Pathology of hypersensitivity pneumonitis

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Current Opinion in Pulmonary Medicine 2008, 14:440–454

Purpose of review

Hypersensitity pneumonitis, caused by inhalation of various antigens, is characterized by interstitial mononuclear cell infiltration, nonnecrotizing granulomas, cellular bronchiolitis, and fibrosis. The pathological picture of chronic hypersensitivity pneumonitis is, however, complicated; it is sometimes difficult to differentiate chronic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis/usual interstitial pneumonia, nonspecific interstitial pneumonia, and connective-tissue-related lung disease. The clinical, radiological, and pathological features of chronic hypersensitivity pneumonitis have recently been described. This study reviews the previously reported information and provides new insights into the pathological features of chronic hypersensitivity pneumonitis.

Recent findings

The pathological features of chronic hypersensitivity pneumonitis comprise overlapping usual interstitial pneumonia-like pattern with subpleural patchy fibrosis, alternating normal alveoli and fibroblastic foci, a nonspecific interstitial pneumonia-like pattern, and centrilobular fibrosis. In contrast to pathological features of acute and subacute hypersensitivity pneumonitis, epithelioid cell granulomas are sparse or absent, but giant cells are seen in the interstitium. Bridging fibrosis between peribronchiolar area and perilobular areas is an outstanding feature of chronic hypersensitivity pneumonitis. Autopsy cases of chronic hypersensitivity pneumonitis have demonstrated not only upper lobe contraction but also lower lobe contraction, mimicking usual interstitial pneumonia pattern and diffuse alveolar damage.

Summary

The present review focuses on the pathological features of chronic hypersensitivity pneumonitis and presents that centrilobular fibrosis and bridging fibrosis are the important hallmarks of chronic hypersensitivity pneumonitis, even with a usual interstitial pneumonia-like pattern.

Keywords

bridging fibrosis, centrilobular fibrosis, chronic hypersensitivity pneumonitis, nonspecific interstitial pneumonia pattern, usual interstitial pneumonia pattern

Curr Opin Pulm Med 14:440–454

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Introduction

Hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, is an immunologically mediated disease caused by inhalation of various antigens containing a variety of organic dusts and chemicals [1–5].

Farmer's lung is the classical and most studied example of hypersensitivity pneumonitis [6–10]. There are increasing cases of summer-type hypersensitivity pneumonitis in Japan related to contaminated home environment by *Trichosporon asahii* or *mucoides* [11,12], bird-related hypersensitivity pneumonitis exposed to avian excretions [12–16], mycobacterial-induced hypersensitivity pneumonitis, known as hot tub lung [17,18], and isocyanate-induced hypersensitivity pneumonitis [19]. Potential offending antigens vary among the geographic locations and influenced by climate, socioeconomic and occupational factors, and new types of hypersensitivity pneumonitis may continuously emerge [5]. To achieve the accurate diagnosis for hypersensitivity pneumonitis, it is essential to integrate clinical, radiological, and pathological features. In this review, pathological features of surgical lung biopsies and autopsy lungs of hypersensitivity pneumonitis will be discussed.

Clinical features

Diagnostic criteria for hypersensitivity pneumonitis have been proposed [1,2,12,20–22], and multicenter study

designed diagnostic criteria as an exposure to a known offending antigen, positive precipitating antibodies to the offending antigens, recurrent episodes of symptoms, inspiratory crackles on physical examination, symptoms occurring 4–8 h after exposure, and weight loss [22]. Further, laboratory-controlled provocation test with the suspicious antigen can be used in chronic hypersensitivity pneumonitis (CHP) [21,23,24]. High-resolution computed tomography (HRCT), bronchoalveolar lavage fluid data, and pathology of surgical lung biopsy can also support to make a confidant diagnosis for hypersensitivity pneumonitis.

Clinical forms of hypersensitivity pneumonitis are usually divided in to acute, subacute, and chronic forms of the disease [2–4,12,15,20,21]. Acute hypersensitivity pneumonitis is caused by an exposure to large amounts of antigen, and the clinical manifestations develop within 4–8 h after exposure and continue for less than 1 month. Farmer's lung disease manifests a prototype of acute hypersensitivity pneumonitis. Subacute hypersensitivity pneumonitis is more common and is caused by intermittent or continuous exposure to an antigen and develops during weeks or months [2,3].

CHP is induced by persistent and recurrent exposure to a low level of antigen, but it is sometimes difficult to identify the causative antigen [3,24]. Cases of CHP are divided into two clinical categories: recurrent cases with recurring acute episodes triggered by repeated antigen exposure and insidious cases characterized by slowly progressive fibrosis with no history of acute episodes [12,25], and the latter are frequently misdiagnosed as idiopathic pulmonary fibrosis (IPF) [12,25,26].

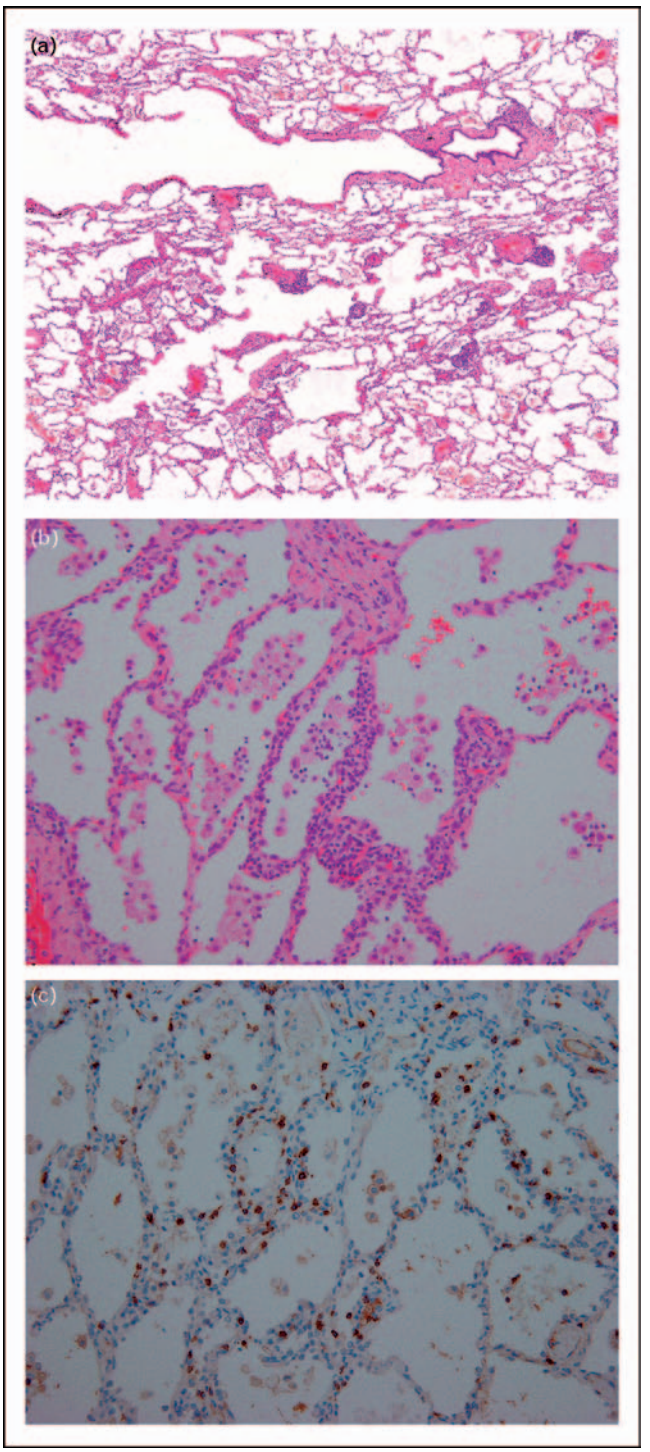
Radiological features

Computed tomography (CT) features of acute and subacute hypersensitivity pneumonitis are characterized by ground-glass attenuation with poorly defined centrilobular nodular opacities and mosaic perfusion [14,27–31], whereas in CHP, there are bronchovascular distribution of fibrosis, reticular pattern, air trapping, traction bronchiectasis, which are indistinguishable features from those of IPF and nonspecific interstitial pneumonia (NSIP) [28–34,35•,36•,37]. Micronodules and mosaic pattern are more frequent in CT features of chronic hypersensitivity pneumonitis in comparison with those of IPF, whereas honeycombing, lower zone, and peripheral zone predominance are common in IPF [35•,36•,37]. Emphysematous change is also seen in the chronic farmer's lung [14,38] and thin-walled cysts in subacute hypersensitivity pneumonitis [39].

