Eosinophilic esophagitis in patients with esophageal atresia and chronic dysphagia

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Author contributions: Kassabian S and Baez-Socorro V wrote the original manuscript; Sferra T helped with editing; Garcia R had seen multiple patients with this association and guided the writing of the manuscript; all the authors contributed to the manuscript.

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Received: March 13, 2014 Revised: July 22, 2014
Accepted: September 18, 2014
Published online: December 21, 2014

Abstract

Esophageal atresia (EA) is defined as a discontinuity of the lumen of the esophagus repaired soon after birth. Dysphagia is a common symptom in these patients, usually related to stricture, dysmotility or peptic esophagitis. We present 4 cases of patients with EA who complained of dysphagia and the diagnosis of Eosinophilic esophagitis (EoE) was made, ages ranging from 9 to 16 years. Although our patients were on acid suppression years after their EA repair, they presented with acute worsening of dysphagia. Esophagogastroduodenoscopy and/or barium swallow did not show stricture and biopsies revealed elevated eosinophil counts consistent with EoE. Two of 4 patients improved symptomatically with the topical steroids. It is important to note that all our patients have asthma and 3 out of 4 have tested positive for food allergies. On one of our patients developed recurrent anastomotic strictures that improved with the treatment of the EoE. A previous case report linked the recurrence of esophageal strictures in patients with EA repair with EoE. Once the EoE was treated the strictures resolved. On the other hand, based on our observation, EoE could be present in patients without recurrent anastomotic strictures. There appears to be a spectrum in the disease process. We are suggesting that EoE is a frequent concomitant problem in patients with history of congenital esophageal deformities, and for this reason any of these patients with refractory reflux symptoms or dysphagia (with or without anastomotic stricture) may benefit from an endoscopic evaluation with biopsies to rule out EoE.

Key words: Eosinophilic esophagitis; Esophageal atresia; Tracheoesophageal fistula; Dysphagia

Core tip: Dysphagia is frequently seen in patients with repaired esophageal atresia (EA). It has been attributed to recurrent strictures, poor esophageal motility and persistent gastroesophageal reflux disease. Anastomotic strictures are common after repair of a gap that is greater than 2.5 cm contributing to this complication. The pathophysiology of later onset dysphagia is not well defined. Eosinophilic esophagitis (EoE) has been reported to play a role in the reoccurrence of strictures in patients with EA. It is very likely that if these patients are treated for EoE early in the course of the disease, stricture formation might be prevented.


INTRODUCTION

Esophageal atresia (EA) and associated tracheoesopha-
Eosinophilic esophagitis (EoE) is a clinicopathological diagnosis, including dysphagia as a common symptom along with abnormal endoscopic findings and esophageal eosinophilia. Its presentation in patients with previous EA has not been fully recognized. We describe 5 patients between the ages of 1-16 years, with a history of EA who presented with dysphagia, not associated with anastomotic strictures. Each patient was subsequently diagnosed with EoE. Our objective is the highlight the possible association of these two disorders and to emphasize the importance of endoscopic evaluation with biopsies in patients with a history of EA who present with dysphagia.

**CASE REPORT**

**Case 1**

A 10-year-old female with VATER association presented with 1 year history of dysphagia, and recent onset of postprandial chest pain. She was born at 29 wk estimated gestational age. She underwent EA and TEF repair soon after birth. During infancy, she experienced recurrent TEs requiring repair. She developed significant gastro-esophageal reflux that was felt to contribute to frequent episodes of aspiration pneumonia and underwent an anti-reflux surgical procedure. She had poorly controlled asthma, eczema, and a history of an elevated serum IgE (2332 IU/mL). The treatment for her asthma included previous use of steroids for asthma exacerbations as well as daily medication which included cetirizine, inhaled fluticasone/salmeterol, montelukast, and albuterol whenever needed. At the time of her presentation her complete blood count and differential were normal. A barium esophagram demonstrated incomplete clearance of the contrast without evidence of an esophageal stricture. Esophagogastroduodenoscopy (EGD) performed after a two month course of lansoprazole, revealed erythema with no thickened folds or erosions. The anti-reflux surgical procedure did not appear to be intact and a moderate hiatal hernia was seen. Histologically, the distal esophagus demonstrated greater than 60 eosinophils per high-power field (eos/hpf) with superficial eosinophilic infiltrate and the proximal esophagus with a maximum of 30 eos/hpf with transmural eosinophilic infiltrate. An esophageal pH impedance study conducted while on proton pump inhibitor (PPI), showed no evidence of pathologic reflux. She was diagnosed with EoE. Skin prick testing revealed reactions to beef, egg, peas and milk. These foods were eliminated from her diet. She was placed on budesonide (0.5 mg in sucralose, twice daily for one month followed by once daily for one month prior to discontinuation) in addition to a PPI. She continued to have similar symptoms with very mild relief. A follow-up examination 6 mo after her previous EGD, revealed a normal caliber esophagus with furrowing distal to the TEF repair, with normal esophageal anastomosis. Mucosal biopsies contained a maximum of 50 eos/hpf with focally superficial eosinophilic infiltrate. She was prescribed fluticasone 0.5 mg twice daily and a more restricted diet (additionally eliminating wheat, seafood, shellfish and peanuts). Nine months after the second EGD, she continued to experience the same symptoms and was unable to comply with the diet restrictions or a trial of an elemental diet. The examined esophagus appeared normal. The site of TEF repair was patent in the proximal esophagus. Biopsies contained a maximum of 42 eos/hpf with focal eosinophilic infiltrate in the surface. At this point she was referred to pediatric surgery for repair of her Nissen fundoplication, hiatal hernia and placement of a gastrostomy. After these surgical interventions she was started on an elemental formula through her gastrostomy and asked to hold oral intake with a planned EGD in the future.

