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Esophageal Stricture in Children with Eosinophilic Esophagitis;Short Segment *vs*. Narrow Caliber Esophagus

Gunasekaran TS*, Vijayalakhsmi Kory, Yu Li, Evelyn Angulo and James Berman

Advocate Children's Hospital, Loyola Medical Center and University of Illinois, Park Ridge, USA

Abstract

Patients with EoE are classified as inflammatory or fibrostenotic, and strictures are an established complication of EoE. We describe EoE pediatric patients with esophageal strictures of the short segmental (SSE) and Narrow Caliber Esophagus (NCE) types.

Aim: Compare clinical features, endoscopy, biopsy, treatment including dilation and outcomes of pediatric patients with SS *vs* NCE.

Methods: In this retrospective study, children with EoE seen between 1/2001 and 4/2019 were included. Stricture was defined as, inability to pass regular endoscope (OD 9 mm) or if scope passed had a mucosal tear. Patients with stricture were included and further sub-classified as short segment strictures-SSE (narrowing<2 cm length) and narrow caliber esophagus-NCE (narrowing more than 1/3 length of the esophagus). Physical findings, CBC, EGD and biopsy of the duodenum, antrum, distal and mid esophagus were captured. Diagnosis of EoE was made as per the Consensus. Treatments included topical steroids, dietary modification, +/- PPIs. Strictures were dilated after initiation of treatment, either with bougies or through-the-scope balloons. Symptom score for dysphagia, nausea, vomiting, regurgitation, early satiety and heartburn were scored as: absent-0, mild-1 and severe-2 except dysphagia with food impaction scored as 3. Follow-up data were recorded.

Results: There were 290 total EoE patients in the entire database. Of these dysphagia=145 (50%) (EoE-D), abdominal pain without dysphagia=87(33.3%), GERD like symptoms=44 (15.2%), failure to thrive=7 (2.4%) and miscellaneous=12 (4.1%). Patients with strictures came from the dysphagia group and=19. Stricture incidence was 6.5% within the entire group and 17.7% within EoE-D. Of the population with strictures, SSE=16 patients and NCE=3 patients. Mean age 13.3 years and 8.7 years (p=0.06). There were no patients with strictures who did not fit into these two groups. Dilation type; balloon=10, Savory=5 dilation by passage of endoscope=4. Total dilations for SSE=40 (mean 2.5) and NCE=12 (mean 4) (p=0.25). Complications: perforations=0, chest pain=6. Follow up: SSE: mean 1.7 years (range 1month -8 years) and NCE 3.4 years (1month-5. 6 yrs). Medical treatment: topical steroids (fluticasone/budesonide)=8, diet=1, combination of both=4 and PPI with topical steroids=6. Symptom improvement; mean dysphagia score in SSE group improved from 2.5 to 1.1 (p=0.001) and in NCE from 2.7 to 0.7 (p=0.01) and composite score from 2.7 to 1.1 (p=0.001) and 2.7 to 0.7 (p=0.01) respectively. EGD score improved from 3.2 to 2.8 (p=0.16) in SSE group and 2.3 to 1.7 (p= 0.16) in NEC. Peak eosinophil count improved from 48 to 36.3 (p=0.59) in SSE group and 45.3 to 5.7 (p=0.11) in NEC.

Conclusion: Incidence of esophageal stricture was 6.5% within 290 EoE patients and 17.7% within the EoE-D group. NCE group required more dilations than the SS group, but difference was not significant. Both groups had significant improvement in dysphagia and composite scores. In both groups EGD scores and PEC had improvement with dilation and treatment, but not statistically significant.

Keywords: Eosinophilic esophagitis; Dysphagia; Strictures; Food impaction; Narrow caliber

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Correspondence:
Thirumazhisai S. Gunasekaran, Advocate Children's Hospital, Loyola Medical Center and University of Illinois, Park Ridge, USA.
Tel: *847-723-7700*
Fax: *847-723-9418*
E-mail: *ts.gunasekaran@aah.com*

