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ORIGINAL ARTICLE

Eosinophilic esophagitis in children: A cross-sectional study from a tertiary care center

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Author contribution: Arghya Samanta contributed to the collection, analysis, and interpretation of data and drafting of the article. Ujjal Poddar conceived and designed the study, analyzed the data, and co-drafted the manuscript. Niraj Kumari examined all histopathological specimens, supervised the study, and critically revised the manuscript for important intellectual content. Moinak Sen Sarma and Anshu Srivastava supervised the study, analyzed the data, and critically revised the manuscript for important intellectual content. Prabhakar Mishra analyzed the data and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript and are responsible for the manuscript.

Abstract

Background and Aim: The prevalence of eosinophilic esophagitis (EoE) is rising in the West. However, data from the Indian subcontinent is limited. In this prospective cross-sectional study, we estimated the prevalence of EoE among children undergoing elective upper gastrointestinal endoscopy (UGIE).
Methods: We enrolled 200 consecutive children (123 boys, median age 10.25 years [interquartile range 8.25–14.5]) between March 2020 and November 2022 at our center. Clinical characteristics, endoscopic findings, and laboratory parameters were noted. A total of 12 mucosal biopsies (3 each from the middle and lower third of the esophagus, stomach, and duodenum) were obtained. EoE was diagnosed if the peak eosinophil count was ≥15/high-power field (HPF) in absence of gastric and duodenal eosinophilia.
Results: The commonest indications for UGIE were gastroesophageal reflux disease-like symptoms (29%), inflammatory bowel disease (22.5%), celiac disease (15%), and abdominal pain (13%). EoE was detected in seven children, suggesting an overall prevalence of 3.5%. Of the 20 children evaluated for dysphagia, 4 (20%) had EoE. Also, two of three (67%) children presented with food bolus impaction along with dysphagia had EoE. Of the seven children with EoE, three (43%) had bronchial asthma, two (28.5%) had peripheral eosinophilia, and one (14%) had elevated serum IgE. Trachealization and linear furrows were found in 57% and 71% cases, respectively. Four children received high-dose proton pump inhibitor (PPI) for 12 weeks, two received PPI+ stricture dilatation, and one received systemic steroids. All achieved clinical, endoscopic, and histopathological remission.
Conclusion: Hospital-based prevalence of EoE among children undergoing elective UGIE was 3.5%. EoE patients had favorable outcomes with PPI.

Introduction

Eosinophilic esophagitis (EoE) is a chronic, antigen-mediated inflammatory disease of the esophagus, characterized clinically by symptoms of esophageal dysfunction and histopathological evidence of eosinophil-predominant inflammation of esophageal mucosa (≥15 eosinophil/high power field [HPF]) in the absence of other causes of eosinophilia.[1] Though EoE was first described in 1978 by Landres *et al.*,[2] its characteristic clinical and histopathological features were established in 1993–1994 only.[3] It is the most frequent cause of esophagitis after gastroesophageal reflux disease (GERD) and the leading cause of food bolus impaction among children and young adults in Europe and North America.[4] However, almost a quarter of children with EoE reported having vague symptoms such as failure to thrive, without having any esophageal symptoms, which may be due to the shorter duration of the disease and the inability of a young child to express their symptoms accurately.[5,6]

The prevalence of EoE has been studied worldwide, but most population-based studies have been conducted in North America,[7] Europe,[8,9] and Australia,[10] with fewer studies in Asia.[11–16] The prevalence tends to be similar in North America,[7] Europe,[8,9] and Australia[10] but much lower in China,[12] Japan,[13] South America,[14] Korea,[15] Turkey,[16] and the Middle East.[11]

The only Indian study so far by Baruah *et al.* in 185 adult patients with GERD-like symptoms showed a prevalence of 3.2%.[17] Pediatric literature is scarce, with most studies being observational ones with small sample sizes.[18–22] EoE has not been reported among Indian children so far. Hence, this prospective cross-sectional study was conducted with the primary aim of determining the prevalence of EoE in children undergoing elective upper gastrointestinal endoscopy (UGIE) in a tertiary care hospital in India; the secondary aim was to assess the clinical, endoscopic, and histopathological features and treatment response of those diagnosed with EoE.

