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Original Contribution

American Registry of Pathology Expert Opinions: Evaluating Patients with Eosinophilic Esophagitis: Practice Points for Endoscopists and Pathologists☆

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1. Overview

Eosinophilic esophagitis is a clinicopathologic condition characterized by a constellation of clinical, endoscopic, and histologic features, all of which must be considered when establishing a diagnosis [1]. The exchange of pertinent information between gastroenterologists and pathologists can greatly facilitate evaluation of patients who present with features suggestive of eosinophilic esophagitis, whereas failure to provide such information can lead to delayed diagnosis or erroneous classification of disease. The purpose of this review is to discuss key points that should be addressed by all clinicians, both gastroenterologists and pathologists, involved in the management of patients who may suffer from eosinophilic esophagitis.

2. Clinical considerations

Endoscopists can facilitate the pathologist's interpretation of esophageal biopsy specimens through several measures that are relatively easy to implement. Provision of key elements of the medical history, such as atopy (e.g. asthma, eczema, allergic rhinitis, food allergies), chronic dysphagia, and food impactions, is helpful when evaluating adults and older children; vomiting, feeding intolerance or aversion, and failure to thrive are other important features to mention when evaluating infants and young children. Esophageal biopsy samples obtained from patients with suspected eosinophilic esophagitis should always be accompanied by a description of the endoscopic findings as well as an assessment of whether those findings are typical of eosinophilic esophagitis (e.g. esophageal rings, furrows, and exudates; Fig. 1) [2]. Ideally, endoscopically obtained specimens are accompanied by a copy of the endoscopy report and associated images.

Clinical guidelines initially required a failed response to proton pump inhibitors to establish a diagnosis of eosinophilic esophagitis, the rationale being that response to proton pump inhibitor therapy was essentially diagnostic of gastroesophageal reflux disease [3]. We now know this notion to be incorrect. Patients with eosinophilic esophagitis can show a partial or complete response to proton pump inhibitor therapy and, in fact, these agents are now considered a first-line option in the treatment of eosinophilic esophagitis [4,5]. Proton pump inhibitors diminish the additive effects of gastroesophageal reflux disease on underlying eosinophilic esophagitis, effectively decreasing mucosal permeability induced by acid exposure. They also alter Th2-mediated inflammation and decrease elaboration of eotaxin-3 by squamous epithelial cells independent of their effects on gastric acid secretion [6,7]. Although cessation of proton pump inhibitor therapy in the weeks preceding diagnostic endoscopy was not routine practice prior to this realization, we now suggest that patients maintained with proton pump inhibitor therapy stop taking their medications 3 to 4 weeks prior to endoscopy whenever eosinophilic esophagitis is a diagnostic consideration [5]. Accordingly, pathologists should be informed when patients are taking medications that could alter mucosal eosinophilia or mask diagnostic features of eosinophilic esophagitis, such as proton pump inhibitors, swallowed, inhaled, or systemically administered corticosteroids, and other immunomodulatory medications.

Eosinophilic esophagitis is often patchy, so sampling error can be a major problem when establishing this diagnosis as well as when assessing its response to therapy. Gonsalves et al. found that a single biopsy sample detected eosinophilic esophagitis with a sensitivity of 55% when diagnostic criteria required ≥15 eosinophils per high power field; diagnostic sensitivity increased to 100% when 5 samples were obtained [8]. More numerous biopsy samples were required to achieve 100% sensitivity when more stringent histologic criteria (i.e. a greater number of eosinophils) were applied. Although eosinophilic esophagitis can show a predilection for the distal esophagus with sparing of its mid and proximal regions, the presence of mucosal eosinophilia in the proximal esophagus strongly supports a diagnosis of eosinophilic esophagitis and can facilitate its distinction from gastroesophageal reflux disease. We recommend that endoscopists take 4 biopsy samples from the distal esophagus 1–3 cm above the squamo-columnar junction as

