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Pathological differentiation of chronic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis/usual interstitial pneumonia

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Pathological differentiation of chronic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis/usual interstitial pneumonia

Aims: To evaluate the histological characteristics differentiating chronic hypersensitivity pneumonitis (chronic HP) with a usual interstitial pneumonia (UIP)-like pattern from idiopathic pulmonary fibrosis (IPF)/UIP.

Methods and results: Surgical lung biopsy specimens from 22 patients with chronic HP diagnosed as having a UIP-like pattern upon histological examination and 13 patients with IPF/UIP were examined and the incidences of bronchiolitis, perilobular fibrosis, centrilobular fibrosis, bridging fibrosis, organizing pneumonia, fibroblastic foci, honeycombing, granulomas, giant cells, lymphocytic alveolitis and lymphoid follicles were compared. Bronchiolitis, centrilobular fibrosis, bridging fibrosis, organizing pneumonia, granulomas, giant cells and lymphocytic alveolitis were significantly more frequent among patients with chronic HP than among patients with IPF (all $P < 0.01$).

Conclusions: Centrilobular fibrosis, bridging fibrosis and organizing pneumonia, in addition to bronchiolitis, granulomas and giant cells, are characteristic features of chronic HP with a UIP-like pattern. These features are therefore important in differentiating chronic HP from IPF/UIP, as management strategies differ for the two disorders.

Keywords: chronic hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, pathological differentiation, usual interstitial pneumonia

Abbreviations: GGO, ground glass opacification; HP, hypersensitivity pneumonitis; HRCT, high resolution computed tomography; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia, UIP, usual interstitial pneumonia

Introduction

Hypersensitivity pneumonitis (HP) is a diffuse interstitial lung disease, caused by inhalation of various antigens, organic dusts and chemicals, and is classified clinically into acute, subacute and chronic forms.[1–3] The histopathological findings in chronic HP have been described recently,[4–7] but histological features overlap with other idiopathic interstitial pneumonias, especially idiopathic pulmonary fibrosis (IPF).[8,9] Indeed, some cases diagnosed initially as IPF have been confirmed later to be chronic summer-type HP.[10,11] Furthermore, the causative antigen can be difficult to determine.[12] Several studies have demonstrated good prognosis in patients with chronic HP showing patterns of non-specific

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interstitial pneumonia (NSIP) and organizing pneumonia (OP), but worse prognosis in those with the usual interstitial pneumonia (UIP) pattern.[4,13–15]

The aim of this study was therefore to evaluate the characteristic histological features of chronic HP exhibiting a UIP-like pattern, to compare them with those of IPF/UIP in order to determine any features that might help to distinguish chronic HP from IPF, and to compare the outcomes of these groups.

Materials and methods

CASE SELECTION

Twenty-two patients with chronic HP in whom biopsy revealed a UIP-like pattern were selected. All the patients had been treated at the Japanese Red Cross Medical Center in Tokyo or the Kanagawa Cardiovascular and Respiratory Center in Yokohama between 1994 and 2010. All patients had been diagnosed as having chronic HP based on the recurrence of respiratory symptoms induced by environmental stimuli, the results of provocation tests for antigens, the appearance of fibrosis on chest X-rays and deterioration on a restrictive pulmonary function test.[16,17] The clinical form of chronic HP was classified as either of insidious onset or recurrent, according to Yoshizawa's[16] criteria. Thirteen cases with IPF/UIP diagnosed using a clinical, radiological and pathological approach according to the American Thoracic Society/European Respiratory Society (ATS/ERS) consensus statement, published in 2002,[8] were selected for comparison.

The smoking habits, high resolution computed tomography (HRCT) findings and follow-up data of the cases with chronic HP and IPF/UIP were compared.

PATHOLOGICAL EVALUATION

For patients with chronic HP, surgical lung biopsies were obtained from the upper and lower lobes in 18 patients, from three lobes in two patients and from only the lower lobes in two patients. In this study, the UIP-like pattern was represented by a patchwork appearance of subpleural or paraseptal fibrosis alternating with normal alveoli, temporal heterogeneity and architectural distortion with or without honeycombing on the histological sections.[8,9]

For patients with UIP/IPF, specimens were obtained from the upper and lower lobes in 10 patients and from three lobes in three patients; histological findings were consistent with concordant UIP.[18] The histological sections were stained with haematoxylin and eosin, elastica van Gieson and Alcian Blue-periodic acid-Schiff (PAS). The histological evaluations of the sections were performed in a blinded manner by two pathologists (T.T., T.A.).

We identified the characteristic histological features in each case, and recorded the extent of chronic bronchiolitis, perilobular (subpleural and paraseptal) fibrosis, centrilobular fibrosis (including peribronchiolar fibrosis), bridging fibrosis, organizing pneumonia with or without progression to interstitial fibrosis,[19] fibroblastic foci, honeycombing, granulomas, giant cells, lymphocytic alveolitis without fibrosis, and lymphoid follicles, in both the chronic HP group and the IPF/UIP group. Areas felt to be respiratory bronchiolitis due to exposure to cigarettes were recorded separately. Bridging fibrosis was defined as the presence of a linear connection between fibrosis in the centrilobular area and fibrosis in the perilobular area (subpleural and paraseptal), as well as between the centrilobular and adjacent centrilobular areas.[7]

Statistical analysis of the incidence of histological features was performed using Fisher's exact probability test or the chi-squared test. A P-value <0.05 was considered significant. This study was approved by the internal review boards of the authors' institutions, and informed consent was obtained from all the patients.

