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Esophageal IgG4: Clinical, Endoscopic, and Histologic Correlations in Eosinophilic Esophagitis

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Abstract

Objective: Recent studies show increased serum and esophageal IgG4 in patients with eosinophilic esophagitis (EoE), suggesting a possible IgG4-involved process. The role of IgG4 in pediatric EoE has not been extensively investigated. Our aim was to analyze IgG4 in esophageal tissue in children in parallel to that in adults with EoE.

Methods: In a retrospective institutional review board-approved study, we performed immunohistochemical staining of IgG4 in esophageal biopsy specimens from 39 subjects: children with EoE (n = 16), adults with EoE (n = 15), children with reflux esophagitis (n = 4), and pediatric controls (n = 4). We assessed the relationships between IgG4 staining and clinical, endoscopic, and histopathologic characteristics.

Results: Patients with EoE were significantly more likely to stain positively for IgG4 than children with reflux esophagitis or controls ($P = 0.015$). Fifteen of 31 (48%) EoE cases stained positively for IgG4. None of the reflux esophagitis or control cases stained positively. IgG4 staining had 48% sensitivity and 100% specificity for EoE. There was a trend toward IgG4 staining being associated with foreign body/food impaction ($P = 0.153$). There was a strong association between distal IgG4 staining and basal zone hyperplasia ($P = 0.003$).

Conclusions: Our study suggests IgG4 is not a consistent finding of EoE at disease diagnosis. Although IgG4 staining was specific for EoE, it had a poor sensitivity with positive staining in only 48% of EoE patients. Further studies are warranted to fully elucidate the role of IgG4 in EoE.

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Keywords

allergy; eosinophilia; eosinophilic esophagitis; IgG4; pediatric

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease of the esophagus characterized clinically by symptoms related to esophageal dysfunction and histologically by esophageal eosinophilia (1). An increase in prevalence and incidence has been noted, with estimates suggesting a prevalence of 0.5 to 1 in 1000 and an incidence of 1/10,000 new cases annually (2). Evidence has suggested a type 2 helper T cell–mediated pathogenesis. The principal antigens are food-based and, less prominently, aeroallergens. Management is challenging, due both to a discrepancy between symptoms and histopathology and the current lack of biomarkers of disease activity.

Several recent studies have implicated a role of IgG4 in EoE. In 1 adult study, patients with EoE had a 45-fold increase in esophageal IgG4 compared to controls, with no significant increase in other IgG subclasses (3). In another study, IgG4 deposits were noted in the esophageal tissue of 76% of adult EoE patients and none of the patients without EoE (4). The IgG4 deposits diminished with therapy, raising the possibility that IgG4 is a marker of disease activity (4). In addition, adults with EoE have been noted to have elevated serum total IgG4 and food-specific IgG4 compared with non-EoE controls (5). A study of 41 pediatric patients with EoE found increased levels of IgG4-positive plasma cells in association with active esophagitis, particularly in those with food allergy (6). Finally, a recent a study of 17 pediatric patients with EoE found esophageal IgG4 levels were elevated in affected patients and correlated with disease activity as assessed by histopathology and transcriptomic features (7). Of note, none of these studies clearly focused on a population naïve to treatment.

The goal of this study was to compare IgG4 quantification in treatment naïve, newly diagnosed EoE patients to pediatric reflux patients and controls. We hypothesized that IgG4 would be present in a greater number of patients with untreated EoE compared to reflux patients and controls. We also aimed to compare esophageal IgG4 in pediatric EoE patients to adult EoE patients, with the hypothesis that IgG4 would be present in a greater number of older patients compared to younger patients. This study expands upon the current body of literature by further evaluating IgG4 in esophageal tissue of EoE patients, particularly the pediatric population.

METHODS

Patient Selection

An institutional review board–approved (#16–001245) retrospective review of patients cared for in the pediatric and adult gastroenterology programs at University of California Los Angeles was performed to identify patients with treatment naïve, newly diagnosed EoE who underwent esophagogastroduodenoscopy (EGD) from February 2012 to February 2017. Inclusion criteria consisted of patients in whom EGD was performed for suspicion of EoE based on clinical symptoms and in whom biopsy specimens were obtained from a distal and

a more proximal level of the esophagus. Patients with previous or ongoing EoE treatment, PPI-responsive eosinophilia, and other esophageal disorders such as scleroderma, Schatzki ring, and Barrett esophagus were excluded.

