

Letter to the Editor

Resolution of acute IgE-mediated allergy with development of eosinophilic esophagitis triggered by the same food

To the Editor:

Eosinophilic esophagitis (EoE) is characterized by isolated eosinophilic infiltration of the esophagus that can present at any age and symptomatically mimic gastrointestinal reflux disease (GERD). The symptoms vary by age from failure to thrive in young children, to abdominal pain, regurgitation, and vomiting seen in school-age children and dysphagia and food impaction in adolescents and adults.¹ Atopy is commonly observed in EoE, with 28% to 86% of adults and 42% to 93% of children having another allergic disease and 71% to 93% of the subjects having positive skin prick test results to aeroallergens.² In addition, high rates of IgE-mediated food allergy (15%-43%) are reported in subjects with EoE, especially in children.³ Foods are the major antigenic trigger for EoE in children and adults, with milk, egg, wheat, and soy being most common.^{2,4}

Genetic analyses and murine model systems have recently identified a role for the cytokine thymic stromal lymphopoietin (TSLP) in promoting eosinophilic esophageal inflammation. We have shown gain-of-function polymorphisms in the TSLP gene to be associated with EoE development in children.^{5,6} Furthermore, in our mouse model, TSLP and basophils contributed to the development of EoE-like disease,⁷ independent of IgE,⁷ and increased basophil responses in human EoE are seen with the TSLP polymorphism. Furthermore, there are reports of children developing EoE after receiving oral immunotherapy (OIT) for food allergy.⁸ Together, this suggests that IgE-dependent mechanisms may not be critical for the development of EoE. However, the relationship between IgE-mediated inflammation and EoE in human subjects is unknown and conflicting.^{1,2,8,9}

We sought to assess the association between IgE-mediated food allergy and EoE in our cohort. We identified a subgroup of 17 children with a history of clinically relevant IgE-mediated food allergy who after outgrowing their IgE-mediated food allergy were found to have EoE to the same food. Thus, IgE-mediated food allergy may proceed, and possibly predispose to, the development of EoE, with the pathogenesis of EoE being distinct from that of IgE-mediated food allergy.

The study was approved by the Children's Hospital of Philadelphia's Institutional Review Board. This is a retrospective cohort study from our database from our Center for Pediatric Eosinophilic Disorders. The diagnosis of EoE was confirmed per 2011 consensus document.¹ IgE-mediated food allergy was confirmed by history and testing. EoE causative foods were confirmed by esophagogastroduodenoscopy (EGD) and biopsy. (See the [Methods](#) section in this article's Online Repository at www.jacionline.org for additional details.)

A total of 1375 subjects were included in the database. A total of 1025 subjects had confirmed EoE, and a definitive causal food was identified by biopsy for 425 subjects. Of these 425, 84 had a history of IgE-mediated food allergy to any food (preceding/concurrent with EoE diagnosis); 17 of the 84 subjects outgrew their IgE-mediated food allergy and subsequently developed EoE to the same food. Two of these 17 subjects had documented normal esophageal biopsies at the time they had

IgE-mediated allergy to the food, but they were diagnosed with EoE only after the food was reintroduced into their diet following a negative oral food challenge.

Consistent with our previous reports,² the most common foods causing EoE in this subgroup of 17 subjects were identical to those seen in the entire cohort ([Table I](#)), with milk, egg, soy, and wheat being the most common. The most common foods causing IgE-mediated allergy in this subgroup are similar to those in the general population: peanut, tree nuts, egg, and milk ([Table I](#)). The most common symptoms of IgE-mediated food allergy were hives (n = 9), emesis (n = 2), anaphylaxis (n = 2), and worsening of atopic dermatitis symptoms (n = 6). For 3 of the 17 subjects (17.6%), more than 1 food was identified as causal for their EoE; in 2 subjects, 2 foods were identified; and in 1 subject, 3 foods were identified. Atopic disease was common among this subgroup of patients, with 82.3% (n = 14 of 17) having another allergic disease ([Table I](#)).

The average time from when the subjects had outgrown their IgE-mediated food allergy to their diagnosis of EoE was 2.4 years. This gradual onset of symptoms suggests that esophageal damage developed slowly over years before the patients noticed symptoms, or, alternatively, repeated exposure over time lead to the development of non-IgE sensitization causing EoE. One patient developed symptoms after only 2 months of exposure to the food, similar to that described in oral immunotherapy,⁹ suggesting possibly multiple mechanisms or variable patient sensitivities.

Interestingly, comparing our subgroup to the 67 subjects with IgE-mediated food allergy and EoE to different food showed that only age appears to be a predictive factor. These patients are younger by about 3.6 years and have not outgrown their IgE-mediated food allergy yet ([Table I](#)).

