Management of Refractory Eosinophilic Esophagitis

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Key Words

Eosinophilic esophagitis · Eosinophil-derived granule proteins · Esophagitis

Abstract

Background/Aims: Whereas most children and adults respond to traditional eosinophilic esophagitis (EoE) treatments, such as exclusion of dietary allergens or the use of topical steroids, a small fraction may not. **Methods:** Based on clinical experience and a review of the literature, the aim of this work is to provide practical advice for caring for 'refractory' patients with EoE. **Results:** The approach to this type of patient continues to evolve and decision-making should consider a number of issues including the patient's age, lack of a complete understanding of the natural history of this disease, risks of monitoring, and side effects of treatments. Next, one needs to define the term 'refractory' in that this can refer either to persistent symptoms or to continued inflammation in the face of presumably effective drug or diet therapy. Before considering alternative treatments, it is important to rule out any other cause of persistent symptoms. For instance, could they be related to an occult esophageal narrowing not identified at the time of endoscopy? Esophagrams may be necessary to identify localized or longitudinal narrowing that could be amenable to dilation. If symptoms and inflammation persist and no narrowing is appreciated, an elemental diet can

be considered; however, the long-term use of this in older children and adults may be difficult. Prednisone or systemic steroids may be indicated to induce remission, but side effects and complications associated with chronic use are limiting. Finally, the use of immunosuppression or biological agents has been reported in case reports and studies; use of these may be limited by side effects or the need to utilize compassionate use protocols. **Conclusions:** As the scope of esophageal eosinophilia continues to evolve, the clinical and molecular characterization of new clinical phenotypes will be important so that new therapeutic targets can be identified.

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Introduction

With the increasing prevalence of eosinophilic esophagitis (EoE), it has been recognized that some patients do not undergo clinicopathological remission with the use of standard of care treatments, diet, drugs, and dilation. Here we discuss representative cases of patients who had 'refractory' disease and provide an approach to this problem. In our practice, these patients are rare and when identified, set into play a number of questions including whether a patient is adherent to treatment, represents a novel phenotype of EoE, or requires additional expertise or perhaps new therapeutic approaches.

Case 1: All That Hurts Is Not EoE

A.B. is a 12-year-old boy with esophageal eosinophilia (72 eosinophils in the distal and 35 in the proximal esophageal sample) identified at the time of an upper endoscopy that was performed to assess abdominal pain. The endoscopic report and images demonstrated esophageal furrowing, friability, and distal ulcerations. Because of this finding, he was treated with 440 µg/day of fluticasone (2 puffs swallowed bid). He experienced no relief of his symptoms. Upon referral, his history was notable for daily heartburn and regurgitation. pH impedance monitoring of the esophagus documented an elevated reflux index of 16.3% and >75% symptom correlation. Treatment with 20 mg of omeprazole daily brought symptom relief.

Discussion

Over the last few years, a number of studies demonstrated two key points regarding esophageal eosinophilia. The first is that this histological finding is associated with a number of different clinical conditions including but not limited to EoE. Dense esophageal eosinophilia, characterized by >15 eosinophils/high-power field can be observed in gastroesophageal reflux disease (GERD), as in this patient, and other conditions. In addition, a new subgroup of patients who present with esophageal symptoms and have a normal pH impedance probe monitoring of the esophagus has dense esophageal eosinophilia, and both symptoms and tissue findings resolve with proton pump inhibitor (PPI) treatment [1]. This group of patients has been described as having PPI-responsive esophageal eosinophilia [2–6]. Whether they represent a variant of GERD or EoE is not certain. This clinical finding brings us to the second key group of studies that have demonstrated an alternative mechanism that PPIs may impact the GI tract. Whereas the traditional target for PPIs is the proton pump, new data has identified the role of PPIs in inhibiting cytokine responses from esophageal epithelia. In these studies, investigators demonstrate that concentrations of PPIs used for acid inhibition are able to impact the expression and release of cytokines such as IL-8 and eotaxin-3, two cytokines thought to participate in GERD and EoE, respectively [7–10]. Taken together, these studies emphasize the importance of interpreting the histological findings in the clinical context of which the biopsies were taken. Friability and ulceration are unusual features of EoE [11], and since GERD is much more common than EoE, an alternative approach would be to treat the patient regardless of the level of eosinophilia, starting with a PPI [12, 13]. Future studies in these areas will need to

determine if alternative biomarkers may be able to separate out different causes of esophageal eosinophilia so that appropriate treatments can be initiated early.