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Introduction

Eosinophilic Esophagitis (EoE) is a chronic, immune mediated disease, associated with eosinophilic inflammation of the esophagus [1,2]. Since its description more than 30 years ago, its incidence has been increasing over the last two decades, particularly in developed countries. The prevalence according to prior studies in adults ranges from 78 to 111 per 100,000 people [3]. In children the incidence of EoE varies from 0.7 to 10/100,000 per person-year and the prevalence ranges

from 0.2 to 43/100,000 [4]. With antigen insult to the esophagus, eosinophilic inflammation starts earliest in the peri-papillary area within the deep layers of the esophagus and then it moves to the top layers of the mucosa. Basal zone hyperplasia and lengthening of lamina propria papillae are secondary changes to the antigen insult and increases with duration of insult [5]. Degranulation of the eosinophils with cytotoxin and cytokine release is another mechanism of inflammation and results in the desquamation or degeneration of cells, and mobilization of more eosinophils and remodeling. Several mediators released from inflammatory cells are involved in driving this esophageal remodeling in EoE, with a particular role for transforming growth factor (TGF)-b1, similar to the one observed in airway remodeling associated with bronchial asthma [6-8]. In addition to TGF-b1 signaling, other mechanisms involved in EoE remodeling include epithelium-mesenchymaltransition and angiogenesis [9,10]. This ongoing remodeling due to persistent inflammation in EoE may adversely affect the esophageal function, leading to dysmotility, esophageal rigidity and, finally stricture formation [11].

Depending on the level and type of inflammatory response in EoE , recently, three phenotypes have been described with different endoscopic features: inflammatory (white exudates and/or furrows), fibro-stenotic (rings, strictures which may be focal or involving a longer segment) and mixed type inflammatory/fibro-stenotic (with combined features) [12,13]. The nature of fibro-stenotic disease in adults has been well characterized. Adult patients with EoE and strictures are grouped into short segment, narrow caliber and extremely narrow caliber esophagus depending on the length of involvement and degree of narrowing [13]. In children published studies are limited in the fibrostenotic phenotype of EoE and its subgroups. Our study brings additional data and knowledge on these different types of strictures in children with EoE .

Aim

Compare clinical features, endoscopic findings and histology, dilation, and outcomes of EoE patients with Segmental Stricture of Esophagus (SSE) and Narrow Caliber Esophagus (NCE).

Methods

In this retrospective study, all children and adolescents with EoE seen over a period of 17. 25 years (1/2001 to 4/2019) were stratified based on the predominant presenting symptom into groups for further analysis as; dysphagia (EoE-D), abdominal pain without dysphagia, GE reflux without dysphagia and FTT/Feeding difficulty [14]. Within the entire group, patients with strictures defined as inability to pass a regular endoscope (Outer Diameter (OD) 9 mm) or when if passed developed a mucosal tear, were included for this study. These strictures were sub-classified as; short segmental strictures of esophagus-SSE (narrowing<9 mm and segment length<2 cm) or narrow caliber esophagus- NCE; narrowing less 9 mm and involving more than 1/3 length of the esophagus, and if in-between as long segmental strictures [15].

Diagnosis of EoE was confirmed as follows: esophageal biopsy with 15 or more eosinophils /HPF, no increased eosinophils in the stomach or duodenum, pre-endoscopy treatment with proton pump inhibitors (PPI-omeprazole 20-40 mg or lansoprazole 30-60 mg) or a negative esophageal pH study (Bravo, Given Imaging, USA) [1,2,14]. Patients with celiac disease, Crohn's disease, drug allergy and increased eosinophils in the stomach or duodenum were excluded. Data was prospectively collected and included; symptoms, physical findings, allergic diseases, complete blood count with differential and complete metabolic profile. Endoscopic findings included were; caliber of stricture, furrows, white spots/exudates, concentric rings and friability and entered as absent-0 or present-1 and scored at diagnosis and follow up. Three- four biopsies were obtained from duodenum, stomach, distal and mid esophagus for histology. A dysphagia score was assigned: absent-0, mild-1 severe-2 [16] and an additional score for food impaction-3 [14]. Food impaction was defined as impacted food requiring endoscopic removal or a visit to the emergency department [2]. Severity of nausea, vomiting, regurgitation, heartburn and early satiety were scored as: absent-0, mild-1 (does not interfere with daily activities), and severe-2 (interferes with daily activities) [14,16]. Peak esophageal eosinophil count based on distal and mid esophageal biopsies were taken at diagnosis and follow up. Prior to dilation the patients were treated with topical steroids; fluticasone 880 mcg/day for age 1-10 years and 1760 mcg/day for 11-18 years, in four divided doses. If a stricture was seen on prior endoscopy, then the patients were treated with budesonide 0.5 mg BID for patients up to 5 feet tall and 1 mg BID for those over 5 feet given for 6-8 weeks. Institutional Review Board approval was obtained through Advocate Aurora Health Care, Downers Grove, Illinois.

