

Chronic hypersensitivity pneumonitis in Japan: A nationwide epidemiologic survey

Yasuyuki Yoshizawa, MD,^a Yoshio Ohtani, MD,^a Hiroshi Hayakawa, MD,^b Atsuhiko Sato, MD,^c Moritaka Suga, MD,^d and Masayuki Ando, MD^d

Tokyo, Hamakita, Kyoto, and Kumamoto, Japan

Background: Pulmonary fibrosis inevitably develops in patients with chronic hypersensitivity pneumonitis (HP).

Objective: We conducted a nationwide epidemiologic study in Japan to evaluate the frequency and clinical characteristics of chronic HP.

Methods: This report is on 36 cases of chronic HP, including 10 patients with summer-type HP, 5 patients with home-related HP, 7 patients with bird fancier's lung, 5 patients with isocyanate-induced HP, 4 patients with farmer's lung, and 5 patients with other types of chronic HP. Chronic HP was further subgrouped into 2 types: one type of patients were first seen with chronic disease (9 patients), and the other type became chronic with fibrosis after repeated acute episodes (27 patients).

Results: The upper lung field was frequently involved in chronic HP (17%). Ground-glass opacities were observed in 57% and air space consolidation in 30% of the patients. Honeycombing was apparent in 37%. Twenty-six of 28 patients had antibodies to the presumptive antigens. Five of 8 patients with chronic HP were positive for antigen-induced lymphocyte proliferation. In 2 cases patients did not have detectable antibodies to causative antigens, although antigen-induced lymphocyte proliferation was detectable. The ratio of CD4 to CD8 in BAL lymphocytes was lowest in isocyanate-induced HP (mean 0.22) and tended to be high in farmer's lung and bird fancier's lung. Granulomas were observed in 39% and Masson bodies in 42% of specimens on histologic examination. Administration of prednisolone was effective in 58% of patients.

Conclusions: The insidious form of chronic HP has probably been misdiagnosed as idiopathic pulmonary fibrosis when a good history was not taken and immunologic (especially antigen-induced lymphocyte proliferation) and BAL testing were not counted. (*J Allergy Clin Immunol* 1999;103:315-20.)

Key words: Chronic hypersensitivity pneumonitis, nationwide survey, antigen-induced lymphocyte proliferation, upper lung field, honeycombing, pulmonary fibrosis

Hypersensitivity pneumonitis (HP) is an immunologically induced lung disease caused by inhalation of a variety of environmental agents.¹ HP is not a uniform disease but rather a complex syndrome characterized by varying intensities of responsiveness to different antigens leading to an immunopathology with variable clinical presentation and natural history.² The long-term outcome of bird fancier's lung and farmer's lung appears to be variable, including persistent obstructive airways disease.^{3,4,5} Continued exposure to antigen does not consistently lead to clinical deterioration, except in some patients such as those with pigeon breeder's disease. Patients with pigeon breeder's disease and farmer's lung frequently progress to pulmonary fibrosis despite avoidance of exposure to pigeon antigens.^{3,4,6}

Classically, the clinical presentation of HP has been divided into acute, subacute, and chronic forms on the basis of clinical features. The clinical features of chronic HP are subjective complaints of cough and dyspnea on exertion, imaging and pulmonary function abnormalities, and a poor prognosis with a strong resemblance to idiopathic pulmonary fibrosis (IPF).⁷ An epidemiologic study of IPF from Japan revealed a significantly higher prevalence among metal production workers, miners, painters, and production woodworkers.⁸ Painting and woodworking are known to be related to HP, which is induced by inhalation of isocyanates and contaminated fungi, respectively.^{9,10} In addition, breeding of birds has been suggested to be a risk factor for the development of IPF.¹¹ Collectively, it is probable that many cases of chronic HP have been incorrectly diagnosed as IPF.

We performed a nationwide epidemiologic study of chronic HP in Japan to determine a better estimate of the frequency and clinical characteristics of chronic HP during the past 10 years.

