

A Clinical Study of Japanese Cedar (*Cryptomeria japonica*) Pollen-Induced Asthma

Yuji Maeda¹, Kazuo Akiyama¹ and Takao Shida²

ABSTRACT

Background: Grass and birch pollens are known to induce asthma. However there are few reports about other pollen-induced asthma. Japanese cedar is the most common allergen in rhinitis in Japan but is controversial on whether it can provoke asthma.

Methods: To clarify Japanese cedar pollen-induced asthma, we studied adult patients who were sensitized only to the Japanese cedar (CAP-RAST ≥ 2) and had symptoms of asthma during the cedar season. We defined cedar asthma as a patient who satisfied the 2 criteria mentioned above.

Results: We found 6 adult asthma patients who fulfilled the two criteria. Five patients suffered from cedar pollinosis in addition to asthma, and 1 patient had no pollinosis. The cedar pollinosis preceded asthma in 3 cases and occurred at almost the same time in the other 2 cases. Pulmonary function was normal in these cases (FEV₁ 1%, mean $\pm$ SD, $76.5 \pm 10\%$), with a high threshold value in the non-specific airway hypersensitivity test (Ach-PC20, 2,696 to 20,000 $\mu\text{g}/\text{ml}$, 9294 ± 2) and low total IgE (101 ± 86 IU/ml). In the allergen provocation test, 3 subjects showed both an immediate and late asthmatic reaction.

Conclusions: We concluded that Japanese cedar pollen could provoke not only pollinosis but also asthma in adults.

KEY WORDS

acetylcholine, bronchial provocation test, Japanese cedar, non-specific airway hypersensitivity, pollen-induced asthma

INTRODUCTION

In Japan, we are exposed to Japanese cedar (*Cryptomeria japonica*, JC) pollen much more than any other pollen during the spring. It is well known that the cedar pollen plays a definite role in provoking allergic rhinitis. On the other hand, it is controversial whether cedar pollen can develop asthma. Because many asthma patients are sensitized not only to the cedar but also to other allergens, we could not conclude that cedar pollen was a causative allergen. We found 6 adult patients who were sensitized to only JC and in whom asthma developed in the spring. We performed some tests on the patients to study their clinical characteristics.

METHODS

DEFINITION OF CEDAR ASTHMA

We defined a patient as a Japanese cedar asthma patient, if he or she satisfied the following criteria. 1) Being sensitized to the Japanese cedar pollen allergen (RAST score ≥ 2) and not to any other allergens which may develop asthma. 2) Having asthma symptoms, such as difficulty in breathing and wheezing occurring in spring and recovering completely after the season without any medications.

INTRA-DERMAL TEST

We used the Japanese cedar allergen extract (1 : 20 w/v) produced by Hollister-Stier Co. (3525 N Regal Street, Spokane, WA 99207-5788) in the intra-dermal test. This 10,000 allergy unit extract contains about

¹Clinical Center of National Hospital Organization Sagamihara Hospital, Kanagawa and ²Shinbashi Allergy Clinic, Tokyo, Japan.
Correspondence: Yuji Maeda, Clinical Center of National Hospital Organization Sagamihara Hospital, Sakuradai 18-1, Sagamihara, Kanagawa 228-8522, Japan.

Email: y-maeda@sagamihara-hosp.gr.jp

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4.4 µg/ml of major allergen, Cry j 1.¹ We applied other allergen extracts, including 7 pollens (sagebrush, orchard grass, alder, ragweed, oak, Japanese hop, zekova), 8 molds (*Aspergillus*, *Alternaria*, *Cladosporium*, *Penicillium*, *Malassezia*, *Neurospora*, *Trichophyton*, *Aureobasidium*), house-dust, house-dust mites and 8 animal allergens (dog, cat, rat, mouse, hamster, guinea-pig, horse, rabbit). With the exception of JC, orchard grass, sagebrush and house-dust mite, all other allergen extracts were produced by Torii Pharmaceutical Co. (Tokyo, Japan). Concentrations of testing allergen extracts were 1 : 10,000 w/v in molds and mites and 1 : 1,000 w/v in other allergens. If results showed both the mean wheal $\geq$ 9 mm and flare diameter $\geq$ 20 mm, the test was considered to be positive. The patients being sensitized to other allergens which may provoke asthma were excluded from this study.