**Case 2**

A 9-year-old male with a history of isolated EA, repaired after birth, was referred to pediatric gastroenterology for evaluation of coffee ground emesis and melena. At the time of referral he had a chronic complaint of dysphagia. He had a history of recurrent symptomatic esophageal stricture requiring dilation. The last dilation was performed 3 years prior. He had asthma, which was treated with montelukast, cetirizine, and inhaled fluticasone. He was receiving lansoprazole (15 mg, daily). This dose was increased to twice a day at the time of presentation (two weeks prior to the first EGD). He had a normal complete blood count and differential. A fluoroscopic barium swallow revealed absent esophageal peristalsis with delayed clearance of contrast from the esophagus. The esophagus was of normal caliber without stricture. At EGD, the proximal esophagus was dilated, the anastomosis site was visualized, no ulcers were noted, the distal esophageal mucosa appeared erythematous with loss of a normal vascular pattern. The biopsies did not specify the number of eos/hpf, but was read as florid intraepithelial eosinophil infiltration and superficial collections of eosinophils most consistent with EoE. He was treated with swallowed fluticasone 0.5 mg twice daily and continued acid suppression (lansoprazole 15 mg, twice daily). Radioallergosorbent test (RAST) evaluation revealed a low positive result for wheat and egg white. He was placed on a diet restricted for milk, wheat, and egg. After three months of therapy, a second EGD revealed a normal appearance to the esophageal mucosa with normal histology. Wheat was reintroduced into his diet. Two months later, a third EGD showed a ringed and furrowed esophagus. Biopsies contained epithelial hyperplasia, edema, and a dense intraepithelial eosinophil infiltrate, greater than 50/hpf. Total IgE at this time was 343, 6 food elimination was initiated, with restriction of milk, soy, egg, wheat, peanuts/tree nuts and fish/shellfish.
Case 3
A 16-year-old male with EA and TEF repaired after birth presented with dysphagia, epigastric abdominal pain, chest pressure and vomiting associated with exercise. He had a history of gastroesophageal reflux disease treated with PPI, which was discontinued at time of presentation and asthma diagnosed at 2 years of age. He required multiple esophageal dilations with the most recent one at 14 years of age. Prior to the age of 6 he experienced intermittent episodes of choking and food impaction requiring dilatation. His current therapy for asthma includes budesonide, loratadine and montelukast. Previous RAST revealed an allergy to milk and egg, but diet continued to contain these two foods. A fluoroscopic barium swallow showed an absence of esophageal motility and no focal esophageal narrowing. He was started on omeprazole 40 mg once daily for one week prior to upper endoscopy. Examination of the esophagus showed diffuse mucosal edema and linear esophageal furrowing throughout the entire length of the esophagus. There was circumferential area in the distal esophagus just above the LES which was erythematous and had mucosal erosions.

Esophageal biopsies of the proximal and distal esophagus revealed 35 eos/hpf. He was then started on fluticasone 440 mcg twice a day with complete resolution of his symptoms after 1 wk of treatment. Skin prick testing was negative. Recommendation of eliminating milk, soy, wheat, egg, peanuts/tree nuts and fish/shellfish was made, but the patient refused to follow the elimination diet. He was also continued on another 4 wk of fluticasone 440 mcg and omeprazole 40 mg once daily. Upon two month follow up he was asymptomatic, continuing his omeprazole. A follow up endoscopy was refused by the patient’s parents since he was doing so well.