Clinical features combined with histopathology reports were used to identify patients with EoE (16 children, 15 adults). Histopathologic diagnosis of EoE was based upon presence of ≥15 eosinophils per high-power field (hpf) in the context of histologic features representative of EoE including basal zone hyperplasia, degranulated eosinophils, eosinophilic microabscesses, lamina propria fibrosis, spongiosis, and superficial layering of eosinophils. For comparison, we included 4 children with diagnosis of reflux esophagitis based upon presence of 1 to 14 eosinophils per hpf in the distal esophagus and absence of histologic features characteristic of EoE. In addition, 4 pediatric control patients with esophageal biopsy specimens that lacked eosinophils and other histologic abnormalities were included. Power calculations suggested these sample sizes would adequately detect significant differences in IgG4 staining between EoE and control patients using 80% power with the usual $\alpha = 0.05$ significance criteria.

Data Collection

During chart review of electronic medical records, data regarding patient demographics, medical history, presenting symptoms, and laboratory results were obtained. Atopy was defined by a diagnosis of eczema, allergic rhinitis, environmental allergies, asthma, and/or food allergies documented in the patient's medical record. Food allergies included a broad spectrum of physician-diagnosed and patient-reported anaphylaxis reactions, hives/rashes, and/or positive skin testing. Dysphagia was defined by a report of difficulty swallowing, including the requirement for copious liquids to pass food boluses. Reflux symptoms were defined by a report of gastroesophageal reflux, regurgitation, heart burn, and/or chest pain related to intake. All laboratory results collected were obtained before or in conjunction with endoscopy. Endoscopic findings including circular rings, exudates, linear furrowing, shearing or fragility, stricturing or narrowing, and ulcerations were obtained through review of gastroenterologist procedure reports. Similarly, the performance of esophageal dilation and foreign body or food impaction removal was also obtained. All clinical characteristics mentioned above were extracted from chart review only and did not rely on ICD-9/10 codes.

Retrospective Histopathologic Reassessment

Pathologist reports of histologic findings were used for the initial classification of patients into groups of EoE, reflux esophagitis, or normal control. Following classification, pathology slides were pulled for confirmation of diagnosis and review of histologic features described above by a masked pathologist. In addition, the 8 features of the Collins histology scoring system were evaluated and scored for grade and stage (8).

Immunohistochemical Staining for IgG4

Paraffin sections were collected on positive-charged slides and baked for 1 hour at 65°C. Immunostaining was performed on Leica Bond III autostainer with onboard deparaffinization and heat-induced antigen retrieval using high pH Ethylenediaminetetraacetic acid buffer for 20 minutes. IgG4 Mouse monoclonal antibody

(clone MRC-44, Cell Marque, 1:50) was applied for 15 minutes. Bond Refine DAB Detection (Leica Microsystems DS9800) was used per manufacturers' instructions. Primary Antibody Diluent alone was used as a negative control.

Immunostaining Review

IgG4 immunostaining, both positively stained plasma cells and extracellular staining, was assessed by a masked pathologist. Predetermined definitions of staining intensity (strong or weak), location (lamina propria, epithelium, or both), and staining distribution (focal or diffuse) were use to characterize the positively stained specimens (Fig. 1). Staining intensity was interpreted as strong or weak based upon the degree of cytoplasmic staining, dark, or pale, respectively, in the majority of the positively stained tissue. Finally, the highest number of IgG4-positive plasma cells per hpf was quantified.

Data Analysis

Standard descriptive analyses were performed and are reported as median (range) or frequency. Statistical analyses included Chisquare, Fisher exact, *t* tests, and Wilcoxon rank-sum analyses. Statistical significance was defined as a P value<0.05.All data analyses were performed with Stata version 11 (StataCorp LP, College Station, TX).

RESULTS

Patient Characteristics

The clinical characteristics of EoE patients are summarized in Table 1. Median (range) age of pediatric and adult EoE patients was 12.5 (6–17) and 33 (20–76) years, respectively. Male sex was less common in pediatric compared to adult patients (50% vs 81%, $P = 0.054$). Eighty-one percent of pediatric EoE patients were atopic; 60% of adult patients were atopic ($P = 0.252$). Pediatric reflux esophagitis patients had a median (range) age of 11 (3–16) years and 50% were boys. Pediatric control patients had a median (range) age of 11.5 (8–16) years and 25% were boys.

