



Review

Eosinophilic esophagitis in cystic fibrosis: A case series and review of the literature ☆☆☆

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Abstract

Patients with cystic fibrosis (CF) frequently experience gastrointestinal symptoms including nausea, emesis, malnutrition and indigestion; diseases such as gastroesophageal reflux disease (GERD), distal intestinal obstructive syndrome, and cholelithiasis are commonly implicated. We have recently diagnosed eosinophilic esophagitis (EoE) in three patients with CF. EoE is a TH-2 driven, allergen-mediated disease which causes esophageal eosinophilia and presents with symptoms of nausea, feeding intolerance, regurgitation, and dysphagia. EoE is diagnosed when esophageal biopsies reveal greater than 15 eosinophils per high power field in the setting of the appropriate clinical scenario and after exclusion of other causes of esophageal eosinophilia. Although described with increasing frequency in the gastrointestinal literature, there have been no prior cases documenting the co-existence of EoE and CF. We speculate that this is related to lack of familiarity with EoE symptoms by CF providers. We present three patients with CF diagnosed with EoE and review the current literature regarding diagnosis and management, focusing on management issues in patients with CF.

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1. Introduction

Eosinophilic esophagitis (EoE) is a chronic, antigen-driven allergic disease characterized by eosinophilic infiltration of the esophagus and symptoms of esophageal dysfunction. First described in the late 1970s and felt to be relatively rare, EoE has exhibited an increasing incidence over the past 5–10 years, due to both increasing recognition of the condition as well as increasing incidence and prevalence [1]. EoE is defined as a clinicopathologic condition, and the correct combination of clinical symptoms and histopathologic findings are required to confirm the diagnosis [2]. In order to diagnose EoE, current guidelines require: 1) symptoms of esophageal dysfunction (dysphagia, food impaction, chest pain, heartburn, and regurgitation, among others); 2) at least 15 eosinophils in at least one high-power microscopy field (eos/hpf) on esophageal biopsy; and 3) exclusion of other potential causes of esophageal eosinophilia [1,2]. While dysphagia and food impaction are the most common symptoms in adults [2,3], symptoms in children can be non-specific and include food intolerance, failure-to-thrive, abdominal pain, nausea, and emesis. Non-specific gastrointestinal (GI) symptoms such as these are common in patients with cystic fibrosis (CF), and may be attributable to CF-related comorbidities such as pancreatic insufficiency with malabsorption, distal intestinal obstruction syndrome (DIOS), gastroesophageal reflux disease (GERD), infections, medication side effects, or other conditions. However, in selected cases, EoE should be considered in the differential diagnosis as it is possible that EoE and CF can coexist, although to our knowledge this has not previously been reported in the medical literature. The purpose of this investigation is to highlight a series of patients with CF who presented with a range of GI symptoms and were ultimately diagnosed with EoE.

2. Case summaries

2.1. Case 1

A 15-year-old female with CF (genotype: F508del/N1303K), mild lung disease (baseline FEV1 of 92% predicted), pancreatic insufficiency, and optimal nutritional status experienced persistent abdominal pain, nausea, and periprandial emesis despite ongoing proton pump inhibitor use. At an outside facility, abdominal ultrasound revealed cholelithiasis and a laparoscopic cholecystectomy was performed. Symptoms did not improve and the patient consequently experienced a 2 kg weight loss. Gastric emptying study, magnetic resonance cholangiopancreatography (MRCP), and a brain MRI were normal. Esophagogastroduodenoscopy (EGD), performed while the patient was taking esomeprazole

20 mg twice daily, was normal; however esophageal biopsies revealed 35 eos/hpf. In the absence of competing causes of esophageal eosinophilia, this finding was consistent with a diagnosis of EoE. RAST testing for common pediatric allergens was negative. After three weeks of treatment with a swallowed budesonide slurry (1 mg/2 ml) twice daily, her symptoms completely resolved. Budesonide therapy was continued for a total of 16 weeks, during which time the medication was slowly tapered off. She remained symptom free off therapy for approximately 18 months, after which she had recurrence of abdominal pain and nausea. Her parents opted not to subject her to the additional risk involved with a second endoscopy, and her symptoms improved with an additional 4 weeks of budesonide therapy and remained in remission over the following 4 months of follow-up.