Case 4
A 17-year-old female with EA and TE fistula repaired after birth with a history of reflux and esophageal stricture requiring multiple dilations. Significant past medical history of failure to thrive, asthma and multiple food allergies including milk, egg, peanut and shellfish, diagnosed by skin prick testing.

She presented with dysphagia, regurgitation and the feeling of meat getting stuck regardless of chewing very well. Her parent reported eosinophils in the esophagus in the past, with no further details. During the initial visit she was taking omeprazole 20 mg twice a day and cetirizine.

At age 13, at the time of EGD an 8.6 mm outer diameter endoscope passed easily through the anastomosis, but there was some post-endoscopic trauma. No dilatation was done during this procedure. Biopsies showed squamous hyperplasia with a moderate number of eosinophils in the proximal esophagus and chronic inflammation with patchy eosinophils in the distal esophagus; interpreted at the time as possible reflux esophagitis. Patient was changed to lansoprazole 30 mg twice daily. Patient had improvement of the reflux symptoms but the dysphagia continued.

Six months later she presented with worsening of the dysphagia requiring pneumatic dilation and triamcinolone injection in the anastomosis area. She was continued on lansoprazole and sucralfate for one week. Due to persistent symptoms of dysphagia this patient underwent several EGDs requiring dilation and triamcinolone injections every 6-8 mo over a 3-year period. The proximal esophagus began to appear furrowed, four years after initial presentation, and the biopsies showed 30 eos/hpf.

At this point she was started on fluticasone, oral steroids, and diet restriction for milk, egg, peanut/tree nut and fish/shellfish, the patient had significant improvement in symptoms and complete resolution of the esophageal eosinophilia. Her last EGD showed biopsies consistent with Barrett’s epithelium with no eosinophils and she has not required any further dilations in the last 15 mo.

Case 5
A 17-mo-old former 28 wk old premature male born with TEF and EA repaired soon after birth. His past medical history is significant for small ASD of no hemodynamic significance, tracheobronchomalacia, chronic lung disease of prematurity, oropharyngeal incoordination, GERD and aspiration requiring G-tube feeds.

At 8 mo of age he required hospitalization for an ALTE. During that hospitalization a pH impedance showed severe acid reflux. He was started on lansoprazole 15mg once daily. His barium swallow showed mild narrowing at the anastomosis site. His EGD showed narrowing at the anastomosis site which did not interfere with the advancement of an endoscope with an outer diameter 5.9 mm.

At 16 mo of age he presented to pediatric gastroenterology with dysphagia for solids. An upper endoscopy was scheduled and dilatation was conducted with a pneumatic dilator, biopsies were also taken during the procedure. His symptoms did not improve post-dilatation. Histology showed epithelial hyperplasia, edema, a dense intraepithelial lymphocytic infiltrate and intraepithelial eosinophils up to 20/hpf, consistent with EoE. A skin prick test was nonreactive. He was placed on an empiric diet restriction of dairy, egg and peanuts/tree nuts. Once the EoE was diagnosed, diet modifications were made, the patient’s symptoms resolved within one month. Esophageal examination four months after initiation of the diet restrictions, showed a benign-appearing, intrinsic mild stenosis measuring less than one cm in length and this was traversed. The biopsies from the proximal and distal esophagus had mild basal cell hyperplasia, scattered mononuclear cells and rare eosinophils (2 eos/hpf). Egg was reintroduced into the diet and milk and dairy were still restricted, he was also continued on the lansoprazole. Three months later a repeat upper endoscopy revealed a normal appearing esophagus. Histology showed mild basal cell hyperplasia, increased mononuclear cells and rare eosinophils (2 eos/hpf).
DISCUSSION

Dysphagia is a frequent symptom in patients with repaired EA\cite{10,23}. Historically this symptom has been attributed to recurrent strictures, poor esophageal motility and persistent GERD. Anastomotic strictures are frequent early complications, that present with dysphagia, in patients with EA repair, with a mean presentation age of 5 months and a frequency of 37%–57\%\cite{4,23,24}. Strictures early in the life of these patients respond well to dilatations\cite{5}. An important factor for the development of subsequent stricture is anastomotic tension which is highly correlated with gap length\cite{5,23,24}.

Gastroesophageal reflux disease (GERD) is common in this population, occurring in up to 58\% of children\cite{4}. Risk factors for GERD in these patients include low birth weight, delayed anastomosis and possibly gastrostomy tube placements\cite{6,23,24}. GERD has been related as a factor for the formation of postoperative stricture and its recurrence\cite{25,4,7,22,24,27,28}. The standardized use of PPIs appears to have decreased the prevalence of GERD related stricture formation in patients with EA\cite{4,23,24}. Proton pump inhibitors have now become a standard treatment in all patients with EA repair\cite{4,23,24}.

