Unmet Diagnostic Needs in Eosinophilic Esophagitis

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Key Words

Eosinophilic esophagitis · Diagnosis · Phenotype

Abstract

The description of eosinophilic esophagitis (EoE) from a clinical, endoscopic, histologic and mechanistic perspective has emerged at a rapid pace. Nevertheless, there are many key areas of diagnosis which remain problematic. The first area is trying to identify a gold standard for EoE, particularly in its differentiation from gastroesophageal reflux disease. As a result, many of the consensus guidelines advise expensive and cumbersome steps with endoscopy and empiric courses of medication that would not be needed should a completely accurate method for identifying EoE be developed. We also grapple with the lack of an accurate test short of endoscopy and biopsy to diagnose and monitor treatment response in EoE. This is particularly problematic in food elimination diets where patients may require up to ten endoscopies to determine precise food avoidance. Finally, it is imperative that we diagnose factors that predict severity and phenotype of the disease. This will yield far clearer guidance concerning the level and duration of therapy needed on EoE patients.

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Introduction

As in any new disease (and many old ones!), there is always a plethora of important questions that need to be answered. This is particularly true in establishing diag-

nostic criteria for eosinophilic esophagitis (EoE). When a new disease is first described, this is ostensibly an easy task given the limited number of cases and ‘classic’ descriptions. As the disease is studied further in greater numbers of patients, variations are demonstrated as well as overlap with other potential diseases. This is most evident in trying to differentiate EoE from gastroesophageal reflux disease (GERD).

Differentiating EoE from GERD

There are several reasons for which this is difficult. First and foremost is the inability to establish a ‘gold standard’ for EoE. Whereas initial descriptions of EoE describe robust tissue eosinophilia and characteristic endoscopic findings such as linear furrowing, rings, strictures and white exudates, broader populations studies demonstrate that patients with GERD may have these findings [1]. Similarly, the personal and family allergic phenotype strongly associated with EoE consists of common diseases also found frequently in the population [1]. Several studies have shown that a response of esophageal eosinophilia to proton pump inhibitors is not specific in revealing etiology [2, 3]. Furthermore, in-depth study of proton pump inhibitors have led to a large number of drug actions independent of acid suppression [4]. These actions include anti-inflammatory effects including inhibition of cytokine secretion described both in GERD and EoE models. Elegant scoring systems combining clinical, endoscopic and pathologic variables have also been pro-

posed with excellent, but without complete, prediction of disease dominance [5].

Further difficulty present in differentiating EoE from GERD is derived from evidence that both diseases may be present in one patient and may in turn have important contributions to the ultimate clinical and pathologic expression of the esophageal eosinophilia. Theories that link these diseases include similar abilities to dilate esophageal epithelial intercellular spaces and facilitate antigen penetration into esophageal mucosa, suppression of cytokine-driven mechanisms and increased esophageal exposure to food antigens in gastric refluxate [6–9].

Genetic studies hold promise both through genome-wide association study techniques and through recent microRNA analysis, but there are caveats to consider [10–12]. First, EoE may be a poly- or multigenic disease; therefore, the hopes of identifying one or two particular gene candidates may not be realistic. This is demonstrated perhaps in inflammatory bowel disease where over 100 genetic abnormalities have now been identified. Identification of a candidate gene also does not rule out finding this in asymptomatic patients or coincidentally in GERD patients who have not expressed the allergic dysfunction derived from the genetic variation consistent with a disease of incomplete penetrance.

Possibly, the most reliable means of differentiating EoE from GERD is not used for practical reasons. In children and to a large degree in adults, histologic response to an elemental diet is accurate in establishing EoE [13, 14]. This makes intuitive sense as there is no clear reason for which GERD would respond to elimination of esophageal exposure to food antigens, but all the reason that EoE would respond. Unfortunately, this has not gained acceptance in the adult world as easily as it has in pediatrics.

