Hypersensitivity Pneumonitis: Spectrum of High-Resolution CT and Pathologic Findings

C. Isabela S. Silva[1]
Andrew Churg[2]
Nestor L. Müller[1]

Silva CIS, Churg A, Müller NL

OBJECTIVE. The purpose of this article is to illustrate the spectrum of pathologic and high-resolution CT features of hypersensitivity pneumonitis (HP).

CONCLUSION. High-resolution CT plays an important role in the diagnosis of HP. A confident diagnosis of subacute HP is based on the presence of ground-glass opacities, poorly defined centrilobular nodules, and mosaic attenuation on inspiratory images and of air trapping on expiratory CT images. Chronic HP is characterized on high-resolution CT by the presence of reticulation due to fibrosis superimposed on findings of subacute HP. Histologically, subacute HP is characterized by the presence of cellular bronchiolitis, noncaseating granulomas, and bronchiolocentric lymphocytic interstitial pneumonitis. Areas of organizing pneumonia also may be seen. The high-resolution CT and pathologic features of chronic HP frequently overlap with those of nonspecific interstitial pneumonia and usual interstitial pneumonia. Awareness of the various manifestations of HP is important for early diagnosis and management.

Keywords: high-resolution CT, hypersensitivity pneumonitis, interstitial lung disease, lung, lung disease

DOI:10.2214/AJR.05.1826

Received October 18, 2005; accepted after revision December 7, 2005.

[1]Department of Radiology, Vancouver General Hospital, University of British Columbia, 899 W 12th Ave., Vancouver, BC, Canada V5Z 1M9. Address correspondence to C. I. S. Silva (isabela.silva@vch.ca).

[2]Department of Pathology, Vancouver General Hospital, University of British Columbia, Vancouver, BC, Canada V5Z 1M9.

AJR 2007; 188:334–344

0361–803X/07/1882–334

Hypersensitivity pneumonitis (HP) is a diffuse granulomatous interstitial lung disease caused by inhalation of various antigenic organic particles [1]. HP is often difficult to diagnose because the clinical manifestations are nonspecific and the radiologic and histologic patterns can mimic those of other interstitial and small airway diseases [2]. HP traditionally has been classified as manifesting in three phases: acute, subacute, and chronic. Although this classification is helpful, patients often present with both subacute and chronic findings [1, 3]. Acute HP is characterized by abrupt onset of symptoms within a few hours after heavy antigen exposure in a previously sensitized patient. Subacute HP is caused by intermittent or continuous exposure to low doses of antigen. Chronic HP results from very low-level persistent or recurrent exposure to antigen and is differentiated from subacute HP by the presence of fibrosis [1, 3].

A high index of suspicion and meticulous acquisition of an environmental and occupational history are essential in making the diagnosis. In as many as 40% of histologically proven cases of HP, however, the offending agent is not identified [4, 5]. High-resolution CT plays an important role in the diagnosis of HP and frequently shows characteristic findings in patients with normal chest radiographic findings [4]. Early recognition of the disease and prevention of long-term antigen exposure are necessary to avoid progression to irreversible fibrosis [5]. The aim of this pictorial essay is to illustrate the spectrum of high-resolution CT and pathologic findings of HP.

Histologic Findings

Acute HP is characterized histologically by the presence of neutrophilic infiltration of the respiratory bronchioles and alveoli. A pattern of diffuse alveolar damage and temporally uniform, nonspecific, chronic interstitial pneumonitis may also be seen [1, 3]. Subacute HP is characterized histologically by the presence of cellular bronchiolitis, noncaseating granulomas, and bronchiolocentric interstitial pneumonitis with a predominance of lymphocytes (Fig. 1). Areas of organizing pneumonia (bronchiolitis obliterans with organizing pneumonia) may be identified [6]. These findings, however, are not present in all cases. Furthermore, in some patients the predominant histologic pattern is nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP). Ohtani et al. [6] analyzed the histologic and clinical characteristics of chronic bird fancier's lung in 26 patients. The NSIP pattern was found in 13 patients, eight of them having fibrotic NSIP-like lesions; the UIP–like pattern in 11 patients; and organizing pneumonia

(bronchiolitis obliterans with organizing pneumonia reaction) in two patients.

In the presence of a history of exposure and consistent clinical and radiologic findings, the diagnosis of HP can be confirmed by visualization of increased numbers of lymphocytes in bronchoalveolar lavage fluid and occasionally by findings at transbronchial biopsy. Surgical biopsy, however, is often needed for the definitive diagnosis of both subacute and chronic HP and for reliable differentiation of chronic HP from idiopathic interstitial pneumonia [3, 4].

High-Resolution CT Findings

The radiologic manifestations of acute HP are those of acute pulmonary edema. Because of the characteristic clinical manifestations and the rapid resolution of the symptoms, high-resolution CT is seldom performed in the evaluation of these patients [1, 7]. The characteristic high-resolution CT manifestations of subacute HP consist of patchy or diffuse bilateral ground-glass opacities, poorly defined small centrilobular nodules, and lobular areas of decreased attenuation and vascularity on inspiratory images and of air trapping on expiratory images (Figs. 2 and 3). The ground-glass opacities primarily reflect the presence of diffuse lymphocytic interstitial pneumonitis; minor degrees of organizing pneumonia, when present, also can contribute to this appearance (Fig. 4). The poorly defined centrilobular nodules may be caused by cellular bronchiolitis, the predominantly peribronchiolar distribution of interstitial pneumonitis (Fig. 1), or focal areas of organizing pneumonia (Fig. 5). The lobular areas of decreased attenuation and air trapping are presumably caused by small-airway obstruction by cellular bronchiolitis or, less commonly, by constrictive bronchiolitis [3, 7].

Chronic HP is characterized on high-resolution CT by the presence of reticulation and traction bronchiectasis and bronchiolectasis due to fibrosis superimposed on findings of acute or subacute HP [7] (Fig. 6). The reticulation in chronic HP can be patchy or random or have a predominantly subpleural and peribronchovascular distribution but typically tends to spare the lung bases [7, 8]. In a small percentage of cases, chronic HP results in subpleural honeycombing [3, 7] (Fig. 7).

Spectrum of High-Resolution CT Findings

Normal High-Resolution CT Findings

In a study by Lacasse et al. [4], 16 (8%) of 199 patients with proven HP underwent high-resolution CT with images acquired at 10-mm intervals and had normal findings. The prevalence of normal findings on high-resolution CT scans is even higher when scans are obtained at greater intervals. The findings on CT can be subtle or be confused with dependent density (Fig. 8).

Atypical Distribution of Ground-Glass Opacities

The ground-glass opacities of HP usually are extensive, bilateral, and symmetric [7]. In some patients, however, they are patchy or asymmetric (Fig. 9). Fine reticulation may be superimposed on the ground-glass opacities and mimic the findings of NSIP on high-resolution CT (Fig. 7) or at histologic examination (Fig. 10). HP should always be considered a possible cause of a CT or histologic pattern of NSIP [2, 3].

