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The Occasional Ebb and Flow between Eosinophilic Esophagitis and IgE-Mediated Food Allergy

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Since initial description in the early 1990s, eosinophilic esophagitis (EoE) has risen from obscurity to a commonly identified condition in children with feeding issues and adolescents and adults presenting with dysphagia or food impaction.[1,2] The updated EoE consensus recommendation in 2011 defined EoE as a chronic, antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil predominant inflammation.[3] Given that the major function of the esophagus is transporting food from the oropharynx to the stomach, resulting in repeated exposure of the permeable esophageal mucosa in patients with EoE to large amounts of various food antigens, it is not surprising that foods have been identified as the most common EoE trigger.

Comorbid allergic diseases, elevated serum IgE levels, positive skin prick tests (SPT) and/or elevated serum specific IgE levels to foods and aeroallergens in the majority of patients with EoE, along with an increased rate of IgE-mediated food allergy (FA) in comparison to the general population, led to early speculation that EoE was likely primarily caused by a form of IgE-mediated allergy to foods and cross-reactive plant allergens. However, subsequent clinical trials revealed that targeted food elimination diets based on the results of SPT were equaled or outperformed by elimination diets empirically removing the most common food allergens.[4,5] Moreover, SPT-negative foods were shown to trigger EoE in some patients.[5] These findings, in combination with the failure of blocking IgE with omalizumab to successfully control or induce disease remission, led to the inevitable conclusion that immune mechanisms other than just FA were largely responsible.[6]

Although current findings clearly support the notion that the pathogenesis of EoE is distinct from that of FA, intriguing clinical experiences suggest an undefined link between the 2 entities. Two clinical situations have been reported in which a portion of patients with FA developed EoE after repeated oral exposure to the causative food allergen. Cases of patients developing EoE while on oral immunotherapy (OIT) to milk, egg, and peanut have been reported, with a recent meta-analysis suggesting that this phenomenon occurs in approximately 2.7% of patients treated with OIT to foods.[7] In addition, the development of

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EoE has been observed in a small portion of patients who outgrew their FA and subsequently added the food to their diet. In one study, 17 of 84 patients who outgrew their FA developed EoE to the same food with an average time to EoE diagnosis of 2.4 years after food introduction.[8]

The finding that some patients with FA develop EoE on prolonged exposure to the causative food raises the antithetical question of whether patients with EoE treated with elimination diets (ED) could develop FA to an eliminated food. This is an important clinical question given that the use of ED is a preferred treatment of EoE. Several lines of evidence suggest this possibility. For example, the use of ED has long been known to result in the development of significant FA in a portion of patients with atopic dermatitis and has been reported more recently in patients with food protein-induced enterocolitis syndrome.[9,10] Additionally, the risk of recurrence of peanut allergy is higher in those who continue to avoid peanut ingestion after resolution of their allergy, leading to the recommendation that peanuts be ingested at regular intervals to maintain tolerance.[11]

In this issue of *JACI In Practice*, Ho and Chehade[12] confirm that patients with EoE placed on an empiric ED can develop FA to an eliminated food. They describe 5 patients with eosinophilic gastrointestinal disorders (4 with EoE, 1 with eosinophilic gastritis) cared for at the Mount Sinai Center for Eosinophilic Disorders between 2010 and 2016 who developed FA to cow's milk (CM) after placement on an empiric ED eliminating CM along with egg, wheat, soy, and, in some patients, also nuts and shellfish. The male:female ratio was the opposite of that usually observed in EoE as 4 were female and 1 was male, although this might be attributable to the small sample size rather than signifying a gender association. Four were children ranging in age from 1.6 years to 12.5 years, but one was a 40-year-old adult, suggesting that occurrence is not limited to children. Four had atopic dermatitis of whom 3 had additional comorbid allergic diseases, but 1 did not. Thus, comorbid allergic disease is not a prerequisite, but possibly a risk factor. All patients regularly ingested CM and had a negative CM SPT before starting the ED. Serum CM-specific IgE levels measured in 2 patients before ED initiation were 4.11 kIU/L in one and undetectable in the other. Symptom resolution and a significant reduction in mucosal eosinophilia were noted in all, but whether CM was a causative food remained undetermined because reintroduction of CM or the other foods individually followed by endoscopy with biopsies was not performed. Sensitization to other eliminated foods determined by SPT or serum food-specific IgE levels was not addressed although it is assumed that allergic reactions to other foods would have been reported. After months on the empiric ED each of the reported patients developed a positive CM SPT and detectable serum CM-specific IgE levels. Two patients after accidental exposure to unbaked milk developed symptoms (generalized urticaria in one and oropharyngeal tingling in the other) that responded to antihistamine treatment. The remaining 3 patients of whom 2 had a CM SPT large enough to suggest a 95% chance of reaction declined the CM challenge. Thus, whether they are truly allergic and their dose threshold remains unknown.

The important findings of this retrospective chart review by Ho and Chehade suggest that approximately 2% of patients with EoE placed on an empiric ED eliminating CM could develop FA to CM. This finding is probably not restricted to milk, as the development of FA

to other eliminated foods is likely. Although the development of FA occurs in a relatively small portion of patients, all patients with EoE considering an ED should be informed of this possibility as it might affect the treatment decision for some. Checking for IgE-mediated sensitization before ED initiation, at reasonable intervals while on the ED, and at least before food reintroduction would aid in identifying those at risk. Reintroduction of the eliminated food under medical supervision in those who become sensitized would help define how many are truly allergic. Monitoring the number who become sensitized, but not allergic, would also be beneficial. In addition, questioning about responses to recent accidental ingestions of eliminated foods at follow-up visits is key.

In summary, clinical experiences suggest an undefined link between FA and EoE, as a portion of patients with FA develop EoE after continuous exposure to a food and a portion of patients with EoE develop FA when a food is eliminated from their diet. Prospective studies are needed to better define and document the frequency of these occurrences, while also detecting risk factors and/or biomarkers that might be used to ascertain the immune mechanisms involved and identify those at higher risk. Thus, there is an occasional ebb and flow between EoE and FA, and identifying the mechanisms involved will undoubtedly lead to a better understanding of both conditions.

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