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Causes and Outcomes of Esophageal Perforation in Eosinophilic Esophagitis

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Abstract

Goals—To characterize patients who suffer perforation in the context of EoE and to identify predictors of perforation

Background—Esophageal perforation is a serious complication of eosinophilic esophagitis (EoE).

Methods—We conducted a retrospective cohort study of the UNC EoE clinicopathologic database from 2001–2014. Subjects were included if they had an incident diagnosis of EoE and met consensus guidelines, including non-response to a PPI trial. Patients with EoE who had suffered perforation at any point during their course were identified, and compared to EoE cases without perforation. Multiple logistic regression was performed to determine predictors of perforation.

Results—Out of 511 subjects with EoE, 10 (2.0%) had experienced an esophageal perforation. While those who perforated tended to have a longer duration of symptoms prior to diagnosis (11.4 vs. 7.0 years, p=0.13), a history of food impaction (OR 14.9; 95% CI 1.7–129.2) and the presence of a focal stricture (OR 4.6; 1.1–19.7) were the only factors independently associated with perforation. Most perforations (80%) occurred after a prolonged food bolus impaction, and only half of individuals (5/10) carried a diagnosis of EoE at the time of perforation; none occurred after dilation. Six patients (60%) were treated with non-operative management, and four (40%) required surgical repair.

Conclusion—Esophageal perforation is a rare but serious complication of eosinophilic esophagitis, occurring in approximately 2% of cases. Most episodes are due to food bolus

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impaction or strictures, suggesting that patients with fibrostenotic disease due to longer duration of symptoms are at increased risk.

Keywords

perforation; eosinophilic esophagitis; food impaction; endoscopy; complication

Introduction

Eosinophilic esophagitis (EoE) is a recently recognized disorder characterized by symptoms of esophageal dysfunction and eosinophilic infiltration of the esophagus that persists despite acid blockade.[1–3] The hallmark symptoms in adolescents and adults with EoE are dysphagia and food impaction, which are often secondary to fibrostenotic changes in the esophagus due to chronic eosinophilic inflammation.[2, 3] Despite being a recently-defined condition, the prevalence of EoE continues to increase, and gastroenterologists and allergists now commonly encounter patients with eosinophilic esophagitis.[4–6]

Esophageal perforation is a potentially life-threatening complication of EoE, and can occur in the setting of prolonged retching as spontaneous Boerhaave's syndrome,[7–9] as a complication of esophageal food bolus impaction or retching during endoscopy, or after mechanical dilation of esophageal strictures in EoE.[9–11] Inflammatory changes and fragility of the esophageal mucosa, as well as esophageal remodeling, are thought to increase the risk for spontaneous or iatrogenic esophageal perforation. Despite once being considered a relatively common complication following endoscopic dilation in EoE,[9–11] rates of iatrogenic perforation in EoE have been shown to be similar to rates after dilation of other stenotic esophageal conditions.[12–17] Esophageal food bolus impaction (EFBI), however, continues to pose significant risk to EoE patients, as unrecognized EoE can dramatically increase the risk of spontaneous perforation following emesis and retching.[7] However, little is known about the context in which esophageal perforation occurs or predictors of perforation.

The aim of this study was to identify and characterize patients with EoE whose course was complicated by esophageal perforation, and to determine risk factors for predictors of perforation.

Materials and Methods

We conducted a retrospective cohort study of the University of North Carolina EoE clinicopathologic database from 2001–2014. This database contains information on patients of all ages who had an incident diagnosis of EoE; details of this database have been published previously.[18–22] Subjects were included if they met consensus guidelines for EoE[1, 3] including symptoms of esophageal dysfunction (such as dysphagia, food impaction, heartburn, or feeding intolerance), an esophageal biopsy with at least 15 eosinophils in at least one high-power field (eos/hpf) after a high-dose trial of a proton pump inhibitor (PPI), and other causes of esophageal eosinophilia excluded. Of note, with the database including dates prior to the 2007 EoE diagnostic guidelines, we required confirmation that patients had

been on a PPI for at least 8 weeks for inclusion in this study, and if we could not find documentation of this, they were excluded.

