

# Eosinophilic Esophagitis: Latent Disease in Patients with Anaphylactic Reaction to Cow's Milk



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**What is already known about this topic?** Food allergy and eosinophilic esophagitis are a substantial and evolving public health issue. Clinicians should know the relationship between these diseases and how one may predispose to the other.

**What does this article add to our knowledge?** This study shows the highest frequency of esophageal eosinophilia yet described in a group of patients with cow's milk allergy and anaphylaxis. Eosinophilic esophagitis is a condition that can coexist "silently" with an IgE-mediated cow's milk allergy and is most often underestimated and underdiagnosed.

**How does this study impact current management guidelines?** This research may help minimize delay in the diagnosis of eosinophilic esophagitis in a subset of patients.

**BACKGROUND:** Food allergy and eosinophilic esophagitis are a substantial and evolving public health issue. Clinicians should know the relationship between these diseases and how one may predispose to the other. This can help minimize misdiagnosis.

**OBJECTIVE:** The objective of this study was to assess esophageal eosinophilia and eosinophilic esophagitis frequency in patients with persistent cow's milk allergy and anaphylaxis manifestations.

**METHODS:** Patients with persistent cow's milk allergy with anaphylaxis manifestations were enrolled from 2012 through 2016 at the São Paulo University Hospital, Brazil. All of them were submitted to endoscopy despite the presence or absence of gastrointestinal symptoms. Demographics data, atopic comorbidities, medication use, endoscopic findings, and esophageal eosinophilia frequency were evaluated.

**RESULTS:** Eighty-nine patients were selected. The median age was 8 years. It was observed that 34 of 89 patients (38.2%; 95% confidence interval [CI]: 28.14%–49.16%) presented with

esophageal eosinophilia. Five patients (7.1%) presented proton pump inhibitor-responsive esophageal eosinophilia, and 10 patients (14.2%) presented eosinophilic esophagitis. We found that 29.4% were asymptomatic patients, 23.5% had nonspecific symptoms, 23.5% had persistent typical symptoms, and 23.5% had intermittent typical symptoms. There was an association with inflammatory endoscopy findings in 21 patients (61.7%). **CONCLUSIONS:** This description demands scientific attention because it is the highest frequency of esophageal eosinophilia yet described in a group of patients with cow's milk allergy presenting with anaphylaxis. Eosinophilic esophagitis is a condition that can coexist "silently" with an IgE-mediated food allergy and is most often underestimated and underdiagnosed. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:451-6)

**Key words:** Anaphylaxis; Milk hypersensitivity; Food hypersensitivity; Eosinophilia; Eosinophils; Eosinophilic esophagitis; Esophagus

Eosinophilic esophagitis (EoE) is an exclusive chronic inflammatory disease of the esophagus first categorized as a distinct clinical pathological disorder 2 decades ago.<sup>1</sup> It has rapidly become recognized as the most prevalent cause of chronic dysphagia in children and young adults.<sup>2</sup> It is immune-mediated primarily by dietary antigens with cow's milk (CM) being a major allergen.<sup>3</sup>

Patients with EoE and food allergies may have late manifestations with symptoms of esophageal dysfunction although some show immediate symptoms including anaphylaxis. The association between anaphylaxis events and EoE has been reported in 9% to 14% of cases,<sup>4,5</sup> but it has not yet been determined whether these conditions had the same trigger and the same temporal order of appearance.

Spergel et al described a group of 17 children who developed EoE approximately 2.4 years after acquiring spontaneous IgE-mediated food allergy tolerance. In both conditions, they had the same food as the triggering antigen, but there was no previous endoscopic study in 15 of them.<sup>6</sup> EoE development during or after cow's milk oral immunotherapy (OIT) has also been

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**Abbreviations used**

CI- Confidence interval  
 CM- Cow's milk  
 EE- Esophageal eosinophilia  
 EoE- Eosinophilic esophagitis  
 eos/hpf- Eosinophils per high-power field  
 OIT- Oral immunotherapy  
 PPI- Proton pump inhibitor  
 PPI-REE- Proton pump inhibitor-responsive esophageal eosinophilia

reported, but these studies also had no baseline endoscopy to exclude the presence of underlying eosinophilic infiltration.<sup>7-9</sup>

There is also another report of a 2-year-old boy who had EoE triggered by CM; 2.5 years after this pathology resolved, he developed a CM IgE-mediated allergy.<sup>10</sup> Thus, there is little doubt that EoE and food allergies coexist and that one may precede another. One relevant question is about the risk of EoE during or after OIT. OIT has been used successfully in IgE-mediated food allergy, but an increased risk of developing EoE associated with OIT has been reported.<sup>7</sup> In the present study, we sought to assess the association between CM persistent allergy (with anaphylaxis manifestations) and esophageal eosinophilic infiltration via endoscopies and esophageal biopsies. The goal was to identify esophageal eosinophilia (EE) and the real frequency of EoE.

