

Esophagitis with Eosinophil Infiltration Associated with Congenital Esophageal Atresia and Stenosis

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Key Words

Eosinophil infiltration · Esophagitis · Congenital esophageal atresia and stenosis

Abstract

Background: The esophagus is physiologically devoid of eosinophils, so their presence would suggest some underlying pathology. The prevalence of eosinophilic esophagitis (EoE) has steadily increased in Western countries. Previous studies have described EoE in association with congenital esophageal atresia (CEA), which is the most common congenital anomaly of the esophagus. However, the association remains unclear. **Methods:** We performed a retrospective histological analysis examining for eosinophil infiltration in the esophagus of patients with CEA following surgical repair or congenital esophageal stenosis (CES) who underwent esophageal biopsy or surgical resection in our hospital between 2005 and 2012. **Results:** There were 6 patients with CEA following surgical repair or CES who had eosinophil-dominant infiltration in the esophagus. All had associated allergic disorders, including food allergies in 4. Moreover, all except for one fulfilled the histological criteria of EoE. Impairment of eosinophil infiltration and symptomatic improvement were observed in those treated with a proton pump

inhibitor (PPI), either alone or in combination with steroids after esophageal dilatation. **Conclusions:** These findings suggest that CEA repair or CES in conjunction with allergic conditions and coexisting gastroesophageal reflux disease (GERD) may induce greater esophageal eosinophilic inflammation. In addition, esophageal dilatation followed by PPI treatment, alone or with steroids, may be a therapeutic strategy that can provide symptomatic relief by reducing eosinophilic inflammation in esophageal strictures or GERD associated with CEA or CES.

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Introduction

Eosinophilic esophagitis (EoE) is an allergic inflammatory disease, which is characterized, clinically, by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [1]. Over the past decade, the recognition and prevalence of EoE has increased, particularly in Western countries [1]. Eosinophils are physiologically present throughout the gastrointestinal tract except in the esophagus [2]. Therefore, the presence of eosinophils in esophagus would suggest some underlying pathology. However, eosinophil in-

filtration in the esophagus is not specific for EoE and has been observed in other diseases such as gastroesophageal reflux disease (GERD), albeit with a lesser extent of infiltration [3]. Thus, GERD should be considered in differential diagnosis of EoE.

Congenital esophageal atresia (CEA) is the most common congenital anomaly of the esophagus and usually requires surgical repair. Anastomotic strictures and GERD are common postoperatively, affecting 30–40% and 40–65% of patients, respectively [4]. GERD in patients with CEA after surgical repair is sometimes refractory, as seen in EoE [4], i.e. it is believed that these patients may have eosinophilic inflammation. Previous case series have described this condition [5–7]; however, the association remains unclear. In this study, we present 6 cases of esophagitis with eosinophilic-dominant infiltration associated with congenital esophageal stenosis (CES) or CEA following surgical repair.

Methods

A retrospective histological review was performed, examining for eosinophilic infiltration in the esophagus of patients with CEA following surgical repair or CES who had undergone esophageal biopsy or surgical resection between 2005 and 2012 at Gunma Children's Medical Center. This study was approved by the ethical committee of the Medical Center. The clinical presentation, laboratory data, endoscopic and histological findings and treatment of these patients were examined. Data were presented as medians with ranges.

Results

Patient Demographics (table 1)

Out of 6 patients, 4 had CEA following surgical repair, 1 had CEA complicated by CES following repair and 1 had CES. Of 5 patients with CEA, 3 had type C esophageal atresia and the remaining 2 had type A esophageal atresia. Furthermore, 1 patient with CEA had VATER association.

The age distribution was bimodal. Three were younger than 2 years old and the other 3 were school-aged or adolescents. The majority of patients were male (n = 4, 66%). All patients were Japanese except for 1 of Peruvian descent.

Five patients received upper gastrointestinal endoscopy with biopsy. Indications were nausea or vomiting in 3 patients and regular esophageal dilatation in 2. One patient who was suspected to have recurrent aspiration

Table 1. Demographic data and symptoms of patients with esophagitis with eosinophilic infiltration associated with CEA/CES

Sex, male/female	4/2
Age at biopsy, years	3.7 (6 months to 14 years)
Diseases	
CEA	5
Type A	2/5
Type C	3/5
CES	2 ¹
Chief complaint	
Nausea or vomiting	3
Regular esophageal dilatation	2
Recurrent fever	1
Past history of allergy	
FA	4
BA + AR	1
AD	1
Family history of allergy	
FA + AR	2
FA	2
AR	1
AD	1

AD = Atopic dermatitis; AR = allergic rhinitis; BA = bronchial asthma; FA = food allergy.

¹ One patient had both CEA and CES.

pneumonia underwent an upper gastrointestinal series, which revealed severe gastroesophageal reflux and prompted surgical management.

