

Possibility of Local Allergic Rhinitis in Japan

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Abstract

Background: The concept of local allergic rhinitis (LAR) has been advocated recently. Allergic rhinitis in Japan is characterized by house dust mites (HDMs) and Japanese cedar pollen (JCP). To investigate LAR in Japan, total IgE and antigen-specific IgE (sIgE) were measured in inferior turbinate mucosa and their relationships with skin test (ST) and nasal allergen provocation test (NAPT) and as well as serum IgE levels were examined.

Methods: Subjects were 50 rhinosinusitis patients for surgery. ST was performed and serum total IgE and sIgE levels were measured preoperatively. Patients with class-0 serum anti-HDM or anti-JCP sIgE levels were subjected to NAPT with HDM or JCP, respectively, or both. In all patients, inferior turbinate mucosa was weighed and mashed, and total IgE and sIgE levels were then measured as local mucosal date per gram and per milligram. Because there is no clinical consensus how to evaluate nasal sIgE yet, both positive NAPT and detectable sIgE in obtained nasal mucosa were adopted as the diagnostic criteria of LAR in order to strictly elucidate the possibility of presence of LAR in Japan.

Results: JCP LAR was definitely diagnosed in 2 of 14 patients (14.3%) and HDM LAR in 5 of 21 (23.8%) in cases with rhinosinusitis symptoms in the absence of positive ST nor serum sIgE.

Conclusion: The present results positively support LAR by HDM or JCP being present in Japan.

Keywords

allergic rhinitis, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, local allergic rhinitis, nasal allergen provocation test, specific IgE, house dust mite, Japanese cedar pollen, skin test

Introduction

Allergic rhinitis (AR) is a type I allergic disease of the nasal mucosa in response to inhaled aeroallergens that exhibits clinical symptoms such as watery rhinorrhea, nasal congestion, itching, and sneezing. Serum-specific IgE (sIgE) measurements and skin tests (STs) against aeroallergens have been routinely employed to diagnose AR. Individuals exhibiting AR symptoms without positive ST or serum sIgE have been considered non-AR patients.¹ However, the concept of local allergic rhinitis (LAR) has recently been advocated as a clinical entity in Europe and North America and is characterized by AR symptoms in the absence of systemic atopy assessed by ST or serum sIgE. The diagnosis of LAR is mainly based on the findings of the nasal allergen provocation test (NAPT) and/or the local synthesis of sIgE.

Almost one decade after the discovery of IgE by Ishizaka et al. in 1966,² Huggins and Brostoff reported that sIgE may be produced in the local nasal mucosa and

induce a local reaction with house dust mite (HDM) even though serum samples and ST were negative.³ The concept of entropy was subsequently proposed,⁴ and LAR, in which serum samples and ST are negative, but sIgE is produced in the local nasal mucosa, causing AR, and the NAPT is positive, was recently reported.^{5,6}

Regarding the pathophysiology of LAR, the production of sIgE with somatic hypermutations and

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class switching has been reported locally in the nasal mucosa.^{7–11} In LAR, the presence of sIgE in nasal secretions has been confirmed after natural allergen exposure,^{12,13} NAPT,^{3,12–15} and periods of nonexposure.^{12,13} Furthermore, local sIgE in LAR has been demonstrated to activate basophils via the high-affinity receptor FcεRI, leading to the release of inflammatory mediators that are characteristic of AR.^{16,17}

The prevalence of AR in Japan is 39.4%, and that of perennial AR and Japanese cedar pollen (JCP) pollinosis is 23.4 and 26.5%, respectively,¹ accounting for a high rate of Japanese AR cases. However, cases of HDM and JCP LAR have not yet been reported in Japan; therefore, their prevalence remains unclear. This study was designed in order to investigate the presence of LAR cases in Japan. Because major antigens are HDM and JCP in Japanese AR cases, LAR by HDM and/or JCP were decided as the targets investigated in this preliminary study. In our operation cases hospitalized for inferior turbinate mucosa resection to reduce nasal obstruction and other symptoms, sIgE by HDM and/or JCP in the turbinate mucosa were analyzed quantitatively and compared with serum sIgE analysis. We hypothesize that LAR suspected cases with positive mucosal sIgE possibly exist among the cases without positive serum sIgE. We investigated the possibility of the presence of LAR in all patients with nasal symptom (rhinorrhea, nasal obstruction, post nasal discharge, sneeze, itchy nose, etc) who underwent nasal surgery at our department.