2.2. Case 2

A 4-year-old female with CF (genotype: F508del/F508del), pancreatic insufficiency, poor nutritional status, and presumed GERD presented at 29 months of age with decreased oral intake. Despite treatment with omeprazole 20 mg twice daily, she subsequently developed severe food aversion and refusal to swallow. These symptoms led to gastrostomy tube placement to ensure adequate nutrition. Upper endoscopy revealed esophageal congestion, linear furrows, punctuate white spots, and decreased vascularity suggestive of EoE. Esophageal biopsies confirmed this impression with increased eosinophils (>50 eos/hpf with eosinophil microabscesses). Further testing revealed allergies to soy, cantaloupe, peas, trees and grasses. Given the severity of her symptoms, she was started on an elemental diet by gastrostomy tube as well as a swallowed budesonide slurry of 0.5 mg twice daily. After six months of therapy with improvement in her symptoms and weight, she underwent repeat endoscopy. While the esophagus had a markedly improved appearance, biopsies revealed persistent eosinophilia (30 eos/hpf). The budesonide dose was increased to 1 mg twice daily and follow-up endoscopic examination revealed a normal esophageal mucosal appearance and normal biopsies. After her initial clinical improvement, she had recurrent symptoms when the oral budesonide therapy was stopped. She subsequently required maintenance on an elemental formula administered via gastrostomy tube for symptom control.

2.3. Case 3

A 12-year-old male with CF (genotype: F508del/F508del), normal lung function values (FEV1 113% predicted), pancreatic insufficiency, and nutritional failure requiring gastrostomy tube placement presented with chronic recurrent abdominal pain and

poor oral intake. Symptoms persisted despite a proton pump inhibitor (PPI) trial of esomeprazole 40 mg twice daily. The patient underwent EGD which showed diffuse granularity of the esophageal mucosa as well as linear furrows and decreased vascularity throughout the esophagus. Biopsies showed 40 eos/hpf, consistent with EoE. Skin prick testing was positive for peanut, egg, soy, wheat, and corn allergies. He was started on a swallowed budesonide slurry and a targeted elimination diet with improvement in his symptoms. Repeat EGD at the end of three months of budesonide therapy showed complete resolution of pathologic findings. The slurry was discontinued but the patient continued with the elimination diet and symptoms of EoE remain under control.

3. Discussion

In this case series, we present three patients with known CF and concomitant non-specific GI symptoms. After extensive evaluations including treatment with high dose PPI therapy, all three patients were diagnosed with EoE after meeting the criteria of the current consensus guidelines [2]. The variable endoscopy findings and clinical outcome in each of these cases is important to emphasize. In each scenario, despite compatible symptoms, the diagnosis of EoE was not clinically suspected prior to obtaining the endoscopy and biopsy results. We believe this is related to a dearth of information in the literature about the possible co-existence of EoE and CF, as well as the fact that EoE has only recently emerged as an important etiology of GI symptoms. We present this case series and literature review to educate CF specialists about the diagnostic possibility of EoE in CF. To our knowledge, the cases presented herewithin document the first published cases of EoE in patients with CF.

3.1. Epidemiology and differential diagnosis

While the true incidence and prevalence of EoE are not known, one survey of GI and allergy providers estimates an overall prevalence of 52 cases/100,000 persons in the United States, similar to a recent report from Europe [4–6]. One difficulty in accurately determining the epidemiology of EoE is that there are a variety of diseases besides EoE which can result in esophageal eosinophilia, making the diagnosis of EoE challenging. These disorders include GERD, eosinophilic gastroenteritis, hypereosinophilic syndrome, connective tissue disorders, celiac disease, Crohn's disease, parasitic infections, and drug hypersensitivity, among others [3].

It is therefore important to note that the finding of eosinophils on an esophageal biopsy specimen in and of itself does not suffice for a diagnosis of EoE. On a practical level, GERD is the most common condition that needs to be differentiated from EoE [7]. The symptoms of GERD overlap with EoE (heartburn, regurgitation, dysphagia). GERD is a common indication for upper endoscopy and is a common cause of esophageal eosinophilia. Therefore, a trial of proton pump therapy is indicated before making a diagnosis of EoE, and this intervention is often done prior to an invasive study such as EGD [3]. Related to the PPI trial is a newly recognized and somewhat controversial subgroup of

patients with a phenomenon termed proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) [2,8]. In this situation, a patient with suspected EoE who has biopsy proven esophageal eosinophilia has a symptomatic and histologic response to PPI treatment alone. While there is preliminary evidence that PPIs may have an anti-inflammatory effect separate from their typical anti-acid effect [9], it is unknown if this PPI-REE subgroup is an EoE phenotype [10], a GERD phenotype, a combination of the two, or a separate condition altogether [2,5].

3.2. Symptoms, endoscopic, and histologic findings

Many of the conditions in the differential diagnosis for esophageal eosinophilia can be seen concomitantly with CF and present with overlapping symptoms. Feeding difficulties and failure to thrive are common in infants and young children with EoE, while school age children tend to present with emesis and abdominal pain. Adolescents and adults may complain of dysphagia, chest or abdominal pain, heartburn, or food impaction [3,7]. While the natural history of EoE is unknown, it is intriguing to speculate that the different presenting symptoms may be related to disease progression over time [3,7]. When asking patients about symptoms of dysphagia, it is important to note that both children and adults with EoE rapidly adapt their eating habits (slow eating, thorough chewing, food avoidance) to minimize symptoms, so questions on history should also address dietary modification [2]. Because the symptoms in EoE are non-specific and are also common in CF, when a patient with CF presents with food avoidance, emesis, regurgitation, heartburn, or dysphagia, EoE should be considered, particularly if symptoms do not respond to empiric treatment and if endoscopic evaluation is contemplated.

