



Perspectives

Are there different subtypes of eosinophilic esophagitis?



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Currently, eosinophilic esophagitis (EoE) is defined by the combination of clinical symptoms and pathologic findings. Patients should have symptoms of esophageal dysmotility and a defined (albeit somewhat arbitrarily so) level of esophageal eosinophilia before being diagnosed with EoE. Thus, on the basis of this definition, the diagnosis of EoE is purely a phenotype, possibly allowing for multiple different causes to funnel into this diagnosis. In this manner, EoE is similar to other conditions, such as asthma, in which treatment strategies are evolving in an era of precision medicine. Should the goal therefore be to one day attempt to subtype EoE?

Are All Patients With EoE Allergic?

From the first well-described cohort of patients with EoE, it was clear that these patients could respond to dietary therapy with diets devoid of protein antigens.¹ Thus, it seemed clear that EoE was an allergic disease caused by food allergens. However, since that time, the scientific study of the disease has increased, and it has become evident that not all patients fall into a clear, well-defined group.

Currently, most studies clearly support the idea that EoE is, for lack of a better term, an *allergy*. Patients with EoE consistently have a T_H2 phenotype locally, with upregulation of *TSLP* and increased production of interleukin (IL) 5, IL-13, and eotaxin 3. Genome-wide association studies have also pointed to *TSLP* as a gene associated with EoE.² Not surprisingly then, in most cohorts, 40% to 80% of patients with EoE have a diagnosis of another atopic disease.³ However, most of these reports rely on medical record diagnoses, a method that may overestimate the prevalence of these concomitant diagnoses. In addition, even with overdiagnosis, 20% to 60% of patients with EoE do not have any other allergic disease (and many have negative skin test and serum test results to any allergen examined). Therefore, it is interesting to speculate that mast cells may play a role in the disease in some patients but not others.

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A recent study⁴ examining the utility of viscous oral cromolyn found that the drug did not work better than placebo but that it worked well for a select group of individuals.

Recently, Hill and Spergel⁵ reported an excellent perspective in this journal regarding how EoE is a part of the atopic march. The argument above does not conflict with this. After all, it is undeniable that some patients with asthma or eczema (parts of the atopic march) do not have any IgE sensitization or other atopic diseases. However, it is well accepted that you can have asthma without allergy, but can the same be said about EoE?

Does IgG4 Play a Role in Some Patients but Not Others?

A few recent studies^{6,7} in adults with EoE have suggested a role of IgG4 and possibly food specific IgG4 in disease pathogenesis. This concept has not been studied or proven in large pediatric cohorts; however, it does lend intriguing evidence to suggest a subtype of patients with EoE. This concept is most interestingly examined in patients (pediatric and adult) undergoing oral immunotherapy (OIT) for food allergy. Although rare, EoE occurs in some patients undergoing OIT.⁸ One Spanish cohort reported EoE in approximately 5% of patients undergoing milk OIT.⁹ Thus, this small group of patients seems to be a unique subset of patients who may or may not be different from other patients with EoE. Ongoing, large-scale studies of peanut OIT are examining this rare adverse event, and perhaps more light will be shed on this group of patients.

Is Proton Pump Inhibitor-Responsive Esophageal Eosinophilia Really a Subtype of EoE?

To date, histologic response to proton pump inhibitors suggested reflux and ruled out EoE. However, studies recently have suggested that patients who have proton pump inhibitor-responsive esophageal eosinophilia may in fact have a molecular profile that suggests a baseline T_H2 phenotype suggestive of EoE and that proton pump inhibitors alone can reverse this T_H2 signature locally and resolve eosinophilia.¹⁰ Thus, perhaps there is a subtype of patients with EoE who could be treated with proton pump inhibitors alone.

Are There Truly Cases of EoE Caused by Aeroallergens?

Several association studies have suggested seasonal variance of EoE symptoms and diagnosis; however, concrete evidence is lacking to support a causal role for seasonal aeroallergens in EoE. Ram et al¹¹ recently found clear seasonal variations in pollen allergic patients during pollen season, with no other changes in medication or diet for their EoE.¹¹ Unfortunately, there have been no well-designed prospective studies regarding this and no proof-of-concept studies showing that allergy immunotherapy to aeroallergens can improve EoE symptoms or histologic findings. Thus, although there may be a subset of patients who have aeroallergens as a trigger this subset, if it exists, has been poorly defined to date.

Other Possible Phenotypes and Questions

Beyond the above examples, there are other possible phenotypes that have been borne out and discussed in the literature. For example, is pediatric EoE different than adult-onset EoE, or is it simply a continuum of the same disease that manifests later in life in patients who had long-term, untreated inflammation? Do all patients who are left untreated develop a fibrostenotic phenotype, or are a subgroup of patients more prone to this manifestation? Is there a subtype of patients who will not respond to topical corticosteroids? Are patients who have concomitant autoimmune disease different than those without?

Conclusions

As we attempt to move into a world of precision medicine, our progress in asthma has taken a great step forward with biologic treatments aimed at targeting specific endotypes. To date, this has not proven to be the case in EoE. Biologic treatments to date have been underwhelming, with anti-IgE and anti-IL-5 not showing great effect and anti-IL-13 having only limited data to date. Perhaps, though, these results are attributable to enrolling a vast array of patients with differing endotypes. However, if we are able to selectively iden-

tify patients based on specific phenotypic criteria, response to therapy could be improved. For research studies, this may mean enrolling individuals to treatment arms based on predefined criteria using a local, esophageal molecular signature pattern. Perhaps simpler would be to enroll individuals based on a phenotype stratification that uses atopic disease history, skin prick testing, serum IgE levels, and peripheral blood eosinophil count. Stratification may need to be based on the selected therapeutic target, such as peripheral eosinophilia or IgE level, as we now are starting to do clinically with asthma. Perhaps it is time that EoE entered the era of precision medicine.

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