Methods

This was a prospective observational study. The subjects comprised 50 rhinosinusitis patients who underwent nasal surgery including deviatomy and resection of the inferior turbinate mucosa at Nippon Medical School Musashikosugi Hospital between April 2016 and December 2017 (1 year and 9 months). They had partial, persistent, or repeated nasal symptoms, such as rhinorrhea, nasal congestion, itching, and sneezing, due to rhinosinusitis, including AR. To estimate the involvement of AR, serum sIgE levels and the ST were preoperatively examined in each rhinosinusitis patient routinely.

Serum was collected, and total IgE and sIgE levels were measured before surgery. The ST and NAPT were performed. After surgery, total IgE and sIgE levels were measured in the local mucosa of the inferior turbinate.

In serum samples, total IgE and sIgE levels (3 items) against JCP, *Dermatophagoides pteronyssinus* (*Der p*), and *Dermatophagoides farinae* (*Der f*) were assessed using AlaSTAT 3g (Siemens Healthcare Diagnostics AG, Erlangen, Germany) with a measurement range of 0.1 to 500 IU/mL employing a chemiluminescent enzyme immunoassay.

Two STs (HDM and JCP) were performed using the extracts for diagnostic use (Torii, Tokyo, Japan) for 47 patients. The control (saline), HDM extract, and JCP extract, at a volume of 0.02 mL each, were intradermally injected into the medial forearm. Skin reactions were measured after 15 minutes, and 20-mm or larger erythema, or the presence of a wheal was judged as positive.

NAPT was performed using the paper disc method routinely employed in Japan for patients with a class-0 serum IgE antibody titer (0.34 IU/mL or lower) against HDM (*Der f* or *Der p*) or JCP. NAPT with HDM and JCP were performed for 22 and 14 patients, respectively. The paper discs were impregnated with the standardized antigen at the highest concentration among commercial standardized antigens before use. HDM and JCP NAPT were both performed for 7 patients. In the NAPT for HDM, 0.01 mL of the mite allergen extract subcutaneous injection for treatment, “Torii” 10 000 JAU (*Der p*: *Der f*=1:1), was dropped onto a control disc. In the NAPT for JCP, 0.01 mL of the standardized allergen extract subcutaneous injection for treatment, “Torii” 2000 JAU JCP, was dropped onto the control disc. A reaction was confirmed using the control disc, and the test was discontinued when sneezing, nasal discharge, or mucosal swelling of the inferior turbinate was noted. For patients who developed no reaction, a disc impregnated with the antigen was placed at a site slightly posterior to the anterior end of the inferior turbinate and judgment was made after 5 minutes. Following the Japanese guidelines,¹ positivity for one of the following 3 items: sneezing/itching, enhanced nasal discharge, or swelling of/pale inferior turbinate, was judged as suspicious ($\pm$), and 2 items was judged as positive (1+). Judgments were reached based on an interview on subjective symptoms and rhinoscopy findings.

The surgically resected inferior turbinate was rinsed with saline to sufficiently remove blood, gently wiped with gauze, and cut into halves. One fragment was immediately frozen in liquid nitrogen. After weighing, the fragment was put into 0.4 mL of phosphate-buffered saline (PBS; pH 7.0) and mashed for 5 minutes manually using a bio masher (Nippi Bio Masher®). The total volume was adjusted to 1 mL by adding 0.6 mL of PBS, followed by centrifugation (300 rpm at 4°C for 10 min). The supernatant was collected and frozen in the deep freezer at –80°C to preserve. Using this supernatant, total IgE levels and 3 sIgE levels (against JCP, *Der p*, and *Der f*) were measured using the AlaSTAT 3G (3ed generation) system (Siemens Healthcare Diagnostics AG). As serum IgE levels were presented as IU/mL, the measured level per gram of sample was calculated (IU/mL/g).

To investigate the possibility of the presence of LAR, diagnostic criteria are required. However, there is no clinical consensus on how to evaluate local sIgE.