Results

CLINICAL FEATURES

The clinical findings of chronic HP with pathological UIP-like pattern are presented in Table 1. The patients with chronic HP comprised 13 men and nine women; their average age was 59.7 years (range 33–74 years). There were two current smokers and nine ex-smokers among the 13 men and two ex-smokers among the nine women, with an average of 33 pack-years. Of the 18 insidious cases, 12 were bird-related and six were home-related, while among the four recurrent cases one was bird-related, two were home-related and one was humidifier-related. The intervals between the onset of symptoms and the time of biopsy ranged from 3 to 108 months. The clinical features of the IPF cases are presented in Table 2. The patients with IPF were all men, with a mean age of 63 years; and all were smokers, with an average of 49 pack-years. The interval between the onset of symptoms and the time of biopsy among the IPF patients ranged from 2 to 60 months. The smoking habits of the IPF cases were significantly different to those of patients with chronic HP ($P < 0.05$).

Table 1. Clinical findings of 22 patients with chronic hypersensitivity pneumonitis

Age/sex	Antigen	Clinical form	Smoking (pack-years)	Onset∼Bx (months)	HRCT findings at biopsy	Biopsy site (histology)	Treatment	Follow-up (months)
53 Male	Bird	I	Ex 15	72	Reticular, nodule, GGO	U (UIP), M (NSIP), L(UIP)	PSL	Alive (144)
60 Female	Home	R	Never	24	Honeycomb, nodule	L2 (UIP)	PSL, Azp	Died (55)
66 Male	Bird	I	Ex 30	5	Reticular, honeycomb	U (UIP), L (UIP)	PSL	Alive (97)
67 Male	Bird	I	Ex 30	8	Reticular, nodules, honeycomb	U (UIP), L (UIP)	No	Alive (89)
33 Male	Bird	I	C 25	36	Nodule, thick BVB	U (UIP), L (UIP)	PSL	Worse (66)
54 Male	Bird	I	Ex 48	36	GGO, reticular	U (UIP), L (UIP)	PSL	Died (16)
64 Female	Home	I	Never	108	GGO, reticular, consolidation	U (UIP), M (NSIP), L (UIP)	PSL	Stable (41)
74 Male	Bird	I	C 55	Unknown*	Reticular, volume loss	L3 (UIP)	PSL	Stable (38)
59 Male	Bird	I	Ex 80	60	GGO, reticular	U (UIP), L (UIP)	PSL	Stable (38)
64 Male	Bird	I	Ex 20	36	Reticular, honeycomb	U (UIP), L2 (UIP)	PSL	Stable (40)
60 Male	Home	I	Ex 52.5	3	Reticular	U (NSIP), L2 (UIP)	No	Stable (30)
58 Female	Home	I	Never	18	Reticular, thick ILS	U (UIP), L2 (UIP)	No	Stable (17)
65 Female	Bird	R	Never	6	Reticular, nodule	U (UIP), L (UIP)	PSL	Worse (73)
64 Female	Bird	I	Never	36	Reticular, thick BVB	U (UIP), L2(UIP)	PSL	Stable (13)
55 Male	Home	I	Ex 25	3	Reticular, thick BVB	U (UIP), L (UIP)	PSL	Died (60)
60 Male	Humidf	R	Never	24	Nodule, thick ILS, GGO	U (UIP), L (UIP)	PSL	Alive (105)
65 Male	Home	R	Never	24	GGO, nodule, thick ILS	U (UIP), L (UIP)	PSL	Worse (65)
66 Female	Bird	I	Ex 30	12	Nodule, GGO, honeycomb,	U (UIP), L (UIP)	No	Died of Ca (21)
41 Male	Bird	I	Ex 5	Unknown*	Nodule, GGO, reticular,	U (UIP), L (UIP)	No	Dropout
69 Female	Home	I	Never	60	Honeycomb, GGO, thick ILS	U (UIP), L2 (UIP)	No	Stable (8)
75 Female	Bird	I	Never	12	Reticular, thick ILS,	U (UIP), L2 (UIP)	No	Stable (6)
61 Female	Bird	I	Ex 15	36	Reticular	U (UIP), L (UIP)	No	Stable (3)

Bird, bird-related antigen; Home, home-related antigen; Humidf, humidifier-related antigen; I, insidious onset; R, recurrent; Ex, ex-smoker; Never, never smoker; C, current smoker; Onset∼Bx, interval between onset of symptoms until biopsy; HRCT: high resolution computed tomography; GGO: ground-glass opacification; BVB: bronchovascular bundle; ILS, interlobular septum; U, upper lobe; M, middle lobe; L, lower lobe; L2, two sites of lower lobe; L3, three sites of lower lobe; UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; PSL, prednisolone; Azp, azathioprine; Died of Ca, died of lung cancer. *Unknown: found at physical examination and no determined onset.