## MATERIALS AND METHODS

### Case definitions

We studied a prospective cohort at the São Paulo University Hospital-Brazil. Patients were enrolled from 2012 through 2016 in our Allergy and Immunology Unit.

We selected patients over 2 years who still had immediate allergic reactions to milk, within the past 12 months, with a history of anaphylaxis. Our database of 120 patients diagnosed with cow's milk allergy was evaluated. Of these, 31 patients were not enrolled in our study because they did not meet inclusion criteria, such as non-IgE-mediated allergy (severe atopic dermatitis, proctocolitis) or IgE-mediated milk allergy without anaphylaxis manifestation. Persistent food allergy was defined as a positive food challenge or parental report of reaction in the previous year consistent with anaphylactic IgE-mediated symptoms. The diagnosis of IgE-mediated food allergy was confirmed by history and testing (cow's milk protein and casein specific IgE). All patients who met these criteria were evaluated with endoscopy despite the presence or absence of gastrointestinal symptoms. There was a minimum of at least 3 months between the last CM reaction and the endoscopy.

EoE was confirmed according to the 2011 consensus document criteria.<sup>11</sup> The patients had to have typical symptoms of esophageal dysfunction and an esophageal biopsy specimen with at least 15 eosinophils per high-power field (eos/hpf) after an 8-week trial of a proton pump inhibitor (PPI). This inhibitor regimen was 1 mg/kg/per dose twice daily with any of the available agents prescribed at the discretion of the clinician. This therapy was necessary to differentiate proton pump inhibitor responsive esophageal eosinophilia (PPI-REE). Other causes of EE were excluded.

Patients who used systemic steroid therapy 1 month before the endoscopy would be excluded; however, none of the patients who fulfilled the selection criteria reported the use of corticosteroids within 1 month of endoscopy.

São Paulo University Ethics Committee approved this study. Patients or their parents provided informed consent and were enrolled before the endoscopy.

### Clinical and endoscopic data

We recorded all data including the demographic characteristics, gastrointestinal symptoms, CM allergy symptoms, atopic conditions, and medication use with a prospective questionnaire. During endoscopy, 4 to 5 esophageal biopsy specimens were obtained from the proximal and distal esophagus. Additional clinical biopsy specimens were taken as indicated at the discretion of the endoscopist to maximize EoE diagnostic sensitivity. Gastric and duodenal biopsy specimens were also collected for research purposes to exclude concomitant eosinophilic gastroenteritis. All specimens were obtained with a 9.8-mm video endoscopy (EG 580 WR, FUJIFILM Europe GmbH, Duesseldorf, Germany).

### Statistical analysis

Continuous variables with normal distribution were described as means and standard deviations and compared using the *t*-test. Those with asymmetrical distribution (analyzed by the Shapiro-Wilk test) were described by medians, interquartile values, and minimum/maximum values, and compared using the Mann-Whitney test. The nominal variables were described by their frequencies and compared using Fisher's exact test. Likelihood estimation analysis (Appendix E1, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)) was performed to predict the percentage of patients who might have EoE after an initial endoscopic diagnosis of EE, regardless of performing a second endoscopy or not. Statistical analysis was performed using SPSS 13.0 statistical software with a significance level of 5%.

## RESULTS

### Demographic data

We enrolled 89 patients with CM anaphylactic allergy. All patients underwent endoscopy. The median age was 8 years (interquartile range, 6-11 years). There were 4 patients over 18 years of age (18, 25, 34, and 49 years old) and none of them presented EE. Of the total group, 63 patients were male and 26 female. Patients without EE (*n* = 55) included 22 female (40%) and 33 male (60%). Regarding patients with EE (*n* = 34), 4 of 34 (11.8%) were female and 30 of 34 patients (88.2%) were male.

Eighty-one patients (91%) had other manifestations of atopic diseases such as allergic rhinitis, asthma, atopic dermatitis, or other food allergies. Of patients with and without EE, 69.6% and 71.1% had allergic rhinitis; 42.4% and 55.7% had asthma; 30.3% and 30.7% had atopic dermatitis; and 27.2% and 19.2% had other food allergies (6 and 8 patients with egg allergy, respectively). The Fisher exact test showed that there was no statistical difference between the presence or absence of atopy in patients with or without EE (*P* = .24).

