MINI-REVIEW

Eosinophilic Esophagitis: A Brief Review

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Abstract
Eosinophilic esophagitis (EoE) is an emerging disease. It is defined as a chronic hypersensitivity disease characterized by localized inflammation of the esophagus. Here we present a focused summary of current medical understanding of the disease, including the diagnostic criteria, management approaches and future directions of research.

Key words: Eosinophilic esophagitis, Chronic hypersensitivity, Disease pattern.

Introduction

Eosinophilic esophagitis (EoE) is an emerging world whide disease (1). Eosinophilic esophagitis was not accepted as a disease in its own right until fairly recently, around the mid-1990s. As such, it is often misdiagnosed and its pathophysiology is largely unknown. However, EoE has been thrust into the spotlight in recent years, as its incidence and prevalence have been on the rise. The estimated cost of treating the illness in the United States is $1.4 billion annually – an unusually high figure for a disease that entered mainstream medical discussions only twenty years ago (1).

This mini-review will attempt to summarize current understanding of eosinophilic esophagitis from a medical professionals' standpoint, as well as identify contemporary pillars of treatment and highlight the frontiers of research into this challenging and poorly understood condition.

Definition

EoE is clinicopathologic diagnosis that describes a localized eosinophilic inflammation of the esophagus. Typically regarded as a chronic immune/hypersensitivity disease, eosinophilic esophagitis may manifest in a variety of ways.

Table 1. The revised diagnostic criteria of eosinophilic esophagitis.
1. Symptoms of esophageal dysfunction.
2. Eosinophilic inflammation localized to the esophagus, both by a) endoscopy (furrowing, edema, erythema, and in some cases, ulceration illustrated in figure 1) and by b) biopsy (defined as esophageal mucosal biopsy specimens with at least 15 eosinophils/high power field or 15/high power field as illustrated in figure 2).
3. Exclusion of other causes of eosinophil proliferation in the esophagus, including eosinophilia that responds to proton-pump inhibitor (PPI) therapy.

Diagnosis

Consensus guidelines for the diagnosis of eosinophilic esophagitis were first published in 2007, with revision in 2011 and 2013 (2). The presence of eosinophils in the esophagus, while not a finding of normal mucosa, is not pathognomonic for EoE because other disorders (including Gastro-esophageal Reflux Disease or GERD, achalasia, reactive esophagitis, and parasitic infections) are known causes of mucosal eosinophilia.

A combination of clinical/endoscopic and histologic evidence is used to arrive at a diagnosis of eosinophilic esophagitis. The Diagnostic criteria are given in Table 1. The last criterion requires that patients be given a clinical trial of PPIs and fail that trial in order to be diagnosed with EoE. Proton pump inhibitor-responsive eosinophilic esophagitis (PPI-REE) is thought of as a disease entity in its own right. However, it remains unknown whether PPI-REE truly represents a distinct disease, whether it belongs on the spectrum with eosinophilic esophagitis, or whether it is a variant of GERD.

Some clinicians and researchers have even speculated that PPIs themselves may be effective in mitigating inflammation via some as-yet unknown mechanism, and thus may be a therapy in their own right for mild cases of EoE (3). This gap in understanding is reflective of the reality that a great deal of research on the pathophysiology of eosinophilic esophagitis remains unfinished.

Clinical Features

While no clinical features are both highly sensitive and specific for the illness, a number of symptoms signify the strong possibility of eosinophilic esophagitis. The differences in presentation can be quite striking between adult and pediatric patients. In adults, these symptoms include dysphagia/food impaction and reflux refractory to conventional medical management. In fact, an estimated 8% of patients reporting refractory heartburn are believed to have EoE (2). Furthermore, "behaviors associated with dysphagia", such as requiring large quantities of water to swallow a food bolus, may also suggest EoE. A good history will include questions about these behaviors.

In children the picture of eosinophilic esophagitis is somewhat different. Children tend to exhibit feeding intolerance, epigastric pain, and vomiting; they may also demonstrate dysphagia and food impaction. Interestingly, in children with EoE who do have dysphagia, it is often out of proportion to radiologic findings and upper endoscopy is usually normal (4). Therefore, a strong index of suspicion is necessary to make the diagnosis. In severe cases, and particularly in low-socioeconomic subgroups, EoE affected children may have failure to thrive.

Endoscopic Findings

Certain other features are common in EoE patients. On endoscopy, patients with eosinophilic esophagitis may be shown to have fixed esophageal rings (also called trachealization, i.e. mimicking the rings of the trachea), transient esophageal rings, whitish exudates, longitudinal furrows, and a narrow-caliber esophagus (Figure 1). According to one study, only 8.8% of adult eosinophilic esophagitis patients will have a normal-appearing esophagus on endoscopy (5, 6). In addition, endoscopic ultrasound in EoE patients reveals thickening of the esophageal wall, including the muscle layer – a finding that may account for dysphagia (2).

