Published in final edited form as:

J Allergy Clin Immunol. 2011 May ; 127(5): 1307–1308.e3. doi:10.1016/j.jaci.2010.12.1118.

Expression of mast cell–associated genes is upregulated in adult eosinophilic esophagitis and responds to steroid or dietary therapy

Karen S. Hsu Blatman, MD^a, Nirmala Gonsalves, MD^b, Ikuo Hirano, MD^b, and Paul J. Bryce, PhD^a

Paul J. Bryce: p-bryce@northwestern.edu

^aDivision of Allergy-Immunology, Northwestern University Feinberg School of Medicine, Chicago, Ill

^bDivision of Gastroenterology, Northwestern University Feinberg School of Medicine, Chicago, Ill

To the Editor:

Eosinophilic esophagitis (EoE) is an eosinophil-dominated disease seen in the esophagi of both children and adults. Despite many similarities, differences exist between pediatric and adult EoE. Adults with EoE typically present with dysphagia and food impaction, whereas children present with failure to thrive or vomiting.¹ Patients with EoE often have a personal and family history of atopic disease. We previously reported differences in the patterns of allergic predisposition between adult and pediatric EoE.² Adults with EoE often have specific IgE for food allergens, aeroallergens, or both but rarely have a history of food-induced anaphylaxis.¹

Although the role of eosinophils in EoE is well established, that of mast cells is less clear.³⁻⁴ In 2001, Straumann et al⁵ identified increased mast cell numbers in adults with EoE.⁵ However, despite much discussion, the roles for mast cells in patients with EoE have not been defined.⁴ Recently, studies by Abonia et al⁶ and Aceves et al⁷ have defined an involvement of mast cells in pediatric EoE. We have concurrently been investigating mast cells in adult EoE. Our results in adults with EoE, described in this article, now support the findings of Abonia et al⁶ and implicate mast cells in the pathogenesis of both pediatric and adult EoE.

Biopsy specimens from the distal esophagus were collected from adult patients undergoing upper endoscopy for evaluation of dysphagia. Biopsy specimens from 7 patients without EoE (3 male and 4 female patients; median age, 54 years; age range, 27–80 years; average peak eosinophil count, 0) and from 21 patients with EoE (17 male and 4 female patients; median age, 40 years; age range, 28–84 years; average peak eosinophil count, 41.3) were studied for expression of several well-defined mast cell–associated genes: the β chain of the high-affinity IgE receptor (*FCER1B*), the histamine-synthesizing enzyme histidine decarboxylase (*HDC*), and 2 mast cell–specific proteases: tryptase $\alpha/\beta 1$ (*TPSAB1*) and carboxypeptidase (*CPA3*). All patients displayed panesophageal endoscopic and histological features, and biopsy specimens from both the proximal and distal sites were taken, as is standard practice at our institution. Initial studies demonstrated similar expression profiles between both locations, and therefore only distal biopsy specimens are reported here.

Disclosure of potential conflict of interest: I. Hirano is on the scientific advisory board for Meritage. The rest of the authors have declared that they have no conflict of interest.

In addition, we investigated the expression in biopsy specimens from additional patients with EoE who had undergone therapy with either swallowed fluticasone (440 µg administered twice daily, $n = 5$) or patients undergoing treatment with a standardized empiric food elimination diet⁸ of 8 foods: milk, egg, soy, peanut, tree nut, wheat, shellfish, and fish. This group included patients who responded initially after the 6-week empiric elimination diet ($n = 6$), those who continued to respond during food reintroduction ($n = 6$), and those who underwent relapse on food reintroduction ($n = 9$). Esophageal biopsy specimens were taken before dietary therapy and after the initial 6-week diet. The 8 food groups were reintroduced one group at a time every 2 weeks, with follow-up endoscopies every 4 weeks with biopsies. Gene expression was determined by using Taqman real-time RT-PCR, and the Institutional Review Board of Northwestern University approved this study. Further classification and methods are available in this article's Online Repository at www.jacionline.org.

Atopic clinical history was common in our patients with EoE (85% with a history of allergic rhinitis or asthma), which is consistent with prior studies.^{1,2,9} However, at the initial visit, no patients were receiving treatment with systemic or swallowed topical steroids, food elimination diet, or elemental diet. Eight-five percent of the patients were undergoing therapy with proton pump inhibitors at the time of index endoscopy with biopsy.

Compared with those from control subjects, biopsy specimens from patients with EoE without treatment had significant increases in expression of mast cell genes for *FCER1B* ($P < .05$), *HDC* ($P < .01$), *TPSAB1* ($P < .01$), and *CPA3* ($P < .01$), as determined by using Student *t* test comparisons. Similar to the findings in pediatric EoE, mast cell-associated gene expression was significantly reduced by treatment with swallowed fluticasone (Fig 1). One patient was found to be nonresponsive on swallowed fluticasone twice daily but did respond to systemic steroids, and mast cell-associated gene expression decreased to levels similar to those seen in the swallowed fluticasone group (data not shown).