Table 2. Clinical findings of 13 patients with idiopathic pulmonary fibrosis

Age/sex	Smoking (pack-years)	Onset~Bx (months)	HRCT findings at biopsy	Biopsy site (histology)	Treatment	Follow-up (months)
56 Male	C 120	14	Reticular	U (UIP), L (UIP)	PSL	Died (100)
53 Male	Ex 19	5	Reticular, honeycomb	U (UIP), M (UIP), L (UIP)	PSL	Died (72)
60 Male	C 60	5	Reticular, honeycomb	U (UIP), M (UIP), L (UIP)	PSL	Dropout
59 Male	Ex 1.9	4	Reticular, nodule	U (UIP), L2 (UIP)	No	Worse, dropout
69 Male	Ex 22.5	Unknown	Reticular, honeycomb	U (UIP), L2 (UIP)	PSL	Died (94)
56 Male	C 75	6	Reticular, honeycomb	U (UIP), L (UIP)	PSL	Worse (91)
71 Male	C 50	2	Reticular, honeycomb	U (UIP), L (UIP)	PSL	Worse, dropout
75 Male	Ex 6	60	Reticular	U (UIP), L (UIP)	PSL	Worse, dropout
71 Male	Ex 62.5	2	Reticular	U (UIP), L (UIP)	PSL	Died of Ca (32)
46 Male	C 20	12	Reticular, volume loss	U (UIP), L (UIP)	PSL	Worse (64)
76 Male	Ex 87.5	3	Reticular, nodule, GGO	U (NSIP), L2 (UIP)	PSL	Worse (40)
72 Male	Ex 30	6	Reticular, honeycomb	U (UIP), M (UIP), L (UIP)	PSL	Worse (89)
57 Male	C 74	36	Bullae, honeycomb, reticular	U (UIP), L (UIP)	PSL	Died of Ca (94)

C, current smoker; Ex, ex-smoker; HRCT, high resolution computed tomography; GGO, ground glass opacification; U, upper lobe; M, middle lobe; L, lower lobe; L2, two sites of lower lobe; UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; PSL, prednisolone; Died of Ca, died of lung cancer.

The HRCT findings in the chronic HP patients at the time of biopsy revealed ground glass opacification (GGO) in nine cases and nodules in 10 cases, compared with GGO in one case and nodules in two cases in the IPF group. GGO was significantly more frequent among the chronic HP cases, compared with the IPF cases ($P < 0.05$).

PATHOLOGICAL FEATURES

The incidences of histological features in chronic HP cases with a UIP-like pattern and in IPF/UIP are summarized in Table 3.

Chronic HP exhibiting a UIP-like pattern commonly revealed perilobular fibrosis combined with centrilobular fibrosis (Figure 1A). In centrilobular fibrosis, the occasional obliteration of respiratory bronchioles by fibrosis and hyperplasia of smooth muscle cells was seen in five cases (22.7%), as shown in Figure 1B. Chronic bronchiolitis was observed in all the chronic HP cases, especially in the recurrent cases, which showed varying degrees of lymphocyte infiltration with occasional lymphoid follicles, loose granuloma formation and fibrosis in the terminal and respiratory bronchioles (Figure 1C). Fibroblastic foci were seen frequently around the respiratory bronchioles, compared with the situation in IPF ($P < 0.01$). In the smokers, respiratory bronchiolitis was observed in both the chronic HP and IPF cases. However, the degree of respiratory bronchiolitis was mild in chronic HP. The histological features in relation to the bronchioles in chronic HP and IPF are presented in Table 4.

Centrilobular fibrosis involving peribronchiolar alveoli was observed in 100% of the chronic HP cases, as opposed to 46% of the IPF cases. Fibroblastic foci were seen occasionally around the bronchioles in the chronic HP cases, as seen at the edge of areas with subpleural and peribronchiolar fibrosis.

Perilobular fibrosis, a key histological feature of UIP, was observed in the subpleural and paraseptal areas in

Table 3. Incidence of histological features of chronic hypersensitivity pneumonitis (HP) with usual interstitial pneumonia (UIP)-like pattern compared with idiopathic pulmonary fibrosis (IPF)/UIP

	Chronic HP (n = 22)		IPF/UIP (n = 13)		
Histological features	Cases (n)	%	Cases (n)	%	P-value
Bronchiolitis	22	100	6	46.2	0.0003
Perilobular fibrosis	22	100	13	100	1.0000
Centrilobular fibrosis	22	100	6	46.2	0.0003
Bridging fibrosis	18	81.8	4	30.8	0.0042
Organizing pneumonia	18	81.8	3	23.1	0.0006
Fibroblastic foci	22	100	13	100	1.0000
Honeycombing	13	59.1	10	76. 9	0.4776
Granulomas	14	63.6	0	0.0	0.0002
Giant cells	15	68.2	0	0.0	<0.0001
Isolated cyst with collagen deposition	3	13.6	0	0.0	0.2790
Lymphocytic alveolitis without fibrosis	19	86.4	4	30.8	0.0022
Lymphoid follicle	17	77.3	5	38.5	0.0268

all the cases of chronic HP with UIP-like pattern. Characteristic bridging fibrosis was observed in 18 cases (81.8%) of chronic HP, as opposed to four cases (30.8%) of IPF. The most frequent pattern of bridging fibrosis was between the respiratory bronchioles and the interlobular septa (Figure 2A) in 15 cases (83%), followed by a connection between respiratory bronchiole and adjacent respiratory bronchiole (Figure 2B) in 11 cases (61%) and the subpleural area in nine cases (50%).

