CLINICAL—ALIMENTARY TRACT

Eosinophilic Esophagitis in Adults Is Associated With IgG4 and Not Mediated by IgE

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This article has an accompanying continuing medical education activity on page e14. Learning Objective: Upon completion of these questions, successful learners will be able to explain the poor performance of IgE-related allergy testing and therapy in adult eosinophilic esophagitis patients and the frequent presence of abundant IgG4.

See Covering the Cover synopsis on page 547.

BACKGROUND & AIMS: Eosinophilic esophagitis is usually triggered by foods, by unclear mechanisms. We evaluated the roles of IgE and IgG4 in the development of eosinophilic esophagitis. METHODS: We performed a prospective, randomized, double-blind, placebo-controlled trial of adults with eosinophilic esophagitis given an antibody against IgE (omalizumab, n = 16) or placebo (n = 14) every 2-4 weeks for 16 weeks, based on weight and serum level of IgE. Endoscopy was performed, esophageal biopsy specimens were collected, and symptoms were assessed at baseline and at 16 weeks. Maximum numbers of eosinophils/high-power field were determined. Homogenates of esophageal biopsy specimens from 11 subjects with eosinophilic esophagitis and 8 without (controls) were assessed for IgM, IgA, and IgG subclasses. In a retrospective analysis, we performed immunofluorescence analysis of IgG4 in fixed esophageal tissues from 2 patients with eosinophilic esophagitis who underwent esophagectomy and 47 consecutive autopsies (controls). We also performed immunofluorescence analysis of IgG4 in esophageal mucosal biopsy specimens from 24 subjects with eosinophilic esophagitis and 9 without (controls). Finally, sera were collected from 15 subjects with eosinophilic esophagitis and from 41 without (controls), and assayed for total and food-reactive IgG4. RESULTS: Omalizumab did not alter symptoms of eosinophilic esophagitis or eosinophil counts in biopsy samples compared with placebo. Homogenates of esophageal tissues from patients with eosinophilic esophagitis had a 45-fold increase in IgG4 compared with controls ($P < 3 \times 10^{-5}$), but no significant increases in other IgG subclasses, IgM, or IgA. Sparse stromal deposits resembling immune complexes were found in 2 of 5 eosinophilic esophagitis biopsy specimens based on ultrastructural analysis. Esophagectomy samples from 2 patients with eosinophilic esophagitis contained 180 and 300 IgG4 plasma cells/maximal high-power field, mainly in the deep lamina propria; these levels were greater than in tissues from controls. Fibrosis essentially was exclusive to the lamina propria. Granular extracellular IgG4 was detected in biopsy specimens from 21 of 24 patients with eosinophilic esophagitis, but in none of the specimens from 9 controls ($P = 6 \times 10^{-6}$). The total serum level of IgG4 increased only slightly in patients with eosinophilic esophagitis, compared with controls. Subjects with eosinophilic esophagitis had increased serum levels of IgG4 that reacted with milk, wheat, egg, and nuts—the 4 foods that most commonly trigger this condition ($P \leq 3 \times 10^{-4}$ for each food). **CONCLUSIONS:** In a prospective trial, omalizumab did not reduce symptoms of eosinophilic esophagitis or tissue eosinophil counts compared with placebo. This finding, along with observed granular deposits of IgG4, abundant IgG4-containing plasma cells, and serum levels of IgG4 reactive to specific foods, indicate that, in adults, eosinophilic esophagitis is IgG4-associated, and not an IgE-induced allergy. ClinicalTrials. gov number: NCT 00123630.

Keywords: EoE; Clinical Trial; Immune Response; B Cell.