BRONCHIAL PROVOCATION TEST (BPT)

Non-specific and allergen specific BPT were performed by Japanese standard tidal breathing method.² Patients were asked to stop taking all medications at least 12 hours before the BPT. Non-specific airway hypersensitivity test was done before the allergen specific BPT.

1. Non-specific BPT with Acetylcholine

The non-specific BPT was performed, using nebulized acetylcholine solution, inhaled for 2 minutes, starting at a dose of 56 µg/ml. Acetylcholine concentration was doubled to a maximal concentration of 20,000 µg/ml. We performed spirometry immediately after the inhalation. The spirometry was done before and after inhaling nebulized 0.9% saline solution (baseline) and each dose of acetylcholine until a 20% fall in FEV_{1.0} from the baseline occurred, or until a maximal dose of 20,000 µg/ml was reached.

2. Allergen Specific BPT

We used the same extract in allergen BPT as used in the intra-dermal test. Because Hollister-Stier's 1 : 20 v/w JC allergen extract contains 50% glycerin and may cause non-specification airway contraction, we therefore reduced the glycerin content to 0.5% by dialysis and adjusted it to a proper concentration. The maximum concentration was 1 : 100 w/v. If there was equal to or more than 20% fall in FEV_{1.0} from the baseline at 10 minutes after inhalation, we found an early asthmatic reaction (EAR) to be positive. Late asthmatic reaction (LAR) was evaluated as follows. On the day before BPT, a monitoring of diurnal variations using Mini-Wright peak expiratory flow meter was performed every hour from 9:00 a.m. to 9:00 p.m. After the EAR evaluation, the patients returned home and measured PEFR every hour until at least 9:00 p.m. If a decrease in PEFR later than 1:00 p.m. was equal to or greater than a 15% decrease (3 hours later

after completion of the inhalation test) and there was no fall in the PEFR on the day before the allergen challenge (control day), we judged that LAR was positive. We informed all patients about the allergen BPT and performed the test on patients who agreed to taking it. The allergen BPT was carried out in spring.

RESULTS

1. CASE REPORT

A 52-year-old woman (case 1 in Table 1) attended our hospital. She has been suffering from pollinosis since she was 30 years old. She experiences sneezing, watery rhinorrhea, stuffed nose and itching eyes from February to April every year. In 1995, she has been experiencing a productive cough from March followed by a difficulty in breathing. She visited our hospital for a detailed examination on April 18th.

According to the patient's past history, she has suffered from no diseases except for pollinosis. She has a brother who is an asthma patient. Physical examination revealed her reddish and swollen nose and no adventitious lung sounds. According to Hansel's standard,³ sputum eosinophil count was 2 plus positive. The pulmonary function test was normal. We observed an 18% increase in the FEV_{1.0} in the airway reversibility test using 2.5 mg salbutamol inhalation. The provocative concentration of acetylcholine which reduced FEV_{1.0} by 20% from the baseline (Ach-PC₂₀) was 8,192 µg/ml. In the intra-dermal test, the patient tested negative in all allergen extracts except for JC pollen. CAP-RAST test was positive in JC and negative in other allergens. In the cedar allergen BPT, she showed both EAR and LAR (Fig. 1). She was treated with β -stimulant and an oral xanthine derivative and recovered from asthma symptoms without any medication after 10th of May.

2. CHARACTERISTICS OF THE JAPANESE CEDAR ASTHMATIC PATIENTS

We have summarized the clinical characteristics of the 6 JC pollen asthma patients (Table 1). All patients began experiencing asthma symptoms from spring, recovered in June and since then, have been completely free from dyspnoeic episodes, chest tightness, cough, and wheezing at night without any medications. They consisted of 1 man and 5 women ranging from 26 to 52 years of age. Except for 1 subject, 5 had JC pollinosis. Three of the 6 had pollinosis before they were given a diagnosis of asthma. Only 1 patient had a family history of allergies.

The CAP-RAST scores ranged from 3 to 6. Lung function test revealed that the %VC ranged from 114 to 89% ($105 \pm 7\%$) and the FEV₁ ranged from 59 to 95% ($77 \pm 10\%$). The total IgE ranged from 17 to 227 IU/ml (mean $\pm$ S.D. 101 ± 86 IU/ml). The Ach-PC₂₀ ranged from 2,696 to 20,000 µg/ml (9294 ± 2). We performed an allergen inhalation test for 3 subjects. All subjects showed both EAR and LAR.