Electronic medical records were reviewed to identify all EoE patients with a history of perforation. An esophageal perforation was defined as objective evidence on an imaging test of esophageal discontinuity. These findings included intrathoracic air, paraesophageal abscess, contrast extravasation, and frank transmural rupture. Based on these findings, we classified the perforation as transmural (evidence of a full thickness disruption of the esophageal wall with contrast extravasation into the mediastinum and intrathoracic air present) or contained (evidence of esophageal disruption with intrathoracic air, but without contrast extravasation into the mediastinum). For subjects experiencing perforation, the suspected cause, treatments, and outcomes were noted. Additional data extracted included demographics, presenting symptoms, endoscopic features (such as rings, strictures, narrowing, white plaques/exudates, linear furrows, and edema), and histologic findings.

Statistical analysis was performed with Stata version 13 (Statacorp, College Station, TX). Descriptive statistics were used to summarize data, and bivariate analyses were performed using Student's t-test, chi-square test, and Fisher's exact test where appropriate to compare features of EoE cases with and without perforation. Multivariable analysis was performed with logistic regression to assess for independent predictors of perforation. This study was approved by the University of North Carolina Institutional Review Board.

Results

Clinical characteristics of EoE cases with and without perforation

Out of 511 subjects with EoE, 10 (2.0%) were identified who experienced an esophageal perforation. Patients with perforation were more likely to have a history of dysphagia (100% vs. 68%, p=0.04) and food impaction (80% vs. 33%, p=0.003) (Table 1). Those who perforated tended to be older at diagnosis (36 vs. 26 years, p=0.10) and have a longer duration of symptoms prior to diagnosis (11.4 vs. 7.0 years, p=0.13) compared to those who did not, although these differences did not reach statistical significance. Rates of atopic disease and food allergies were similar in both groups. Patients suffering perforation tended to have more typical EoE findings on upper endoscopy, including a diffuse narrowing (30% vs. 14%, p=0.15) and focal stricturing (60% vs. 18%, p=0.004). Maximum esophageal eosinophils did not differ between the two groups (Table 1). In a multivariate regression model including length of symptoms prior to diagnosis, age at EoE diagnosis, history of food impaction, and presence of a focal stricture on EGD, a history of food impaction was the strongest predictor of experiencing esophageal perforation (OR 14.9; 95% CI 1.7–129.2). The only other factor independently associated with experiencing perforation was the presence of a focal stricture (OR 4.6; 1.1–19.7).

Perforation details, treatments, and outcomes

Details for all 10 patients who experienced a perforation are presented in Tables 2 and 3, and representative images are shown in Figure 1. At the time of esophageal perforation, patients had a mean age of 33.5 years. 80% (8/10) of perforations occurred in the setting of a food

impaction, either spontaneously or after attempted endoscopic removal of a food bolus. Four individuals had perforations during or post-endoscopy; patients carried a diagnosis of EoE in 1/4 of these cases. Overall, only half of individuals who experienced perforation (5/10) carried a diagnosis of EoE at the time of perforation, and none of these individuals were on topical steroids when the perforation occurred (note: topical steroids are not approved by the FDA for treatment of EoE). Perforation occurred in a community practice setting for 60% of the cases (6/10) and in an academic/tertiary care center for the other four cases (40%). Six patients (60%) were treated with non-operative management, usually consisting of bowel rest and IV antibiotics. The remaining four (40%) required surgical repair of the esophageal perforation; posterior thoracotomy was performed in three and left thoracotomy was performed in one. No minimally-invasive surgical approaches or endoscopic stenting/closure techniques were used. The esophagus could be closed primarily in 3 cases, but due to tissue disruption and inflammation, a T-tube was used to repair the esophagus in the fourth case. Four of the six patients with a transmural esophageal perforation were preferentially managed with surgical intervention. No individuals with a contained perforation underwent surgery. Patients stayed a mean of 7.3 days in the hospital (range 3–12) after their perforation, with those having surgery requiring more time (9.5 vs. 5.8 days on average).

Discussion

Esophageal perforation is a serious and feared complication of EoE, but it has not been extensively investigated. In this study, we analyzed a large cohort of more than 500 adults and children with EoE, and found that only 10 had previously suffered esophageal perforation. 40% of these cases required surgical repair, and there were no deaths related to either surgery or perforation. Notably, more than three-quarters of the perforations were complications of esophageal food impaction, three were likely iatrogenic from endoscopic manipulation, and none of the patients who perforated were on anti-inflammatory EoE-specific treatment at the time of perforation.

