Histopathology of Eosinophilic Esophagitis

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Key Words

Eosinophilic esophagitis · Pathology · Differential diagnosis · Gastroesophageal reflux disease · Proton pump inhibitor-responsive esophageal eosinophilia

Abstract

Eosinophilic esophagitis (EoE), a chronic relapsing antigen-driven disease, is associated with characteristic esophageal histopathology, including ≥ 15 intraepithelial eosinophils in at least one high-power field (HPF), and alterations in the epithelium and subepithelial connective tissue. Currently, the pathologic changes in EoE are characteristic but not pathognomonic: the differential diagnosis includes gastroesophageal reflux disease, proton pump inhibitor-responsive esophageal eosinophilia, EoE with significant eosinophilic inflammation in other parts of the gastrointestinal tract (eosinophilic gastrointestinal disorder), etc. EoE biopsy pathology does not vary according to age, sex, or familial predisposition. Genetic analyses of EoE esophageal biopsies have identified a characteristic transcriptome that includes upregulation of several genes that relate to histopathology, such as periostin, thymic stromal lymphopoietin, and desmoglein. Diagnostic pitfalls include the patchy distribution of the characteristic EoE pathology; examining multiple biopsies increases the disease detection rate. The method used to quantitate eosinophils, including the size of the HPF,

influences the diagnostic yield, but excellent interobserver variability is achieved among pathologists who agree to a uniform methodology. Therapy for EoE includes diet-based approaches to eliminate offending antigens, topical steroid therapy, and novel biologic agents including monoclonal antibodies. Following appropriate therapy, biopsies may revert to normal histology, but signs and symptoms of esophageal dysfunction may persist. A potential explanation is that endoscopic biopsies obtain very small superficial fragments of tissue from an organ that has complex underlying neuromuscular components; unseen pathology in those loci may influence the clinical state of patients with normal epithelial biopsies.

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Eosinophilic esophagitis (EoE) is an inflammatory esophageal disease that has characteristic clinical findings indicating esophageal dysfunction and eosinophil-predominant inflammation in the esophageal epithelium [1]. A conceptual definition has emerged of EoE as a chronic disease resulting from immune/antigenic stimulation [2–5]. An exceedingly important component of the definition is that EoE is a clinicopathologic diagnosis – neither biopsies nor clinical findings can be used in isolation to diagnose the disease; both are required.

Fig. 1. **a** Normal esophageal squamous epithelium exhibits a basal layer that is not more than 3 cell layers thick or more than 15% of the total epithelial thickness (bar with arrow). Lamina propria is not thickened (asterisk). **b** Esophageal epithelium from a patient with EoE shows a markedly thickened basal layer (bar), numerous intraepithelial eosinophils (arrows), dilated intercellular spaces (white arrow), and thickened fibers in the lamina propria (asterisk). **c** In this EoE biopsy that is not well oriented, peripapillary basal layer hyperplasia is apparent (bar). Numerous intraepithelial eosinophils are seen including eosinophil abscesses at the surface (arrows). Dilated intercellular spaces are also seen (white arrow).

Microscopic Pathologic Features

Inflammatory Cells

The most characteristic microscopic pathologic feature of EoE is intraepithelial eosinophil inflammation (fig. 1). Eosinophils are normally found in the mucosa of the gastrointestinal tract, except for the esophagus [6]. Eosinophils are easily recognized in sections of tissue, fixed in formalin, that are stained with hematoxylin and eosin; special stains are not required. Frequently, esophageal biopsies at the time of EoE diagnosis demonstrate very large numbers of intraepithelial eosinophils that may form abscesses and align parallel to the luminal surface [1, 4, 7]. Methods of counting eosinophils vary and the

size of the microscopic field in which they are counted may vary significantly among microscopes, which complicates the ability to compare counts obtained from different pathologists and even counts obtained in the same pathology department over time. Expressing the eosinophil number per unit area would help to diminish variations, and in fact excellent interobserver agreement is achieved among pathologists who decide upon and routinely use selected methods of evaluating EoE biopsies [8]. Mean counts obtained from quantitating eosinophils in several or all high-power fields (HPF) in esophageal biopsies may be suitable for research purposes, but currently a carefully obtained peak count is sufficient to suggest that, in the proper clinical setting, a biopsy is consistent with EoE.