Methods

We prospectively studied consecutive children (<18 years of age) who underwent elective UGIE in our center from March 2020 to November 2022.

Patients were excluded from the study if they met any of the following criteria:

1. Undergone UGIE for variceal screening or upper gastrointestinal bleeding;
2. Had thrombocytopenia or coagulopathy;
3. Were on steroid therapy for any underlying disease;
4. Previously diagnosed as drug-induced esophagitis or infectious esophagitis;
5. Refusal of consent to participate in the study.

Clinical and demographic profiles such as a history of heartburn, regurgitation (suggestive of GERD), dysphagia, nausea, chest pain, failure to thrive, and so on, associated comorbidities such as asthma, food, and air-borne allergies, and treatment history (history of intake proton pump inhibitor, treatment duration, and symptom response) were noted. Absolute eosinophil count (AEC) in peripheral blood and serum IgE level were measured in diagnosed cases of EoE.

Endoscopy procedures. All endoscopies were performed by experienced pediatric gastroenterologists who had been informed about the study protocol, and all of them completed a data collection sheet at the time of endoscopy. All the procedures were carried out using conscious sedation (intravenous midazolam and ketamine) with an Olympus gastroscope with 8.6 mm outer diameter (GIF-Q180, Olympus Corp., Tokyo, Japan). A complete examination of the esophagus, stomach, and first and second parts of the duodenum was carried out. The Los Angeles classification was used to describe and grade erosive esophagitis.[23] Other endoscopic findings such as hiatus hernia, erosion or ulcer, linear furrows, concentric rings, plaques, strictures, small-caliber esophagus, and white exudates, if present, were noted down. During the upper gastrointestinal examination, using standard biopsy forceps, a minimum of three biopsies each were obtained from the predefined mid-esophagus (7–10 cm above the z-line), the lower end of the esophagus (4–7 cm above the z-line), body of the stomach, and second part of duodenum. Any intervention (dilation) or additional biopsies were performed at the discretion of the endoscopist.

Histopathological examination of the tissue biopsies. After obtaining biopsy samples in 10% neutral buffered formalin, they were then transported to the Department of Pathology. The samples were kept in the fixative for 5–6 h and thereafter embedded in the paraffin blocks after orienting them properly. Multiple step-sections were examined from all the biopsy fragments after HE staining. One dedicated and experienced gastrointestinal pathologist examined all the biopsy blocks.

The number of eosinophils per high-power field (400× magnification, Olympus, BX50 microscope) was counted, based on the average eosinophil count in all the biopsy fragments. Other histopathological features of EoE (eosinophilic microabscess [>4 eosinophils in cluster], layering of eosinophils, basal zone hyperplasia, elongation of rete-peg) were also examined in all biopsy samples. The presence of parasites or fungal profiles, sub-epithelial stromal changes, and the presence or absence of epithelial dysplasia or malignancy were noted. All the biopsy results were adequate to interpret and none were excluded.

Diagnosis of EoE. The diagnosis of EoE was established in the presence of ≥15 eosinophils/HPF (peak eosinophil count at the site of maximum density) in either the lower half or upper half of esophageal mucosal biopsy sample with the absence of eosinophils in the gastric and duodenal mucosa, irrespective of symptoms.[24]

Ethics. The study was performed after obtaining clearance from the Institutional Ethics Committee (IEC-2020-63-DM-EXP-15) and was conducted in a manner to conform with the Helsinki Declaration of 1975, as revised in 2000 and 2008, concerning human and animal rights. All endoscopic procedures were carried out after obtaining informed consent from either parent.