Bronchoalveolar lavage

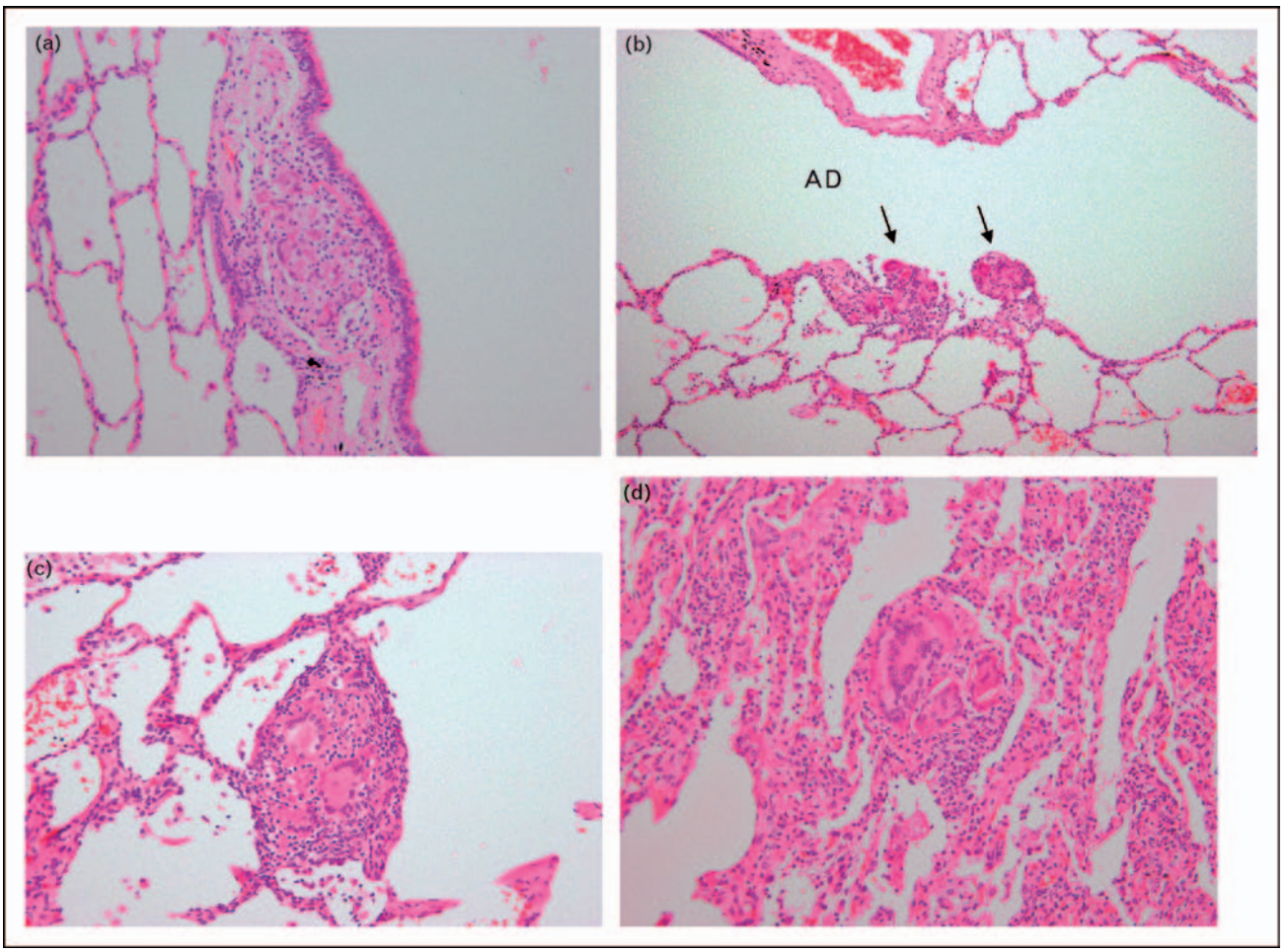
Lymphocytic alveolitis in hypersensitivity pneumonitis reflects on lymphocytosis of bronchoalveolar lavage fluid. In the acute and subacute hypersensitivity pneumonitis,

Figure 1 Lymphocytic alveolitis in subacute hypersensitivity pneumonitis



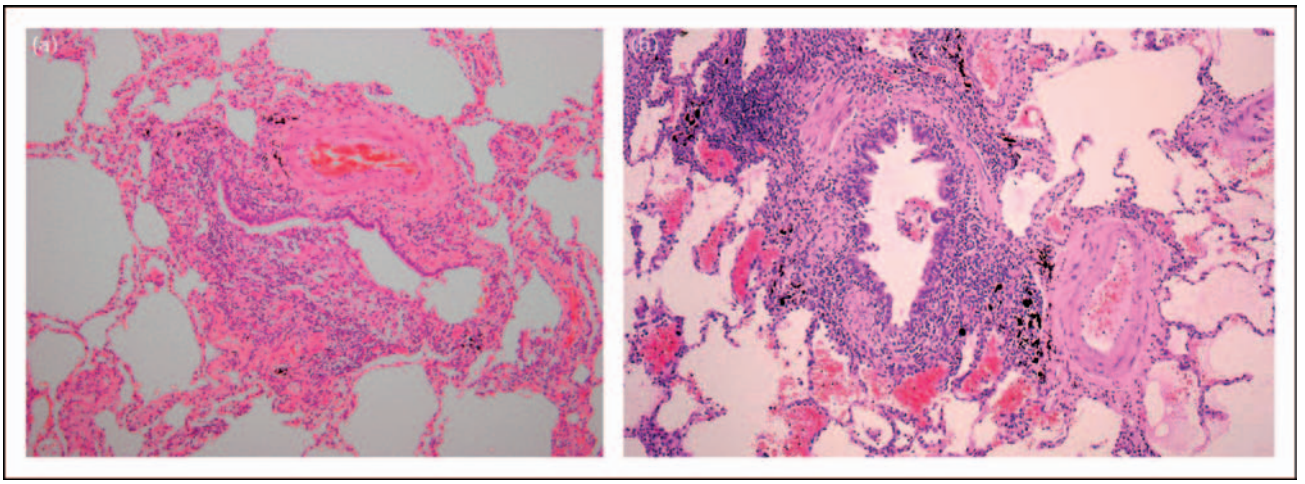
(a) Lymphocytic alveolitis in subacute bird fancier's lung; low-power view shows accentuation of respiratory bronchiole and alveolar duct (HE, ×2). (b) Lymphocyte infiltration of the alveolar walls (hematoxylin and eosin, HE, ×20). (c) CD8+ lymphocytes are predominantly infiltrating in the alveolar walls (HE, ×20).

Figure 2 Distribution and morphology of nonnecrotizing granulomas



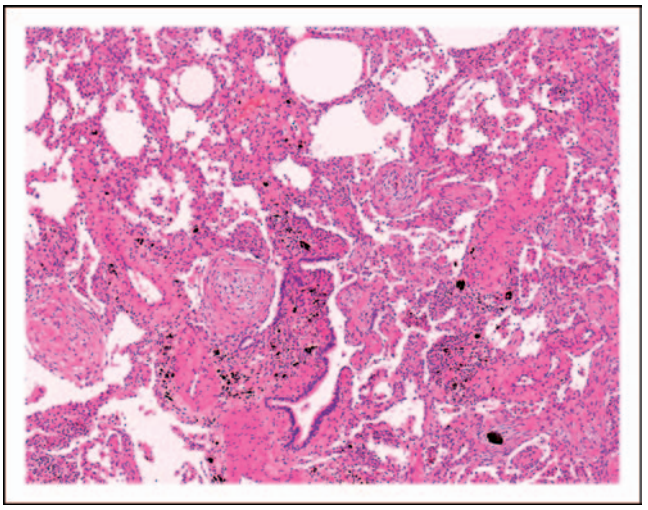
(a) A poorly formed granuloma in the bronchiolar wall (HE, ×20). (b) Small granulomas (arrows) protruding into the alveolar duct (HE, ×20). AD, alveolar duct. (c) A granuloma with giant cells in the wall of alveolar duct (HE, ×20). (d) Cholesterol-laden giant cell granuloma is observed (HE, ×20).

Figure 3 Cellular bronchiolitis in a case of subacute hypersensitivity pneumonitis



(a) Lymphocyte infiltration of the respiratory bronchiole and occasional small granulomas (HE, ×10). (b) Small lymphoid follicle around a membranous bronchiole (HE, ×10).