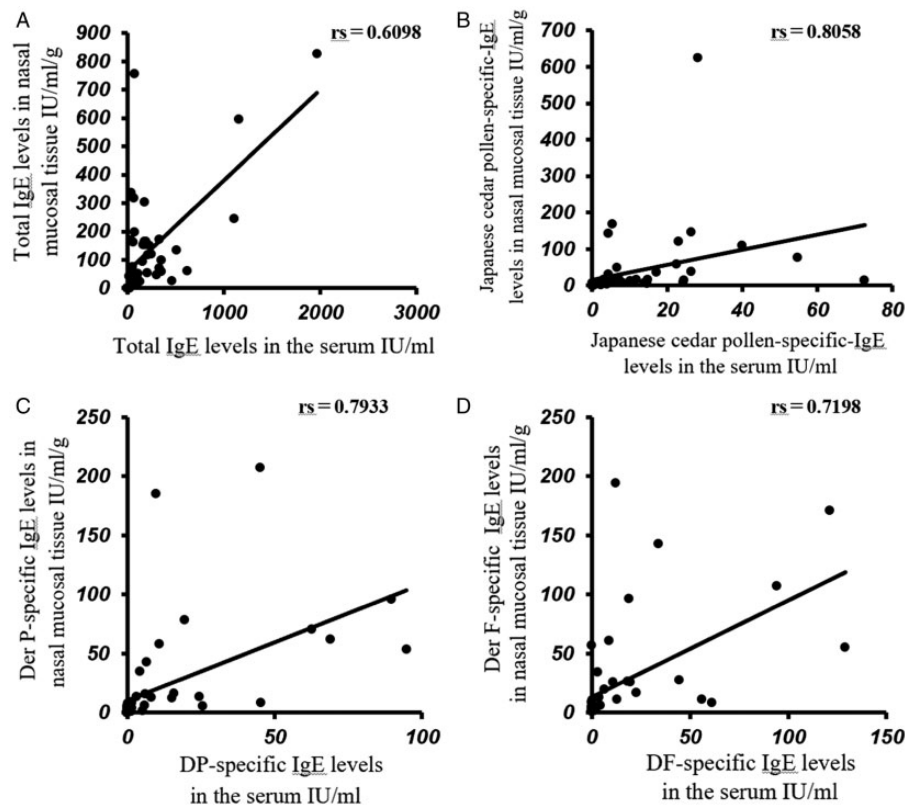


Figure 1. Relationship between IgE levels in serum and nasal mucosal tissue samples. A, Total IgE levels in serum and nasal mucosal tissue samples ($r=.61$). B, Japanese cedar pollen-specific IgE levels in serum and nasal mucosal tissue samples ($r=.81$). C, *Der p*-specific IgE levels in serum and nasal mucosal tissue samples ($r=.79$). D, *Der f*-specific IgE levels in serum and nasal mucosal tissue samples ($r=.72$).

According to Rondon et al., positive NAPT and/or detectable nasal sIgE are allergologically important examinations.⁵ In this study, both positive NAPT and detectable sIgE in the obtained nasal mucosa were adopted as the diagnostic criteria for LAR in order to strictly clarify the presence of LAR in Japan.

In statistical analyses, the relationship between 2 groups was analyzed using Spearman's rank correlation, and the significance of differences between 2 groups was analyzed using the Mann-Whitney *U* test. An IgE level lower than 0.1 IU/mL was regarded as 0.

This study was performed after approval by the ethics committee of Nippon Medical School Musashikosugi Hospital (receipt number: 314-28-11), and informed consent was received from each patient enrolled in this study.

Results

Thirty-five and 15 patients were male and female, respectively, and their ages ranged from 18 to 79 years (median: 45 years). Ten patients underwent surgery during the JCP pollinosis season (February–May) and 40 underwent surgery in other seasons.

1. Relationship between IgE levels in serum and nasal mucosal tissue samples.

A positive correlation was noted between serum and local IgE levels for 4 items: total IgE, sIgE against JCP, *Der p*, and *Der f* ($P<.01$) (Figure 1).

2. Comparison of local sIgE levels between patients with positive and negative ST.

On ST with JCP and HDM, local sIgE levels were significantly higher in the positive test score group than in the negative test score group (JCP: $P=.0003$, *Der p*: $P=.0026$, *Der f*: $P=.0151$) (Figure 2).

3. Comparison of local sIgE levels between patients with positive and negative NAPT.

No significant differences were noted in local sIgE levels between the negative and suspicious/positive NAPT score groups in any of the items tested (JCP: $P=.279$, *Der p*: $P=.525$, *Der f*: $P=.528$) (Figure 3).