On endoscopy, there are several typical findings of EoE, including esophageal rings, esophageal strictures or a narrow-caliber esophagus, linear furrows in the esophageal mucosa, white plaques or exudates, and mucosal pallor, congestion, or decreased vascularity. However, similar to symptoms of EoE, no single endoscopic finding can be considered pathognomic for EoE. Therefore, it is important to maintain a high index of suspicion and obtain esophageal biopsies when the diagnosis of EoE is clinically suspected. Increasing biopsy numbers yield higher diagnostic sensitivities [11], and biopsies should be taken even if there is no gross evidence of esophageal abnormalities as up to 10% of endoscopies may be visually normal [12].

On histopathologic examination of the esophageal biopsy, a dense eosinophilic infiltration, eosinophilic microabscesses, eosinophil granules, fibrosis, and basal cell hyperplasia can be seen [13]. Current diagnostic guidelines recommend that in addition to the eosinophil count, other pertinent findings should be reported because in isolation, none of the pathologic features are pathognomic for EoE. Because there is no single finding that differentiates EoE from other conditions, the diagnosis of EoE can only be made by linking compatible clinical symptoms with histopathologic findings and excluding other potential causes of esophageal eosinophilia. Prior to the 2007 consensus diagnostic guidelines for EoE [1,2], there was substantial variability in diagnostic criteria, which makes some of the

medical literature difficult to interpret and could cause clinical confusion as well [12]. In the future, more specific staining of the esophageal biopsies might aid with diagnosis, as several studies have suggested that eosinophil granule deposition and staining for esophageal mast cells may help diagnose EoE more efficiently [14–17]. In addition, eotaxin-3 has been found to be over-expressed in patients with EoE but not GERD [18] and this may also be helpful for diagnosis in the future.

With regards to diagnosing EoE in CF, there are several special considerations. First, since an EGD, an invasive procedure requiring sedation with its associated risk of aspiration, is required for diagnosis, it makes sense to minimize the number of procedures needed and combine the procedure with any other sedated procedures that may be required. Secondly, many patients with CF are routinely maintained on a PPI, either for symptomatic GERD or to enhance pancreatic enzyme efficacy. When EoE is a clinical consideration, if the patient is not already on a PPI, he or she should be placed on a high-dose twice daily PPI for at least 8 weeks prior to the procedure. Since CF patients are known to require high doses of PPI for adequate acid suppression, the clinician might also consider obtaining ambulatory pH monitoring to ensure appropriate neutralization of gastric and esophageal acid. Finally, inadvertent swallowing of a small amount of an inhaled corticosteroid used for asthma may mask the underlying diagnosis of EoE. If it is considered safe, this medication should be held prior to the endoscopy to avoid missing the diagnosis.

3.3. Allergic associations and pathogenesis

The underlying pathogenic mechanism of EoE is still being clarified, but the current belief is that EoE is an immune-mediated condition in which allergens prompt a Th2 response where IL-5 and IL-13 stimulate the esophageal epithelium to produce eotaxin-3, a potent eosinophil chemokine. This chemokine recruits eosinophils into the esophagus and may lead to decreased barrier function [19]. The cytokine IL-5 deserves special mention as it promotes the production of eosinophils from the bone marrow. IL-5 has been identified in EoE biopsy specimens and is known to induce eosinophil-mediated esophageal remodeling in mouse models [2].

Clinically, atopic diseases are commonly associated with EoE, including asthma, atopic dermatitis, allergic rhinitis, sinusitis, and food allergies [20]. Radioallergosorbent testing for specific IgE and skin prick testing are the most common diagnostic testing for food allergens, but atopy patch testing (for delayed, Type IV, non-IgE mediated reactions) can also be used [3]. Interestingly, patch testing suggests that the range of food protein allergy in EoE is much more extensive than typical IgE-mediated food allergy [21], though this modality is not universally available. In most patients with EoE, culprit food allergens can be identified through a range of allergy testing, and an elimination or elemental diet is effective in controlling symptoms. When offending food allergens are reintroduced, symptoms and esophageal eosinophilia recur, and unlike typical food allergies, patients with EoE do not usually outgrow their allergic response to the offending foods [22–24]. Seasonality has also been shown to be a factor in the diagnosis of EoE, corresponding to the season with the most

aeroallergens for the patient [3,7], but on a practical level it is difficult to eliminate all environmental allergens to determine if they are etiologic.

