Summary of presentation

Eosinophilic Esophagitis: From the Bench to the Bedside

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Eosinophilic Esophagitis: From the Bench to the Bedside

Clinical Features of Eosinophilic Gastrointestinal Diseases (EGIDs)

An increasing body of evidence suggests that the eosinophil plays a role in gastrointestinal (GI) diseases. A number of different diseases are associated with eosinophilic inflammation of the gastrointestinal tract, including gastroesophageal reflux disease; eosinophilic gastroenteritis; eosinophilic colitis; eosinophilic ganglionitis; intestinal infections (parasites and fungus); celiac disease; hypereosinophilic syndrome; food or drug hypersensitivity reactions; inflammatory bowel diseases; and transplant-associated eosinophilic enteritis [1]. Since symptoms associated with these diseases are overlapping and common, a mucosal biopsy and other ancillary testing are required to complete a diagnostic evaluation. When diseases such as the more common GERD (abnormal pH monitoring, response to proton pump inhibition), infections (stool cultures, serological testing) and inflammatory bowel diseases (radiographic studies and histological assessment) are ruled out, the diagnosis of EGID can be made.

Incumbent on the physician is the task of determining which part of the GI tract is involved, as this will impact treatment and potentially long-term management. For instance, if the patient is found to have eosinophilic esophagitis (EoE), current experience suggests that esophageal strictures are a potential long-term complication of ongoing inflammation, a risk not typically observed with the mucosal form of eosinophilic gastroenteritis.

During the last 5 years, clinical observations declared the emergence of eosinophilic esophagitis (EoE) as a cause of upper intestinal symptoms that are unresponsive to maximal acid suppression [2]. While the exact diagnostic criteria are still undergoing definition, it is safe to say that EoE is a clinicopathological diagnosis requiring upper intestinal symptoms and an esophageal biopsy that contains large numbers (>20 eosinophils/HPF), both of which are unresponsive to proton pump inhibition. Symptoms associated with EoE include feeding difficulties, vomiting, and abdominal pain in young children and dysphagia and food impaction in adults.

The classic patient is a young male with a history of atopic disease, peripheral eosinophilia and a family history of atopic disease. At endoscopy, the esophageal mucosa can appear normal but usually displays features of acute or chronic inflammation such as longitudinal furrowing, whitish exudates and circular rings [3]. The exudates can be confused with Candida infection or swallowed topical anesthetic spray. The rings can be fixed or transient. The one endoscopic finding that is likely unique to EoE is longitudinal shearing or splitting of the esophageal mucosa following minor trauma such as the passage of the endoscope. Radiographic features include proximal strictures and a small caliber esophagus that represents long segment narrowing. Histological specimens reveal increased numbers of eosinophils,
eosinophilic microabscesses and superficial layering of eosinophils along the esophageal lumen. These features can be seen in the proximal and distal esophagus. Importantly, the stomach and small intestine are normal, showing no evidence of increased eosinophils. The natural history of EoE is unknown but adult studies suggest the possibility of fixed strictures that are unresponsive to medical management.

Pathophysiological Mechanisms of Eosinophilic Esophagitis

The eosinophil is a powerhouse of a leukocyte containing a number of biologically potent mediators [4]. Not only does it store its unique pre-formed granule proteins (major basic protein, eosinophilic cationic protein, eosinophilic-derived neurotoxin and eosinophilic peroxidase), but it also has the capacity to synthesize and secrete proinflammatory cytokines and leukotrienes. Eosinophils are born in the bone marrow under the direction of interleukin-5, interleukin-3 and GM-CSF and when called by chemokines such as eotaxin, eosinophils migrate to the vascular space. When signaled, eosinophils roll, attach, and transmigrate through the endothelium into the mucosal tissues. Upon appropriate stimulation, eosinophils can synthesize and/or release mediators leading to an inflammatory nidus [5].

The pathophysiological mechanism(s) of EoE are presently unknown, but a significant body of clinical and basic evidence suggests that it is driven by an allergic stimulus. Basic studies developed a murine model in which esophageal eosinophilia develops following sensitization and challenge with an ubiquitous aeroallergen, Aspergillus fumigatus [6]. This eosinophilic inflammation is dependent on the Th2-type cytokine, interleukin-5. Further basic studies have demonstrated a role for the Th2-cytokine IL-13. For instance, exogenous IL-13 leads to eosinophilic esophageal inflammation response in mice [7]. Clinical studies show increased expression of IL-5 in affected esophageal tissues and one case report documented the utility of an anti-IL-5 antibody in clinicopathological features of EoE [8,9]. Basic evidence suggests that eosinophil granule proteins induce cytokine production, histamine release, and smooth muscle contraction and alter barrier function [5,10-13]. Taken together, these studies suggest that the eosinophilic inflammation is based in a Th2-type response and begin to explain the effectiveness of anti-allergic treatments.

Treatment of Eosinophilic Gastrointestinal Diseases

After other causes of gastrointestinal eosinophilia have been ruled out (see above), the clinician is faced with a number of treatment options for EGIDs. Below are approaches to treatment based on the published literature and clinical experiences.