E lemental and food elimination diet studies strongly implicate foods in eosinophilic esophagitis.¹⁻⁶ Eosinophil, mast cell, interleukin 5, and interleukin 13 involvement, and the frequent presence of high serum IgE and atopy suggest that eosinophilic esophagitis could be an IgE-mediated allergy.⁷ However, although allergy skin testing predicts trigger foods in children,⁶ skin testing does not predict trigger foods in adults.¹⁻³ The mast cell stabilizer cromolyn sodium has no apparent effect.⁸ Some otherwise typical adult eosinophilic esophagitis patients lack mucosal mast cell IgE.⁹ Two adult eosinophilic esophagitis subjects failed to respond to omalizumab.¹⁰ Together, these findings raise doubts about whether adult eosinophilic esophagitis is an IgE-mediated allergy.

Abbreviation used in this paper: IRB, Institutional Review Board.

To determine whether eosinophilic esophagitis is an IgEmediated allergy, we treated eosinophilic esophagitis patients with omalizumab (a humanized anti-IgE) and analyzed the effects on symptoms and inflammation. When this showed no effect, we then quantitated other immunoglobulin classes and subclasses in esophageal mucosal biopsy specimens, then further studied IgG4, specifically the site of IgG4 production and the serum IgG4 immunoreactivity, in eosinophilic esophagitis.

Materials and Methods

All human studies were approved by the University of Utah Institutional Review Board (IRB) by written participant consent. The omalizumab trial was registered at ClinicalTrials.gov as NCT 00123630, and approved by the University of Utah IRB (protocol 13623). Tissue and sera for IgG4 studies also were IRB approved (protocols 47802, 14543, and 67489). For all studies, eosinophilic esophagitis subjects met standard criteria (>15 eosinophils/high-power field in esophageal biopsy specimen, not responsive to maximal-dose proton pump inhibitors).^{7,11} Except for 3 subjects in the omalizumab trial ages 15-17 years, all subjects were adults (age, \geq 18 y). Statistical tests used were the Mann-Whitney U test, the Wilcoxon matched pairs test, the Fisher exact test, and the Fieller method for confidence intervals of ratios. All statistical comparisons were based on blinded analysis of number-coded slides, tissue homogenates, sera, or of subjects for whom treatment status was known only by a research pharmacist. Antibodies used are listed in Supplementary Table 1. Authors had access to the study data and reviewed and approved the final manuscript.

Omalizumab Trial

This prospective, double-blind, randomized, placebocontrolled study of omalizumab (Xolair; Novartis, East Hanover, NJ) in eosinophilic esophagitis was designed to test the hypothesis that eosinophilic esophagitis is IgE-mediated. Thirty eosinophilic esophagitis subjects were treated with omalizumab or placebo subcutaneously every 2-4 weeks for 16 weeks, using a weight and serum IgE-based dosing protocol (Supplementary Table 2). Endoscopy with esophageal biopsy and symptom assessment were performed at baseline and at 16 weeks. The primary end point was reducing esophageal biopsy eosinophil content. A secondary end point was a reduction in dysphagia symptoms. Biopsy specimens were collected for electron microscopy, and 5 cases were examined ultrastructurally. For details, see the Supplementary Materials and Consort Methods, Supplementary flowchart. and Supplementary Table 3.

Given the unexpected lack of an omalizumab effect, an additional (not prespecified) test was performed to confirm the validity of the results. The esophageal biopsy specimens were immunostained for IgE and mast cell tryptase to confirm depletion of mast cell IgE.

Tissue Immunoglobulin Quantitation

This tissue was from a published elemental diet study¹ and a prospective proteomics study in eosinophilic esophagitis. Esophageal mucosal biopsy specimens from 11 eosinophilic esophagitis subjects and 8 healthy controls (Supplementary Table 4) were frozen in cOmplete protease inhibitor (Roche Applied Science, Madison, WI). The tissue was homogenized at $0^{\circ}-4^{\circ}$ C. Supernatant protein content was measured (Bicinchoninic acid (BCA) method, Pierce/Thermo Scientific, Rockford, IL), and adjusted to 100 μ g protein/mL. Immunoglobulin quantitation by class/subclass (IgM, IgA, IgG1, IgG2, IgG3, and IgG4) was performed using the Luminex 100 system (Luminex, Austin, TX), at Eve Technologies (Calgary, Alberta).