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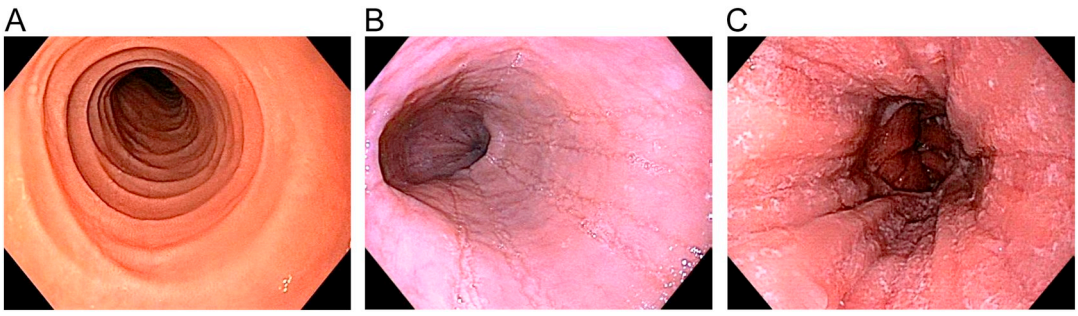

Fig. 1. Fixed circumferential rings are classic endoscopic features of eosinophilic esophagitis (A). Some patients have furrows, which have been termed longitudinal furrows or vertical lines (B). Exudates, variably termed plaques and white spots, are commonly present, and often accompany furrows or other features of eosinophilic esophagitis (C).

well as 4 biopsies from the more proximal esophagus when evaluating patients for possible eosinophilic esophagitis. Samples from these two locations should be submitted to the pathology laboratory in separate formalin-filled containers. There is no need to obtain biopsy material from the squamo-columnar junction when considering a diagnosis of eosinophilic esophagitis; its distinction from gastroesophageal reflux disease in this area is often difficult, or impossible, because the squamo-columnar junction can be affected by intense acid exposure even in asymptomatic individuals [9].

Some patients with eosinophilic esophagitis also have a widespread eosinophilic gastrointestinal disorder (i.e. eosinophilic gastroenteritis) affecting the stomach, small bowel [1,10]. These patients generally do not respond to conventional therapy for eosinophilic esophagitis and may require systemic treatment. The endoscopic and histologic features of isolated eosinophilic esophagitis are indistinguishable from those of esophagitis associated with eosinophilic gastroenteritis. Sampling of the gastric antrum and duodenal mucosae can be helpful in distinguishing between these entities; detection of mucosal eosinophilia at these sites would support a diagnosis of eosinophilic gastroenteritis. There is also some literature suggesting a relationship between eosinophilic esophagitis and celiac disease, so sampling of the duodenum may be helpful when evaluating patients with upper gastrointestinal symptoms [11]. For these reasons, we recommend that the endoscopist obtain tissue samples from the gastric antrum and duodenum to assess for this condition when establishing an initial diagnosis of eosinophilic esophagitis.

Endoscopists frequently perform interval endoscopic examinations to assess patients with established eosinophilic esophagitis for response to therapy and, in this situation, the endoscopist should relay such information to the pathologist. Knowledge of the clinical context will alert the pathologist of the need to compare findings in the interval biopsy specimens with those of earlier specimens. Attempts should be made to obtain the slides or, at least, the pathology report in the event that prior procedures were performed at another institution. Interval samples of the antrum and duodenum are unnecessary, provided that these sites have already been assessed for the possibility of a generalized eosinophilic gastrointestinal disorder during a prior procedure. Gastroenterologists should bear in mind the patchy nature of eosinophilic esophagitis and issues related to sampling errors when they receive pathology reports related to interval procedures. Comparisons between biopsy sets can be misleading, especially if attention is directed only toward the numbers of eosinophils present in biopsy samples. Comprehensive assessment of the response to therapy requires consideration of clinical and endoscopic features as well as histologic findings in biopsy material.