Clinical Presentation

As shown in Table 1, clinical symptoms varied by age, with 50% of pediatric EoE patients presenting with dysphagia compared to 100% of adult patients ($P = 0.002$). Other common pediatric presentations included reflux symptoms (50%) and weight loss or poor weight gain (44%). Comparatively, nearly half of adult patients (47%) presented with food impaction, one third (33%) with reflux symptoms, and few (13%) with weight loss.

Laboratory Tests

Laboratory studies were not performed universally before or at the time of diagnosis. Of the patients in whom a complete blood count was obtained, 50% (6/12) of pediatric and 14% (1/7) of adult EoE patients had peripheral eosinophilia, defined by an absolute eosinophil count >0.5×10^3/mL. Median (range) eosinophil count was 7×10^3/μL ($2.1–15.1 \times 10^3$/μL) in children; median (range) eosinophil count was 5.8×10^3/μL ($0.4–15.3 \times 10^3$/μL) in adults.

All 6 pediatric patients in whom serum IgE level was obtained demonstrated elevated IgE, defined as IgE >100kU, with a median (range) of 263kU (146–1206kU).

Endoscopic Findings and Interventions

Endoscopic findings are presented in Table 1. All pediatric EoE patients had abnormal findings, with linear furrowing and exudates as the most common, in 81% and 63% of patients, respectively. Exudates were significantly more common in children compared to adults with EoE (63% vs 20%, $P = 0.029$). Circular rings were significantly more common in adults compared to children with EoE (67% vs 19%, $P = 0.011$). Esophageal strictures were observed in 2 pediatric (13%) and 5 adult (33%) EoE patients. Three adults with esophageal strictures underwent esophageal dilation during EGD. One pediatric (6%) and 3 adult (20%) patients required removal of a food impaction.

Histologic Findings

As shown in Table 2, histologic features were similar in children and adults except for a trend toward increased basal zone hyperplasia in proximal esophageal biopsies in adult patients ($P = 0.054$). In the biopsy specimens which included lamina propria, lamina propria fibrosis was present in all adult tissue and nearly all pediatric specimens (100% proximal, 75% distal). There were no significant differences in esophageal eosinophil counts in pediatric and adult EoE patients. Pediatric EoE patients had a median (range) of 35 (0–164) and 45 (7–124) eosinophils per hpf in the distal and proximal esophageal level, respectively. Adult EoE patients had a median (range) of 46 (13–95) and 47 (20–117) eosinophils per hpf at the distal and proximal esophageal level, respectively. There were 3 patients (2 pediatric, 1 adult) with <15 eosinophils per hpf at 1 level, but all had >15 eosinophils per hpf at the other level and additional histologic features of EoE at both levels. Pediatric reflux esophagitis patients had a median (range) of 6 (1–12) eosinophils per hpf at the distal level. No eosinophils were seen in the esophageal biopsies of the control patients.

IgG4 Staining

A summary of IgG4 staining results is shown in Table 3. Patients with EoE were significantly more likely to stain positively for IgG4 than children with reflux esophagitis or controls ($P = 0.015$). Fifteen of 31 (48%) EoE cases stained positively for IgG4. None of the reflux esophagitis or control cases stained positively for IgG4. IgG4 staining was found to have 48% sensitivity and 100% specificity for EoE.

Esophageal Level—Most positive cases stained in both the distal and proximal esophageal biopsy specimens, but 3 of 15 (20%) cases, including 1 pediatric and 2 adult cases, stained at 1 esophageal level only.

Intensity—Intensity of IgG4 staining varied: 8 of 15 (53%) cases stained with strong intensity, 5 of 15 (33%) cases with weak intensity, and 2 (13%) cases with both strong and weak intensity based on the esophageal level. There was a trend toward strong IgG4 staining being associated with basal zone hyperplasia in the distal esophagus, with basal zone hyperplasia seen in only 14 of 22 cases with no or weak staining compared to 9 of 9

cases with strong staining ($P = 0.068$). Aside from this, there was no correlation between staining intensity and number of eosinophils per hpf or other histopathologic findings.

Location—Lamina propria was the most common location of IgG4 staining, with 13 of 15 (87%) cases staining in the lamina propria. Two cases had staining in the epithelium in addition to the lamina propria. Two adult cases had staining limited to the epithelium, one of which did not have lamina propria present in the specimen for assessment.

Distribution—The distribution of the staining was most often focal, with 8 of 15 (53%) cases demonstrating focal staining and 4 of 15 (27%) cases demonstrating diffuse staining. In the remaining 3 cases, the staining pattern was not uniform amongst the distal and proximal specimens, revealing focal staining at 1 esophageal level and diffuse staining at the other level.