Esophagectomies From Eosinophilic Esophagitis Patients

Transmural sections from formalin-fixed, paraffinembedded tissue from 2 previously reported esophagectomies in eosinophilic esophagitis subjects were studied.^{12,13} As controls, consecutive adult autopsy cases (47 cases) (Supplementary Table 5) meeting these criteria were used: autopsy fewer than 24 hours after death, adequate esophageal tissue, no history of esophageal or gastric disease, and no esophageal abnormality in routine sections. Paraffin sections were stained immunofluorescently for IgG4, as explained later.

Esophageal Biopsy Specimens and Tissue Immunostaining

The esophagectomies and autopsy controls, as well as esophageal mucosal biopsy specimens from a different cohort of 24 eosinophilic esophagitis subjects and 9 normal controls (Supplementary Table 6), were immunostained for IgG4. Sections of formalin-fixed, paraffin-embedded tissue underwent EDTA-based antigen retrieval (Trilogy; Cell Marque, Rocklin, CA), and then were treated with Image-IT FX (Life Technologies, Carlsbad, CA). All primary and secondary antibody incubations for immunofluorescent staining were for 12 hours at 4°C. Immunoperoxidase staining for IgG4 was performed using mouse anti-IgG4 in a Benchmark Ultra Immunostainer (Ventana, Tucson, AZ). Immunoperoxidase and immunofluorescent stains, using different methods and primary antibodies, identified similar numbers of IgG4 plasma cells.

For the omalizumab study, mast cell IgE immunostaining was quantified by examining Cy3 fluorescence of 10 tryptasestaining mast cells in each biopsy specimen, using an Olympus microscope (Center Valley, PA) with a Retiga 2000R detector (Q Imaging, Surrey, British Columbia, Canada).

Serum IgG4 Studies

Sera from 15 eosinophilic esophagitis subjects and 41 controls with no known alimentary tract or other disease were used (Supplementary Table 7). Inclusion criteria for eosinophilic esophagitis subjects were adults (age, ≥ 18 y) with active eosinophilic esophagitis (esophageal biopsy within 3 months with ≥ 15 eosinophils/maximal high-power field while on maximal-dose proton pump inhibitors, not currently treated with steroids). Inclusion criteria for controls were healthy adults (age, ≥ 18 y) with no known medical diseases.

Ninety-six-well plates (Microlon 600; Greiner Bio-One, Frickenhausen, Germany) were coated with target antigen (fat-free milk, wheat gluten, mixed fresh peanut and almond, or total egg) at 20 μ g/mL protein in 0.1 mol/L carbonate buffer, pH 9.5, overnight at 4°C, and then blocked with bovine serum albumin (fraction V; Sigma-Aldrich, St. Louis, MO). The plates

	Omalizumab	Placebo
Number of subjects	16	14
Eosinophils/high-power field, before treatment	41 ± 17	37 ± 9
Eosinophils/high-power field, after treatment	39 ± 15	33 ± 12
Change in mean eosinophil content	-1.3	-4.2
Dysphagia score before treatment	4.0 ± 0.7	5.5 ± 0.5
Dysphagia score after treatment	2.8 ± 1.0	3.8 ± 0.6
Change in dysphagia score after treatment	-1.2 ^ª	-1.7 ^a

NOTE. Omalizumab trial, showing a lack of effectiveness. Results are expressed as the means \pm 95% confidence interval. The primary end point was a decrease in esophageal eosinophil content. Pretreatment and post-treatment eosinophil content were not statistically different. A secondary end point was a decrease in dysphagia symptoms. Both placebotreated and omalizumab-treated subjects had significantly decreased dysphagia scores after treatment (P = .017 and .046, respectively, Wilcoxon matched pair test). However, the change in dysphagia score in the omalizumab vs the placebo group was not statistically different (P = .95, Mann–Whitney U test).