### Esophageal eosinophilia, eosinophilic esophagitis, and proton pump inhibitor responsive esophageal eosinophilia frequency

We observed that 34 of 89 patients (38.2%; 95% confidence interval [CI]: 28.14%-49.16%) presented at least 15 eos/hpf in at least 1 hpf from endoscopic esophageal biopsy. Figure 1 shows that 15 of the 34 patients with EE received a full dose of PPI for 8 weeks and were then examined with follow-up endoscopy. There was no parenteral permission to perform new endoscopy

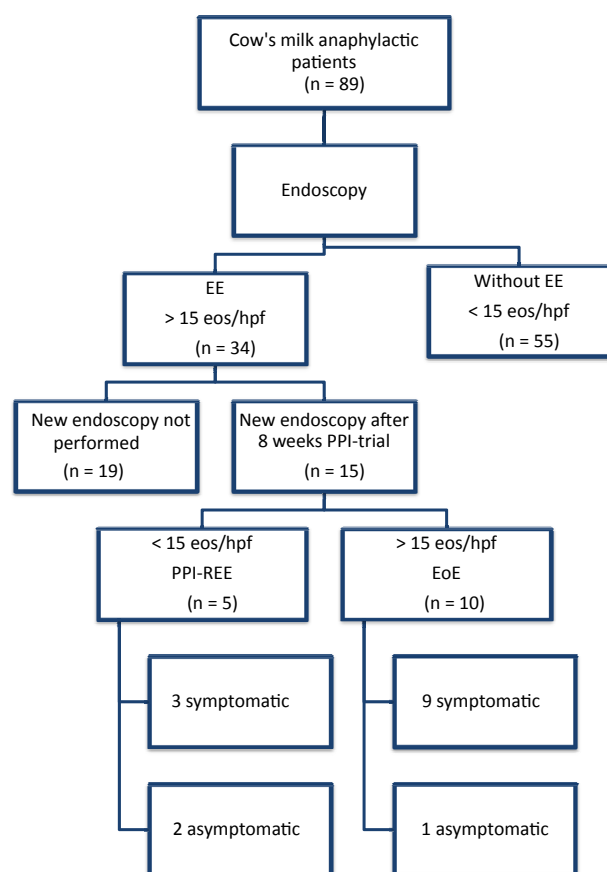


**FIGURE 1.** Esophageal eosinophilia classification according to gastrointestinal symptoms and proton pump inhibitor response. *EE*, Esophageal eosinophilia; *EoE*, eosinophilic esophagitis; *eos/hpf*, eosinophils per high power field; *PPI*, proton pump inhibitor; *PPI-REE*, proton pump inhibitor-responsive esophageal eosinophilia.

after PPI use in the remaining 19 patients with EE. Therefore, these 19 patients were not included in frequency estimates for EoE and PPI-REE. After the second endoscopy, 7.1% patients (5/70) presented PPI-REE. The remaining 14.2% patients (10/70) presented a second endoscopy with more than 15 eos/hpf; 9 received EoE diagnoses (clinical and histological criteria) and 1 presented asymptomatic EoE.

### Gastrointestinal manifestations and medications use

As presented in Table I, not all patients had gastrointestinal symptoms. After complete evaluation, 12.8% of patients (9/70) had EoE diagnosis (clinical manifestations associated with at least 15 eos/hpf after the PPI trial). In 1 patient, eosinophilic infiltration remained after PPI use and he was asymptomatic from a gastrointestinal perspective. There is no literature consensus on this group, and this condition was defined as asymptomatic eosinophilic esophagitis. Among the 5 patients with PPI-REE, 3 had gastrointestinal symptoms and 2 were asymptomatic.

Clinical manifestations in patients who had eosinophilic infiltrate ( $n = 34$ ) were quite variable and many of them were only reported after directed anamnesis as the patients' parents did not associate these symptoms with a possible allergy. Despite eosinophilic infiltrate, there were 10 patients completely

**TABLE I.** Esophageal eosinophilia classification according to gastrointestinal symptoms and PPI response

| First endoscopy >15 eos/hpf<br>(n = 34)  | Symptomatic | Asymptomatic |
|------------------------------------------|-------------|--------------|
| >15 eos/hpf after the PPI trial (n = 10) | 9           | 1            |
| PPI-REE                                  | 3           | 2            |
| <15 eos/hpf after the PPI trial (n = 5)  |             |              |
| New endoscopy not performed (n = 19)     | 12          | 7            |

*eos/hpf*, Eosinophils per high power field; *PPI*, proton pump inhibitor; *PPI-REE*, proton pump inhibitor-responsive esophageal eosinophilia.

asymptomatic from a gastrointestinal point of view. The frequency of symptoms reported is described in Table II. Besides, 22 patients (64.7%) used topical nasal and/or inhaled corticosteroids.