Eosinophilic Colitis

In the majority of cases, allergic proctocolitis occurs in infants and toddlers. The treatment revolves around the identification and removal of food antigens [14,15]. Once these foods are eliminated, clinical symptoms and tissue histology improve within 4 to 6 weeks. By 9 to 24 months of age, these foods can be reintroduced without clinical or histologic sequelae.
Eosinophilic Gastroenteritis

First, it is important to assess the severity of the patient’s clinical symptoms. Many patients with this disorder are often quite ill, presenting either with severe weight loss, dehydration, GI bleeding, or ascites. It must be determined whether or not therapy needs to be conducted on an inpatient or an outpatient basis. At times, the best mode of treatment is to hospitalize these patients, make them NPO and provide central hyperalimentation. However, the majority of these patients can be treated as outpatients. In the past, the typical therapies that have been effective include the use of an elemental diet or the use of systemic corticosteroids [16,17]. Less commonly used medications include sodium chromoglycate, antihistamines, leukotriene receptor antagonists and immunosuppressive agents such as Purinethol.

Eosinophilic Esophagitis

Several treatment options are available to patients diagnosed with eosinophilic esophagitis. Currently, most investigators do not believe that esophageal acid exposure is the cause of EoE; however, because of the severity of mucosal and submucosal disease seen in EoE, secondary acid reflux often occurs. Additionally, because there may be some histologic overlap between patients with EoE and those with GERD, it is important to exclude acid reflux as a cause of esophageal inflammation. Therefore, most investigators believe that the initial use of proton pump inhibitors is essential in any patient who has clinical symptoms of EoE so that GERD can be excluded [18]. The diagnosis of EoE cannot be made unless a documented biopsy is performed while the patient is on aggressive acid blockade. If a severe EoE exists despite the use of an aggressive acid blockade, EoE must be considered. Patients with EoE may show partial response to aggressive acid blockade.

Adult gastroenterologists have reported the use of esophageal dilatation for their patients who present with esophageal strictures secondary to EoE [19]. While esophageal dilatation using rigid esophageal dilators can relieve dysphagia, many of these physicians have described esophageal tearing during dilatation. In addition, there have been several reports of esophageal tearing simply with the introduction of the endoscope in patients with EoE. Thus, gastroenterologists should be extremely careful whenever performing endoscopy or dilatation on a patient with EoE as perforation is a distinct possibility.

The first medical treatment that was shown to be effective in improving both symptoms and esophageal histology was systemic steroids [20]. Oral corticosteroids should be used whenever patients have severe dysphagia (with or without strictures) or other clinical symptoms that may be contributing to possible hospitalization because of a feeding disorder, poor weight gain or dehydration. While systemic steroids work rapidly, their disadvantages include that they cannot be used chronically, that they do not cure the disease, and that they often have serious side effects with prolonged use (bone, growth, and mood abnormalities).

Instead of prescribing systemic steroids, topical corticosteroids can be
utilized [21]. These medications, such as fluticasone, can be sprayed in the pharynx and swallowed. Both clinical symptoms and esophageal histology dramatically improve with the use of this therapy. The advantage of using topical steroids is that their side effects are less than that seen with systemic steroids. The disadvantage of using this medication is that it does not treat the disease fully, the disease generally recurs when the treatment is discontinued, and side effects (esophageal candidiasis) may occur with its chronic use. Recently, the use of a swallowed viscous solution containing budesonide has been reported with some effectiveness.

Several other medications have also been used. Some investigators have used cromolyn sodium as an adjunct to therapy for EoE. However, no studies have been conducted to prove its effectiveness. Leukotriene receptor antagonists have also been utilized to treat EoE. Initial doses of 10 to 100 mgs per day have been prescribed with reports of symptomatic improvement; however, on repeat biopsy, there was no significant change in the patient’s esophageal eosinophilia [22]. The advantage of using a leukotriene receptor antagonist is that it has minimal side effects and it may alleviate the patient’s clinical symptoms. However, there have been no reports documenting improvement in the patient’s histology. Additionally, in the majority of patients, both tissue inflammation as well as clinical symptoms recurred when the medication was discontinued.

Dietary therapy either by removing suspected food antigens or by providing the strict use of an amino acid-based formula has been shown to significantly improve both the clinical symptoms and the esophageal histology [23-25]. Two types of diets have been tried: 1) the elimination diet (removal of specific food antigens by utilizing clinical history and allergy testing); 2) strict elemental diet utilizing an amino acid-based formula. Because of the inaccuracies of present day allergy testing and the difficulties of obtaining a perfect dietary history, elimination diets are often not successful. In contrast, several investigators have demonstrated greater than a 98% clinical and histologic response with the strict use of an elemental diet. Once the diet is initiated, the patient’s clinical symptoms improve within ten days and the tissue histology normalizes within one month.

Finally, there have been reports of the development of other medications that will target specific chemokines and other inflammatory mediators that are involved in the activation of the eosinophil. Medications such as anti-interleukin-5, very late activating antigen, and monoclonal eotaxin antibody may benefit those patients who have severe EoE [26]. Drs. Ngo and Furuta have recently written a summary of the currently accepted medical treatments for EoE [27].

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References


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