Organizing pneumonia with or without incorporation into the interstitium was observed in 18 cases (81.8%) and frequently involved the region of the alveolar ducts (Figure 3A,B). Alveolar collapse was also seen around the bronchioles and along the alveolar duct and interlobular septum (Figure 3C). However, the frequency of subpleural collapse was not different in chronic HP and IPF cases. Lymphocytic alveolitis (86.4%) was observed focally in chronic HP cases exhibiting a predominantly UIP-like pattern. These histological features were not specific to various antigen species of chronic HP in this study. An isolated cystic lesion was observed in the lung parenchyma adjacent to atelectasis in three cases of chronic HP, exhibiting collagen deposition within the cyst wall with scattered multinucleated giant cells and macrophages in the inner surface.

Honeycombing (59.1%) and fibroblastic foci (100%) were both common findings in chronic HP, as they were in cases of IPF/UIP. However, the perilobular fibroblastic foci were more numerous in the IPF cases than in the chronic HP cases, while they were observed more frequently around the respiratory bronchioles in the chronic HP cases. The granulomas were poorly formed and present mainly in the fibrous area around the respiratory bronchioles. Giant cells were present in the fibrous areas with frequent cholesterol clefts in the cytoplasm.

Among the histological parameters, bronchiolitis (P = 0.0003), centrilobular fibrosis (P = 0.0003), bridging fibrosis (P = 0.0042), organizing pneumonia (P = 0.0006), poorly formed granulomas (P = 0.0002), giant cells (P < 0.0001), lymphocytic alveolitis, (P = 0.0022) and lymphoid follicles (P = 0.0268) were significantly more common in the chronic HP cases than in the IPF cases. Granulomas and giant cells in the fibrotic areas were not observed in the IPF cases.

FOLLOW-UP DATA

The patients with chronic HP were recommended to avoid antigen exposure. Fourteen cases were treated with corticosteroids, of whom four deteriorated and