METHODS

The Research Committee on Diffuse Pulmonary Diseases, organized and sanctioned by the Japanese Ministry of Welfare, conducted a survey of chronic HP. A questionnaire was sent to qualified hospitals throughout Japan, and the diagnostic criteria of chronic HP was given to the physician in charge for the collection of as

From ^aPulmonary Medicine, Tokyo Medical and Dental University, Tokyo;

^bthe Department of Internal Medicine, National Sanatorium, Tenryu Hospital, Hamakita; ^cKyoto Preventive Medical Center, Kyoto; and ^dFirst Department of Internal Medicine, School of Medicine, Kumamoto University, Kumamoto.

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Reprint Requests: Yasuyuki Yoshizawa, MD, PhD, The Pulmonary Medicine, Tokyo Medical and Dental University, 5-45, Yushima 1-chome, Bunkyo-ku, Tokyo 113-8519, Japan.

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TABLE I. Summary by type of chronic HP

Type	No of patients (M:F)	Mean age (y)	Time lapsed to first visit (mos)	Observation period (y)
SHP (n = 10)	10 (2:8)	57.7	15.9	4.7
HR (n = 5)	5 (1:4)	61.6	9.0	7.1
TDI (n = 5)	5 (5:0)	54.0	2.9	4.6
BFL (n = 7)	7 (3:4)	60.7	74.0	4.5
FL (n = 4)	4 (3:1)	61.3	105.0	5.8
Other (n = 5)	5 (3:2)	49.4	13.0	5.2
Total (n = 36)	36 (17:19)	57.7 ± 8.1	31.9 ± 83.0	5.2 ± 4.0

SHP, Summer-type HP; HR, home-related HP; BFL, bird fancier's lung; TDI, isocyanate-induced HP; FL, farmer's lung; Other, other HP.

TABLE II. Smoking percentage

Type	Cases of repeated acute episodes (smoker: nonsmoker)	Cases of insidious onset (smoker:non-smoker)
SHP (n = 10)	9 (3:6)	1 (0:1)
HR (n = 5)	2 (2:2)	1 (0:1)
TDI (n = 5)	4 (3:1)	1 (1:0)
BFL (n = 7)	4 (2:2)	3 (1:2)
FL (n = 4)	2 (0:2)	2 (1:1)
Other (n = 5)	4 (2:2)	1 (1:0)
Total (n = 36)	27 (12:15)	9 (4:5)
Smoking rate	44.4%	44.4%

SHP, Summer-type HP; HR, home-related HP; BFL, bird fancier's lung; TDI, isocyanate-induced HP; FL, farmer's lung; Other, other HP.

Abbreviations used

HP: Hypersensitivity pneumonitis
HRCT: High-resolution computed tomography
IPF: Idiopathic pulmonary fibrosis
PSL: Prednisolone

many cases as possible. The data of each patient were described by members of the Research Committee or by members of the Japan Respiratory Society on staff at the hospitals. In addition, the authors discussed each case to confirm the diagnosis of chronic HP on the basis of the descriptions received from the various hospitals. Patients who had repeated acute episodes with intermittent disease-free periods were excluded from this analysis. Data from a total of 75 patients were collected from the various hospitals. According to the current diagnostic criteria described below, the patients were presented to us as 41 definite and 14 probable cases of chronic HP. We excluded 19 of these 55 patients because of insufficient data or lack of evidence of pulmonary fibrosis. Therefore 36 patients, ranging in age from 43 to 70 years (mean age, 58 ± 8.3 SD), were evaluated. The current diagnostic criteria for chronic HP was 3 or more of the following (including 5, either 2 or 3, and either 1 or 6): (1) reproduction of symptoms of HP by an environmental provocation or laboratory-controlled inhalation of the causative antigen; (2) evidence of pulmonary fibrosis with or without granulomas; (3) honeycombing on computed tomography scans; (4) progressive deterioration of a restrictive impairment on pulmonary function over 1 year; (5) over 6 months duration of respiratory symptoms related to HP; or (6) antibodies and/or lymphocyte proliferation to the presumptive antigen. The determination of antibody to the causative antigen was performed by Ouchterlony agar-gel diffusion, an indirect fluorescent method, or ELISA, with the antigens prepared at the individual institutions.