Centrilobular Nodules

Small centrilobular nodules may be the predominant or only high-resolution CT abnormality in patients with subacute HP [4]. Although they usually are numerous, the nodules can be few (Fig. 11) or have an atypical distribution (Fig. 12). Irregular nodules larger than 10 mm in diameter are uncommon and usually represent focal areas of organizing pneumonia [3] (Fig. 13).

Decreased Attenuation and Vascularity

Areas of decreased attenuation and vascularity with air trapping on expiratory CT, often in a lobular distribution, represent indirect signs of bronchiolar obstruction in HP [3]. Although they are seen in as many as 90% of patients, these findings usually are limited in extent [7] (Fig. 14).

Reticulation

HP can cause bilateral predominantly lower lung zone ground-glass opacities with superimposed fine reticulation and traction bronchiectasis resembling fibrotic NSIP [2] (Fig. 7). It also can cause bilateral reticulation and honeycombing in a predominantly subpleural and basal distribution that resembles idiopathic pulmonary fibrosis [2]. However, the centrilobular nodules and lobular areas of air trapping typically seen in HP are uncommon in idiopathic NSIP and idiopathic pulmonary fibrosis.

Airspace Consolidation

Consolidation in patients with HP can be caused by organizing pneumonia (Fig. 13) or a superimposed complication such as infection; less commonly it is caused by acute exacerbation with diffuse alveolar damage. Diffuse alveolar damage is an uncommon but potentially fatal complication of HP that can result from extensive exposure to antigens in a sensitized patient. It also occasionally occurs in patients who do not have apparent acute exposure (Fig. 15).

Cysts

Cysts have been reported in 13% of patients with subacute HP [9]. The cysts are typically few, range from 3 to 25 mm in diameter, and are associated with ground-glass opacities (Fig. 16). The cysts in HP resemble those of lymphoid interstitial pneumonia and, like the cysts of lymphoid interstitial pneumonia, are presumably caused by partial bronchiolar obstruction by the peribronchiolar lymphocytic infiltrate present in patients with HP [9].

Emphysema

Most patients with chronic HP have evidence of fibrosis with reticulation and traction bronchiectasis. Patients with chronic farmer's lung, however, including lifelong nonsmokers, are more likely to develop emphysema than they are interstitial fibrosis [10] (Fig. 17). The pathogenesis of emphysema in these patients is not known.

HP Not Related to Inhaled Organic Antigens

HP reaction can be seen as a manifestation of drug-induced lung disease (Fig. 3), inhalation of *Mycobacterium avium-intracellulare* complex organisms (e.g., hot tub lung) (Fig. 18), or exposure to low-molecular-weight chemicals [1, 3] (Fig. 7). The histopathologic and radiologic features usually are indistinguishable from those of HP secondary to immunologic reaction to inhaled organic antigens, except for hot tub lung, which characteristically at histologic examination has large numbers of granulomas, sometimes necrotizing, and a relatively minor interstitial inflammatory component.

Summary

A confident diagnosis of subacute HP on high-resolution CT is based on the presence of ground-glass opacities, poorly defined centrilobular nodules, and mosaic attenuation on inspiratory images and of air trapping on expiratory CT images. Chronic HP is characterized on high-resolution CT by the presence of reticulation due to fibrosis superimposed on findings of subacute HP. Histologically subacute HP is characterized by the presence of cellular bronchiolitis, noncaseating granulomas, and bronchiolocentric lymphocytic in-

terstitial pneumonitis. High-resolution CT and pathologic features of chronic HP frequently overlap with those of NSIP and usual interstitial pneumonia. Awareness of the various manifestations of HP is important for early diagnosis and management to avoid progression to irreversible fibrosis.

References

1. Mohr LC. Hypersensitivity pneumonitis. *Curr Opin Pulm Med* 2004; 10:401–411
2. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002; 165:277–304
3. Travis WD, Colby TV, Koss MN, Rosado-de-Christenson ML, Müller NL, King TE Jr. Idiopathic interstitial pneumonitis and other diffuse parenchymal lung diseases. In: *Atlas of nontumor pathology non-neoplastic disorders of the lower respiratory tract.* Washington, DC: American Registry of Pathology and the Armed Forces Institute of Pathology, 2002:115–123
4. Lacasse Y, Selman M, Costabel U, et al. Clinical diagnosis of hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2003; 168:952–958
5. Vourlekis JS, Schwarz MI, Cherniack RM, et al. The effect of pulmonary fibrosis on survival in patients with hypersensitivity pneumonitis. *Am J Med* 2004; 116:662–668
6. Ohtani Y, Saiki S, Kitaichi M, et al. Chronic bird fancier's lung: histopathological and clinical correlation—an application of the 2002 ATS/ERS consensus classification of the idiopathic interstitial pneumonias. *Thorax* 2005; 60:665–671
7. Hansell DM, Wells AU, Padley SP, Müller NL. Hypersensitivity pneumonitis: correlation of individual CT patterns with functional abnormalities. *Radiology* 1996; 199:123–128
8. Patel RA, Sellami D, Gotway MB, Golden JA, Webb WR. Hypersensitivity pneumonitis: patterns on high-resolution CT. *J Comput Assist Tomogr* 2000; 24:965–970
9. Franquet T, Hansell DM, Senbanjo T, Remy-Jardin M, Müller NL. Lung cysts in subacute hypersensitivity pneumonitis. *J Comput Assist Tomogr* 2003; 27:475–478
10. Cormier Y, Brown M, Worthy S, Racine G, Müller NL. High-resolution computed tomographic characteristics in acute farmer's lung and in its follow-up. *Eur Respir J* 2000; 16:56–60

