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The Extreme Narrow-Caliber Esophagus is a Treatment Resistant Sub-Phenotype of Eosinophilic Esophagitis

Swathi Eluri, MD[1], **Thomas M. Runge, MD, MPH**[1], **Cary C. Cotton, MPH**[1], **Caitlin M. Burk, BA**[1], **W. Asher Wolf, MD, MPH**[1], **John T. Woosley, MD, PhD**[3], **Nicholas J. Shaheen, MD, MPH**[1,2], and **Evan S. Dellon, MD, MPH**[1,2]

[1]Center for Esophageal Diseases and Swallowing, University of North Carolina School of Medicine, Chapel Hill, NC

[2]Center for Gastrointestinal Biology and Disease, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

[3]Department of Pathology and Laboratory Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

Abstract

Background and aims—Some patients with eosinophilic esophagitis (EoE) have an extremely narrowed esophagus, but the characteristics of this group have not been extensively described. We aimed to characterize the narrow-caliber phenotype of EoE, determine associated risk factors, and identify differences in treatment response in this sub-group of patients.

Methods—This retrospective cohort study from 2001 to 2014 included subjects with a new diagnosis of EoE per consensus guidelines. Demographic, endoscopic, histologic, and treatment response data were extracted from medical records. An “extreme narrow-caliber esophagus” was defined when the neonatal endoscope was required to traverse the esophagus due to inability to pass an adult endoscope. Cases with and without the extreme narrow-caliber esophagus were compared. Multivariable logistical regression was performed to assess treatment outcomes.

Results—Of 513 patients with EoE, 46 (9%) had an extreme narrow-caliber esophagus. These cases were older (33 vs 22 years; $p<0.01$), had longer symptom duration (11 vs 3 years; $p<0.01$), more dysphagia (98% vs 66%; $p<0.01$), and food impactions (53% vs 31%; $p<0.01$). Dilation was more common with extreme narrowing (69% vs 17%; $p<0.01$). Narrow-caliber patients were more refractory to steroid treatment, with lower symptom (56% vs 85%), endoscopic (52% vs 76%), and histologic (33% vs 63%) responses ($p<0.01$ for all), and these differences persisted after multivariate analysis.

Corresponding Author: Evan S. Dellon MD, MPH, CB#7080, Bioinformatics Building, 130 Mason Farm Rd., UNC-CH, Chapel Hill, NC 27599-7080, Phone: (919) 966-2513, Fax: (919) 843-2508, ; Email: edellon@med.unc.edu.

Conclusion—The extreme narrow-caliber esophagus is a more treatment-resistant sub-phenotype of EoE and is characterized by longer symptom duration and requirement for multiple dilations. Recognition at diagnosis of EoE can provide important prognostic information.

Keywords

Eosinophilic esophagitis; narrow-caliber esophagus; phenotype; diagnosis; outcomes

Introduction

Eosinophilic esophagitis (EoE) is a chronic antigen-mediated disease characterized by a dense eosinophilic infiltrate and esophageal dysfunction [1]. With the increasing prevalence of EoE over the past decade, there has been a greater understanding of the variability in disease manifestation [2-6]. It is well established that adults and children have different clinical presentations [7-9]. Children commonly present with difficulty feeding, vomiting, heartburn, and abdominal pain, whereas adults typically have symptoms of dysphagia, strictures, and food impactions [10-13]. It is unknown whether these symptomatic differences represent distinct phenotypes of EoE or a progressive disease course that evolves from an inflammatory to a fibrostenotic stage in a time-dependent manner [14].

Distinct clinical and endoscopic features differentiate inflammatory and fibrostenotic EoE phenotypes [15]. Inflammatory changes on endoscopy manifest as white exudates, linear furrows, and edema, and patients typically present with symptoms such as nausea and abdominal pain [15, 16]. Patients with fibrotic features experience dysphagia and tend to have rings, strictures, and crepe paper mucosa on examination [10]. In addition, approximately 10% of EoE patients have a diffusely stenotic esophagus described as a narrow-caliber or small-caliber esophagus [1]. This can be characterized as a narrowed esophagus with a fixed internal diameter that can either extend the entire length of the esophagus or skip segments [13, 17], which differs from a stricture that is focal [17]. Although the narrow-caliber esophagus has been recognized as a distinct manifestation of EoE previously, the features of this group of patients has not been described in detail. Currently, there is no standardized definition of a narrow-caliber esophagus, and it is unknown whether it represents a new sub-phenotype of EoE.

The primary aim of this study is to characterize EoE patients with a narrow-caliber esophagus, determine associated risk factors, and identify differences in treatment response to topical steroids for this sub-group. We hypothesize based on clinical experience that the extreme narrow-caliber esophagus is a distinct EoE sub-phenotype and is associated with older age, longer disease duration, and treatment resistant disease compared with patients with a regular-caliber esophagus.

Methods

Study Design, Study Population, and Data Source

This is a retrospective cohort study conducted at the University of North Carolina (UNC) using the UNC EoE clinicopathology database from 2001 to 2014. The development and

characteristics of the database have been previously reported [15, 18, 19]. All subjects included in the study were patients at UNC with an incident diagnosis of EoE who met consensus diagnostic guidelines [1, 20, 21], including symptoms of esophageal dysfunction, ≥15 eosinophils per high-power field (eos/hpf) (hpf area = 0.24 mm^2), non-response to a proton pump inhibitor trial, and exclusion of competing causes. EoE cases were categorized as having an extreme "narrow-caliber" esophagus if the endoscopy report documented a requirement to use a neonatal endoscope (<6 mm diameter) to traverse the esophagus due to inability to pass an adult upper endoscope secondary to narrowing (Fig. 1). Cases of EoE that allowed passage of an adult upper endoscope despite a decrease in esophageal luminal diameter are referred to as "regular-caliber" for the purposes of this study. Of note, presence of focal esophageal strictures could be present in either group. The study was approved by the University of North Carolina Institutional Review Board.