Fifty-five patients had no eosinophilic infiltrate at endoscopy; 13 of them had gastrointestinal symptoms, and 5 of these were suggestive of esophageal dysfunction (dysphagia or gagging) (Table II). However, 5 of these symptomatic patients were using topical nasal steroids and 4 also used inhaled corticosteroids, all at a low or medium dose (up to 400  $\mu$ cg budesonide or equivalent per day according to Global Initiative for Asthma 2015). Bivariate analysis using Fisher's exact test showed no significant difference regarding the use of nasal steroids ( $P = .82$ ), low-dose inhaled corticosteroids ( $P = .24$ ), and medium-dose inhaled corticosteroids ( $P = .75$ ) between the groups with and without EE.

### Endoscopic findings

The main endoscopic findings in patients with EE are presented in Table III. This indicates that there was inflammatory phenotype predominance in this study group of patients with EE.

Ten patients had EoE, and we found that only 1 had normal endoscopy. This asymptomatic patient had edema, and there were longitudinal furrows and exudate in his first endoscopy. Of the 34 patients with EE, 8 (23.5%) had a normal endoscopy. There was an association with inflammatory alterations in the esophagus in 21 patients (61.7%).

We found some cases with endoscopic alterations in patients with no evidence of esophageal eosinophilic infiltration in biopsies. We note that 3 patients presented whitish exudates and 2 of them had typical gastrointestinal symptoms. They were using inhaled corticosteroids, and this might have influenced the finding of eosinophils in the esophageal mucosa. Fungal culture has not been performed in any of these cases to rule out the presence of *Candida*.

### Eosinophils count

The median values of esophageal eosinophils in patients with EE are listed in Table IV. When there was no description of the site where the biopsy was collected, it was called "without specific location."

### Laboratory findings

Overall, the EE group presented higher values for all tests; significant differences were found for peripheral blood eosinophils, IgE to cow's milk,  $\beta$ -lactoglobulin, and casein. Table V compares the IgE values, peripheral eosinophils, specific IgE to cow's milk,  $\alpha$ -lactalbumin,  $\beta$ -lactoglobulin, and casein between the groups.

**TABLE II.** Frequency of gastrointestinal symptoms in patients with and without esophageal eosinophilia

| Gastrointestinal symptoms                                    | Patients with esophageal eosinophilia (n = 34) | Patients without esophageal eosinophilia (n = 55) |
|--------------------------------------------------------------|------------------------------------------------|---------------------------------------------------|
| Absent gastrointestinal symptoms, n (%)                      | 10 (29.4%)                                     | 42 (76.3%)                                        |
| Persistent typical symptoms (at least once a week)           |                                                |                                                   |
| Abdominal pain, n (%)                                        | 3 (8.8%)                                       | 2 (3.6%)                                          |
| Vomiting, n (%)                                              | 4 (11.7%)                                      | 2 (3.6%)                                          |
| Gagging, n (%)                                               | 3 (8.8%)                                       | 2 (3.6%)                                          |
| Dysphagia, n (%)                                             | 4 (11.7%)                                      | 1 (1.8%)                                          |
| Impaction, n (%)                                             | 2 (5.8%)                                       | 0                                                 |
| Intermittent typical symptoms (reported up to twice a month) |                                                |                                                   |
| Abdominal pain, n (%)                                        | 3 (8.8%)                                       | 4 (7.2%)                                          |
| Vomiting, n (%)                                              | 4 (11.7%)                                      | 1 (1.8%)                                          |
| Gagging, n (%)                                               | 3 (8.8%)                                       | 1 (1.8%)                                          |
| Dysphagia, n (%)                                             | 0                                              | 1 (1.8%)                                          |
| Impaction, n (%)                                             | 1 (2.9%)                                       | 0                                                 |
| Nonspecific symptoms                                         |                                                |                                                   |
| Drinking liquids with meals habits, n (%)                    | 5 (14.7%)                                      | 1 (1.8%)                                          |
| Coughing while feeding, n (%)                                | 5 (14.7%)                                      | 1 (1.8%)                                          |
| Sialorrhea, n (%)                                            | 2 (5.8%)                                       | 0                                                 |
| Nonspecific sore throat, n (%)                               | 1 (2.9%)                                       | 0                                                 |
| Hiccups, n (%)                                               | 2 (5.8%)                                       | 0                                                 |
| Inappetence, n (%)                                           | 2 (5.8%)                                       | 0                                                 |
| Liquid/paste food preference, n (%)                          | 1 (2.9%)                                       | 0                                                 |
| Slowly eating, n (%)                                         | 1 (2.9%)                                       | 0                                                 |
| Early satiety, n (%)                                         | 1 (2.9%)                                       | 0                                                 |

