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CASE IN POINT

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Eosinophilic Esophagitis as a Complication of Sublingual Immunotherapy

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An 11-year-old boy presented with a 3-month history of chest pain and epigastric pain. He described the pain as if he had been punched in the stomach. He reported a burning sensation at the epigastrium and throat pain.

No particular foods exacerbated his symptoms except for gumbo and pizza. He initially had seen his pediatrician, because over-the-counter antacids had not relieved the pain. He was started on esomeprazole daily; despite a trial of the proton-pump inhibitor (PPI), his symptoms persisted. He was referred to a gastroenterologist, who started him on esomeprazole, 40 mg twice daily, along with antacids for a month, which had led to minimal relief. The subsequent month, he also had developed dysphagia and globus sensation.

Medical history. The patient's medical history included allergic rhinitis, with results of a previous skin-prick test showing sensitization to grass, tree pollen, and cat dander. He had been

treated for his allergies with sublingual immunotherapy (SLIT) drops for grass and tree pollen for almost 1 year. He was taking no other medications at the time of presentation.

Physical examination. His vital signs at presentation were within normal limits. His abdomen was soft but tender at the epigastrium, nondistended, and without a mass or organomegaly. The rest of the physical examination findings, including those of skin and nasal examinations, were normal.

Diagnostic tests. Five days prior to presentation, the patient had undergone a diagnostic esophagogastroduodenoscopy (EGD), which had revealed furrowing of the mid to distal esophagus. Biopsy results showed up to 35 eosinophils per high-power field (**Figure**) and superficial layering of eosinophils, findings that were consistent with eosinophilic esophagitis (EoE).