Data were abstracted from the UNC electronic medical records, endoscopy reports, and pathology reports. Patient demographics, symptom characteristics, and duration before diagnosis, history of atopic disease, and food allergy (documented by presence of allergic symptoms with reintroduction of a food or by testing directed by an allergist) were collected. Endoscopic findings obtained included presence of rings, linear furrows, white plaques or exudates, decreased vascularity, crêpe-paper mucosa, strictures, and therapeutic interventions such as dilations. For histologic data, the maximum eosinophil count (eos/hpf; hpf area = 0.24 mm^2) [22] was used, as determined by pathologist review of biopsy samples. Finally, data on topical corticosteroid treatment, prescribed at the discretion of the gastroenterologist, were recorded. Steroid treatment at our institution consistent of an 8-week course of budesonide (0.5-1 mg twice daily mixed into a slurry with 5 g sucralose) [23, 24] or fluticasone (440-880 ug twice daily) [25]. Patients were treated exclusively with topical steroids and did not receive concomitant dietary therapy. All subjects who completed an 8-week course of topical steroid treatment with either budesonide or fluticasone were evaluated for treatment effect.

Definition of Measures

In addition to characterizing the features of the narrow-caliber esophagus, 3 outcomes were also extracted from medical records to assess response to an 8-week course of topical corticosteroid treatment. Symptom response was defined as a subjective patient report of global improvement of prior symptoms (such as dysphagia, food impaction, abdominal pain, nausea, vomiting, heartburn, chest pain, failure to thrive) characterized as yes or no. Endoscopic response was defined as the resolution of previously present features such as rings, furrows, and plaques. Finally, histologic response was defined as achieving an eosinophil count of <15 eos/hpf after a completed course of steroid treatment.

Statistical Analysis

Descriptive statistics were used to examine subject characteristics, and bivariate analyses were performed to determine the relationship between each independent variable and the presence of an extreme narrow-caliber esophagus, using the Student *t* test and Wilcoxon rank-sum for continuous variables and the Pearson chi-square tests for categorical variables. Multivariable logistic regression was used to estimate the odds of symptomatic, endoscopic,

and histologic response to steroid treatment in patients with an extreme narrow-caliber esophagus compared with regular-caliber, after adjusting for potential confounding factors. An additional sub-group analysis was performed to assess outcomes when comparing EoE cases with a narrow-caliber, to cases with a regular-caliber esophagus but with strictures. Based on these models, adjusted and unadjusted odds ratios and 95% confidence intervals were calculated. All analyses were performed using Stata 13 (College Station, Tex).

Results

Clinical Characteristics of the Narrow-Caliber Sub-Phenotype

Out of 513 subjects, 46 (9%) had an extreme narrow-caliber esophagus (Table 1). Mean age at diagnosis of EoE was significantly higher in the narrow-caliber group at 33 years, with only 13% being children less than 18 years, compared with 22 years in the regular-caliber subjects ($p<0.01$). There were no differences between the 2 groups in terms of race and sex. Narrow-caliber patients had longer symptom duration (11 vs 3 years, $p<0.01$) and higher rates of dysphagia (98% vs 66%) and food impaction (53% vs 31%). Both groups were comparable for having a history of atopic diseases, allergy, and asthma. Between 2001 and 2014, the proportion of narrow-caliber cases diagnosed per year did not change with time.

Endoscopic and Histologic Characteristics of the Narrow-Caliber Sub-Phenotype

Endoscopic findings of rings, furrows, white plaques, and crêpe-paper mucosa were significantly more common in the narrow-caliber group (Table 2), and 72% had strictures compared with only 13% with a regular-caliber. All of the narrow-caliber subjects required dilation therapy at some point with a median number of 3 dilations required per patient. In addition, 33% ($n = 15$) of the narrow-caliber group who were dilated underwent repeat dilation within 8 weeks. In contrast, only 26% of the regular-caliber patients underwent dilations with a majority requiring only a single dilation. There was no difference in the maximum number of eos/hpf with a median of 78 and 60 eosinophils in the narrow and the regular patients.

Response to Steroids: Narrow-caliber versus Regular-caliber

Narrow-caliber esophagus patients had less improvement of symptoms, endoscopic findings, and histology after topical steroid treatment (Table 3). Only 56% reported a global subjective improvement in esophageal and gastrointestinal symptoms compared with 85% with a regular-caliber, $p<0.01$. Similarly, fewer in the narrow-caliber group had improvement of endoscopic findings characteristic of EoE (52% vs 76%, $p<0.01$) or histologic response (33% vs 63%, $p<0.01$), as evidenced by a higher median eosinophil count when compared with the regular-caliber subjects (45 vs 3 eos/hpf, $p<0.01$).

These findings persisted after multivariable analysis adjusting for symptom duration, history of dilation, and age. Those with a narrow-caliber esophagus had decreased odds of improvement in symptoms (OR, 0.28; 95% CI, 0.08-0.96), endoscopic findings (OR, 0.31; 95% CI, 0.10-0.90), and histology (OR, 0.27; 95% CI, 0.09-0.74), after a course of steroids compared with the regular-caliber patients (Table 4).