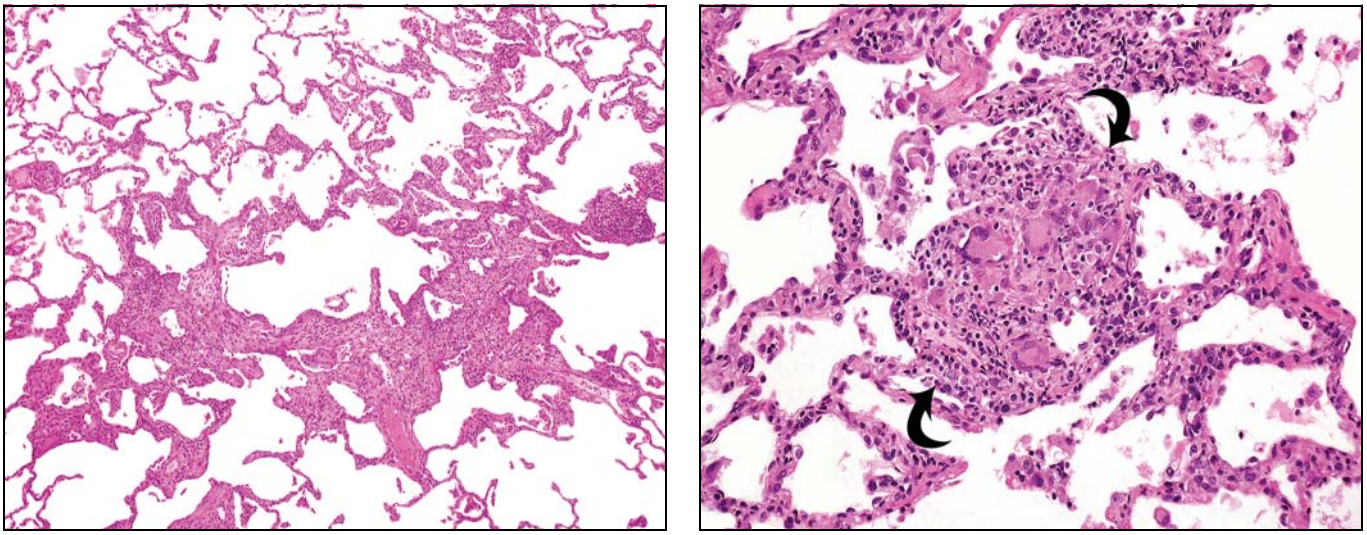


Fig. 1—35-year-old woman with subacute hypersensitivity pneumonitis (bird fancier's lung).
A, Photomicrograph of histopathologic specimen obtained at surgical lung biopsy shows moderate, diffuse, bronchiolocentric chronic lymphocytic inflammatory infiltrate. (H and E, ×60)
B, Magnified view of different area from **A** shows poorly formed granuloma (*arrows*) and chronic interstitial inflammatory infiltrate. (H and E, ×200)

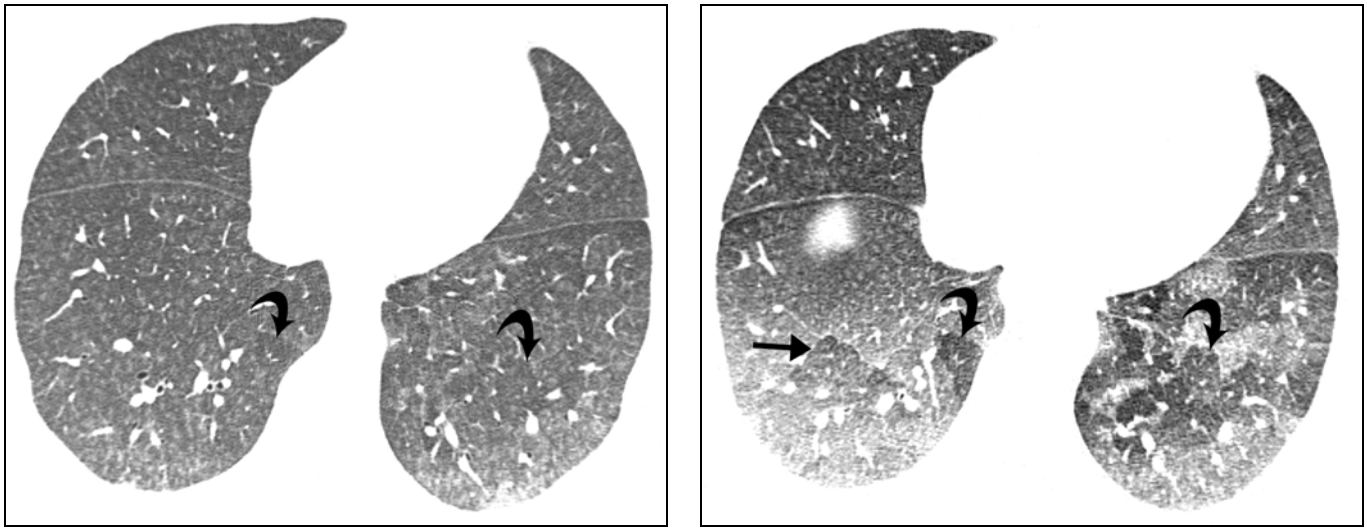


Fig. 2—41-year-old man with subacute hypersensitivity pneumonitis.
A, High-resolution CT image shows bilateral poorly defined centrilobular nodules and ground-glass opacities. Also evident are lobular areas (*arrows*) of decreased attenuation.
B, Expiratory high-resolution CT scan at same level as **A** shows air trapping in lobules (*curved arrows*) that had decreased attenuation on inspiratory CT and in other lung regions (*straight arrow*).

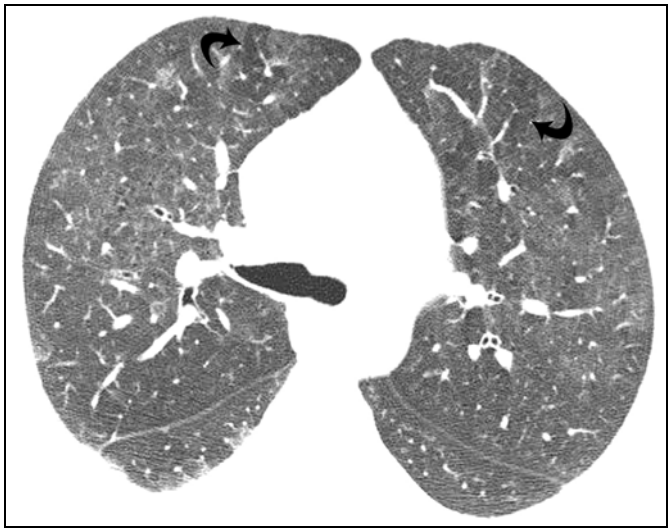


Fig. 3—36-year-old woman with hypersensitivity pneumonitis caused by selective serotonin reuptake inhibitor sertraline. High-resolution CT image shows bilateral ground-glass opacities and lobular areas (*arrows*) of decreased attenuation and vascularity. Patient was taking oral sertraline for management of depressive illness.

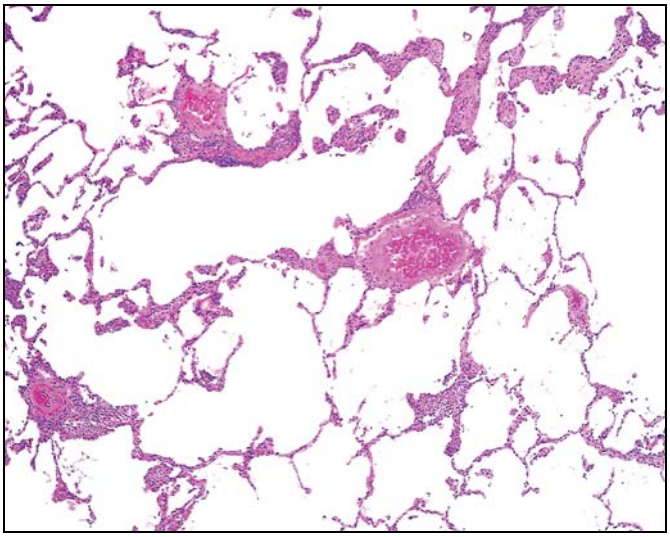


Fig. 4—74-year-old man with hypersensitivity pneumonitis (bird fancier's lung). Low-power view of surgical lung biopsy specimen shows mild interstitial mononuclear cell infiltrate that correlates with areas of ground-glass opacities seen on high-resolution CT. (H and E, ×60)