In vitro proliferation of PBMCs with the relevant antigen was performed as described previously.³ Briefly, each cell suspension (2 ×

10⁵ cells in 100 μL of RPMI 1640-10% FCS) was incubated in the presence of various concentrations of the relevant antigens. Cultures were done in triplicate in a humidified chamber with 5% CO₂ in air for 5 days. The uptake of ³H-thymidine by PBMCs was counted 16 hours after the PBMCs were pulsed with 1 μCi of ³H-thymidine.

Of the above 36 patients with chronic HP, 10 patients had summer-type HP (3 smokers and 7 nonsmokers), 5 had home-related HP (2 smokers and 3 nonsmokers), 7 had bird fancier's lung (3 smokers and 4 nonsmokers), 5 had isocyanate-induced HP (4 smokers and 1 nonsmoker), 4 had farmer's lung (1 smoker and 3 nonsmokers), and 5 had other types of chronic HP (3 smokers and 2 nonsmokers) (Tables I and II).

These patients with chronic HP were also classified into 2 subtypes: one subtype was first seen with chronic disease (insidious onset), and the other subtype had pulmonary fibrosis after repeated acute episodes (acute onset). The breakdown of patients on the basis of either acute or insidious onset was as follows: (1) summer-type chronic HP, 9 acute onset and 1 insidious onset; (2) home-related chronic HP, 4 acute onset and 1 insidious onset; (3) bird fancier's chronic HP, 4 acute onset and 3 insidious onset; (4) isocyanate-induced chronic HP, 4 acute onset and 1 insidious onset; (5) farmer's lung chronic HP, 2 acute onset and 2 insidious onset; and (6) other chronic HP, 4 acute onset and 1 insidious onset.

RESULTS

Characteristics of each HP group

The mean age of patients was 57.7 years. A predominance of male patients was observed in occupation-related HP, and a predominance of female patients was observed in home-related HP.

In isocyanate-induced HP, the duration of HP-associated respiratory symptoms was 2.9 months before the first visit to the hospital, the shortest interval among the 5 chronic HP groups. In the remainder of the HP groups, the time from onset of symptoms to the first hospital visit ranged from 9 to 105 months. The mean observation period of chronic HP was 5.2 years. Among the 36 patients with chronic HP, 9 had experienced no acute episodes, suggesting that they were first seen with chronic disease of insidious onset (Table II). Patients with bird fancier's lung and farmer's lung tended to be first seen with an insidious onset (3 of 7 cases of bird fancier's lung and 2 of 4 cases of farmer's lung). Over 41% of the patients were smokers, a larger proportion than that reported for acute HP.¹²

Symptoms and physical findings

The major symptoms were cough (80%) and dyspnea on exertion (80%) followed by low-grade fever (50%). Clubbed finger was observed in 8 of 36 cases (22%), and

Symptoms of Chronic Hypersensitivity Pneumonitis (36 cases)

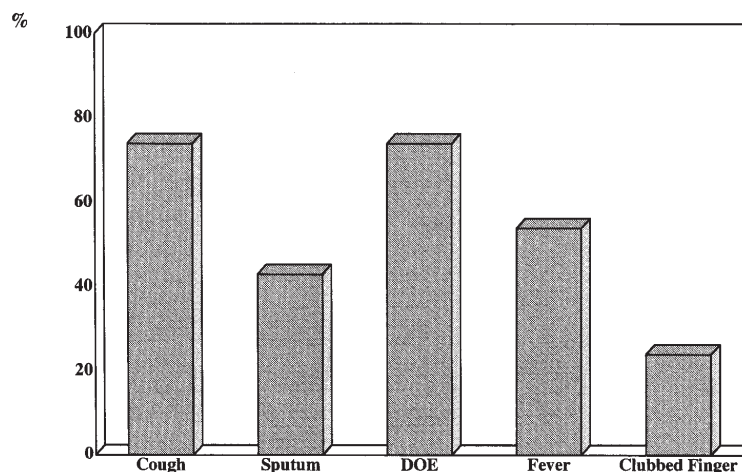


FIG 1. Symptoms of chronic HP (36 cases).