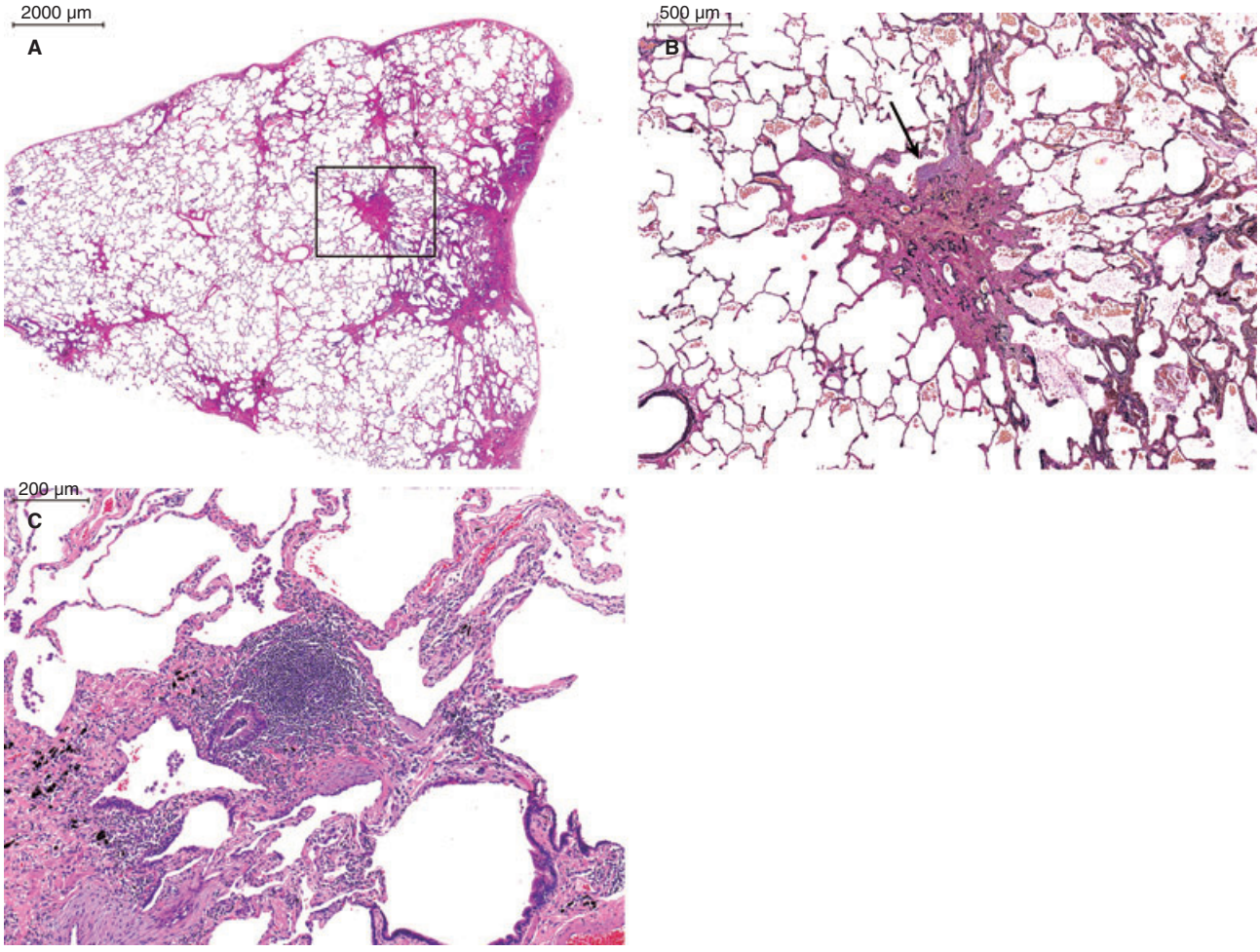

Figure 1. Centrilobular and bridging fibrosis in chronic hypersensitivity pneumonitis exhibiting a usual interstitial pneumonia (UIP)-like pattern. **A**, Subpleural fibrosis and centrilobular fibrosis (shown in box) in bird-related chronic HP (bar, 2 mm; haematoxylin and eosin). **B**, Fibrous obliteration of respiratory bronchiole (box in A) with smooth muscle hyperplasia and a fibroblastic focus (arrow) at the edge of the fibrosis (bar, 500 μm; elastica van Gieson). **C**, Lymphoid follicle in the wall of a respiratory bronchiole (bar, 200 μm; haematoxylin and eosin).

Table 4. Histological features of bronchioles in chronic hypersensitivity pneumonitis (HP) with usual interstitial pneumonia-like pattern compared with idiopathic pulmonary fibrosis (IPF)

Histological feature	Chronic HP (n = 22) cases (%)	IPF (n = 13) cases (%)	P-value
Respiratory bronchiolitis	9 (40.9)	9 (69.2)	0.1017
Lymphocyte infiltration	22 (100)	6 (46.2)	0.0003
Fibrosis of RB	22 (100)	7 (53.8)	0.0011
Obliteration of RB	5 (22.7)	1 (7.7)	0.2569
Fibroblastic foci	14 (63.6)	1 (7.7)	0.0013
Lymphoid follicle	8 (36.4)	0	0.0091
Granuloma or giant cell	4 (18.2)	0	0.0077

RB, respiratory bronchiole.

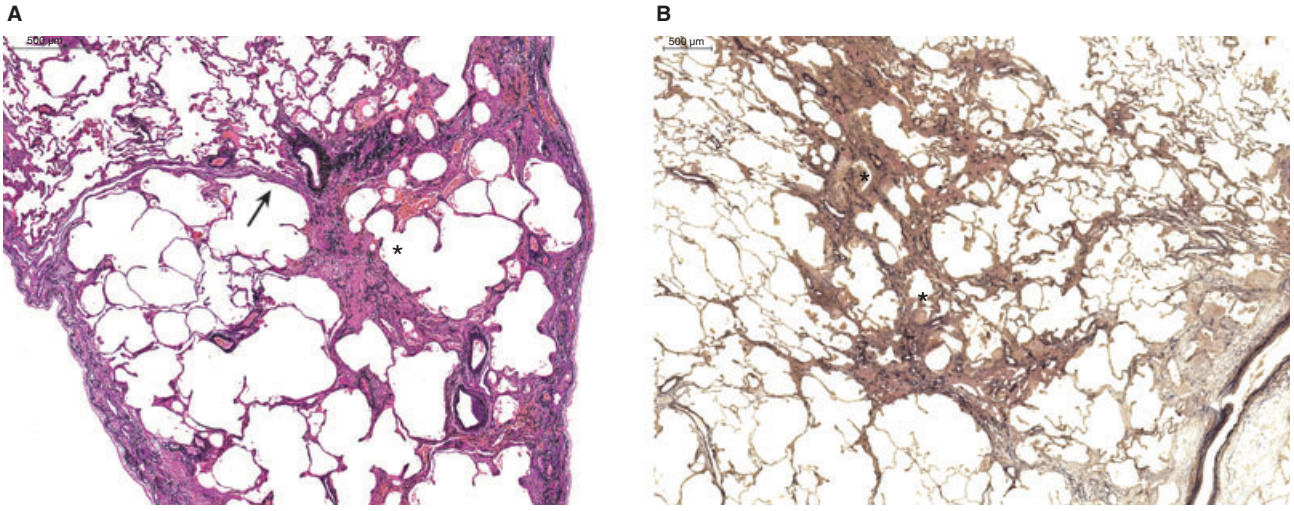

Figure 2. Bridging fibrosis in chronic hypersensitivity pneumonitis. **A**, Bridging fibrosis between centrilobular area and the interlobular septum (bar, 500 μm; elastica van Gieson). **B**, Peribronchiolar fibrosis with a connection to a neighbouring respiratory bronchiole (bar, 500 μm; elastica van Gieson). *Respiratory bronchiole. Arrow, interlobular septum.

eight were stable. As the biopsies of three cases were performed within 1 year, the follow-up times ranged from 3 months to 12 years in the chronic HP group. Four patients died, one of lung cancer. In the IPF group, the follow-up times ranged from 2 to 8 years. Five patients died within 8 years after their biopsy, two of lung cancer, and all the survivors showed disease progression. The Kaplan–Meier survival curves for the chronic HP and IPF cases were not statistically different (Figure 4).