Gene expression for *FCER1B*, *HDC*, *TPSAB1*, and *CPA3* was also significantly reduced by the 8-food elimination diet (Fig 2). Gene expression remained decreased during food reintroduction when patients denied any symptoms. Conversely, expression of these genes remained increased in nonresponders and was increased in those patients experiencing food reintroduction-induced relapse. Expression of stem cell factor was similarly affected (see this article's Fig E1 in the Online Repository at www.jacionline.org).

Eotaxin-3 (*CCL26*) is highly expressed in pediatric EoE¹⁰ and correlated with *CPA3* expression in pediatric EoE.⁶ In our adult samples eotaxin-3 was also highly expressed compared with that seen in control samples (data not shown) and also correlated with *CPA3* expression ($r = 0.58$; $P < .05$, Spearman correlation; Fig 3). A similar correlation was seen with *HDC* and *TPSAB1* also (see this article's Fig E2 in the Online Repository at www.jacionline.org).

In summary, our data suggest that adult EoE is associated with local upregulation of mast cell responses and that these alterations are highly responsive to therapy with either steroids or a food elimination diet. Our study supports the recent studies demonstrating mastocytosis in esophageal biopsy tissue.^{5,6} The upregulation of mast cell-associated gene expression and its responsiveness to therapy and correlation with disease recurrence on food-induced relapse indicate that mast cells likely participate in the pathogenesis of EoE. Consequently, mast cells might be an important target for treatment of both pediatric and adult disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

P.J.B. received support from National Institutes of Health/National Institute of Allergy and Infectious Diseases grant R01AI076456-03.

REFERENCES

1. Rothenberg ME. Biology and treatment of eosinophilic esophagitis. *Gastroenterology*. 2009; 137:1238–1249. [PubMed: 19596009]
2. Gonsalves N, Anh T, Zhang Q, Kagalwalla A, Ditto A, Hirano I. Distinct allergic predisposition of children and adults with Eosinophilic Esophagitis. *Gastroenterology*. 2006; 130:A579.
3. Lucendo AJ, Bellon T, Lucendo B. The role of mast cells in eosinophilic esophagitis. *Pediatr Allergy Immunol*. 2009; 20:512–518. [PubMed: 18681944]
4. Wershil BK. Exploring the role of mast cells in eosinophilic esophagitis. *Immunol Allergy Clin North Am*. 2009; 29:189–195. xiii. [PubMed: 19141354]
5. Straumann A, Bauer M, Fischer B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J Allergy Clin Immunol*. 2001; 108:954–961. [PubMed: 11742273]
6. Abonia JP, Blanchard C, Butz BB, Rainey HF, Collins MH, Stringer K, et al. Involvement of mast cells in eosinophilic esophagitis. *J Allergy Clin Immunol*. 2010; 126:140–149. [PubMed: 20538331]
7. Aceves SS, Chen D, Newbury RO, Dohil R, Bastian JF, Broide DH. Mast cells infiltrate the esophageal smooth muscle in patients with eosinophilic esophagitis, express TGF-beta1, and increase esophageal smooth muscle contraction. *J Allergy Clin Immunol*. 2010; 126:1198–1204. e4. [PubMed: 21047675]
8. Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2006; 4:1097–1102. [PubMed: 16860614]
9. Gonsalves N, Policarpio-Nicolas M, Zhang Q, Rao MS, Hirano I. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest Endosc*. 2006; 64:313–319. [PubMed: 16923475]
10. Blanchard C, Wang N, Stringer KF, Mishra A, Fulkerson PC, Abonia JP, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest*. 2006; 116:536–547. [PubMed: 16453027]

FIG 1.

Changes in *FCERIB* (A), *HDC* (B), *TPSAB1* (C), and *CPA3* (D) gene expression in esophageal biopsy specimens from control subjects, patients with EoE, or patients with EoE receiving swallowed steroid treatment normalized to the glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) housekeeping gene.

FIG 2.

Changes in *FCERIB* (A), *HDC* (B), *TPSAB1* (C), and *CPA3* (D) gene expression induced by empiric 8-food elimination diet normalized to the glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) housekeeping gene.

FIG 3.

Correlation of eotaxin-3 expression with *CPA3* expression. Correlation between the relative gene expression of eotaxin-3 and *CPA3* was determined for each biopsy specimens. *GAPDH*, Glyceraldehyde-3-phosphate dehydrogenase.