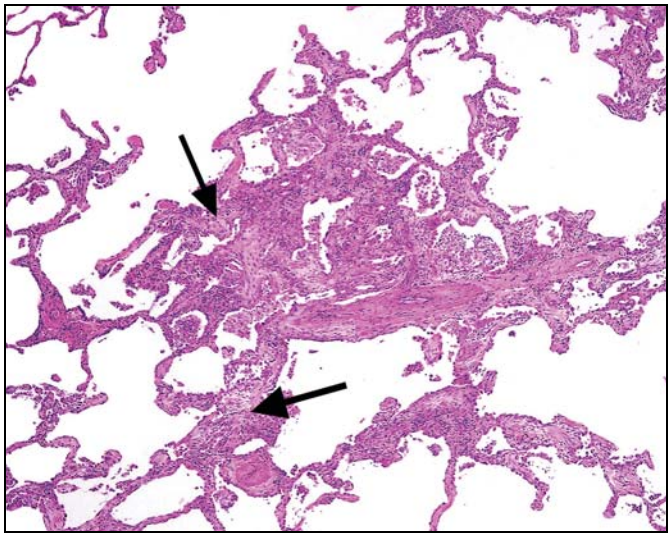


Fig. 5—65-year-old man with hypersensitivity pneumonitis (bird fancier's lung). Photomicrograph of surgical lung biopsy specimen shows chronic inflammatory infiltrate with focal area (*arrows*) of organizing pneumonia. (H and E, ×60)

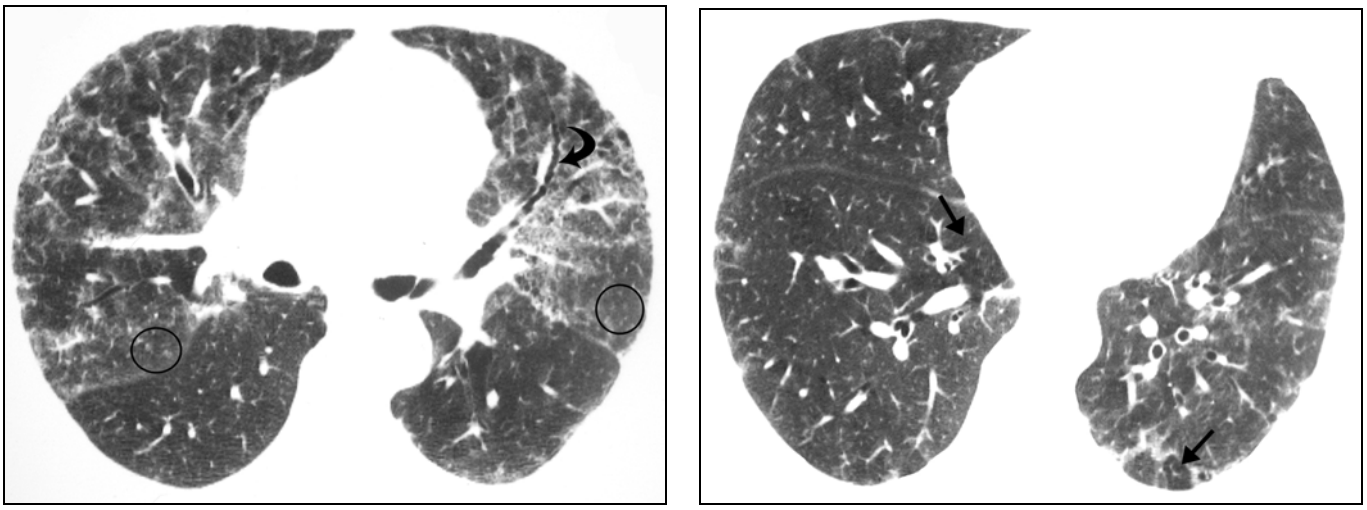


Fig. 6—65-year-old man with chronic and subacute hypersensitivity pneumonitis due to exposure to red cedar.
A, High-resolution CT image at level of left upper bronchus shows bilateral patchy areas of ground-glass opacities, fine reticulation, and traction bronchiectasis (*arrow*). Bilateral centrilobular nodules (*circles*) also are evident.
B, High-resolution CT image at level of lung bases shows relative sparing with minimal reticulation. Lobules (*arrows*) with decreased attenuation and vascularity are evident in lower lobes.
(Fig. 6 continues on next page)

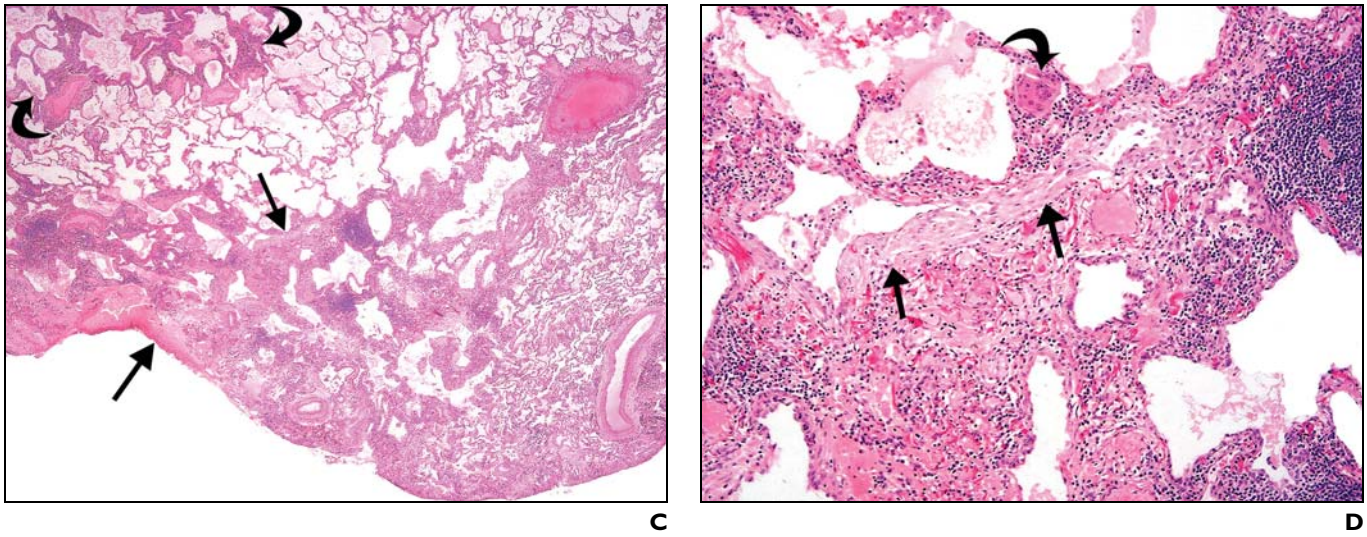


Fig. 6 (continued)—65-year-old man with chronic and subacute hypersensitivity pneumonitis due to exposure to red cedar.
C, Low-power view of surgical lung biopsy specimen shows areas of subacute (*curved arrows*) and chronic (*straight arrows*) changes of hypersensitivity pneumonitis. (H and E, ×40)
D, Higher-power view shows chronic interstitial inflammatory infiltrate and interstitial fibrosis. Also evident are giant cell (*curved arrow*) and fibroblast focus (*straight arrows*). (H and E, ×400)

