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Case Report

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# Eosinophilic esophagitis induced by sublingual immunotherapy with cedar pollen: a case report

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## ABSTRACT

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease associated with eosinophilic infiltration of the esophageal mucosa mostly due to exposure to allergens. However, the causes and pathogenesis of EoE are not fully understood. We encountered a case of EoE that was triggered by sublingual immunotherapy (SLIT) for cedar pollen allergy. A 40-year-old man who was treated with Japanese cedar pollen tablet SLIT for cedar pollen allergy developed heartburn 3 weeks after the initiation of the treatment. He took vonoprazan for the heartburn, but the heartburn did not improve. Then, esophagogastroduodenoscopy was performed; it revealed longitudinal furrows and white spots on the esophageal mucosa, decreased vascular permeability, and erosions. Consequently, the patient was diagnosed with EoE. Heartburn and chest discomfort disappeared 1 week after the discontinuation of Japanese cedar pollen tablet SLIT, and the patient tested positive for drug allergy to Japanese cedar pollen tablet SLIT. In this study, we found that if heartburn persists during SLIT for cedar pollen allergy, and does not improve on administration of vonoprazan or proton pump inhibitors, EoE should be suspected. In addition, the occurrence of EoE due to drug allergy is indicated.

**Keywords:** Sublingual immunotherapy; Eosinophilic esophagitis; Reflux esophagitis; Drug-induced lymphocyte stimulation test; Heartburn

## INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease associated with eosinophilic infiltration of the esophageal mucosa mostly due to exposure to allergens [1]. It is presumed that dietary antigens, airborne microorganisms, and pollen, which are ingested via the oral or nasal cavity, may adhere to the esophageal epithelium, and trigger a localized immune response, which is dominated by the Th2 system [1]. However, its pathogenesis has not been fully elucidated. Here, we report a case of EoE triggered by a sublingual immunotherapy (SLIT) for cedar pollen allergy. Although, there is a reported case of EoE induced by sublingual drop of cedar pollen extract in 2018 [2], to the best of our knowledge, this is the first report of EoE induced by the administration of a Japanese cedar pollen tablet (JCPT) (CEDARCURE Japanese Cedar Pollen Sublingual Tablet Torii Pharmaceutical Co., Ltd., Tokyo, Japan).

**Conflict of Interest**
The authors have no financial conflicts of interest.

**Author Contributions**
Conceptualization: Daisuke Suto, Takaaki Otake, Mitsuhiro Okano. Formal analysis: Daisuke Suto, kazumoto Murata, Takaaki Otake. Investigation: Daisuke Suto, Kazumoto Murata, Takaaki Otake. Methodology: Daisuke Suto, Kazumoto Murata, Takaaki Otake. Project administration: Daisuke Suto, Takaaki Otake, Mitsuhiro Okano, Yutaka Kohgo. Writing - original draft: Daisuke Suto, Kazumoto Murata, Yutaka kohgo. Writing - review & editing: Daisuke Suto, Kazumoto Murata, Takaaki Otake, Eiichiro Ichiishi, Kiichi Sato, Shinya Okada, Mitsuhiro Okano, Yutaka Kohgo.

## CASE REPORT

A 40-year-old man visited an otolaryngologist for nasal congestion. Blood tests did not reveal eosinophilia (eosinophils: 2.3% of white blood cells). The serum total immunoglobulin E (IgE) levels were normal (81 IU/mL), but specific IgE tests (ImmunoCAP, Thermo Fisher Diagnostics K.K., Tokyo, Japan) were positive for cedar pollen allergy. Therefore, the patient was started on SLIT at a dose of 2,000 Japanese allergy units (JAU) of JCPT. According to the manufacturer's instructions, the patient was advised to swallow the JCPT after holding it under his tongue for 1 minute. One week after the initiation of JCPT administration, the dose was increased from 2,000 JAU to 5,000 JAU. Three weeks after the initiation of JCPT administration, the patient started experiencing occasional heartburn, and consequently, self-administered vonoprazan (10 mg/day) without a doctor's consultation; however, his symptoms were not alleviated. Four weeks after the initiation of JCPT administration, the patient's heartburn worsened, and was referred to our outpatient clinic. Esophagogastroduodenoscopy (EGDS) revealed a longitudinal groove with white spots and erosions in the esophageal mucosa (**Fig. 1A**). No abnormal findings were found in his stomach or duodenum. Histology revealed multiple eosinophilic infiltrates in the esophageal epithelium with more than 70 eosinophils per high-power field (**Fig. 1B**). Consequently, he was diagnosed with EoE. We increased the dose of vonoprazan to 20 mg, but this did not alleviate his symptoms. Then, we reduced the dose of JCPT from 5,000 JAU to 2,000 JAU and changed the method of administration from sublingual-swallow to sublingual-spit out; however, this also did not alleviate his symptoms. Therefore, we discontinued JCPT administration. The heartburn completely disappeared one week after the discontinuation of JCPT, and vonoprazan administration was continued until the heartburn resolved. The drug-induced lymphocyte stimulation test (DLST), which measures the proliferation of T cells in response to a drug *in vitro*, was positive for JCPT. An EGDS performed 2 months after the resolution of his symptoms revealed marked improvement (**Fig. 1C**) and histology revealed no eosinophilic infiltration (**Fig. 1D**). The patient has been stable for the past 6 months since the discontinuation of JCPT without a relapse of his symptoms and without requiring vonoprazan. He has been taking antiallergic medication for slight heartburn-like chest discomfort and rhinitis during spring. The patient has provided written informed consent for the publication of this report. This case report was approved by the Institutional Review Board at the International University of Health and Welfare Hospital (approval number: 21-B-462) and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