Search for a Noninvasive Test to Monitor EoE Disease Activity

It is clear that EoE is to a large degree (if not completely) a food antigen-driven disease in which esophageal eosinophilia and its sequelae lead to chronic inflammation and fibrosis. Unfortunately, despite this strong foundation, there has been no practical means of reliably determining which food antigens trigger the disease in individual patients. Diligent work by a handful of investigators have been able to show some accuracy with combinations of noninvasive allergic testing such as RAST, skin tests and patch tests [15], but outside of a specialized

center, these tests are either not available or not as predictive. Other investigators have also carefully demonstrated the most common food antigens to trigger this disease in general are wheat, milk and others that comprise the six-food elimination diet [16, 17]. Unfortunately, there is marked variation among individual patients in terms of which foods, how many of these foods and food antigens existing outside of the six most common foods. As a result, the most established means of monitoring disease activity remains endoscopy and esophageal biopsy. For those patients and physicians electing to use topical steroid therapy as a primary therapy, the number of endoscopies is limited, but by consensus guidelines still require three procedures: diagnosis, lack of response to proton pump inhibitors and successful response to steroids. For those patients choosing food elimination therapy, endoscopy and esophageal biopsy are required between every withdrawal and reintroduction of a specific food. In the few studies that have applied this strategy, up to ten procedures could be required. This comes with considerable expense and risk to the patient.

One promising less invasive diagnostic tool is the esophageal string test [18]. This test, developed by Dr. Glenn Furuta, applies an old test once used to diagnosis *Giardia* infection to EoE. Specifically, patients are asked to swallow a capsule with a string after an overnight fast (and perhaps only an hour), and the string migrates into the stomach and perhaps more distally. The string, emerging from the mouth, is then withdrawn and is scraped for secretions. These secretions are stained for eosinophil-derived proteins such as major basic protein, eosinophil-derived neurotoxin and eosinophilic cationic protein. The measures of these proteins correlate well with the eosinophil count on biopsy. Due to the accuracy of the test in addition to its safety and cost, it may be the future of noninvasive testing in EoE. The only difficult aspects identified so far are patient tolerance with gagging in some and the ability of routine laboratories to assay for eosinophil-derived proteins.

Another less invasive test being evaluated still in the most preliminary stages is the cytosponge [19]. This test employs swallowing a capsule containing an abrasive sponge that deploys in the stomach and then withdrawing the device with a string. The cytosponge has been used in hundreds of patients for esophageal cancer and Barrett's esophagus screening with excellent results. Its application to EoE is new, but its advantage is that the sponge yields a cytology specimen and in some cases a tissue specimen eliminating the need for assessment of markers [Fitzgerald and Katzka, unpubl. data]. Concerns exist, however,

in patients with tight strictures in which the capsule may not pass, or conversely, may cause trauma upon withdrawal.

The Holy Grail for assessing EoE activity might be a blood test. A few groups have examined serum eotaxin in patients with EoE and have shown good correlation with disease activity [22]. Unfortunately, there is still overlap in patients in remission and in those with GERD.

Identification of EoE Disease Progression and Phenotypes

One of the key and unknown questions in EoE is its long-term natural history. As this disease has only been well recognized for approximately two decades, we still have little idea what the lifetime course of EoE is in an individual patient. Important data from Drs. Straumann and Schoepfer have revealed that with increasing disease duration and ongoing inflammation, the risk of stricture formation is higher [20, 21]. This makes good general sense but does not explain why some patients of equal age and with similar disease duration have an end-stage small caliber esophagus while others have a normal caliber with minimal stricture formation. It is unclear if severity reflects the degree of antigen exposure, the strength of the allergic response or upregulation of esophageal inflammation by extraesophageal factors. So far, studies from Dr. Straumann's laboratory have not been able to find these factors other than disease duration and ongoing inflammation.

It is also important to consider, as in inflammatory bowel disease, whether different disease phenotypes exist. Whereas for years it was assumed that Crohn's disease follows a general course of chronic inflammation leading

to fibrosis and stricture formation, landmark work from Dr. Gary Lichtenstein suggested there are two types of Crohn's disease: structuring/obstruction types and fistulizing/perforating types [23]. This observation has stood the test of time with the existence now of potential serum markers that predict the severity and type of Crohn's disease. This type of testing could be extremely helpful in diagnosing the 'type' of EoE present and in turn guiding treatment by expected phenotype and severity.

Conclusion

Many characteristic features of EoE have been characterized from a clinical, histologic and pathogenesis perspective, but no gold standard exists. While this has allowed effective treatment to be developed, it has been at the expense of potentially unnecessary treatment regimens, guided by consensus, to arrive at a diagnosis of EoE. Furthermore, in many patients there may be a combination of both GERD and EoE contributing additionally or synergistically, making clarification of pathogenesis difficult in individual patients and default management by maximum combination therapy. Better diagnosis is also needed to determine if the pathogenesis of EoE is similar in all patients, or has varying intensity and phenotypic presentation allowing for identification of patients at higher risk and therefore greater need for potent and sustained therapy.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the content of the article.

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