Figure 4 Intraluminal polypoid fibrosis in a case of subacute bird-fancier's lung



(HE, ×10).

CD8+ T cells are predominant, whereas in the chronic form with fibrosis, CD4/8 increased [11,12,40–45]. Phenotype of infiltrating lymphocytes is different in the stage of disease and depends on the antigen species, for example, low CD4/CD8 in summer-type hypersensitivity pneumonitis, more in farmer's lung and bird-fancier's lung [11,12,41–43,46].

Pathogenesis of hypersensitivity pneumonitis

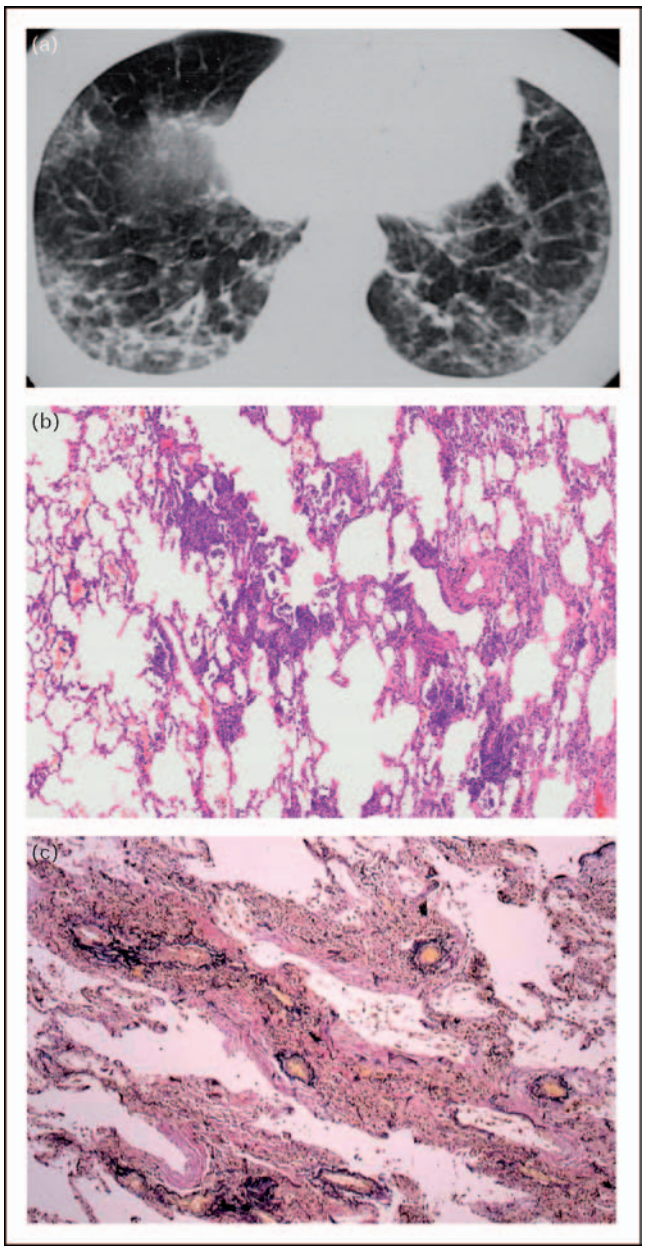
Inhaled antigenic particles less than 3 μm in diameter may reach to the pulmonary parenchyma and then move to the lymphatic vessels and preferably deposit at the respiratory bronchiole [47]. The pathogenesis of hypersensitivity pneumonitis is complex of immune-complex-mediated (type III) and T-cell-mediated (type IV) hypersensitivity reactions in the genetically susceptible people [2,3,48,49]. As for the immune reaction of hypersensitivity pneumonitis, positive serum precipitating antibodies against causative antigen, and immunoglobulin and complement were demonstrated in vessel walls [50,51], and fluorescein-labeled γ-globulins from farmer's lung serum deposited to the bronchiole wall [52]. T-cell-mediated immune response is more important in the pathogenesis of hypersensitivity pneumonitis. Th1-type cytokine network plays an important role in the development of hypersensitivity pneumonitis [49], and then Th2-like immune response develops in the chronic form [53]. Smoking is also related to the pathogenesis of hypersensitivity pneumonitis, because hypersensitivity pneumonitis occurs more frequently in nonsmokers than in smokers, and chronic form of hypersensitivity pneumonitis occurs more severely in smokers [54,55].

Table 1 Histopathological characteristics of surgical biopsy specimens of lung from cases of chronic hypersensitivity pneumonitis

	Number of cases	Cellular bronchiolitis (%)	CLF/peribronchiolar fibrosis (%)	UIP-like pattern (%)	Honeycomb change (%)	Fibroblastic foci (%)	fibrotic NSIP-like pattern (%)	c-NSIP/OP pattern (%)	Bridging fibrosis (%)	Lymphoid follicle (%)	Giant cells (%)	Granulomas (%)
Hayakawa [69]	10	6 (60)	5 (50)	4 (40)	NA	NA	NA	8 (80)	NA	8 (80)	NA	4 (40)
Ohtani *et al.* [70]	26	14 (54)	+ (% NA)	11 (42)	16 (62)	17 (65)	8 (31)	7 (27)	NA	19 (73)	19 (73)	5 (19)
Churg *et al.* [71]	13	NA	3 (23)	9 (69)	NA	10 (77)	4 (31)	7 (54)	3 (23)	NA	11 (85)	7 (54)
Takemura *et al.* [72]	20	10 (50)	16 (80)	14 (70)	14 (70)	14 (70)	12 (60)	6 (30)	16 (80)	10 (50)	7 (35)	6 (30)

CLF, centrilobular fibrosis; c-NSIP, cellular nonspecific interstitial pneumonia; NA, not available; OP, organizing pneumonia.

Figure 5 Chronic bird fancier's lung with recurrent acute episodes



(a) Computed tomography (CT) revealed ground-glass attenuation and a traction bronchiectasis. (b) Histology reveals centrilobular accentuation of infiltration of the alveolar walls by lymphocytes (HE, ×10). (c) Foci of mural incorporation fibrosis along the alveolar ducts and alveolar walls like fibrotic NSIP pattern are observed (Elastica van Gieson, ×20).

Pathological characteristics

We describe here the pathological characteristics of hypersensitivity pneumonitis, according to the clinically acute, subacute, and chronic form of the disease. Lung biopsy is rarely performed in the patients with acute hypersensitivity pneumonitis. On the contrary, variable interstitial pneumonia patterns appear in the lung with subacute and CHP, and it is necessary to differentiate from the other interstitial lung diseases.

Acute hypersensitivity pneumonitis

The pathological features of acute hypersensitivity pneumonitis in farmer's lung have been described [6,8–10]: neutrophil and eosinophil infiltration of the alveolar spaces and small-vessel vasculitis [8,9]. Diffuse alveolar damage (DAD) was also reported in an autopsy case [9]. Immunopathological studies [9,50,51] have revealed immunoglobulin and complement depositions in the vessels.

Subacute hypersensitivity pneumonitis

The histopathological features of subacute hypersensitivity pneumonitis comprise a triad of lymphocyte-dominant interstitial inflammatory cell infiltration, poorly formed nonnecrotizing granulomas, and cellular bronchiolitis [56–60]. There are also foci of bronchiolitis obliterans and intra-alveolar fibrosis [57,58,61]. The interstitial infiltrates resemble those of cellular NSIP [58,62].

Lymphocytic alveolitis

Lymphocytic alveolitis is accentuated at the peribronchiolar areas. Lymphocytes infiltrating in the alveolar walls are predominantly composed of CD8+ lymphocytes (Fig. 1). The lymphocyte infiltration is also seen in the visceral pleura, interlobular septa and vascular walls. Lymphoid follicles are often present around the bronchioles [63], but fewer than in collagen vascular diseases.