EoE may be distributed in a patchy manner throughout the esophagus, impairing the ability to diagnose the disease. Increasing the number of biopsies submitted for histologic examination increases the diagnostic yield, and examining 5 biopsies increases the yield to 100% for a threshold peak count of ≥ 15 eosinophils/HPF [9]. Patchy distribution of eosinophil infiltrates may result in biopsies showing eosinophil inflammation, but the peak eosinophil count is less than the recommended threshold value for diagnosis of 15/HPF; EoE is a clinicopathologic diagnosis and clinical judgment is required to determine if individuals whose biopsies do not display ≥ 15 eosinophils/HPF have EoE [4]. Pathologists should obtain additional sections of such biopsies because deeper sections may yield higher counts. Eosinophil infiltrates having a peak count ≥ 15 /HPF peak count may be found in proximal esophageal biopsies in patients who have gastroesophageal reflux disease (GERD) or proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) and therefore are not pathognomonic of EoE [10]. Abnormalities of the mucosa identified at endoscopy of EoE are characteristic [11], but the mucosa may appear normal in a significant number of patients [2], and normal gross mucosal appearances should not deter endoscopists from obtaining biopsies from patients with characteristic EoE clinical findings. Biopsies from the stomach and duodenum should also be obtained to identify eosinophil-related or other pathologies at those sites. As with esophageal biopsies, biopsies at those sites should be obtained even if the mucosa appears normal because, for example, children and adults who have eosinophil gastritis may have normal-appearing gastric mucosa at endoscopy [12].

Other inflammatory cells including lymphocytes and mast cells are increased in esophageal biopsies from patients who have EoE [13–16], and generally their increase parallels the increase in eosinophils.

Additional Pathology

The epithelial alterations most characteristic of EoE are basal layer hyperplasia and dilated intercellular spaces (fig. 1). Biopsy orientation may diminish the ability to evaluate hyperplasia, but significant hyperplasia can be appreciated even in tangentially oriented sections. Dilated intercellular spaces are often seen, with or without basal layer hyperplasia. The epithelial alterations tend to be most impressive in biopsies that contain large numbers of intraepithelial eosinophils [1], but some biopsies with apparently few eosinophils show marked hyperplasia and intercellular space dilation; these may be biopsies in which eosinophil concentrations are quite patchy. Lamina propria may show

changes suggestive of fibrosis/remodeling [17–19], which may be reversible [20–22]. Many esophageal biopsies obtained endoscopically do not exhibit lamina propria.

History and Significance of EoE Pathology

Although allergic esophagitis is an apparently new disease, the histopathology of EoE is not new. Review of esophageal biopsy slides obtained from adults and children prior to the recognition of EoE as a disease entity has confirmed that esophageal biopsies contained numerous intraepithelial eosinophils and associated pathology, including eosinophil abscesses, basal layer hyperplasia, and lamina propria fibrosis [23–26]. The significance of intraepithelial eosinophils in esophageal biopsies is emphasized by the fact that patients who had intraepithelial eosinophils (as few as 5/HPF in esophageal biopsies and were not treated for EoE with antigen elimination, etc.) were significantly more likely to experience dysphagia and food impaction in subsequent years compared to patients whose biopsies contained less than 5 eosinophils/HPF [27].

Differential Diagnosis

These esophageal epithelial pathologic features are not pathognomonic of allergic EoE. Esophageal epithelial biopsies obtained from patients who have systemic disorders such as hypereosinophilic syndrome may show these features, as well as patients who have significant eosinophil infiltrates in the mucosa of one or more other sites in the gastrointestinal tract (eosinophilic gastrointestinal disorder) or unrelated diseases such as celiac disease or idiopathic inflammatory bowel disease [1, 4, 5]. Predisposing conditions include a family history of EoE [28] and a connective tissue disorder characterized by hypermobility [29]. There are no features on hematoxylin and eosin-stained slides that identify subjects with predisposing or associated conditions from those without such history.

More common causes of esophageal biopsies that show the features of allergic EoE are GERD [30, 31] and PPI-REE [10, 32–35]. PPI-REE is increasingly being recognized as a cause for clinical findings and biopsies that resemble EoE. There are no pathologic features that predict response to PPI [32–35]. The clinical and histologic responses may be transient [33], and close clinical follow-up is prudent. Whether PPI-REE represents an unusual phenotype of GERD or EoE is not yet known [36].

