

EDITORIAL

EoE-like, EoE-light, or EoE-not? Pursuing variations of a new disease

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'Eosinophilic esophagitis represents a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation' (1). Is this really true? One of the intriguing aspects of clinical research after the description of a classic form of a disease is the attempt to further define possible variations. This can be challenging in deciding how many characteristics of this variant need be present to fulfill the criteria of being related to the original diagnosis. On the other hand, it is important to expand the definition of a disease to include possible variants so that more patients may receive appropriate diagnosis and treatment. Furthermore, defining these variations of the disease may yield important molecular and physiologic insights into the disease and establish predictors of prognosis and severity.

In this issue of *Allergy*, Straumann, and colleagues described the existence of a potential eosinophilic esophagitis (EoE) variant (2). It makes sense that this Swiss group, arguably the leading group worldwide in adult eosinophilic esophagitis, and certainly, the group that has followed patients with eosinophilic esophagitis the longest should have the experience to recognize such a variant. This group of patients consists of five patients with years of solid food dysphagia without eosinophil-predominant esophageal inflammation but from families in which there were first degree relatives with proven eosinophilic esophagitis. This description satisfies one of the characteristics, particularly the family history of EoE. Indeed, studies demonstrated an approximate 1.8–2.4% risk of EoE if related to a first degree relative with the disease (3). Still, we need to examine more closely the strength of the characteristics that tie this group of patients to those with EoE. Certainly, some of the most compelling data used to establish a relationship between diseases is with genetic analysis of tissue. This is supported by the finding of some positivity of the EoE diagnostic panel (EDP) in all five patients. This panel consists of an array of 94 EoE genes representative of the EoE transcriptome (4). In the present study of EoE-like patients, transcriptome analysis demonstrated some genes to be abnormally expressed to similar degrees as EoE patients but others less so. Specifically, the authors found that in EoE-like disease, *CDH26*, *KCNJ2*, and *UPKB* were strongly upregulated and *MUC4* was upregulated to a degree seen on EoE. Eotaxin-3 and *DSG1* were only dysregulated in EoE as expected given the lack of eosinophils and barrier defect in EoE-like disease. As discussed, EoE-like is not EoE, and the finding of overlap but not an identical transcriptome analysis is what one might expect.

Thus, do these tissue features help confirm a relationship of these five patients to EoE-likely. It might be more compelling if there was greater overlap of the gene panel though variants of diseases commonly show a mismatch of gene profiles, particularly when the disease is polygenic and/or of variable penetrance. For example, earlier research putatively established inflammatory bowel disease (IBD) as an abnormality of the *NOD2* gene (5). Today, there are at least 100 such genetic abnormalities identified in IBD with marked variation in the presence and penetrance among those affected (6, 7). Another issue, however, is understanding the limitations of the EDP. Studies demonstrate an approximate 96% sensitivity and 98% specificity for discriminating EoE from GERD and controls (4). Although this is superb accuracy, these five patients derived from a pool of 417 patients with EoE, which might fit within the error margin of the EDP. Furthermore, it is unclear what the EDP findings are in family members of EoE index patients. Thus, is the mRNA esophageal expression profile data enough to feel comfortable calling this an EoE-like illness—more likely than not.

The second avenue of comparison is tissue analysis, particularly for defining mechanisms compatible with EoE. Although there were no eosinophils or degranulation products on biopsy, the five patients exhibited several features that are shared with EoE patients including the presence of mast cells and increased T cells. There were also increased levels of cytokines, TSLP, and TNF-alpha in some EoE-like patients. Yet, some of the key features of EoE were lacking, most notably evidence of barrier defect thought to be the mechanism of facilitated antigen entry and initiation of the Th2 pathway in EoE patients (3, 8–10).

The third area of comparison takes into account some of the clinical features of this new group. Curiously, all five patients had dysphagia yet all had a normal endoscopy and barium esophagram. This appears paradoxical, but then again, it is possible these patients have esophageal mural fibrosis without clear evidence of narrowing on endoscopic or radiographic visualization. This could be confirmed with use of EndoFLIP (11) where EoE patients can have a normal caliber esophagus clearly abnormal esophageal wall compliance. Thus, it appears a safe assumption to assume some loss of esophageal distensibility is present in these five patients. These patients were also older than your typical patient with EoE (mean age 60) but then again, many diseases such as ulcerative colitis or cystic fibrosis have been described as having less aggressive forms presenting in older patients. Similar to EoE, however, EoE-like patients had a long history of

dysphagia before a diagnosis was proposed. Thus, do these clinical differences and similarities dissuade us from a relationship between EoE and EoE-like. Not completely.

By the end of such a study, one has to make a decision as to whether these are two distinct phenotypes of a similar disease or two independent processes with similar characteristics. This is more difficult in EoE where no gold standard exists, hence, defined by a statement of compatible characteristics. As a result, one has to consider the sum of the evidence as opposed to the strength of individual findings. I suspect the authors have identified a disease that is genetically and phenotypically related to EoE. Furthermore, who better to have the insight and experience to define a new

EoE-like disease than the Swiss EoE group. Clearly, following the natural history of this new group and exploring other large EoE centers for similar patients will be of benefit. At the very least, the authors deserve great credit for pushing the boundaries of defining a disease where most of us are trying to define clearer limits.

Conflict of interest

The authors declare that they have no conflicts of interest.

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