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EDITORIAL

Eosinophilic esophagitis: when pathologists make the difference☆

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Eosinophilic esophagitis (EoE) is a chronic relapsing esophageal inflammatory disease-causing esophageal dysfunction and damage. A substantial rise in incidence and prevalence has been reported in the last decades both in adults and in children throughout the world.[1,2] Although EoE is increasingly recognized and a matter of research for different health care specialists, a specific symptom or non-invasive validated biomarker is still lacking, and delayed diagnosis, missing cases, and incomplete histological reports still occur.[2,3] In addition, natural history and prognostic factors for both responses to treatments and disease progression need to be fully clarified. The detection of severe eosinophilic infiltration in the esophagus beyond the threshold of 15 for high power field (HPF) is the gold standard diagnostic feature.[1]

Vieira et al.[4] explored how different pathologist expertise may influence the identification of the eosinophilic infiltration and additional histological changes included in the eosinophilic esophagitis histologic scoring system (EoEHSS). Fifty esophageal biopsies from pediatric patients with EoE were analyzed by pathologists with high or low experience, after being considered adequate samples from the most expert one.[4]

The EoEHSS is a histological score including eight esophageal features: eosinophilic density, abscesses and surface layering; basal zone hyperplasia, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis. The severity (grade) and extent (stage) of all abnormalities are scored from 0 (normal) to 3 (maximum change) creating a 4-point scale for each finding.[5] The EoEHSS was first proposed by Collins et al.[5] in 2017 to provide a tool to objectively assess histologic changes in the esophagus of EoE patients considering not only eosinophil peak number but also epithelial and mucosal changes. Reliability was demonstrated by strong to moderate agreement among three pathologists who scored biopsies independently. The authors observed that EoE patients frequently presented basal zone hyperplasia, dilated intercellular spaces, and thickened connective tissue fibers in the lamina propria in addition to severe eosinophilic inflammation. Moreover, the score accurately discriminated against treated from untreated patients and appeared utilizable by pathologists after minimal training.[5] In another study, the composite EoEHSS and all items except dyskeratotic and surface epithelial alteration were associated with substantial reliability when 45 biopsies from adult patients with EoE were assessed by four expert gastrointestinal pathologists.[6]

The clinical relevance of EoEHSS is important to explore because of the currently limited evidence of symptom correlation, the lack of an accurate biochemical marker of EoE, the occurrence of repeated endoscopies in most patients, and the need of findings an objective measure of response to treatment beyond the eosinophilic peak.

Vieira et al. were the first to assess the concordance of the EoEHSS in Brazilian children with EoE. The agreement was excellent for identifying the EoE diagnostic cut-off score of $\geq$ 15 eosinophils / HPF whereas it was poor for other individual items of EoEHSS, particularly among the least experienced pathologists.[4] Based on their results, the authors suggest that specific training of pathologists is required for the correct identification of all EoEHSS features that may be useful in the evaluation of response to treatment and in the correlation with clinical manifestations and endoscopic findings.[4]

There is a wide spectrum of clinical presentation of EoE, including irritability, vomiting, poor weight gain, feeding

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disorders, dysphagia, bolus impaction, and epigastric pain. More frequent gastroesophageal reflux-like manifestations are reported in young children and obstructive symptoms in teenagers and adult patients.[1-3] However, because there is no specific symptom or questionnaire or blood test that accurately identifies EoE and relapse, diagnosis may be delayed or missing mostly in absence of bolus impaction and in young patients.[2,3,7] Likewise, esophageal endoscopic appearance may reveal signs of mucosal inflammation, erosions, white plaques, furrowing, and stenosis but also being completely normal.[1-3] Thus, the detection and monitoring of EoE are exclusively dependent on costly and invasive esophageal biopsies and histopathology reports revealing an esophageal infiltration of $\geq$15 eosinophils per high power field (HPF) on microscopy.[1] An intra and inter-observer substantial agreement for esophageal count is essential for the diagnosis but would be also important for improving mechanistic knowledge and for the evaluation of the response to treatment when considering a throughout assessment of the esophageal sample, as proposed by the EoEHSS.[1,4,5]

A self- or by parent proxy reported symptoms tool (PEESS v2.0) has been developed and validated in treated and untreated pediatric patients with EoE.[8] The questionnaire domains well-identified dysphagia, reflux symptoms, nausea, vomiting, and pain. Only dysphagia correlated strongly with overall histopathology changes, eosinophil peroxidase immunohistochemical staining, and mast cell-specific gene transcript levels. On the other hand, eosinophil levels were more associated with pain than dysphagia.[8] Because awareness and proper report of symptoms may help in identifying children to submit to endoscopy and esophageal biopsies to identify EoE, this score has recently been translated and culturally adapted to be used in Brazilian children.[9]