Response to Steroids: Narrow-caliber versus Strictures

There were 60 patients with EoE who had strictures but did not have the extreme narrow-caliber phenotype (Table 5). When these patients were compared with the narrow group (n = 46), there were no significant differences in terms of age at biopsy, race, atopic history, symptom duration, and maximum eosinophil count before treatment. As with the primary analysis, significantly fewer in the narrow-caliber group had symptomatic (56% vs 89%), endoscopic (52% vs 88%), and histologic (33% vs 68%) response to steroids with a higher maximum eosinophil count (median eos/hpf (IQR): 45 (3-90) versus 2 (0-16)) after steroids, compared with those with strictures but a normal-caliber esophagus ($p<0.01$ for all) (Table 6). These findings also persisted on multivariable analysis with the narrow-caliber esophagus subjects having decreased odds of symptom (OR, 0.16; 95% CI, 0.04-0.67), endoscopic (OR, 0.14; 95% CI, 0.04-0.55), and histologic (OR, 0.24; 95% CI, 0.08-0.71) improvement compared with the stricture group.

The effect of steroid type and dose on histologic response was assessed when comparing the narrow-caliber group to those with strictures and to the regular-caliber patients. No differences in histologic response or mean number of eosinophils after treatment were noted based on steroid type or dose in all 3 groups (data not shown).

Discussion

In this study, we aimed to further characterize a possible new sub-phenotype of EoE, the extreme narrow-caliber esophagus. Narrow-caliber patients were predominantly adults with longer symptom duration and delayed diagnosis, with frequent symptoms of dysphagia, high rates of food impaction, and a universal requirement for esophageal dilation. Importantly, patients in the narrow-caliber group were treatment resistant to topical steroids, with profoundly decreased odds of having symptomatic, endoscopic, and histologic response to treatment when compared with EoE patients with a regular-caliber esophagus. Moreover, these clinical outcomes appeared to be specific to the narrow-caliber group, and were not seen in EoE cases with a regular-caliber esophagus and focal strictures, though the groups had similar clinical and histologic characteristics. Due to these differences in clinicopathological presentation and non-response to steroid treatment, identifying the sub-group of EoE patients with a narrow-caliber esophagus can have important prognostic implications.

Although the inflammatory and fibrostenotic phenotypes of EoE have been previously described [14, 15], there is limited literature on the narrow-caliber esophagus. One of the earliest studies demonstrated that the narrow-caliber was a common finding in young patients with dysphagia, which was difficult to detect, and was characterized by the presence of long rents after dilation [26]. Since then, the reported prevalence of narrow-caliber in EoE has ranged from 5% to 28% based on endoscopy with larger studies documenting 9% to 10%, which is comparable with the prevalence in our data [1, 13, 27-30]. It is plausible that the prevalence is even higher as a recent study highlighted that the narrow-caliber may be missed on endoscopy [31]. Endoscopically, the narrow-caliber esophagus has been described as a diffuse decrease in the caliber of the thoracic esophagus [32], and on barium esophagram as narrowing with a mean length of >15 cm and diameter <20 mm [32, 33].

Despite the recognition of the narrow-caliber as an endoscopic and radiographic sign of EoE, there have been no studies to date to our knowledge that have characterized it as a distinct sub-phenotype of EoE.

In our study, the clinical and endoscopic features of the narrow-caliber esophagus are consistent with sequelae of esophageal remodeling and fibrostenosis. Driven by a chronic inflammatory process, esophageal remodeling involves basal cell hyperplasia, subepithelial and transmural fibrosis, and smooth muscle hypertrophy [34-40], which leads to a decrease in esophageal luminal diameter and compliance [41]. Therefore, the pathogenesis of EoE may be an evolution from an inflammatory to a fibrostenotic state [10, 15], as evidenced by the low prevalence of strictures in children and a high prevalence of strictures or esophageal narrowing in those with longer symptom duration before diagnosis [14, 15, 42, 43]. In addition, EoE patients with strictures or a narrow-caliber have lower esophageal distensibility [44]. This raises the question of whether the narrow-caliber esophagus represents a more severe and end-stage manifestation or a treatment-resistant variant of the fibrostenotic phenotype. Although findings such as the increased prevalence of narrow-caliber in adults, longer symptom duration, fibrosis and lower esophageal distensibility suggest an end-stage fibrostenotic state, the decreased response to steroids compared with the regular-caliber cases and those with focal strictures is a new finding, and argues that it is likely a separate sub-phenotype. Reasons for the poor steroid response, which was not explained by steroid dose or type, remain unclear and need to be further elucidated.

Recognizing disease phenotypes that are treatment resistant is important for prognostic implications. There is some evidence that patients with strictures do not respond as effectively to steroids when compared with those with inflammatory symptoms [19, 45-47]. Because patients with a narrow-caliber sub-phenotype have even lower odds of symptomatic, endoscopic, and histologic improvement with topical steroids, these patients may benefit more from sequential dilation therapy, particularly from the symptom response standpoint. However, more aggressive dilation therapy would not result in an improvement of the poor histologic response noted in the narrow-caliber group. Therefore, it is possible that the narrow-caliber group may require higher doses of steroids, longer duration of steroids, or primary dietary therapy, but this requires further study.

The interpretation and generalizability of our study results are limited by its retrospective single-center design. Because of this, patients' symptom response could only be reported as a subjective dichotomous variable of yes or no, and validated symptom scores were not used. Similarly, different endoscopists performed the procedures and a formalized endoscopic scoring system [48] could not be used resulting in minor differences in reporting of endoscopic findings. However, we do not anticipate that this affected the results in a significant manner because the same parameters were used across both comparison groups, but we acknowledge that future prospective studies should be conducted to confirm our response data possibly using standardized endoscopic criteria and documentation of esophageal luminal diameter. We acknowledge that there was no formal assessment of the luminal diameter in defining the narrow-caliber cases other than the use of a neonatal endoscope at the endoscopist discretion. Due to this, there may have been misclassification of some stricture cases as narrow-caliber esophagus. In order to address this, we compared

groups with strictures to the narrow-caliber cases and found a significantly decreased treatment response that persisted in the narrow-caliber group. Therefore, any misclassification of stricture cases as narrow-caliber would have biased our results towards the null hypothesis. Finally, because the patients in this study were treated with topical steroids, we were not able to comment about treatment response with dietary elimination.

