Familial Summer-type Hypersensitivity Pneumonitis: A Review of 25 Families and 50 Cases in Japan

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Abstract

Summer-type hypersensitivity pneumonitis (SHP) is the most common form of pneumonitis in Japan; it accounts for 74% of all cases. It has been reported that 19.5-23.8% of SHP cases occur in families who live in the same house. We present our SHP cases and review 50 familial cases in 23 families that were reported in Japan (including our own) and 48 cases that were previously described in 22 articles published between January 1982 and October 2011. To the best of the authors' knowledge, this is the first review article in English to document the familial occurrence of SHP in Japan.

Key words: summer-type hypersensitivity pneumonitis, *Trichosporon*, HLA-DQ

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Introduction

Hypersensitivity pneumonitis (HP) is an immunologically induced lung disease caused by repeated inhalation of a variety of causative antigens (1). A previous epidemiologic study of 621 HP cases in Japan demonstrated that summer-type hypersensitivity pneumonitis (SHP) is the most common form of HP in Japan; it accounts for 74% of all cases (2). SHP most often occurs in the western part of Japan, where the summer weather typically consists of high temperatures and high humidity. It has been reported that 19.5-23.8 % of SHP cases occur in families who live in the same house (2, 3). The familial occurrence of SHP is considered to be related, not only to environmental factors, but also to hereditary factors such as the presence of the human leukocyte antigen (HLA) (4, 5). In 1982, Kohaku et al. published the first report of familial SHP cases; since then, a total of 50 Japanese patients in 23 families with familial SHP have been reported, including our cases which we report here. In this article, we present our cases and review all of the previously reported cases of familial SHP in Japan, published between January 1982 and October 2011 (5-26). To the best of the authors' knowledge, this is the first review article in English, to document the familial occurrence of

SHP in Japan.

Case Reports

Patient 1

Patient #1 was a 19-year-old man who had never smoked and had no history of allergic diseases. Visiting a local hospital, he complained of exertional dyspnea and a dry cough lasting for one month from August 2011. He was admitted to the hospital and diagnosed with atypical pneumonia by laboratory findings and chest radiography. Intravenous antibiotics and steroid pulse therapy were initiated and his symptoms rapidly improved. He was discharged after 14 days of hospitalization. However, he experienced a recurrence 2 days after discharge and was referred to our hospital.

Patient 2

Patient #2 was the mother of Patient #1. She was 49 years of age and had never smoked. She presented a fever and general fatigue of one month in duration from August 2011. She came to take her son to our hospital, and then consulted us. In both the mother and the son, a mild elevation of inflammatory reactions such as C-reactive protein

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Table 1. Patients' Characteristics.

Characteristics	Patients No (%)	
Mean age, years (range)	33.5 (2 - 74)	
Sex		
Male	22 (44)	
Female	28 (56)	
Smoking history (n=31)†		
Never	20	(65)
Ex-smoker	7	(23)
Current smoker	4	(13)
N.D.	19	
Month of onset (n=49)†		
May	2	(4)
June	2	(4)
July	8	(16)
August	26	(53)
September	7	(14)
October	3	(6)
November	1	(2)
N.D.	1	
Symptoms on initial visit (n=48)†		
Cough	43	(90)
Sputum	11	(23)
Fever	40	(83)
Dyspnea	38	(79)
N.D.	2	
Blood relation of the families (n=23)		
Blood relation	15	(65)
Not blood relation	8	(35)
Treatment		
Elimination of the antigen	25	(50)
Steroid therapy	25	(50)
Mean duration from living to occurrence of HP (Months, range)	15.0 (0.5 - 396)	
Mean house age (Years, range)	20.4 (14.0 - 33.0)	
Movement (n=47)†		
Needed	19	(40)
Not needed	28	(60)
N.D.	3	

*N.D. means not described in the paper.

†The cases not described in the paper, were excluded in the table.

(CRP), erythrocyte sedimentation rate (ESR) were found. High resolution chest computed tomography showed diffuse centrilobular nodules. A bronchoalveolar lavage fluid (BALF) analysis revealed a high proportion of lymphocytes with a decreased CD4/CD8 ratio and transbronchial lung biopsy specimens showed alveolitis associated with granuloma. They were diagnosed with SHP on the basis of the detection of anti-*Trichosporon asahii* antibodies in both the BALF and serum.

The condition of both patients improved within one week after admission by the avoidance of antigens, without any medication. Both of them were positive for a provocation test, which consisted of returning home. This resulted in them moving to another house. There was no recurrence during the 6-month observation period.

Their 50-year old wooden house was found to be damp and dusty, especially in the room of Patient #1. *Trichosporon asahii*, an arthrospore-forming yeast, which was isolated in their house environment, was the likely causative agent (27). They had lived in the house for 18 years.

We reviewed 50 familial SHP cases of 23 families that have been reported in Japan, including our own in this study and 48 cases that were detailed in 22 previously published articles. The results are shown in Table 1.