3. Histologic considerations

In 2007, Furuta, et al. recommended that the diagnosis of eosinophilic esophagitis requires a minimum of 15 eosinophils per high-power field in esophageal mucosal biopsy samples [3]. This arbitrary number was derived from several pathologist-driven studies describing the morphologic features of eosinophilic esophagitis, many of which required a minimum of 15 eosinophils per high-power field for classification [12,13]. However, the presence of 15 eosinophils in a high-power field was never intended to be a diagnostic criterion for eosinophilic esophagitis or a discriminatory variable in its distinction from gastroesophageal reflux disease. There are no data, for example, to suggest that patients with 14 eosinophils per high-power field are substantially different than those with 16 eosinophils per high-power field. Pathologists and gastroenterologists should be aware that some patients with eosinophilic esophagitis have mucosal samples containing fewer than 15 eosinophils per high-power field, particularly when they have concurrent atopic conditions that are managed with corticosteroid therapy [8]. Nonetheless, gastroenterologists have come to place considerable weight on the importance of 15 eosinophils per high-power field and they tend to expect pathologists to count eosinophils in samples obtained from patients with suspected eosinophilic esophagitis.

Counting eosinophils is straightforward when they are present in relatively low numbers, but quantitation becomes exponentially challenging when high numbers of eosinophils are encountered. It is essentially impossible to count eosinophils with any degree of accuracy when they are degranulated, present in microabscesses, or located in parakeratotic crust (Fig. 2). It is also worth mentioning that the field diameter of a high-power field varies among microscopes. Those with larger eyepiece field number diameters have larger fields of view than those with smaller diameters, so eosinophil counts vary depending on the type of microscope used for assessment [14]. Finally, endoscopically obtained fragments of squamous epithelium are tiny so the piece containing the highest number of eosinophils may not occupy the entire visual field. These factors, in combination with the fact that eosinophilic esophagitis is a patchy disease, call into question the clinical value of reporting precise eosinophil counts.

We acknowledge that the threshold value of 15 eosinophils per high-power field for diagnosing eosinophilic esophagitis has become entrenched in clinical practice and it is not onerous for pathologists to provide gastroenterologists with information regarding eosinophilia in relation to this number. However, precise quantification of eosinophils when they are more numerous is of unclear clinical utility, so we believe rough estimates of mucosal eosinophilia are probably adequate. Given that there are no data suggesting a relationship between clinical symptoms and absolute eosinophil numbers, we recommend reporting eosinophil counts up to 15 per high-power field, then providing ranges of mucosal eosinophilia (e.g. 15–50, >50, or >100 per high-power field) when higher numbers are present. Mentioning other common features of eosinophilic esophagitis, such as eosinophil clusters/abscesses, extensive eosinophil degranulation, eosinophils and/or eosinophil granules in sloughed parakeratotic material, and hyalinized lamina propria fibrosis, can be helpful to pathologists who review follow-up material.