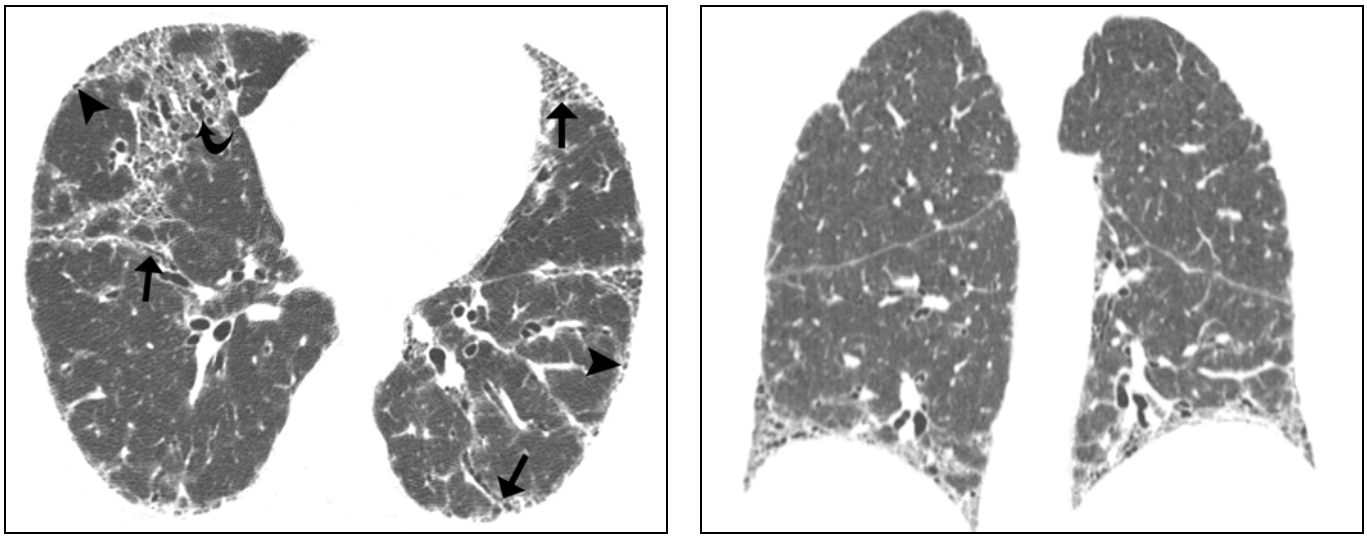
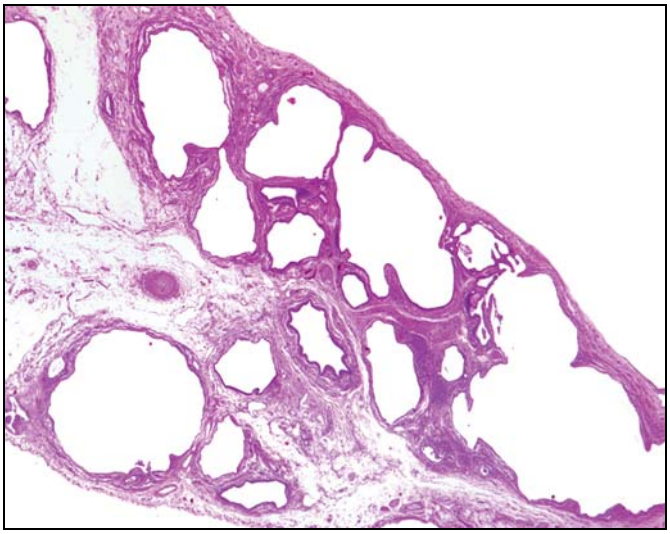
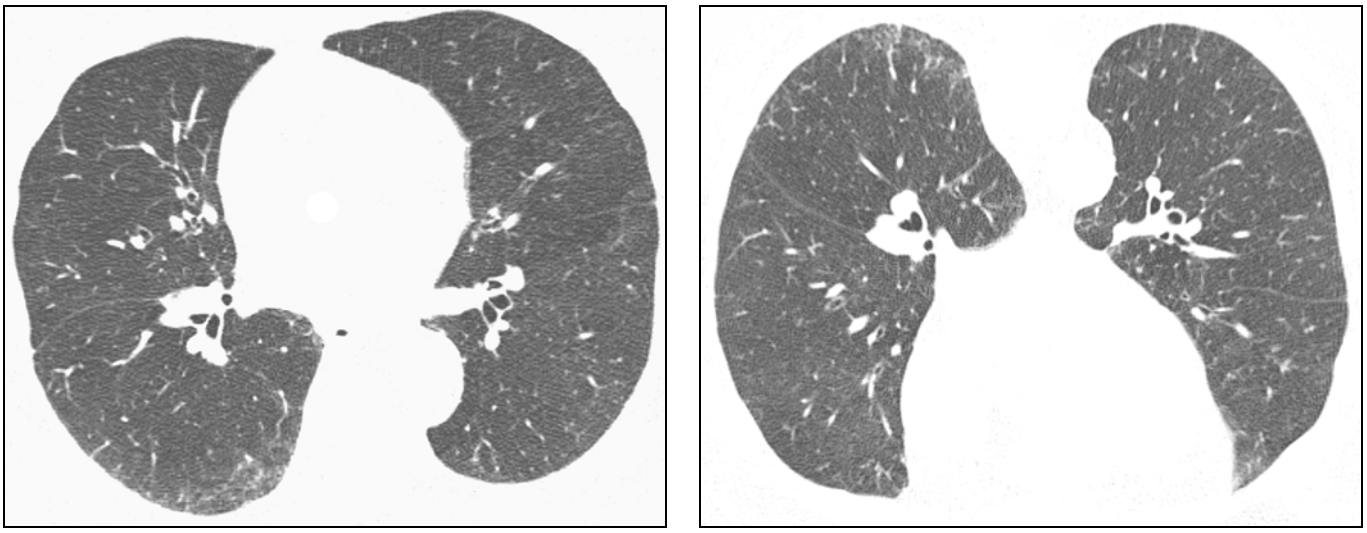


Fig. 7—56-year-old man with chronic hypersensitivity pneumonitis due to occupational exposure to isocyanate compounds in paint.
A, High-resolution CT scan shows bilateral reticulation, traction bronchiectasis (*curved arrow*), and traction bronchiolectasis (*straight arrows*). Also evident are subpleural cysts consistent with mild honeycombing (*arrowheads*). Area of ground-glass opacity with superimposed reticulation is present in right middle lobe. These high-resolution CT findings resemble those of nonspecific interstitial pneumonia.
B, Coronal reformatted image shows predominance of abnormalities in subpleural and basal regions.
(Fig. 7 continues on next page)



C

Fig. 7 (continued)—56-year-old man with chronic hypersensitivity pneumonitis due to occupational exposure to isocyanate compounds in paint.
C, Photomicrograph of surgical lung biopsy specimen shows nondiagnostic honeycombing and moderate mononuclear interstitial infiltrate. (H and E, ×20)



A B

Fig. 8—80-year-old woman with hypersensitivity pneumonitis due to exposure to mold.
A, High-resolution CT scan shows subtle ground-glass opacities and minimal subpleural reticulation in dorsal regions of lower lobes that can be interpreted as normal dependent density.
B, Prone high-resolution CT scan at same level as **A** shows persistent abnormalities in dorsal regions of lower lobes. Diagnosis of hypersensitivity pneumonitis was made clinically. Samples of air in patient's apartment grew *Penicillium* organisms.