4. LAR of JCP (Table 1)

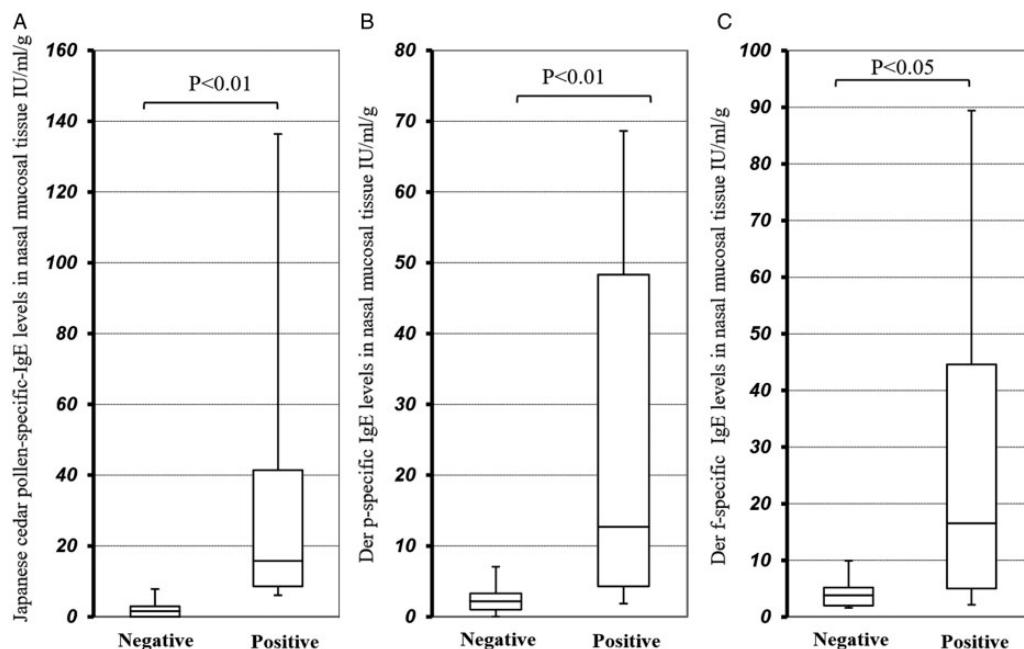


Figure 2. Comparison of local sIgE levels between patients with a positive and negative ST. A, Japanese cedar pollen. $P = .0003$; JCP ST—negative: $n = 23$, positive: $n = 24$. B, Der p. $P = .0026$; HDM ST—negative: $n = 24$, positive: $n = 23$. C, Der f. $P = .0151$; HDM ST—negative: $n = 24$, positive: $n = 23$.

