ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Prateek Sharma, MD

Challenges in Differentiating and Diagnosing Gastroesophageal Reflux Disease vs Eosinophilic Esophagitis

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G&H What is the current understanding of gastroesophageal reflux disease and eosinophilic esophagitis, and why is it important to distinguish them?

ED Gastroesophageal reflux disease (GERD) and eosinophilic esophagitis (EoE) are two distinct conditions. They have different pathophysiologies, treatment approaches, outcomes, and complications. It is important to distinguish them, to accurately diagnose when one is present and one is not, and to understand that patients may have both at the same time. Diagnosis can be complicated because not only can EoE and GERD overlap, they can also impact each other. The answer may not be as simple as saying, EoE *yes* and GERD *no*. For historical perspective, EoE was first defined by the absence of GERD, meaning that the patient had not responded to GERD treatment with a high-dose proton pump inhibitor (PPI) trial. It is known now that not only can the two conditions coexist and influence each other but both can be treated with PPIs, potentially through independent mechanisms. Although the conditions may share some of the same symptoms, the same histologic and endoscopic findings, and even the same treatment, it is important to understand where the differences are. For example, performing an antireflux surgical procedure to treat what is thought to be refractory reflux in an EoE patient will result in suboptimal outcomes.

G&H What are the key differentiating diagnostic clinical, endoscopic, and histologic features of GERD vs EoE?

ED The primary symptoms of EoE particularly in adolescents and adults are dysphagia and food impaction. With reflux, patients typically have symptoms of heartburn and regurgitation. However, what is tricky is that patients with EoE can have heartburn and chest discomfort, and patients with GERD can have trouble swallowing potentially from a peptic stricture. Clinically, a careful history is needed to understand whether a patient's symptoms are the classic, typical symptoms of reflux, with pyrosis that travels in a cranial direction and is worse when lying down and at night, and that patients respond to simple antacids, for example. On endoscopy, the patient may have evidence of erosive esophagitis or Barrett esophagus,

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and these are considered definitive signs of diagnosis. A patient with GERD would also have abnormal pH exposure when tested off antisecretory therapy. The presence of a hiatal hernia in the absence of erosive disease may explain regurgitation or symptoms of volume reflux.

In contrast, although these findings are not pathognomonic, rings, edema, furrows, and exudates on endoscopy are much more likely to indicate EoE than GERD. It is not usual to see erosive esophagitis or erosions in a patient who has EoE, so these findings can help distinguish the conditions. Regarding histologic features, it is a little tricky because for years it was thought that eosinophils in a biopsy sample were a hallmark of reflux, and it was a finding that was not clinically actionable. Additionally, ablation therapy for Barrett esophagus may increase the level of esophageal eosinophils.

This is why the last step in the EoE diagnostic algorithm is to consider other non-EoE conditions that could contribute to esophageal eosinophilia. Often the question is, to what extent is reflux present? There is no one definitive thing that can answer this question. Even the presence of distal eosinophilia alone does not distinguish between GERD and EoE. In all patients with EoE, eosinophil counts actually are higher distally than proximally. Therefore, it comes down to synthesizing data on the history, symptoms, endoscopic findings, and biopsies. Sometimes ancillary testing is needed.

G&H How do diagnostic considerations change at different stages in a patient's life?

ED Age does not impact either the likelihood of reflux or EoE. However, because reflux is seen far more often than EoE, the pretest probability of GERD in a patient with symptoms of reflux is much higher than that of EoE, and that is true whether the patient is an infant or 80 years old. In general, EoE is thought of as a condition that tends to develop in people who are younger; however, because it is a chronic disease, the epidemiology is changing. EoE is more likely to be diagnosed in adulthood than in childhood. Children who have EoE become adults with EoE. In a younger patient with nonspecific upper gastrointestinal symptoms such as heartburn, vomiting, and regurgitation, which could be consistent with either reflux or EoE, if food allergies, asthma, and eczema are present, then that should raise the suspicion for EoE.

G&H How can recent advances in the pathogenesis of EoE help distinguish it from GERD?