TABLE III. Laboratory findings on admission

Type	WBC (μ L)	CRP (mg/dL)	PaO ₂ (mm Hg)	PaCO ₂ (mm Hg)	VC (%)	FEV ₁ (%)	DLco (%)
SHP (n = 10)	8073	2.8	54.1	35.1	59.2	84.4	54.4
HR (n = 5)	6200	4.3	64.2	40.7	64.4	80.5	42.5
TDI (n = 5)	8620	5.0	71.3	40.2	68.3	74.9	45.4
BFL (n = 7)	7967	0.5	77.2	37.5	68.9	78.1	45.1
FL (n = 4)	5570	1.6	77.8	39.1	63.7	80.1	53.5
Other (n = 5)	9580	5.1	75.3	34.8	87.8	83.7	57.6
Total (n = 36)	7795	3.1	67.8	37.6	67.4	80.7	49.7

VC, Vital capacity; DLco, carbon monoxide diffusing capacity of the lungs; SHP, summer-type HP; HR, home-related HP; BFL, bird fancier's lung; TDI, isocyanate-induced HP; FL, farmer's lung; Other, other HP.

the frequency of clubbing was similar in the repeated acute episodes group and the insidious onset group (Fig 1).¹³

Laboratory data

The mean white cell counts were within normal limits, except for the 5 cases of other chronic HP (mean, 9580/mm³) (Table III). C-reactive protein was positive in summer-type chronic HP, home-related chronic HP, and isocyanate-induced chronic HP. C-reactive protein was weakly positive in farmer's lung and negative in bird fancier's lung.

Pulmonary function tests

The mean PaO₂ was 67.8 mm Hg and was lowest in summer-type chronic HP (54.1 mm Hg) (Table III). There was a restrictive impairment (67.4% [mean] of the predicted vital capacity and 49.7% [mean] of the predicted carbon monoxide diffusing capacity of the lungs).

Imaging

Radiologic findings on chest X-ray scans and computed tomography scans were evaluated on the basis of the characteristics of shadows (nodular, ground-glass, consolidation, honeycombing, volume loss) and the distribu-

tion of shadows (peripheral, centrilobular, upper, middle, and lower lung fields) (Table IV). Abnormal chest shadows were distributed throughout the whole lung field in 8 of 36 patients with chronic HP. The distribution of shadows was predominant in the middle to lower lung field in 6 patients (1 with summer-type HP, 1 with bird fanciers' lung, 2 with isocyanate-induced HP, and 2 with other chronic HP). In contrast, the upper lung field was dominant in 2 patients (1 with farmers' lung and 1 with summer-type HP). The upper lung field was also involved with the midlungs in 3 patients (1 with summer-type HP, 1 with bird fanciers' lung, and 1 with farmers' lung); the upper lung field and lower lung field was involved in 1 patient (with isocyanate-induced HP). Therefore the upper lung field was frequently involved in chronic HP (17%) compared with IPF.

High-resolution computed tomography (HRCT) was obtained in 30 patients with chronic HP, and characteristics of shadows were expressed as diffuse increased density (ground-glass), air space consolidation, honeycombing, and nodular shadows (Table IV). Ground-glass opacities were observed in 17 of 30 patients (57%) (5 with summer-type HP, 1 with home-related HP, 2 with bird fancier's lung, 5 with isocyanate-induced HP, 1 with farmer's lung, and 3 with other chronic HP).

TABLE IV. Image findings

	Linear		Ground-glass		Nodular		Air space consolidation		Honeycombing		Volume loss		Peripheral zone predominance	Centri-lobular
	X-ray		X-ray	CT	X-ray	CT	X-ray	CT	X-ray	CT	X-ray	CT	CT	CT
SHP (n = 10)	3/10		6/10	5/10	9/10	6/10	1/10	1/10	1/10	2/10	4/8	0/9		5/10
HR (n = 5)	1/4		1/4	1/3	4/4	2/3	0/4	0/3	0/4	1/3	3/4	1/2		1/2
TDI (n = 5)	1/5		4/5	5/5	2/5	1/5	2/5	2/5	0/5	2/5	2/5	2/4		2/4
BFL (n = 7)	4/6		3/6	2/5	4/6	4/5	1/6	2/5	1/6	3/5	3/5	3/3		1/5
FL (n = 4)	2/4		1/4	1/4	1/4	2/4	1/4	3/4	3/4	3/4	3/3	2/4		1/2
Other (n = 5)	3/5		4/5	3/3	3/5	1/3	0/5	1/3	0/5	0/3	1/2	1/3		3/3
Total (n = 36)	14/34 (41.2%)		19/34 (55.9%)	17/30 (56.7%)	23/34 (67.6%)	6/30 (53.3%)	5/34 (14.7%)	9/30 (30.0%)	5/34 (14.7%)	11/30 (36.7%)	16/27 (59.3%)	9/25 (36.0%)		13/26 (50.0%)