This report greatly augments the literature regarding perforation in the setting of EoE. In the existing literature, spontaneous esophageal perforation has been described in 22 cases published over 16 articles (Table 4), and 13 cases were associated with food impaction.[7, 8, 23–35] When the 10 cases presented here are added to those previously reported in the literature,[7, 8, 23–35] 21 out of a total of 32 reported perforations in EoE have been associated with food bolus impaction. This association may be explained by several factors. First, EoE patients can have mucosal fragility, commonly manifest by shearing or tearing of the esophageal wall with passage of the endoscope.[36, 37] Second, EoE can lead to fibrostenotic changes in the esophagus, including deposition of collagen in the laminal propria, focal stricturing, diffuse narrowing, decreased compliance, and altered motility.[18, 38–40] These mechanical changes cause dysphagia and predispose to food impaction. In certain individuals, this process can deteriorate into a severe phenotype in which the esophagus is narrowed along its entire length.[417, 9, 30, 42–45] Third, patients with EoE often have a long duration of symptoms prior to diagnosis[15, 17, 30, 46–48] and modify their eating behaviors to minimize symptoms. Because they may be used to transient impactions, they may not seek care rapidly, which might lead to esophageal injury from the impacted food. Finally, when food is acutely impacted and endoscopy is performed, it is a

higher risk procedure. For example, in the Swiss EoE database, of 87 patients experiencing 137 food impactions, there were three perforations, two during rigid esophagoscopy to remove the food bolus and one Boerhaave's syndrome due to retching during the procedure.[7]

In the literature overall, esophageal perforation is reported to have a high morbidity and mortality, and among those with spontaneous perforation the mortality is reported at approximately 33%.[49, 50] While the mortality from perforation is not known in EoE, we did not identify any deaths in our cohort or in the published EoE literature. This would suggest that mortality from esophageal perforation may be lower than that associated with perforation in the general population. One factor that could impact this is the severity of the perforation, whether it is contained or transmural with mediastinal or pleural contamination. Of our cases with transmural perforation, 4 required surgery and had longer hospitalizations and recoveries. In the EoE literature, there are 12 cases with documented full-thickness perforations identified by contrast leak or frank pneumomediastinum out of a total of 22 reported perforations.[7, 8, 23–35] In addition, EoE patients who suffer perforation do so at a relatively young age (mean 32.5 yrs in this cohort), and this likely improves their morbidity after surgery.

Methods to reduce the risk of perforation have not been elucidated. Data from pediatric EoE cohorts suggest reversal of lamina propria fibrosis with topical steroid or dietary elimination therapy,[51, 52] but similar results have not been seen in adults where fibrosis at both the microscopic and macroscopic/endoscopic level tends to persist after anti-inflammatory treatment.[53–55] Additionally, adults with EoE are likely to have longer periods of untreated inflammation, increasing the risk of fibrotic complications such as food impaction,[38] as well as endoscopic findings such as diffusely narrow esophagus or strictures.[18, 38, 56] However, even in adulthood, there may be opportunities to reduce the risk of perforation. In a retrospective study, Kuchen et al found that treatment with topical corticosteroids significantly reduced the risk of food impaction (OR 0.41).[57] In addition, dilation of strictures or narrowing may decrease the risk of food impactions, but this has not been studied in detail.[13, 14, 16, 58]

There may be practical ways to reduce perforation risk as well, especially in the peri-procedural period. In our series, 4 out of 8 patients who presented for acute EFBI had an upper endoscopy shortly after presentation. In 3 cases (patients 2, 7, and 8) the perforation was identified either in the endoscopy suite or over the next few hours; in 1, dilation was performed during the urgent endoscopy after the food was removed (done at an outside center). Based on this, we feel the following suggestions should be considered. First, we recommend that endoscopists do not blindly push the bolus forward, as this could cause injury or perforation at a more distal stricture or narrowing site. Second, the endoscopist should always visualize the tip of the instrument they are using (e.g., roth net, grasper device, etc) and avoid passing these instruments blindly. Third, dilation in the setting of an EFBI is likely high-risk due to underlying mucosal injury from the food bolus, and we typically do not dilate patients at the time of an acute food bolus impaction. However, we do agree with the recommendation to obtain routine esophageal biopsies at the time of the food impaction, because the pretest probability of EoE in this setting is high.[2, 59, 60] If a

recognized or suspected esophageal perforation occurs, urgent surgical consultation is recommended to assist in management.