IgG4-positive Plasma Cells—There was no significant difference in number of IgG4-positive plasma cells per hpf in the distal versus proximal esophagus, with a median (range) of 7 (1–29) in the distal esophagus and 5 (1–21) in the proximal esophagus. The number of IgG4-positive plasma cells was, however, higher in patients with strong compared with weak intensity staining ($P = 0.010$), with a median (range) of 8.5 (4–29) in strongly stained biopsies and 3 (1–12) in weakly stained biopsies.

Collins Histology Scoring System—Based on the Collins histology scoring system, basal zone hyperplasia (grade and stage), dilated intercellular spaces (grade), and lamina propria fibrosis (grade) scores were higher in patients with positive compared to negative IgG4 staining, as shown in Supplementary Table 1 (Supplemental Digital Content, http://links.lww.com/MPG/B531). In addition, composite scores tended to be higher in patients with positive IgG4 staining, meeting statistical significance in biopsies from the proximal esophagus. There was no association between higher composite scores and stronger intensity IgG4 staining.

Clinical Correlations—There was a trend toward distal IgG4 staining being associated with foreign body/food impaction, which was seen in 7 of 14 (50%) patients with distal IgG4 staining compared to 4 of 17 (24%) patients without ($P = 0.153$). Reflux symptoms, however, were less common in patients with distal IgG4 staining; reflux symptoms were seen in 3 of 14 (21%) patients with distal IgG4 staining compared to 10 of 17 (59%) patients without ($P = 0.067$). Finally, there was a strong association between distal IgG4 staining and basal zone hyperplasia, with basal zone hyperplasia seen in all 14 (100%) patients with IgG4 staining compared to only 9 of 17 (53%) patients without ($P = 0.003$). No other identifiable clinical, gross, or histologic differences between the positive cases and the rest of the cohort were present.

DISCUSSION

Our study is the largest report of esophageal IgG4 staining in patients with treatment naïve, newly diagnosed EoE, and 1 of only 3 analyses of esophageal IgG4 in pediatric EoE patients. Our work further supports the recently recognized association between EoE and

IgG4 staining, and complements this with clinical, endoscopic, and additional histologic correlations and comparisons between the pediatric and adult EoE populations. We show that a similar proportion of both pediatric and adult EoE patients stain positively for IgG4. None of the reflux esophagitis or control cases stained positively for IgG4, yielding a high specificity of IgG4 staining for EoE.

Several recent studies implicate the role of IgG4 in adult EoE patients. One study showed IgG4 content in esophageal mucosal biopsy tissue homogenates from EoE patients had a 45-fold increase compared with controls (3). Another study observed that the presence of IgG4 deposits in the esophageal tissue of EoE patients could distinguish them from patients with gastroesophageal reflux disease (4). A third study noted elevated serum total IgG4 and food-specific IgG4 in EoE patients (5). Our study compares esophageal tissue in pediatric and adult EoE populations, showing that both populations are significantly more likely to stain positively for IgG4 than controls and that a similar proportion of esophageal biopsies in pediatric and adult EoE patients stain for IgG4.

Similar to our findings, 2 recent pediatric studies have also described an association between IgG4 staining and EoE. The first found increased levels of IgG4-positive plasma cells in association with active esophagitis, particularly in children with food allergy (6). The second study found esophageal IgG4 levels were elevated in patients with EoE and correlated with disease activity as assessed by esophageal eosinophilic counts, histologic scores, and transcriptomic features (7). Similar to our findings, basal zone hyperplasia was found to have the strongest correlation with tissue IgG4 levels. This second study also found that tissue IgG4 levels were related to type 2 immunity and T regulatory cytokines, especially interleukin-10 (7). Finally, recent data also suggest that high-titer serum IgG4 to cow's milk is more common in pediatric patients with EoE, further implicating IgG4 as a biomarker of disease in EoE (9).

Clinical presentation of our patient cohort is fairly consistent with findings in the literature. As expected, presentation varied according to age, with poor weight gain, vomiting, and abdominal pain seen in pediatric EoE patients and food impaction more frequent in adult EoE patients. Although circular rings were the most common endoscopy finding in adults, only a minority of children with EoE had this finding. Pediatric and adult EoE patients had a similarly high occurrence of fibrosis, but strictures were seen in nearly 3 times as many adults as children. It is recognized that fibrostenotic disease is a complication of EoE, particularly when there is a delay in treatment and with increased time since disease onset (10,11). Both pediatric and adult EoE patients in our study are newly diagnosed cases; thus, the extent of fibrostenotic complications may correlate with the duration of symptoms before diagnosis, information which is not uniformly identified in this study.