**TABLE III.** Endoscopic findings

| Findings                        | Patients with esophageal eosinophilia (n = 34) | Patients without esophageal eosinophilia (n = 55) |
|---------------------------------|------------------------------------------------|---------------------------------------------------|
| Pallor or decreased vasculature | 12 (35.2%)                                     | 1 (1.8%)                                          |
| Linear furrows                  | 16 (47%)                                       | 0                                                 |
| White plaques or exudates       | 7 (20.5%)                                      | 3 (5.4%)                                          |
| Esophageal rings                | 0                                              | 0                                                 |
| Strictures                      | 1 (2.9%)                                       | 0                                                 |
| Narrow-caliber esophagus        | 1 (2.9%)                                       | 0                                                 |
| Erosive esophagitis             | 3 (8.8%)                                       | 6 (10.9%)                                         |
| "Crepè" paper                   | 1 (2.9%)                                       | 0                                                 |
| Normal                          | 8 (23.5%)                                      | 45 (81%)                                          |

## DISCUSSION

Data on EoE prevalence currently vary widely, perhaps because it is an emerging disease and there is a lack of medical knowledge, with less clinical suspicion. There are reports of prevalence ranging from 0.4% in the general population (based on endoscopies with biopsies) up to 15% (based on endoscopies performed in patients with dysphagia).<sup>12-15</sup>

The onset of EoE after OIT has been repeatedly described in up to 2.7% of patients with IgE-mediated food allergy undergoing this treatment strategy.<sup>7</sup> Although these reports can dampen enthusiasm for this treatment option, there have been no previous studies into the presence of eosinophils in the esophageal mucosa before treatment was initiated in either of these reports.

In this way, this research shows that there are significant eosinophilic infiltrates in patients with CM-persistent allergy and

anaphylaxis manifestations. In some of these patients, there were endoscopic findings compatible with EoE that were associated with mild or even absent gastrointestinal symptoms. Symptoms of EoE were not always valued and reported spontaneously by the patient or family. Many of the patients reported gastrointestinal symptoms only after medical questioning. Therefore, it would be important for physicians to ask questions about EoE symptoms even for patients with IgE-mediated food allergy, apparently asymptomatic from the gastrointestinal point of view. This suggests the possibility of an insidious development of EoE in a large proportion of anaphylactic patients. The causal relation between EoE and OIT is still controversial, as EoE could be consequent to a pre-existing condition or EoE could precede IgE-mediated food allergy.

Of the 89 patients studied, 34 (38.2%) had EE. Among the 34 patients with EE, the estimated probability of a patient being

**TABLE IV.** Eosinophils count per high power field in esophageal mucosa

|                           | Median | Minimum value | Maximum value | Interquartile range |
|---------------------------|--------|---------------|---------------|---------------------|
| Proximal esophagus        | 0      | 0             | 100           | 24                  |
| Midesophagus              | 20     | 0             | 120           | 32                  |
| Distal esophagus          | 26     | 0             | 84            | 20                  |
| Without specific location | 28     | 18            | 150           | 30                  |

**TABLE V.** Laboratory findings in patients (n = 89)

|                                       | Patients without esophageal eosinophilia,<br>median (range) | Patients with esophageal eosinophilia,<br>median (range) | P value     |
|---------------------------------------|-------------------------------------------------------------|----------------------------------------------------------|-------------|
| Total IgE (UI/mL)                     | 664 (57-8880)                                               | 1013 (81-3000)                                           | .57         |
| Eosinophils/ $\mu$ L                  | 447 (54-1330)                                               | 788 (110-1530)                                           | <b>.004</b> |
| IgE to cow's milk (kUA/L)             | 33.5 (0.35-100)                                             | 77.8 (1.7-100)                                           | <b>.043</b> |
| IgE to $\alpha$ -Lactalbumin (kUA/L)  | 9.1 (0.35-100)                                              | 22.7 (0.35-100)                                          | .060        |
| IgE to $\beta$ -Lactoglobulin (kUA/L) | 7.3 (0.35-100)                                              | 21.1 (0.35-100)                                          | <b>.047</b> |
| IgE to Casein (kUA/L)                 | 22.3 (0.35-100)                                             | 63.6 (2.2-100)                                           | <b>.018</b> |

Bold values indicate statistical significance ( $P < .05$ ).

diagnosed with EoE is 0.33 (90% CI: 0.14-0.60). Frequencies of EE, EoE, and PPI-REE in the present study were higher than we might expect considering the EoE prevalence in the general population and even among the group of patients with gastrointestinal symptoms. In a large retrospective study examining electronic medical records data and performing manual chart reviews in a subset of patients, Hill et al<sup>16</sup> have investigated the association between IgE-mediated food allergy and EoE in children and adolescents. The prevalence of EoE in patients with IgE-mediated food allergy was 4.7%, and IgE-mediated allergy to milk, egg, or shellfish was significantly associated with an EoE diagnosis. Our group of patients had a higher EoE prevalence, and the frequency of EE, EoE, and PPI-REE in CM anaphylactic patients is being described for the first time here. Thus, phenotypes never reported before were found such as asymptomatic patients with eosinophilic infiltrate and endoscopic findings suggestive of EoE.