Esophageal dilation

Under general anesthesia a standard upper endoscope, (Olympus Medical Systems Corporation, Tokyo, Japan; OD 9 mm and channel size 2.8 mm) was passed carefully. If a stricture was identified, the stricture was gently "maneuvered" with the scope to see if it traversed. If the endoscope did not traverse or was felt to be "tight then a small caliber endoscope (Olympus Medical Systems Corporation, Tokyo, Japan; OD 5.5 mm) was passed to assess the esophageal stricture. Dilation was performed with Savary-Gillard hollow-centered dilators passed over an endoscopically placed guide wire, for all NCE patients. For SSE strictures either balloon dilation via the endoscope or Savary-Gillard dilation was performed per the endoscopist preference. Size of the first dilation was carefully chosen based on the visual assessment of the stricture lumen. Balloon size increments were one mm and bougie size increment was three French. Post dilation endoscopic assessment was always done during and after the dilation to assess for mucosal tears. In select cases post-dilation contrast esophagram was done. Unless a perforation was observed, patients were discharged home on the same day.

Results

During the study period of 17.25 years a total of 290 EoE patients were seen. Within this entire group, the following were the predominant presetting symptom; dysphagia=145 (50%) abdominal pain without dysphagia=87 (33.3%), GERD like symptoms=44 (15.2%), failure to thrive=7 (2.4%) and miscellaneous=12 (4.1%). Nineteen patients had esophageal strictures, and all were within the dysphagia group. Stricture incidence was 6.5% within entire group and 17.7% within the EoE-Dysphagia sub-group. Sixteen patients had SSE and three patients had NCE and their mean ages were 13.3 (range 1-18) and 8.7 years (range 6-11) (p=0.06) respectively. There were no patients with strictures who did not fall into of these two groups. Dilation was done by balloon dilation in 10 patients, Savory-Gillard dilation in 5 patients and dilation by passage of endoscope alone in four patients. Total dilations for SSE group was40 (mean 2.5) and for NCE group 12 (mean 4) (p=0.25). Stricture size improved from 8.6 to 11.3 mm in the SSE and from 5 to 13.6 mm in the NCE group. (French units were converted to mm for uniformity of

Table 1: Demographics and clinical features.

Demographics	Segmental Stricture (n=16)		Narrow Caliber Esophagus (n=3)		
	n	%	n	%	*p* Value
Male	13	81%	2	67%	0.57
Mean Age (yrs)	13.4		8.7		0.06
Presenting Symptoms					
Dysphagia	16	100	3	100	1
Food Impaction	11	69%	2	67%	0.9
Associated Allergies	6	38%	3	100	0.09
Vomiting	2	13%	1	33%	0.4
GI Bleeding	1	6%	0	0	1

Table 2: Endoscopy and biopsy findings.

	Segmental Stricture (n=16)		Narrow Caliber Esophagus (n=3)		
EGD	n	%	n	%	*p* Value
Edema	6	38%	1	33.3	1
Rings	7	44%	1	33.3	1
Exudates	10	63%	1	33.3	0.5
Furrows	9	56%	1	33.3	0.6
Stricture	16	100	3	100	1
Biopsy at diagnosis					
Peak Eosinophil count	41.8	-	45.3	-	0.9

calculation). There were no perforations seen, chest pain was seen in six patients and there were no deaths. Follow up period was; for SSE group mean 1.03 years (range 1-16 months) and in NCE group was 2.07 years (1month- 5.06yrs). Treatments given were; topical steroids (fluticasone/budesonide) for eight patients, diet exclusion one patient, combination of diet and medication in four patients and PPI with topical steroids in six patients. Symptom improvement; mean dysphagia score in SSE group improved from 2.5 to 1.1 (p=0.001) and in NCE from 2.7 to 0.7 (p=0.01) and composite score from 2.7 to 1.1 (p=0.001) and 2.7 to 0.7 (p=0.01) respectively. EGD score improved from 3.2 to 2.8 (p=0.16) in SSE group and NCE from 2.3 to 1.7 (p=0.16). Peak eosinophil count improved from 48 to 36.3 (p=0.59) in SSE group and 45.3 to 5.7 (p=0.11) in NEC.