It is clear that anastomotic strictures are common after repair of a gap that is greater than 2.5 cm and certain types of EA/TEF as well as vascular compromise contributing to this complication\cite{23}. The pathophysiology of later onset of dysphagia in these patients is not well defined. Multiple publications have noted that numerous factor including dysmotility, GERD and strictures play a role\cite{4,23,24}. We propose an additional etiology to consider when a patient complains of dysphagia. Eosinophilic esophagitis should be considered and further investigated by an upper endoscopic evaluation with proximal and distal biopsies.

In the 2011 Consensus Recommendations of the International Gastrointestinal Eosinophil Researchers defined eosinophilic esophagitis as a chronic, immune/antigen mediated, esophageal disease characterized by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation\cite{10,31}. Symptoms of EoE can be confused with GERD-like symptoms that do not respond to conventional anti-reflux therapies\cite{4,23}. There is an increasing prevalence of EoE in recent years as well as a male predominance shown in several studies\cite{3,11,20-22,32,33}.

EoE, has been reported to play a role in the reoccurrence of strictures in patients with EA. To our knowledge there has only been a couple of case series relating EA and EoE\cite{12,14}. Taking into account previous case series and our experience from case 4, strictures that develop later in the course of patients with EA repair and EoE do not respond as well to pneumatic dilators unless the eosinophilia is treated. It is very likely that if these patients are treated for EoE early in the course of the development of the disease, stricture formation might be prevented, although to date we do not have evidence of this.

All our patients presented with either dysphagia and/or food impaction years after initial repair. These patients had endoscopic and histological findings consistent with EoE. We did not see any evidence of significant anastomotic stricture on the esophagrams and endoscopic evaluations of our five patients. In one patient we found a narrowing of the anastomosis site that did not impede the passage of the 8.6 mm endoscope and dilation did not resolve the patient’s dysphagia. Symptoms of dysphagia and reflux improved with the treatment of the EoE. Four had significant atopic history; all carrying the diagnosis of asthma and 3 out of 5 with known food allergy. Three of our 5 patients did not have stricture in the anastomosis area. The other patient initially had a mild narrowing of the anastomosis and subsequently required multiple dilations with no relief of the dysphagia. Once biopsies were taken from the esophagus and the diagnosis of EoE was made and treated, the symptoms did not reoccur. This suggests that the dilations were not adequate treatment in this patient, until the underlying diagnosis was made and treated effectively.

In conclusion, when presented with symptoms such as dysphagia later on in the life of a patient with EA repair, the diagnosis of EoE should seriously be considered and adequate biopsies should be taken prior to committing a patient to recurrent anastomotic dilations. It is very important to consider the atopic history of these patients, especially when they begin to have complaints such as dysphagia. It is well known that asthma is more common in patients with esophageal atresia than in controls\cite{4,23,28}. So the diagnosis of EoE should be highly suspected and is a logical association in patients. Through our experience we found that these patients’ EoE is more difficult to treat. Likely a combination of their baseline poor motility due to the underlying EA along with EoE complicating the course. When a patient with a history of EA presents with dysphagia a diagnosis of EoE should be considered and further investigated.

COMMENTS

Case characteristics

Dysphagia is a common symptom among patients with a history of esophageal atresia, it can also be found concurrently with other esophageal conditions like Eosinophilic esophagitis.

Clinical diagnosis

Biopsies to confirm eosinophilic esophagitis (EoE) is an essential part of the evaluation of these patients and it allowed for different therapeutic options.

Differential diagnosis

Dysmotility, gastroesophageal reflux disease are among the other diagnosis that should be considered.

Laboratory diagnosis

Unfortunately there are no good laboratory testing methods to confirm the diagnosis of EoE in patients. Sometime peripheral eosinophilia or an elevated IgE might be present.

Imaging diagnosis

Imaging is an important part of evaluating patients, esophagrams can identify possible strictures.

Pathological diagnosis

Pathologic findings of greater than 15 eos/hpf are necessary to diagnose EoE.
Kassabian S et al. Eosinophilic esophagitis in esophageal atresia patients

without associated eosinophilia in the stomach or duodenum.

Treatment
Once diagnosis of EoE is made, therapy should be aimed at treating the EoE, based on patient’s atopic history, dietary restrictions can be an option, other times topical steroids are the best option.

Experiences and lessons
Biopsies are important to obtain in patients with the history of esophageal atresia who present with dysphagia. Treating strictures with dilation may not be an effective therapy if a patient has underlying EoE.

Peer review
Weakness is limited volume of patients, and underlying cause of EoE is unknown. Strength is outcome of the patients improved with the treatment of EoE.


Kassabian S et al. Eosinophilic esophagitis in esophageal atresia patients