Pathologic Findings

Along with clinical and radiologic features, histopathology is the main tool for confirming the diagnosis of EoE. Currently, all patients must undergo endoscopy with biopsy in order to establish the diagnosis. Two to four biopsy specimens should be collected from at least two separate locations in the

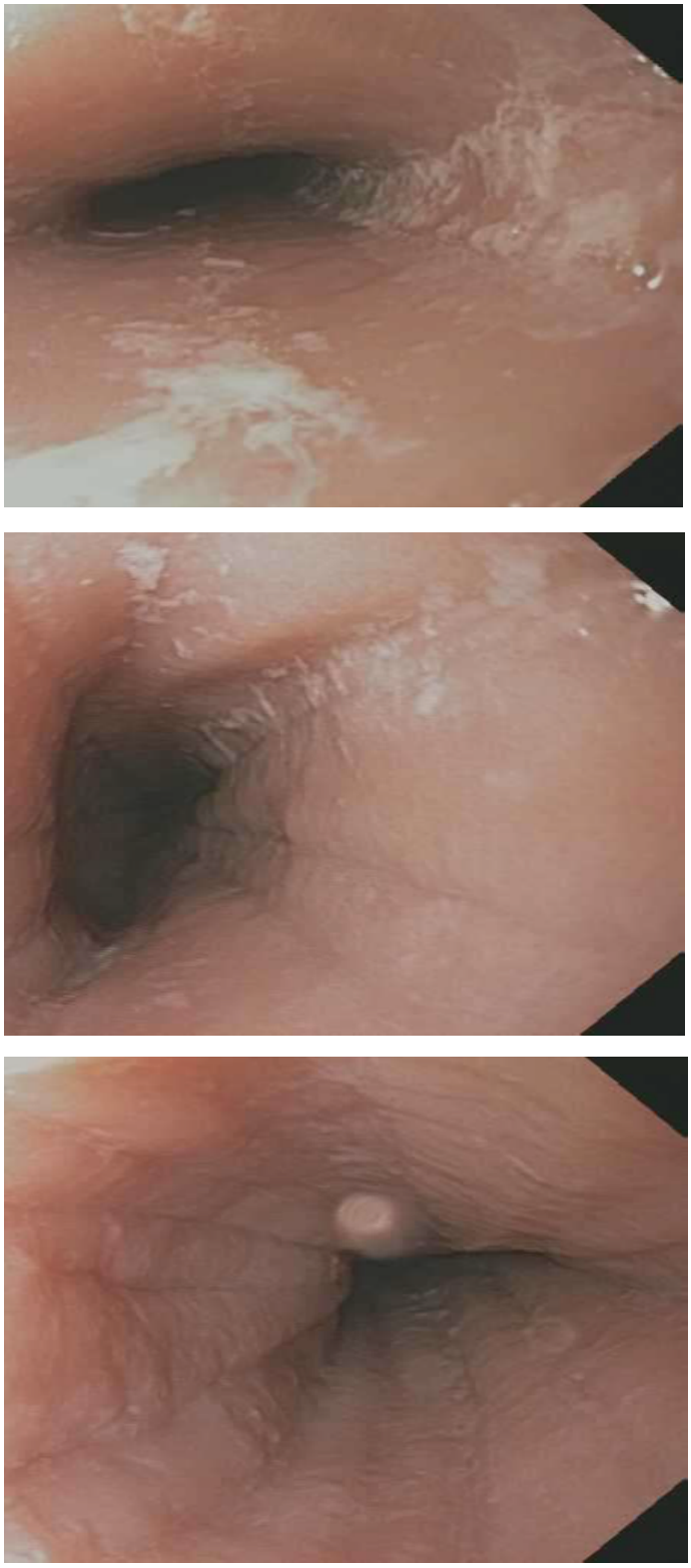

Figure 1. Classic features of eosinophilic esophagitis on endoscopy: whitish exudates (upper), linear furrowing (middle and lower), and edema with narrowing of the esophageal lumen (lower).

esophagus, which the guidelines recommend to be in the distal and mid-esophagus. In the proper clinical context, the pathologic finding of 15 or more eosinophils per high power fields in the esophageal mucosa support the diagnosis of EoE (Figure 2). The convention is to report the peak number of eosinophils per high power field rather than the average from all fields (2).