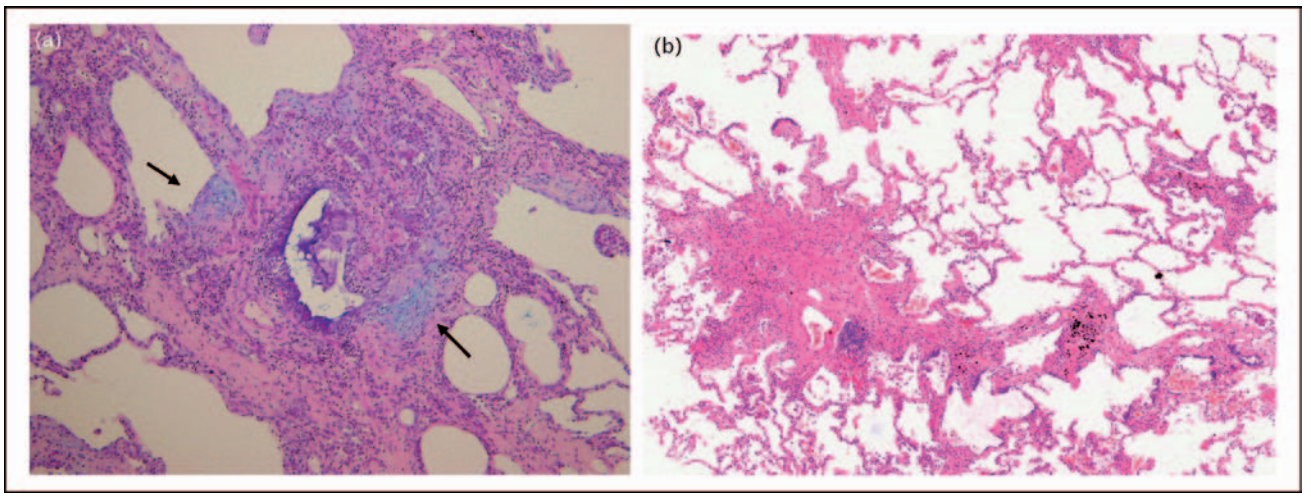
Characteristics of granulomas

Small, loose nonnecrotizing epithelioid cell granulomas are commonly observed in the bronchiolar wall and alveolar ducts in subacute hypersensitivity pneumonitis, and they are less than 150 μm in diameter, smaller than in sarcoidosis [56–60]. However, the size of the granulomas depends on the antigens inhaled, for example, larger granulomas are seen in the farmer's lung [9,10]. The distribution of granulomas is predominantly in the bronchiolar walls, alveolar ducts, alveolar spaces, and rarely granulomas are seen in vessel walls [64]. Loose granulomas are occasionally observed in the alveolar lumina, and cholesterol clefts are often in the granulomas (Fig. 2). Granulomas may last 6 months and disappear after avoiding antigen exposure [65]. The granulomas in hypersensitivity pneumonitis seldom become hyalinized. When there are hyalinization and fibrosis associated with the granuloma, other granulomatous diseases such as infection, sarcoidosis, and berylliosis should be differentiated [57].

Cellular bronchiolitis

Cellular bronchiolitis is an important feature of hypersensitivity pneumonitis and predominantly involves the

Figure 6 Peribronchiolar fibrosis and centrilobular fibrosis in a case of chronic hypersensitivity pneumonitis with an insidious course



(a) Marked fibrosis of the respiratory bronchiolar wall and fibroblastic foci (arrows) (Alcian blue-PAS staining, ×10). (b) Luminal narrowing of a respiratory bronchiole by fibrosis and hyperplasia of smooth muscle cells (HE ×10).

respiratory bronchiole and peribronchiolar lymphoid hyperplasia sometimes occurs [63,66] (Fig. 3). The pathological features indicate airway inhalation and deposition of antigenic particles preferably at the respiratory bronchiole level. Peribronchiolar fibrosis and luminal obstruction later develop, and they result in peribronchiolar and centrilobular fibrosis.

Intraluminal fibrosis

Intraluminal fibrosis, also called Masson's body, is frequently observed in the alveolar ducts and occasionally in the respiratory bronchiolar lumina in the form of bronchiolitis obliterans [56–61] (Fig. 4). Foamy macrophages sometimes accumulate in the alveolar lumina. Widespread intraluminal fibrosis occasionally occurs in a lobule and develops to organizing pneumonia pattern and atelectatic fibrosis.

Chronic hypersensitivity pneumonitis

The histopathological features of CHP are overlapping of various patterns of usual interstitial pneumonia (UIP)-like, NSIP-like, organizing pneumonia pattern, centrilobular fibrosis with or without granuloma [67–72]. Ohtani *et al.* [70] were the first to correlate the histopathological and clinical findings in bird fancier's lung, applied by American Thoracic Society (ATS)/European Respiratory Society (ERS) 2002 classification [73]. Among the 26 cases studied, the organizing pneumonia pattern and cellular NSIP pattern predominated in the cases with recurrent acute episodes, and the fibrotic NSIP (f-NSIP) and UIP pattern were dominant in the cases with insidious onset. Churg *et al.* [71] reported 13 cases of CHP, in which the UIP pattern and f-NSIP pattern were intermingled with peribronchiolar fibrosis and Schaumann bodies were frequent. In the following sections we describe the characteristic pathological features of surgical biopsy and autopsy lung specimens from CHP cases of our own and in the literature.

Surgical biopsy specimens

The histopathological features of surgical lung biopsy specimens from the cases with CHP are a mixture of various interstitial pneumonia patterns. Table 1 presents the pathological characteristics summarized from the previous reports and our own.

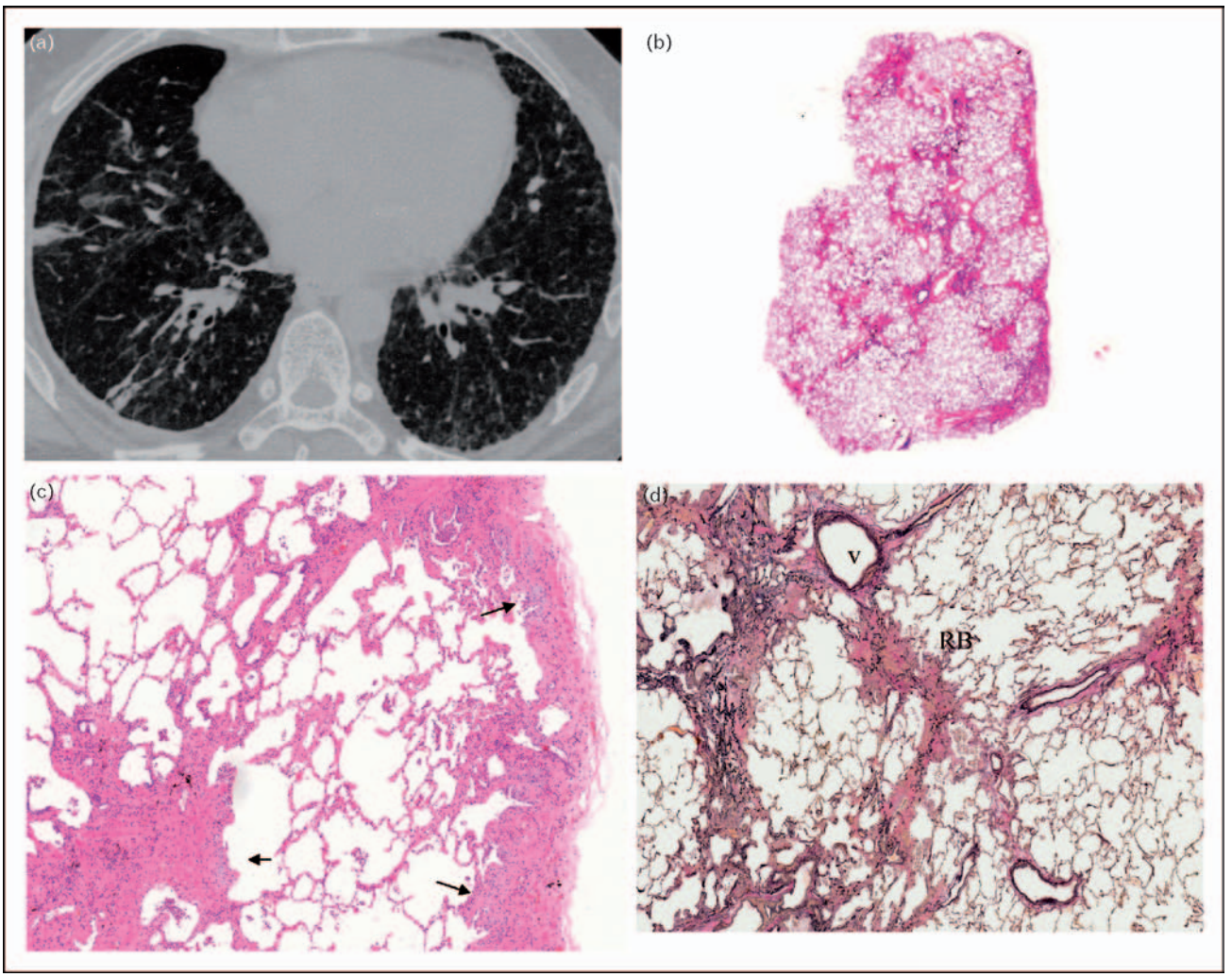
Nonspecific interstitial pneumonia-like pattern

The NSIP-like pattern is frequently observed in the cases with recurrent episodes showing infiltration by mononuclear cells of alveolar walls, occasionally intra-alveolar fibrosis and in some places, mural incorporation fibrosis along the alveolar walls. CT scans show a ground-glass appearance, reticular shadows along the bronchovascular bundle and traction bronchiectasis (Fig. 5).