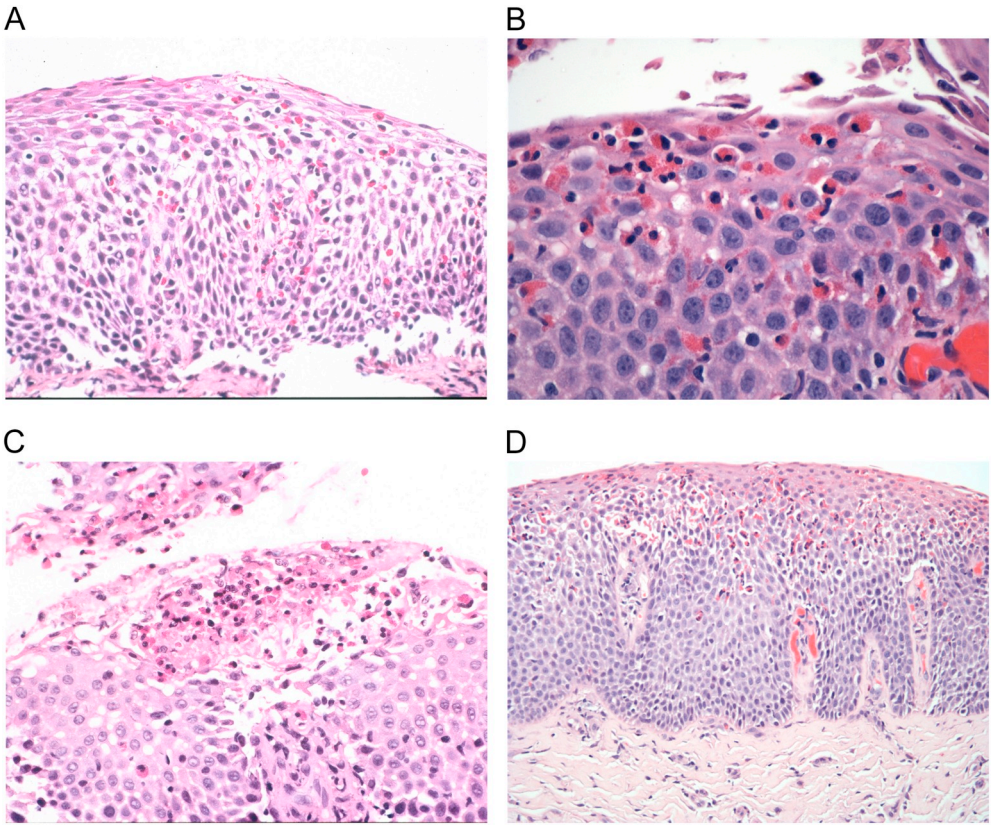

Fig. 2. Histologic features of eosinophilic esophagitis include increased intraepithelial eosinophils accompanied by scattered lymphocytes, mucosal edema, and basal zone hyperplasia (A). Extensive eosinophil degranulation and clustered eosinophils are diagnostic when present (B). Eosinophil-rich squamous debris accounts for the endoscopic appearance of mucosal plaques (C). Lamellar fibrosis of the lamina propria is a helpful diagnostic feature, particularly when eosinophils are present in low numbers (D).

Gastroenterologists commonly sample the squamocolumnar junction when patients present with dysphagia or other esophageal symptoms, even though this practice generally is discouraged by gastroenterology societies. It is not uncommon for cardiac-type mucosa to show chronic inflammation with or without neutrophils, but this observation does not necessarily correlate with clinical symptoms or detection of inflammation in samples from the tubular esophagus. Moreover, it is not uncommon to detect a few eosinophils in the adjacent squamous epithelium unaccompanied by evidence of mucosal injury, such as basal zone hyperplasia and edema. These findings are of unclear clinical significance and should not be interpreted to represent esophagitis. However, pathologists can certainly raise the possibility of eosinophilic esophagitis when sampling from this area shows high numbers of eosinophils ($\geq$15 per high-power field) or other features of eosinophilic esophagitis, even if they are not provided with material from the mid or proximal esophagus.

Most patients with eosinophilic esophagitis undergo subsequent endoscopic procedures to assess for response to therapy. In this situation, pathologists should compare current findings with those of prior samples and explicitly state whether there is any improvement in the severity of mucosal eosinophilia (Fig. 3). Although gastroenterologists assess therapeutic response using a variety of parameters, information regarding interval changes in histologic abnormalities can be helpful when planning further management.

4. Conclusions

Although clinical, endoscopic, or histologic findings alone may strongly suggest a diagnosis in some patients, establishing a diagnosis of eosinophilic esophagitis generally requires clinicopathologic correlation. Close communication between endoscopists and pathologists can greatly facilitate this effort and minimize the possibility of a misdiagnosis in patients who have non-classic disease manifestations or other disorders that simulate eosinophilic esophagitis. Clinicians can help pathologists create useful reports by providing them with relevant clinical information and submitting an adequate number of tissue samples from the distal and mid/proximal esophagus. Biopsy material from different sites in the esophagus must be submitted in separate containers to assist pathologists in the distinction of eosinophilic esophagitis from its mimics. On the other hand, pathologists can help direct clinical care by providing endoscopists with information regarding the density of mucosal eosinophilia. They can also help endoscopists determine whether patients have responded to treatment for eosinophilic esophagitis by assessing the extent of inflammatory changes in current material compared with that from prior procedures.