This study has several limitations. As a retrospective study, there is potential loss to follow-up, so individuals who had a perforation but sought care at another institution would not be captured in these data. This would lead to an underestimation of the risk of perforation in our cohort. There was no standardized protocol for how a perforation should be diagnosed/confirmed and our patients presented with a variety of clinical manifestations of perforation. We also could not fully characterize the details of the food bolus impaction, including the length of time the bolus had been present. Additionally, we present data from a single tertiary center, so the results may not be generalizable to other settings. However, strengths of the study include a large cohort of EoE cases, with detailed demographic and clinical characteristics reported using standardized criteria, that allowed for an analysis of predictors of perforation. We also report the largest series of esophageal perforations yet described in EoE, increasing the number of perforations reported in the literature by more than 50%.

In conclusion, esophageal perforation is a rare but severe complication of eosinophilic esophagitis. Most perforations occurred either at the time of a food impaction in patients with unrecognized EoE, or in patients who were not actively being treated for EoE and had a food impaction. No perforations were seen after dilation. Despite greater recognition of EoE by gastroenterologists, patients have long delays in diagnosis, and it is difficult to predict who may develop severe complications of EoE such as esophageal perforation. Therefore, physicians should have a high suspicion for previously unrecognized or untreated EoE in patients presenting with food impaction, as well as for the possibility that esophageal perforation can complicate food impaction. Future study of mechanical and medical treatment of adults with EoE is needed to determine the optimal way to mitigate perforation risk in this population.

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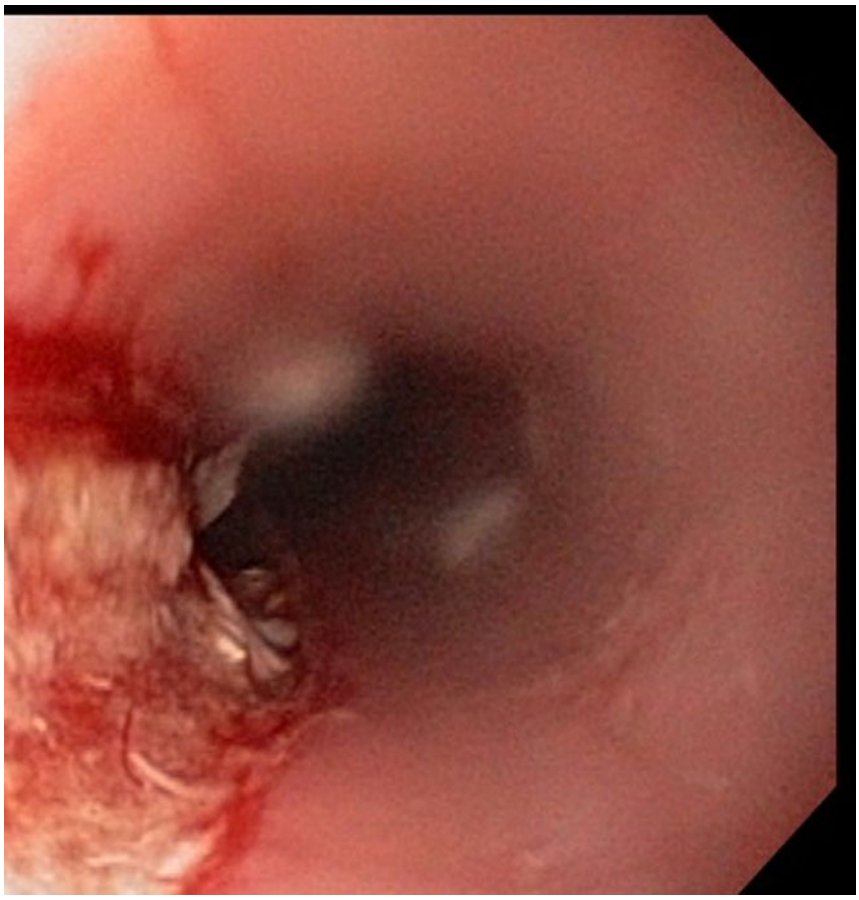