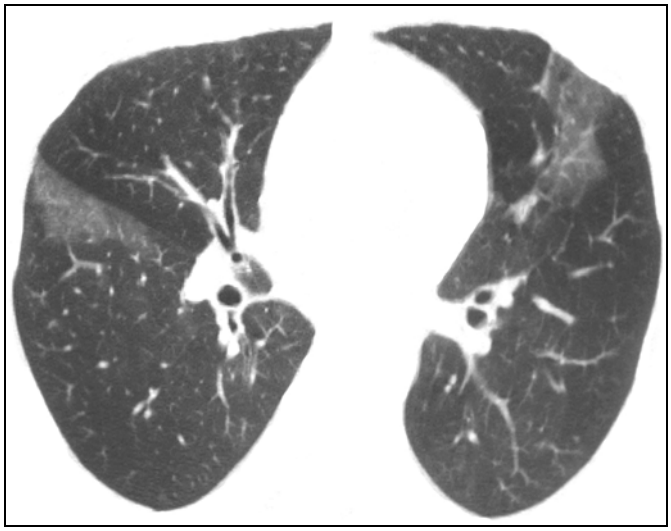
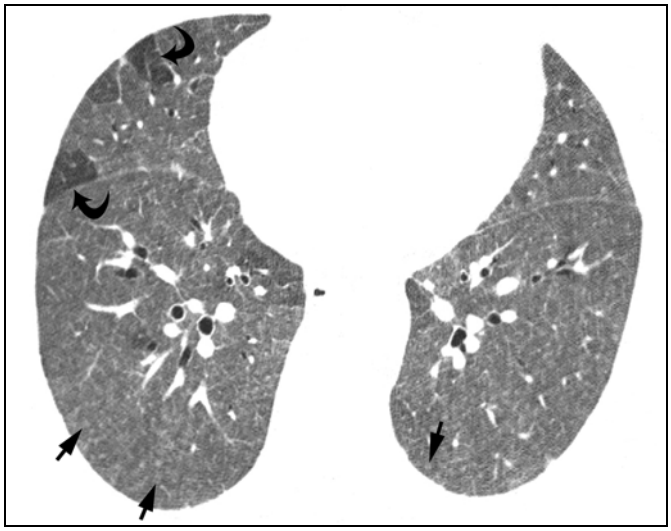
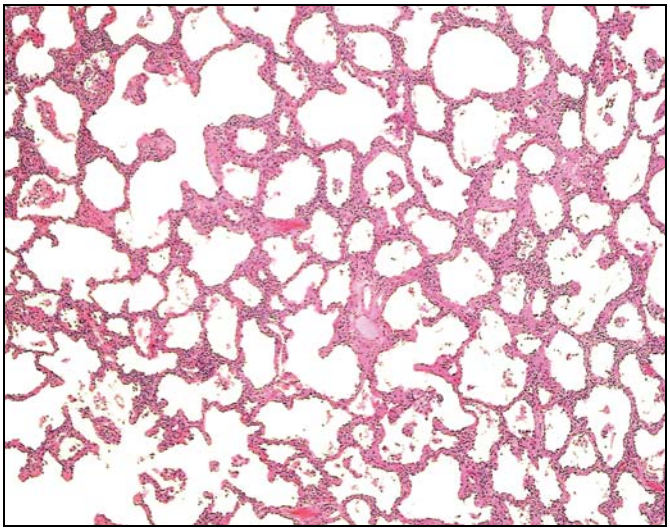


Fig. 9—47-year-old man with subacute hypersensitivity pneumonitis (bird fancier's lung). High-resolution CT image shows patchy ground-glass opacities in right lower lobe and lingula.



A



B

Fig. 10—53-year-old man with hypersensitivity pneumonitis.
A, High-resolution CT image shows extensive bilateral ground-glass opacities, poorly defined small centrilobular nodules (*straight arrows*), and lobular areas (*curved arrows*) of decreased attenuation and vascularity in right middle lobe. These findings are characteristic of subacute hypersensitivity pneumonitis.
B, Surgical lung biopsy specimen of right lower lobe shows thickening of alveolar wall by mild to moderate inflammation consisting mostly of lymphocytes and plasma cells. Histologic findings are those of nonspecific interstitial pneumonitis. Diagnosis of hypersensitivity pneumonitis was based on radiologic and clinical findings. Patient had positive results for *Aspergillus precipitins,* but specific etiologic agent for hypersensitivity pneumonitis was not identified. (H and E, ×40)

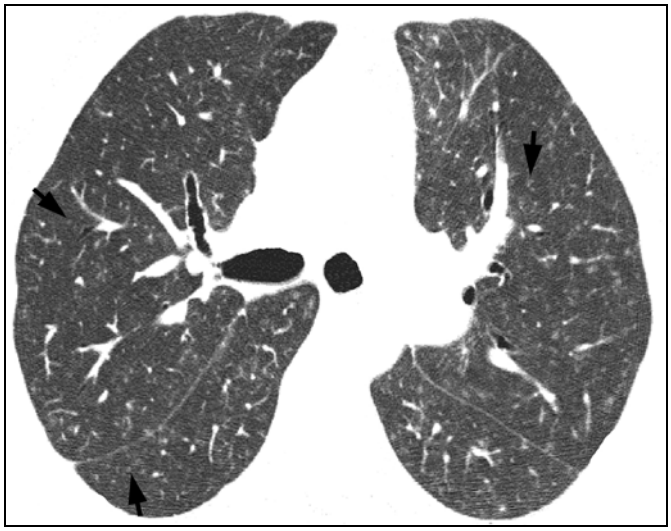


Fig. 11—45-year-old woman with subacute hypersensitivity pneumonitis (winemaker's lung). High-resolution CT image at level of right upper bronchus shows bilateral small centrilobular nodules (*arrows*).

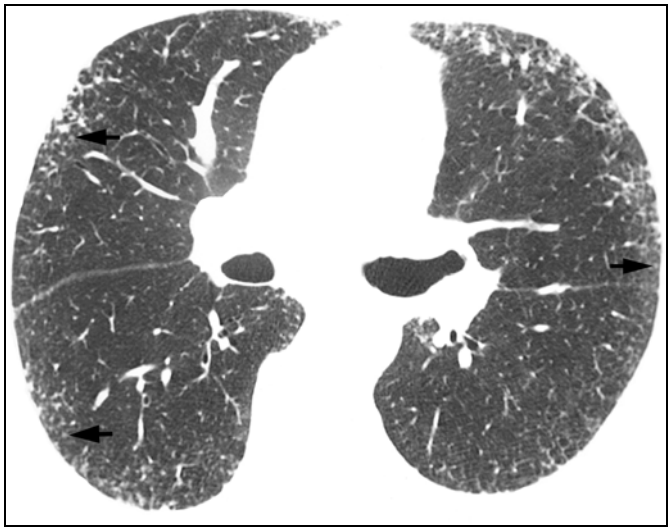


Fig. 12—77-year-old man with chronic hypersensitivity pneumonitis (bird fancier's lung). High-resolution CT image shows mild reticulation and micronodules (*arrows*) in peripheral lung regions.