Our study has important strengths as well. To our knowledge, this is the first study to characterize the extreme narrow-caliber esophagus in detail and this was possible due to our large sample size. Second, our study is also the first to demonstrate that the narrow-caliber group is more treatment resistant to steroids and this can have significant clinical implications. Third, the data extraction protocol was standardized and extensive, and our analysis allowed stratification by presence of stricture, to show that the narrow-caliber cases had worse treatment response than focal stricture cases, arguing that it is likely a different EoE sub-phenotype rather than end-stage fibrostenotic disease.

In summary, we characterized a new sub-phenotype of EoE, the extreme narrow-caliber esophagus defined by the need to use a neonatal endoscope to traverse the esophagus due to inability to pass an adult endoscope secondary to severe narrowing. Narrow-caliber occurs primarily in adults with longer symptom duration and shares many of the fibrostenotic features, but is more treatment resistant to steroids with poor symptomatic, endoscopic, and histologic response when compared with non-narrowed EoE patients or those with strictures. Therefore, it may be a group that needs more aggressive dilation, higher doses of steroids, or other therapies. Recognizing this group of EoE patients can be helpful in driving treatment decisions and predicting treatment response.

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References

1. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. The Journal of allergy and clinical immunology. 2011; 128:3–20.e6. quiz 1-2. [PubMed: 21477849]
2. Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? The Journal of allergy and clinical immunology. 2005; 115:418–9. [PubMed: 15696105]
3. Kapel RC, Miller JK, Torres C, Aksoy S, Lash R, Katzka DA. Eosinophilic esophagitis: a prevalent disease in the United States that affects all age groups. Gastroenterology. 2008; 134:1316–21. [PubMed: 18471509]
4. Sealock RJ, Rendon G, El-Serag HB. Systematic review: the epidemiology of eosinophilic oesophagitis in adults. Aliment Pharmacol Ther. 2010; 32:712–9. [PubMed: 20662785]
5. Prasad GA, Talley NJ, Romero Y, Arora AS, Kryzer LA, Smyrk TC, et al. Prevalence and predictive factors of eosinophilic esophagitis in patients presenting with dysphagia: a prospective study. The American journal of gastroenterology. 2007; 102:2627–32. [PubMed: 17764492]
6. Dellon ES. Epidemiology of eosinophilic esophagitis. Gastroenterology clinics of North America. 2014; 43:201–18. [PubMed: 24813510]
7. Gonsalves N. Distinct features in the clinical presentations of eosinophilic esophagitis in children and adults: is this the same disease? Digestive diseases (Basel, Switzerland). 2014; 32:89–92.

8. Straumann A, Aceves SS, Blanchard C, Collins MH, Furuta GT, Hirano I, et al. Pediatric and adult eosinophilic esophagitis: similarities and differences. Allergy. 2012; 67:477–90. [PubMed: 22313241]
9. Dellon ES, Liacouras CA. Advances in Clinical Management of Eosinophilic Esophagitis. Gastroenterology. 2014; 147:1238–54. [PubMed: 25109885]
10. Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. Gastroenterology. 2003; 125:1660–9. [PubMed: 14724818]
11. Baxi S, Gupta SK, Swigonski N, Fitzgerald JF. Clinical presentation of patients with eosinophilic inflammation of the esophagus. Gastrointestinal endoscopy. 2006; 64:473–8. [PubMed: 16996334]
12. Lucendo AJ, Sanchez-Cazalilla M. Adult versus pediatric eosinophilic esophagitis: important differences and similarities for the clinician to understand. Expert review of clinical immunology. 2012; 8:733–45. [PubMed: 23167685]
13. Potter JW, Saeian K, Staff D, Massey BT, Komorowski RA, Shaker R, et al. Eosinophilic esophagitis in adults: an emerging problem with unique esophageal features. Gastrointestinal endoscopy. 2004; 59:355–61. [PubMed: 14997131]
14. Schoepfer AM, Safroneeva E, Bussmann C, Kuchen T, Portmann S, Simon HU, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology. 2013; 145:1230–6.e1-2. [PubMed: 23954315]
15. Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointestinal endoscopy. 2014; 79:577–85.e4. [PubMed: 24275329]
16. Fox VL. Eosinophilic esophagitis: endoscopic findings. Gastrointestinal endoscopy clinics of North America. 2008; 18:45–57. [PubMed: 18061101]
17. Vasilopoulos S, Shaker R. Defiant dysphagia: small-caliber esophagus and refractory benign esophageal strictures. Current gastroenterology reports. 2001; 3:225–30. [PubMed: 11353559]
18. Dellon ES, Chen X, Miller CR, Woosley JT, Shaheen NJ. Diagnostic utility of major basic protein, eotaxin-3, and leukotriene enzyme staining in eosinophilic esophagitis. The American journal of gastroenterology. 2012; 107:1503–11. [PubMed: 22777338]
19. Wolf WA, Cotton CC, Green DJ, Hughes JT, Woosley JT, Shaheen NJ, et al. Predictors of response to steroid therapy for eosinophilic esophagitis and treatment of steroid-refractory patients. Clinical Gastroenterology and Hepatology. 2015; 13:452–8. [PubMed: 25086190]
20. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). The American journal of gastroenterology. 2013; 108:679–92. quiz 93. [PubMed: 23567357]
21. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, et al. Eosinophilic Esophagitis in Children and Adults: A Systematic Review and Consensus Recommendations for Diagnosis and Treatment: Sponsored by the American Gastroenterological Association (AGA) Institute and North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition. Gastroenterology. 2007; 133:1342–63. [PubMed: 17919504]
22. Dellon ES, Aderoju A, Woosley JT, Sandler RS, Shaheen NJ. Variability in diagnostic criteria for eosinophilic esophagitis: a systematic review. The American journal of gastroenterology. 2007; 102:2300–13. [PubMed: 17617209]
23. Dellon ES, Sheikh A, Speck O, Woodward K, Whitlow AB, Hores JM, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. Gastroenterology. 2012; 143:321–4.e1. [PubMed: 22561055]
24. Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. Gastroenterology. 2010; 139:418–29.e1. [PubMed: 20457157]
25. Konikoff MR, Noel RJ, Blanchard C, Kirby C, Jameson SC, Buckmeier BK, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. Gastroenterology. 2006; 131:1381–91. [PubMed: 17101314]

