ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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The Epidemiology and Characteristics of Eosinophilic Esophagitis

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G&H When was eosinophilic esophagitis first reported, and what did these first reports describe?

PB This is a difficult question to answer confidently. The most likely answer is that eosinophilic esophagitis (EoE) was first described in the 1970s in adults with dysphagia and esophageal rings. Several subsequent reports in the 1980s and 1990s described patients with multiple esophageal rings with or without a narrow-caliber esophagus, findings that were believed to be congenital or related to gastroesophageal reflux disease (GERD). Histologic evidence of esophageal eosinophilia in association with these features was reported by the late 1970s and early 1980s. Thus, esophageal eosinophilia with dysphagia and multiple-ringed esophagus were reported in parallel. By the late 1990s, it became apparent that these 2 disorders were related and likely the same entity. In children, the disorder was recognized as being distinct from GERD in the mid-1990s by its responsiveness to an amino acid–based formula.

Interestingly, the characteristic finding of esophageal rings in patients with EoE provides indirect evidence that the disease had its onset sometime in the 1950s or 1960s. This estimate assumes that there is a 10- to 15-year latency period from disease onset to the development of the ringed esophagus. Multiple rings were not described in earlier literature of patients undergoing barium radiography for dysphagia. The majority of such patients had peptic strictures or other anatomic causes of dysphagia.

G&H What is the current understanding of the characteristics of EoE?

PB A complete picture of EoE is still evolving. The very name of the disease includes its hallmark feature, esophageal eosinophilia. However, the presence of esophageal eosinophilia is insufficient as a defining feature because it can be seen in a variety of disorders. An accumulation of mast cells also is invariably present (although it is more difficult to observe); thus, the disease could just as well have been labeled mast-cell esophagitis. As a result, EoE has been considered a clinicopathologic diagnosis.

However, it has been a challenge to define the clinical and histologic features that establish an unequivocal diagnosis. This is an area in which there has been much progress in the last decade. Consensus definitions of the disease require that the diagnosis be established only in patients with compatible clinical features and persistent esophageal eosinophilia despite treatment with a proton pump inhibitor (PPI). The requirement of an incomplete response to a PPI stems from the recognition that a subset of patients has clinical and histologic features that resemble EoE but respond entirely to treatment with a PPI. Controversy remains as to what threshold of residual esophageal eosinophilia is sufficient after treatment with a PPI to establish the diagnosis of EoE. The current consensus (a peak eosinophil count of ≥15 eosinophils per high-power field) may not prove to be optimal because it is possible that treatment for EoE may also be helpful in patients with lesser degrees of esophageal eosinophilia. Ongoing studies will help clarify this issue.

It is possible that EoE represents a heterogenous disorder with various pathways leading to a similar phenotype. As a result, the response to treatment may become a defining characteristic of the disease. The allergic underpinnings of the disease have been increasingly appreciated in the past decade, with growing evidence in adults and children that the disorder can respond to elimination of food allergens. Thus, a clinical and histologic response to an elimination diet (with the gold standard being an elemental diet) may prove to be a defining characteristic of the disease. On the other hand, such a definition is clinically impractical and somewhat circular. Furthermore, it is unclear if all patients respond to an elimination diet.

There has also been tremendous progress in characterizing the disorder on a genetic and molecular level. Indeed, a gene array profile may prove to be clinically useful for diagnosis of the disorder. Emerging data have demonstrated that such profiling can distinguish patients with EoE from healthy controls and those with GERD while also helping to forecast responsiveness to treatment.

G&H What are the etiology and pathogenesis of EoE?

PB The etiology and pathogenesis of EoE remain incompletely understood. Although the immunology of EoE has been revealed with increasing detail, the cause of EoE remains uncertain. Patients with EoE are more likely than controls to have a family history of the condition, be male and white, and have a history of allergies, but none of these characteristics alone or in combination predicts a substantially elevated risk of EoE.

As noted earlier, many patients respond to elimination of certain foods. Wheat, dairy, and, to a lesser extent, eggs and soy are often implicated. A relationship to food allergies has been most persuasively demonstrated by a clinical and histologic response to an elemental diet. An unanswered question is how such patients became allergic to these foods in the first place. There are many theories, but none has been proven. A related question is why certain patients who appear to have EoE phenotypically respond to a PPI alone. Although it is tempting to attribute the response to pathologic esophageal acid exposure, PPI-responsive eosinophilia likely has more complex underpinnings.

Furthermore, the extent to which food allergies are responsible for EoE remains unclear. Some experts believe that all patients with EoE would respond to an elemental diet, thereby proving that EoE is caused by food allergies, although, as of yet, there are inadequate data to confirm such a view. Even if this were the case, it does not necessarily reveal the mechanistic etiology of the disorder. For example, some patients with EoE related to milk allergy can tolerate milk in baked foods, suggesting that food processing may be important. Similarly, seasonal variation in the incidence of EoE suggests that aeroallergens may be important in modifying disease expression. Elimination of major food groups, such as wheat and dairy, also means the elimination of various other substances that are ingested along with them, which may confound the observed association. Finally, EoE has developed in patients undergoing oral immunotherapy for pollen allergy, suggesting that foods are not the only cause.

