‘Stuck on You’ – A Familial Tale of Eosinophilic Esophagitis

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INTRODUCTION

Eosinophilic esophagitis (EoE) is an IgE-mediated allergic condition of the esophagus characterized by dense eosinophilic infiltrates. The prevalence of EoE has been increasing over the last few decades and has become an important entity encountered by primary care physicians, gastroenterologists and allergists.[1] An association with atopic conditions suggests that EoE may be driven by both genetic and environmental factors, including food-related exposures.[2] Here, we present two cases of EoE in adult brothers with an update on the known genetic involvement in this disease.

Case Report

An 18 year-old male with allergic rhinitis and food allergies presented with abdominal pain, foul-smelling bowel movements and weight loss for one year. Esophagogastroduodenoscopy (EGD) revealed linear furrows throughout the esophagus (Figures 1a and b). Biopsies demonstrated eosinophilia up to 150 per high-power field (HPF) consistent with eosinophilic esophagitis (EoE). Serum allergen testing indicated an elevated serum IgE (380 IU/ml) and multiple food sensitivities. The patient was initially placed on a proton pump inhibitor (PPI) and scheduled for a repeat EGD to assess response and confirm the suspected EoE diagnosis. In the interim, the patient began experiencing dysphagia primarily to liquids but also to solids. Repeat EGD showed unchanged linear furrows in the mid and proximal esophagus (Figures 1c and d), however biopsies showed significant reduction in eosinophilia to 22/HPF. The patient’s symptoms improved after an 8-week PPI course and he has not required further treatment with topical steroids.

His brother is a 36 year-old with a history of gastroesophageal reflux disease (GERD) and one year history of progressive dysphagia to solids. He has no known allergies or atopic conditions. On initial EGD, the esophageal mucosa appeared normal (Figures 1e and f); however, biopsies yielded eosinophilia up to

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150/HPF, concerning for EoE. His serum allergen panel was negative with a mildly elevated IgE (163 IU/ml). The patient completed an 8-week PPI course with improvement in dysphagia but has not undergone a follow-up EGD at the time of this manuscript. He is being followed by an allergist and primary care physician for further evaluation of potential food-triggers.

Discussion

Eosinophilic esophagitis is an increasingly prevalent condition encountered by various health care providers. Until recently, the entity has been poorly understood and this has led to delayed diagnosis and treatment increasing the risk of complications including esophageal strictures.[3] Understanding the heterogeneous clinical presentation and underlying patient demographics and risk factors, principally family history and association with atopic conditions, is crucial for timely and accurate diagnosis.

Here we describe two adult male siblings who presented with symptomatic EoE within the same year. Both were diagnosed with a high burden of eosinophilia on endoscopic biopsies, with some differences in the details of their clinical presentations and serologic and endoscopic findings. One patient demonstrated classic endoscopic findings of linear esophageal furrows with a history of atopic disease (food allergies and allergic rhinitis), whereas his sibling had a normal appearing esophagus and no history of atopy. The patients presented in the second and fourth decades of life, respectively, illustrating the delayed diagnosis and varying latency periods of disease manifestation seen in the adult population.

Studies support a heritable component in EoE with recurrence risk ratios (RRR) in first-degree relatives of patients ranging from 10-64 compared to the general population, which is a stronger relationship than that observed in other atopic diseases such as asthma.[4] The RRRs were found to be highest in brothers (64) and fathers (42.9) of probands, compared to sisters and mothers.[4] However, research on the relative contribution of genetics and environment to this condition is limited. Alexander *et al.* provides insight through analysis of nuclear family and twin cohorts of EoE probands. The authors estimate that the combined gene-environment heritability for the nuclear family cohort was 72% with common environment accounting for most of the observed variation.[4] Furthermore, dizygotic twins had