The patients with familial SHP included 22 males and 28 females, with a mean age ($\pm$ SD) of 33.5 ± 18.0 years. Eighteen (36%) patients were younger than the age of 20 years. All of the families lived in traditional Japanese wooden houses which were damp. Forty-one of the 49 cases (84%) occurred between July and September in summer in Japan (Table 1). All of the familial occurrence of SHP occurred within 2 months of the first case of HP within the family. Eight patients of the 23 families (35%), were not blood relations of another patient in the same family. In terms of host and genetic factors, there is a relatively high incidence of HP in housewives and nonsmokers. Fifty-six percent of SHP patients were females and 44% were males. Four of the patients (13%) in our study were current smokers. In terms of treatment, 25 patients (50%) received steroid therapy, while the remaining 25 (50%) improved without any medication. Nineteen (40%) patients needed to move to another house.

Discussion

It is supposed that less frequent smoking and a longer duration of exposure to antigens would be related to HP occurring more frequently in women than in men (28). Furthermore, it has already been reported that cigarette smoking has a suppressive effect in patients susceptible to

Table 2. Laboratory Data and Pulmonary Function Test.

	Elder brother (Patient #1)	Mother (Patient #2)	Father	Young brother
Age	19	49	52	14
Sex	Male	Female	Male	Male
Hematology				
WBC (/mm ³)	5,300	8,400		
Neu (%)	56	91		
Lym (%)	31	8		
Eos (%)	6	0		
Biochemistry				
LDH (IU/L)	333	279		
ESR (mm/hr)	25	32		
Serology				
CRP (mg/dL)	1.33	0.95		
KL-6 (IU/mL)	1,130	2,150		
SP-D (ng/mL)	257	144		
Anti- <i>Trichosporon asahii</i> antibody	positive	positive	positive	negative
Blood gas analysis				
PaO ₂ (mmHg)	67.7	74.5		
PaCO ₂ (mmHg)	37.2	36.1		
Pulmonary function test				
VC (L)	2.81	2.61		
%VC (%)	65.8	101.2		
FEV _{1.0} (L)	2.07	2.13		
FEV _{1.0} (%)	50.0	95.9		
%DLCO (%)	38.6	70.7		
BALF analysis				
Total cell count (/μL)	825	875		
Neu (%)	7	5		
Lym (%)	74	62		
Eos (%)	5	6		
Mφ (%)	14	27		
CD 4 /8 ratio	0.37	0.1		
HLA type				
A	A24	A24	A2, A24	A24
B	B48, B52	B48, B51	B52, B54	B48, B54
DR	DR9, DR15	DR9, DR14	DR15	DR9, DR15

WBC: white blood cell, Neu: neutocyte, Lym: lymphocyte, Eos: eosinophil, LDH: lactate dehydrogenase, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, KL-6: Krebs von den Lungen-6, SP-D: surfactant protein D, VC: vital capacity, FEV_{1.0}: forced expiratory volume in one second, DLCO: diffusing capacity for carbon monoxide, BALF: bronchoalveolar lavage fluid, Mφ: macrophage, HLA: human leukocyte antigen

HP (29, 30). The prevalence of anti-*T. asahii* antibody was significantly lower in smoker (29, 31). It is presumed that cigarette smoking stimulates the production of alveolar macrophages and accelerates the clearance of the lungs. In addition, some physicians demonstrated that the elevation of estrogen could correlate with lung injury and pulmonary fibrosis (32, 33). This suggests that gender plays an important role in the occurrence of HP.

Due to the close relationship between the immune system and HLA, some physicians have reported the possibility of a genetic predisposition linked to this system.

Ando et al. documented the increased frequency of HLA-DQw3 in Japanese patients with *T. asahii*-induced SHP (2). The occurrence of SHP has also been reported to be related to HLA-A2 and DR9 (3). Table 2 shows the results of the laboratory data, pulmonary function test and HLA type in

the family of our cases. In our cases, both of the HP patients had HLA-DR9. While the father of Patient #1 had HLA-A2, and did not show anti-*T. asahii* antibody-positive HP. This suggests that the occurrence of HP may not only be related to the environmental factors such as the duration of inhalational exposure and climate but also to the host's hereditary susceptibility to the antigens.

As for home environmental factors, the old wooden houses were found to be damp, dusty and poorly ventilated, especially in the room of Patient #1. *T. asahii* was also isolated in their house. The arthrospore-forming yeast, was the likely causative agent (27). They had lived in a moldy house for 13 years. Both Patients #1 and #2 often stayed in the room of Patient #1. In contrast, the younger brother and father did not visit the room although they were positive for anti-*T. asahii* antibodies. The duration of inhalational expo-

sure could affect sensitization to *Trichosporon* antigens and the occurrence of SHP.

In terms of clinical symptoms, about 90% of the SHP patients presented with cough, fever and dyspnea. All of the patients' houses were wooden and the mean house age was 20.4 years. Ando et al. documented the clinical symptoms and the length of time that SHP patients had resided in their homes. Coughing was the most common symptom, and fever was seen in about 90% of patients. Exertional dyspnea was also seen in approximately 80% of patients. The patients' houses were 89.5% wooden and 10.5% non-wooden, with a mean house age of 20.5 years for wooden houses and 12.3 years for non-wooden ones. Thus, there was no difference in the patient characteristics of the familial and non-familial cases of SHP (28).

In conclusion, familial SHP does sometimes occur. Clinicians must therefore consider the possible occurrence of familial SHP, even in cases where household members are not blood relations.

The authors state that they have no Conflict of Interest (COI).

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