Statistical analysis. IBM SPSS statistical software version 20 (SPSS, Chicago, IL, USA) was used to perform the statistical tests. A P-value of <0.05 was considered statistically significant. Continuous variables are expressed as median with interquartile range (IQR) and discrete variables as proportions. Comparisons of continuous variables between two groups were performed using the independent t-test and the Mann–Whitney U test as per normality of data distribution. Paired t-test was used to compare two variables within the group. Variables with skewed distribution were compared using the Kruskal–Wallis test followed by the Mann–Whitney test with adjusted P-values.

Results

A total of 226 children underwent elective UGIE during the study period, of whom esophageal biopsy was not obtained in 6 because of thrombocytopenia and 20 had a history of taking steroids (18 had Crohn's disease and 2 inflammatory bowel disease [IBD] unclassified) and hence excluded. Thus, 200 patients (123 boys, median age 10.25 years [IQR 8.25–14.5]) were finally included in the study (Fig. 1).

Indications of elective UGIE in our study are listed in Table 1. The most common indications were evaluations for GERD-like symptoms (29%), IBD (22.5%), celiac disease (15%), and abdominal pain (13%). Twenty (10%) children presented with dysphagia, three of them with food bolus impaction.

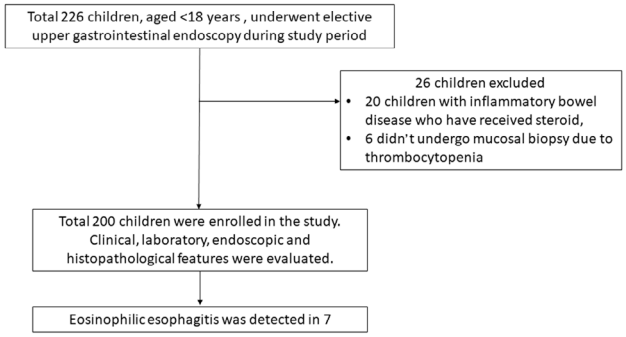

Figure 1 Study flow diagram.

Table 1 Primary indications of elective upper gastrointestinal endoscopy ($n = 200$) in our study

Symptoms/ disease		*N* (%)
Gastroesophageal reflux-like symptoms	Chest pain/heartburn	30 (15%)
	Vomiting	15 (7.55%)
	Belching	2 (1%)
	Regurgitation	3 (1.5%)
	Refusal to feed	4 (2%)
	Night cough	4 (2%)
Dysphagia	Peptic stricture	5 (2.5%)
	Post-esophageal atresia repair anastomotic stricture	6 (3%)
	Congenital stricture	2 (1%)
	Achalasia cardia	4 (2%)
	Food bolus impaction	3 (1.5%)
Pediatric intestinal pseudo-obstruction		5 (2.5%)
Evaluation of abdominal pain		26 (13%)
Celiac disease		30 (15%)
Inflammatory bowel disease	Crohn's disease	38 (19%)
	IBD unclassified	7 (3.5%)
Cow's milk protein allergy		5 (2.5%)
Other	Total	11 (5.5%)
	Cyclic vomiting syndrome	3
	Rumination syndrome	2
	Primary intestinal lymphangiectasia	2
	Systemic lupus erythematosus	3
	Juvenile idiopathic arthritis	1

EoE was found in 7 out of 200 children undergoing elective UGIE, indicating the overall prevalence of EoE of 3.5%. Out of the 20 children evaluated for dysphagia, 4 (20%) had EoE, while 2 (67%) out of the 3 children presenting with food bolus impaction had EoE. Among the 45 children with IBD, EoE was detected in 1 (2%), while it was found in 1 (3.3%) out of 30 children with celiac disease. We had six children with post-esophageal atresia repair anastomotic stricture; among them, one (16.6%) had EoE. Thus, the prevalence EoE in children without known esophageal atresia, IBD, and celiac disease was 4 out of 119 (3.4%).

The demographics, endoscopic and histopathological characteristics, and treatment outcomes of EoE cases are listed in Table 2. On comparing children with EoE *versus* without EoE, factors associated with EoE were a history of bronchial asthma (3 of 7 *vs* 3 of 193, $P < 0.001$) and the presence of peripheral eosinophilia (2 of 7 *vs* 1 of 193, $P = 0.003$).

