A case of food and aeroallergen sublingual immunotherapy inducing eosinophilic esophagitis

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Eosinophilic esophagitis (EoE) has been reported secondary to aeroallergen sublingual immunotherapy (SLIT) and food allergen oral immunotherapy. Gastrointestinal symptoms with food allergen SLIT are uncommon, with no prior reports of cases of food allergen SLIT inducing EoE. Here we report a patient who developed EoE secondary to food and aeroallergen SLIT therapy that resolved with SLIT cessation. (J Allergy Clin Immunol Global 2023;2:100125.)

Key words: *Eosinophilic gastrointestinal disease, food allergy*

Abbreviations used
EoE: Eosinophilic esophagitis
SIgE: Specific IgE
OIT: Oral immunotherapy
OVB: Oral viscous budesonide
SLIT: Sublingual immunotherapy
SPT: Skin prick testing

Eosinophilic esophagitis (EoE) secondary to aeroallergen sublingual immunotherapy (SLIT) has been demonstrated in case reports and case series resulting in EoE being a contraindication to initiation of SLIT.[1-3] At present, there are no case reports demonstrating EoE secondary to food allergen SLIT.[1] Here we report a patient who developed EoE after food and aeroallergen SLIT. This article was determined to be institutional review board–exempt by the Colorado Multiple Institutional Review Board. Informed consent was obtained from the patient's parents.

A male patient who is currently 7 years of age was born at full term via normal spontaneous vaginal delivery without complications. In his first few months of life, he developed mild atopic dermatitis that was successfully treated with moisturizer therapy. His family history was notable for both parents having allergic rhinitis but no other allergic disorders. At 10 months of age, he ingested scrambled egg for the first time and developed immediate hives and coughing. He was referred to an allergist and was noted to be sensitized to peanut (before introduction) and egg white (egg white skin prick testing [SPT] resulted in a 5-mm wheal and serum specific IgE [sIgE] level of 7.32 kUA/L, and peanut SPT resulted in a 7-mm wheal and sIgE level of 2.76 kUA/L). The results of SPT to tree nuts (almond, hazelnut, cashew, pistachio, walnut, and pecan) were negative. At the age of 15 months, the patient underwent oral food challenge to baked egg, which that he passed (tolerance), and oral food challenge to peanut, which he failed (reaction).

At 2 years of age, he had 2 reactions concerning for additional food allergies. He ingested cashew butter for the first time and developed urticaria and lip swelling. He ingested hummus containing tahini and developed urticaria and ocular angioedema. He was tolerating select tree nuts (almond and hazelnut) as well as chickpea. Testing demonstrated persistent sensitization to egg white and peanut (egg white SPT resulted in a 4-mm wheal and sIgE level of 1.92 kUA/L, and peanut SPT resulted in an 11-mm wheal and sIgE level of 3.71 kUA/L) with additional sensitization noted to cashew, pistachio, and sesame consistent with his clinical history (cashew SPT resulted in a 12-mm wheal and sIgE level of 2.12 kUA/L, pistachio SPT resulted in a 7-mm wheal and sIgE level of 3.84 kUA/L, and sesame SPT resulted in a 15-mm wheal and sIgE level of 4.91 kUA/L). The results of testing to walnut and pecan were negative. The patient passed (tolerated) food challenge to unbaked egg.

At 3 years of age, the patient continued to avoid peanut, cashew, pistachio, and sesame. He developed mild congestion and sneezing around dogs and was sensitized (SPT resulted in a 5-mm wheal) without ever having had a dog in the home. The results of testing for seasonal and perennial aeroallergens were negative. The patient was additionally noted to have persistent hypertension and was ultimately diagnosed with renal artery stenosis by nephrology.

At 4 years of age, his parents sought SLIT for treatment primarily for his food allergies. Before initiation of therapy, he was noted to have persistent sensitization to his known food allergens and dog, with development of aeroallergen sensitization to tree pollens, cat, and dust mite. His SLIT therefore contained peanut, cashew, pistachio, sesame, tree, cat, dog, and dust mite extracts. He had no gastrointestinal symptoms such as dysphagia, feeding difficulties, or reflux before initiation of SLIT; his growth was normal.