In this context, we emphasize the controversial PPI-REE phenotype because current data have not shown relevant differences in endoscopic and immunohistochemical comparisons with EoE.<sup>17-19</sup> So, these findings allow for the hypothesis that there could be different stages of the same disease.<sup>20</sup> This assumption is strengthened by the proposed anti-inflammatory mechanism of PPI over control of EE: barrier healing, acid suppression, and eotaxin-3 downregulation, although the clinical relevance of this observation still needs to be determined.<sup>19</sup>

In the EoE group (n = 10), there were 4 patients with nonspecific symptoms, 4 with persistent typical symptoms, 1 with intermittent typical symptoms, and 1 with absent gastrointestinal symptoms. The asymptomatic patient presented inflammatory alterations in endoscopy, such as esophageal edema, furrows, and exudate. Likewise, there were 3 patients with nonspecific symptoms and 2 patients with persistent typical symptoms with the same alterations in endoscopy.

A similar phenomenon was seen in all patients with EE (n = 34): 29.4% of asymptomatic patients, 23.5% patients with nonspecific symptoms, 23.5% with persistent typical symptoms, and 23.5% with intermittent typical symptoms. There was an association with inflammatory alterations in esophagus

endoscopy in 21 patients (61.7%) including the presence of lacerations and narrowing in 1 patient with an absent clinical picture. Therefore, 8 patients (23.5%) had normal endoscopy similar to the literature data that described up to 25% of normal endoscopies in the patients with EoE.<sup>21</sup>

This description demands scientific attention because it is the highest frequency of EoE reported in a particular group of patients. It is one of the highest EoE in a determined group of patients. This fact begs the question of which risk factor has a greater impact: anaphylaxis or persistent IgE-mediated CM allergy, or perhaps both.

Thus, we suggest that EE is a condition that can coexist "silently" with an IgE-mediated food allergy that is often underestimated and underdiagnosed. Its diagnosis during or after cow's milk OIT does not necessarily mean a side effect caused by immunotherapy.

Although it was not possible to confirm the EoE diagnosis in the total group of patients with EE, there was a high presence of esophageal inflammatory alterations in all patients, even including fibrostenotic remodeling in 1 patient. This group advises us about the possible existence of a higher frequency of EoE in patients with cow's milk anaphylaxis. Recent studies suggest that delay in the EoE diagnosis increases the risk for stricture formation in a time-dependent manner.<sup>22,23</sup> Our group of patients was characterized by predominantly inflammatory and not fibrostenotic endoscopic phenotype, but little is known about progression of stricture formation. Thus, early diagnosis is essential to prevent severe esophageal remodeling in the future.

An important aspect analyzed in the present study was the great predominance of EE in males. Even in the general group of cow's milk anaphylactic patients, there was a higher prevalence among boys (70.7%). This became more pronounced when we observed the EE group. The male group presented a 5-fold increase in EE frequency (odds ratio 5, 95% CI 1.5-15.7). A possible explanation for this higher EoE prevalence in males is related to the pathophysiology of the disease. One of the main cytokines involved in the genesis of inflammatory stimulus, thymic stromal lymphopoietin, has its gene receptor on chromosome Yp11.3.<sup>24</sup>

We question if other genetic factor could be involved and promote cow's milk anaphylaxis associated with EoE.

Although EoE is currently recognized as a non-IgE-mediated hypersensitivity disease,<sup>25</sup> sensitization to food and environmental allergens has been observed in 75% and 79% of pediatric patients with EoE, respectively.<sup>4</sup> Among foods, milk sensitization is most commonly seen in patients with EoE; however, anti-IgE therapy has not been effective in inducing remission of EoE,<sup>26</sup> and elimination diets based on detection of specific IgE to food allergens, either by the skin prick test or by specific IgE, have not proven successful for the identification of causative foods in EoE.<sup>27,28</sup> Thus, the link that we observed in this study between EoE and IgE-mediated milk allergy could not be explained solely by the IgE-mediated food hypersensitivity.

Recently, the possibility of EoE onset after the development of spontaneous tolerance for the same food that previously caused immediate IgE-mediated events has been described.<sup>6</sup> This issue has been questioned, including the role of IgE in the pathophysiology of EoE. However, facing these results, there is a need to revise and evaluate the possibility of IgE-mediated food allergy-associated cellular mechanisms.