Discussion

As described earlier, ongoing inflammation in EoE with resulting remodeling and fibrosis leads to strictures. This remodeling and fibrosis occur with duration of untreated disease and this may be the reason for strictures to be less common in children. However, when strictures occur, dilation is the treatment of choice in children with similar techniques to adults. There is a dual goal in the management of EoE strictures; one to relieve the mechanical narrowing and second heal the underlying inflammation to prevent recurrence of the stricture. Our study, by addressing both these issues adds knowledge to the management and outcomes of EoE with fibrostenotic-strictures in children.

Our study showed a male predominance in both groups of strictures, similar to previous publications in children and adults [1-4]. The stricture incidence is 6.5% within the 290 EoE patients, and 17.7% within the group of 107 patients presenting with dysphagia as a predominant symptom. There were no strictures in other EoE groups. In previously published work we showed that categorizing children with EoE into subgroups demonstrated that EoE in children presenting with dysphagia versus abdominal pain- without dysphagia as the predominant symptom, have differences in EGD, histology and outcomes [14,17]. Esophageal stricture occurrence in adults varies from 7-25% [13,18,19]. From a large series of children with EoE, Liacouras reported from a total of 381 children 6.3% had strictures [20]. A study from Saudi Arabia, by Al Hussaini, reported 11 out of 50 (22%) children with EoE had strictures [15]. The authors' hypothesis for this high incidence in Saudi children is that, it may be a genetic predisposition from a higher rate of consanguinity in that population. The genetic hypothesis may have some relevance to our study. Narrow caliber esophagus was more common in younger children, with a mean age of 8.7 years versus short segment esophagus was more common in slightly older children with a mean age of 13.3 years. Additionally, in our study, a sibling of one child in NCE group had stricturing Crohn's disease and there is evidence that these two diseases have similarities [21].

Dysphagia, as expected was the predominant symptom in both groups and food impaction was seen in about two thirds of the patients. A study from Switzerland analyzed 251 patients with EoE for food impaction and perforation [22]. Within this group, 87 (34.7%) adults and adolescents experienced 134 food impactions requiring endoscopic bolus removal, but the study did not subgroup the patient with strictures. The reason that not all patients with strictures have food impaction may be, because these patients have a gradual onset of dysphagia. So they learned to avoid certain foods, carefully chew before swallowing, or take extra fluids to follow the swallow, in order to avoid food impaction. Additionally, impaction may also depend on the underlying smooth muscle dysfunction, which when present, increases the risk of food becoming lodged [23,24].

Associated allergic diseases were more common in NCE (100%) *versus* in SSE (38%), but the difference was not significant (p=0.09). Allergic diseases such as asthma, atopic dermatitis or allergic rhinitis are present in approximately half or more of EoE patients [25]. The contribution of this added atopy and increased Th2 inflammatory load from uncontrolled allergy has been ascribed as the cause of tissue remodeling and fibrosis both in asthma and EoE [26]. On the contrary cohort studies of children and adult patients, found that atopy is more likely to be seen in patients of the inflammatory phenotype compared to the fibrostenotic phenotype [27], but this is not the focus of our study. In a separate retrospective cohort of adults and children, comparing 46 patients with extremely narrow caliber esophagus and 467 patients with regular caliber esophagus, no significant difference in atopy was seen between the groups [28]. These studies suggest associated atopic diseases have a role in the pathogenesis of EoE inflammatory burden but how it influences the disease course and stricture formation is yet to be understood.

Endoscopic findings of edema, exudates, furrows and specifically rings, which are associated with fibrosis, were more common in SSE versus NCE, but the difference was not significant. Submucosal fibrosis, an important histologic characteristic, is difficult to include in the analysis, as the mucosal biopsies may not always be deep enough to evaluate fibrosis. Peak eosinophil counts, the manifestation of the inflammation, were almost similar in both groups. A recent study in adults with EoE strictures, showed histologic remission, <15 eosinophils/hpf, was significantly associated with achieving a final esophageal diameter>15 mm [13]. This finding validates prior

observations that histologic remission results in better outcomes with stricture dilation in EoE stricture patients [29-31].