SHP, Summer-type HP; HR, home-related HP; BFL, bird fancier's lung; TDI, isocyanate-induced HP; FL, farmer's lung; Other, other HP.

Twenty-five patients were described, with a peripheral zone predominance of abnormal shadow observed in 9 (36%). Centrilobular distribution of nodular shadows was described in 13 of 26 of the patients (50%).

Immunologic findings

All patients with summer-type HP, isocyanate-induced HP, and farmer's lung showed positive antibody activity to *Trichosporon asahii* (formerly *T. cutaneum*), isocyanate, and *Faenia rectivirgula*, respectively. Three patients with other types of chronic HP had positive test results to the presumptive antigen, and 1 patient with other chronic HP showed a positive antibody to wheat flour; the other 2 patients with other types of chronic HP were reactive to damp straw. Overall, 26 of these examined 28 patients (93%) showed positive antibodies to the relevant antigens.

Lymphocyte proliferation responses to the relevant antigen were positive in 5 of 8 (63%) examined patients with chronic HP. Two patients with bird fancier's lung showed lymphocyte proliferation of peripheral and BAL lymphocytes to bird sera with no demonstrable antibody activity.

Bronchoalveolar lavage

At the time of diagnosis of chronic HP, BAL was performed on 24 patients with chronic HP (7 with summer-type HP, 3 with home-related HP, 4 with isocyanate-induced HP, 5 with bird fancier's lung, 3 with farmer's lung, and 3 with other types of chronic HP) (Table V). Although small numbers were studied in BAL analyses, only small differences were observed regardless of the group of chronic HP.

The proportion of BAL lymphocytes was variable from 15% to 83% of BAL cells. The characteristic finding in isocyanate-induced HP was the lowest ratio of CD4 to CD8 lymphocytes among the 5 HP groups. The

ratio of CD4/CD8 lymphocytes ranged from 0.11 to 3.9 in summer-type HP and 0.43 to 3.8 in bird fancier's lung. Two patients with bird fancier's lung (insidious onset) had high CD4/CD8 (3.5 and 3.8, respectively). In patients with farmer's lung, the proportion of BAL lymphocytes ranged from 23% to 83%, and the CD4/CD8 ranged from 0.6 to 8.3. The BAL findings were variable even in the same chronic HP group, probably dependent on the time point when the BAL was conducted.^{11,12}

Histologic findings

The details of histologic findings will be published in a separate paper (manuscript in preparation). Histologic examination of specimens obtained by transbronchial lung biopsy was evaluated in 31 patients; 8 patients were evaluated by using specimens obtained by either open lung biopsy or video-assisted thoracoscopic surgery. Alveolitis was observed in 29 of 31 patients (9 of 9 with summer-type HP, 3 of 3 with home-related HP, 4 of 5 with isocyanate-induced HP, 5 of 6 with bird fancier's lung, 3 of 3 with farmer's lung, and 5 of 5 with other chronic HP). Masson bodies were seen in 13 of 31 patients (42%) (2 of 9 with summer-type HP, 1 of 3 with home-related HP, 3 of 5 with isocyanate-induced HP, 4 of 6 with bird fancier's lung, 1 of 3 with farmer's lung, and 3 of 5 with other chronic HP). Granulomas were observed in 12 of 31 patients (39%) (4 of 9 with summer-type HP, 3 of 5 with isocyanate-induced HP, and 1 of 6 with bird fancier's lung).