## DISCUSSION

Our patient developed EoE after SLIT with pure pollen allergenic extracts. The typical symptoms of EoE are dysphagia, vomiting, and food impaction in the esophagus. Food impaction is present in approximately half of the cases of EoE reported from the United States and Europe [3]. However, our patient presented with atypical symptoms of EoE with heartburn as the main symptom making it difficult for us to differentiate EoE from reflux esophagitis [4]. EoE should be suspected if the feeling of choking or heartburn persists even after proton pump inhibitors are administered, as proton pump inhibitors are ineffective against EoE.

It has been reported that the etiology of EoE is due to genetic factors in 20% and environmental factors in 80% of the cases [5]. In fact, the seasonality of the onset of EoE is

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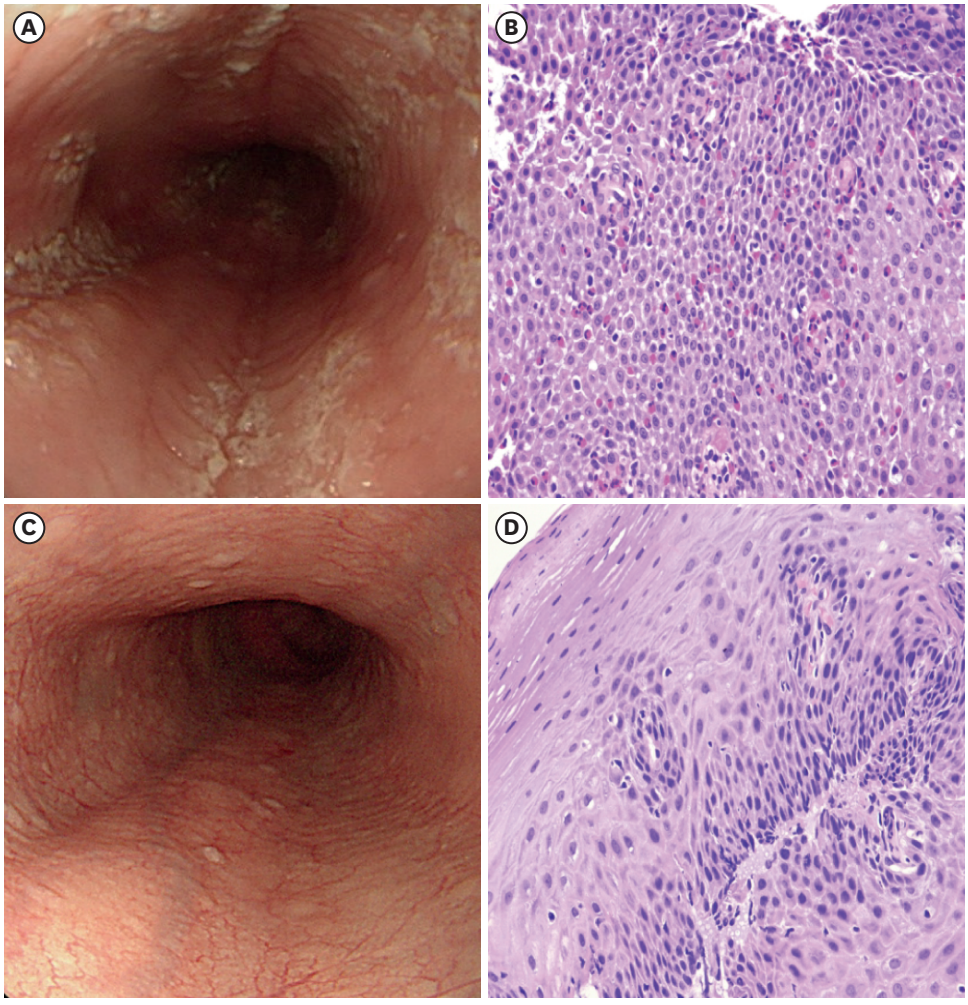