Of special interest are 2 patients with IgE-mediated food allergy who both underwent EGD as part of a failure to thrive workup, both revealing no ongoing EoE at the time. The first child had urticaria attributed to milk, diagnosed at 10 months, and then passed an oral food challenge at 25 months and was regularly consuming milk. At 5 years, this child had a second EGD after developing EoE-concerning symptoms (GERD/abdominal pain/early satiety), which was positive in the setting of a negative skin prick test result to milk, but with a positive atopy patch test to milk. Her EoE responded to milk elimination on repeat biopsy ([Fig 1](#)). The second child's symptoms, attributed to soy, were airway symptoms (rhinorrhea, tearing, cough, decreased breath sounds) and worsening of atopic dermatitis. This child passed an oral food challenge at 5 years and was regularly consuming soy. At 6 years, a second EGD for EoE-concerning symptoms (GERD/abdominal pain/emesis) was positive. His EoE responded to soy elimination on repeat biopsy.

The pattern seen for these 2 patients would suggest that the pathogenesis of EoE is distinct from that of IgE-mediated food allergy. This is further supported by 2 studies in which EoE was unaffected by the removal of free IgE from serum with omalizumab (monoclonal anti-IgE antibody) therapy. In OIT protocols, select patients have developed EoE because OIT has been seen to induce EoE as IgE-mediated food allergy resolves, indicating 2 separate mechanism.^{8,9}

TABLE I. Clinical characteristics of patients

	17 subjects who outgrew IgE-mediated allergy and developed EoE to the same food	67 subjects with IgE-mediated food allergy and EoE to different foods	P value
Average age (y) (range)	12 (7-21)	8.4 (2-19)	.01
Gender (male: female)	3:1	3.2:1	NS
Concurrent atopic disease	14 of 17*	65 of 67†	NS
Average age at EoE presentation (y) (range)	6.5 (1.5-8)	5.4 (1-14)	NS
Average age at which IgE allergy outgrown (y)	4.3 (2-16)	—	
Average time from when IgE allergy outgrown until EoE diagnosis (y)	2.4	—	

NS, Not significant.

*A total of 59% had allergic rhinitis, 53% asthma, and 29% atopic dermatitis.

†A total of 61% had allergic rhinitis, 46% asthma, and 38% atopic dermatitis.

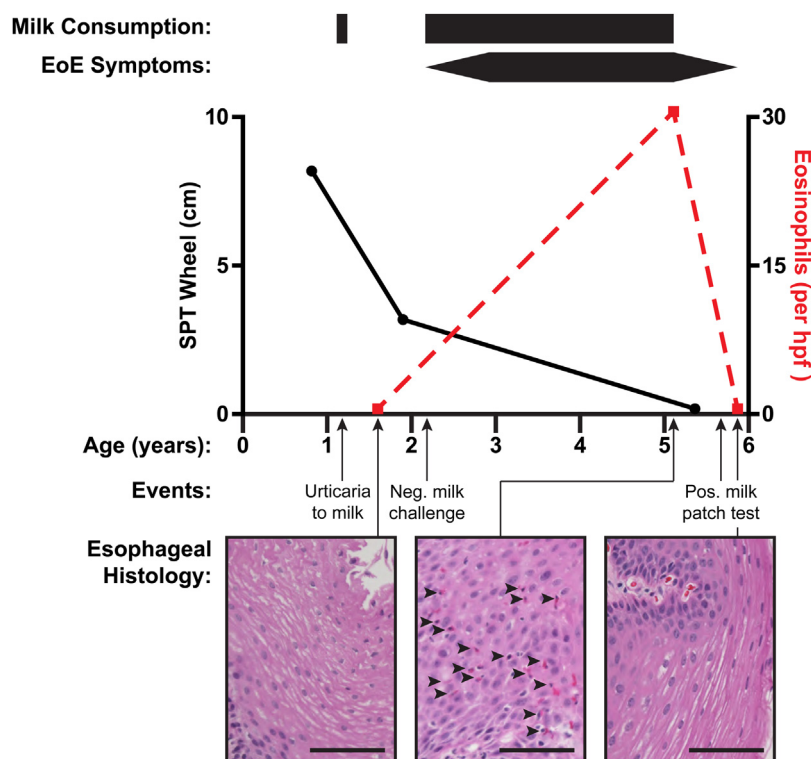


FIG 1. Clinical scenario of patient outgrowing IgE reaction to milk and developing EoE to milk. Wheal skin test size (mm) indicated on left axis and solid lines. Maximum eosinophil count per hpf indicated on the right axis and dashed lines. Clinical history and hematoxylin and eosin staining indicated on the x-axis. Neg., Negative; Pos., positive.