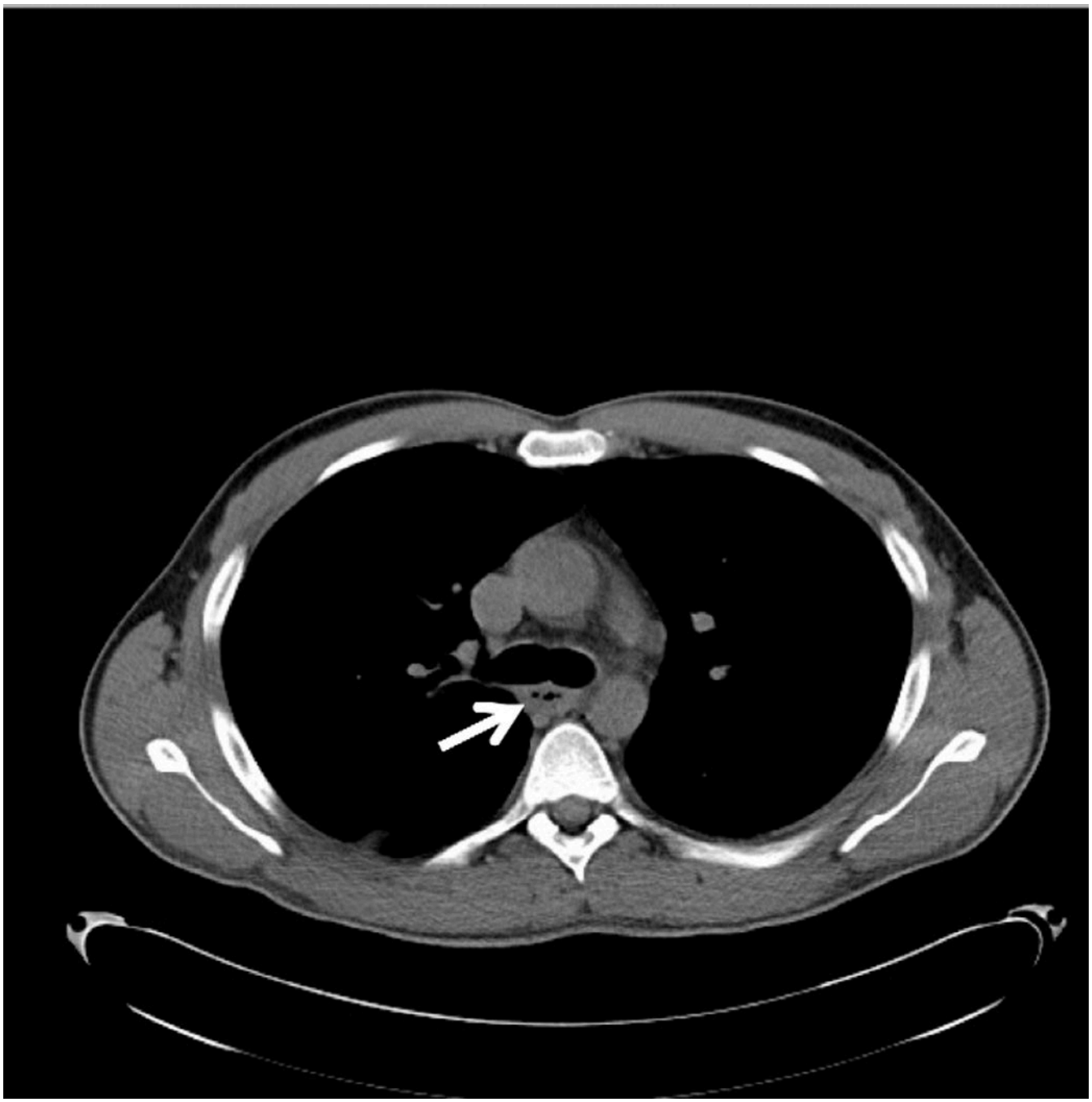

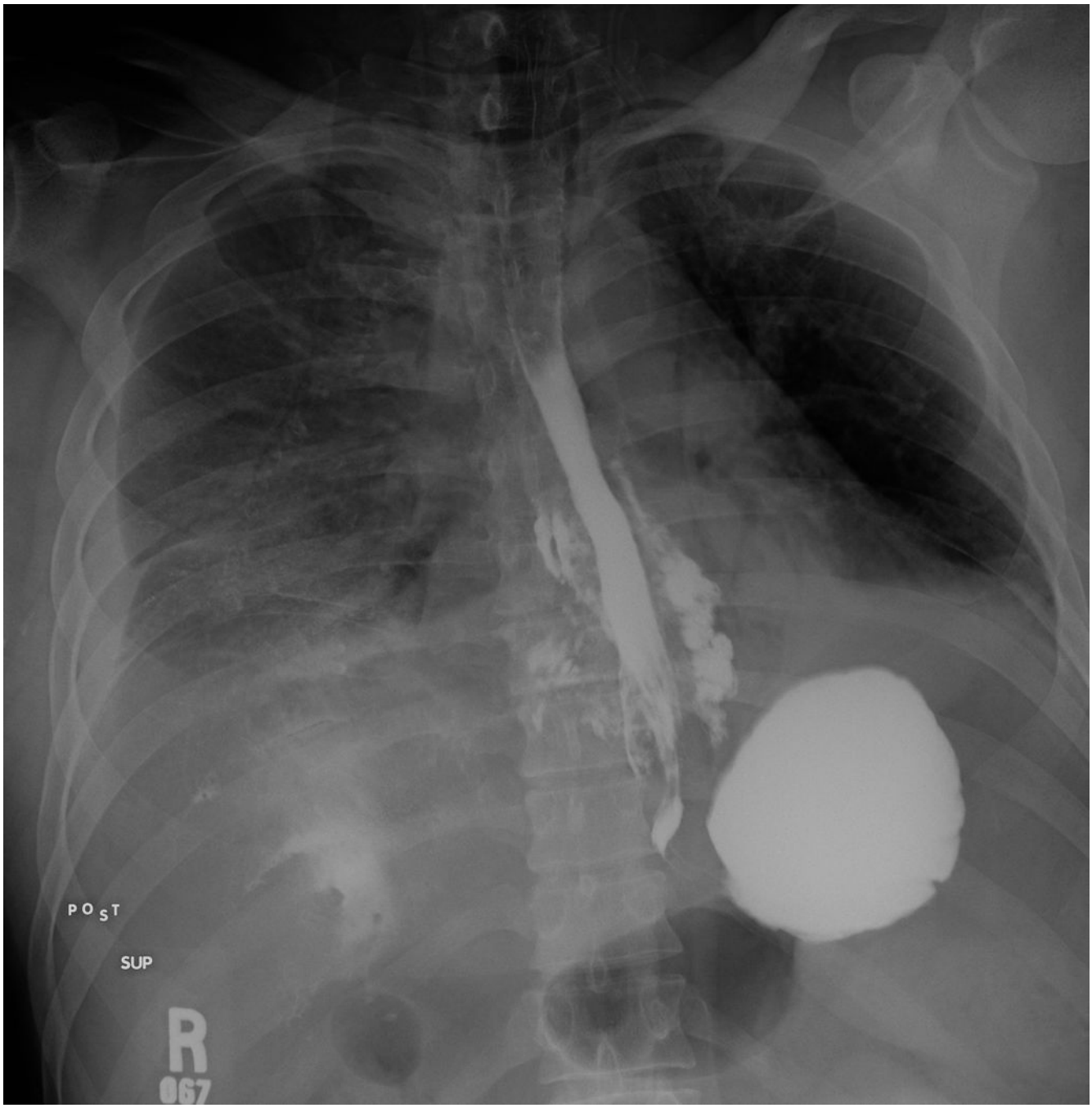

Figure 1.

Examples of esophageal perforations in EoE patients. **(A)** Endoscopic view of a deep mucosal rent concerning for an esophageal perforation. **(B)** Noncontrasted chest CT scan in a different patient demonstrating diffuse esophageal wall thickening with associated paraesophageal stranding. A small amount of free mediastinal air can be seen (arrow), as well as paraesophageal fluid suggestive of phlegmon vs. abscess, suggesting a transmural

perforation. **(C)** Barium swallow in a different patient with free extravasation of contrast into the mediastinum consistent with a transmural perforation.