26. Vasilopoulos S, Murphy P, Auerbach A, Massey BT, Shaker R, Stewart E, et al. The small-caliber esophagus: an unappreciated cause of dysphagia for solids in patients with eosinophilic esophagitis. Gastrointestinal endoscopy. 2002; 55:99–106. [PubMed: 11756928]
27. Remedios M, Campbell C, Jones DM, Kerlin P. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. Gastrointestinal endoscopy. 2006; 63:3–12. [PubMed: 16377308]
28. Sgouros SN, Bergele C, Mantides A. Eosinophilic esophagitis in adults: what is the clinical significance? Endoscopy. 2006; 38:515–20. [PubMed: 16767590]
29. Kim HP, Vance RB, Shaheen NJ, Dellon ES. The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2012; 10:988–96.e5. [PubMed: 22610003]
30. Pasha SF, DiBaise JK, Kim HJ, De Petris G, Crowell MD, Fleischer DE, et al. Patient characteristics, clinical, endoscopic, and histologic findings in adult eosinophilic esophagitis: a case series and systematic review of the medical literature. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE. 2007; 20:311–9.
31. Gentile N, Katzka D, Ravi K, Trenkner S, Enders F, Killian J, et al. Oesophageal narrowing is common and frequently under-appreciated at endoscopy in patients with oesophageal eosinophilia. Aliment Pharmacol Ther. 2014; 40:1333–40. [PubMed: 25287184]
32. White SB, Levine MS, Rubesin SE, Spencer GS, Katzka DA, Laufer I. The small-caliber esophagus: radiographic sign of idiopathic eosinophilic esophagitis. Radiology. 2010; 256:127–34. [PubMed: 20505062]
33. Tamhankar, A.; Huprich, J.; Bremner, C.; Portale, G.; Tafazzoli, A.; Chandrasoma, P., et al. Gastroenterology. WB Saunders CO; Independence Square West Curtis Center, STE 300, Philadelphia, PA 19106-3399 USA: 2004. The small caliber esophagus: clinical features and radiological diagnosis; p. A447-A.
34. Mishra A, Wang M, Pemmaraju VR, Collins MH, Fulkerson PC, Abonia JP, et al. Esophageal remodeling develops as a consequence of tissue specific IL-5-induced eosinophilia. Gastroenterology. 2008; 134:204–14. [PubMed: 18166354]
35. Aceves SS, Newbury RO, Dohil R, Bastian JF, Broide DH. Esophageal remodeling in pediatric eosinophilic esophagitis. The Journal of allergy and clinical immunology. 2007; 119:206–12. [PubMed: 17208603]
36. Aceves SS, Ackerman SJ. Relationships between eosinophilic inflammation, tissue remodeling, and fibrosis in eosinophilic esophagitis. Immunology and allergy clinics of North America. 2009; 29:197–211. xiii–xiv. [PubMed: 19141355]
37. Rubinstein E, Cho JY, Rosenthal P, Chao J, Miller M, Pham A, et al. Siglec-F inhibition reduces esophageal eosinophilia and angiogenesis in a mouse model of eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2011; 53:409–16. [PubMed: 21970996]
38. Chehade M, Sampson HA, Morotti RA, Magid MS. Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2007; 45:319–28. [PubMed: 17873744]
39. Hirano I, Aceves SS. Clinical implications and pathogenesis of esophageal remodeling in eosinophilic esophagitis. Gastroenterology clinics of North America. 2014; 43:297–316. [PubMed: 24813517]
40. Cheng E, Souza RF, Spechler SJ. Tissue remodeling in eosinophilic esophagitis. American journal of physiology Gastrointestinal and liver physiology. 2012; 303:G1175–87. [PubMed: 23019192]
41. Kwiatek MA, Hirano I, Kahrilas PJ, Rothe J, Luger D, Pandolfino JE. Mechanical properties of the esophagus in eosinophilic esophagitis. Gastroenterology. 2011; 140:82–90. [PubMed: 20858491]
42. Lipka S, Kumar A, Richter JE. Impact of Diagnostic Delay and Other Risk Factors on Eosinophilic Esophagitis Phenotype and Esophageal Diameter. Journal of clinical gastroenterology. 2015
43. Lipka S, Kumar A, Richter JE. Impact of Diagnostic Delay and Other Risk Factors on Eosinophilic Esophagitis Phenotype and Esophageal Diameter. J Clin Gastroenterol. 2015

44. Lin Z, Kahrilas P, Xiao Y, Nicodème F, Gonsalves N, Hirano I, et al. Functional luminal imaging probe topography: an improved method for characterizing esophageal distensibility in eosinophilic esophagitis. Therapeutic advances in gastroenterology. 2012:1756283X12470017.

