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Is eosinophilic esophagitis a member of the atopic march?

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The Atopic March refers to the natural history of allergic diseases as they develop over the course of infancy and childhood. As we detail in our accompanying review (see pages 131–137 in this issue), "the March" classically begins with atopic dermatitis (AD), and progresses to immunoglobulin E (IgE)–mediated food allergy (FA), asthma, and allergic rhinitis (AR). In addition to its characteristic progression, members of the March have been shown to predispose to the development of subsequent allergic conditions. This is likely due to a shared genetic and environmental propensity for allergic inflammation, available routes of allergen exposure, and utilization of common immunologic pathways.

The identification of the 4 major members of the March (AD, FA, asthma, AR) is the result of considerable epidemiologic and basic research that has established their clinical co-occurrence and related pathophysiology. However, it is important to consider the potential for new members of the March that fit with the established model of characteristic progression, predisposition, and shared pathophysiology. In particular, we believe there is reasonable evidence to suggest that eosinophilic esophagitis (EoE), a food allergy that causes esophageal inflammation and dysfunction, may be an additional component of the March.

Most fundamentally, EoE is an allergic condition that shares immunologic pathways with other members of the March.[1] As such, like AD, FA, asthma, and AR, EoE is responsive to allergen avoidance and therapy with corticosteroids. Furthermore, EoE shares several susceptibility loci with other March members. Polymorphisms in thymic stromal lymphopoietin and signal transducer and activator of transcription 6 are independently associated with AD, FA, asthma, and EoE, further implicating the involvement of common immunologic pathways in the pathophysiology of these conditions.[2] Finally, fitting with a shared pathophysiology, clinical associations between EoE and other members of the March have been described. In a recent study of 449 patients with EoE, 46.1% had AD, 39% had asthma, 61.9% had AR, and 21.6% had all 3 atopic comorbidities.[3]

In our cohorts, we found the peak age of diagnosis of EoE to be approximately 3 years—after that of AD, IgE-mediated FA, and asthma, and concurrent with that of AR.[4] Although this does not constitute direct evidence of EoE being a member of the March, it does fit with

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the model, allowing for risk analyses to be performed. Toward this end, we found that the presence of AD increased risk of developing EoE in our cohorts (data not shown). We also recently sought to ascertain whether significant epidemiologic associations exist between FA and EoE in children.[5] By examining the concurrence of FA and EoE in our subspecialty care network of 35,528 children and adolescents, we determined that the prevalence of EoE in patients with FA was higher than that of the general population (4.7% vs 0.04%). In addition, we found increased odds ratio to FA to egg (2.27; 1.91–2.64), milk (4.19; 3.52–4.97), and shellfish (1.55; 1.24–1.92) to be significantly associated with EoE. These observations further support a role for EoE in the March.

An additional feature of EoE that suggests a link to the March is the observation that aeroallergens can exacerbate EoE in some individuals. In a case series of 1,180 EoE patients, we found that 160 (14%) were suspected of having aeroallergen-associated triggers by history, and 32 had biopsy-confirmed seasonal variation of esophageal eosinophilia.[6] It has also been shown that new diagnoses of EoE and the incidence of esophageal food impactions are higher in the spring—2 observations that further support a role for aeroallergen exposure in esophageal inflammation.[7] Finally, direct evidence of a role for aeroallergen in EoE exacerbations comes from patients exposed to large volumes of allergen due to environmental exposure or immunotherapy.[8]

Given the clinical associations between AD, FA, AR, and EoE, it is reasonable to consider the role of IgE in EoE. Although often compared, there are several lines of evidence from animal and human studies indicating that EoE and IgE-mediated FA have distinct pathophysiology.[9] However, associations have also been made between EoE and sensitization to pollens with homology with food proteins, as well as comorbid oral allergy syndrome.[10] As such, it is likely that IgE is a marker of underlying allergen-specific T-cell responses, and a contributing factor in pollen-mediated EoE flares, even if not required for food-triggered esophageal inflammation.

In conclusion, it is important that the field of allergy consider a role for new and emerging allergic conditions in the Atopic March. It is reasonable to hypothesize that EoE is a “fifth member of the March,” as it shares clinical features, immunologic pathways, susceptibility loci, and risk with other March members. It is also reasonable to hypothesize that prevention of the March, via optimal AD control or other means, may subvert EoE development in some individuals. However, it is also important to note that EoE can occur beyond childhood, and in otherwise non-atopic individuals. Indeed, EoE patients with atopic comorbidities tend to be younger.[3] As such, distinct EoE endotypes may exist, as with AD and asthma. Additional research into epidemiology of EoE in the context of other atopic conditions, as well as basic research into its underlying pathophysiology, will be necessary to improve our understanding of EoE and its relationship to other members of the Atopic March.

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