By making reference to the known model of atopic march compared with the current knowledge about the natural history of food allergy, this frequency allows us to question whether EoE precedes or even predisposes to food anaphylaxis and may be an underlying disease of insidious onset. Early diagnosis would avoid future complications. Moreover, when observing the present changes of cow's milk allergy history, which is becoming more persistent over the years and with a growing association with anaphylaxis,<sup>29</sup> it will be inevitable to raise doubts about the reasons involved in these changes: could cellular immune mechanisms associated with IgE-mediated allergy alter the natural course of the disease? Although it is not possible to answer this question, the connection between EE, anaphylaxis, persistent allergy, and factors that suggest genetic interference (male dominance) in this study was very high.

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## REFERENCES

- Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci* 1993;38:109-16.
- Dellon ES. Diagnosis and management of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2012;10:1066-78.
- 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). *Am J Gastroenterol* 2013;108:679-92. quiz 693.
- Assa'ad AH, Putnam PE, Collins MH, Akers RM, Jameson SC, Kirby CL, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. *J Allergy Clin Immunol* 2007;119:731-8.
- Sugnanam KKN, Collins JT, Smith PK, Connor F, Lewindon P, Cleghorn G, et al. Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. *Allergy* 2007;62:1257-60.
- Maggadottir SM, Hill DA, Ruymann K, Brown-Whitehorn TF, Cianferoni A, Shuker M, et al. Resolution of acute IgE-mediated allergy with development of eosinophilic esophagitis triggered by the same food. *J Allergy Clin Immunol* 2014;133:1487-9.
- Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2014;113:624-9.
- Ridolo E, De Angelis GL, Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. *Ann Allergy Asthma Immunol* 2011;106:73-4.
- Sánchez-García S, Rodríguez Del Río P, Escudero C, Martínez-Gómez MJ, Ibáñez MD. Possible eosinophilic esophagitis induced by milk oral immunotherapy. *J Allergy Clin Immunol* 2012;129:1155-7.
- Hill DA, Shuker M, Cianferoni A, Wong T, Ruchelli E, Spergel JM, et al. The development of IgE-mediated immediate hypersensitivity after the diagnosis of eosinophilic esophagitis to the same food. *J Allergy Clin Immunol Pract* 2015;3:123-4.
- Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3-20.
- De la Cruz-Patiño E, Ruíz Juárez I, Meixueiro Daza A, Grube Pagola P, Roesch-Dietlen F, Remes-Troche JM. Eosinophilic esophagitis prevalence in an adult population undergoing upper endoscopy in southeastern Mexico. *Dis Esophagus* 2015;28:524-9.
- Veerappan GR, Perry JL, Duncan TJ, Baker TP, Maydonovitch C, Lake JM, et al. Prevalence of eosinophilic esophagitis in an adult population undergoing upper endoscopy: a prospective study. *Clin Gastroenterol Hepatol* 2009;7:420-6. 426.e1-2.
- Merves J, Muir A, Modayur Chandramouleeswaran P, Cianferoni A, Wang M-L, Spergel JM. Eosinophilic esophagitis. *Ann Allergy Asthma Immunol* 2014;112:397-403.
- 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. *Am J Gastroenterol* 2007;102:2627-32.
- Hill DA, Dudley JW, Spergel JM. The prevalence of eosinophilic esophagitis in pediatric patients with IgE-mediated food allergy. *J Allergy Clin Immunol Pract* 2016;5:369-75.
- Warners MJ, van Rhijn BD, Curvers WL, Smout AJPM, Bredenoord AJ. PPI-responsive esophageal eosinophilia cannot be distinguished from eosinophilic esophagitis by endoscopic signs. *Eur J Gastroenterol Hepatol* 2015;27:506-11.
- Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. *J Allergy Clin Immunol* 2015;135:187-197.e4.
- Molina-Infante J, Rivas MD, Hernandez-Alonso M, Vinagre-Rodríguez G, Mateos-Rodríguez JM, Dueñas-Sadomil C, et al. Proton pump inhibitor-responsive oesophageal eosinophilia correlates with downregulation of eotaxin-3 and Th2 cytokines overexpression. *Aliment Pharmacol Ther* 2014;40:955-65.
- Rothenberg ME. Molecular, genetic, and cellular bases for treating eosinophilic esophagitis. *Gastroenterology* 2015;148:1143-57.
- Müller S, Pühl S, Vieth M, Stolte M. Analysis of symptoms and endoscopic findings in 117 patients with histological diagnoses of eosinophilic esophagitis. *Endoscopy* 2007;39:339-44.
- Lipka S, Kumar A, Richter JE. Impact of diagnostic delay and other risk factors on eosinophilic esophagitis phenotype and esophageal diameter. *J Clin Gastroenterol* 2016;50:134-40.
- 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.
- Sherrill JD, Gao P-S, Stucke EM, Blanchard C, Collins MH, Putnam PE, et al. Variants of thymic stromal lymphopoietin and its receptor associate with eosinophilic esophagitis. *J Allergy Clin Immunol* 2010;126:160-165.e3.
- Simon D, Cianferoni A, Spergel JM, Aceves S, Holbreich M, Venter C, et al. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. *Allergy* 2016;71:611-20.
- Rocha R, Vitor AB, Trindade E, Lima R, Tavares M, Lopes J, et al. Omalizumab in the treatment of eosinophilic esophagitis and food allergy. *Eur J Pediatr* 2011;170:1471-4.
- Liacouras CA, Spergel JM, Ruchelli E, Verma R, Mascarenhas M, Semeao E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005;3:1198-206.
- Spergel JM, Brown-Whitehorn TF, Beausoleil JL, Franciosi J, Shuker M, Verma R, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr* 2009;48:30-6.
- Hochwallner H, Schulmeister U, Swoboda I, Spitzauer S, Valenta R. Cow's milk allergy: from allergens to new forms of diagnosis, therapy and prevention. *Methods* 2014;66:22-33.

