Induction of Eosinophilic Esophagitis by Sublingual Pollen Immunotherapy

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Key Words
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Abstract
Sublingual immunotherapy (SLIT) is increasingly investigated and utilized for the treatment of food and pollen allergies. Previous case reports suggested that eosinophilic esophagitis (EoE) might develop as a long-term complication in children after completion of oral immunotherapy. Here, we describe a 44-year-old female with a medical history of pollinosis who for the first time in her life developed complete manifestation of EoE (peak eosinophils 164/high power field) 4 weeks after initiation of SLIT using specific soluble allergens (hazelnut, birch, alder) according to previous specific serum IgE testing. After discontinuation of SLIT, EoE resolved completely within 4 weeks without any other medical intervention. During a follow-up of 12 months the patient remained free of any esophageal symptoms. This is the first case report demonstrating a close and therefore likely causative association between pollen SLIT and EoE in an adult patient.

Introduction
Sublingual immunotherapy (SLIT) is increasingly investigated and utilized for the treatment of food and pollen allergies. While SLIT is generally considered to be safe, a recent meta-analysis of randomized controlled trials has identified limitations in the standardization of adverse events [1]. Previous case reports suggested that eosinophilic esophagitis (EoE) might develop as a long-term complication in children several months after comple-
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The clinical course together with all findings is highly suggestive of SLIT as the causative factor for EoE in this patient. The final proof that SLIT was the trigger for EoE would require re-exposition with confirmation of relapse. We did not perform this procedure due to ethical considerations. Our patient developed a complete manifestation of EoE about 4 weeks after initiation of SLIT using hazelnut, birch and alder, which are typically airborne antigens. According to the manufacturer’s description, dysphagia appears to be a rare but well-recognized side effect of SLIT. The incidence and the exact cause of dysphagia during SLIT, however, are currently unknown. Therefore, we hypothesize that SLIT may be a potential trigger for EoE due to high antigen exposure of the esophagus in predisposed individuals.

EoE is a chronic inflammatory, immune/antigen-mediated esophageal disease increasingly recognized during the last decade [5]. Although the common belief is that EoE is pri-
mainly a food allergen-triggered disease, several lines of evidence suggest that both airborne and food allergens may be involved in the etiology of EoE. For example, a seasonal and geographical pattern of EoE which may be compatible with increased airborne allergen exposure has been described [6, 7]. On the other hand, a recent prospective study in adults with EoE confirmed previous observations that a six-food elimination diet significantly improved both endoscopic and histological features of EoE and its symptoms [8]. Furthermore, reintroduction of the individual food components resulted in recurrence of EoE, with wheat and milk being the most frequent causes. Finally, several cases of de novo EoE following high-volume exposure of aeroallergens has recently been reported [9].

The immunological effects induced by allergens introduced through the mouth are quite variable and depend on the dose and type of the allergen, low doses inducing immune deviation and high doses resulting in deletion of antigen-specific T cells [10, 11]. Since the present literature on SLIT indicates a shift in the immune response resulting in regulatory T cells [12], we can assume that the concentrations of allergens that are used in therapy do not result in deletion of allergen-specific T cells as seen in high-dose oral tolerance. In some cases, while reducing allergen-specific IgE levels, sublingually administered pollen extracts induced IL-10, IL-5 and Foxp3 expression T cells [13]. Since IL-5 is a key mediator in eosinophil activation, such immunological effects of SLIT can result in EoE. Even though EoE has not been reported previously in subjects undergoing SLIT, there are several reasons that we believe may have influenced this. First, most SLIT studies have been done in adults, and the symptoms of EoE in this population can be very subtle (such as altered feeding behavior), and the questionnaires of SLIT protocols do not address this question [5]. Second, the time of induction of an eosinophilic disease can be much longer than what it takes to develop an IgE-mediated allergy. Most IgE-mediated food allergies present in the pediatric age group as opposed to EoE, which can present in all age groups [5]. It is possible that it may take many years from the time sensitization starts to becoming clinically symptomatic, hence the EoE side effects of SLIT may not become evident many years later. Finally, the frequent occurrence of abdominal symptoms in patients receiving oral immunotherapy for desensitization for foods such as milk and egg [2, 3] suggests the possibility of eosinophilic gastrointestinal disease, but this has not been addressed systematically.

Our case report, in conjunction with similar recently published cases, suggests that both food and pollen SLIT could be a trigger for EoE in predisposed individuals. Giving the strongly rising incidence of EoE [14], physicians evaluating patients with dysphagia, e.g. gastroenterologists and otolaryngologists, should be aware of this potential and clinically relevant complication of SLIT and consider it in patient care and follow-up. Furthermore, EoE-specific questionnaires should be incorporated into clinical trials involving allergens introduced orally or sublingually, and proper endoscopic assessments should be implemented in symptomatic individuals.

References


Fig. 1. Endoscopic (a) and histological findings (b) 4 weeks after initiation of SLIT. b Hematoxylin & eosin staining, magnification ×150.
Fig. 2. Endoscopic (a) and histological findings (b) 4 weeks after withdrawal of SLIT. b Hematoxylin & eosin staining, magnification ×150.