**Fig. 1.** Endoscopic (A) and histological (hematoxylin and eosin stain: ×20) (B) appearance of the esophageal mucosa at the time of diagnosis of eosinophilic esophagitis, 28 days after initiation of sublingual immunotherapy. Endoscopic (C) and histological (hematoxylin and eosin stain: ×20) (D) appearance of the esophageal mucosa 8 weeks after the discontinuation of sublingual immunotherapy.

similar to that of pollen dispersal, suggesting that inhaled antigens such as pollen may play a role in the development of the disease [5]. A retrospective study by Moawad et al. [6] analyzed 127 patients who were diagnosed with EoE on biopsy. Pollen counts were measured daily and correlated with the date of each diagnosis. The results showed that 33% of the patients developed EoE in spring and 16% in winter. Since the patient in this case was aware of chest discomfort in early spring, we speculate that pollen extracts may be a factor in the etiology and seasonal onset of EoE and aerosol allergens.

In this case, the DLST of JCPT was positive, suggesting that the patient was allergic to pollen extracts. DLST is quite useful in diagnosing patients with drug allergy [7]. Eosinophilic drug reactions are type IV b hypersensitivity reactions [8], which are th2-mediated immune responses involving the secretion of IL-4, IL-13, and IL-5 and production of IgE by B cells. IL-5 is an important regulator of growth, differentiation, and activation of eosinophils, which are inflammatory cells characteristic of certain drug responses [9]. IL-5 and IL-13 induce eosinophilic infiltration of the esophageal epithelium and intrinsic layer of the mucosa [10]. Therefore, SLIT-induced drug allergy may have caused EoE in this case. However, it is


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necessary to construct a model to elucidate the mechanism of SLIT-induced EoE induced by pollinosis extracts.

The pathogenesis and pathophysiology of this condition are poorly recognized and not fully understood. Large cohort studies are required to determine the incidence of EoE due to SLIT and cedar pollen. EGDS should be performed for patients complaining of heartburn after SLIT with cedar pollen.

## REFERENCES

1. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME; First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology 2007;133:1342-63.
PUBMED | CROSSREF
2. Kawashima K, Ishihara S, Masuhara M, Mikami H, Okimoto E, Oshima N, Ishimura N, Araki A, Maruyama R, Kinoshita Y. Development of eosinophilic esophagitis following sublingual immunotherapy with cedar pollen extract: a case report. Allergol Int 2018;67:515-7.
PUBMED | CROSSREF
3. Sperry SL, Crockett SD, Miller CB, Shaheen NJ, Dellon ES. Esophageal foreign-body impactions: epidemiology, time trends, and the impact of the increasing prevalence of eosinophilic esophagitis. Gastrointest Endosc 2011;74:985-91.
PUBMED | CROSSREF
4. Dellon ES, Gibbs WB, Fritchie KJ, Rubinas TC, Wilson LA, Woosley JT, Shaheen NJ. Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2009;7:1305-13.
PUBMED | CROSSREF
5. Alexander ES, Martin LJ, Collins MH, Kottyan LC, Sucharew H, He H, Mukkada VA, Succop PA, Abonia JP, Foote H, Eby MD, Grotjan TM, Greenler AJ, Dellon ES, Demain JG, Furuta GT, Gurian LE, Harley JB, Hopp RJ, Kagalwalla A, Kaul A, Nadeau KC, Noel RJ, Putnam PE, von Tiehl KF, Rothenberg ME. Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis. J Allergy Clin Immunol 2014;134:1084-92.e1.
PUBMED | CROSSREF
6. Moawad FJ, Veerappan GR, Lake JM, Maydonovitch CL, Haymore BR, Kosisky SE, Wong RK. Correlation between eosinophilic oesophagitis and aeroallergens. Aliment Pharmacol Ther 2010;31:509-15.
PUBMED | CROSSREF
7. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. Allergy 2004;59:809-20.
PUBMED | CROSSREF
8. Pichler WJ. Delayed drug hypersensitivity reactions. Ann Intern Med 2003;139:683-93.
PUBMED | CROSSREF
9. Kuruvilla M, Khan DA. Eosinophilic drug allergy. Clin Rev Allergy Immunol 2016;50:228-39.
PUBMED | CROSSREF
10. Davis BP. Pathophysiology of eosinophilic esophagitis. Clin Rev Allergy Immunol 2018;55:19-42.
PUBMED | CROSSREF