At present, this pathologic definition is based on expert consensus rather than any randomized controlled trial. Other exam findings correlated with eosinophilic esophagitis include histologic evidence of eosinophilic micro-abscesses (aggregates of three or more eosinophils on the surface epithelium), esophageal manometry studies demonstrating decreased motility, and peripheral eosinophilia, which is found in 40-50% of patients (5).

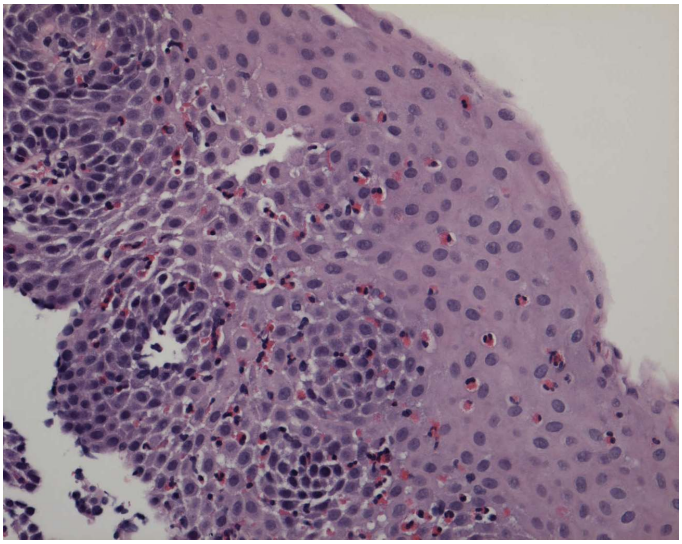

Figure 2. Photomicrograph of Esophageal mucosa showing infiltrates of eosinophils (more than 30/high power fields) which is a strong evidence of EoE diagnosis (H&E stain, 40X magnification).

Possible Causes and Etiology

Much has been made of eosinophilic esophagitis as an allergic condition characterized by an antigen-mediated response (7). Some proposed models of molecular pathogenesis in EoE will be discussed later in this review. However, it should be noted that eosinophilic esophagitis occurs in patients with other atopic diseases at a higher rate than in the general population. An estimated 30-50% of children with EoE also have asthma, while 50-75% have allergic rhinitis (in American children as a whole these figures are 10% and 30%, respectively) (8). Additionally, 10-20% of children with

EoE have food allergies, and the seasonal pattern of EoE-related medical visits parallels that of environmental allergies (7). In adults affected by EoE these numbers do not appear to be as dramatic, but atopy is still more prevalent than in the general population. In one study, 18 of 23 EoE patients (78%) had other atopic tendencies but no large scale surveys have been done to establish such a high figure (9).

In line with the trends in other atopic conditions, particularly allergies, the incidence and prevalence of eosinophilic esophagitis have been rising over the past two decades. While greater awareness and thus increased identification is partly responsible, it was demonstrated in a recent study Switzerland that the increased number of documented cases locally did indeed represent a true increase in the population of EoE patients and was not simply a result of heightened sensitivity to diagnosis (5).

The current incidence of EoE is 1 case per 10,000 per year (2). An estimated 40 to 55 individuals per 100,000 are believed to be affected by EoE, which is roughly the same prevalence as Crohn's disease (5). Men are affected three times as often as women and Caucasians more often than any other ethnic group. As with other atopic conditions, the frequency of disease is higher in cold and arid zones. Additionally, its incidence is higher in urban environments than in rural parts (10).

Management

The mainstays of eosinophilic esophagitis management are diet modification and corticosteroid therapy. Food elimination diets constitute the first main category of eosinophilic esophagitis treatment described here. EoE has been associated with food allergies since its initial description, and elimination diets seek to withdraw the inciting agent for the eosinophilic reaction. The single most effective therapy for EoE is switching the patient to a pure-liquid, elemental, amino acid formula diet (6). Some studies have reported histological evidence for disease regression in as many as 94% of treated patients (6).

Realistically, however, the long-term maintenance of such an extreme diet is infeasible considering its impracticality, high cost, and unsavory taste. The ideal dietary treatment would involve identifying the trigger(s) for EoE and eliminating them from consumption. Skin Allergen Testing-directed therapy has been by and large unsuccessful; thus, patients are usually treated with 6-food or 4-food elimination diets (SFED and FFED, respectively). The SFED targets the foods most commonly associated with food allergies in children: milk protein, soy, eggs, wheat, peanuts, and seafood. In one study, 26 of 35 children (74%) showed complete remission via endoscopic biopsy-evidence after being treated with SFED for 6 weeks (6). A subsequent study on European adults revealed histological remission in 73% of subjects, with all reporting symptomatic improvement while following the diet (6). The less strict FFED forbids eggs, gluten, milk protein, and legumes. This very recent strategy was proposed as an easier alternative that may increase patient compliance. Early results have shown promise, with 57% of patients achieving histologic remission. Interestingly, when non-responding patients were offered SFED as a rescue therapy, the total percentage of responders jumped to 88% (6).