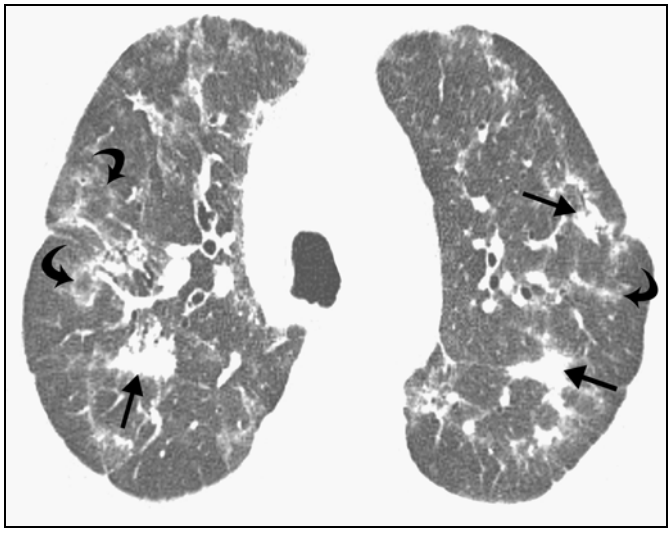


Fig. 13—55-year-old man with hypersensitivity pneumonitis due to exposure to mold. High-resolution CT image of upper lobes shows patchy bilateral ground-glass opacities, nodular areas of consolidation (*straight arrows*), and perilobular opacities (*curved arrows*). These high-resolution CT findings resemble those of organizing pneumonia (bronchiolitis obliterans organizing pneumonia).

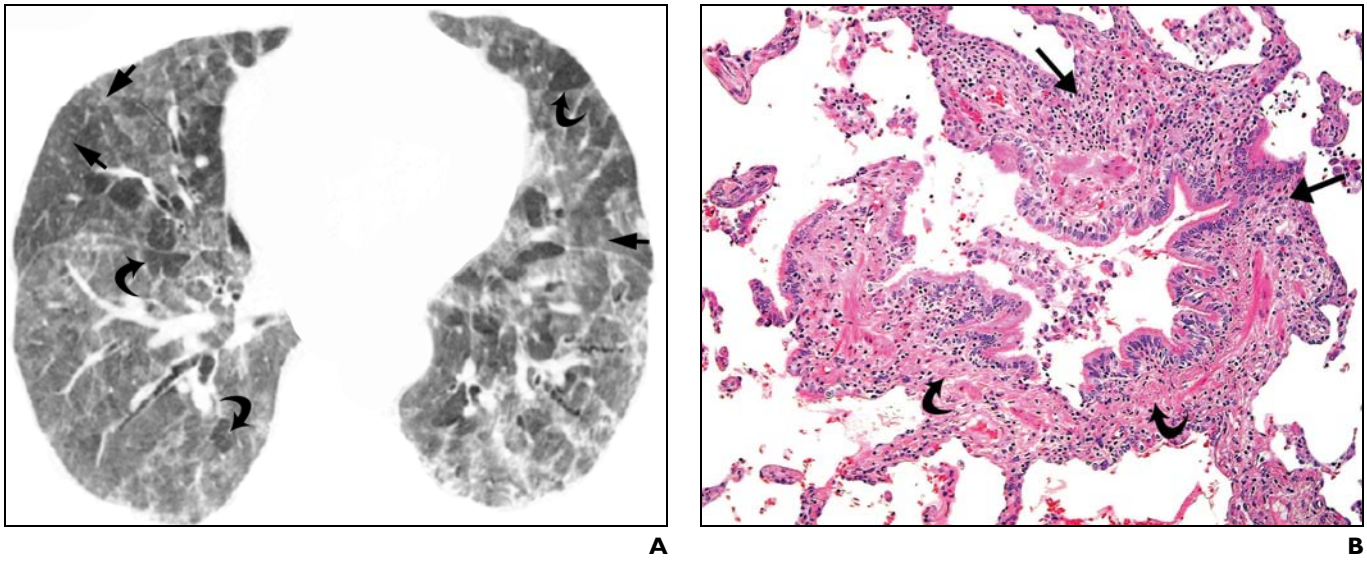


Fig. 14—74-year-old man with chronic and subacute hypersensitivity pneumonitis (bird fancier's lung).
A, High-resolution CT image shows mild reticulation and extensive bilateral ground-glass opacities. Also evident are bilateral centrilobular nodules (*straight arrows*) and localized areas (*curved arrows*) of decreased attenuation and vascularity.
B, Surgical lung biopsy specimen shows cellular bronchiolitis with infiltrate of chronic inflammatory cells (*straight arrows*), thickening wall (*curved arrows*), and narrowing lumen. This type of bronchiolitis presumably accounts for lobular areas of decreased attenuation and vascularity seen on high-resolution CT. (H and E, ×160)