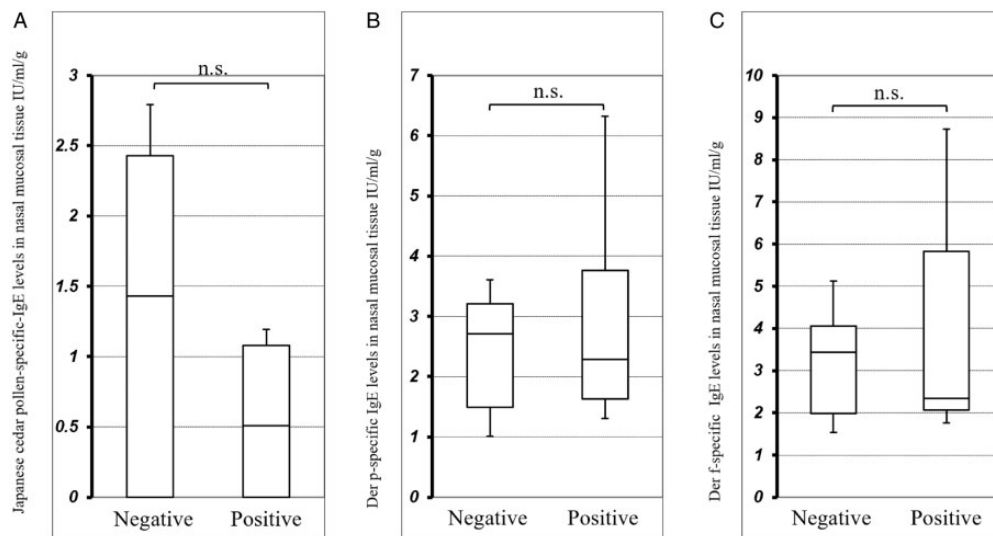


Figure 3. Comparison of local sIgE levels between patients with a positive and negative NAPT. A, Japanese cedar pollen. $P = .28$; JCP NAPT—negative: $n = 10$, positive: $n = 4$. B, Der p. $P = .53$; HDM NAPT—negative: $n = 10$, positive: $n = 11$. C, Der f. $P = .53$; HDM NAPT—negative: $n = 10$, positive: $n = 11$. n.s., not significant.

Rhinosinusitis symptoms were noted in 14 patients with a class-0 blood anti-JCP sIgE level and negative ST. Among these patients, the local anti-JCP sIgE level was class 2 or higher (0.7 IU/mL or higher) in 8 patients, and the local sIgE-positive rate was 57% (8/14). Three

patients were positive on the NAPT for JCP, 1 was suspicious, and 10 were negative. Two patients were positive on both the NAPT for JCP and local anti-JCP sIgE. The age distribution of the 14 patients and the ratio of LAR patients are shown in Figure 4(A).

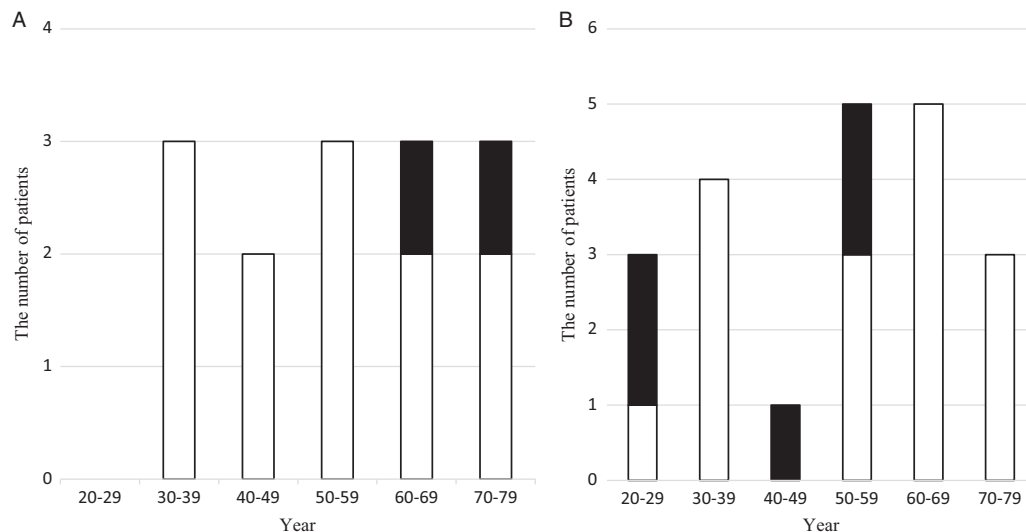


Figure 4. Age distribution and ratio of local allergic rhinitis. White columns are non-LAR (including suspicious LAR) and black columns are LAR. A, Japanese cedar pollen (n = 14). B, house dust mites (n = 21).

5. LAR of HDM (Table 2).

Rhinosinusitis symptoms with a class-0 blood anti-HDM sIgE level and a negative ST were noted in 21 patients. The local anti-*Der p* sIgE level was class 2 or higher in 17 patients, and the local anti-*Der p* sIgE-positive rate was 80.9% (17/21). The local anti-*Der f* sIgE level was class 2 or higher in all 21 patients, and the positive rate was 100%. Five patients were NAPT-positive, 6 were suspicious, and 10 were negative. Five patients were positive for both HDM NAPT and local HDM sIgE. The age distribution of the 21 patients and the ratio of LAR patients are shown in Figure 4(B). Pathological preparations of the inferior turbinate mucosa of 2 patients are shown (Figures 5 and 6).

6. Incidence of LAR (Tables 1 and 2).

The rates of being definitively diagnosed with and being suspicious for JCP LAR were 14.3% (2/14) and 57.1% (8/14), respectively, and those for HDM LAR were 23.8% (5/21) and 76.2% (16/21), respectively.