ED The pathogenesis of EoE is distinct from GERD. EoE is primarily an allergic disease. It is thought that food antigens or environmental allergens interact with an impaired esophageal barrier. This triggers a characteristic allergic inflammatory response, also called a T-helper type-2 response, that leads to elevations of allergic cytokines (eg, interleukin [IL]-4, IL-5, IL-13), some of which are targets for treatment of EoE. This inflammatory cascade results in recruitment of a host of allergic cells into the esophagus, notably eosinophil and mast cells, and leads to gene expression changes in the esophageal epithelium. If this pathogenesis is used for diagnostic testing, for example, with either gene transcription assessment or staining the esophageal biopsies for mast cells, EoE can be diagnosed with a high degree of confidence. The elevated mast cell counts and gene expression changes that are characteristic of EoE are not seen in GERD.

A key point is that before proceeding to surgery with fundoplication for a patient with presumed refractory GERD, it is critical to rule out EoE with endoscopy and biopsy.

G&H In what instances may both GERD and EoE overlap?

ED There are several ways in which GERD and EoE interact or can overlap that were initially highlighted by Spechler and colleagues. First, a person has EoE and GERD simultaneously and the two conditions are unrelated. Second, because the esophagus is inflamed and has decreased compliance in EoE, patients can have secondary reflux. The motility may be altered in these patients, and they may have issues with clearing of physiologic normal reflux. Third, a patient who has reflux can either have erosive disease (where there are clearly breaks in the esophageal barrier) or microscopic impairment of the barrier that will allow egress of allergens from the esophageal lumen into the mucosa. In this case, a secondary EoE-like picture develops that may be more driven by GERD. In these instances, if EoE and GERD are interacting, it takes some time to understand what the driving feature is and how best to target therapy to the appropriate patient and underlying mechanism. A key point is that before

proceeding to surgery with fundoplication for a patient with presumed refractory GERD, it is critical to rule out EoE with endoscopy and biopsy.

G&H What findings lead to misdiagnosis of GERD as EoE and vice versa?

ED One way GERD can be mistaken as EoE is when eosinophils in the esophagus are related to reflux and not to allergy. A patient may have, for example, 30 eosinophils on a biopsy of the esophagus. The biopsy report interpretation in the absence of any clinical information may say, consistent with EoE, because of the elevated eosinophils. However, if that patient had heartburn, regurgitation, Los Angeles grade B esophagitis, and a 4-cm hiatal hernia, even if there are some endoscopic findings typical of EoE, most likely GERD is the primary driver of symptoms. This is an instance where it is important to take the whole situation into account. If a corticosteroid or a biologic was given for what is thought to be EoE, there is a good chance the patient would not respond because it would not treat the underlying GERD physiology.

On the flip side, in a patient with asthma and eczema who is undergoing endoscopy for dysphagia and heartburn, there could be subtle endoscopic findings of EoE that may not be appreciated. If the patient also had a stricture in the distal esophagus, a 1-cm hiatal hernia, and a low level of eosinophils on the biopsy (eg, 20 eosinophils distally), there could be a misdiagnosis of GERD when the cause is actually EoE.

An EoE diagnosis can also be missed when the patient undergoes endoscopy on a PPI. A patient who has, for example, dysphagia, heartburn, and regurgitation but also has asthma and environmental allergies is empirically placed on a PPI and then has an endoscopy. If the endoscopy and biopsy findings look normal, the patient could be inappropriately considered to have nonerosive reflux disease, when in fact the PPI is treating the underlying EoE. When there is a clinical suspicion of EoE, it is much better to have the patient undergo endoscopy off PPI therapy. For EoE, a PPI washout for 2 to 3 months may be needed for the diagnosis. In contrast, for a patient who has dysphagia-predominant symptoms, there is no need for a PPI, and EoE is less likely to be missed when endoscopy is performed. Consideration of diagnostic endoscopy off PPI therapy will likely become more routine, as recent GERD guidelines recommend stopping PPI therapy before endoscopy in patients to facilitate a definitive diagnosis of GERD with the findings of erosive esophagitis. It is critical that when there is a clinical consideration of EoE and the first endoscopy was normal on a PPI, for a patient to undergo endoscopy off the PPI at some point to confirm whether EoE is the cause.

G&H When is a PPI trial appropriate or not appropriate?