All patients had associated allergic disorders. Four had food allergies, 1 had prior bronchial asthma and allergic rhinitis and 1 had atopic dermatitis. One had moderate recurrent wheezing in addition to food allergies. There was a positive family history of allergic disorders in all patients: food allergies in 3 and allergic rhinitis and food allergies in 1.

Upper Gastrointestinal Endoscopic and Histological Findings (table 2)

Upper gastrointestinal endoscopy was performed in 5 patients. Esophageal strictures were observed in all 5 and in the remaining patient who underwent surgery. Circumferential inflammation was noted in 2 patients. Erosive lesions were noted in 1 patient and scarring lesions in another. Interestingly, the characteristic findings of EoE such as furrows or white plaques were not observed in any of the patients.

Basal epithelial cell hyperplasia or elongation of papillae along with eosinophil infiltration was found in all 6. In addition to eosinophil infiltration, lymphocytic infil-

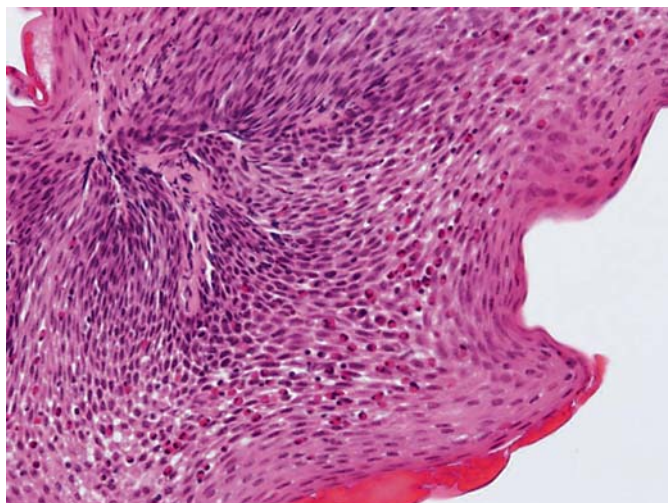


Fig. 1. Esophagitis with marked eosinophil infiltration in a patient with CEA following surgery. Histological analysis of the esophagus of a patient with CEA after repair was performed. HE. $\times 200$.

tration was observed in 5, neutrophil infiltration in 4 and plasma cells in 2.

The number of tissue eosinophils per high-power field (HPF) was evaluated. Two patients showed marked higher eosinophil infiltration (fig. 1). With the exception of 1 patient with only a slightly lesser extent of eosinophilia, all fulfilled the histological criteria of EoE (≥ 15 eosinophils/HPF).

Laboratory Findings (table 2)

Total and allergen-specific IgEs were measured in 4 patients, with 2 having higher levels of total IgE. One patient was positive only for environmental/seasonal allergens. Sensitizations to food allergens alone and food allergens together with cedar pollen were found in 1 and 2 patients, respectively. Peripheral blood eosinophil counts were relatively low in all patients (≤ 500 eosinophils/ mm^3).

Treatments (table 3)

Esophageal dilatation was performed in all patients, except for 1 who underwent a Bianchi procedure. Esophageal dilatation alone was effective in 1 patient with CES. Of 4 patients with CEA after surgical repair, 3 underwent esophageal dilatation followed by proton pump inhibitor (PPI) treatment for symptomatic improvement, while another was treated with systemic and intralesional steroids. All 4 patients, except for 1 who was lost to follow-

Table 2. Laboratory data, endoscopy and histology of patients with esophagitis with eosinophilic infiltration associated with CEA/CES

IgE, IU/ml (n = 4)	279.5 [15.7–1,956]
Positive allergens (n = 4) ^a	
Foods and cedar pollen	2
Foods	1
Environmental/seasonal	1
White blood cell count, / mm^3	10,250 [8,000–14,400]
Eosinophil count, / mm^3	316 [105–500]
Endoscopy (n = 5) ^b	
Stricture	5
Circumferential inflammation	2
Erosive lesion	1
Scarring lesion	1
Histology (detectable other cells ^b)	
Lymphocytes	5
Neutrophils	4
Plasma cells	2
Tissue eosinophils, /HPF	
<15	1
15–50	3
>100	2

^a Positive for specific IgEs.

^b Overlapping.

Table 3. Treatments of patients with esophagitis with eosinophilic infiltration associated with CEA/CES

Treatments just after biopsy	
Esophageal dilatation + PPI	3
Esophageal dilatation + steroids + PPI	1
Esophageal dilatation only	1
Diet modification	2 ¹
Operation	1
Reduction of eosinophil number after treatment (n = 3)	3/3
Improvement (short-term)	6/6

¹ Overlapping.

up just after the treatment, had esophageal biopsies before and after treatment, with a reduction of eosinophil infiltration observed in all 3. In terms of long-term prognosis, 2 were lost to follow-up due to relocation. With the exception of 1 patient who underwent surgery, a Bianchi procedure, the remaining 3 ultimately required fundoplication and 1 of them also underwent end-to-end anastomosis for CES.