^a01 < P < .05.

were incubated with diluted serum, then biotin anti-IgG4, followed by Europium streptavidin-based detection in a Victor V3 1420 counter (Perkin Elmer, Waltham, MA). For standards, human IgG4 (Protos Immunoresearch, Burlingame, CA) was added to wells coated with anti-IgG (10 μ g/mL in 0.1 mol/L carbonate buffer, pH 9.5). IgG-coated wells with highly diluted subject sera were used for total IgG4 assays.

Results

Omalizumab Trial

In the omalizumab trial, treated subjects had no significant reduction in esophageal eosinophil content and no decrease in symptoms relative to placebo controls (Table 1 and Supplementary Figure 1). Immunostaining confirmed mast cell IgE depletion after treatment (Supplementary Figure 2), without significant changes in the controls. Serum IgE was increased significantly after treatment in omalizumab subjects (P < .001) (Supplementary Table 3) but not the placebo controls, also confirming treatment effect.

Esophageal Biopsy Specimens

To determine if tissue contents of immunoglobulins other than IgE are altered in eosinophilic esophagitis, we measured them in esophageal biopsy tissue homogenates. The mean mucosal IgG4 content was increased 45-fold in the eosinophilic esophagitis biopsy specimens relative to controls ($P < 3 \times 10^{-5}$) (Table 2 and Figure 1*A*). Tissue IgG4 comprised a mean of 17% of total IgG among the eosinophilic esophagitis subjects vs 0.92% in controls ($P < 3 \times 10^{-5}$) (Figure 1*A*). IgG1, IgG2, IgG3, IgA, and IgM were not increased significantly (Table 2).

IgG4 immunofluorescent staining of the biopsy specimens showed granular intercellular immunostaining in 21 of 24 eosinophilic esophagitis subjects vs 0 of 9 normal controls ($P = 6 \times 10^{-6}$) (Figure 1*B* and *C*). Complement staining was consistently absent. Rare IgG4 plasma cells, all of which stained for CD138, were seen in the subepithelial tissue in 7 of 24 eosinophilic esophagitis subjects (Supplementary Figure 3). All control mucosal biopsy specimens lacked IgG4 plasma cells.

There were no significant correlations between either patient age or the duration of disease symptoms and either the tissue IgG4 content or IgG4 immunostaining. However, all but one of the cases had 3 or more years' duration of symptoms, and all the subjects were adults.

Electron Microscopy

Given the granular intercellular staining for IgG4, we wondered whether the staining resembled immune complexes. Electron microscopy was performed on biopsy specimens from the omalizumab study. In 2 of the 5 cases examined, densities resembling immune complexes were seen in the fibrovascular stroma near both plasma cells and blood vessels (Supplementary Figure 4).

Table 2	Esophageal	Mucosal	Tissue	IgG4	s Strikingly	and S	pecifically	/ Increased

	Normal controls	Eosinophilic esophagitis	Eosinophilic esophagitis/control ratio
lgM, mg/g protein	0.16 ± 0.07	0.38 ± 0.21	2.4 (0.91–5.5)
IgA, mg/g protein	0.32 ± 0.15	0.51 ± 0.18	1.6 (0.84–3.5)
IgG1, mg/g protein	2.2 ± 0.73	3.1 ± 1.1	1.4 (0.78–2.4)
IgG2, mg/g protein	0.76 ± 0.14	1.4 ± 0.64	1.8 (0.88–2.9)
lgG3, mg/g protein	0.10 ± 0.05	0.15 ± 0.092	1.5 (0.48–3.7)
lgG4, mg/g protein	0.029 ± 0.013	1.3 ± 0.99^{a}	45 (7.5–109)
IgG4, % total IgG	0.92 ± 0.43	17 ± 7.7 ^a	18 (8.4–40)

NOTE. Immunoglobulin content in esophageal mucosal biopsy tissue homogenates (mg/g total protein, mean \pm 95% confidence interval). In eosinophilic esophagitis, there was a 45-fold increase in IgG4 content relative to controls and an 18-fold increase in IgG4 as a fraction of total IgG. In contrast, there were 1.4- to 2.4-fold increases in contents of IgM, IgA, and the other IgG subclasses, which was not significantly different from controls. ^a $P < 3 \times 10^{-5}$ for both.