In our study, a small and specifically pediatric cohort of patients with reflux esophagitis and normal esophageal biopsies was chosen, given that tissue from controls has previously been shown to lack IgG4 staining (4,6). Although IgG4-positive staining was specific for EoE, it had a poor sensitivity with positive staining in only 48% of EoE patients. In addition, even when positive, IgG4 staining was not always present at both distal and proximal levels. This may be a reflection of the patchy nature of the disease, as we know that 6 biopsies,

taken from multiple levels of the esophagus, have a diagnostic sensitivity for EoE of 100% (12). With positively stained esophageal biopsies, IgG4 varied in intensity, location, and distribution. This is in line with the previously published reports of IgG4 staining in patients with EoE, which also showed varying patterns (3,4,6). The variance of these characteristics may reflect the nonuniformity of disease. Importantly, our findings suggest that higher composite scores on the Collins histology scale are associated with IgG4 staining. This scoring system has been found to discriminate between treated and untreated patients with EoE (8). Given that our study is the first to focus on newly diagnosed EoE, it is possible that the pattern and intensity of staining may change after treatment. Therefore, future studies should address differences in IgG4 staining in treatment naïve patients compared to those who have failed therapy and those who have been successfully treated. Ultimately, enhancement of the evaluation of both the degree and extent of pathologic features in biopsies from patients with EoE may improve our ability to diagnosis and treat their underlying disease.

Our study is limited by the retrospective study design and small patient cohort. As is true of EoE in clinical practice, care providers of the patients characterized in our study lacked uniform clinical intervention. There is no serum IgG4 parallel with which to relate the esophageal IgG4 staining. Nor did we look at esophageal or serum IgE nor food-specific IgE, which was recently observed to assist in predicting the probability of esophageal eosinophilia (13). Our potential to capture the association of IgG4 with fibrostenosis is limited, because our patient cohort did not undergo esophagograms, which may have detected subtle strictures unrecognized on endoscopy (14). Despite these limitations, our study remains 1 of only 3 evaluations of IgG4 staining in the pediatric EoE population.

CONCLUSIONS

We show EoE patients are significantly more likely to have esophageal biopsies that stain positively for IgG4 than pediatric control patients, and that approximately half of both pediatric and adult EoE patients stain for IgG4. With poor sensitivity, IgG4 is not a reliable marker of EoE, at least at disease diagnosis. IgG4, however, does have high specificity for EoE. Post-treatment evaluation of esophageal biopsies in patients with positive IgG4 staining at diagnosis should provide important insight into the role of IgG4 as a marker of disease activity. Future studies should address whether there is an association between the pattern of IgG4 staining and treatment responsiveness and/or likelihood of complications. Certainly, further studies are warranted to fully elucidate the role of IgG4 in EoE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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What Is Known

- IgG4 has been implicated in patients with eosinophilic esophagitis.
- The role of IgG4 in eosinophilic esophagitis is not fully elucidated.

What Is New

- Esophageal IgG4 has a high specificity for eosinophilic esophagitis at disease diagnosis.
- Further studies are warranted to fully investigate IgG4 in eosinophilic esophagitis.

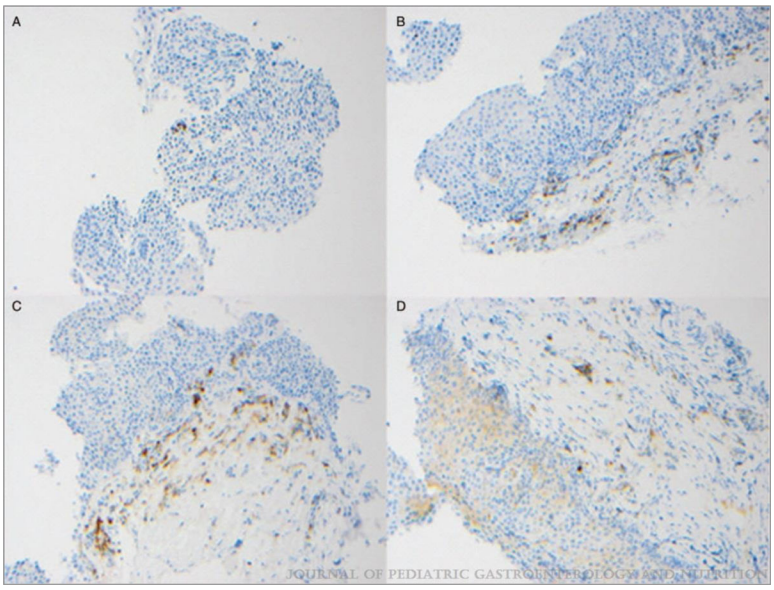

FIGURE 1.

