alveoli or interstitium. The radiographic appearance of the lungs is often abnormal, but high-resolution CT is more sensitive in depicting ground-glass opacification, poorly defined centrilobular ground-glass opacities, and air trapping. Fibrosis, honeycombing, and emphysema also may be seen. The histologic and radiographic findings may mimic those of UIP or NSIP. The CT findings that are most suggestive of hypersensitivity pneumonitis in such cases are centrilobular opacities and air trapping. Fluid from BAL usually demonstrates an increased number of white cells,

at least 20%–30% of which are lymphocytes. That finding, when accompanied by characteristic CT features, strongly suggests a diagnosis of hypersensitivity pneumonitis. Treatment includes avoidance of the antigen, and, in those with severe symptoms, a short-term regimen of systemic corticosteroid therapy. Over time, symptoms generally improve, even in patients with continued exposure to the allergen; in a few, symptoms progress to severe respiratory impairment.

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Hypersensitivity Pneumonitis: A Historical, Clinical, and Radiologic Review

Hirschmann et al

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Publications have delineated numerous types of hypersensitivity pneumonitis, particularly from occupational exposures, but sometimes from hobbies, recreational activities, or contaminated air systems. The reported culprits have included microbes, animal and plant proteins, and low-molecular-weight chemicals that combine with host proteins to form haptens.

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Although symptoms occasionally develop after just a few weeks of contact with the allergen, most cases of hypersensitivity pneumonitis occur following months or years of continuous or intermittent inhalation of the inciting agent. For example, the average duration of exposure before symptom onset is approximately 9 years among those with bird fancier's disease, 5 years among those with mushroom worker's lung, 11 years among those with mollusk shell hypersensitivity pneumonitis, and 2 years among those with hot tub lung.

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Most cases of hypersensitivity pneumonitis, whether acute or insidious, include the following four histologic features in variable amounts and combinations: (1) cellular bronchiolitis, which is the presence of chronic inflammatory cells lining the small airways, sometimes with resultant epithelial ulceration; (2) diffuse chronic interstitial inflammatory infiltrates, primarily consisting of lymphocytes and plasma cells but often including eosinophils, neutrophils, and mast cells; (3) poorly circumscribed interstitial nonnecrotizing (noncaseating) granulomas consisting of lymphocytes, plasma cells, and epithelioid histiocytes, with or without giant cells; and (4) individual giant cells in the alveoli or interstitium.

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The typical high-resolution CT abnormalities in hypersensitivity pneumonitis of acute onset and insidious onset without fibrosis include ground-glass opacity, air trapping, and centrilobular ground-glass opacities.

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This finding is the most common bronchoalveolar lavage feature in hypersensitivity pneumonitis: The white blood cell count is increased, with lymphocytes accounting for at least 20%–30% of white blood cells, but commonly more than 50%.