Centrilobular fibrosis and peribronchiolar fibrosis

Centrilobular fibrosis is an outstanding pathological feature of CHP, but is seen in the other interstitial lung diseases [74–76]. The respiratory bronchioles are most involved in CHP, showing peribronchiolar fibrosis, scarring, and luminal occlusion and smooth muscle hyperplasia (Fig. 6). Fibroblastic foci are frequently observed at the margin of the areas of peribronchiolar and alveolar duct fibrosis, suggesting a continuous antigen exposure at the bronchiole level. Peribronchiolar inflammation and subsequent irreversible bronchiolar change sometimes develop. It is difficult to differentiate airway-centered

Figure 7 Bridging fibrosis seen in chronic bird fancier's lung disease in a 33-year-old man



(a) Computed tomography (CT) shows traction bronchiectasis and centrilobular small nodular opacity. (b) Lower power view reveals centrilobular fibrosis and patchy subpleural fibrosis. (c) Centrilobular fibrosis is extending to the subpleural area and small fibroblastic foci (arrows) are located at the edge of the centrilobular and subpleural fibrosis (HE, ×4). (d) Bridging fibrosis is located between respiratory bronchiole and interlobular septa (Elastica van Gieson, ×4). RB, respiratory bronchiole; V, interlobular vein.

interstitial pneumonia and bronchiolocentric interstitial pneumonia from CHP [74,75].

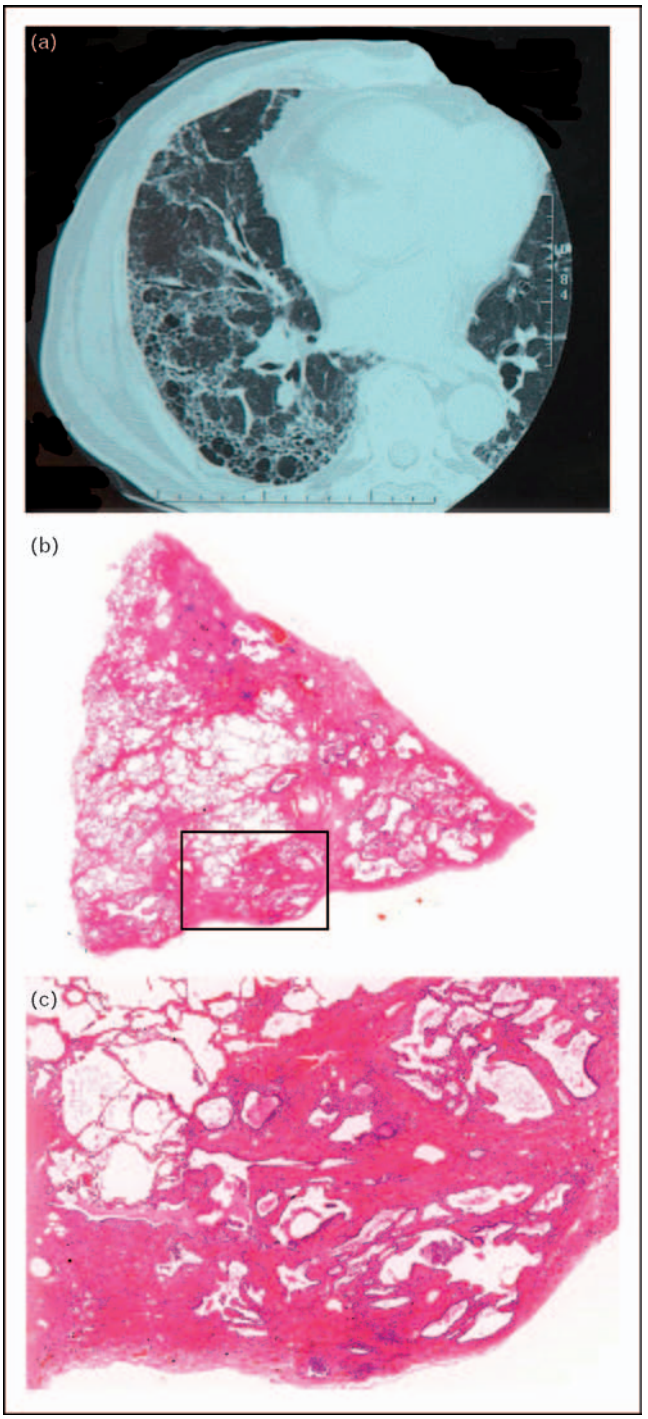
Bridging fibrosis

Churg *et al.* [71] described continuous fibrosis between the centrilobular and subpleural location. Bridging fibrosis between centrilobular and perilobular areas such as supleural areas and areas close to the interlobular septa is frequently seen in CHP (Fig. 7). This pattern of fibrosis is considered a histopathological hallmark of CHP. Inase *et al.* [26] described bridging fibrosis in 70% of their cases with chronic summer-type hypersensitivity pneumonitis. CT scans reveal irregular linear bronchovascular bundles and reticular shadow, correlated to histological bridging fibrosis. Bridging fibrosis may be attributable to unresolved foci of organizing pneumonia and consequent atelectasis along the alveolar duct and peribronchiolar area.

Usual interstitial pneumonia-like pattern

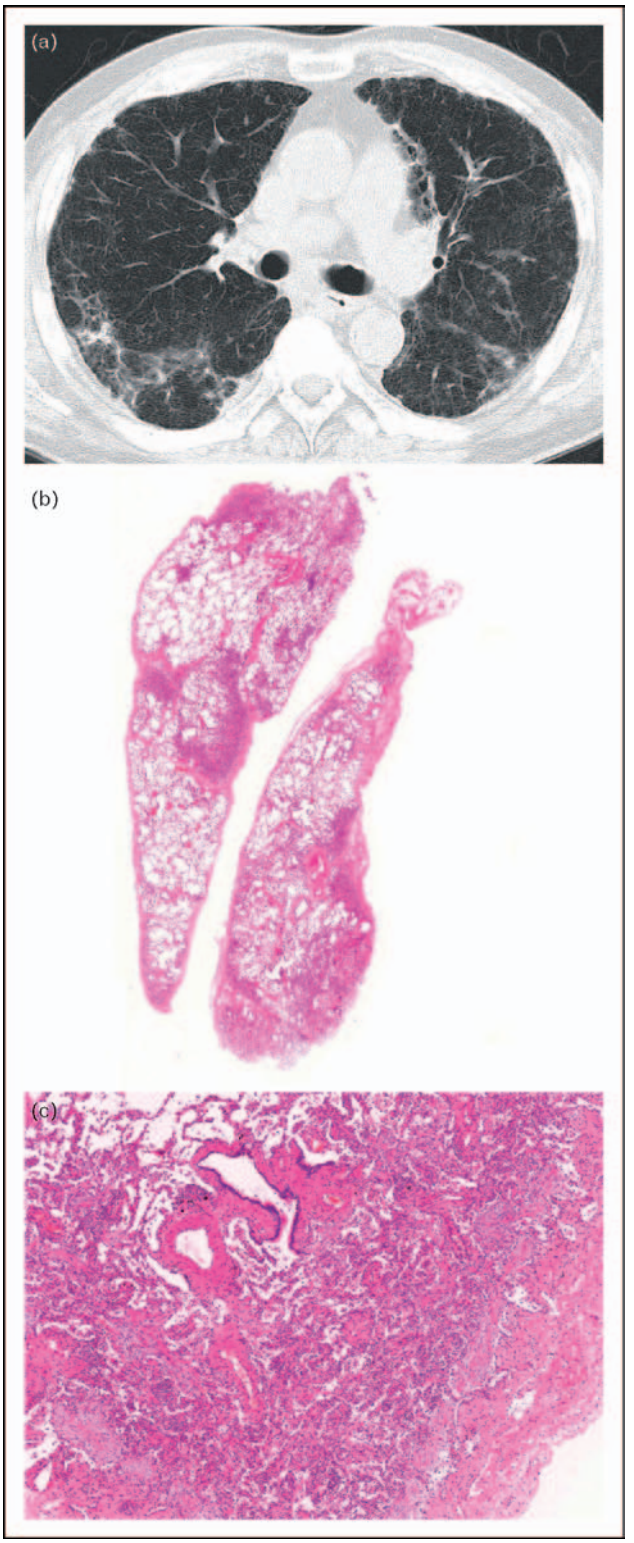
Insidious cases have frequently revealed patchy perilobular (subpleural area and along the interlobular septa) fibrosis alternating with normal alveoli and honeycomb change (Fig. 8). The reason why perilobular fibrosis coexists with centrilobular fibrosis in CHP is related to the sites of deposition of inhaled antigenic particles [47]. Fibroblastic foci are frequently observed at the edge of areas of established fibrosis. Compared with HRCT findings of IPF, the centrilobular nodules and the absence of lower zone predominant abnormalities are the best differentiated features of CHP [36•]. Centrilobular fibrosis and bridging fibrosis are common even in cases exhibiting the UIP pattern.