ED PPI therapy is now an accepted EoE treatment, and a PPI trial is not needed to diagnose EoE. As I mentioned, it could mask the diagnosis. This was a significant change in the field about 5 years ago, and prior to that, failure of a PPI trial was required for EoE diagnosis. It turns out that there are several mechanisms whereby PPIs can treat EoE in an acid-independent fashion. For example, PPIs decrease expression of the chemokine eotaxin-3, which in turn decreases eosinophil recruitment in the esophagus; they may improve esophageal barrier function; and they improve epithelial homeostasis in the esophagus as well. PPIs can also help if there is overlapping secondary reflux or coexisting reflux in a patient. Use of a PPI is recommended as one of the first-line treatment options for EoE, and a histologic response of about 40% to 50% is seen with this approach. However, it is important to know why the PPI is being used, because the approach is different for reflux, and the rationale should be explained to patients. In EoE, double dosing is used, which is off-label. In reflux, the standard approved PPI doses are used. The decision comes down to clinical suspicion. If there is clinical suspicion that reflux is causing a patient's symptoms, then empiric treatment with a PPI is recommended.

G&H How effective is risk factor modification as a diagnostic tool in patients with signs and symptoms of GERD and/or EoE?

ED There is currently no role for risk factor modification in EoE. However, lifestyle modifications are very helpful for GERD and should certainly be tried. These include avoidance of the typical reflux food triggers, losing weight, elevating the head in bed, and not eating late at night or before lying down. In practice, many patients have already tried lifestyle modifications before being prescribed medicine or even before coming to the doctor. Also in practice, many patients are not adherent to the lifestyle modifications.

G&H What do the guidelines recommend regarding further testing to distinguish GERD from EoE in equivocal cases?

ED It is a little tricky because typical reflux tests are not recommended for regular use in EoE. A negative reflux test is not needed to diagnose EoE because it is possible to have both EoE and superimposed reflux. I think further testing comes into play when the clinician is having difficulty clinically distinguishing the conditions. An example is a patient who has dysphagia and heartburn and

endoscopically has classic EoE findings but also has a hiatal hernia, although may not have erosive esophagitis and is not responding to PPI or corticosteroid therapy. For this patient, it is important to understand whether the driving factor is reflux or allergy. That may be a time to consider either pH-impedance monitoring performed while the patient is on a PPI or wireless reflux monitoring off the PPI to try to settle the diagnosis.

G&H What might future diagnostic methods to distinguish GERD and EoE entail?

ED There are two methods that might potentially be used, although many are being studied. As I mentioned, staining biopsies for mast cells or for other inflammatory factors related to EoE have been shown to be effective at distinguishing the conditions, and are potentially more accurate than the eosinophil count. Although these tests are not used routinely in clinical practice, they can be an option to consider in particularly difficult cases because most pathology laboratories can stain for mast cells, for example, on request. The EoE Diagnostic Panel (EDP) is a molecular test that analyzes gene expression for EoE-related genes in the esophagus. It has a nearly perfect ability to discriminate EoE and GERD, and although it is not commercially available currently and is mostly used as a research tool, EDP has potential utility in the future.

Disclosures

Dr Dellon has received research funding from Adare/Ellodi Pharmaceuticals, Allakos, Arena Pharmaceuticals/Pfizer, AstraZeneca, Eupraxia Pharmaceuticals, GSK, Meritage Pharma, Miraca Life Sciences, Nutricia, Celgene/Receptos/BMS, Regeneron Pharmaceuticals, Revolo Biotherapeutics, and Shire/Takeda; consulting fees from Abbott Laboratories, AbbVie, Adare/Ellodi Pharmaceuticals, Aimmune Therapeutics, Akesobio, Alfasigma, ALK, Allakos, Amgen, Aqilion, Arena Pharmaceuticals/Pfizer, Aslan Pharmaceuticals, AstraZeneca, Avir Pharma, Biorasi, Calypso Biotech, Celgene/Receptos/BMS, Celldex Therapeutics, Eli Lilly, EsoCap Biotech, Eupraxia Pharmaceuticals, Ferring Pharmaceuticals, GSK, Gossamer Bio, Holoclara, Invea Therapeutics, Knightpoint, Landos Biopharma, Lucid Diagnostics, Morphic Therapeutic, Nexstone Immunology/Uniquity, Nutricia, Parexel/Calyx, Phathom Pharmaceuticals, Regeneron Pharmaceuticals, Revolo Biotherapeutics, Robarts/Alimentiv, Salix Pharmaceuticals, Sanofi, Shire/Takeda, Target RWE, and Upstream Bio; and educational grants from Allakos, Holoclara, and Invea Therapeutics.

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