Timing of the dilation is a critical decision for the clinician to make; dilate and then treat-to- heal or treat-to-heal and then dilate or do both simultaneously. There was a reported higher rate of perforation when gastroenterologists were dilating ahead of treat-to-heal the inflammation [30]. This ensuing experience combined with the knowledge that the inflamed mucosa in EoE is fragile and dilation is only a mechanical procedure, led to the adoption of treat-to-heal the inflammation first and follow with dilation [30,31]. The period of treat-to-heal may vary from 8-12 weeks. This method of, "treat-to-heal and then dilate" has helped the patients with significant improvement of dysphagia and decreased the perforation rate to significantly less than 1% compared to an initial rate much more than this [30,31]. An extension of this method adopted in EoE patients with healed post esophageal perforations, is if one follows "….start low and go slow, and you will like it," the outcomes are good with dysphagia improvement and no recurrence of perforation [32]. Except one, all of our patients were treated with steroids in some form, or with combination therapy and then dilated, but medical treatment alone is not adequate to relieve dysphagia. Topical steroids or diet treatment alone can improve the stricture lumen and decrease the frequency of dilation in adults by about 65%, but dilation should be part of the management for optimal return of the esophageal lumen [30]. Dilation is done either with through the scope balloons or with Savory-Gillard bougie dilators. Bougie dilation would be more effective with multiple sites of strictures or with NCE and this method additionally gives a tactile feeling to the endoscopist, guiding safer dilation. Balloon dilation has the advantage of direct visualization during dilation and is generally used for segmental strictures. Balloon dilation has also been used for multiple sites of dilation in adults with dilating each stricture at a time or inflate the balloon distally and slowly, "pull-through". This method also provides the benefit of direct visualization [33]. Our patients needed a total of 52 dilations, and about half were done with balloon dilation and the rest between Savory-Gillard dilators or with gentle passage of the endoscope. There were no perforations, and like earlier reports the most common side effect was chest pain, seen in six patients. Post dilation tears were seen but were not included as a complication as this was an evidence of successful dilation and not a complication [30].

With the method of "treat and then dilate" both groups of our patients showed significant improvement in dysphagia and the composite scores and the strictures opened up as well. A meta-analysis of EoE stricture dilation, included 525 adult EoE patients requiring 992 dilations and showed 75% improvement in dysphagia [18]. This study was expanded and published three years later in 2016, from the same group, and included 845 patients including 87 children with 1820 dilations and showed a 95% improvement of dysphagia. The mean number of dilations was 3 (range 1-35) and perforation occurred in 0.38% [19]. Another meta-analysis of 1607 dilations showed that perforation and chest pain was seen in 0.61% and 0.06% respectively, and supports that the perforation rates are very low [34]. Perforation risk may be higher with proximal strictures, initial diameter less than 6 mm, strictures of long standing duration, when done with simultaneous food bolus removal or food bolus removed with rigid endoscope [18,19,22]. The target esophageal diameter, post dilation is a potentially important issue. Our patients were dilated to 11.3 and 13.6 mm. Adult patients are dilated to 13-15 mm as this diameter allows the patient to eat a normal diet [13]. Pediatric data varies from 12.8 mm for children less than 5 years and 14 mm for older children or up to 15 mm [15,33]. Studies have shown that with topical steroid use and improvement in PEC there is a higher success rate of stricture improvement. Once final diameter is achieved, these patients will need maintenance treatment, diet or medication, based on the understanding that EoE this a chronic inflammatory disease [20,36]. Hence adequate dilation and healing the inflammation leads to better outcomes in these patients with strictures.

With dilation, improvement in the dysphagia score was significant in both groups; however the EGD scores and peak eosinophil counts though improved numerically but were not significant. This discordance between dysphagia versus EGD and PEC improvement is similar to earlier reports of similar observations. One potential explanation is that the esophageal muscle function abnormality improves earlier with treatment, facilitating better motility and swallow [23].

The strengths of our study are; a reasonably large sample of pediatric EoE strictures and the first to compare short segment and narrow caliber esophagus in children. The study also outlines the management of NCE, including safe bougie dilation. This is important because the adult literature shows that the group with diffuse narrowing has an aggressive course and potential for higher rate of perforation. Our study adds to the limited literature available on strictures in children with EoE. The weaknesses are its retrospective nature and the sample size. Though large in pediatrics it is still not powered sufficiently to arrive at statistically significant differences. Endoscopy and dilation were done by more than one endoscopist and so the endoscopic findings and stricture assessment may not be uniform. In spite of these limitations the study provides fruitful ideas for future work on the analysis of different types of EoE strictures and its outcomes in children.

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