Figure 1. (*A*) Esophageal tissue homogenate IgG4 content, as milligrams per gram of total protein, is increased 45-fold (95% confidence interval, 7.5–109; $P < 3 \times 10^{-5}$). Esophageal tissue homogenate IgG4 content is a mean of 17% ± 8% of total IgG in the eosinophilic esophagitis subjects and 0.92% ± 0.43% in normal controls ($P < 3 \times 10^{-5}$). (*B*) Immunofluorescent staining for IgG4 in an eosinophilic esophagitis subject shows patchy granular intercellular IgG4, in red, with a blue DAPI nuclear counterstain. (*C*) The control has no IgG4 staining. (*B* and *C*) Co-staining for complement 9 (green) is negative. Granular IgG4 is found in 21 of 24 eosinophilic esophagitis cases and in 0 of 9 controls ($P = 6 \times 10^{-6}$).

Esophagectomy Findings

Given the 45-fold increase in tissue IgG4 content, we wondered about the source of the tissue IgG4, and examined 2 eosinophilic esophagitis esophagectomies. Case 1, a 68-year-old man with eosinophilic esophagitis and solid-food dysphagia for 20 years, developed an esophagogastric junction adenocarcinoma, requiring resection.¹² Case 2, a 46-year-old man with eosinophilic esophagitis had recurrent food impactions, leading to a perforation, which was resected.¹³

In both cases, there was extensive fibrosis limited to the lamina propria (Figure 2*A*). Dense clusters of plasma cells were present mainly in the deep lamina propria (Figure 2*B*–*D*), with lesser involvement in the contiguous muscularis mucosae, superficial lamina propria, and near lymphoid aggregates. Case 1 had plasma cell infiltrates in 22% of the high-power fields of the esophageal mucosa. Intraepithelial eosinophils were most abundant over and near the lamina propria plasma cell infiltrates. Case 2 had essentially confluent deep lamina propria plasma cells.

IgG4 immunostaining showed up to 180 and 300 IgG4 plasma cells/high-power field (Figure 2*E* and *F*). Essentially all the plasma cells stained for IgG4. The IgG4 plasma cells were predominantly in the deep lamina propria, although a few were just under the surface epithelium or in the muscularis mucosae (Figure 2*E* and Supplementary Figure 5). In contrast, autopsy controls (47 cases) had a mean of 4.6 IgG4 plasma cells/maximal high-power field (range, 0–25) (Supplementary Figure 6), in a similar deep lamina propria–predominant distribution. Esophagectomy lymph nodes had up to 50 IgG4 plasma cells/high-power field (Supplementary Figure 7).

Serum IgG4 and IgG4 Food-Specific Antibodies

Given that eosinophilic esophagitis is food-triggered and the abundant esophageal mucosal IgG4, we examined total serum IgG4 and IgG4 immunoreactivity to each of the 4 most common trigger foods (wheat, milk, egg, and nuts). Serum IgG4 was 1.9-fold increased in eosinophilic esophagitis relative to normal controls (P = .016) (Figure 3), but rarely reached the high levels typical of an IgG4-related disease (1 of 15 eosinophilic esophagitis subjects > 1400 μ g/mL). In contrast, serum IgG4 reactive to each of the 4 common trigger foods and to the highest anti-food antibody content per subject, were increased highly significantly in eosinophilic esophagitis subjects relative to controls ($P \leq 3 \times 10^{-4}$ for each comparison, Mann–Whitney *U* test) (Figure 3). There were no significant correlations between either patient age or the duration of disease symptoms and either the total serum IgG4 content or the maximal anti-food IgG4 content in a given subject.