Provocation challenge tests

Environmental provocation tests were conducted in 23 patients, resulting in 16 positive responses (70%) (6 of 9 with summer-type HP, 3 of 4 with home-related HP, 3 of 3 with isocyanate-induced HP, 1 of 3 with bird fancier's lung, 1 of 1 with farmer's lung, and 3 of 4 with other

TABLE V. BAL findings at the time of diagnosis as chronic HP

Type	Alveolar macrophages (%)	Lymphocytes (%)	Neutrophils (%)	Eosinophils (%)	CD4/CD8
SHP (n = 7)	33.7	55.1	10.1	2.1	1.02
HR (n = 3)	59.2	32.8	6.1	3.3	1.57
TDI (n = 4)	45.8	46.0	2.4	5.5	0.22
BFL (n = 5)	60.4	28.9	10.1	0.6	2.35
FL (n = 3)	39.4	51.5	6.4	0.1	4.01
Other (n = 3)	30.1	62.8	4.3	2.5	2.11
Total (n = 24)	44.3	46.3	7.1	2.0	1.70

SHP, Summer-type HP; HR, home-related HP; BFL, bird fancier's lung; TDI, isocyanate-induced HP; FL, farmer's lung; Other, other HP.

chronic HP). The major symptoms following environmental provocation testing are as follows, in decreasing order of frequency: cough, fever, and dyspnea. Controlled inhalation challenge tests with the presumptive antigens were conducted in 7 patients with 6 positive responses; only 1 patient with bird fancier's lung did not have symptoms of HP.

Treatment

Administration of prednisolone (PSL) was initiated in 26 patients (6 with summer-type HP, 5 with home-related HP, 5 with isocyanate-induced HP, 6 with bird fancier's lung, 2 with farmer's lung, and 2 with other chronic HP). The efficacy of PSL was categorized into effective and ineffective as assessed by symptoms, pulmonary function tests (including blood gas analysis), and imaging. Treatment with PSL was effective in 15 of 26 patients (58%) (4 of 6 with summer-type HP, 5 of 5 with home-related HP, 2 of 5 with isocyanate-induced HP, 1 of 6 with bird fancier's lung, 2 of 2 with farmer's lung, and 1 of 2 with other chronic HP). PSL was ineffective in 11 cases (42%). The relative ineffectiveness of PSL in bird fancier's lung was apparent. In addition, antigen avoidance per se did not cause a reversal of chronic HP. It is a very important concept that when inflammatory lung diseases or organ diseases per se progress into fibrosis, they are not susceptible to corticosteroids, and they may even progress when patients avoid the causative antigens.

DISCUSSION

On the basis of the current survey in Japan, as well as other data in the literature, chronic HP can be characterized as follows. Pulmonary fibrosis inevitably develops in these patients, and therefore they have a poor prognosis. In some cases antibodies to the presumptive antigens cannot be detected, although PBMC proliferation to the causative antigens is usually detected. Because these patients have pulmonary fibrosis, their clinical response to corticosteroids is poor. By contrast, fibrosis does not develop in patients with acute HP, and therefore their response to corticosteroids is excellent. They invariably have detectable antibodies to the causative antigens, and their PBMC proliferative response to the causative antigen is also usually positive.

This nationwide epidemiologic study of chronic HP in

Japan revealed that only a small proportion of patients with summer-type HP have chronic HP compared with patients with bird fancier's lung, farmer's lung, and isocyanate-induced HP. A previous epidemiologic study of HP from Japan demonstrated that summer-type HP represents most HP in Japan (>74% of all 621 cases of the disease).¹⁴

This study has also confirmed that the chronic form of HP can be subgrouped into 2 types: one subgroup initially seen with chronic disease and another subgroup that becomes chronic with ensuing fibrosis after repeated acute episodes. The insidious form of chronic HP has probably been misdiagnosed as IPF when a good history was not taken and immunologic testing and BAL were not conducted.

Another interesting finding in this study is that greater than 40% of patients with chronic HP are smokers when they note the symptoms of HP. Smoking has been shown to inhibit antibody production to the causative antigen, thereby reducing the probability of acute HP development.^{12,15-17} A better estimate of the prevalence of chronic HP among smokers should be obtained to determine the relationship between smoking and the development of chronic HP. However, because smoking modulates cytokine secretion from lymphocytes and alveolar macrophages, an altered cytokine response is another possible factor for the development of HP. Other factors are concentration and duration of inhaled antigen exposure, chemical nature of the antigen, age, and genetic predisposition of the patient.

