Limitation of Symptoms as Predictors of Remission in Eosinophilic Esophagitis: The Need to Go Beyond Endoscopy and Histology

See "Symptoms have modest accuracy in detecting endoscopic and histologic remission in adults with eosinophilic esophagitis," by Safroneeva E, Straumann A, Coslovsky M, et al, on page 581.

Since its initial description in the early 1990s, eosinophilic esophagitis (EoE) was considered a clinicopathologic syndrome, for which the diagnostic hallmark consisted of esophageal symptoms coupled with high concentrations of intraepithelial eosinophils in esophageal biopsies. Over the past few years, we have gained significant knowledge on EoE, including its epidemiology,[1] full clinical spectrum, classification of endoscopic findings,[2] characterization of abnormal esophageal motility patterns,[3] the potential pathogenic role of acid exposure,[4] insight on its genetic signature,[5] and the efficacy of several therapeutic options, including dietary modifications,[6] proton pump inhibitors,[7] topical steroids,[8] and endoscopic esophageal dilation.[9] However, none of these scientific breakthroughs has altered the former diagnostic definition for EoE, provided >2 decades ago. Consecutive consensus guidelines published in 2007 and 2011 still consider EoE as "a chronic, immune/antigen-mediated, esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation."[10,11] Both clinical and pathologic information should be taken into consideration and neither of these parameters should be interpreted in isolation. The commonly described clinicopathologic dissociation in patients with EoE[12,13] has reinforced the need of a joint analysis of both variables, since asymptomatic periods do not necessarily imply resolution of eosinophilic inflammation and dysphagia or food impaction may occur in patients without eosinophilic inflammation. Notably, both symptoms and biological activity have been reported to be major determinants for patient's quality of life.[14]

Given that EoE is a chronic disease with remarkable diagnostic delay,[15] patients usually develop adaptive behaviors that allow them to better cope with symptoms. In this regard, adult EoE patients may avoid dysphagia by food avoidance, modification in the consistency of foods consumed, altering eating pace, or restricting their social activities. Therefore, assessment of dysphagia in EoE may be challenging, because it depends not only on the activity of the disease, but also on the effectiveness of behavioral adaptation strategies taken by the patients to minimize symptoms. For these reasons, "classic" scales to assess dysphagia, on the basis of quantifying the frequency and intensity of factual esophageal symptoms, have shown limited utility in EoE patients.[13,16] To overcome these limitations, an international group of experts developed and validated the EoE activity index (EEsAI), a patient-reported outcome (PRO) instrument for adult patients that quantifies both difficulties foreseen by patients in eating 8 different food consistencies and dietary or behavioral modifications for these specific foods.[17] The EEsAI instrument, thus, helps to guide clinical decision making and define outcome parameters for research in EoE.

In this issue of *Gastroenterology,* researchers from the group that originally developed the EEsAI instrument report important data on the accuracy of esophageal symptoms to predict the biological activity of EoE.[18] In a multinational cohort of 269 adult EoE patients, sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of distinct EEsAI PRO score cutoff values were correlated with endoscopic (according to the Endoscopic Reference Score classification and grading system [EFERS])[2] and histologic remission (<15 eos/high-power field [HPF]). A EEsAI score of 20 showed the best predictive capacity to detect both endoscopic and histologic remission, although sensitivity and specificity were markedly low. Sensitivity and specificity values for an EEsAI PRO score of 20 to predict histologic remission (peak eosinophil count, <15/HPF) were 48.6% and 70.9%, respectively. These cutoff points showed an overall poor diagnostic accuracy, with an area under the receiving operator characteristics curve of 0.61. Results did not improve when defining a deeper histologic remission (<5 eos/HPF). Moreover, the EEsAI instrument could not adequately predict remission of endoscopic findings, being that an EEsAI score of 15 points had the best predictive capacity (66.9%). Analysis of data according to the treatment received in the previous 3 months for EoE, including hypoallergenic diets or topical steroids, did not enhance the predictive capacity of the EEsAI instrument. It is worth noting that only endoscopic dilation during the previous year (a mechanical procedure that can improve esophageal symptoms without any effect on inflammatory features) significantly improved the predictive capacity of the EEsAI instrument.

Overall, this study draws a relevant message for clinical practice, because esophageal symptoms alone showed a modest predictive capacity for estimating the presence of either histologic or endoscopic remission in adult patients with EoE. Contrary to this information, a recent multicenter

study conducted in adult EoE patients underscored that gastroenterologists still rate EoE activity mainly on the basis of endoscopic findings and symptoms and, to a lesser extent, on histologic findings.[19] The study conducted by Safroneeva et al[18] is, therefore, pivotal to understand that clinicians should not make assumptions about the biological activity of EoE exclusively upon symptoms, so histologic analysis through endoscopy for diagnosis and monitoring of the disease currently continues to be necessary.