7. Patients with a positive serum sIgE level and undetectable local sIgE level.

The local anti-JCP sIgE level was undetectable in 7 patients, 2 of whom were positive for serum sIgE (0.27 [very weakly positive] in one and 0.39 [class 1] in the other). ST results were 2+ and negative, respectively.

The local anti-*Der p* sIgE level and peripheral serum level were undetectable in 3 patients. Local anti-*Der f* sIgE was detected in all 50 patients.

Discussion

Cases considered to be LAR were suspected to exist as cases of HDM- and JCP-induced AR at our department. A correlation was observed between serum and local IgE levels, and local sIgE levels were significantly higher in the ST-positive group than in the ST-negative group. In general, the blood and ST results reflect antigen-specific antibody production in the nasal mucosa, being diagnostically significant. However, these are not applicable in some cases, including LAR.

In the Japanese guidelines for AR, AR is definitively diagnosed when 2 or more of the following items are positive: eosinophils in nasal discharge, ST, serum sIgE, and NAPT.¹⁸ The description on LAR in the Japanese guidelines only suggests that LAR is included in “vasomotor rhinitis,” and “eosinophilic rhinitis” classified as nonallergic.¹ In Allergic Rhinitis and its Impact on Asthma (ARIA),¹⁹ the concept of a local nasal allergic reaction is described as follows: “The concept is not sufficiently supported by currently available data and routine measurement of IgE in nasal discharge is not recommended.” The International Consensus Statement on Allergy and Rhinology contains an item concerning local IgE production and LAR, which describes that when AR-like symptoms are present despite a negative serum sample and ST, LAR is diagnosed based on a positive NAPT, and/or the detection of nasal sIgE and/or a positive basophil activation test.⁶ This study clarified that LAR is possibly present in Japan, although the number of cases may be small.

A local sIgE measurement method to diagnose LAR has not yet been established in Japan,^{20,21} and practical provocation tests are now routinely performed using commercial paper discs. The basophil activation test is

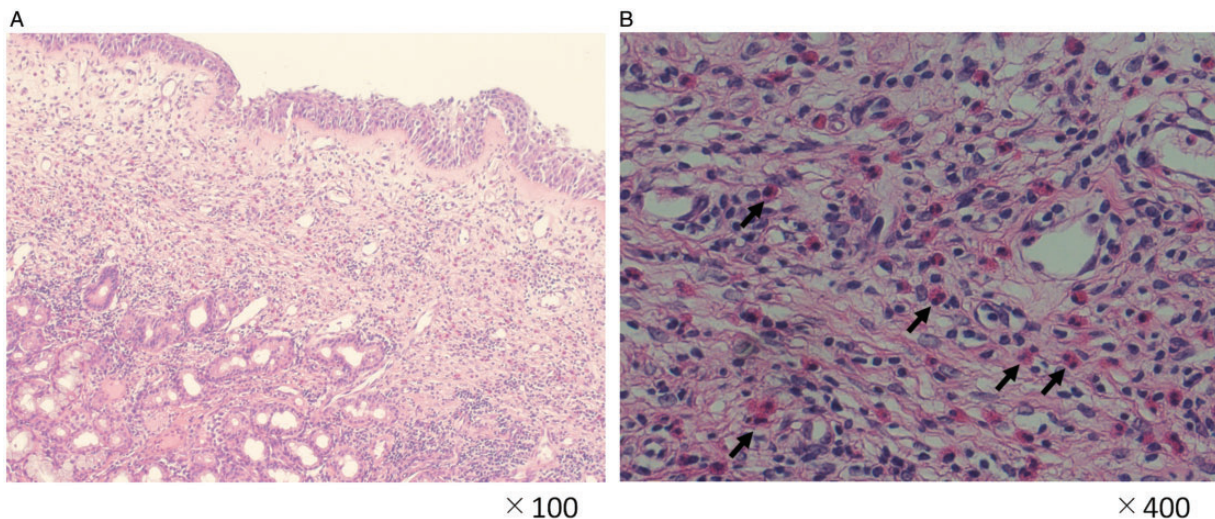


Figure 5. Pathology of nasal mucosal tissue. The resected nasal mucosal tissue from a 61-year-old male was positive for Japanese cedar pollen-specific IgE in a nasal mucosal tissue sample and had a positive NAPT and marked number of infiltrating eosinophils in the subepithelial region. Hematoxylin and eosin staining. Original magnification: arrow: eosinophil $\times 100$ (A) and $\times 400$ (B). NAPT, nasal allergen provocation test.