45. Langdon DE. Fluticasone in eosinophilic corrugated ringed esophagus. The American journal of gastroenterology. 2001; 96:926–7. [PubMed: 11280589]

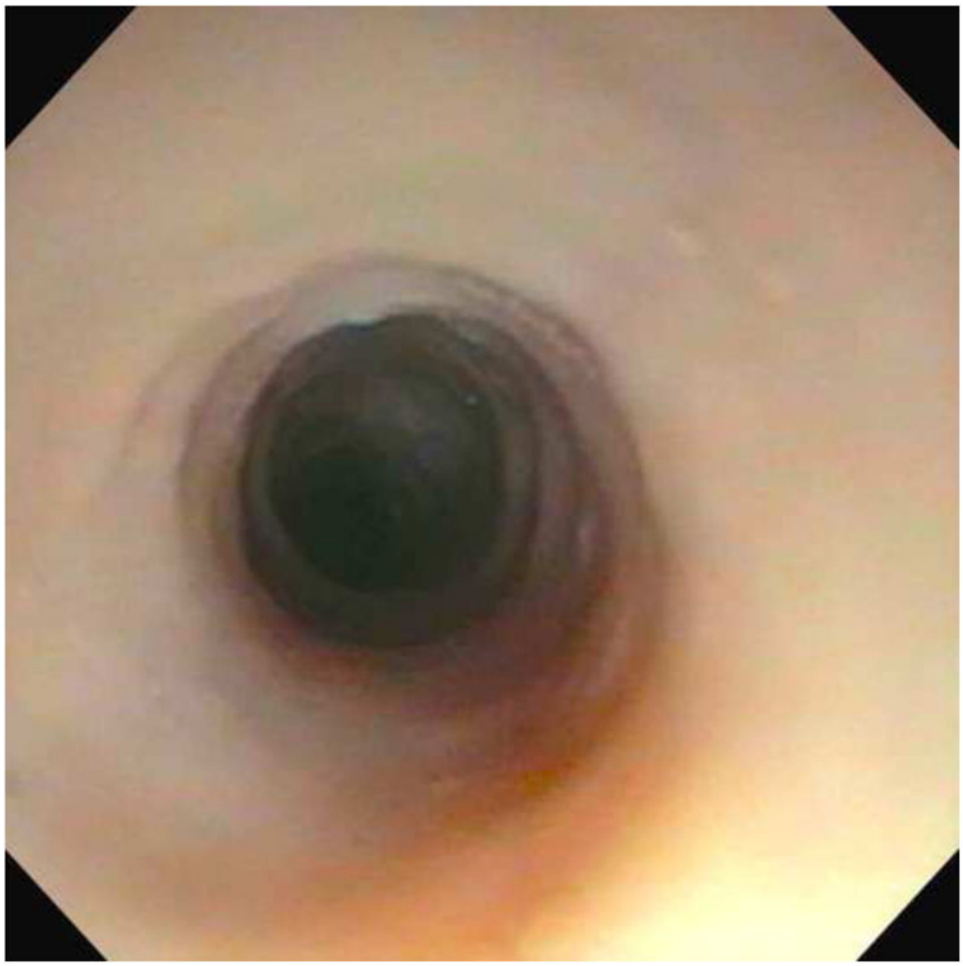
46. Straumann A, Conus S, Degen L, Felder S, Kummer M, Engel H, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology. 2010; 139:1526–37. 37 e1. [PubMed: 20682320]

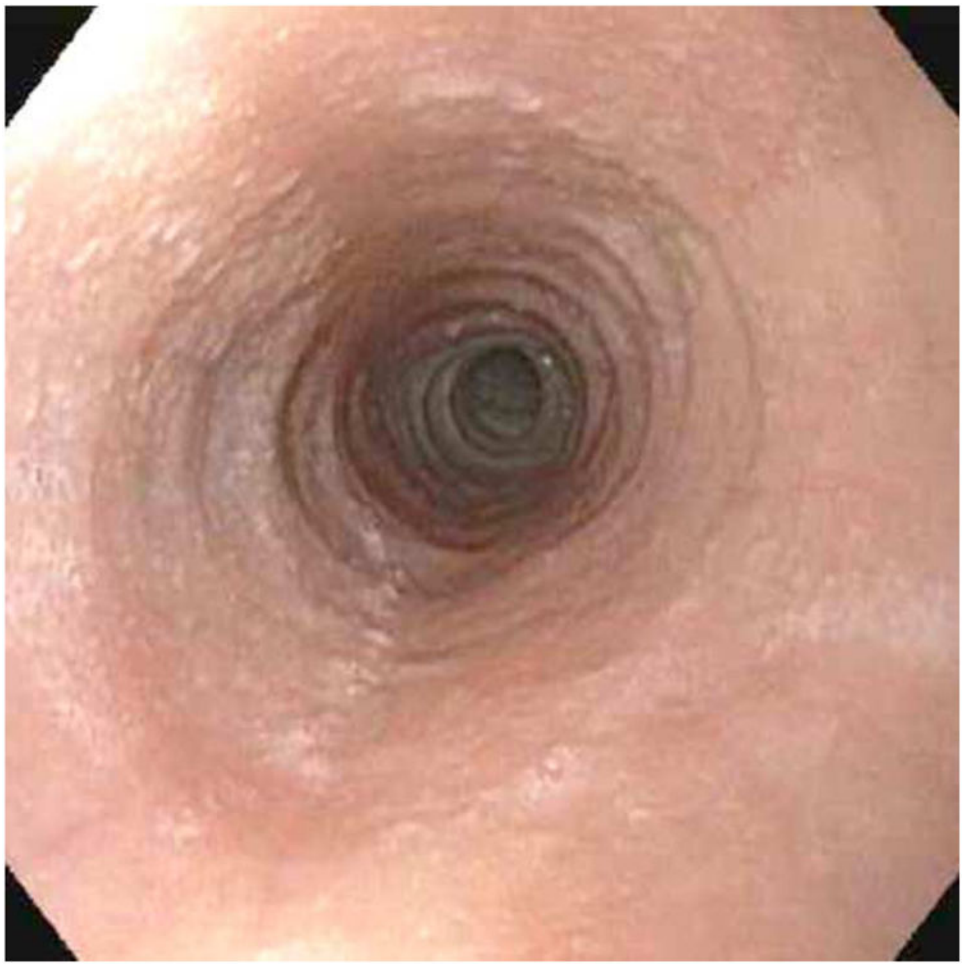
47. Lucendo AJ, Arias A, De Rezende LC, Yague-Compadre JL, Mota-Huertas T, Gonzalez-Castillo S, et al. Subepithelial collagen deposition, profibrogenic cytokine gene expression, and changes after prolonged fluticasone propionate treatment in adult eosinophilic esophagitis: a prospective study. The Journal of allergy and clinical immunology. 2011; 128:1037–46. [PubMed: 21880354]

48. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut. 2013; 62:489–95. [PubMed: 22619364]

Acronyms

EoE	eosinophilic esophagitis
eos/hpf	eosinophils per high power field
OR	odds ratio





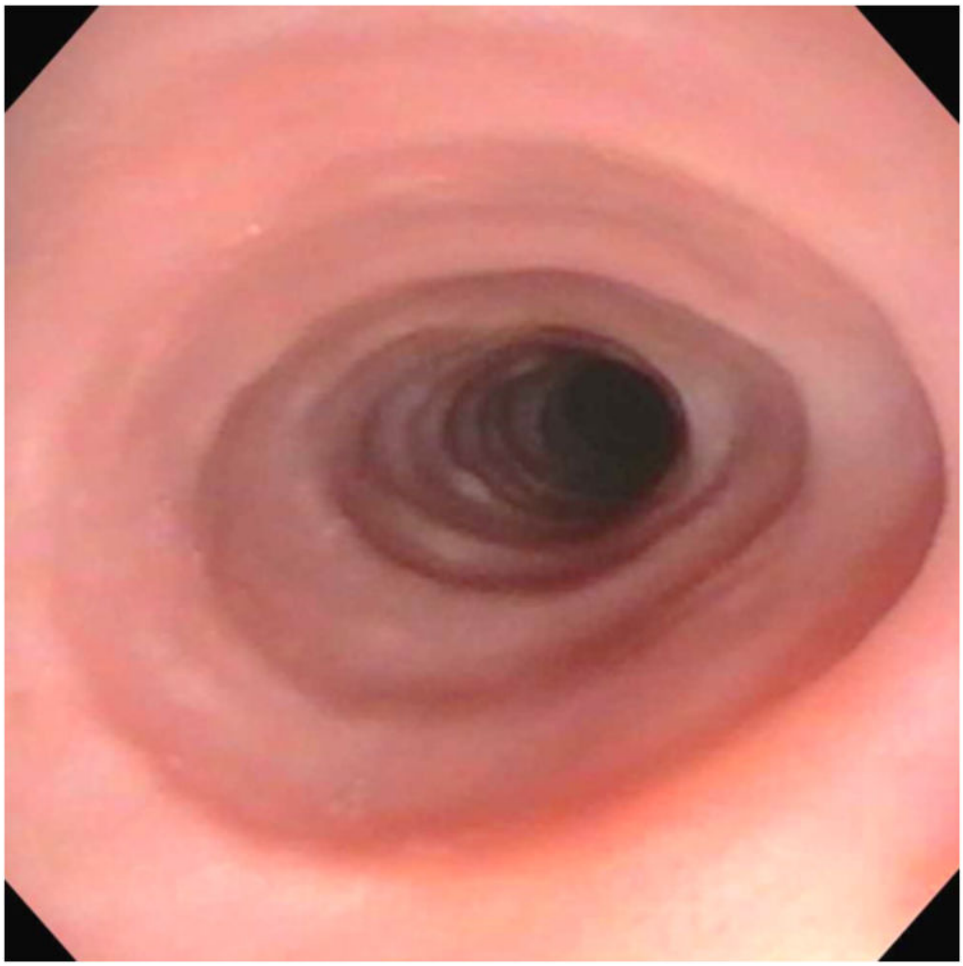


Figure 1.

These images demonstrate the endoscopic appearance of the extreme narrow-caliber esophagus characterized by significant narrowing of the luminal diameter. All 3 images show the presence of esophageal rings and edema and also white plaques/exudates in the third image.

Table 1

Demographic and clinical characteristics of patients with extreme narrow-caliber and regular-caliber esophagus

	Narrow-caliber[a] (n = 46)	Regular-caliber (n = 467)	*P* value[b]
Age at biopsy (mean years, SD)	33.4 (13.1)	22.1 (19.2)	<0.01
Children <18 years (n, %)	6 (13.0)	216 (46.3)	<0.01
Male (n, %)	32 (70)	332 (71)	0.83
Whites (n, %)	42 (93)	373 (81)	0.40
Symptoms (n, %)			
Dysphagia	45 (98)	302 (66)	<0.01
Food impaction	24 (53)	138 (31)	<0.01
Chest pain	5 (11)	46 (10)	0.88
Heartburn	11 (24)	179 (40)	0.04
Abdominal pain	2 (4)	106 (24)	<0.01
Nausea	1 (2)	57 (13)	0.04
Vomiting	7 (16)	124 (28)	0.07
Failure to thrive	1 (2)	57 (13)	0.04
Symptom length before diagnosis (median years, IQR)	11.0 (5-15)	3.4 (1-9)	<0.01
Atopic diseases (n, %)	21 (47)	154 (35)	0.12
Allergic rhinosinusitis (n, %)	28 (64)	218 (51)	0.13
Asthma (n, %)	14 (31)	96 (22)	0.16
Food allergy (n, %)	14 (33)	93 (24)	0.19
History of steroid treatment (n, %)	39 (85)	310 (67)	0.01

[a] Characterized by inability to pass an adult upper endoscope.