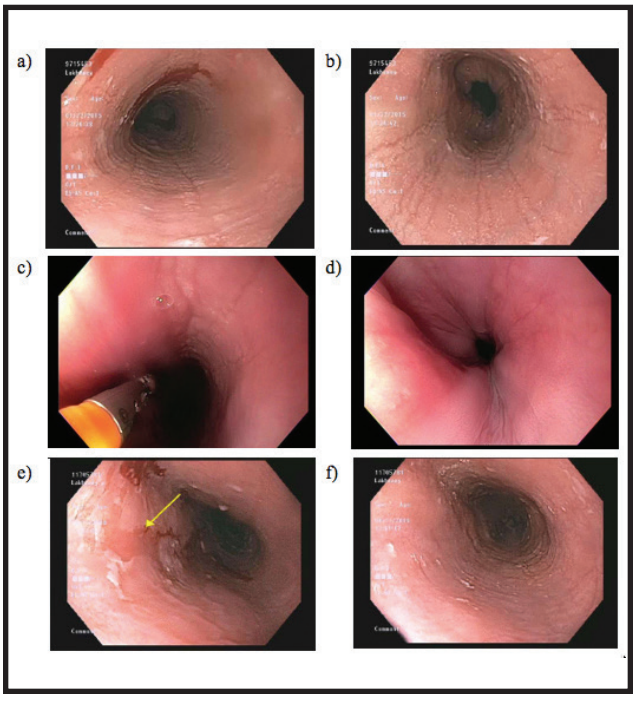

Figure 1.

a significantly higher frequency of EoE than non-twin siblings, which suggests not only the importance of a shared environment but also the timing of early life exposures that may influence genetically-susceptible family members.[4] In a population-based study, findings support an increased risk in first degree relatives but extend their analysis to include more distant relatives. Both second-degree relatives and first cousins showed an increased odds ratio (OR) of concordant disease, supporting the role of a heritable component in family members less likely to share common environments.[5]

Clinically, the heterogeneity of presentation as well as symptom overlap with more common conditions such as GERD have proven roadblocks to timely and accurate diagnosis of EoE. As discussed, our two patients presented with different clinical presentations in terms of disease latency, symptoms, and endoscopic appearance. While prior studies have not shown a statistically significant difference in signs and symptoms, endoscopic appearance, or atopic status between familial and sporadic EoE patients, our case study suggests there may be more variability within the familial EoE population than previously recognized.[6]

Despite different clinical presentations, the histopathologic similarity between the two patients presented here is consistent with reports of a genomic

"EoE transcriptome" that may be conserved across EoE patients regardless of sex, age, or atopic/allergic status.[7] The *eotaxin-3* (eosinophil-specific chemoattractant) gene has been identified as a highly over-expressed gene in the transcriptome, with end-organ eosinophilia being strongly correlated with both *eotaxin-3* mRNA levels as well as disease severity.[7] The gene expression profile also differed from patients with chronic esophagitis, including GERD, highlighting a potentially unique downstream pathway for diagnosis and treatment of EoE.

According to the 2013 ACG Practice Guidelines, the first step in management of suspected EoE is an 8-week PPI trial followed by repeat EGD to assess clinical and histological response. A lack of PPI-response is consistent with EoE but a positive response places a patient in a category known as PPI-responsive esophageal eosinophilia (PPI-REE), requiring the physician to rule out GERD as a possible cause of this eosinophilia.[8] Interestingly, in our two patients, both had clinical responses to an 8-week PPI trial, one of whom also showed endoscopic evidence of response with significantly reduced esophageal eosinophilia.

There is growing evidence that PPI-REE is not a separate clinical entity, but rather lies within the spectrum of patients with EoE. Patients with EoE and PPI-REE not only share the same demographics, clinical presentations, and endoscopic characteristics, but also have indistinguishable downstream immuno-histochemical profiles of certain inflammatory markers, including eotaxin-3.[9] Furthermore, these same markers were useful in identifying EoE patients compared to controls with GERD or dysphagia.[9] The strict cutoff of persistent eosinophilia ≥15/HPF for failing a PPI trial also blurs the distinction between these two entities. Strictly speaking, our patient would qualify as a failed responder despite clinical improvement and drastic reduction in esophageal eosinophilia, which is not uncommon in patients with typical EoE presentations. As such, there is growing support to reclassify PPI-REE as a subtype of EoE in which a PPI trial is a safe and effective first-line therapy rather than a diagnostic test.[10]

In conclusion, EoE represents an increasingly important condition to recognize in various clinical settings. Proper diagnosis and treatment can reduce the risk of long-term consequences such as esophageal strictures, and is also useful for family members who may have yet-undiagnosed disease. New insights into the genetic susceptibility and importance of early life exposures support a complex pathogenesis of this disease, of which our understanding is improving. Our case study adds to the growing body of evidence to support a familial inheritance of EoE while simultaneously highlighting the diverse clinical presentations that create additional challenges for healthcare providers. ■

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