The findings from chest X-ray and computed tomography scans were analyzed from a perspective of pattern, extent, and distribution. This study has shown that ground-glass attenuation and honeycombing were seen in 17 and 11 of 30 patients, respectively. Therefore honeycombing seems to be present in about 36% of patients with chronic HP. Adler et al¹⁸ reported that all patients with chronic HP had evidence of fibrosis by HRCT as indicated by irregular linear areas and architectural distortion. Fibrosis was located predominantly either in the middle lung zones or showed no zonal predominance. Honeycombing was identified in 11 of 16 patients on HRCT and was predominantly subpleural in 7 of these patients. Ground-glass attenuation was observed in 15 of 16 patients by HRCT. Similar observations were reported by Remy-Jardin et al.¹⁹

Immunologic findings were conducted in a limited number of patients; 26 of 28 patients had an antibody response to the relevant antigens, and peripheral lymphocyte proliferation to the corresponding antigen was positive in 5 of 8 patients examined. Unfortunately, methods for immunologic data are limited in some of the participating institutions, especially lymphocyte proliferation.

BAL findings were variable both in the numbers of BAL lymphocytes, as well as the ratio of CD4 to CD8 lymphocytes, dependent on the time point at which the material was obtained. The mean ratio of CD4 to CD8 in the 7 patients with summer-type HP was higher compared with that in the patients with acute summer-type HP.²⁰ The most characteristic findings were the lowest CD4/CD8 and the high percentage of BAL lymphocytes in the isocyanate-induced HP group. In addition, patients first seen with an insidious onset tended to show higher CD4/CD8, except for 1 patient with summer-type HP.²¹

Histologic examination of specimens obtained by open lung biopsy or video-assisted thorascopic surgery was evaluated in only 8 patients; 5 of these patients showed granulomas. It is interesting that fibrosis was observed in centrilobular, as well as perilobular, areas. However, a few patients cannot be distinguished between usual interstitial pneumonia and chronic HP histologically, even on specimens obtained by transthoracic biopsy.

The response to environmental or controlled aerosol antigen provocation differs when comparing patients with acute HP with those with chronic HP. Patients with acute HP always respond with dyspnea, leukocytosis, fever, and changes in pulmonary function. On the other hand, patients with chronic HP have more variable and less intense response to provocation challenge. Environmental provocation testing was conducted in 23 patients, with 16 positive responses. Controlled antigen inhalation testing was done in 7 patients, with 6 positive response. In 1 of the 6 patients with positive responses to antigen inhalation, testing showed no acute symptoms other than increased leukocytosis, positive C-reactive protein, and a decrease in PaO₂ of more than 10 mm Hg. No antibodies to the causative antigen were detected in sera or BAL fluid. It is therefore likely that positive responses were induced by cellular hypersensitivity. However, it should be noted that it is not known whether acute symptoms, neutrophilia, positive C-reactive protein, a decrease of PaO₂, or carbon monoxide diffusing capacity of the lungs are reproducible by controlled antigen inhalation if the patient had no acute episodes during the development of disease.²²

Finally, the efficacy of steroid administration was limited in chronic HP in contrast to its efficacy in acute HP. In addition, antigen avoidance did not result in improvement of pulmonary function tests, imaging, and dyspnea on exertion. In fact, some patients show a gradual deterioration.³⁻⁶

