
Eosinophilic Esophagitis Caused by Grass Pollen Sublingual Immunotherapy With Tolerance to a Subcutaneous Extract

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Eosinophilic esophagitis (EoE) is an immune-mediated chronic esophageal disorder characterized by symptoms of esophageal dysfunction and predominantly eosinophilic inflammation with >15 eosinophils per high-power field. It is due to a type 2 cell-mediated immune response, mainly to food allergens.

EoE may develop during oral immunotherapy in patients with IgE-mediated food allergy, affecting between 2.7% and 5.7% of those undergoing induction of oral tolerance to milk, egg, or peanut [1]. Involvement of airborne allergens in EoE has been less frequently confirmed, and the association between EoE and sublingual immunotherapy (SLIT) has received very little attention in the literature.

A 39-year-old woman was referred to our allergy unit in September 2014 with a 10-year history of seasonal rhinoconjunctivitis and mild allergic asthma due to grass pollen sensitization. She reported ocular-nasal symptoms despite daily antihistamines, as well as daily cough, wheezing, and mild dyspnea. One year earlier, during the preseason (January to March), she initiated SLIT with a standardized grass mix and *Cynodon dactylon* pollen extract (Sublingual Spray Maxi, Diater SA). She had no history of food allergy.

The patient also had a 20-year history of recurring digestive symptoms consisting in nausea, heartburn, and burning stomach pain. At the age of 18, she was diagnosed with peptic esophagitis and chronic gastritis by esophago-gastro-duodenoscopy (EGD) and started treatment with proton pump inhibitors (PPIs). She also underwent eradication of *Helicobacter pylori*, which led to improvement of her symptoms, although occasional heartburn persisted. No esophageal biopsies were taken at the time. Nonetheless, in January 2014, an abrupt worsening of her previous digestive symptoms necessitated a new EGD, which was performed in March; this revealed erythematous

mucosa in the distal esophagus. An esophageal biopsy revealed >25 eosinophils per high-power field. Treatment with polyezymes, dimethicone, succinate, and metoclopramide led to a progressive improvement.

After taking a meticulous clinical history, we established the timeline of the patient's symptoms, linking the relapse to the initiation of the second season of SLIT and the resolution to completion of SLIT. A new EGD carried out in December 2014 revealed complete remission of the disease, with no signs of local inflammation or presence of eosinophils in esophageal biopsy specimens. The patient was not taking PPIs or corticosteroids at that time.

Seasonal respiratory symptoms improved after 2 years of SLIT, and the patient asked to continue pollen immunotherapy. Sensitization to grass pollen was confirmed by prick test and determination of specific IgE (rPhl p 1 and 5, 63 kU_A/L; total IgE, 114 kU/L). Allergy tests were negative to foods. Subcutaneous immunotherapy (SCIT) with a grass pollen extract (Depigoid, LETI Pharma) was initiated, and the patient completed 5 years of treatment with a favorable response. The bronchial symptoms ceased, and rhinoconjunctival symptoms remained mild, requiring treatment with antihistamine exceptionally. She seldom experienced digestive complaints, although these responded satisfactorily to on-demand PPIs. A follow-up EGD in December 2017, after 3 years of SLIT and without taking PPIs, confirmed full remission of EoE, with persistent antral gastritis.

We report the case of a woman who developed EoE caused by a sublingual grass pollen extract. The cause-effect relationship was supported by a chronological correlation with both clinical symptoms and endoscopic/histologic findings.

Apart from the well-established role of food antigens in EoE, the involvement of inhaled airborne allergens in an inflammatory response in the lung and esophagus has been proved in murine models [2]. Some studies established a connection between the pollen season and the display of EoE symptoms and diagnosis, although these hypotheses were rebutted in a systemic review [3]. Nevertheless, there are singular case reports of seasonal clinical exacerbation and histological aggravation of otherwise well-controlled EoE caused by significant exposure to airborne allergens.

Despite the growing use of SLIT for environmental and food allergy, this approach has been exceptionally related to EoE, with 7 cases published in the literature to date (Table). In 2013, Miehke et al [4] reported the first case, which involved a 44-year-old woman who developed dysphagia 4 weeks after initiation of a hazelnut/birch, alder/oak pollen sublingual extract. Subsequently, 2 cases were reported following initiation of SLIT with dust mites [5,6], 2 were triggered by grass pollen [7,8] and 1 was triggered by a cedar pollen extract [9]. The most recent case was reported in a 38-year-old woman after 3-year maintenance of SLIT with a latex extract [10]. Esophageal symptoms developed in 6 of these 7 patients within less than 6 weeks of the beginning of immunotherapy. The SLIT extract was discontinued in all cases. In the only case in which SLIT was switched to SCIT, the patient experienced a relapse of esophageal symptoms. However, this 10-year-old boy had had histologically confirmed EoE before starting immunotherapy, and no subsequent biopsies were performed, thus establishing the association between EoE and SLIT/SCIT based merely on clinical symptoms [8].

Table. Cases of SLIT-Induced Eosinophilic Esophagitis Reported in the Literature

Authors	Sex age, y	Allergen extract	Time to onset of symptoms	Endoscopic findings	Biopsy findings	Intervention	Outcome
Miehke et al, 2013 [4]	Female 44	Hazelnut, birch, alder	8 wk	Whitish exudates, longitudinal furrows	164 eos/hpf	Discontinued SLIT	Negative biopsy at 4 wk
Antico et al, 2014 [7]	Male 23	Timothy grass	4 wk	Not found	18-24 eos/hpf	Discontinued SLIT	Negative biopsy at 3 mo
Béné et al, 2016 [5]	Female 10	Dust mite	6 wk	Focal congestion of gastric mucosa	100 eos/hpf	Discontinued SLIT, PPIs	Negative biopsy at 4 wk
Rokosz et al, 2017 [6]	Male 9	Grass, tree, dust mite	13 mo	Not mentioned	57 eos/hpf	Discontinued SLIT, PPIs	Negative biopsy at 12 mo
Kawashima et al, 2018 [9]	Male 53	Cedar	18 d	Linear furrows, concentric rings, whitish exudates	61 eos/hpf	Discontinued SLIT, PPIs	Negative biopsy at 8 wk
Wells et al, 2018 [8]	Male 10	Five grass mix	10 mo	Not mentioned	Not mentioned	Discontinued SLIT, PPIs, budesonide slurry	Clinical resolution, no biopsy, recurrence with SCIT
Nucera et al, 2020 [10]	Female 38	Latex	3 y	Circular rings, linear furrows, whitish exudates	25 eos/hpf	Discontinued SLIT, PPIs	Negative biopsy at 12 wk

Abbreviations: eos/hpf, eosinophils per high power field; PPI, proton pump inhibitor; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

We present the case of a woman with chronic gastritis that portrays the development of EoE due to SLIT with a grass pollen extract. The chronology of onset of symptoms, histological confirmation, and remission of symptoms and inflammation after discontinuation of SLIT points to a cause-effect relationship. Our conclusions are also supported by the long follow-up period (>5 years).

We demonstrated tolerance to a subcutaneous pollen extract, suggesting that direct contact of the allergen with esophageal mucosa may be mandatory for EoE to develop. To our knowledge, this observation has not been previously reported in the literature.

Although extremely uncommon, EoE can constitute an unwanted adverse effect of SLIT. The allergist must remain alert in order to detect characteristic symptoms and thus discontinue therapy and provide proper care for the patient. Continuation of specific immunotherapy may be feasible by changing the route of administration (SCIT), always with close clinical and endoscopic monitoring. Further clinical investigation of these cases is needed for a full understanding of this phenomenon.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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