[b] p values for significant difference in distribution of proportions and p value for difference in mean age and median symptom length.

Table 2

Endoscopic and histological findings in patients with narrow-caliber and regular-caliber esophagus

	Narrow-caliber[a] (n = 46)	Regular-caliber (n = 467)	*P* value[b]
Endoscopic findings (n, %)			
Rings	40 (87)	188 (41)	<0.01
Linear Furrows	31 (67)	214 (46)	<0.01
White Plaques	19 (41)	119 (26)	0.02
Decreased Vascularity	15 (33)	100 (22)	0.09
Crêpe-paper mucosa	6 (13)	17 (4)	<0.01
Strictures	33 (72)	60 (13)	<0.01
History of dilation (n, %)	46 (100)	123 (26)	<0.01
Number of dilations (median, IQR)	3.0 (1-6)	1.0 (1-2)	<0.01

[a] Characterized by inability to pass an adult upper endoscope.

[b] *P* values for significant difference in distribution of proportions and *P* value for difference in median number of dilations.

Table 3

Response to steroid[a] treatment in patients with narrow-caliber and regular-caliber esophagus

	Narrow-caliber[b] (n = 39)	Regular-caliber (n = 310)	*P* value[c]
Symptom response to steroids (n, %)	14 (56)	175 (85)	<0.01
EGD response to steroids (n, %)	17 (52)	146 (76)	<0.01
Histologic response to steroids (n, %)	11 (33)	119 (63)	<0.01
Maximum eosinophil count before steroids (median, IQR) eos/hpf	77.5 (33-100)	60.0 (37-100)	0.38
Maximum eosinophils after steroids (median, IQR) eos/hpf	45 (3-90)	3 (0-34)	<0.01

[a] Defined as any topical swallowed corticosteroid formulation.

[b] Characterized by inability to pass an adult upper endoscope.

[c] *P* values for significant difference in distribution of proportions and *P* value for difference in maximum eosinophil count.

Table 4

Association between presence of narrow-caliber esophagus and symptomatic, endoscopic, and histologic[a] response to steroid[b] treatment

	Unadjusted odds ratio (95% CI)	Adjusted[c] odds ratio (95% CI)
Symptom response to steroids (n, %)	0.22 (0.09-0.53)	0.28 (0.08-0.96)
EGD response to steroids (n, %)	0.33 (0.15-0.70)	0.31 (0.10-0.90)
Histologic response to steroids (n, %)	0.29 (0.13-0.64)	0.27 (0.09-0.74)

[a] Defined as <15 eosinophils/hpf.

[b] Defined as any topical swallowed corticosteroid formulation.

[c] Adjusted for symptom duration, history of dilation, and age at biopsy.

Table 5

Demographic and clinical characteristics of patients with extreme narrow-caliber and patients with strictures

	Narrow-caliber[a] (n = 46)	Strictures[b] (n = 60)	*P* value[c]
Age at biopsy (mean years, SD)	33.4 (13.1)	36.7 (15.5)	0.26
Male (n, %)	32 (70)	47 (78)	0.30
Whites (n, %)	42 (93)	52 (87)	0.37
Symptoms (n, %)			
Dysphagia	45 (98)	56 (97)	0.70
Food impaction	24 (53)	23 (46)	0.48
Chest pain	5 (11)	5 (10)	0.83
Heartburn	11 (24)	16 (31)	0.45
Abdominal pain	2 (4)	3 (6)	0.75
Nausea	1 (2)	3 (6)	0.36
Vomiting	7 (16)	4 (8)	0.25
Failure to thrive	1 (2)	1 (2)	0.94
Symptom length before diagnosis (median years, IQR)	11.0 (5-15)	8 (3-19)	0.97
Atopic diseases (n, %)	21 (47)	18 (37)	0.33
Allergic rhinosinusitis (n, %)	28 (64)	23 (51)	0.23
Asthma (n, %)	14 (31)	13 (27)	0.62
Food allergy (n, %)	14 (33)	9 (22)	0.28
History of steroid treatment (n, %)	39 (85)	40 (67)	0.03
History of dilation (n, %)	46 (100)	49 (82)	<0.01

[a] Characterized by requiring a neonatal endoscope to traverse the esophagus.

[b] Patients with strictures and without a narrow-caliber esophagus.

[c] *P* values for significant difference in distribution of proportions and *P* value for difference in mean age and median symptom length.

Table 6

Response to steroid[a] treatment in patients with strictures without a narrow-caliber esophagus and narrow-caliber esophagus

	Narrow-caliber[b] (n = 46)	Strictures[c] (n = 60)	*P* value[d]
Symptom response to steroids (n, %)	14 (56)	24 (89)	<0.01
EGD response to steroids (n, %)	17 (52)	23 (88)	<0.01
Histologic response to steroids (n, %)	11 (33)	17 (68)	<0.01
Maximum eosinophil count before steroids (median, IQR) eos/hpf	78 (33-100)	73 (36-111)	0.81
Maximum eosinophils after steroids (median, IQR) eos/hpf	45 (3-90)	2 (0-16)	<0.01

[a] Defined as any topical swallowed corticosteroid formulation.

[b] Characterized by inability to pass an adult upper endoscope.

[c] Patients with strictures and without a narrow-caliber esophagus.

[d] *P* values for significant difference in distribution of proportions and *P* value for difference in maximum eosinophil count.