Discussion

In this study, we compared the pathological features in a patient cohort with chronic HP showing a predominantly UIP pattern with those in a cohort with IPF/UIP, and demonstrated several characteristic pathological features capable of differentiating chronic HP from IPF.

The fibrosis pattern in chronic HP, which exhibits a predominantly UIP-like pattern histologically, is characterized by centrilobular fibrosis, bridging fibrosis and intraluminal fibrosis, in addition to the subpleural and paraseptal fibrosis that is seen commonly in UIP cases.[8,9] We reported previously in an autopsy study that centrilobular fibrosis and bridging fibrosis were significantly more conspicuous in the cases with chronic HP than those with IPF/UIP.[20] In chronic HP, the fibrosis is more bronchiolocentric in distribution, rather than being predominantly subpleural and paraseptal as in UIP.[21] Centrilobular fibrosis is related to the bronchiolar lesion due to the deposition of inhaled antigen. An experimental model of chronic HP has demonstrated that inflammation occurs initially in the respiratory bronchioles and alveolar ducts.[22] A high-resolution computed tomography study has also revealed centrilobular nodules in confirmed images of chronic HP, compared with images of IPF and NSIP.[23]

Bridging fibrosis, namely a connection between centrilobular and perilobular or centrilobular fibrosis, is observed frequently in patients with chronic HP. The most frequent form of bridging fibrosis consists of connections between respiratory bronchioles and the interlobular septum. Organizing pneumonia, which is localized and limited to the alveoli and alveolar ducts, presents as alveolar injury, due probably to antigen exposure. It seems reasonable to suppose that unresolved organizing pneumonia and the consequent collapse of alveoli lead to the development of bridging fibrosis. However, bridging fibrosis is not specific to chronic HP; a similar connection between centrilobular and perilobular fibrosis occurs in occupational lung diseases, such as asbestosis. Akira *et al.*[24] reported that subpleural and peribronchiolar fibrosis are connected histologically, and recognised as a curvilinear line in HRCT. They demonstrated that curvilinear lines are correlated pathologically with peribronchiolar fibrosis combined with the collapse of the alveoli.[24,25]

Bronchiolar alterations in patients with chronic HP are characterized by lymphoid aggregates, occasional granulomas or giant cells and fibroblastic foci in the respiratory bronchioles. These histological features of the bronchioles, especially the respiratory bronchioles, suggest that such areas are affected preferentially by