Table 1

Characteristics of EoE patients with and without esophageal perforation

	Perforation (n = 10)	No perforation (n = 501)	p*
Age at diagnosis, mean yrs ± SD	36.3 ± 9.4	26.3 ± 18.9	0.10
Symptom length prior to diagnosis, mean yrs ± SD	11.4 ± 7.2	7.0 ± 8.7	0.13
Male, n (%)	7 (70)	358 (72)	1
White, n (%)	9 (90)	405 (82)	1
Symptoms, n (%)‡			
Dysphagia	10 (100)	335 (68)	0.04
Food impaction	8 (80)	156 (33)	0.003
Heartburn	2 (20)	187 (39)	0.19
Chest pain	2 (20)	49 (10)	0.28
Abdominal pain	1 (10)	107 (22)	0.70
Failure to thrive	0 (0)	57 (12)	0.38
Food allergies	3 (30)	103 (24)	0.71
Any atopic disease	3 (30)	173 (37)	0.75
Baseline endoscopic findings, n (%)			
Normal endoscopy	0 (0)	75 (15)	0.37
Rings	7 (70)	219 (44)	0.12
Narrowing	3 (30)	68 (14)	0.15
Stricture	6 (60)	88 (18)	0.004
Linear furrows	6 (60)	237 (48)	0.53
White plaques	3 (30)	136 (27)	1
Decreased vascularity	2 (20)	113 (23)	1
Max eosinophil counts, mean eos/hpf ± SD	76.3 (84.9)	79.8 (75.3)	0.89

SD, standard deviation; *eos*, eosinophils; *HPF*, high-power field

* *P* values calculated using Student's t-test for continuous variables and chi-squared test for categorical variables.

‡ Information on symptoms collected at time of diagnostic endoscopy. Information available for eleven out of twelve individuals who suffered perforation

Table 2

Clinical details and EoE history among those with perforation

	Overall (n = 10)	Perforation before 10/2007** (n=4)	Perforation after 10/2007** (n=6)
EoE diagnosed at time of perf, n (%)	5 (50)	1 (25)	4 (80)
On treatment at time of perf *	0 (0)	0 (0)	0 (0)
Occurred in community	6 (60)	2 (40)	4 (67)
Associated with food impaction	8 (80)	3 (75)	4 (67)
Required surgery	4 (40)	2 (50)	2 (33)
Prior esophageal dilation ǂ	2 (20)	1 (25)	1 (17)

SD, standard deviation

*Among those carrying a diagnosis of EoE

**Before or after release of consensus recommendations on diagnosis and treatment of EoE.

ǂDenotes patient who received esophageal dilation at any point during course of disease prior to developing perforation

Table 3

Clinical vignettes of individuals with esophageal perforation

Case #	Patient age (years)	Sex	Prior symptoms	Presentation/Course	Had surgery?	Final dx	EoE Dx known?	Assoc with food impaction?	Ever dilated prior?
1	25	Male	History of chronic dysphagia, heartburn	4 days of severe abdominal pain. CT showed paraesophageal abscess, no visible air. Barium swallow showed no contrast extravasation. Treated conservatively with IV antibiotics and bowel rest. Discharged after 8-day hospitalization.	No	Contained perforation	Yes	No	Yes
2	36	Female	Allergic rhinitis and sinusitis, dysphagia for 8–10 years	Presented with inability to swallow secretions after eating cereal. Had urgent endoscopy at outside center, during which food was dislodged and balloon dilation was performed. Returned 5 hours post-procedure with severe abdominal pain and chest pain. Negative barium swallow. CT Chest performed, showed pneumomediastinum. Treated with IV antibiotics and bowel rest. Discharged after 7-day hospitalization.	No	Transmural perforation	No	Yes	No
3	32	Male	Asthma, dysphagia, hx of food impactions.	Presented to ER with chest pain and hematemesis 3 hours after eating lettuce. Then vomited food and blood. Barium swallow showed intramural esophageal tear. Chest CT showed gas	No	Transmural perforation	Yes	Yes	No