Figure 8 Usual interstitial pneumonia-like pattern of chronic hypersensitivity pneumonitis with an insidious course



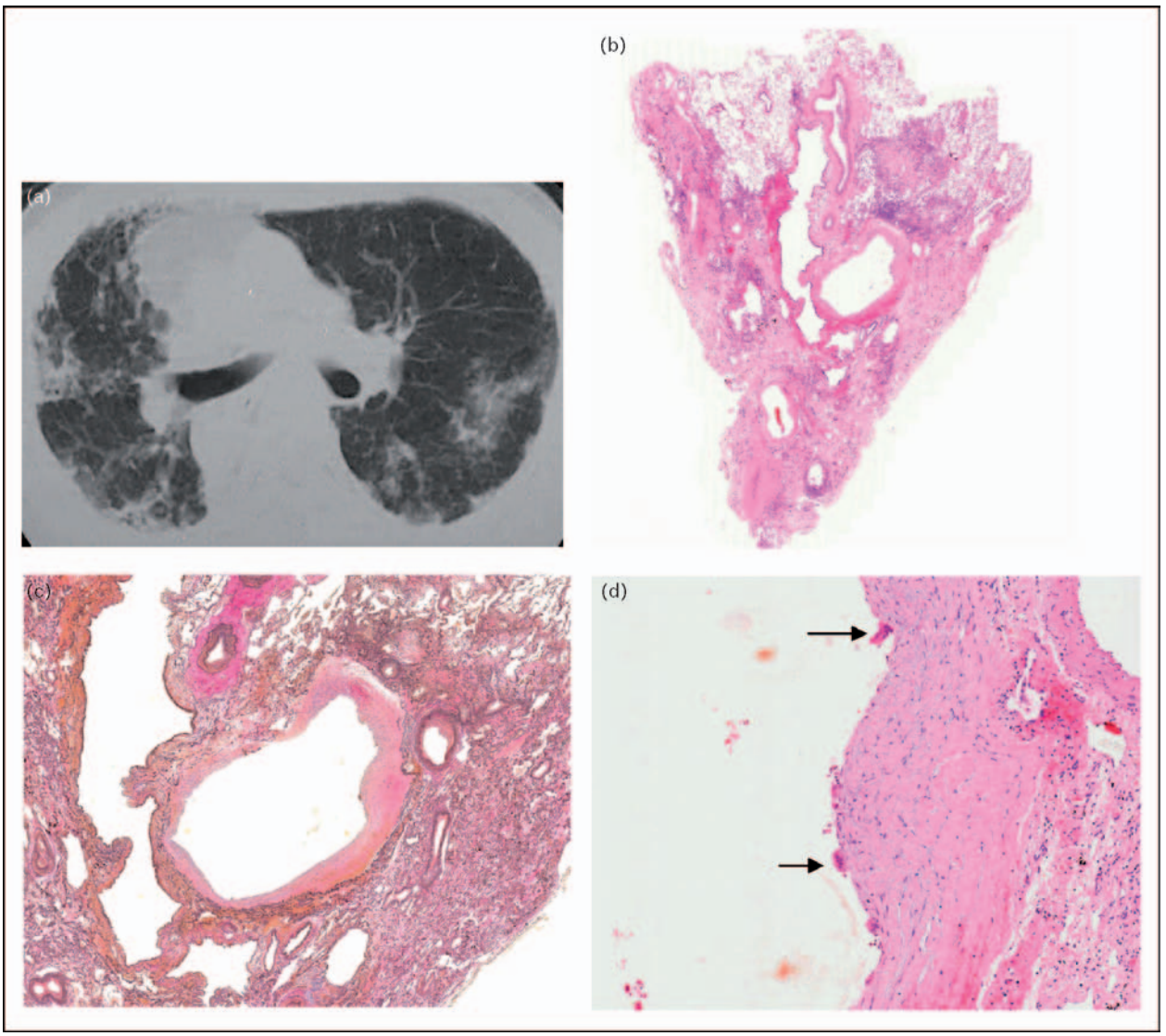
(a) Computed tomography (CT) scan showing reticular shadow of the lobule, with honeycomb change in the posterior segment. (b) Low-power view shows patchy subpleural fibrosis with alternating normal alveoli and honeycomb change, similar to that seen in usual interstitial pneumonia (UIP)/idiopathic pulmonary fibrosis (IPF). (c) Microscopic appearance of the area of honeycomb change and peribronchiolar dense fibrosis (rectangular area of b) (HE, ×2).

Figure 9 Organizing pneumonia pattern in chronic bird fancier's lung



(a) High-resolution computed tomography (HRCT) reveals ground-glass attenuation and patchy subpleural fibrosis in both lung fields. (b) A low-power view reveals patchy subpleural fibrosis and patchy distribution of air space consolidation. (c) Intra-alveolar polypoid fibrosis and alveolitis are observed beneath the level of a respiratory bronchiole (HE, ×10).

Figure 10 Atelectasis and a cystic lesion in an insidious case of chronic bird fancier's lung



(a) Computed tomography (CT) scan shows patchy consolidation in the subpleural area and centrilobular ground-glass attenuation. (b) Low-power microscopic view showing subpleural atelectasis and an adjacent cyst lesion. (c) Dense atelectatic fibrosis in the upper lobe and marked elastosis (Elastica van Gieson, ×4). (d) Note dense collagen deposition lining a cyst with no epithelium, and scattered giant cells (arrows) (HE, ×20).

Organizing pneumonia pattern

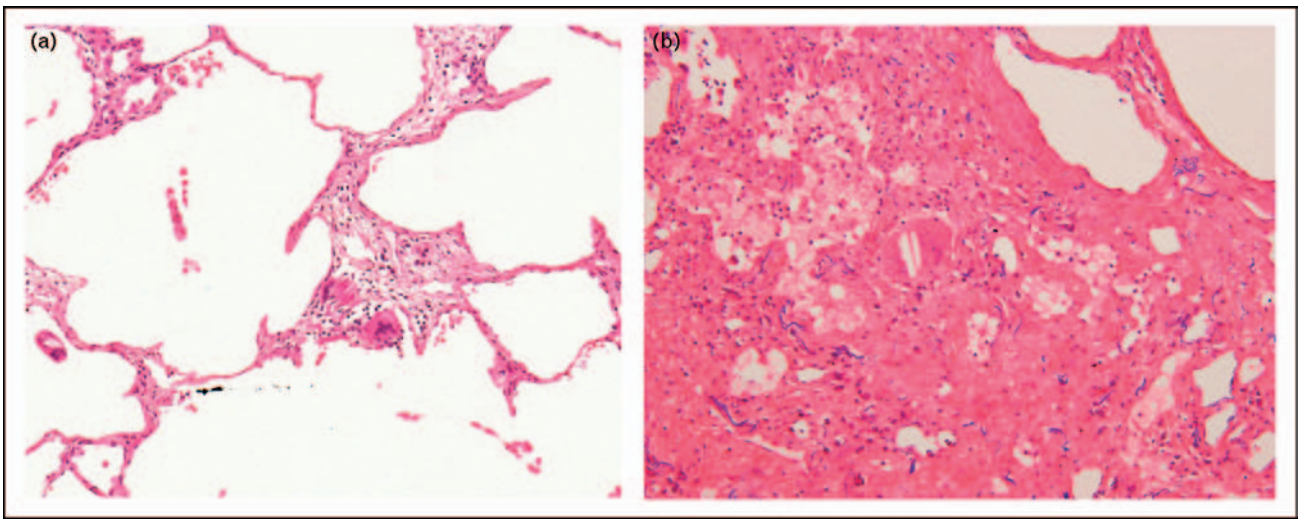
Intraluminal polypoid fibrosis, mainly affecting the alveolar duct and respiratory bronchioles, is frequently observed in subacute hypersensitivity pneumonitis [56–61], which corresponds to the patchy ground-glass appearance on the CT images. Organizing pneumonia pattern occurred in the cases with recurrent episodes at the centrilobular area and at the periphery of the lobules (Fig. 9).

