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Allergy International

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Letter to the Editor

Development of eosinophilic esophagitis following sublingual immunotherapy with cedar pollen extract: A case report

Dear Editor,

Eosinophilic esophagitis (EoE), a chronic inflammatory immune-mediated disease characterized by esophageal dysfunction and dense eosinophilic infiltration of the esophageal epithelium,¹ is considered to be caused by exposure of esophageal mucosa to food and airborne allergens. Although previous reports have noted that oral immunotherapy (OIT) for immunoglobulin E (IgE)-mediated food allergy may cause development of EoE,² whether the disease is induced by sublingual immunotherapy (SLIT), particularly that for aeroallergens, has not been fully elucidated. Here, we present the first known possible case of EoE induced by SLIT with pure cedar pollen extract.

We encountered a 53-year-old female who had suffered for several years from severe allergic rhinitis caused by Japanese cedar (JC) pollen, with exacerbation mainly seen in March and April. In addition to allergic rhinitis, she reported a melon food allergy. Ten months prior to the initial visit to our institution, the patient underwent successful *Helicobacter pylori* eradication, which was confirmed by results of a urea breath test. No esophageal symptoms were detected prior to undergoing SLIT. On July 8, 2016, she began to receive SLIT with daily administrations of standardized JC pollen extract (CEDARTOLEN® SUBLINGUAL DROP, Torii Pharmaceutical, Tokyo, Japan) according to the standard procedure.³ Thirteen days after initiation of therapy, the patient felt mild retrosternal discomfort. The symptom gradually increased in intensity and she visited the emergency unit of our hospital 18 days after starting SLIT, because of severe dysphagia and frequent vomiting. Complete blood cell count and liver function test results were normal, while chest computed tomography (CT) findings demonstrated diffuse wall thickening of the esophagus (Fig. 1). An upper gastrointestinal endoscopy examination performed the following day revealed several longitudinal linear furrows, multiple concentric rings, and whitish exudates (Fig. 2A), which were highly suggestive of EoE, as previously reported. A biopsy sample obtained from esophageal mucosa showed 61 eosinophils per high powered field (hpf), which confirmed a diagnosis of EoE (Fig. 2B) based on the recent guidelines published in Europe.⁴ In addition, approximately one-third to one-half of the infiltrate in the mucosa specimen was composed of lymphocytes as compared to eosinophils, whereas no mast cell infiltration was detected. Serological findings revealed that total IgE in serum was elevated to 868 IU/ml (normal ≤ 173.0) and the allergen-specific IgE to Japanese cedar pollen was strongly positive.

The eosinophilic ratio in the white blood cell count ($3800/\mu\text{l}$) findings was not elevated at 1.1%.

SLIT for JC pollenosis was discontinued the same day as the endoscopy examination, because it was considered to be a possible cause of EoE in this case. Additionally, the patient was started on rabeprazole at 20 mg daily and continued for 8 weeks, and the symptoms gradually improved. At 8 weeks after stopping SLIT, dysphagia had disappeared, though mild retrosternal discomfort remained. An upper endoscopy examination performed at that time showed that the previous findings of linear furrows, multiple rings, and whitish exudates had disappeared (Fig. 2C). Histological results were also improved, with a peak of only 4 eosinophils/hpf in an esophageal biopsy specimen (Fig. 2D). In the present case, discontinuation of SLIT and administration of rabeprazole were quite effective for treatment of EoE.

The present patient was an adult female in whom development of EoE was considered to have been caused by SLIT with pure JC pollen extract. In a literature search, we found several case reports of EoE that developed after SLIT for pollen allergy, with a variety of different aeroallergens noted in those cases, including a wide range of pollens, such as hazelnut, birch, and alder.^{5,6} Accordingly, the present is the first known report of EoE caused by SLIT with pure cedar pollen extract. Therefore, we suggest that SLIT with cedar pollen extract may be a causative factor in EoE development. The present findings are also considered to be important for understanding the pathogenesis of this disease, since airborne allergens causing it have yet to be identified. We speculate that JC pollen is one of the airborne allergens responsible for EoE development and a possible reason for seasonal variation of its occurrence.

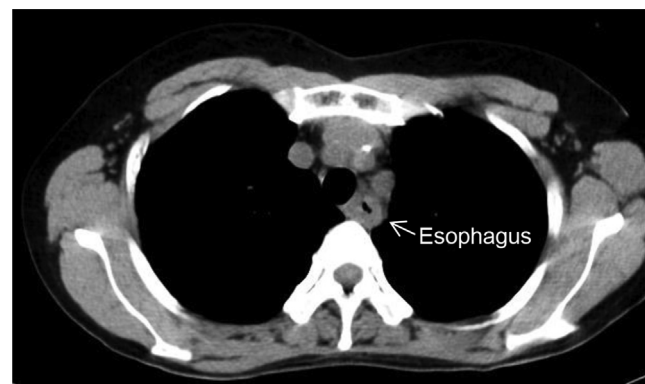


Fig. 1. Chest computed tomography findings at first hospital visit (18 days after initiation of sublingual immunotherapy).