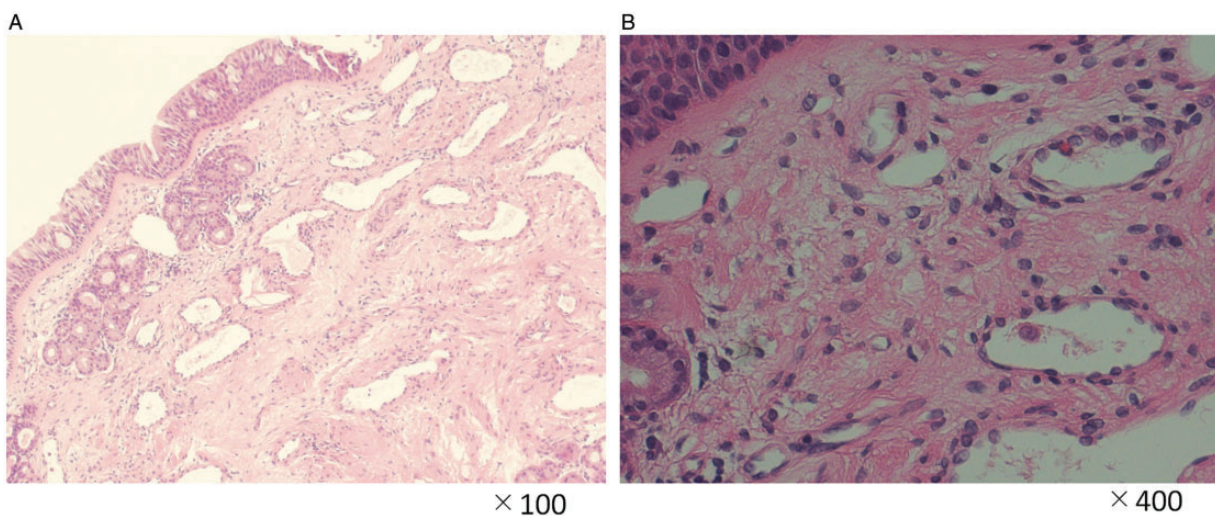


Figure 6. Pathology of nasal mucosal tissue. The resected nasal mucosal tissue from a 65-year-old male was positive for house dust mite-specific IgE and had a negative NAPT, and inflammatory cells including eosinophils were scarce or absent in the entire examined sample. Hematoxylin and eosin staining. Original magnification $\times 100$ (A) and $\times 400$ (B). NAPT, nasal allergen provocation test.

not covered by the national health insurance system in Japan and is not a general test in routine medical practice. In Japan, LAR may not be diagnosed as AR because it is considered nonallergic due to the reasons described above, in addition to the absence of diagnostic criteria in the guidelines.

Previous studies in Europe suggested that 47% to 62.5% of patients with perennial or seasonal symptoms have LAR.⁵ In this study, the frequency of LAR was lower than those reported in previous studies.⁵ We only diagnosed double-positive cases as LAR: positive for local IgE production and NAPT (positive for 2

items), and this may have been the reason for the lower frequency. NAPT is currently considered to be the gold standard for diagnosing LAR²²; however, local anti-JCP sIgE was negative even though the provocation test was positive in 1 patient. Although we strictly diagnosed patients to clarify the actual prevalence of LAR, the clinical diagnostic criteria for LAR remain unclear, including the judgment of a smaller number of unexceptional cases.

Regarding the difficulties associated with local nasal mucosal IgE measurements, measured levels may vary depending on the timing of mucosa sampling.

Table 1. Japanese Cedar Pollen Nasal Allergen Provocation Test Scores and sIgE in Nasal Mucosal Tissue.

sIgE in nasal mucosal tissue	NAPT		
	Negative	Suspicious	Positive
Negative	4	1	1
Positive	6	0	2 (14.3%)

Abbreviations: NAPT, nasal allergen provocation test; sIgE, specific IgE. Local allergic rhinitis due to Japanese cedar pollen 2/14 (14.3%), either NAPT or sIgE, in nasal mucosal tissue 8/14 (57.1%).