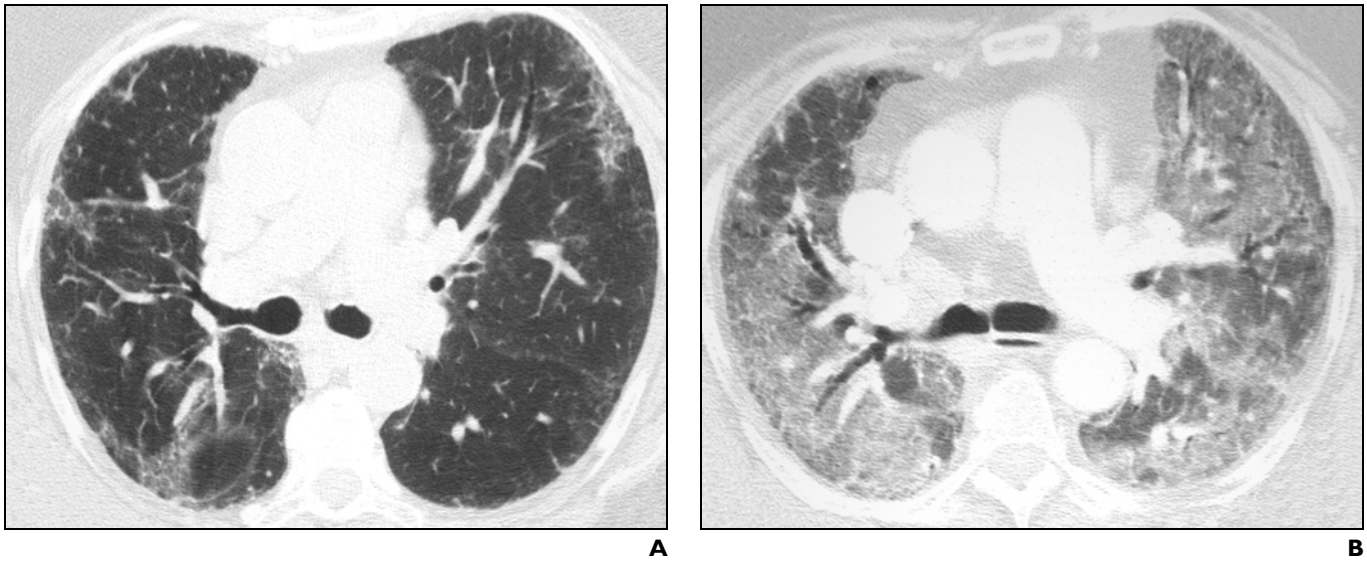


Fig. 15—70-year-old woman with acute exacerbation of biopsy-proven chronic hypersensitivity pneumonitis.
A, High-resolution CT image at level of right upper lobe shows patchy bilateral ground-glass opacities and peripheral reticulation.
B, High-resolution CT image at same level as **A** obtained 7 years after **A** when patient developed acute exacerbation shows extensive bilateral ground-glass opacities.

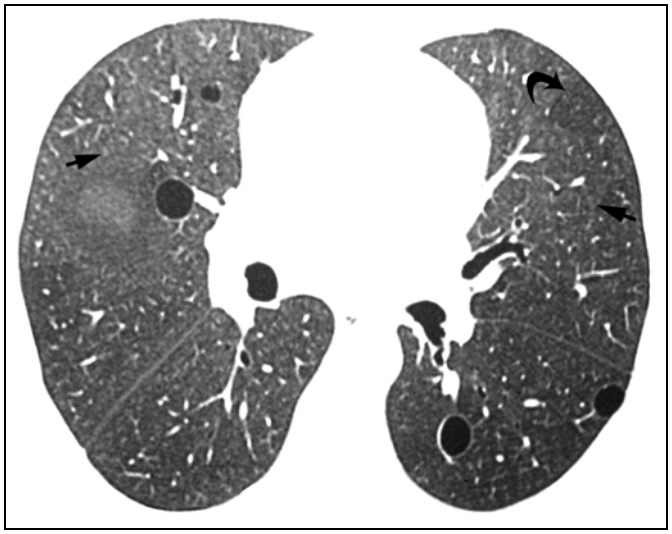


Fig. 16—45-year-old woman with subacute hypersensitivity pneumonitis. High-resolution CT image shows bilateral ground-glass opacities, poorly defined centrilobular nodules (*straight arrows*), and thin-walled cysts. Also evident is lobular area (*curved arrow*) of decreased attenuation in left upper lobe. Patient was lifelong nonsmoker. (Reprinted with permission from [9])

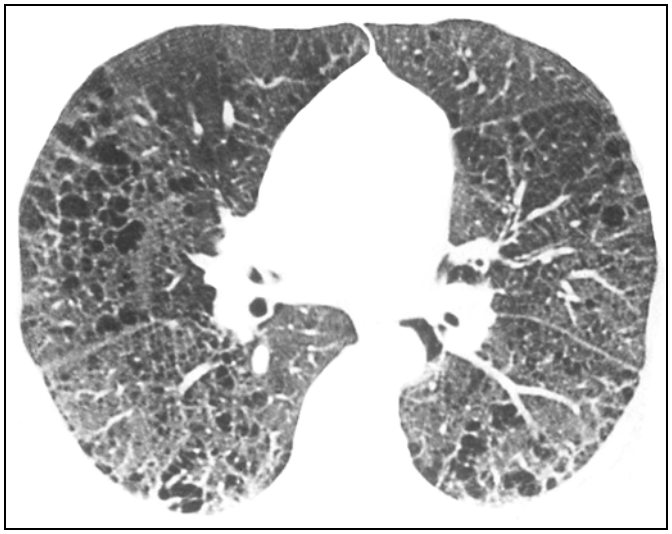
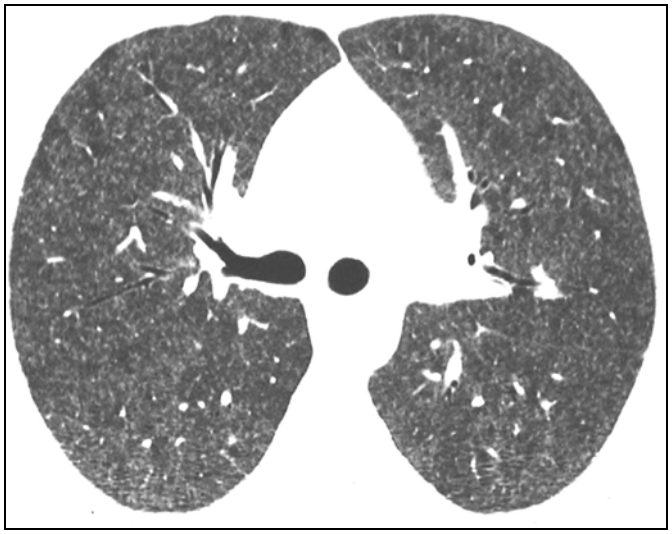
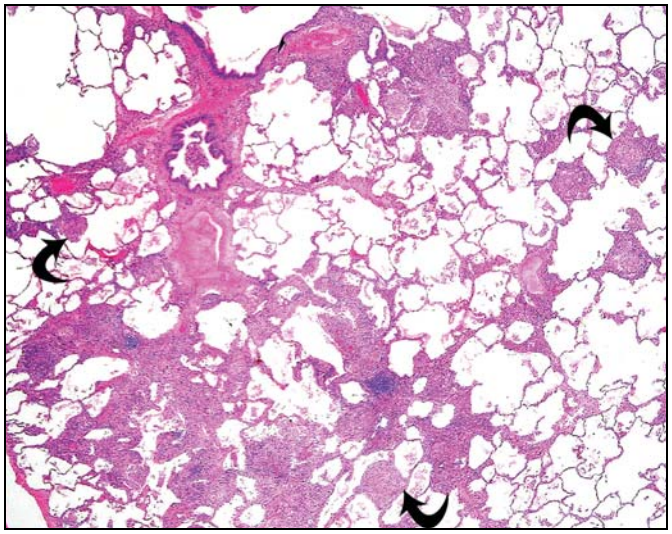


Fig. 17—44-year-old man with chronic hypersensitivity pneumonitis (farmer's lung). High-resolution CT image shows bilateral ground-glass opacities and centrilobular emphysema. Patient was lifelong nonsmoker. (Courtesy of Dr. Yvon Cormier, Quebec, Canada)



A



B

Fig. 18—35-year-old man with hot tub lung.
A, High-resolution CT image shows diffuse bilateral poorly defined small nodules.
B, Low-power view of surgical lung biopsy specimen shows numerous nonnecrotizing granulomas (*arrows*) accompanied by chronic interstitial inflammatory infiltrate. Histologic findings are characteristic of hot tub lung. (H and E, ×40)