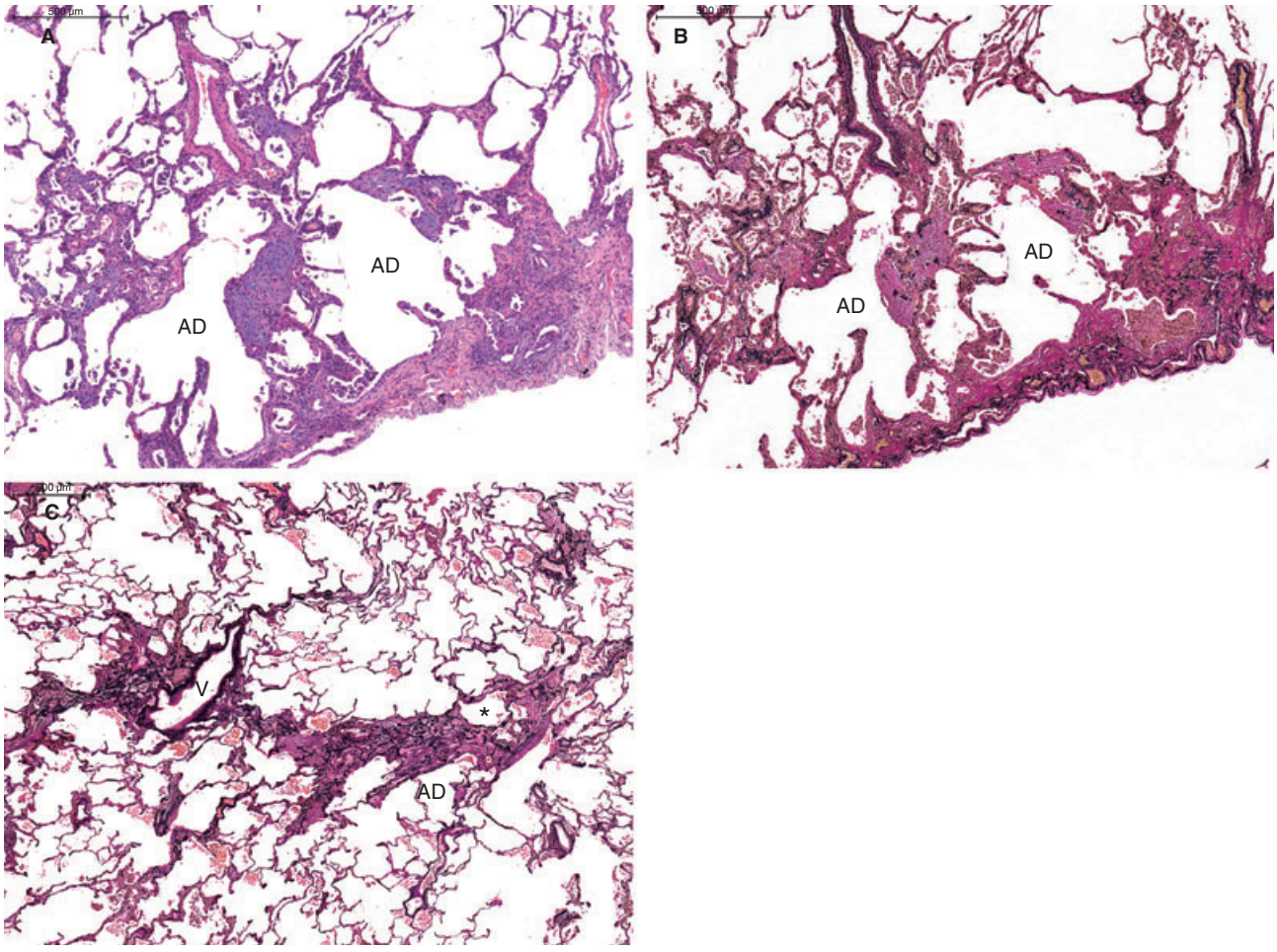

Figure 3. Organizing pneumonia in the alveolar duct and atelectasis. **A**, Organizing pneumonia in the alveolar duct with mural incorporation in a patient with bird-related chronic hypersensitivity pneumonitis (bar, 500 μm; haematoxylin and eosin). **B**, Same area stained with elastica van Gieson (bar, 500 μm). **C**, Atelectatic fibrosis along the alveolar duct connecting to the interlobular septum (bar, 500 μm; elastica van Gieson). AD, alveolar duct. *Respiratory bronchiole; V, interlobular vein.

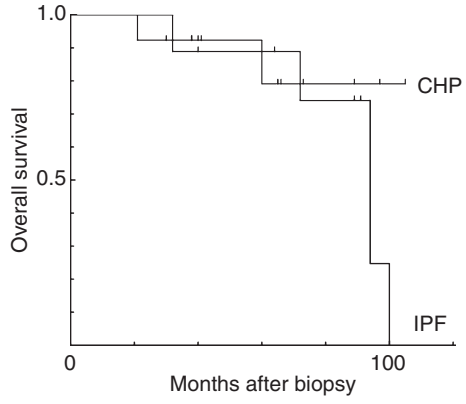

Figure 4. Kaplan–Meier survival curves for chronic hypersensitivity pneumonitis (CHP) with a usual interstitial pneumonia-like pattern, and idiopathic pulmonary fibrosis (IPF).

inhalation of antigens, and centrilobular fibrosis then develops. Perez-Padilla *et al.*[26] reported a spectrum of bronchiolar lesions from mononuclear inflammation to fibrosis with smooth muscle hyperplasia in patients with chronic pigeon breeder's disease, compared with IPF. They reported a higher incidence of inflammation, fibrosis and squamous metaplasia of membranous bronchioles among patients with pigeon breeder's disease than among those with UIP, and demonstrated small airway disease due to chronic inflammation and fibrosis, parallel to the damage in the parenchyma.

Poorly formed granuloma and giant cells with frequent cholesterol clefts were observed in areas of fibrosis in the cases with chronic HP, but they were not found in the IPF cases. These features are characteristic of chronic HP.[4,5] This finding suggests that the

possibility of chronic HP should be considered in cases with granulomas and giant cells in the areas of fibrosis in patients with a UIP pattern.

Lung cysts were reported by Franquet *et al.*[27] in subacute HP and also in chronic HP[23] as thin-walled cysts present in areas of GGO on HRCT. Franquet *et al.*[27] postulated that cysts are related to peribronchiolar lymphocytic infiltration. However, the cysts in this study sometimes had relatively thick fibrous walls with scattered multinucleated giant cells on the inner surface, as described previously.[7] As the cystic lesions in our study were located in the atelectatic parenchyma with occasional destruction of alveoli, interstitial emphysema might be one of the mechanisms contributing to cyst formation in chronic HP, although their precise pathogenesis remains to be elucidated.

Previous studies of the outcome in chronic HP have revealed the poor prognosis of cases with a UIP pattern, compared with those with NSIP or OP patterns.[4,13–15] In this study, the Kaplan–Meier survival curves suggest that the prognosis of chronic HP with a UIP-like pattern is similar to that of IPF. However, by avoidance of antigen exposure patients with the former tend to have a longer period of stability than those with IPF. This study involved a relatively small number of cases, and a more precise comparison of the outcomes for patients with HP with a UIP-like pattern and those with IPF will require examination of larger series.

In conclusion, the presence of centrilobular and bridging fibrosis in addition to bronchiolitis, localized organizing pneumonia, lymphocytic alveolitis, granulomas, giant cells and lymphoid follicles is highly suggestive of chronic HP in cases that demonstrate perilobular fibrosis mimicking IPF/UIP. It is important to differentiate chronic HP from IPF/UIP on histological examination, since avoidance of antigen exposure can prevent disease progression and improve patient outcome.[2] Depending on their histological findings, pathologists should advise clinicians to explore the possible causative antigens.