Acute exacerbation in chronic hypersensitivity pneumonitis

Acute exacerbations were observed during the follow-up of chronic bird fancier's lung disease [77–79]. Pathological examination reveals epithelial damage, an intra-alveolar fibrinous exudate, and intra-alveolar fibrosis. This acute lesion is limited or widespread in a lobule.

Epithelial injury and apoptosis in CHP recently have been examined [80]. The regenerative epithelia in UIP-like pattern revealed more increased positive p21 and p53 than those of NSIP-like pattern. Fas ligand is strongly expressed in the epithelium in the UIP-like pattern, and terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick end-labelling (TUNEL)-positive cells are more numerous in the UIP-like pattern than in the NSIP-like pattern. These findings suggest that epithelial apoptosis may be related to disease progression in CHP, the same as in UIP/IPF [81].

Figure 11 Giant cells in chronic summer-type hypersensitivity pneumonitis



Scattered giant cells in the wall of alveolar duct (a) and giant cell with cholesterol cleft (b) in the fibrous interstitium (HE, ×20).

Atelectatic fibrosis

Atelectasis with elastosis to variable degrees is frequently seen in the lobules of CHP, resulting in traction bronchioloectasis (Fig. 10). CT has revealed irregular patchy consolidation in the subpleural and intralobular area. The atelectasis is induced by unresolved organizing pneumonia and subsequent contraction in the lobule, suggestive of the presence of the organizing pneumonia pattern in the subacute phase.

Emphysema and cyst formation

Chronic farmer's lung is associated with an increased risk of emphysema [38]. Emphysematous changes are common in 50% of cases of CHP [14] and thin-walled cysts are seen in 13% of cases with subacute hypersensitivity pneumonitis [39]. There have been a few pathological studies of cyst formation in CHP. We have observed not only thin-walled cystic lesions but also thick-walled cysts with collagen fiber deposition on the inner surface and no epithelial lining and scattered multinucleated giant cells in the cyst walls (Fig. 10). The pathogenesis of cysts in CHP is related to lymphocytic alveolitis such as cyst in Sjogren syndrome or a partial bronchiolar obstruction [34,39].

Interstitial giant cells

Epithelioid cell granulomas are rarely seen or absent in CHP, except in the acute phase of CHP cases. Scattered interstitial giant cells with cholesterol clefts or Schaumann bodies are characteristic findings in CHP [70,71]. They are usually observed around bronchioles and alveolar ducts, but are sometimes seen in perilobular areas (Fig. 11).

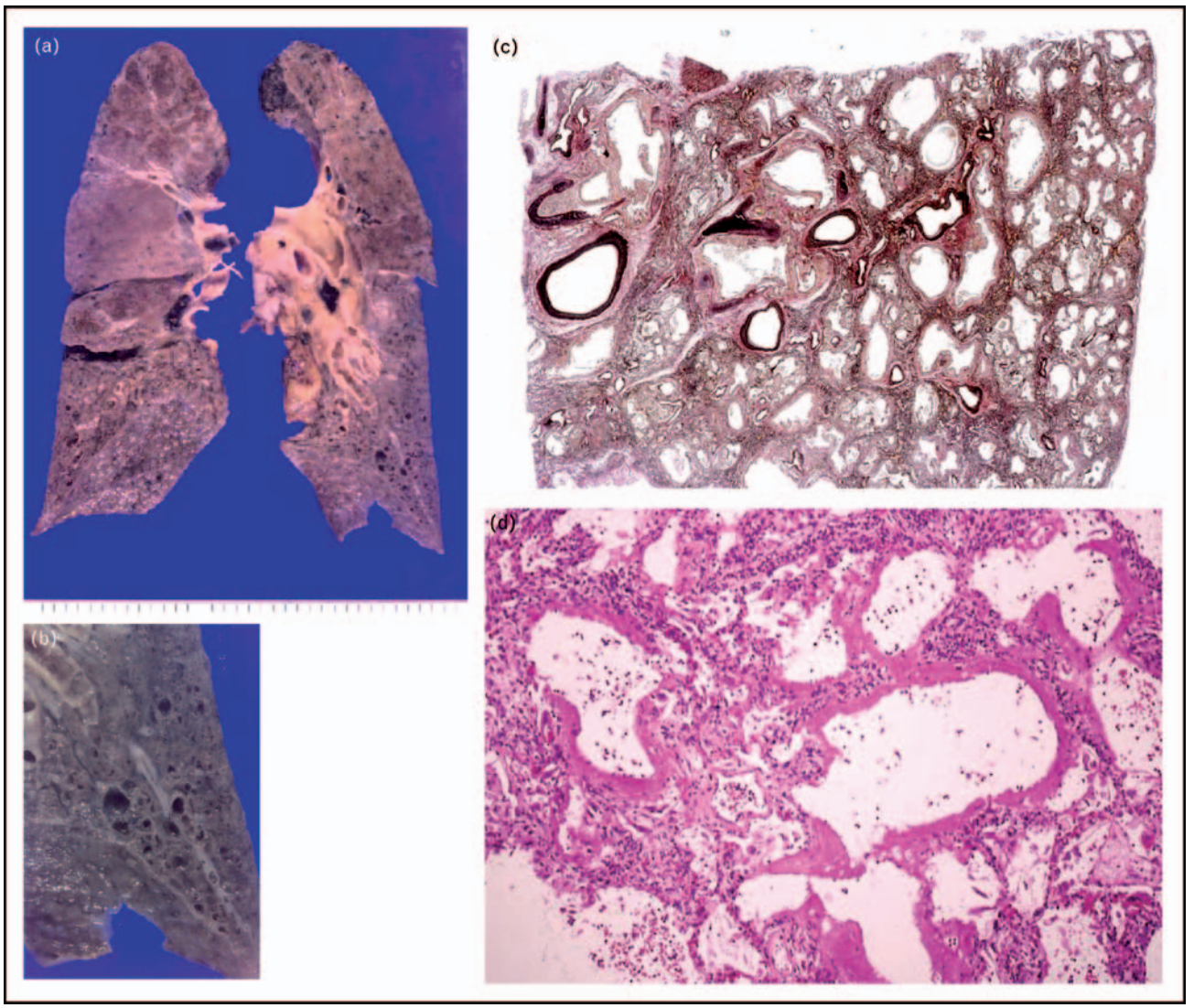
On the basis of the histopathological observations, the pivotal pathological factors in the progression of CHP are interstitial inflammatory cell infiltration, continuous bronchiolitis, organizing pneumonia pattern, and fibroblastic foci. Continuous insult to the bronchioles may progress to bronchiolar and peribronchiolar fibrosis, and ultimately to bronchiolar obstruction, and then progress to centrilobular fibrosis. Bridging fibrosis, an outstanding feature of CHP, may develop as a result of unresolved organizing pneumonia and subsequent atelectasis along the alveolar ducts and peribronchiolar area, which connects to the fibrosis in the peripheral area of the lobule.

Autopsy lungs from chronic hypersensitivity pneumonitis cases

The prognosis of chronic farmer's lung is considered to be poor [2,15]. Pathological and HRCT evidence of fibrosis of hypersensitivity pneumonitis indicates poor prognosis [35•,36•,38,82–84]. Mortality rates of CHP have been reported by several countries and institutions [85–87], and the increasing hypersensitivity pneumonitis mortality has been reported in the agricultural industries [88].