Five out of the seven cases were symptomatic (dysphagia two, food bolus impaction three), while two cases (Crohn's disease and primary intestinal pseudo-obstruction one case each) were asymptomatic for esophageal dysfunction. Endoscopic features of trachealization and furrowing were found in four (57%) and five (71.4%) children, respectively, while UGIE was normal in two (28.6%) (Table 2, Fig. 2). The peak eosinophil count was >15/HPF in the middle and lower esophagus in all seven cases, while eosinophilic micro-abscess and basal-layer hyperplasia were seen in six cases each (85.7%) (Table 2, Fig. 3). In the non-EoE group, one (0.5%) child with GERD-like symptoms had trachealization on endoscopy, while none had linear furrows or white exudates.

Treatment and outcome. The treatment modalities and responses in each case are summarized in Table 2. Four children received esomeprazole at a dose of 2 mg/kg/day for 12 weeks, two children received esomeprazole in addition to controlled radial expansion dilatation of esophageal strictures, and the child with Crohn's disease plus EoE received systemic steroid induction as a part of Crohn's disease treatment. Among those four children who received exclusive PPI, three had endoscopic abnormalities and all three showed endoscopic healing at the end of PPI induction. Of the two who received PPI plus endoscopic dilatation, endoscopic features disappeared and histopathological remission was seen in both. Histopathological response was reported in the child with Crohn's disease and EoE treated with steroids. Normalization of AEC was reported in both children with peripheral eosinophilia and serum IgE level in a child with elevated IgE, after PPI therapy. All seven children showed histopathological remission (<5 eosinophils/HPF) at the end of induction therapy. They were given maintenance therapy with PPI at 1 mg/kg/day for 6 months, and all of them remained asymptomatic.

Discussion

In this prospective, cross-sectional study, we have found the overall prevalence of EoE among children undergoing elective UGIE to be 3.5%. Among children presenting with dysphagia and food bolus impaction, the prevalence of EoE was higher (20% and 67%, respectively), compared to children without dysphagia (1.6%). There was a clear male preponderance (86%), a strong association with atopic diseases like asthma (43%), peripheral eosinophilia (28.5%), and an increased prevalence of EoE in patients with esophageal atresia (16.5%).

Table 2 Summary of the clinical, endoscopic, and histopathological features and treatment outcome in all seven cases of eosinophilic esophagitis in our study

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age/gender	7 years/boy	10 years/boy	8 years/girl	13 years/boy	8.5 years/boy	16 years/boy	7 years/boy
Symptoms							
Dysphagia	Yes	Yes	No	No	No	Yes	Yes
Chest pain/heartburn	Yes	Yes	No	No	No	Yes	Yes
Regurgitation	No	Yes	No	No	No	Yes	No
Abdominal pain	No	Yes	No	No	No	No	No
Food impaction	No	No	No	Yes	No	Yes	Yes
History of atopy							
Asthma	Yes	Yes	No	No	No	No	Yes
Food allergy	No	No	No	No	No	No	No
Atopic dermatitis	No	No	No	No	No	No	No
Family history	No	No	No	No	No	No	No
Absolute eosinophil count (AEC) in peripheral blood	1530/mm^3	320/mm^3	320/mm^3	270/mm^3	240/mm^3	180/mm^3	1840/mm^3
Indication of UGIE	Esophageal stricture	Esophageal stricture, duodenal biopsy	Upper gastrointestinal biopsy	Food bolus impaction	Upper gastrointestinal biopsy	Dysphagia	Dysphagia
Concomitant disease	Post-EA repair anastomotic stricture	Down's syndrome with celiac disease	Crohn's disease	None	Small intestinal and colonic pseudo-obstruction	None	None
Endoscopic features							
Trachealization	Yes	Yes	No	Yes	No	Yes	Yes
Linear furrows	Yes	Yes	No	No	No	Yes	Yes
White exudates	Yes	Yes	No	No	No	Yes	No
Plaque	No	No	No	No	No	No	No
Stricture	Yes	Yes	No	No	No	No	No
Erosion	Yes	No	No	No	No	No	No
Histopathological features							
Peak eosinophil count at lower esophagus	43/HPF	37/HPF	19/HPF	27/HPF	20/HPF	27/HPF	22/HPF
Peak eosinophil count at middle esophagus	25/HPF	28/HPF	17/HPF	23/HPF	18/HPF	17/HPF	19/HPF
Eosinophilic microabscess	Yes	Yes	Yes	Yes	Yes	No	Yes
Basal cell hyperplasia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Elongation of rete peg	Yes	Yes	No	Yes	No	No	Yes
Treatment	PPI × 12 weeks, CRE balloon dilatation	PPI × 12 weeks, CRE balloon dilatation	Systemic steroid	PPI × 12 weeks	PPI × 12 weeks	PPI × 12 weeks	PPI × 12 weeks
Response							
Symptom	Yes	Yes	N/A	Yes	N/A	Yes	Yes
AEC	180/mm^3	N/A	N/A	N/A	N/A	N/A	240/mm^3
Endoscopic	Yes	Yes	N/A	Yes	N/A	Yes	Yes
Histopathological	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AEC, absolute eosinophil count; CRE, controlled radial expansion; EA, esophageal atresia; N/A, not applicable; PPI, proton pump inhibitor.

