

Gastrointestinal Eosinophil-Mediated Disorders and Their Treatment

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Eosinophilic esophagitis has become a diagnosis familiar to allergists and immunologists who treat pediatric patients presenting with complaints of recurrent vomiting, feeding difficulty, abdominal pain, dysphagia, and food impaction. Over the past 3 years, published research has addressed several clinically important issues, including incidence among special patient populations, adult patients and familial cases, diagnostic features, natural history and complications, therapies with topical steroids, and pathogenesis with distinct genetic markers of the disorder.

Introduction

Although eosinophilic gastrointestinal diseases, including gastroenteritis and colitis, have been studied for a long time, the clinical entity of eosinophilic esophagitis (EE) has taken center stage. It has been the subject of many reviews and research studies. In fact, the number of reviews written about EE exceeded the number of publications of original research until late in 2007 and early 2008, when a wealth of relevant original research was published. Allergists/immunologists and gastroenterologists have remained the main players, with valuable contributions coming from pathologists and radiologists. A collaborative group of clinical physicians and researchers has been formed, and a systematic review and consensus recommendations for diagnosis and treatment have been published [1•]. Parental support groups also have emerged rapidly and became driving forces in raising research funds and pushing for recognition of the disorder by national organizations and government authorities regulating clinicopathologic coding. Although

most reports had described EE in pediatrics, more published reports are examining the disorder in adults in an attempt to unravel the natural history. Because atopy has been associated with this disorder, several procedures conducted by allergists/immunologists have become an integral part of evaluating patients with EE, generating knowledge on the phenotype.

Several questions have been posed and debated, and although no definitive answers have emerged, practitioners have started to develop their own approaches based on a synthesis of the varied opinions expressed by researchers and clinicians in the field. The most frequently pondered questions have been the following: is this a new disorder, or have we missed it in the past? Now that we recognize the disorder, is it increasing in incidence to the point of becoming an epidemic, or is the incidence rather stable? Although these questions parallel a similar question regarding an increase in atopic disorders in general and are asked in search of an etiology, other questions about the diagnosis' validity seem more relevant. Mainly, a question of the differentiation from, and overlap with, gastroesophageal reflux disease is frequently asked: is this the other end of the spectrum of gastroesophageal reflux disease or a separate disorder? The frequent coexistence of atopy has raised the question of whether ingested and inhaled allergens should be sought out. If yes, which test is most predictive of a role for the identified allergen in the disorder? The occurrence of the disorder in several generations of families and its diagnosis in very young infants has raised this question: is there a genetic basis for the disorder? If yes, what is the mechanism by which this gene causes or influences the disorder? Finally, without definitive answers to the above questions, can we present well-studied diagnostic and therapeutic modalities to patients and advise them on the prospects of cure or control of the disorder?

This review highlights the most recent publications to address the above questions and suggests an approach to practicing allergists/immunologists.

Is This a New Disorder, or Have We Missed It in the Past?

In 2004, Noel et al. [2] calculated the incidence of EE in children 0 to 19 years of age in Hamilton County, Ohio,

from 2000 to 2003. The number of cases was 22, 24, 24, and 31 in each of the 4 consecutive years. The cumulative prevalence was 4.296 per 10,000 children.

Four new publications in 2007 addressed the same question. Gill et al. [3] reviewed pathology specimens from esophageal biopsies over 10 years (1995–2004) in West Virginia and found only 44 cases of EE during that period. They calculated the cumulative prevalence at 0.73 per 10,000 children, much lower than the Noel et al. [2] estimate.

Wang et al. [4] conducted a retrospective review of the cases of EE seen at Riley Hospital in Indianapolis, Indiana, over 6 years (1998–2004). They found 234 children with the diagnosis. Although they did not specifically report an annual incidence, dividing 234 by 6 years gives a rough incidence of 39 cases per year.

Vanderheyden et al. [5] reviewed all the pathology specimens obtained in Iowa University Hospital from the esophagi of patients of all ages, excluding cases of cancer and Barrett's metaplasia, and compared two groups 15 years apart. They found 7% cases of EE—defined as more than 20 eosinophils per high-power field (HPF)—of 115 and 150 biopsies in 1990 and 2005, respectively.

Globally, Martin de Carpi et al. [6] reported approximately 11 cases of EE diagnosed in Spain over a 6-year period (1997–2003), with characteristics very similar to the cases reported from the United States.