EoE was first associated with TSLP gain-of-function polymorphisms in 2010.^{5,6} TSLP is known to induce T_H2 responses, support IgE production, activate dendritic cells, and expand a subpopulation of basophils.⁶ Our previously reported murine model of EoE-like disease suggests that TSLP and basophils, but not IgE, are required for the development of the disease.⁷ The subgroup of 17 subjects with EoE we report here who outgrew their IgE-mediated food allergy and subsequently were diagnosed with EoE to the same food raises important questions regarding the pathophysiology of EoE and supports that the pathogenesis of EoE may be distinct from that of IgE-mediated food allergy. Although further studies are needed, TSLP and basophils appear to be an intellectually satisfying theory for the pathogenesis of EoE. Also, importantly, our data demonstrate that an individual can develop different types of

allergy or reactions to the same food. Importantly, the limitations of our study are small cohort and available baseline EGDs only for 2 patients. Thus, smoldering EoE cannot be ruled out. However, previous observations of EoE development in children after OIT treatment support a mechanism separate from IgE. Of note, it is unusual to develop tolerance to foods causing EoE, while it is common to develop tolerance to many IgE-mediated foods.

Taken together, the current data suggest that EoE pathogenesis is distinct from that of IgE-mediated food allergy, while at the same time both can occur in the same individual to the same food.

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REFERENCES

1. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3-20.e6; quiz 1-2.
2. Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol* 2012;130:461-7.e5.
3. Spergel JM, Brown-Whitehorn T, Beausoleil JL, Shuker M, Liacouras CA. Predictive values for skin prick test and atopy patch test for eosinophilic esophagitis. *J Allergy Clin Immunol* 2007;119:509-11.
4. Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults: food reintroduction identifies causative factors. *Gastroenterology* 2012;142:1451-9.e1; quiz e14-5.
5. Rothenberg ME, Spergel JM, Sherrill JD, Annaiah K, Martin LJ, Cianferoni A, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. *Nat Genet* 2010;42:289-91.
6. Siracusa MC, Saenz SA, Hill DA, Kim BS, Headley MB, Doering TA, et al. TSLP promotes interleukin-3-independent basophil haematopoiesis and type 2 inflammation. *Nature* 2011;477:229-33.
7. Noti M, Wojno ED, Kim BS, Siracusa MC, Giacomini PR, Nair MG, et al. Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. *Nat Med* 2013;19:1005-13.
8. Sánchez-García S, Rodríguez Del Río P, Escudero C, Martínez-Gómez MJ, Ibáñez MD. Possible eosinophilic esophagitis induced by milk oral immunotherapy. *J Allergy Clin Immunol* 2012;129:1155-7.
9. Ridolo E, De Angelis GL, Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. *Ann Allergy Asthma Immunol* 2011;106:73-4.

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METHODS

Definition of EoE

All patients with confirmed EoE had isolated eosinophils (>15 eosinophils/hpf) in the esophagus after other diseases were ruled out. All patients with confirmed EoE were treated for at least 8 weeks with a high-dose proton pump inhibitor before the defining upper endoscopy and biopsies were performed. The maximal eosinophil count in the most severely affected esophageal biopsy specimen was used to determine response to therapy. Patients were receiving a stable dose of inhaled steroids for their asthma and intranasal steroids for their allergic rhinitis as needed.

All patients had a minimum of 4 biopsies in the esophagus and separate biopsies in the stomach and duodenum. The numbers of eosinophils per hpf were abstracted from the surgical pathology reports and reviewed and confirmed.

Definition of IgE-mediated food allergies

The diagnosis of food allergy was confirmed on the basis of previously defined criteria.^{E1} All patients had a clear clinical history of a reaction on 2 or more occasions and documented IgE by positive skin prick test (SPT) result or specific serum IgE levels meeting 95% positive predictive values, as published by Sampson and Ho.

Allergy skin testing

SPTs and atopy patch tests were performed as previously described.^{E1} Briefly, all patients underwent SPTs to foods on the basis of their clinical history in addition to a standard panel. If patients were not ingesting the foods in the diet, they were not tested to those foods. Atopy patch tests were then conducted for the same foods unless the patient had a positive wheal-and-flare reaction (>3-mm wheal) on an SPT.

Identification of foods causing EoE

Definitive foods causing EoE were determined on the basis of the addition of a food causing an esophageal biopsy specimen to change from normal (0 eosinophils/hpf) to more than 15 eosinophils/hpf or removal of a food leading to normalization of the esophageal biopsy specimen.^{E1}

REFERENCE

- E1. Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol* 2012; 130:461-7.e5.