## ONLINE REPOSITORY

### APPENDIX E1: ESTIMATION ANALYSIS

Goal: Estimation of the prevalence of a disease based on a sampling of individuals at risk.

Procedure: To detect “the disease,” 2 endoscopies must be performed: (1) a first endoscopy screens “diseased” individuals, but other diseases are also positive (false positive). Treatment is carried out among first positive persons aiming to eliminate false positives. (2) Then a second endoscopy is performed among first positive persons. If positive, this person is confirmed as diseased.

Sampling: The risk group comprises  $n = 89$  patients. A first endoscopy resulted in  $n_1 = 34$  positive persons ( $n_0 = 55$ ). Among them,  $n_{10} = 19$  refused to undergo a second endoscopy. After a specific treatment, a second endoscopy among  $n_2 = 15$  caught up  $n_{22} = 5$  as carrying the disease ( $n_{20} = 10$ ).

Assumptions: (1) Endoscopy results positive for a diseased person (probability for one who is carrying disease to be positive by endoscopy); (2) second endoscopy does not bear error (diseased if the second endoscopy is positive); and (3) given that the first endoscopy is positive, the probability of this person undergoing the second endoscopy is the same, regardless of being a carrier or not of the disease.

Definitions of probabilities: (1)  $P$  is the probability of a person being diseased; (2)  $P_1$  is the probability of a nondiseased person resulting in positive endoscopy (false positive); (3)  $P_2$  is the probability of person undergoing a second endoscopy, given that

the first endoscopy was positive; (4)  $P_3$  is the probability of a person, after the first endoscopy being positive, carrying disease regardless of the second endoscopy.

Transitions: (1) The probability of the second endoscopy being positive ( $n_{22} = 5$ ) is  $P \cdot P_2$ ; (2) the probability of the second endoscopy being negative ( $n_{20} = 10$ ) is  $(1 - P) \cdot P_1 \cdot P_2$ ; (3) the probability of refusing the second endoscopy, given that the first endoscopy was positive ( $n_{10} = 19$ ) is  $[P + (1 - P) \cdot P_1] \cdot (1 - P_2)$ ; and (4) the probability of the first endoscopy being negative ( $n_0 = 55$ ) is  $(1 - P) \cdot (1 - P_1)$ .

Likelihood estimation :

$$\frac{\overline{pP}}{pP} = \frac{n_{22}/(n_{22} + n_{20})}{n/n_0} = \frac{5/15}{89/34} = 0.127; \quad (1)$$

$$\frac{\overline{pP_2}}{pP_2} = \frac{n_{22} + n_{20}}{n_0} = \frac{15}{34} = 0.441; \quad (2)$$

$$\frac{\overline{pP_1}}{pP_1} = \frac{n_{20}/n}{pP_2(1 - \overline{pP})} = 0.292; \text{ and} \quad (3)$$

$$\frac{\overline{pP_3}}{pP_3} = \frac{\overline{pP}}{pP + (1 - \overline{pP})\overline{pP_1}} = 0.333.$$

Confidence interval: The confidence interval for  $P$  and  $P_3$  are obtained by bootstrap samplings, considering a sample of 89 with estimated probabilities. The confidence intervals with 90% (quantiles 0.05 and 0.95) are: (1) (0.047, 0.21) for  $P$  and (2) (0.14, 0.60) for  $P_3$ .

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