G&H Does the recent escalation in EoE diagnosis reflect a true emerging epidemic of a new disease, or is it due to increased physician recognition or misclassification with GERD?

PB Interpretation of the literature examining the epidemiology of EoE requires careful attention to how cases were classified and how they were identified. As described above, the definition of EoE has evolved over time to its current consensus definition, which requires a threshold level of residual esophageal eosinophilia despite treatment with a PPI. Not all epidemiologic studies use such a definition; thus, these cases have not been identified using methods that readily permit direct comparisons across studies. The available data have focused on populations of patients who were identified in various ways, further complicating comparisons. For example, some focused on patients undergoing upper endoscopy, whereas others examined pathology databases.

Despite these limitations, there are a few studies that have focused on well-defined populations and used consistent methods to identify patients with presumed EoE over time. These observations suggest that the disease burden related to EoE is increasing and cannot be fully explained by increased recognition or misclassification with other disorders, such as GERD. One such report from the United States estimated the incidence of EoE to be 9.45 per 100,000 person-years between 2001 and 2005, a rate that demonstrated a steady increase from earlier years. The prevalence of EoE was estimated to be 55 per 100,000 persons in 2006. A later study from the United States reported a nearly identical prevalence of 56.7 per 100,000 persons. A rising incidence over 20 years was also reported in adults in Switzerland, and a meta-analysis of 25 studies in children also found an increasing incidence (ranging from 0.7 to 10 per 100,000 person-years). On the other hand, a rising incidence has not been confirmed in all studies, and some have suggested that there is regional variability in disease burden within the United States. Thus, we do not have a full picture of the epidemiology of EoE. Reports from outside of the United States have also demonstrated wide variations in disease burden, possibly providing insights into the pathogenesis of this disorder.

G&H What then is the relationship between EoE and GERD?

PB The relationship between EoE and GERD is complex, and our understanding is still evolving. Several possible associations have been proposed. One theory is that GERD leads to mucosal injury that could predispose patients to EoE. By contrast, it is also possible that EoE predisposes patients to GERD, possibly because of esophageal dysmotility, impaired acid clearance, or hormonal mechanisms. Interestingly, celiac disease, another disorder related to food allergy and possibly EoE, is associated with esophagitis that responds to a gluten-free diet. Thus, it is possible that food allergies predispose patients to EoE and GERD. Yet another theory suggests that treatment of GERD with antisecretory agents predisposes patients to EoE, possibly by prolonging the exposure of patients to labile food proteins and increasing the chance of sensitization.

PPI response in patients who appear phenotypically identical to those with EoE adds to the puzzle. Although it is possible that such patients have GERD and not EoE, it is also possible that such patients have underlying EoE that is exacerbated by esophageal acid exposure and is correspondingly improved with acid suppression. PPIs also impair exotoxin 3 expression, a potent stimulator of eosinophil recruitment, suggesting that the observed benefit might be related to an immunomodulator effect rather than an antisecretory effect.

In principle, the requirement that EoE be diagnosed only after a therapeutic trial of a PPI provides a clinically practical way to distinguish GERD or PPI-responsive esophageal eosinophilia from EoE. Still, GERD is common, making it likely that some patients have both disorders. EoE does not appear to be a common diagnosis in patients with PPI-refractory GERD.

Interestingly, there is no reference standard for establishing the diagnosis of GERD in patients with EoE. Histology is insufficient for distinguishing GERD from EoE because the histologic findings are similar. In some reports, patients with EoE were more likely to have a greater density of eosinophils, more microabscesses, a more prominent layer of eosinophils on the mucosal surface, and more basal cell hyperplasia. However, none of these features alone or in combination reliably distinguishes GERD from PPI-responsive esophageal eosinophilia. The distribution of eosinophils has been helpful in some studies (more likely to be GERD if eosinophils predominate in the distal compared with the proximal esophagus), but such a pattern of distribution is insufficiently specific to make a confident distinction. Traditional criteria defining pathologic reflux on ambulatory pH studies may not be applicable to patients with concomitant EoE in whom esophageal inflammation may create increased sensitivity to even physiologic esophageal acid exposure.

Because of the above considerations, some practitioners continue a PPI in patients with established EoE. In some cases, PPI therapy is used in the hope of improving symptoms in patients who are not on EoE-specific therapy, whereas in other cases, PPI therapy is used as cotherapy with dietary or pharmacologic treatment for EoE.

G&H What are the next steps of research in this area?

PB There are several areas of ongoing research, some that will help elucidate the epidemiology, diagnosis, pathogenesis, and management of EoE and other areas that focus on new therapeutic approaches. However, there are 3 research areas that I believe are underrepresented: greater emphasis needs to be placed on finding noninvasive methods to diagnose the disease and monitor response to treatment; more high-quality investigation needs to be conducted to evaluate how environmental changes could predispose patients to loss of tolerance to common food groups; and more research is needed on methods to reinduce tolerance in patients in whom food allergies that drive EoE have developed.

Dr Bonis has no relevant conflicts of interest to disclose.

Suggested Reading

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