Two months after initiation of SLIT, he experienced weight loss (0.91 kg) and was referred to pediatric gastroenterology. He had feeding difficulties, requiring drinking liquids and using sauces to help swallow denser textures, prolonged meal times, and poor appetite. The results of routine bloodwork were notable for an absolute eosinophil count of 670 cells/μL. Because of concern

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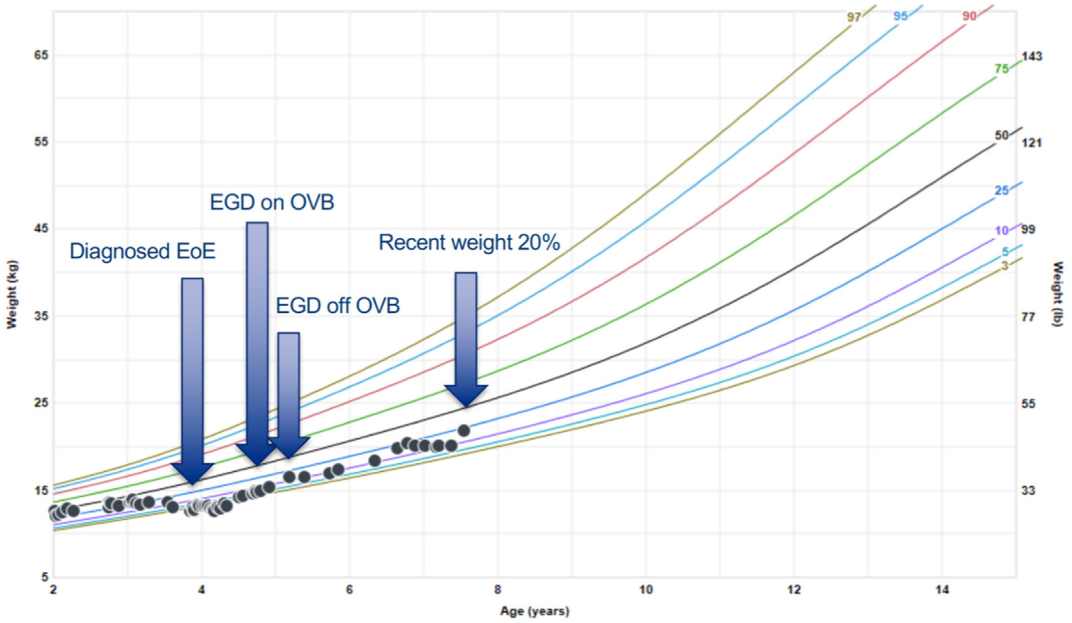

FIG 1. Patient growth curve. Patient World Health Organization growth curve of weight (in kg) with arrows indicating key clinical time points. *EGD,* Esophagogastroduodenoscopy.

for EoE, he underwent endoscopy, revealing mild edema, exudates, and furrows and was diagnosed with EoE, with biopsy specimens revealing proximal and distal esophageal mucosa containing 16 eosinophils/hpf and 22 eosinophils/hpf, respectively.[4]

After diagnosis of EoE, SLIT was discontinued, and he started taking oral viscous budesonide (OVB), 0.25 mg, thickened with Neocate Nutra (Nutricia, Hoofddorp, The Netherlands) swallowed twice daily. Although discontinuation of SLIT only as treatment was considered, given the patient's renal artery stenosis and need for a nephrectomy, there was a desire to maximize esophageal healing and nutritional status before surgery, which was ultimately performed successfully. The results of an endoscopy at 6 months after discontinuation of SLIT and initiation of OVB were normal (proximal and distal esophagus with zero eosinophils/hpf), indicating histologic remission of EoE. The patient experienced improvement in growth and feeding, so OVB was discontinued (Fig 1). A subsequent endoscopy 8 months after discontinuation of SLIT and 2 months after discontinuation of OVB demonstrated 10 eosinophils/hpf in the proximal and distal esophagus, meeting the criteria for histologic remission.[4] For the past 2 years, the patient has continued to experience improvement in terms of weight gain (Fig 1) and absence of feeding difficulties, and he has not resumed SLIT as treatment for EoE.