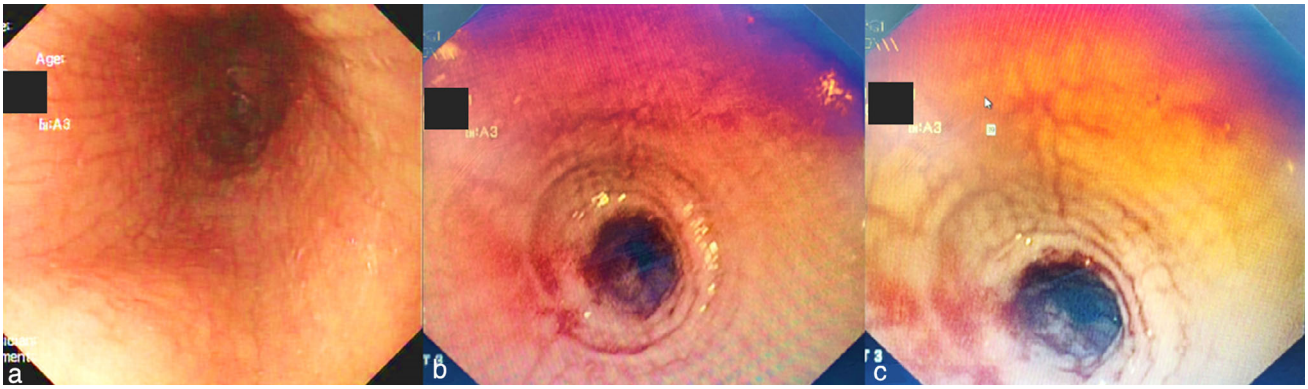

Figure 2 Endoscopic images of esophagus showing (a) linear furrows and (b, c) fixed concentric rings (trachealization).