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REFERENCES

- Salvaggio JE, Millhollon BW. Allergic alveolitis: new insights into old mysteries. *Respir Med* 1993;87:495-501.
- Kaltreider HB. Hypersensitivity pneumonitis. *West J Med* 1993;159:570-8.
- Yoshizawa Y, Miyake S, Sumi Y, Hisauchi K, Sato T, Kurup VP. A follow-up study of pulmonary function tests, bronchoalveolar lavage cells, and humoral and cellular immunity in bird fancier's lung. *J Allergy Clin Immunol* 1995;96:122-9.
- Barbee RA, Callies Q, Dickie HA, Rankin J. The long-term prognosis in farmer's lung. *Am Rev Respir Dis* 1968;97:223-31.
- Bourke SJ, Carter R, Anderson K, Boyd J, King S, Douglas B, et al. Obstructive airways disease in non-smoking subjects with pigeon fanciers' lung. *Clin Exp Allergy* 1989;19:629-32.
- Lalancette M, Carrier G, Laviolette M, Ferland S, Rodrigue J, Begin R, et al. Farmer's lung: long-term outcome and lack of predictive value of bronchoalveolar lavage fibrosing factors. *Am Rev Respir Dis* 1993;148:216-21.
- Perez-Padilla R, Salas J, Chapela R, Sanchez M, Carrillo G, Perez 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.
- Iwai K, Mori T, Yamada N, Yamaguchi M, Hosoda Y. Idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1994;150:670-5.
- Baur X. Hypersensitivity pneumonitis (extrinsic allergic alveolitis) induced by isocyanates. *J Allergy Clin Immunol* 1995;95:1004-10.
- Dykewicz MS, Laufer P, Patterson R, Roberts M, Sommers HM. Woodman's disease: hypersensitivity pneumonitis from cutting live trees. *J Allergy Clin Immunol* 1988;81:455-60.
- Hubbard RB, Lewis SA, Richards KA, Johnston IDA, Britton J. Pet birds as a risk factor for cryptogenic fibrosing alveolitis (CFA). *Am J Respir Crit Care Med* 1995;151:A198.
- Warren CPW. Extrinsic allergic alveolitis: a disease commoner in non-smokers. *Thorax* 1977;32:567-9.
- Sansores R, Salas J, Chapela R, Barquin N, Selman M. Clubbing in hypersensitivity pneumonitis. Its prevalence and possible prognostic role. *Arch Intern Med* 1990;150:1849-51.
- Ando M, Konishi K, Yoneda R, Tamura M. Difference in the phenotypes of bronchoalveolar lavage lymphocytes in patients with summer-type hypersensitivity pneumonitis, farmer's lung, ventilation pneumonitis, and bird fancier's lung: report of a nationwide epidemiologic study in Japan. *J Allergy Clin Immunol* 1991;87:1002-9.
- Thomas W, Holt PG, Keast D. Effect of cigarette smoking on primary and secondary humoral responses of mice. *Nature* 1973;243:240-1.
- Kusaka H, Homma Y, Ogasawara H, Munakata M, Tanimura K, Ukita H, et al. Five-year follow-up of *Micropolyspora faeni* antibody in smoking and nonsmoking farmers. *Am Rev Respir Dis* 1989;140:695-9.
- Arima K, Ando M, Ito K, Sakata T, Yamaguchi T, Araki S, et al. Effect of cigarette smoking on prevalence of summer-type hypersensitivity pneumonitis caused by *Trichosporon cutaneum*. *Arch Environ Health* 1992;47:274-8.
- Adler BD, Padley SPG, Muller NL, Remy-Jardin M, Remy J. Chronic hypersensitivity pneumonitis: high-resolution CT and radiographic features in 16 patients. *Radiology* 1992;185:91-5.
- Remy-Jardin M, Remy J, Wallaert B, Muller NL. Subacute and chronic bird breeder hypersensitivity pneumonitis: sequential evaluation with CT and correlation with lung function tests and bronchoalveolar lavage. *Radiology* 1993;189:111-8.
- Ando M, Arima K, Yoneda R, Tamura M. Japanese summer-type hypersensitivity pneumonitis. Geographic distribution, home environment, and clinical characteristics of 621 cases. *Am Rev Respir Dis* 1991;144:765-9.
- Murayama J, Yoshizawa Y, Ohtsuka M, Sato T, Yano H, Honma T, et al. Lung fibrosis in hypersensitivity pneumonitis: association with CD4+ cell dominant alveolitis and insidious onset. *Chest* 1993;101:47-51.
- Hendrick DJ, Marshall R, Faux JA, Krall JM. Positive "alveolar" responses to antigen inhalation provocation tests: their validity and recognition. *Thorax* 1980;35:415-27.