The pathological features of autopsy lungs of five cases of farmer's lung had been described [9]; upper lobe contraction was predominant, and interstitial fibrosis, cystic change and pulmonary hypertension were the principal findings. We have examined 17 autopsy cases of CHP, consisting of 13 cases of bird fancier's lung and four cases of summer type with total duration of observation between 15 and 152 months [72], all of which fulfilled the diagnostic criteria for CHP [23,25]. The upper lobe contraction was seen in seven cases, whereas nine cases exhibit lower lobe contraction, similar to that seen in IPF/UIP. All the cases exhibited honeycomb lesions containing microscopic cysts, ranging from 2 to 4 mm in

Figure 12 Autopsy lung of a case of chronic bird fancier's lung with insidious course



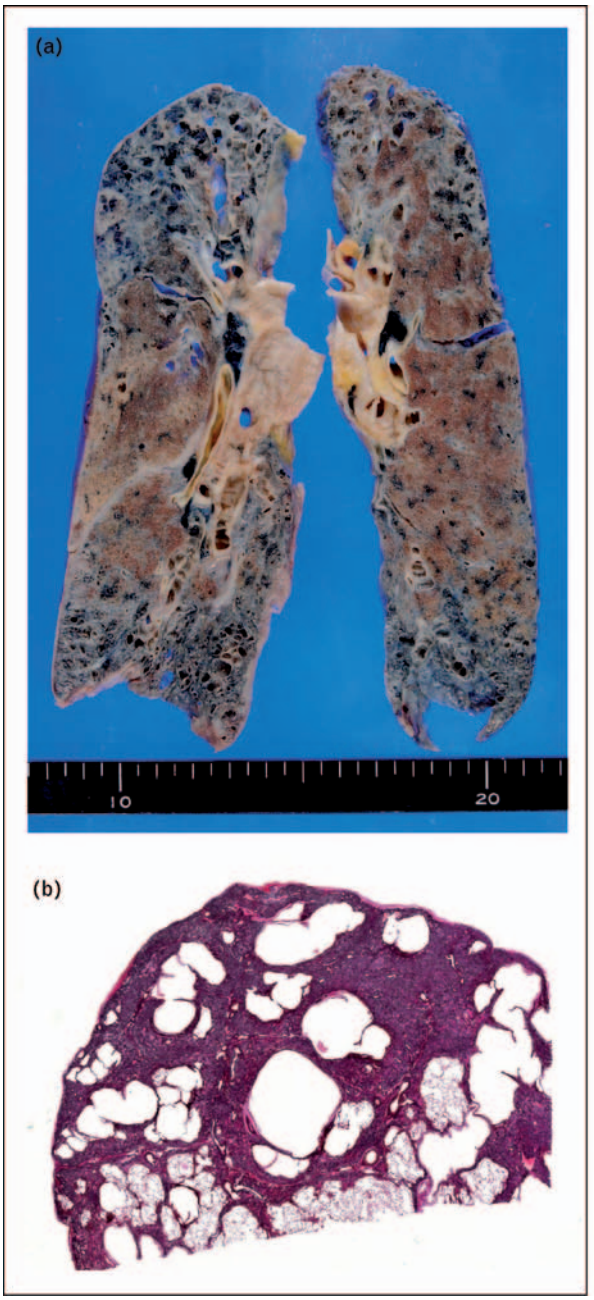
(a) The lungs showed lower lobe contraction with honeycomb change, mimicking usual interstitial pneumonia (UIP)/idiopathic pulmonary fibrosis (IPF). (b) Small size honeycomb change of the lower lobe. (c) Microscopic appearance of honeycomb change in the lower lobe (EvG, ×1). (d) Hyaline membrane formation in the upper lobe of the same case (HE, ×20).

diameter, and they were found both in the lower lobes and in the upper lobe (Fig. 12a–c). Subpleural atelectasis and cystic lesions were frequently observed (Fig. 13). These cystic lesions are closely associated with atelectatic fibrosis. Thus, cyst formation may be associated with bronchiolar obstruction due to bronchiolitis and traction by the atelectatic fibrosis. Cholesterol-laden giant cells were observed in the interstitium in nine cases, whereas no epithelioid cell granulomas were observed in any of the 17 cases. DAD had developed in seven cases of insidious onset of chronic bird fancier's lung and in two cases with recurrent episodes of summer-type hypersensitivity pneumonitis (Table 2). Histological features of DAD are the same as those of IPF/UIP (Fig. 12d), showing hyaline membrane formation of acute stage and organizing stage [89,90].

Differential diagnosis

The pathological features of hypersensitivity pneumonitis are nonspecific and should be differentiated from other interstitial lung diseases, for example, sarcoidosis, lymphoid interstitial pneumonia (LIP), NSIP, and UIP (Table 3). Granulomas are usually poorly formed and become resolved in hypersensitivity pneumonitis, compared with well packed, persistent granulomas in sarcoidosis. The granuloma in hypersensitivity pneumonitis is preferably distributed to the centrilobular area and

Figure 13 Atelectasis and cystic change in the upper lobe from a case of chronic bird fancier's lung



(a) Note the atelectatic fibrosis, cystic change and traction bronchiectasis of the upper lobes. (b) Marked atelectasis and elastosis with cystic change of the upper lobe (EvG, ×1).

alveolar ducts, compared with lymphangitic distribution, that is, broncovascular bundles and pleura in sarcoidosis. Interstitial lymphocyte infiltration is more prominent in LIP, but it is difficult to separate from cellular NSIP [59,62]. Cellular bronchiolitis and subsequent peribronchiolar fibrosis are more frequent in hypersensitivity pneumonitis than LIP. Fibrosis is variable in CHP and frequently similar to that of fibrotic NSIP and UIP; however,

Table 2 Pathological features of autopsy lungs from cases of chronic hypersensitivity pneumonitis

Type of CHP (observation period)	Number of cases	Upper lobe contraction	Lower lobe contraction	Honeycomb change	Fibrotic NSIP-like pattern	CLF	Bridging fibrosis	Atelectatic fibrosis	Cystic change	Cholesterol-laden giant cells	DAD
Bird fancier's Lung (13 cases) (15–144 months)	Insidious (12 cases)	5	6	12	5	12	8	4	10	7	7
	Recurrent (1 case)	0	0	1	1	1	1	0	0	0	0
Summer-type HP (4 cases) (24–152 months)	Insidious (2 cases)	1	3	2	2	2	1	2	1	1	0
	Recurrent (2 cases)	1	0	2	2	2	0	0	1	1	2

CHP, chronic hypersensitivity pneumonitis; CLF, centrilobular fibrosis; DAD, diffuse alveolar damage; HP, hypersensitivity pneumonitis; NSIP, nonspecific interstitial pneumonia.

Table 3 Comparison of histological features between hypersensitivity pneumonitis, sarcoidosis, lymphoid interstitial pneumonitis, NSIP and UIP

	HP	Sarcoidosis	LIP	NSIP	UIP
Granuloma morphology	Poorly formed	Well formed	Well formed or poorly formed	Absent	Absent
Distribution	Random, peribronchiolar	Lymphangitic	Random		
Interstitial infiltrate of inflammatory cells	Prominent peri-bronchiolar	Minimal	Extensive, diffuse	Diffuse, moderate	Minimal
Intraluminal fibrosis	Moderate	Minimal	Absent	Moderate	Absent, rare
Cellular bronchiolitis	Frequent	Minimal	Minimal	Minimal	Minimal
Fibrosis interstitial	Frequent in chronic	In advanced cases	Unusual	Frequent	Frequent
CLF	Frequent in chronic	Occasional	Absent	Minimal	Minimal
Honeycomb	Frequent in chronic	Occasional in advanced cases	Absent	Occasional in fibrotic NSIP	Frequent
Fibroblastic foci	Occasional	Absent	Absent	Occasional	Frequent

CLF, centrilobular fibrosis; HP, hypersensitivity pneumonitis; LIP, lymphoid interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia.

centrilobular fibrosis is prominent in CHP. When pathological features are suggestive of hypersensitivity pneumonitis, the final diagnosis of hypersensitivity pneumonitis requires clinical findings and identification of the causative antigens.

Conclusion

The histopathological features of CHP consist of a mixture of UIP-like, NSIP-like, and organizing pneumonia patterns with the presence of centrilobular fibrosis and bridging fibrosis. In addition to these features, atelectatic fibrosis in the lobule is also an important feature in relation to distortion of the lung architecture.

CHP has been extracted from cases previously diagnosed as IPF/UIP, based on the HRCT and pathological features. It is important to differentiate CHP from IPF, because avoidance of antigen exposure may improve or stop the progression of CHP. However, once irreversible fibrosis develops, the disease progression and the subsequent events are similar to those of IPF, and DAD occurs in the terminal stage.

Acknowledgements

The authors thank Dr O.P. Sharma for his kind review of this manuscript and Dr M. Oritsu, Japanese Red Cross Medical Center, Dr T. Ogura. Kanagawa Cardiovascular Respiratory Center and Dr Y. Yamada, JR Tokyo General Hospital for contribution of valuable cases.

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- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 503).

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