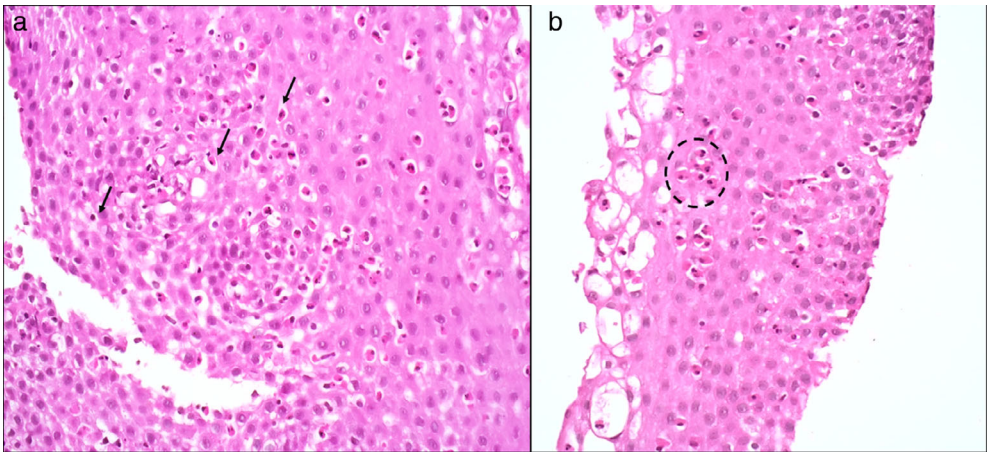

Figure 3 Photomicrograph showing (a) dense eosinophilic infiltration in the esophageal epithelium (HE, 400×) (black arrows) and (b) eosinophilic micro-abscess (HE, 400×) (black circle).

Most of the children (71%) with EoE in our study had typical endoscopic features, and all of them showed endoscopic healing after a 12-week course of PPI therapy. Histopathological remission was achieved in all seven cases after medical therapy. To the best of our knowledge, this is the first pediatric study from the Indian sub-continent to estimate the prevalence of EoE among children undergoing elective UGIE and adds to the limited pediatric literature on the prevalence of EoE in Asia.

Veerappan *et al.*[25] and Sealock *et al.*[26] reported an EoE prevalence rate of 6.5% in 400 adult patients and 2.4% in 1357 adult American patients undergoing elective UGIE, respectively, while Saeed *et al.*[27] reported a prevalence rate of 7.4% among 94 Pakistani adults undergoing elective UGIE. Pediatric studies from Asia have yielded similar results.[19,20,22] In a study among 88 children from Singapore undergoing elective UGIE for any indication, Tan *et al.* found EoE in 4.5% of cases, consistent with our finding.[19] In two separate studies evaluating the prevalence of EoE among Saudi children undergoing elective UGIE for all indications, Saeed *et al.*[20] and Assiri *et al.*[22] reported prevalence rates of 9.3% in 398 children and 4.8% in 229 children, in agreement with our results.

When endoscopy was done for the evaluation of dysphagia, the prevalence of EoE was higher (ranging from 9% to 33%), similar to our results (20%).[20,25,28,29] Veerappan *et al.* found that the prevalence of EoE was higher in the patient subgroup with dysphagia as compared to those without dysphagia (10% *vs* 3.9%), similar to our findings (20% *vs* 1.6%).[25] The yield of UGIE and esophageal biopsy was highest (>50%) in children with food bolus impaction in the studies by Hurtado *et al.*[30] and Ettyreddy *et al.*[31] from the United States, which was seen in our study as well (67%).

EoE is an antigen-driven, eosinophil-predominant disorder with Th2 cytokine profile and has been frequently associated with asthma, atopic dermatitis, food allergies, and aeroallergens.[32] History of atopic diseases is reported in 30–50% of children with EoE, with bronchial asthma being the commonest, as was seen in our cohort.[19–22] The presence of peripheral eosinophilia was reported in 8.6–33% of patients, similar to our findings.[18,20]

The classic endoscopic findings of EoE include linear furrows, concentric rings (trachealization), whitish plaques, and strictures. In the study by Saeed *et al.*, the majority (72%) of

EoE patients had one of these findings.[20] Similarly, the study by Assiri *et al*. reported that 71% of the patients had endoscopic abnormality, linear furrows being the commonest (52%), similar to our findings.[22]

