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Mucosal inflammation, esophageal eosinophilia and celiac disease; A little "pinch" will have to do you

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When a mucosal surface is injured, inflammatory responses ensue. These responses are characterized by the well-orchestrated accumulation of reparative leukocytes that protect and heal the mucosa during a process that often goes unrecognized. In other circumstances, genetically predisposed hosts encounter exogenous or endogenous triggers that lead to pathological inflammation, tissue damage and organ dysfunction. The gastrointestinal (GI) tract is the target site for this process in a number of diseases including inflammatory bowel diseases, celiac disease and eosinophilic esophagitis (EoE).

To date, clinicians are able to directly assess the inflamed mucosal surface only with mucosal pinch biopsies. This is problematic since both clinical and laboratory based studies demonstrate inflammatory responses likely extend deeper into the tissues, outside of the grasp of the 3 mm biopsy forceps. In the case of both celiac disease and EoE, this is certainly the case as evidenced by the systemic manifestations of celiac disease and the submucosal changes observed with imaging studies and in surgical resections of EoE patients. In this light, a broader view of both of these diseases, and in fact, any GI disease characterized by mucosal inflammation is timely and necessary. The recent article by Ahmed and colleagues supports this view as they identify the difficulties in fully interpreting

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inflammatory patterns associated with *esophageal eosinophilia* and the associated clinical implications in patients with celiac disease. (1)

These authors, and others, note that a high degree of confusion is emerging regarding whether *esophageal eosinophilia* is a representative pattern associated with celiac disease alone or celiac disease and EoE. Answers to this question are important for both scientific and clinical reasons. The scientific understanding of pathogenetic mechanisms leading to *esophageal eosinophilia* will lead to definition of novel therapeutic targets. From a clinical standpoint, a number of immediate questions have arisen. Does a patient need both a gluten free diet and topical steroids? Are long-term risks of the esophageal inflammation the same? Do repeat endoscopies need to be performed?

Ahmed and colleagues begin to address these issues, by performing a retrospective study that characterizes two subject groups, one with celiac disease and one without, who underwent endoscopy for other clinical reasons. They then go on to determine how many subjects in each group have esophageal biopsies that are characterized by *esophageal eosinophilia*. When comparing pediatric subjects with well-defined celiac disease to the control group, they found that *esophageal eosinophilia* occurred similarly in both groups (6.5 % vs. 7.7 % celiac vs. controls). Their results are consistent with an adult study in which 4.2% of adults with celiac disease had *esophageal eosinophilia*. (2) Ahmed et al conclude that *esophageal eosinophilia* occurs without regard to the presence of celiac disease. The authors should be commended for including a control group of patients to make their comparison since this supports the conclusion that *esophageal eosinophilia* is not an uncommon histological finding in the general population undergoing endoscopy or in patients with celiac. It was no doubt tempting to classify their subjects as having EoE, especially in light of their overall EoE-like symptom pattern with dysphagia predominance, but they did not. We applaud them for using the term *esophageal eosinophilia* and by sticking to recent Consensus Recommendations in their design and analyses. In doing so, we think their results provide a much higher degree of clarity. (3, 4) In comparison, a number of previous studies reporting “EoE” and celiac disease and a recent “mini-analysis”, reported that 0.97–8.2% of patients had “EoE” and celiac disease. (5) While these reports provide similar percentages to Ahmed et al, the use of the term “EoE” is not appropriate, at least to date, since the diagnosis of EoE can only be made after other causes of *esophageal eosinophilia* are excluded. As they note, a prospective study to fully answer the next set of questions would require a large population of very well defined subjects. Overall, this study sets the stage to define who and why a subset of patients with celiac disease develops *esophageal eosinophilia*.

As the finding of *esophageal eosinophilia* is uncovered in patients with and without symptoms referable to the esophagus, previous have determined, and upcoming studies will focus on, genetic patterns in well-defined patient populations. For instance, a number of studies provided well-defined risk alleles for celiac disease and an emerging body of evidence is beginning to do this for those with EoE. In this light, Lucendo et al examined the celiac disease HLA risk alleles in adult EoE subjects and found no association. (6)

As suggested by the authors, a second tier of studies may begin to examine common inflammatory protein patterns between celiac and EoE in an attempt to link the understanding of the histological finding of *esophageal eosinophilia* between these diseases. One possible link may be of this could relate to interleukin-15 (IL-15) a 'hallmark' of celiac disease. (7) IL-15 is also increased in patients with EoE and in EoE mouse models. (8)

Finally, is there commonality in exogenous triggers or epigenetics that relate to *esophageal eosinophilia*? As the microbiome's role in intestinal health and disease continues to undergo definition, studies are beginning to identify microbial patterns that may initiate or perpetuate disease activity in celiac patients and IBD. (9, 10) The esophageal microbiome has been reported in "healthy" and GERD subjects but remains to be identified in EoE. (11) Comparison of microbiome diversity and load in the esophagus and duodenum in patients with EoE and celiac will certainly be of interest.

So how can we practically use the results of this study and many others that are based on the limited, but realistic, assessments from a small fraction of the esophageal mucosal surface? In our opinion, the clinical evaluation of a patient with esophagitis should be based on a reasonable assessment of symptoms, and treatment should be focused on maximizing growth and development. Both evaluations and treatments should be established on best available evidence and balance risks and benefits of testing and treatments with quality of life. Most importantly, patients with esophagitis, like those defined by Ahmed et al, need to be followed over time to fully establish a diagnosis so that appropriate treatment can be provided. To date, there is limited support for the use of gluten free diet in patients with *esophageal eosinophilia* and celiac disease. In small case series of patients with *esophageal eosinophilia* and celiac disease, esophagitis responded to gluten free diet in 0 to 33% of 21 patients (12–16) Because of the limited data and potential co-morbidities and impact on quality of life of additional EoE treatments, we treat patients with celiac disease and *esophageal eosinophilia* with a proton pump inhibitor and gluten free diet first. Depending on the clinical response and/or the presenting symptomatology, we would then consider either additional dietary elimination or topical corticosteroids.

Esophageal eosinophilia is "real" in patients with celiac disease. Ahmed et al provide evidence that this association may be incidental rather than causal. As our understanding of the pathogenesis of esophageal inflammation continues to increase, new diagnostic approaches, biomarkers and therapeutic targets will be defined that can be able to be applied to this unique group and ultimately answer the question of what "real" means, how it occurs and what to do about it.

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