Peer review under responsibility of Japanese Society of Allergy.

<https://doi.org/10.1016/j.alit.2018.03.003>

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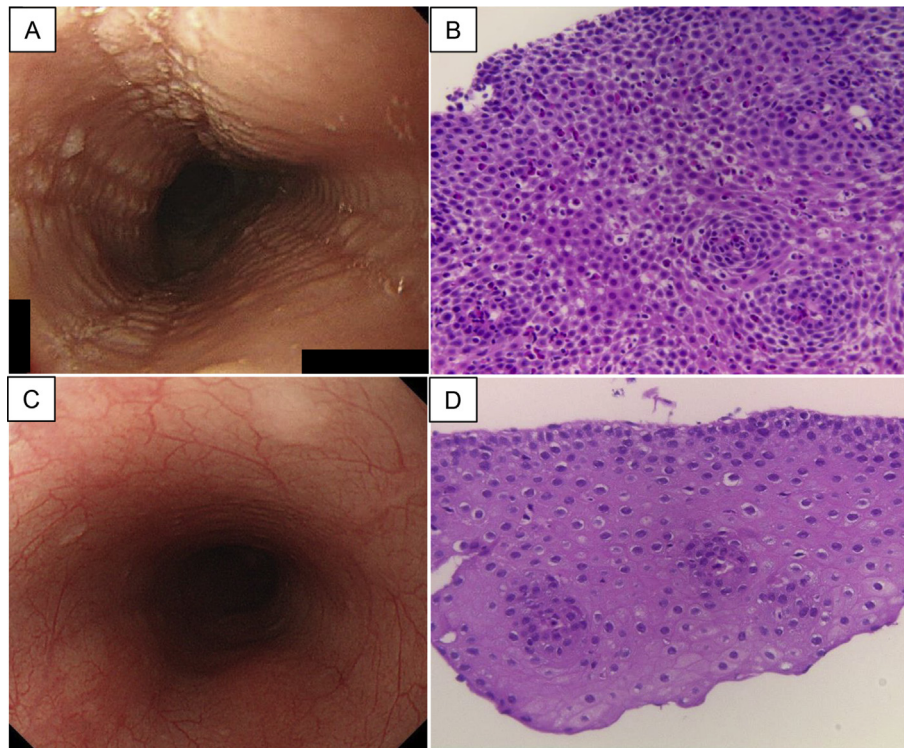


Fig. 2. Endoscopic (A) and histological (B) findings at diagnosis of EoE (19 days after initiation of sublingual immunotherapy). Endoscopic (C) and histological (D) findings at 8 weeks after discontinuation of sublingual immunotherapy.

EoE is considered to be distinct from standard acute type food allergies and IgE is not thought to be responsible for its development. Despite the existence of various types of food allergen-specific IgE in cases of EoE, a standard six-food elimination or elemental diet was reported to induce histological remission in more than three quarters of patients with EoE.⁷ In addition, a meta-analysis revealed that OIT for IgE-mediated food allergy resulted in occurrence of EoE in 2.7% of related cases.² On the other hand, seasonal variations related to the prevalence of EoE in correlation with increased pollen levels have also been reported.⁸ Therefore, aeroallergens are considered to have a potential role in the pathogenesis of EoE. In experiments with animal models, increased numbers of eosinophils in the esophagus have been found after exposure to dust mites, cockroach allergens, or *Aspergillus* antigens. Furthermore, several cases of EoE induced by exposure to a large volume of aeroallergens have been reported.⁹

On the other hand, as compared to many reports of EoE induced by OIT, there are few regarding its development caused by SLIT for aeroallergens.^{5,6,10} In each of those reports, SLIT with several different aeroallergens containing a wide range of pollens were administered, while SLIT with dust mites was administered in 2 of those cases. In the present patient, pure cedar pollen extract was used for SLIT. Our findings may explain, at least in part, why EoE frequently occurs during the spring season in Japan, as that is when JC pollens are densely present in the atmosphere.⁸

SLIT has been approved by the World Health Organization as treatment for allergic disorders, and is widely utilized throughout the world because of proven safety as well as efficacy.^{3,11} Although the frequency of EoE induced by SLIT for aeroallergens may be lower than that induced by OIT, it is important to be aware of EoE-related symptoms following initiation of SLIT, such as retrosternal discomfort, difficulty with swallowing, and vomiting. A future prospective investigation to clarify the incidence of EoE induced by SLIT may be necessary.

Based on our experience with the present case, we speculate that SLIT with cedar pollen extract is a potential cause of EoE and consider that exposure of esophageal mucosa to a large volume of cedar pollen might trigger its development.

Conflict of interest

The authors have no conflict of interest to declare.

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Received 28 December 2017

Received in revised form 23 February 2018

Accepted 4 March 2018

Available online xxx