More is known about the relationship between EoE and food allergen oral immunotherapy (OIT) with the prevalence of biopsy-confirmed EoE after initiation of OIT, ranging from 3% to 5%.[5,6] However, this is likely an underestimation, as gastrointestinal symptoms are common and not all patients undergo endoscopy after initiation of OIT.[6] The prevalence of EoE secondary to aeroallergen SLIT is not well characterized and is limited to case reports.[3] However, given that there is a clear role for aeroallergen-triggered (aeroallergen-exacerbated) EoE in a subset of patients,[7] it is possible that EoE secondary to aeroallergen SLIT is more common than reported. The majority of patients with EoE have comorbid allergic rhinitis and are sensitized to aeroallegens.[7] Although aeroallergens are the primary antigen exposure driving EoE in individual case reports only,[8] they contribute to seasonal exacerbations of EoE in a subset of patients,[9,10] and perennial aeroallergen sensitization is associated with a lack of response to standard EoE therapies.[11] Thus, it is reasonable to suspect that delivery or aeroallergens via SLIT would contribute to EoE in a similar subset of patients. Case reports of biopsy-confirmed EoE secondary to aeroallergen SLIT, which are summarized elsewhere,[1,2] notably include SLIT for tree pollen[2,12-14] and SLIT for dust mite,[2,15] which were similarly received by our patient.

There are no previously published cases of food allergen SLIT inducing EoE. In general, SLIT for food allergens has a more modest desensitization effect than OIT does; however, this is balanced with a more favorable side effect profile,[16] with gastrointestinal symptoms being uncommon (noted in only 0.3% of patients in a study of pediatric patients undergoing long-term peanut SLIT).[17] On the basis of our case, EoE secondary to food allergen SLIT is possible, although it is likely less common than EoE secondary to OIT given the smaller exposure dose and infrequent gastrointestinal symptoms. However, the relative contribution of foods versus aeroallergens leading to EoE development in our patient's case is unknown. Although one could consider restaring SLIT for food allergens only to better elucidate the culprit, this was thought to be unethical, as the patient's family was not interested in pursuring future treatments for food allergy given the prominence of his symptoms and weight loss.

Recent data have better characterized the relationship between OIT and EoE, as patients with IgE-mediated food allergies are at increased risk for EoE,[18] so whether patients have subclinical disease before initiation of therapy is unclear. In a substudy of adult patients undergoing peanut OIT, endoscopies were performed before therapy initiation, at the end of buildup, and during maintenance therapy. The substudy demonstrated that 24% of patients had preexisting esophageal eosinophilia without symptoms suggestive of EoE,[19] with a transient increase in esophageal eosinophilia noted during buildup that resolved during maintenance without intervention in most patients. Only 1 patient developed EoE.[20] Although

gastrointestinal symptoms were common, they were not closely correlated with esophageal eosinophilia,[20] demonstrating that not all patients with gastrointestinal symptoms or esophageal eosinophilia ultimately develop EoE, although currently unidentified factors may render certain individuals more susceptible.

Although EoE is a contraindication to use of the US Food and Drug Administration–approved peanut OIT product, given the more widespread use of OIT, there are likely patients who will develop EoE while undergoing OIT and would like to continue therapy. In these scenarios, it may be appropriate to consider shared decision making based on how the family weighs the risk of an accidental exposure and anaphylaxis versus that with chronic treatment of EoE with long-term medications and procedures such as endoscopy.[21] Use of the Esophageal String Test or Cytosponge may aid in monitoring patients old enough to swallow a capsule, thereby reducing the frequency of endoscopies.[22] Although not specifically studied in SLIT, similar principles and treatment options are likely appropriate. In this patient's case, we could have considered long-term OVB therapy or potentially dupilumab, given its recent approval in an older age group,[23] as a means to continue SLIT. However, given the presentation of weight loss in a child who needed to undergo nephrectomy, the treatment would have likely remained unchanged.

In conclusion, EoE secondary to food and aeroallergen SLIT is less common than EoE secondary to food allergen OIT, but it can occur. EoE secondary to SLIT or OIT typically resolves with discontinuation of therapy through removal of chronic antigen exposure, as was shown in our patient's case.[1,5] It is prudent for physicians to inquire about gastrointestinal symptoms before initiation of and during ongoing SLIT and OIT. With more widespread use of OIT, future studies are needed to guide the optimal monitoring and management of patients who develop gastrointestinal symptoms and/or EoE while undergoing these forms of immunotherapy.

DISCLOSURE STATEMENT

Disclosure of potential conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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