Key points

1. The diagnosis of eosinophilic esophagitis requires open communication between endoscopists and pathologists to facilitate clinicopathologic correlations.
2. At least 4 samples should be obtained from both the proximal and distal esophagus in order to increase the likelihood of detecting eosinophilic esophagitis and these samples should be placed in separately labeled containers. Sampling of the gastric antrum and duodenum should be performed during the first endoscopic evaluation to exclude the possibility of an eosinophilic gastrointestinal disorder. Biopsy of the squamocolumnar junction should be avoided when trying to diagnose eosinophilic esophagitis.
3. Pathologists should report the highest number of eosinophils present per high-power field when esophageal samples contain only mildly increased eosinophils ($<$20/hpf). Estimates, such as $>$50 or $>$100/high-power field are more appropriate when eosinophils are more numerous.
4. Pre-treatment biopsy samples and/or pathology reports should be compared to current specimens when patients undergo interval endoscopic procedures and biopsies are performed following treatment for eosinophilic esophagitis. Pathologists should provide a

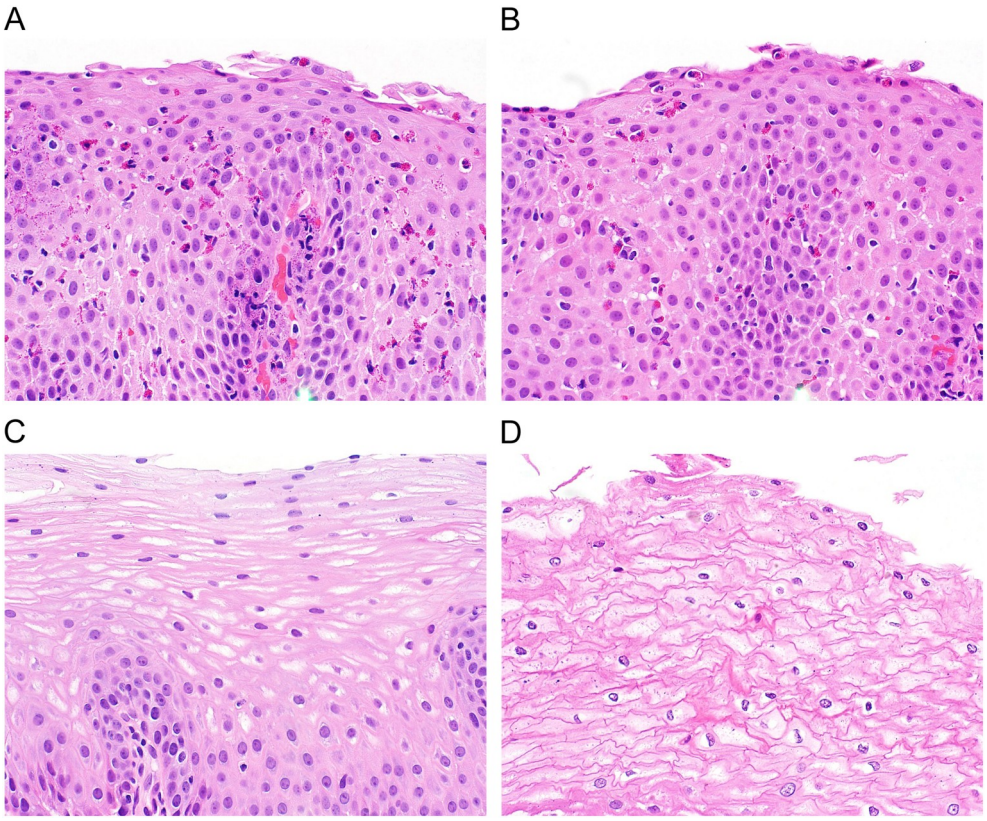

Fig. 3. Proton pump inhibitors can markedly decrease the inflammatory infiltrate of eosinophilic esophagitis. Initial biopsy samples from this patient contained numerous intraepithelial eosinophils and eosinophil granules (A) as well as superficial eosinophilic microabscesses (B). Interval biopsies following proton pump inhibitor therapy revealed normal squamous epithelium (C) with complete resolution of eosinophilia (D).

comment regarding improvement, or lack thereof, when prior materials are available.

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