Distinguishing biopsies of EoE from GERD would be helpful clinically to reduce additional testing and accelerate the time to a proper diagnosis. In esophageal biopsies obtained from children, mast cell activation defined as IgE-positivity has been suggested to distinguish EoE from GERD [37]; however, the patient populations in the study were assigned diagnoses based on intraepithelial eosinophil counts, and additional crucial clinical information such as use of PPI or results of pH monitoring was not provided. In biopsies obtained from children and adults diagnosed with EoE or GERD according to consensus guidelines, mast cells were significantly increased in EoE biopsies compared to those from patients who had GERD, and the combination of peak eosinophil count plus the number of mast cells successfully distinguished the groups in a high proportion of cases [38]. However, the number of intraepithelial eosinophils in the GERD biopsies was significantly less than the number in EoE biopsies. In a study of esophageal biopsies from patients who had EoE (normal pH monitoring results) versus GERD (abnormal pH monitoring results) and increased intraepithelial eosinophil counts that did not differ between the groups, the median but not mean number of tryptase-positive mast cells was increased in EoE compared to GERD [39]. Some of these patients, however, may have had PPI-REE. More studies of mast cells in esophageal biopsies of patients with EoE and patients with GERD who have comparable amounts of eosinophilic inflammation are required to determine if mast cells can distinguish the diseases.

Therapy

Several prospective randomized placebo-controlled clinical trials of various therapies to treat EoE have been reported. Topical corticosteroid therapy, in the form of swallowed fluticasone in children [40] and adults [41] or oral budesonide in children [42], adolescents, and adults [43], reduced eosinophilic inflammation in esophageal epithelium consistently. Monoclonal antibodies to IL-5 also significantly reduced intraepithelial eosinophilic inflammation in esophageal biopsies from children enrolled in trials that tested the efficacy of high doses versus low doses of antibody [44] or antibody versus placebo [45].

EoE diagnosis depends on the correlation of clinical signs and symptoms with esophageal biopsy pathology in the proper clinical setting, e.g. lack of clinical and histopathologic response to PPI therapy. After therapy targeted to treat EoE, both biopsy and clinical symptoms may improve [44, 45]. However, a strong placebo effect may

Table 1. Dysregulated genes and pathologic features of EoE

Dysregulated gene	Pathologic feature	Reference
Eotaxin-3	inflammation	14, 16
Carboxypeptidase A3, tryptase	inflammation	15, 16
TSLP	inflammation	46, 48
Periostin	inflammation	49
Filaggrin	epithelium	50
microRNA:		
miR-221, miR-223, miR-375	inflammation	51, 52

obscure the significance of the clinical improvement [45]. In some studies, inflammation was significantly diminished following therapy, including reduction of eosinophil granule-associated proteins, but symptoms did not improve significantly [41]. One possible explanation is that topical therapy does not result in improvements in the esophageal wall that surrounds the epithelium.

Genetics

EoE is diagnosed using both clinical and pathologic criteria in combination – truly a clinicopathologic diagnosis. EoE is also a ‘genopathologic’ disease. A unique transcriptome is identified in esophageal biopsies from affected patients [14], and several of those dysregulated genes correlate with several features of EoE esophageal biopsies (table 1). Eotaxin-3 is the most upregulated gene and it strongly promotes eosinophil infiltration into tissue [14, 16]. Thymic stromal lymphopoietin is a cytokine involved in multiple allergic processes that also promotes tissue inflammation in EoE [46–48]. Periostin, an extracellular matrix protein, is overexpressed in EoE and facilitates eosinophil adhesion to fibronectin [49]. Filaggrin is a member of the epithelial differentiation complex of genes and filaggrin expression is decreased in EoE, consistent with expansion of the less differentiated basal cell layer and reduction of the more differentiated suprabasal layers [50]. Several microRNAs are dysregulated in biopsies of active EoE and appear to contribute to Th2-polarized responses [51, 52]. A recently developed test provides rapid evaluation of gene expression in esophageal tissue [53].

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the content of the article.

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