Case 2: Instructions Matter

C.D. is a 5-year-old boy who had a diagnosis of EoE established 6 months ago. Topical steroids (44 µg of fluticasone, 2 puffs swallowed bid) were prescribed, but he did not experience any improvement in his presenting symptom of vomiting. Further questioning determined that he rinsed his mouth out immediately after taking his fluticasone. Within 3 weeks after receiving the medications properly, his vomiting stopped and he was completely well.

Discussion

Topical steroids represent the only medical treatment effective in inducing a clinicopathological remission in patients with EoE. Whether administered with a metered dose inhaler, nebulizer, or in a viscous solution, this treatment induces remission in over 75% of patients [14–18]. To date, no US Food and Drug Administration medicine has been approved for EoE, and thus instructions for off-label use and administration are lacking. To address this, we and the advocacy group American Partnership for Eosinophilic Disorders (www.APFED.org) have developed instructional aids and two short videos to assist families and patients (http://youtu.be/L_l86ze9I-4 and <http://youtu.be/XkP2JDmp-zA>).

If, in fact, this patient was taking the medication correctly, an alternative explanation has arisen based on molecular studies of patients with EoE. Gene analysis of mucosal biopsies has revealed that some patients have altered expression of FKBP51, a finding associated with increased responsiveness to topical steroids [19, 20]. Future gene-based studies may provide therapeutic guidance and a personalized approach to EoE care.

Case 3: Ask for Help

E.F. is a 4-year-old boy with EoE who vomits and ‘refuses to eat’. Mealtime is chaotic and his growth is impaired. His mother needs to chase him around the house to have him sit down to eat, uses distractions such as the television to keep him at the table and provides rewards to have him open his mouth. Treatment with dietary avoidance of milk decreased vomiting, but feeding refusal and growth disturbances persisted. Upon referral, the dietician

identified hidden sources of milk and removal resulted in prompt cessation of vomiting and resolution of eosinophilia, but feeding problems persisted. Over the course of the next 3 months, intensive feeding therapy led to improved oral intake and normalized mealtimes at home.

Discussion

This case presents three important features in the care of the more complicated EoE patient. First, while a number of studies have demonstrated the benefits of dietary treatment of EoE, little has been published to determine the best way to provide nutritional support. In this regard, one study determined that physicians were the primary educators for dietary advice. While this may be straightforward for some, the knowledge and time to educate parents completely is not likely available for most physicians, thus emphasizing the importance of a dietitian in the care of children with EoE. Dietitians will provide knowledgeable advice for label reading, practical suggestions for food alternatives, and critical input to insure adequacy of calories, protein, and micronutrients [21]. Second, while symptoms improved, feeding problems did not resolve after complete milk avoidance. To ascertain whether the symptoms were due to persistent inflammation or learned behavior, a second endoscopy and biopsy was needed. This procedure is not taken lightly because of potential complications associated with it and anesthesia/sedation, but it is necessary to allow the progression of additional treatments. In this case, feeding therapy would not be effective if inflammation persisted. Third, significant feeding problems are not unusual as a part of the clinical features of EoE [22–24]. When the normal development of eating skills is disrupted early in life, the acquisition of necessary motor skills may not occur. In addition, when the child does not want to eat because of pain or fear of symptoms with food intake, dysfunctional patterns of eating can develop, and parents may inadvertently reinforce these patterns in a desperate attempt to maintain nutrition by ‘whatever means necessary’. This is often remedied by the expertise of a skilled feeding therapist to teach eating skills that may not have been mastered and develop an environment for eating that is family friendly.

Case 4: Reevaluate the Patient

G.H. is a 6-year-old girl with a long-standing history of ‘food impactions’ secondary to her EoE. Otherwise, she is well with normal growth and nutrition. Her meals last far

longer than the rest of her family and she chews her solid food until it reaches a near liquid state. She avoids bulky foods such as bagels. Treatment with swallowed 44 µg of fluticasone swallowed bid did not improve her symptoms. Over the course of 18 months, three endoscopies revealed no stricture and a normal mucosa compared to her original biopsy. Upon further investigation, an esophagram revealed esophageal narrowing from the proximal to middle esophagus. Subsequent balloon dilation led to complete resolution of symptoms for over 1 year.