Discussion

In addition to primary EoE defined in consensus guidelines, there are 2 subtypes of secondary eosinophil-associated esophageal disorders [3]: the first associated with systemic eosinophilic disorders and the second observed in noneosinophilic disorders. Esophagitis with eosinophil infiltration in CEA and CES may be classified as secondary eosinophilic esophageal diseases derived from noneosinophilic disorders.

Primary EoE is considered an allergic disorder, with the majority of patients sensitive to food allergens and/or aeroallergens based on IgE-mediated test results [1]. In addition, an allergic insult on mucosal epithelium by food antigens or aeroallergens plays a role in the onset of EoE [8]. Indeed, 4 patients had food allergies in this study. The food impactions by esophageal stricture associated with CEA repair or CES might facilitate mucosal damage resulting in esophageal eosinophil infiltration. Therefore, an allergic response may provoke or exacerbate esophageal stricture following CEA repair.

Males are more likely to be affected than females in both EoE and CEA [1, 9]. In our study, the majority of patients were male. The bimodal age distribution we observed may be due to the updated indications for esophageal biopsy in patients with GERD requiring that EoE be distinguished from GERD.

The number of eosinophils may be useful in order to differentiate EoE from GERD, as suggested by previous studies [10]. Up to 7 eosinophils/HPF is suggestive of GERD, whereas 7–24 eosinophils/HPF indicates a combination of GERD and allergic response and >20–24 eosinophils/HPF is more likely to be EoE. In our study, 5 of 6 patients had a relatively greater extent of tissue eosinophilia, suggestive of EoE. Previous studies have also reported 9 patients with similar histological findings [5–7]. Esophagitis with eosinophil infiltration associated with CEA or CES cannot be explained by GERD alone. Furthermore, genetic similarities between CEA and EoE have recently been proposed [6]. It would be suggested that the eosinophil infiltration in the patients who had esophagitis associated with CEA or CES may be a primary effect as well as a result of acid reflux from the stomach as seen in GERD. Therefore, a greater extent of eosinophilia may be due to a combination of GERD, allergic disorders and CEA, implying that eosinophils appear not to be bystanders but effector cells in these conditions.

An increase of peripheral blood eosinophils ($>300\text{--}350/\text{mm}^3$) has been described in 40–50% of patients with

primary EoE [1]. However, a greater extent of eosinophilia, as observed in eosinophilic gastroenteritis, would be uncommon in EoE [11]. Our patients with esophageal eosinophilic inflammation associated with CEA or CES also had relatively lower peripheral blood eosinophil counts. Peripheral blood eosinophilia may be an unsuitable marker for suspecting the development of esophageal eosinophilic inflammation in the patients with CEA repair or CES.

The majority of patients were treated with esophageal dilatation followed by PPI treatment alone or with systemic or intralesional steroids. Systemic or intralesional steroids have been occasionally and successfully used for refractory esophageal stenosis following CEA repair [12, 13]. However, the use of steroids mostly did not target eosinophil infiltrations in early patients as little was known at the time concerning EoE. A subset of patients with esophageal eosinophilia suggestive of EoE has been found to respond well to PPI treatment. According to the new consensus guidelines, these patients have PPI-responsive esophageal eosinophilia [1]. Interestingly, a recent report showed that PPIs significantly inhibit IL-4-stimulated eotaxin-3 expression by reducing the binding of STAT6 to the eotaxin-3 promoter in esophageal cells, independently of their effects on gastric acid secretion [14]. In our study, 2 patients treated with esophageal dilatation followed by PPI experienced a significant improvement with regard to eosinophil infiltration. Hence, despite the potential for a refractory esophageal stricture, a subset of esophagitis with eosinophil infiltration associated with CEA or CES may resemble that of PPI-responsive esophageal eosinophilia. All taken together, PPI and/or steroids after esophageal dilatation could be a promising therapeutic approach for esophagitis with eosinophil infiltration associated with CEA or CES as well as EoE and PPI-responsive esophageal eosinophilia.

In conclusion, we described 6 patients with esophagitis with marked eosinophil infiltration suggestive of EoE associated with CEA or CES. All patients had coexisting allergic disorders, with a high incidence of food allergies in particular. The development of allergic disorders, particularly food allergies, in patients following CEA repair or with CES may provoke eosinophil infiltration and consequently exacerbate esophageal strictures or GERD. Our findings suggest that esophageal dilatation followed by PPI either alone or in combination with steroids may be an effective treatment strategy to help provide symptomatic relief by reducing eosinophil infiltration in esophageal strictures or GERD associated with CEA or CES.

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Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of this article.

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