Table 1 Characteristics of Japanese cedar pollen-induced asthma

Name	Age/ Gender	Asthma symptoma- tic month	Asthma onset age (yo)	Pollinosis onset age (yo)	Ach-PC20 (μ g/ml)	%VC	FEV1.0%	FH	BPT	IgE (IU/ml)	CAP- RAST score
1) FH	52/F	3–5	52	30	8192	112	71	N	Dual	ND	6
2) KA	47/F	2–3	47	N	20000	101	79	N	Dual	17	3
3) TS	44/M	3–5	38	38	ND	89	59	N	ND	35	3
4) KI	35/F	3–6	32	14	20000	114	85	N	Dual	227	4
5) EW	33/F	3	33	31	7850	104	70	N	ND	189	6
6) NN	26/F	2–5	26	26	2696	111	95	N	ND	36	3
40 $\pm$ 8					9294 $\pm$ 2	105 $\pm$ 7	77 $\pm$ 10			101 $\pm$ 86	4.2 $\pm$ 1.2

Asthma symptomatic month, 2 (February) – 6 (June); yo, year-old; Ach-PC20, Acetylcholine concentration at 20% fall in FEV1.0 from baseline value; BPT, Bronchial Provocation Test with Japanese cedar allergen extract (month when BPT done); Dual, Dual Asthmatic Reaction (both Early Asthmatic Reaction and Late Asthmatic Reaction); FH, Family History on allergic diseases (asthma, allergic rhinitis, atopic dermatitis); N, non; ND, not done.

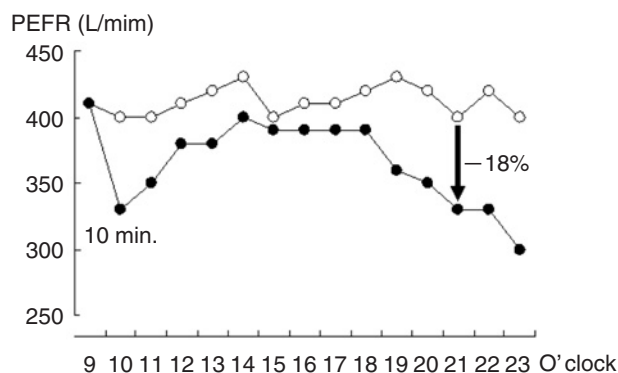


Fig. 1 Bronchial provocation test with Japanese cedar pollen allergen extract. Figure shows bronchial provocation test with Japanese cedar pollen extract in case 1. She exhibited both early and late asthmatic reaction. Early asthmatic reaction is evaluated with FEV1.0 at 10 minutes after the allergen inhalation. When FEV1.0 falls to equal or for more than 15%, early asthmatic reaction is considered to be positive. After the evaluation of early asthmatic reaction, the patient returns home and measures the peak expiratory flow rate every hour with Mini-Wright peak flow meter at least until 9 p.m. (closed circle). If a peak flow value falls to equal or for more than 15% from the control day (open circle, the day before the challenge) 3 hours after test completion, a late asthmatic reaction is considered to be positive.

DISCUSSION

Some pollen increases the risk of hospital admission for asthma.⁴⁻¹⁰ These reports provoked us to pay attention to the relationship between pollen and asthma.¹¹ However we have little knowledge about pollen-induced asthma other than grass and birch.^{5,12,13}

In our data, about 80% of adult rhinitis patients and 60% of adult asthma patients are sensitized to Japa-

nese cedar pollen in Japan. We had two reasons why we could not prove that the JC pollen could cause asthma. We had never seen that the pollen sensitized asthma patients with pollinosis complained of worsening in their asthma symptoms distinctly during the season. With the exception of a few children,¹⁴ a discordance of asthma symptoms and the pollen season has made an obscure correlation between the cedar pollen and asthma in adult patients. These asthma patients have already had some anti-asthmatic medications before an evaluation of the cedar pollen affect on asthma was made. The medications may make it unclear to determine what caused the worsening in asthma symptoms. Another reason is the multiple sensitization to other aero-allergens. We see many asthma patients who are sensitized to other spring aero-allergens and or perennial allergens. The multiple sensitizations make it difficult to decide which allergen is responsible for causing asthma.