An increased risk of EoE has been described in patients with successful repair of esophageal atresia (EA) owing to post-surgery GERD and esophageal dysmotility, causing increased exposure to food allergens, and the genetic abnormalities common to both conditions: the microdeletion involving the Forkhead box transcription factor (*FOXF1*).[33–35] *FOXF1* binding sites have been found not only in the promoter region of genes critical for the mesenchymal proliferation of the esophagus and trachea but also in the promoter region of pro-inflammatory genes, including eotaxin.[34,35] By 2019, 101 cases of EoE in EA were reported worldwide, mostly in the form of case series with prevalence rates ranging from 6 to 17%.[33–36] The largest reported cohort of EoE in EA patients was in a study by Dhaliwal *et al*. from Australia, where a retrospective review of all biopsies from an esophageal atresia cohort of 103 patients showed an incidence of 17%.[33] Yamada *et al*.[35] reported clinical and histopathological remission in 33% of patients with PPI plus endoscopic dilatation, while Dhaliwal *et al*.[33] and Yasuda *et al*.[36] found treatment response to PPI therapy alone in 28% and 32% of patients, respectively. In our cohort, we studied six children with EA, and EoE (16.6%) was detected in a 7-year-old boy, who was refractory to regular dilatation sessions. Treatment with 12 weeks of PPI led to a reduction in esophageal eosinophil count as well as the need for further endoscopic dilatation. Further research is needed to establish the etiological association between these two conditions.

EoE and IBD are immune-mediated disorders of the intestine, both involving helper T cells as well as abnormalities in epithelial barrier function.[37] Given these shared pathologic mechanisms, co-occurrence of both diseases in the same patient is not uncommon.[38,39] Moore *et al*.,[38] in a large multicenter retrospective study among 4515 American children with IBD, reported that the prevalence of EoE in the IBD population was 1.5%, while Aloi *et al*.[39] in another retrospective study based on the Italian Society for Pediatric Gastroenterology (SIGENP) national registry study found EoE in 11/3090 (0.35%) children with IBD, between 2009 to 2021, similar to our finding. Larger, well-powered studies evaluating the genetics of these populations will be needed in the future to better understand these observations.

Treatment modalities include an elimination diet, PPI, and topical steroids; however, there is a dearth of randomized control trials to define the optimum approach. The use of PPIs has been one of the biggest advances in the management of EoE.[40] Over the course of just one decade, PPIs, initially developed to inhibit acid gastric secretion, have evolved from being an agent to rule out GERD as a cause of esophageal eosinophilia, to the defining factor of PPI-responsive esophageal eosinophilia and, finally, to constitute a definitive treatment for EoE.[40] Beyond its anti-acid secretory properties, downregulation of gene expression of eotaxin-3/CCL26 and interleukin (IL)-5 and IL-3 in biopsies from patients with EoE was found for PPI, similar to that of patients treated with topical corticosteroids.[41] Additionally, PPIs restore the integrity of the damaged esophageal mucosa and reverse fibrosis, as demonstrated by Navarro *et al*.[42] The effectiveness of PPI therapy to induce symptomatic and histopathological remission of EoE has been demonstrated in multiple observational studies.[42–44] A systematic review with meta-analysis of 33 studies found that PPIs given at double doses led to histopathological remission in 50.5% and symptomatic improvement in 60.8% of patients, irrespective of patient age, study design, or type of PPI evaluated.[45] In a prospective study of 57 children, Gutiérrez-Junquera *et al*. observed that 67% of children achieved clinical and histopathological remission after 8 weeks of high-dose PPI therapy, and 70% of those children with PPI-responsive EoE showed sustained histopathological remission with maintenance half-dose treatment at 12 months of follow-up, similar to our results.[44]

Our study has the limitation of small sample size due to the ongoing pandemic during the study period. Our findings reflect data from a single tertiary care hospital. Larger multicentric studies are required to substantiate our findings. Also, pH-metry was not performed in any of our children presenting with GERD-like symptoms.

In conclusion, in our tertiary care hospital-based study, the prevalence of EoE among children undergoing elective UGIE was found to be 3.5%. All patients achieved endoscopic and histopathological remission after 12 weeks of induction therapy. Gastroenterologists need to be aware of this disease entity, especially in children with refractory GERD, dysphagia, or food bolus impaction.

Data availability statement. The data that support the finding of this study are available on request from the corresponding author. The data are not publicly available for privacy or ethical restrictions.

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