Case #	Patient age (years)	Sex	Prior symptoms	Presentation/Course	Had surgery?	Final dx	EoE Dx known?	Assoc with food impaction?	Ever dilated prior?
				dissecting into wall of esophagus and bilateral pleural effusions. Treated with IV antibiotics and bowel rest. Discharged after 5-day hospitalization.					
4	47	Male	History of asthma, esophageal perforation in past	Presented to ER with sore throat ×1 week, fever to 101° F for 1 day. CT demonstrated circumferential thickening of the distal esophagus with a loculated paraesophageal fluid collection. Treated with IV antibiotics, fluids, and bowel rest. Discharged home after 3-day hospitalization.	No	Contained perforation	Yes	No	Yes
5	43	Male	None	Presented to ER with 6 hours of abdominal pain, chest pain, after eating nachos. Barium swallow showed extravasation of contrast and moderate R pleural effusion. Taken to OR, underwent R thoracotomy with evacuation of empyema and primary closure of esophagus. Discharged after 11-day hospitalization.	Yes	Transmural perforation + empyema	No	Yes	No
6	19	Male	Childhood allergies to cats, dogs	Presented to ER with inability to swallow secretions 4 hrs after eating steak. Had EGD with disimpaction of food, but returned to ER with severe chest pain. Barium swallow negative for	No	Contained perforation	Yes	Yes	No

Case #	Patient age (years)	Sex	Prior symptoms	Presentation/Course	Had surgery?	Final dx	EoE Dx known?	Assoc with food impaction?	Ever dilated prior?
				contrast extravasation. CT showed para-esophageal gas and pneumomediastinum. Treated with IV antibiotics and bowel rest. Discharged home after 7-day hospitalization.					
7	42	Male	Asthma, GERD	Presented to ER with chest pain and feeling that food was stuck, 8 hrs after eating chicken. EGD performed, food bolus removed piecemeal. Immediately post-procedure, had severe chest pain, crepitus. CXR showed pneumomediastinum with air tracking into neck. The pt. underwent left thoracotomy with primary closure of the esophagus. He was discharged home after 6-day hospitalization.	Yes	Transmural perforation	No	Yes	No
8	29	Female	None	Presented to ER with inability to swallow secretions after eating meat, passed after glucagon administration. Several days later, had routine outpatient EGD, scope unable to be passed. Perforation observed during procedure. Patient given IV antibiotics, bowel rest, and observed. Discharged after 5-day hospitalization.	No	Transmural perforation	No	Yes	No

Case #	Patient age (years)	Sex	Prior symptoms	Presentation/Course	Had surgery?	Final dx	EoE Dx known?	Assoc with food impaction?	Ever dilated prior?
9	33	Female	Seasonal allergies, GERD	Presented to ER with severe abdominal pain 15 hours after eating chicken, after several episodes of emesis. Barium swallow showed contrast extravasation and pneumomediastinum. Pt was taken to the OR for thoracotomy; had primary closure of the esophagus. Discharged after 12-day hospitalization.	Yes	Transmural perforation	No	Yes	No
10	28	Male	None	Presented to outside ER with severe chest and epigastric pain ×3–4 hours after eating a piece of pot roast. CXR showed pneumomediastinum. Patient emergently transferred for surgical evaluation. Underwent a left thoracotomy with T-tube repair of esophagus. Discharged after 9-day hospitalization.	Yes	Transmural perforation	Yes	Yes	No

Table 4

Literature Review – Prior Studies That Describe Spontaneous Esophageal Perforation in EoE.

Author	Year	# Perfs	# Associated with food impaction	# Treated Surgically	Method of Diagnosis (n)
Fischer	2015	1	0	0	EGD
Jacobs	2015	2	2	0	CT Chest
Vernon	2015	2	1	0	CT Chest, EGD
Van Rhijn	2014	1	1	0	Chest X-ray
Jackson	2013	4	0	2	CT Chest
Predina	2012	1	1	0	Chest X-ray
Fontillon	2012	1	1	1	EGD
Lucendo	2011	2	2	2	CT Chest, Chest X-ray
Quiroga	2009	1	0	0	Barium swallow
Liguori	2008	1	1	1	CT Chest
GÓmez	2008	1	1	0	CT Chest
Straumann	2008	1	0	1	EGD
Cohen	2007	1	0	1	CT Chest
Prasad	2005	1	1	0	CT Chest
Mecklenberg	2005	1	1	0	EGD
Riou	1996	1	1	1	Barium swallow
TOTALS, n (%)		22	13 (59)	9 (41)	CT Chest: 12 (55) EGD: 5 (23) Chest X-ray: 3 (14) Barium swallow: 2 (9)