From these results, it seems that the findings of EE in esophageal biopsies did not increase over time; however, recognition of the disorder as a separate entity from reflux-related eosinophilic infiltration of the esophagus is the novelty in the current era.

Is This the Other End of the Spectrum of Gastroesophageal Reflux Disease or a Separate Disorder?

At the heart of this debate is the question of how many eosinophils per HPF in an esophageal biopsy constitute EE. Then, after the diagnosis is made, how many eosinophils per HPF constitute resolution and cure? A thorough review of the FIGERS (First International Gastrointestinal Eosinophilic Research Symposium) group and its results published in the consensus report clearly indicated that the number of eosinophils in a biopsy is not to be taken in isolation of the global assessment of the status of the esophagus. This is to include the visual inspection during endoscopy and the number of biopsies taken, with a larger number of biopsies correlating with a higher degree of accuracy in the diagnosis. Clinicians should search for other features of the histopathology, namely basal zone hyperplasia, superficial layering of the eosinophils, and eosinophilic abscesses, in addition to a count of more than 15 eosinophils per HPF [1•]. EE and gastroesophageal reflux disease have common

symptoms, and both include the presence of eosinophils on the histopathology of the esophagus; therefore, it has become a common clinical practice to initiate treatment with proton pump inhibitors for 2 to 3 months, followed by esophagogastroduodenoscopy. A complete resolution of the histopathologic findings, including a return of the number of eosinophils to baseline, should be the goal. Studies that have evaluated a response to endoscopic treatment have adhered to the stringent criterion of return of the number of eosinophils per HPF to 0 or 1 [7•].

Should Ingested and Inhaled Allergens Be Sought Out?

Previously published data have clearly demonstrated that sensitization to foods and environmental allergens is more common in pediatric patients diagnosed with EE than in the general pediatric population [8]. The same relationship was recently addressed in a case series of adults with EE consisting of 16 men and 7 women with a median age of 34 years (range, 18–57 years) [9]. Eighteen of 23 had an atopic diathesis, with allergic rhinitis being the most common. Seventeen of 21 patients tested were sensitized to environmental allergens, and 19 of 23 (82%) had serum IgE specific for one or more food-associated allergens (median, five foods), with wheat, tomato, carrot, and onion identified most commonly. Of note, this list of food sensitization is quite different from the most common food sensitizations seen in the pediatric population.

How Often Is the Diagnosis Made in the Presence of the Characteristic Symptom?

This is a very important question, as physicians are often presented with symptoms rather than a diagnosis. The symptoms of EE in young pediatric patients are nonspecific, so designing a study that looks at the diagnostic yield of an esophageal biopsy in children with the symptom of vomiting would be difficult. Pentiuk et al. [10] found 15 patients who were diagnosed with EE among infants and toddlers referred to a feeding team over 3.5 years (1999–2003). The main symptom of EE in adults is dysphagia. Kerlin et al. [11] reported the results of the esophageal biopsies of 29 adults who presented with acute food impaction and found that half qualified for a diagnosis of EE, whereas the other half had peptic esophagitis. Whereas Lee et al. [12] found that 50% of the 32 patients with the symptom of intermittent dysphagia and who underwent dilation between 1989 and 2004 had EE, Byrne et al. [13] found EE to be the cause of food impaction in only 9 of 75 (12%) patients aged 18 to 100 years. In a prospective study, Prasad et al. [14] found EE in 33 of 222 (15%) patients with dysphagia.

Once Diagnosed, What Is the Best Course of Treatment? Does It Vary Between Adult and Pediatric Patients?

Adult patients

Dilatation

There are no systematic studies of treatment for EE in adults. The presenting symptom of dysphagia has been classically treated with esophageal dilatation or bougienage.

Schoepfer and colleagues [15] presented a retrospective analysis of 10 adult patients with EE who had symptomatic esophageal stenosis unresponsive to topical corticosteroids and who were treated with bougienage. Eight patients had one single stricture, one patient had two, and another had three; mean stricture length was 2.1 cm (range, 1–6 cm). Bougienage led to prompt symptom relief. Apart from transient postprocedural odynophagia, no severe complications occurred. During the follow-up (mean, 6 months; range, 2–11 months), all patients enjoyed sustained treatment response.