The pathogenesis of CF does not appear to overlap with that of EoE, and food allergies in CF have rarely been reported [25]. However, atopic diseases are widespread, and when atopy is encountered in patients with CF and GI symptoms, EoE should be a diagnostic consideration. Anecdotal evidence suggests that food allergies may be quite common but are often overlooked clinically and not reported in the literature. When EoE and CF overlap, clinicians should search for food allergies. In our small series, two of the three patients were found to have specific food allergies.

3.4. Treatment options

There are several options for treatment of EoE, including pharmacologic agents and dietary elimination. Consensus recommendations advocate for first line treatment of either swallowed (“topical”) corticosteroids or dietary therapy, depending on patient preference, severity of illness, and availability of local expertise [2]. Reflecting this, a survey of 1800 adult and pediatric gastroenterologists and allergists indicated that 44% prescribed swallowed corticosteroids and a PPI as first line therapy, with another 39% selecting an elimination diet as first line therapy [4]. PPI therapy alone is not effective for EoE (though by definition it is appropriate for PPI-REE, as discussed above).

While there are no FDA-approved medications for EoE, the use of swallowed corticosteroid is a mainstay of EoE therapy. In this approach, a steroid inhaler such as fluticasone is puffed into the mouth and then swallowed, or aqueous budesonide respules can be mixed into a syrup with sucralose or another thickening agent and swallowed directly. Efficacy of both of these agents has been confirmed in recent randomized placebo-controlled clinical trials [26,27]. It is important to note that EoE frequently recurs when steroid therapy is discontinued, and the approach to long-term maintenance medical therapy is still unclear [2]. Although well tolerated compared to systemic steroids, swallowed corticosteroids do carry a small risk of candidal esophagitis [28].

Dietary therapy can be very effective in children if culprit food allergens are identified, and recent data show efficacy in adults as well [22–24]. Strategies that have been shown to be effective include eliminating the most common food allergens from the diet (“six-food elimination diet” where wheat, soy, milk, egg, nuts, and seafood are restricted), performing food allergy testing and eliminating offending agents (“targeted elimination diet”), or using an allergen-free diet consisting only of an elemental formula (“elemental diet”). Although the most restrictive and least appropriate for most patients in the long term, studies have shown that amino acid based elemental diets are the most effective in eliminating esophageal eosinophilia [22]. In general, proven food triggers likely need to be restricted permanently [2].

In the context of CF, EoE treatment presents some special concerns. While medical treatment with topical steroids is usually well tolerated, this does add another medication to an already

complicated treatment regimen. In addition, at high doses, even swallowed/topical steroids can impact the adrenal axis and bone health, which can already be affected in CF. Restrictive dietary therapy in EoE may be at odds with nutritional approaches in CF where patients are instructed to consume large amounts of calories due to increased metabolic demands. Consultation with a registered dietician is warranted to ensure adequate nutritional intake, especially if multiple allergens are identified and need to be eliminated from the diet.

3.5. Prognosis and importance of EoE in CF

EoE is a chronic, immune mediated condition defined by eosinophilic-predominant esophageal inflammation associated with clinical symptoms of esophageal dysfunction [2]. The natural history of EoE is incompletely described, but while EoE is chronic and symptoms persist without treatment and generally recur if treatment stops, it does not yet appear to progress to other eosinophilic GI conditions or malignancy [3,29]. A number of disease complications, including food impaction and esophageal stricture are common, but esophageal rupture is noted only in a minority of patients. [2,30]. In patients with CF, underlying EoE may clinically result in persistent emesis, food aversion, and failure to thrive. The association of CF lung disease and nutritional failure is well documented, so timely diagnosis of a potentially treatable condition such as EoE is imperative. The association of EoE and CF is likely not mechanistically related, since EoE is a Th-2 allergen-mediated process and CF is a genetically determined disease. However, when EoE is suspected in a patient with CF, it is important for the clinician to relay concerns about potential EoE to the endoscopist, as biopsies need to be taken to evaluate for the disease regardless of the endoscopic appearance of the esophagus. If the concern for EoE is not adequately conveyed to the endoscopist, the diagnosis could easily be missed.

We believe these are the first reported cases of EoE diagnosed in patients with CF and it is possible that EoE has been underappreciated in CF because of symptom overlap with other common GI disorders in CF, including GERD, cholelithiasis, pancreatic insufficiency, and adverse drug reactions. EoE should be considered as a potential diagnosis in children presenting with a compatible clinical scenario, failure to respond to PPI therapy, and after exclusion of other potential GI causes. Because symptoms of EoE are non-specific, a high degree of suspicion is necessary to diagnose this entity in the CF population.

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