Table 2. House Dust Mite Nasal Allergen Provocation Test Scores and sIgE in Nasal Mucosal Tissue.

sIgE in nasal mucosal tissue	NAPT		
	Negative	Suspicious	Positive
Negative	0	0	0
Positive	10	6	5 (23.8%)

Abbreviations: NAPT, nasal allergen provocation test; sIgE, specific IgE. Local allergic rhinitis due to house dust mites 5/21 (23.8%), either NAPT or sIgE, in nasal mucosal tissue 16/21 (76.2%).

Furthermore, sIgE and eosinophilic cation protein (ECP) levels in nasal discharge increase with time after antigen exposure.²³ The timing of surgery was not in the pollen dispersal season for patients definitively diagnosed with JCP LAR; however, the timing of sampling, pollen dispersal, and other seasons need to be considered, particularly for JCP.

There were some difficulties associated with conducting NAPT. As the disc was moistened with the drug solution, it was challenging to distinguish it from nasal discharge, and judgment was made after 5 minutes. Therefore, it was not possible to evaluate the late phase of the allergic reaction. As a method to evaluate the reaction over time using a visual analog scale and acoustic rhinometry is available,²⁴ standardization of objective evaluations of NAPT is necessary. The local level of sIgE against *Der f.* was higher than the sensitivity in all 50 patients. On analysis of LAR against HDM, 10 patients were positive for local sIgE but negative for NAPT. This phenomenon highlights the problems with the appropriate threshold and presymptomatic sensitized cases. The detection of local sIgE alone is insufficient to diagnose LAR and a satisfactory NAPT is essential.

In Rondon's diagnostic flow chart,²⁵ ST-positive cases and serum sIgE-positive cases consistent with the medical history do not require NAPT, and these cases are diagnosed as AR. Thus, we did not perform NAPT for ST- or serum sIgE-positive patients in this study.

No clear global guidelines are available for provocation tests, and they are currently under discussion. We performed NAPT using a method that is easy to

perform in routine medical practice, but we think that these conditions, such as the antigen concentration, were insufficient. If the NAPT method changes, the epidemiology of LAR is likely to change. Thus, the frequency of LAR observed in this study may be arbitrary. However, for the objective of this study, "investigation of the presence of LAR mainly against JCP and HDM in Japan," such cases supposed to be present. It is necessary to increase the accuracy of the diagnostic methods, including NAPT, for the epidemiology on the assumption of the possibility.

Regarding the mechanism of LAR, in flow cytometry studies on nasal discharge, LAR was accompanied by increases in eosinophils and CD3-positive T cells in nasal discharge, similar to those in AR patients, and CD45-positive cell, neutrophil, eosinophil, and basophil levels were equivalent.^{12,13} Immediate- and late-phase allergic reactions occur in NAPT, and local sIgE production, and mast cell and eosinophil activity develops, producing viscous nasal discharge containing tryptase and ECP.^{26,27} Eosinophil infiltration was noted under the mucosal epithelium of the inferior turbinate in pathological preparations from patients diagnosed with LAR.

On comparison between the ST-negative and -positive groups, the ST score, and local anti-HDM and anti-JCP sIgE levels were significantly higher in the positive group. ST results reflected local sIgE levels.

Local sIgE was negative in 2 patients with very weakly positive and positive serum anti-JCP sIgE levels, respectively. A local reaction was noted without a systemic allergic reaction in some LAR patients, whereas sIgE production was not detected in the local nasal mucosa, and systemic allergy was present in others; however, this was the only case among a very small number of patients.

Regarding the natural course of LAR, Rondon et al. performed a 10-year prospective study and concluded that LAR does not progress to normal AR and is an independent disease. In addition, the aggravation of nasal symptoms and progression to asthma were observed in LAR patients for whom an early diagnosis of LAR and immunotherapy are necessary.²⁸

Patients with HDM and JCP LAR have been reported in Japan. Although there are difficulties associated with strictly diagnosing LAR in routine medical practice, it is important to actively perform NAPT when LAR is suspected based on symptoms even if the serum and ST are negative. Thus, it needs to be utilized for diagnosis and treatment.

Authors' Note

This study was presented at the *Rhinology World Congress*, Hong Kong, held on September 1–3, 2017.

Author Contributions

Mariko Ishida and Shoji Matsune designed the study and wrote the manuscript. Nozomu Wakayama, Ryuji Ohashi, and Kimihiro Okubo contributed to data collection.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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