Discussion

Omalizumab failed to reduce tissue eosinophils and symptoms. Eosinophilic esophagitis subjects had a 45-fold increase in esophageal tissue IgG4. Extracellular IgG4 staining was granular, resembling immune complexes. The eosinophilic esophagitis resection had a striking IgG4 plasma cell infiltrate. Abundant IgG4 antibodies to the common trigger foods were present in most eosinophilic esophagitis subjects. None of our subjects had a parasitic infection. Only 1 of the resection cases had a tumor, and the IgG4 plasma cells were not present in or near the carcinoma. The failure of omalizumab, the abundant tissue IgG4, and the serum IgG4 antibodies reactive to common trigger foods, provide strong evidence that despite the frequent presence of IgE-bearing mast cells, adult eosinophilic esophagitis is not an IgE-mediated allergy, possibly because of blocking IgG4 antibodies.

We show evidence for the presence of IgG4 in eosinophilic esophagitis. Similar to systemic IgG4-related diseases, eosinophilic esophagitis responds to steroids, is associated



Figure 2. (A) Trichrome stain shows dense lamina propria fibrosis. (B) Clusters of inflammatory cells were found in the deep lamina propria. (C) The deep lamina propria infiltrates are often perivascular, particularly around small blood vessels, with increased endothelial cellularity. (D) These infiltrates are mainly plasma cells, with sparse lymphocytes, eosinophils, and neutrophils. (E) IgG4 immunostaining shows abundant IgG4 plasma cells mostly in the deep lamina propria, with only sparse IgG4 cells superficially. (F) IgG4 immunoperoxidase staining showed up to 300 IgG4 plasma cells high-power per field. Nearly all the plasma cells are IgG4 positive. Note also occasional the lgG4 plasma cells in the muscularis mucosae at lower right and the superficial lamina propria at upper left. There are granular extracellular deposits in the superficial lamina propria. (C and E) Images are from case 2; (A, B, D, and F) images are from case 1.

with atopy, eosinophilic infiltrates, numerous IgG4 plasma cells, granular IgG4 deposits resembling immune complexes, fibrosis, and is male predominant.^{14,15} In contrast, typical IgG4-related diseases, which have been reported in the esophagus,^{16,17} have distinct masses or strictures, unlike the widespread, shallow lamina propria fibrosis of eosinophilic esophagitis. Typical IgG4-related diseases often have storiform fibrosis and obliterative phlebitis, both absent in our resection cases. Total serum IgG4 is increased minimally in eosinophilic esophagitis, unlike typical IgG4-related diseases, potentially because of the small tissue compartment (esophageal deep lamina propria) involved. Given these differences, we call eosinophilic esophagitis IgG4-associated rather than IgG4-related to avoid confusion with systemic IgG4-related diseases.

IgG4 plays a role in the immune response to invasive parasites, avoiding elephantiasis, and in allergy desensitization.^{18,19} In both settings, the IgG4 response follows an

IgE-mediated response, presumably blocking IgE-mediated mast cell activation. Also, allergy skin testing predicts trigger foods in children⁶ but not adults¹⁻³ with eosinophilic esophagitis. Given this, we speculate that eosinophilic esophagitis might be IgE-associated or mediated initially, then becomes an IgG4-associated process with repeated trigger food exposure. The lack of an association with symptom duration or age in our subjects does not exclude this possibility; we did not study young children or those with recent disease onset. Given the limited number of omalizumab-treated subjects and the occasional failure of IgG4 antibodies to develop in patients with filariasis or with allergen desensitization therapy, it is plausible that a few adult or long-term eosinophilic esophagitis patients might retain IgE reactivity and lack an IgG4 response.

