
Trichosporon asahii-induced asthma in a family with Japanese summer-type hypersensitivity pneumonitis

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Background: *Trichosporon* species frequently induce summer-type hypersensitivity pneumonitis (SHP), which is the most prevalent type of hypersensitivity pneumonitis (HP) in Japan, but have not been reported to induce asthma.

Objective: Evaluation of a case of asthma induced by *Trichosporon asahii*.

Methods and Results: This report describes a 46-year-old Japanese man who developed asthma induced by *T. asahii*, following symptoms of HP attributable to the same pathogen, in a case of familial occurrence of SHP. This patient lacked typical findings of HP in his radiograph but had an elevated level of eosinophils in his bronchoalveolar lavage fluid. Open lung biopsy, however, revealed typical pathologic findings of HP when he was free of asthmatic symptoms. His serum was also positive for anti-*T. asahii* antibody, as are the sera of SHP patients. Nevertheless, provocation tests, including returning home and inhalations of *T. asahii* antigen, reproduced asthmatic features such as airway hyperresponsiveness and reversible bronchoobstruction, but not the features of HP. A skin test with the same antigen also evoked an immediate allergic reaction. An IgE mechanism was suspected but could not be proven by radioallergosorbent test. The patient's son and daughter displayed typical features of SHP, associated with compatible results in their radiographs, bronchoalveolar lavage fluid analysis, serologic and pathologic examinations, and provocation and skin tests.

Conclusions: To our knowledge, this is the first case of extrinsic asthma, and of coexistent asthma and HP, induced by *T. asahii*. The patient initially displayed symptoms typical of SHP, which were subsequently replaced by more typical asthmatic symptoms.

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INTRODUCTION

Summer-type hypersensitivity pneumonitis (SHP), which is caused by the inhalation of *Trichosporon* species during the muggy summers after the rainy season, is the most prevalent type of hypersensitivity pneumonitis (HP) in Japan and has also recently been found in other Asian countries.^{1–3} *Trichosporon asahii* and *Trichosporon mucoides* (formerly termed *Trichosporon cutaneum* serotypes II and I, respectively) are the most clinically im-

portant *Trichosporon* species, as they cause both SHP and deep-seated infection.^{4–6} We report here the first case of extrinsic asthma induced by *T. asahii*. The asthmatic features in this patient appeared following typical symptoms of HP because of exposure to the same pathogen over a period of several weeks. This patient was a member of a family with familial occurrence of SHP in Japan caused by *Trichosporon*. Only 1 of the 3 patients in this family exhibited asthmatic features on admission and exhibited typical pathologic findings of HP when he was asymptomatic of asthma.

CASE REPORTS

We examined a family living together in an 18-year-old wooden house. Di-

agnosis of SHP was made in accordance with the diagnostic criteria of the Research Committee on Diffuse Pulmonary Disease organized by the Japanese Ministry of Welfare.⁷ Table 1 shows the symptoms and the serum antibody activities against *T. mucoides* TIMM 1573 (formerly *T. cutaneum* serotype I) and *T. asahii* TIMM 1318 (formerly *T. cutaneum* serotype II) antigens for patient 1 and his family members, including patients 2 and 3. The antibodies in serum were detected by the indirect fluorescent antibody method (titers of 32× or more were considered positive).^{2,7}

Patient 1 was a 46-year-old male farmer who was an ex-smoker and had no previous history of allergic rhinitis or asthma. In late July 1994, patient 1 experienced the insidious onset of a cough with yellowish sputum; he felt feverish and experienced general fatigue. The symptoms repeatedly subsided and recurred over a 1-month period. On August 30, 1994, he experienced shortness of breath and was later admitted to our hospital when asthmatic symptoms recurred on October 19.

Physical examination showed only diffuse wheezing. Laboratory studies showed: leukocyte count, $6.8 \times 10^9/L$, with 7.0% eosinophils; C-reactive protein, 0.221 mg/dL; erythrocyte sedimentation rate, 25 mm in the first hour; hepatic and renal function test results, normal. The total serum level of immunoglobulin (Ig)E was normal at 15 U/mL. Arterial blood gas analysis in room air showed pH 7.465, PaO₂ 65.6 mm Hg, and Paco₂ 37.1 mm Hg. Pulmonary function testing showed percentage of vital capacity was 86.5%,

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Table 1. Symptoms on Admission, and Anti-*Trichosporon* Antibody Activities of the Patients and an Asymptomatic Family Member