Pediatric patients

Steroids: oral and topical

Although topical steroids administered to the esophagus by swallowing puffs from a metered-dose inhaler gained a place in the treatment of EE after a placebo-controlled study was published [7•], a new study compared the previous therapy with oral steroids in a randomized design. The therapies, prednisone or fluticasone (puffed and swallowed), were given for 4 weeks, followed by an 8-week weaning protocol. Esophageal histology was evaluated at baseline and after 4 weeks of therapy, and clinical assessments were performed for up to 24 weeks. Histologic improvement and resolution of the presenting symptoms were seen at almost the same rate with both treatments. However, a high rate of symptom relapse was observed in 45% of patients by week 24, highlighting the need for maintenance treatment protocols [16]. Another retrospective analysis of symptoms, endoscopic and histologic findings, efficacy, and safety of treatment in children with EE demonstrated the beneficial effect of another form of topical steroids—budesonide solution mixed in Splenda (McNeil Nutritionals, Fort Washington, PA) to a consistency of a slurry, termed *oral viscous budesonide*—in the treatment of EE in children. This can be used to treat children who may not be able to receive the inhaled steroid from a metered-dose inhaler [17].

Familial Occurrence

Many clinicians have found family histories of EE. A small case series of seven families showed that EE spanned two generations in four families and involved two brothers in one family [18]. Recently, a larger study that included histologic evidence of EE (threshold peak number ≥ 24 eosinophils/HPF) reported on 59 members (41 males, 18 females) of 26 families. The family mem-

bers were 3 months to 47 years of age (mean age, 10.3 years) at diagnosis and were all white. Familial EE characteristics—clinical, endoscopic, pathologic, and global esophageal transcript expression profile analysis—were similar to those of sporadic EE. Using genome-wide microarray analysis, no significant differences were observed in the genetics between familial and sporadic EE. The diagnosis therefore should be considered in symptomatic family members of patients who have EE [19•].

Complications

The natural history of EE has been described as one with periods of resolution followed by relapses. However, there is no clear estimate of the rate of complications from EE on prolonged follow-up. Straumann et al. [20] examined the Swiss Esophageal Esophagitis Database and documented 251 confirmed cases of EE. A chart review identified which patients had required endoscopic bolus removal and/or experienced transmural esophageal perforation/rupture [20]. They reported that during an 18-year period, 87 patients (34.7%) experienced 134 food impactions, which were removed by flexible endoscopy in 92.5% and by rigid endoscopy in others. The latter procedure was associated with transmural perforation in 2 of 10 patients and with one esophageal rupture. Another study, by Chehade and colleagues [21•], demonstrated a 57% occurrence of esophageal subepithelial fibrosis among 21 patients with EE and the correlation of symptoms of dysphagia and food impactions with fibrosis. Fibrosis was not associated with duration of symptoms or increasing numbers of infiltrating eosinophils/mast cells, but it was associated with eosinophil degranulation. Taken together, the above studies strongly suggest that close follow-up and continued therapy for EE may be necessary to prevent complications.

Genetics

In EE patients, Blanchard et al. [22•] initially showed that the gene encoding the eosinophil-specific chemoattractant eotaxin-3 (*CCL26*) is the most highly induced gene compared with its expression level in healthy individuals. They also showed that esophageal eotaxin-3 mRNA and protein levels strongly correlate with tissue eosinophilia and mastocytosis. These results implicated eotaxin-3 as a critical effector molecule for EE. Subsequently, the same group showed that the interleukin (IL)-13 mRNA level was increased 16-fold in esophageal biopsy specimens from patients with EE compared with those from healthy individuals. Also, esophageal epithelial cells markedly produced eotaxin-3 after IL-13 stimulation through a transcriptional mechanism dependent on signal transducer and activator of transcription 6 [23]. Increased IL-13 mRNA levels and the EE transcriptome were largely reversible with glucocorticoid treatment in vivo.

Conclusions

Much progress toward a better delineation of the clinical entity of EE has been made over the past 3 years. Future directions of research will include an understanding of the remodeling of the esophagus that may lead to complications of EE, treatments for the patients who do not respond to current treatment or who experience the commonly observed recurrence or relapse, and novel therapies based on our understanding of the pathogenesis of the disorder and its genetic basis.

Disclosure

No potential conflict of interest relevant to this article was reported.

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