The primary drawback of dietary elimination is long-term compliance. To counter this, some EoE specialists have developed a strategy of food elimination, followed by single food reintroduction and response-monitoring (2, 6). For instance, a patient may be started on SFED, and then once he/she has achieved remission, be reintroduced to eggs, undergo biopsy to look for evidence of disease recurrence, and if none is present, be reintroduced to the next potential food trigger, and so on.

Corticosteroid therapy works by modulating the inflammatory response, thereby suppressing the number of eosinophils in the esophagus. Both systemic and local steroid therapy have been shown to be effective, and equally so, with symptomatic and histologic evidence of improvement in 95% of patients (2).

However, local treatment is preferred as first line therapy due to its much lower adverse effect profile. Topical steroid preparations for the esophagus come in a variety of forms, including oral viscous, nebulized, and large-particle nebulized. Of these, the nebulized form is most frequently used, and comes packaged as a traditional inhaler resembling that used in asthmatics and chronic obstructive pulmonary disease patients. EoE patients are instructed to spray the inhaler directly into their mouths and then swallow the medication. This can be awkward and difficult to accomplish, so true compliance is unknown and certainly sub-optimal. Moreover, oral

viscous budesonide treatment has been shown to be the most effective out of these preparations, with large-particle nebulized treatment coming in second place (8). These preparations are scarcely available at the present time. But with current trends in EoE diagnosis, oral viscous corticosteroid treatment in particular will likely become widely accepted and implemented.

Finally, in cases of advanced eosinophilic esophagitis, patients are often treated with balloon dilation to relieve constriction. Dilation results in symptom improvement for 92% of patients and relieves dysphagia for 20-23 months on average (8). For long term management, the ideal care of an EoE patient would be handled by a multidisciplinary team composed of allergists, gastroenterologists, pathologists, and dieticians (8).

Future Research Directions

Even when the knowledge from all aforementioned subspecialties is compiled, our understanding of EoE remains incomplete. What we do know is that eosinophilic esophagitis is an immune, antigen-mediated disease whereby food or environmental antigens stimulate an inflammatory response. This response takes the form of eosinophilic infiltration, and by some unknown mechanism, local tissue damage and fibrosis (3).

Research is mostly aimed at uncovering the molecular pathogenesis of EoE in order to devise more effective therapies. A more complete picture of pathogenesis will also make clear the true definition of eosinophilic esophagitis, which is currently based on expert opinion alone, and almost certainly enables false positive and true negative diagnoses. Furthermore, a detailed pathogenesis may shed light on the reason for EoE's increased incidence. Eotaxin-3, also known as CCL26, is a chemokine associated with antigen-mediated eosinophil recruitment. Overexpression of the gene for eotaxin-3 has been linked with EoE more strongly than any other genetic abnormality (11). A diagnostic method that relies on measuring cytokine mRNA expression from biopsy specimens may lead to greater sensitivity for the diagnosis of eosinophilic esophagitis.

It has been proven that EoE, like many eosinophilic diseases, has a predominantly Th2 type immune response. The roles of individual cytokines and other cell signaling molecules in this response are currently the subject of intense research. Interleukin (IL)-13 and IL-5 are both known to regulate EoE. Some ongoing clinical trials are evaluating the effectiveness at anti-IL-13 therapy as a potential treatment. Isolated IL-5 blockade has previously been shown to be ineffective (3).

Another area of research is on the pathogenesis of esophageal tissue remodeling, which leads to the fibrosis and strictures observed in patients. One current hypothesis argues that the proliferation of inflammatory cells causes production of tumor growth factor (TGF)-B1 to skyrocket, which in turn induces transformation of the epithelium (3). This is of course a gradual process. Children with EoE do not outgrow the disease, which, if the hypothesis is true, may explain why adults tend to present more often with dysphagia and pediatric patients more often with chest pain and reflux symptoms.

Concluding Remarks

In summary, eosinophilic esophagitis is an allergic/immune disease of the gastrointestinal tract with a rising global incidence. Revealing the molecular physiology of the disease will lead to the development of more sophisticated and effective therapies for EoE patients. Until then, EoE is best managed by a multidisciplinary team including gastroenterologists, allergists, and pathologists.

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