Dysphagia in adult EoE patients is complex and incompletely understood, with 2 different major contributing mechanisms: esophageal dysmotility and structural changes related with fibrous remodeling. Several altered motility patterns have been identified in EoE patients with standard and high-resolution manometry tests.[3] However, the dynamic effect leading to dysphagia was first assessed by using simultaneous manometry and endoscopic ultrasound in a series of 10 adult patients.[20] Esophageal dysmotility was explained to occur through a dyscoordination of longitudinal muscle layer of the esophagus, which showed weaker and asynchronic water swallow-induced contractions, while the circular muscle was unaffected. In addition, fibrous remodeling develops as a consequence of long lasting eosinophil-predominant inflammation, leading to collagen deposits in esophageal lamina propria that progress into the formation of esophageal strictures, the prevalence of which correlates with the duration of untreated disease.[15] Therefore, dysphagia might be a dynamic symptom and fibrous remodeling and its effects toward the formation of esophageal strictures may change dysphagia over time, from an intermittent muscular phenomenon to a constant obstructive rigidity.

However, there may be also "underlying" explanations to justify the disconnection between esophageal symptoms and the biological activity of EoE, by the recent recognition of EoE as a transmural disease in which the eosinophilic infiltration permeates deep into the submucosa, the muscle layers, and the neuronal plexus.[21] Hence, transmural disease would promote fibrous remodeling, intense collagen deposition, and smooth muscle hypertrophy, which collectively alter the mechanical properties of the esophageal wall and reduce esophageal distensibility. Additionally, not only eosinophils, but also mast cells included in the inflammatory infiltrate contribute to symptoms and functional disturbances in EoE.[22] In the study conducted by Safroneeva et al,[18] most of the recruited patients (59.1%) presented with long-standing symptoms for >5 years, but lamina propria tissue was underrepresented, preventing assessment of fibrosis, and mast cells were not evaluated. Regarding endoscopic features, the EFERS classification system[2] has shown an excellent capacity to predict a diagnosis of EoE in adults,[23] but it has also exhibited an incomplete interobserver agreement among the gastroenterologists who participated in its development and is limited for classifying a particular patient in disease phenotypes (inflammatory, fibrostenotic), whose characteristic features frequently overlap. Moreover, endoscopy tends to overlook esophageal narrowing identified by barium esophagography in EoE patients suffering from dysphagia.[24] Collectively, not only the presence of esophageal-related symptoms, but also the current standard for diagnosing and monitoring EoE (endoscopy and histology) may provide, at best, a very limited picture of the full-thickness esophagus in EoE.

The EEsAI PRO score, therefore, may merely reflect what happens in the whole organ extent and thickness, which may not be characterized adequately by endoscopy and esophageal biopsies. Presently, no alternative technique beyond endoscopic ultrasonography has allowed the examination of changes in deep esophageal layers or their consequences on organ function. The recent release of Endoluminal Functional Lumen Imaging Probe (EndoFLIP; Crospon, Inc, Carlsbad, CA), which demonstrated a significant reduction in esophageal distensibility in EoE,[25] may change this scenario in the future, but further testing is needed. Accordingly, the relationship between symptom severity (as captured with the EEsAI PRO instrument) and changes in esophageal compliance (determined by using EndoFLIP) requires further research to establish the capacity of the former as a full-organ evaluation tool.

In conclusion, symptoms cannot accurately predict remission in EoE, so the disease will remain defined for the time being as a clinicopathologic disorder. The unique characteristics of EoE as a full-thickness esophageal disorder, with overlapping inflammatory (not necessarily by eosinophils alone) and fibrostenosing features, underscore the limitations of endoscopy (which helps to assess superficial esophageal eosinophilia) to understand what happens beyond the mucosal surface. Until we manage to discover accurate noninvasive biomarkers for EoE, the addition of EndoFLIP to the EEsAI PRO instrument in the diagnostic workup of EoE will likely improve the correlation between perception of dysphagia by patients and the real biological activity of the disease. As hinted by Safroneeva et al,[18] this combined diagnostic strategy may be useful to ascertain which patients will clinically benefit best from endoscopic dilation, beyond histologic remission, thereby enhancing the predictive capacity of the EEsAI PRO instrument.

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Conflicts of interest
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