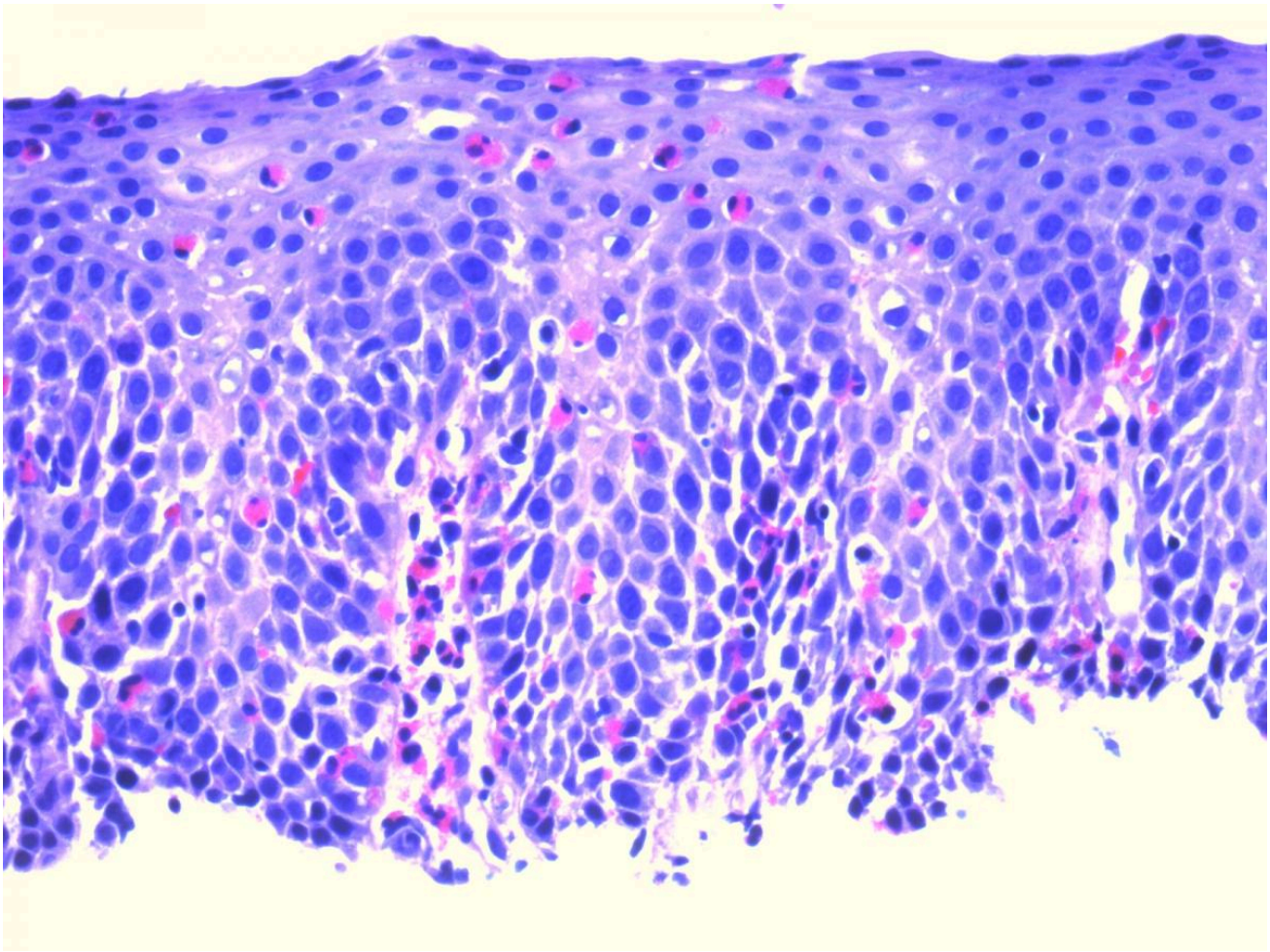

Figure 1. *Increased intraepithelial eosinophils (arrows) with superficial layering and spongiosis.*

Results of skin-prick tests, which were performed after the EGD, for allergies to common foods including meats and corn were negative.

SLIT-induced EoE was suspected, and his oral immunotherapy was discontinued. The gastroenterologist suggested he continue esomeprazole, 40 mg twice daily, for 1 more month. At the allergist's suggestion, he was started on swallowed fluticasone propionate for 1 month, which led to complete resolution of his symptoms. A repeated EGD was not pursued, because discontinuing SLIT was curative.

Discussion. EoE was initially described as a chronic clinicopathologic disease characterized by esophageal dysfunction, with symptoms including dysphagia in adults and feeding intolerance and reflux in children.[1] Histologically, the diagnosis requires the presence of 15 or more eosinophils per high-power field on esophageal biopsy results and the exclusion of other disorders, especially gastroesophageal reflux disease, by the use of high-dose PPIs prior to biopsy or normal pH monitoring.[1] In 2011, new consensus recommendations for EoE defined it as representing "a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation."[2]

The estimated US prevalence of EoE is 56.7 cases per 100,000 individuals.[3] Symptoms generally differ by age and are nonspecific. Infants and toddlers commonly present with feeding difficulties and failure to thrive. Adolescents typically present with vomiting, abdominal pain, and dysphagia (symptoms similar to those of our patient, who was in this age group). Adults typically present with dysphagia and food impaction.

Given that a normal esophagus is devoid of eosinophils, the pathologic process in EoE is the infiltration of eosinophils in the esophageal mucosa. The pathogenesis is incompletely understood. Many factors, including genetic, environmental, and host immune system factors, may contribute to the pathogenesis. An adaptive type 2 helper T cell (T_H2)-mediated response produces interleukin 5 (IL-5) and interleukin 13 (IL-13) in response to antigenic proteins, which more commonly originate from food triggers rather than inhalation triggers.[4] IL-13 triggers expression of the eotaxin-3 gene, causing recruitment of eosinophils from the circulation.[4] T_H2 cells activated by antigens produce IL-5, which is primarily responsible for eosinophil growth, activation, and increased survival.[5]

Triggers of EoE in most patients include foods as the inciting event for non-immunoglobulin E–mediated T_H2 inflammation.[6-8] Based on clinical improvement with various elimination diets and normalization of esophageal biopsy findings, food antigenic triggers are associated with the pathogenesis of EoE. EoE also is associated with other allergic conditions such as environmental allergies, asthma, and atopic dermatitis. Crohn disease, celiac disease, and connective tissue disorders also are associated with esophageal eosinophilia.[9-11]

Subcutaneous immunotherapy is a traditional and efficacious treatment for allergic respiratory diseases, but an alternative approach, which is more convenient and has a lower risk for

diseases, but an alternative approach, which is more convenient and has a lower risk for anaphylaxis, is emerging. SLIT is self-administered sublingually via tablets, but oral drops are also available. A 5-grass tablet, short ragweed tablet, and timothy-grass tablet are available but have not gained much acceptance in the United States as they have in Europe. EoE has been reported as a rare complication in oral immunotherapy using milk, peanut, and oral tolerance induction for egg. Only one case of EoE with SLIT drops has been reported when using birch, hazelnut, and alder extract, but no cases have been reported as a complication of purely grass SLIT tablets.

As patients elect to avoid invasive therapy such as subcutaneous immunotherapy in favor of oral options, EoE should be considered as an adverse effect and should be studied further, given that the incidence of EoE has increased in recent years. In all of the reported cases, including our patient's cases, treatment involved removing the offending agent, which led to complete resolution of symptoms and histologic disease.

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