Determining the relative contributions of individual esophageal features, grade and stage scores, as well as the correlation with clinical and endoscopic findings could lead to better management of EoE patients. Indeed, a full assessment and classification of histological type, grading and staging have long been recognized as fundamental in oncology to define the patient's appropriate therapeutic protocol and prognostic issues. Likewise, in inflammatory bowel diseases the histologic examination of both severity and extent of inflammation have provided essential clinical information. A throughout and precise assessment of the tissue samples leads to clear discrimination between Crohn's disease, ulcerative colitis, and other form of colitis, is necessary to correctly classify different disease subtypes and guides the choice and the change of treatment.[10,11] More than 25 years ago, disagreement between ulcerative colitis and Crohn's diagnosis ranged from 25% to 35% among pathologists with gastrointestinal interest when assessing the same biopsy specimen. The absence of visible ulcers was early considered as a feature of complete response, but, although it was simple to apply in clinical practice, it did not allow for a quantification of overall improvement.[11] Over the years considerable progress has been made in the correct classification and description of inflammatory bowel diseases. In addition, mucosal healing is now commonly indicated as a 'true' measure of remission and the ultimate treatment target, particularly in pediatric patients.[12] Emerging data also indicate that early mucosal healing could be important for predicting sustained long-term remission.[11]

Up to now, in EoE, quantification of eosinophilic infiltration has been considered as the most important, if not the unique feature to ascertain, as it represents the hallmark of the disease. However, different phenotypes and endotypes of EoE have been recently described and are likely influencing the natural evolution of this condition. In a cross-sectional study, different histologic, endoscopic, and molecular features of esophageal biopsies from pediatric and adult EoE subjects were evaluated.[13] By analyzing active EoE, the authors identified three clusters of distinct endotypes (termed EoEe1−3) despite similar eosinophil levels. EoEe1 was associated with normal endoscopy and mild histologic and molecular changes. EoEe2 demonstrated an inflammatory and steroid-refractory phenotype and showed the highest expression of cytokines and steroid-responding genes. EoEe3 was associated with a narrow-caliber esophagus and histological severity.[13] Early diagnosis and effective treatment of EoE are currently considered as the key to prevent some of the long-term consequences of esophageal inflammation and progression to fibrosis.[14,15]

In hepatology, epidemiological studies have demonstrated that staging of fibrosis has a significant impact on patient morbidity and mortality, no matter the cause of liver disease.[16] Several non-invasive methods, such as magnetic resonance and fibroscan have been introduced and tested to screen hepatic fibrosis, but they are not precise enough for the correct staging of fibrosis that is important to enact interventions to block the progression of liver damage.[17]

The importance of early detection of epithelial and lamina propria alteration, ongoing and regress of inflammatory findings and fibrosis in EoE still need to be determined.

Noteworthy, in the study of Vieira et al.[4] fibrosis was not easily recognized and no agreement for this item was reported.

Nowadays, treatment of EoE includes proton pump inhibitors, corticosteroids and biologic agents, elimination diet, and endoscopic esophageal dilation. The initial and subsequent best therapeutic strategy remain poorly understood, but the choice of different therapeutic options should consider EoE phenotype (i.e. inflammatory *versus* fibrostenotic) and endotype; patient's clinical characteristics, preference, and tolerance; drug/diet efficacy, cost and adverse effects and also clinician expertise.[3,18]

However, the patient's management is still challenging and response to treatment is not predictable on the basis of clinical presentation, endoscopic appearance or the excess of eosinophilic concentration.

Maximizing the report of the biopsies with an accurate assessment of all histological features is therefore of the utmost importance to unravel possible risk factors for EoE relapse, progression, and resistance to one or other treatment. To improve pathologist agreement different strategies have been proposed. When a teaching session, digitized slide set, and validated protocol were used, an excellent agreement between pathology trainees and expert pathologists was reported for eosinophil counts, a very good agreement for eosinophil degranulation and spongiosis while less concordance was found for microabscesses.[19] More recently, an automated approach was introduced for quantifying eosinophils using deep image segmentation. A U-Net model and post-processing system were applied to generate results for eosinophils, to describe disease severity and progression.

These histology statistics were collected at the diagnosis and then compared with patient metadata consisting of clinical and treatment phenotypes. A detailed classification model was applied to discover features other than eosinophils that can be considered for the diagnosis using, for the first time, a deep learning computer vision approach. Moreover, this system could provide an automated process for tracking disease severity and progression.[20]

As outlined by Vieira et al.[4] the increased incidence and prevalence of EoE at all ages and worldwide determine an urgent need for pathologist training and of consensus on esophageal biopsy reports among and outside reference centers. Finding genetic, esophageal impedance signs or other biomarkers that can reliably identify the acute and recurrent stages of the disease are still an unmet need. In the meantime concordance on histology findings and recognition of causes of discrepancies are pivotal to avoid misinterpretation of the biopsies and to proper diagnosis and monitoring of EoE.

Whether the presence of specific additional histology features is linked to a worse prognosis or a high frequency of relapse and disease progression has not yet been well-studied and is an important metric to pursue in future larger studies. Nonetheless, making an accurate diagnosis and a complete histology report may provide new insights on EoE pathophysiology and on the progression of the disease. Moreover, it increases reproducible results, enables clinicians to more clearly identify prognoses and monitor treatment efficacy, and help to consider other therapeutic options.

Conflicts of interest

The author declares no conflicts of interest.

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