If we give a diagnosis of JC pollen induced asthma to a subject, we need to show that at least two criteria have been met. First, patients must be sensitized to the pollen. Second, the asthma symptoms need to coincide with the pollen season. We believe that an allergen provocation test is not necessary when making a diagnosis.¹⁵ If a patient is sensitized to pollen, he or she has the pollen specific IgE on mucosal mast cells in the lower respiratory tract and may show a bronchoconstriction in the allergen inhalation test. The most important criterion is that a change in asthma symptoms coincides with the air-borne pollen count. For example, in rhinitis, we observed that many patients sensitized to JC pollen alone have rhino-conjunctivitis symptoms only during the spring. Therefore it is easy to make a diagnosis of JC pollinosis.

In 1995, we had an extremely high JC pollen count, 10 to 20 fold more than the average year and discovered 6 JC pollen asthma patients. It can be said that the higher the pollen counts, the higher the risk of asthma worsening.⁹ The existence of JC pollen

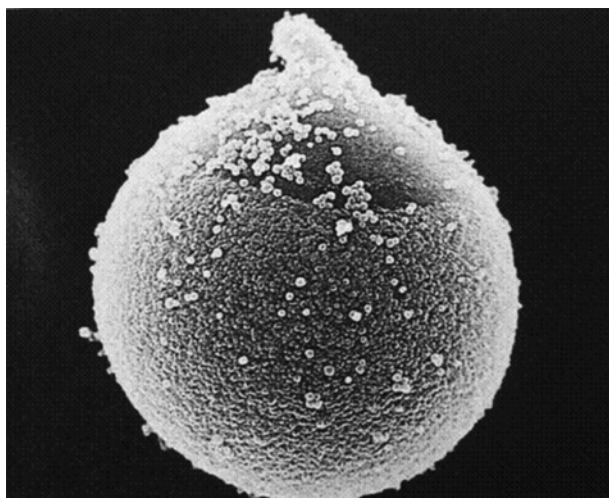


Fig. 2 Morphology of the Japanese cedar pollen. The Japanese cedar pollen grain is about 30 μm size in diameter and covered with a numerous number of fine particles, called orbicules, which comes off easily from the pollen surface.

asthma shows that the Japanese cedar is a novel pollen which can provoke asthma. Generally, pollen grains are too large to penetrate into the lower respiratory tract. Rosenberg reported that an intact pollen grain itself hardly provoked asthma symptoms but the crushed pollen could induce asthma.¹⁶ Therefore, a minute particle may have a key role in provoking asthma.

Allergenic activities of small particles on grass pollen and birch have been studied.¹⁷⁻¹⁹ These small particles are reported to be of micron size and considered to be a starch granule which consists of the pollen grain. Grass pollen adsorbs water during a thunder storm and then bursts⁴ and disperses the inner starch granule into the atmosphere. The starch granule contains a major grass allergen, *Lol p V*,²⁰ which can provoke asthma attacks.

The JC pollen grain has a unique form and is about 30 micrometers in diameter (Fig. 2)²¹ and is too large to penetrate into the lower respiratory tract. Therefore, we believe that there might be some submicronic components in JC pollen. Such a small particle exists in the atmosphere during the cedar season²² and disperses along with the pollen grain itself.²³ This small component can pass through a 5 μm filter and contains Cry j 1 allergen activity and is thought to be an orbicle which adheres to the pollen surface.²⁴ These findings suggest that other pollens which have a similar morphology, as in the Japanese cedar pollen, can induce asthma. The large pollen grain and a crushed one may be inhaled into lower airway respiratory tract likely to induce an asthma attack.

There may be other mechanisms which induce pollen asthma. One attractable hypothesis is that JC

asthma patients are more sensitive to Cry j 1 allergen which is the only allergen of the orbicle, and not sensitive to Cry j 2 which is the only allergen of the pollen starch granule. We must investigate that there is a difference in allergen sensitivity between the asthma and pollinosis patients. A pollinosis patient without asthma shows allergic inflammation in the lower respiratory tract after the pollen season.²⁵⁻²⁷ It is unclear what the main mechanism of allergic inflammation in the lower airway is, and its indirect affect on upper airway inflammation or direct allergen inhalation. We require further study on the relationship between pollen and asthmatic symptoms.

We conclude that the Japanese cedar pollen can provoke not only pollinosis but also asthma in adults. Further studies on cedar asthma, may add a novel relationship to pollen and asthma.

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