Subject	Sex	Age	Symptoms on admission	Anti- <i>Trichosporon</i> antibodies	
				<i>T. asahii</i> TIMM1318	<i>T. mucoides</i> TIMM1573
Patient 1	Male	46	shortness of breath, stridor	× 64	× 8
Patient 2 (son of patient 1)	Male	17	fever, cough, sputum	× 64	× 64
Patient 3 (daughter of patient 1)	Female	21	fever, cough, sputum	× 256	× 64
Asymptomatic family member (wife of patient 1)	Female	43	none	× 8	× 8

percentage of forced expiratory volume in 1 second (FEV₁) 30.2%, and percentage of diffusing capacity of lung for carbon monoxide 70.8%, indicating obstructive respiratory dysfunction. Neither x-ray nor thoracic computed tomography showed typical findings of HP. The bronchoalveolar lavage fluid (BALF) exhibited an extremely high percentage of eosinophils, a slightly elevated percentage of lymphocytes, and a decreased CD4/CD8 ratio when the patient displayed the symptoms of asthma (Table 2). The symptoms and signs subsided on the second day and disappeared on the third day of hospitalization. Open biopsy of the lung was performed when the patient was asymptomatic 1 week after the last asthma attack. Tissue sections were stained with hematoxylin and eosin. Microscopic examination of the sections revealed diffuse focal non-foamy histiocytes associated with alveolar and interstitial infiltration of plasma cells. Giant cells and Masson bodies, typical findings of HP, were also observed. Fungal cultures of sputum, BALF, and material from the lung biopsy were negative. Serum anti-*Aspergillus fumigatus* antibody was negative.

A provocation test consisting of the return of the patient to his home was positive for causing recurrence of the

asthmatic symptoms but not the HP symptoms. An inhalation test and a skin test^{2,7} were administered to patient 1 to determine whether provocation produced immediate, late, or both kinds of allergic reaction. First, patient 1 inhaled a total of 2.0 mg of *T. asahii* TIMM1318 antigen (0.2 mg/mL). This is widely used as the standard method for inhalation challenge and skin tests to diagnose SHP attributable to *T. asahii* in Japan.⁷ The culture-filtrate antigen was prepared by the double dialysis method of Edwards,⁸ and the lyophilized crude antigen was dissolved in sterile phosphate-buffered saline at a concentration of 10 mg/mL.^{2,7} The antigen was used after appropriate dilution in sterile phosphate-buffered saline. During the next 48 hours, symptoms and signs were recorded, and body temperature, peripheral leukocytes, and C-reactive protein were measured. One week later, the patient inhaled 20 mg of culture-filtrate antigen (2 mg/mL). In both inhalation tests, the patient complained of a sore throat just after inhalation; shortness of breath with stridor occurred 15 minutes after the beginning of the inhalation, suggesting that an immediate reaction had occurred. Diffuse wheezing became audible in the lung fields. The symptoms and wheezing resolved after the patient inhaled orciprenaline

sulfate. In the second inhalation test, %FEV₁ was monitored, and decreased in value from 46.5% to 28.7% 30 minutes after the challenge. Respiratory resistance also increased from 3.2 to 4.8 cm H₂O/L/second during the same time period. After the inhalation of orciprenaline sulfate, %FEV₁ and the respiratory resistance improved to the initial levels, indicating airway hyper-responsiveness and reversible bronchoobstruction. Over the 48-hour period after the asthmatic symptoms had improved, no cough or fever were observed in either (2 and 20 mg antigen) inhalation test. There was also no increase in peripheral leukocytes and no elevation of C-reactive protein. A skin test involving intradermal injection of 0.02 mL of a 1-mg/mL solution of culture-filtrate antigen of *T. asahii* TIMM1318 was performed. Reactions with indurations of 100 mm² or larger were considered to be positive.⁷ The skin test was positive 15 minutes after provocation (234-mm² diameter). The induration 3 hours after challenge diminished to 91 mm² and then enlarged to 120 mm² 6 hours after the challenge. The indurations 12, 24, and 36 hours after provocation were 513, 1,140, and 600 mm², respectively. The results demonstrated that immediate, late, and delayed allergic reactions all occurred. Specific IgE levels against *T. asahii*

Table 2. BALF Findings of the Patients

Subject	Total cell number	% macrophages	% lymphocytes	% neutrophils	% eosinophils	CD4/CD8 ratio
Patient 1, with symptoms	5.5 × 10 ⁶	47.0	12.0	0.0	41.0	0.50
Patient 1, without symptoms	2.1 × 10 ⁶	79.0	8.0	3.0	10.0	ND
Patient 2	3.3 × 10 ⁶	13.0	79.0	2.0	6.0	0.38
Patient 3	2.4 × 10 ⁶	15.6	83.9	0.0	0.5	0.19

ND, not done.

TIMM 1318 and other mold antigens were measured by radioallergosorbent test (RAST) using a capsulated hydrophilic carrier polymer (Pharmacia, Uppsala, Sweden) system.⁹ For this study, capsulated hydrophilic carrier polymer was newly produced by the coating of freeze-dried *T. asahii* TIMM 1318 cells (Pharmacia). RAST values were arbitrarily classified into categories corresponding to those used for the Phadebas RAST system (Pharmacia). Specific IgE against *T. asahii* TIMM 1318 was not detected in the serum or BALF of patient 1 in this study. IgE RAST for house dust, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Penicillium notatum*, *Cladosporidium herbarum*, *A. fumigatus*, and *Candida albicans* were also all negative in patient 1.