Discussion

Tools to assess the esophagus in EoE continue to be developed for clinical care and research. Over the course of the last 5 years, a number of tools to assess clinical outcomes have been developed, including the EoE Symptom Activity Index (EESAI), Pediatric EoE Symptom Score (PEESS), and the Endoscopic Reference System (ERES) [25–28]. Validation of these tools continues in both pediatric and adult populations. In this regard, as shown in this case, clinical experience suggests that endoscopy may not always be the best test to assess for esophageal narrowing in children with EoE. The reasons for this are not certain and include the fact that not all EoE children have discrete strictures, but rather may develop more diffuse narrowing (‘narrow-caliber esophagus’) because of EoE’s panesophageal pattern of injury. Esophagrams may be a better test in some patients to identify narrowing [29–31]. Alternatively, empiric dilation may be used if esophageal narrowing is suggested by symptoms or subtle traction sensed upon the passage of the endoscope, especially in a known EoE patient whose mucosa appears normal endoscopically and histologically [32, 33]. Future studies using EndoFLIP or high-resolution manometry may become critical tools as indicators of esophageal function, which was indicated by a recent study that identified potential threshold compliance predictive of food impaction [32, 33].

Case 5: Problems with Polypharmacy

I.J. is a 7-year-old boy with a recent diagnosis of steroid-dependent asthma treated with 110 µg of fluticasone (2 puffs inhaled bid). He was initially started on therapy for EoE with 220 µg of fluticasone (2 puffs swallowed bid), but at the time of referral was having both an increase in vomiting/food refusals and a sudden worsening in his asthma control leading to two emergency room visits. Upon referral, it became obvious that he and his family

were quite confused over the difference between the two regimens and were frequently using the wrong dosages for each condition, i.e. 110 µg for the EoE and vice versa. In addition, the instructions to swallow the fluticasone for EoE had led to an inability to properly inhale the medication for asthma control, leading to subpar treatment of both conditions. His EoE medication regimen was changed to 0.5 mg of budesonide mixed in a slurry and swallowed bid (see video in Case 2 above), and he was re-educated as to the proper use of his inhaled corticosteroid therapy for asthma. With this, he has had complete symptomatic and histologic resolution of his EoE and his asthma has been under good control for over a year.

Discussion

Many patients with EoE suffer from other atopic diseases concurrently, many of which require similar therapies. In the case of asthma therapy, it is crucially important that a child's use of medications for EoE does not adversely affect the ability to control their asthma, and it is well understood that training a young child to properly use an inhaler is challenging [34]. This case also highlights the need for more research into the cumulative effect of multiple steroid formulations (swallowed, inhaled, and topical) on children with multiple atopic conditions [34].

Case 6: Families Often Know Best

K.L. is an 8-year-old boy with EoE that was diagnosed at age 6 following a presentation of vomiting and abdominal pain. He was initially treated with a six-food elimination diet with mild improvement in symptoms and histology. His therapy was then changed to 220 µg of swallowed fluticasone (2 puffs bid), again with only marginal improvements in symptoms and histology. His family then requested a trial of combined six-food elimination diet and fluticasone prior to any change to the elemental formula, and he had complete symptomatic, endoscopic, and histologic improvement. Subsequently, he has had all foods reintroduced successfully with the exception of milk, which caused both abdominal pain and marked esophageal eosinophilia consistent with his original endoscopy.

Discussion

This case highlights the fact that sometimes treatment for these challenging cases requires creative therapies that are not established in the literature (in this case the combination of diet and topical steroids). This child has a

clear response to a dietary antigen (milk), but removal of milk alone is not sufficient to control his symptoms or inflammation. There are a number of scenarios to account for this, including a possible role for an additional unidentified food trigger. An alternative hypothesis is that there may be an environmental inhaled antigen which is driving inflammation in addition to the dietary trigger, and which requires the addition of the corticosteroid to control. This has been suggested in the literature both from animal models showing respiratory exposure is sufficient to drive esophageal eosinophilia as well as from epidemiologic data showing seasonal trends in EoE [35–38]. A more rigorous collection and study of patients requiring this sort of combination therapy might help uncover additional clinical phenotypes that could be useful in determining therapeutic options.

Summary

Since most EoE patients respond to one of the '3 Ds' (drugs, dilation, and diet) [33], the care of the refractory or 'stubborn' patient, one who does not respond as predicted, often requires reassessing the diagnosis, reviewing instructions, asking for additional expertise, and using additional studies to improve outcomes. Overall tenets to guide care include using treatments to maximize a child's growth and development, balancing risks of treatment with severity of illness, and considering impacts on quality of life for the patient and family.

Future studies are needed to better define patterns of eosinophilia and understand their relationship with symptoms, patient-reported outcomes and clinical outcome measures, and to determine mechanisms by which eosinophils impact the esophagus. In addition, it is also necessary to foster the development of novel therapeutic strategies, identify and validate biomarkers to both make a diagnosis and monitor the effects of treatment, and characterize the natural history of EoE to improve the care of children and adults with EoE.

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