IgG4 staining in representative cases demonstrating (A) focal versus (B) diffuse staining and staining located in the (C) lamina propria versus (D) lamina propria and epithelium. All at 100×.

TABLE 1.

Clinical and endoscopic characteristics of eosinophilic esophagitis patients

	Pediatric EoE patients (n = 16)	Adult EoE patients (n = 15)	*P*
Median age (range), y	12.5 (6–17)	33 (20–76)	<0.001
Male, no. (%)	8 (50)	13 (87)	0.054
Documented atopy, no. (%)	13 (81)	9 (60)	0.252
Presenting symptoms, no. (%)			
Abdominal pain	4 (25)	0	0.101
Dysphagia	8 (50)	15 (100)	0.002
Foreign body/food impaction	4 (25)	7 (47)	0.273
Reflux symptoms	8 (50)	5 (33)	0.473
Weight loss/poor weight gain	7 (44)	2 (13)	0.113
Vomiting	5 (31)	1 (7)	0.172
Endoscopic findings, no. (%)			
Circular rings	3 (19)	10 (67)	0.011
Exudates	10 (63)	3 (20)	0.029
Furrows	13 (81)	9 (60)	0.252
Normal	0	2 (13)	0.226
Shearing/fragility	3 (19)	0	0.226
Stricture/narrowing	2 (13)	5 (33)	0.220
Ulcerations	2 (13)	0	0.484
Endoscopic interventions, no. (%)			
Dilation performed	0	3 (20)	0.101
Food impaction removed	1 (6)	3 (20)	0.333

EoE = eosinophilic esophagitis.

TABLE 2.

Histologic characteristics of eosinophilic esophagitis patients

	Esophageal level	Pediatric EoE patients, n = 16	Adult EoE patients, n = 15	*P*
Intraepithelial eosinophils per high powered field, median (range)	Distal	35 (0–164)	46 (13–95)	0.947
	Proximal	45 (7–124)	47 (20–117)	0.980
Histologic features, no. (%)				
Basal zone hyperplasia	Distal	11 (69)	12 (80)	0.685
	Proximal	8 (50)	13 (87)	0.054
Degranulated eosinophils	Distal	15 (94)	11 (73)	0.172
	Proximal	15 (94)	14 (93)	1.000
Eosinophilic microabscesses	Distal	5 (31)	7 (47)	0.473
	Proximal	7 (44)	6 (40)	0.833
Lamina propria fibrosis *	Distal	9 (75)	8 (100)	0.242
	Proximal	11 (100)	7 (100)	1.000
Spongiosis	Distal	14 (88)	15 (100)	0.484
	Proximal	13 (81)	15 (100)	0.226
Superficial layering of eosinophils	Distal	5 (31)	8 (53)	0.285
	Proximal	7 (44)	6 (40)	0.833

EoE = eosinophilic esophagitis

* Lamina propria was present in a subset of pediatric (12/16 distal esophageal specimens and 11/16 proximal esophageal specimens) and adult (8/15 distal esophageal specimens and 7/15 proximal esophageal specimens) EoE cases.

TABLE 3.

IgG4 staining in eosinophilic esophagitis patients

EoE patients by age group	Any positive IgG4 staining, no. (%)*	Esophageal level	IgG4 staining strong intensity, no. (%)	IgG4 staining lamina propria location, no. (%)	IgG4 staining epithelium location, no. (%)	IgG4 staining focal distribution, no. (%)
Pediatric, n = 16	8/16 (50)	Distal	6/7 (86)	7/7 (100)	4/7 (57)	4/7 (57)
		Proximal	5/8 (63)	7/8 (88)	4/8 (50)	5/8 (63)
Adult, n = 15	7/15 (47)	Distal	3/7 (43)	5/7 (71)	4/7 (57)	5/7 (71)
		Proximal	2/5 (40)	3/5 (60)	2/5 (40)	3/5 (60)

EoE = eosinophilic esophagitis

*Patients with EoE were significantly more likely to stain positively for IgG4 compared to children with reflux esophagitis or healthy controls (15/31 vs 0/8, $P = 0.015$).