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References

1. Selman M. Hypersensitivity pneumonitis: a multifaceted deceiving disorder. *Clin. Chest Med.* 2004; **25;** 531–547.
2. Mohr LC. Hypersensitivity pneumonitis. *Curr. Opin. Pulm. Med.* 2004; **10;** 401–411.
3. Hanak V, Golbin JM, Ryu JH. Causes and presenting features in 85 consecutive patients with hypersensitivity pneumonitis. *Mayo Clin. Proc.* 2007; **82;** 812–816.
4. 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.
5. Churg A, Muller NL, Flint J, Wright JL. Chronic hypersensitivity pneumonitis. *Am. J. Surg. Pathol.* 2006; **30;** 201–208.
6. Trahan S, Hanak V, Ryu JH, Myers JL. Role of surgical lung biopsy in separating chronic hypersensitivity pneumonia from usual interstitial pneumonia/idiopathic pulmonary fibrosis: analysis of 31 biopsies from 15 patients. *Chest* 2008; **134;** 126–134.
7. Takemura T, Akashi T, Ohtani Y, Inase N, Yoshizawa Y. Pathology of hypersensitivity pneumonitis. *Curr. Opin. Pulm. Med.* 2008; **14;** 440–454.
8. 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.
9. Raghu G, Collard HR, Egan JJ *et al.* An official ATS/ERS/JRS/ALAT statement. Idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am. J. Respir. Crit. Care Med.* 2011; **183;** 788–824.
10. Inase N, Ohtani Y, Usui Y, Miyazaki Y, Takemura T, Yoshizawa Y. Chronic summer-type hypersensitivity pneumonitis; clinical similarities to idiopathic pulmonary fibrosis. *Sarcoidosis Vasc. Diffuse Lung Dis.* 2007; **24;** 141–147.
11. Ohtani Y, Ochi J, Mitaka K *et al.* Chronic summer-type hypersensitivity pneumonitis initially misdiagnosed as idiopathic interstitial pneumonia. *Intern. Med.* 2008; **47;** 857–862.
12. Patel AM, Ryu JH, Reed CE. Hypersensitivity pneumonitis: current concepts and future questions. *J. Allergy Clin. Immunol.* 2001; **108;** 661–670.
13. Perez-Padilla R, Salas J, Chapela R *et al.* Mortality in Mexican patients with chronic pigeon breeder's lung compared with those with usual interstitial pneumonia. *Am. Rev. Respir. Dis.* 1993; **148;** 49–53.
14. Sahin H, Brown KK, Curran-Everett D *et al.* Chronic hypersensitivity pneumonitis: CT features-comparison with pathologic evidence of fibrosis and survival. *Radiology* 2007; **244;** 591–598.
15. Churg A, Sin DD, Everett D, Brown K, Cool C. Pathologic patterns and survival in chronic hypersensitivity pneumonitis. *Am. J. Surg. Pathol.* 2009; **33;** 1765–1770.
16. Yoshizawa Y, Ohtani Y, Hayakawa H, Sato A, Suga M, Ando M. Chronic hypersensitivity pneumonitis in Japan: a nationwide epidemiologic survey. *J. Allergy Clin. Immunol.* 1999; **103;** 315–320.
17. Ohtani Y, Kojima K, Sumi Y *et al.* Inhalation provocation tests in chronic bird fancier's lung. *Chest* 2000; **118;** 1382–1389.
18. Flaherty KR, Travis WD, Colby TV *et al.* Histologic variabilities in usual and nonspecific interstitial pneumonias. *Am. J. Respir. Crit. Care Med.* 2001; **164;** 1722–1727.
19. Basset F, Ferrans VJ, Soler P, Takemura T, Fukuda Y, Crystal RG. Intraluminal fibrosis in interstitial lung disorders. *Am. J. Pathol.* 1986; **122;** 443–461.
20. Akashi T, Takemura T, Ando N *et al.* Histopathologic analysis of sixteen autopsy cases of chronic hypersensitivity pneumonitis and comparison with idiopathic pulmonary fibrosis/usual interstitial pneumonia. *Am. J. Clin. Pathol.* 2009; **131;** 405–415.

21. Corrin B, Nicholson AG, eds. Occupational, environmental and iatrogenic lung disease. In *Pathology of the lung*. Philadelphia, PA: Churchill Livingstone, Elsevier, 2011; 266–367.
22. Mitaka K, Miyazaki Y, Yasui M *et al.* Th2-biased immune responses are important in a murine model of chronic hypersensitivity pneumonitis. *Int. Arch. Allergy Immunol.* 2011; **154;** 264–274.
23. Silva CI, Muller NL, Lynch DA *et al.* Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. *Radiology* 2008; **246;** 288–297.
24. Akira M, Yamamoto S, Yokoyama K *et al.* Asbestosis: high-resolution CT-pathologic correlation. *Radiology* 1990; **176;** 389–394.
25. Akira M, Yamamoto S, Inoue Y, Sakatani M. High-resolution CT of asbestosis and idiopathic pulmonary fibrosis. *Am. J. Roentgenol.* 2003; **181;** 163–169.
26. Perez-Padilla R, Gaxiola M, Salas J, Mejia M, Ramos C, Selman M. Bronchiolitis in chronic pigeon breeder's disease. Morphologic evidence of a spectrum of small airway lesions in hypersensitivity pneumonitis induced by avian antigens. *Chest* 1996; **110;** 371–377.
27. Franquet T, Hansell DM, Senbanjo T, Remy-Jardin M, Muller NL. Lung cysts in subacute hypersensitivity pneumonitis. *J. Comput. Assist. Tomogr.* 2003; **27;** 475–478.