The IgG4 immunoreactivity to foods that commonly trigger eosinophilic esophagitis, granular IgG4 immunostaining, and electron microscopic deposits together suggest

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Figure 3. Serum lgG4 antibodies to common eosinophilic esophagitis trigger foods often are present. Serum total IgG4 in eosinophilic esophagitis (top left) is increased 1.9fold (*P = .016), broadly overlapping the controls. Serum IgG4 reactivity to the 4 most common trigger foods (wheat, milk, egg, and nuts) and to the highest serum IgG4 anticontent food of anv tested food are all increased in eosinophilic esophagitis (each ** $P \leq$ 3 \times 10⁻⁴). However, for each food studied, 1 or more controls had abundant food-specific IgG4 antibodies.

possible food-IgG4 immune complexes. Complement staining is absent in the deposits, in keeping with IgG4's known inability to activate complement.²⁰ Although IgG4 immune complexes could be causal, we have no evidence to support that over other mechanisms. If IgG4, particularly IgG4 immune complexes, were causal, esophageal plasma cells could be important, increasing local IgG4 concentration and minimizing Fab arm exchange because the IgG4 would be mostly freshly, locally secreted. Fab arm exchange, in which IgG4 light plus heavy chain pairs trade with other light plus heavy chain pairs (making the IgG4 effectively monovalent), would reduce immune complex development.²⁰ IgG4 undergoes Fab arm exchange in vivo over hours to 1 day.²¹ Although IgG4 has, relative to other IgG subclasses, a higher affinity for the inhibitory receptor FcyRIIB, eosinophils and mast cells lack this inhibitory receptor.²² Particulate IgG4 (bound to sepharose beads), like IgA and the other IgG subclasses, can induce eosinophil degranulation.²³

Food elimination studies for eosinophilic esophagitis are prolonged and costly; foods are tested by trial and error and repeated endoscopy is required. Serum-based prediction of the trigger foods would be helpful. However, abundant IgG4 anti-food antibodies are seen in some controls. Anti-milk IgG4, present in some of our controls, is seen in resolved cow's milk allergy, a common, often transient, pediatric allergy that results in persistent serum IgG4 anti-milk.²⁴ Increased intestinal IgG4 plasma cells are associated with a variety of processes including autoimmune pancreatitis (at the major duodenal papilla),^{25,26} and intestinal inflammatory disorders such as collagenous sprue,²⁷ and inflammatory bowel disease.²⁸ Although there is a highly statistically significant association between eosinophilic esophagitis and IgG4 antibodies to common trigger foods, serum IgG4 antifood antibodies might be of limited to poor specificity in predicting trigger foods, as are IgG4 antibodies in other circumstances. A prospective food elimination study is

needed to determine whether serum food-specific IgG4 antibodies (potentially with food-specific IgE or IgM antibodies) would identify the trigger foods. Further work also is needed to address the role of IgG4, if any, in the pathogenesis of eosinophilic esophagitis, in pediatric or recent-onset eosinophilic esophagitis, and in proton pump inhibitor-responsive esophageal eosinophilia.

The diffuse lamina propria distribution of fibrosis in the esophagectomies suggests a possible mechanism for dysphagia. Mucosal fibrosis would reduce esophageal distensibility, a prominent finding in eosinophilic esophagitis correlating with food impaction,²⁹ a characteristic eosinophilic esophagitis symptom.³⁰

In summary, in eosinophilic esophagitis, IgE depletion with omalizumab did not alter tissue eosinophil content or symptoms. There was a striking increase in esophageal tissue IgG4 content and granular IgG4 deposits in most cases, often with serum IgG4 to the common trigger foods. The esophagectomies had mucosal fibrosis and abundant deep lamina propria IgG4 plasma cells. Eosinophilic esophagitis in adults is not an IgE-mediated allergy, but instead an IgG4associated process, often with food-immunoreactive IgG4 that presumably blocks IgE-allergen binding.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.05.036.

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Reprint requests

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Conflicts of interest

The authors disclose no conflicts.

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