Patients 2 and 3, who were the 17-year-old son and 21-year-old daughter of patient 1, experienced fever, cough, and yellowish sputa during the summer of 1994 and were admitted to our hospital on September 7 and October 26, 1994, respectively. The total IgE levels in patients 2 and 3 were 48 and 154 U/mL, respectively. The serum of patient 2 showed high RAST values for house dust (14.16 Ua/mL), *D. pteronyssinus* (13.73 Ua/mL), and *D. farinae* (9.05 Ua/mL). Both patients 2 and 3 improved a few days after admission without any medication. Typical findings of SHP were observed in the radiographs, anti-*Trichosporon* antibody assays (Table 1), BALF (Table 2), and pathologic examinations of the trans-bronchial lung biopsy materials of these patients. Upon the provocation test consisting of returning home, both patients were positive for recurrence of the features of HP. They were negative for an immediate allergic reaction against *T. asahii* by the skin test performed as described above.

The other family member, the wife of patient 1, was negative for anti-*Trichosporon* antibodies and had no symptoms during the summer season. Environmental examination was performed in October 1994. Although no live *Trichosporon* species were isolated from their house environment,

the house was found to be damp and dusty, especially in the room of patient 2. Decayed wood was observed in the bathroom, kitchen, and dining room.

DISCUSSION

It is well known that inhalation of diisocyanates can produce the features of both asthma and HP.¹⁰⁻¹² A case of a farmer with coexistent HP and extrinsic asthma has also been reported.¹³ However, it is generally recognized that asthma is an unusual concomitant of HP.¹⁴ Further, SHP patients have normal IgE levels, eosinophilia is usually absent, and the incidence of SHP is not higher in atopic than in nonatopic patients.¹⁵ In SHP patients, the inhalation test with 15 mg of *Trichosporon* antigen generally produces symptoms and signs that appear 4 to 6 hours after the challenge and subside 2 to 6 hours thereafter, whereas an immediate allergic reaction has not been reported hitherto in SHP patients.⁷ The time course of the skin test response is identical to that of the symptoms and signs that appear after inhalation.⁷

An immediate asthma-type reaction attributable to inhalation of *T. asahii* occurred in the Japanese farmer described here (patient 1) during the summer, when two of his children living in the same house experienced typical SHP. Patient 1 initially displayed symptoms typical of SHP, which occurred and subsided over a period of several weeks, and were then replaced by more typical asthmatic symptoms. The patient had obvious wheezing and had 7% eosinophils in his blood when he arrived at our hospital and also showed an elevated percentage of eosinophils in his BALF, in line with diagnosis of asthma. The asthmatic symptoms recurred upon the inhalation of the *T. asahii* antigen widely used in standard sensitivity tests for the diagnosis of SHP and by the returning-home test. A skin test also showed an immediate allergic reaction to this antigen. To our knowledge, extrinsic asthma induced by *T. asahii* has not been reported. We suspect that the asthma and the immediate allergic reactions in the inhalation and skin tests

in this patient were IgE-mediated, but we could not prove this because the RAST failed to detect the specific IgE in serum and BALF. However, the sensitivity of RAST was probably too low because the crude antigen used for RAST was not IgE-specific. In addition, it is a general finding that RAST has high specificity, but lower sensitivity than the provocation test.¹⁶ In particular, RAST has been considered to be less sensitive than the skin test for mold antigens.¹⁷ It is also possible that an IgG antibody (most likely IgG4)-mediated immediate response¹⁸ to *Trichosporon* was involved.

Patients with mild cases of HP sometimes have normal chest x-rays, and the chronic form of HP may show relatively mild symptoms in response to natural or bronchial inhalation challenges with the offending antigens.¹⁹ Further, it has been reported that even high-resolution computed tomography did not reveal abnormal findings in 6 of 11 HP patients who were swimming pool employees.²⁰ Therefore, it is possible that patient 1 developed spontaneous chronic SHP after the recurrence of typical SHP and showed no typical findings in radiographs, and that specific IgE against *T. asahii* was produced during the repeated natural inhalation. Allergic bronchopulmonary fungus was also suspected but ruled out because the radiographs of the patient lacked central bronchiectasis, which is thought to be the most specific finding for allergic bronchopulmonary aspergillosis according to the diagnostic criteria of Rosenberg et al.²¹

HLA-DQw3 antigens are frequently detected in SHP patients.²² This suggests that the susceptibility of hosts to the antigens inducing HP may be genetically controlled. In our study, however, HLA-DQw3 was not detected in the patients (data not shown). Additionally, we found no HLA antigen specific to the wife, suggesting that she did not have a genetically specified resistant phenotype (data not shown).

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