

Tissue remodeling in patients with eosinophilic esophagitis: What lies beneath the surface?

Seema S. Aceves, MD, PhD San Diego, Calif

Key words: Asthma, eosinophilic esophagitis, tissue remodeling

The concept of eosinophil-associated tissue remodeling and fibrosis has its roots in the hypereosinophilic syndrome and asthmatic airways.¹ In asthmatic patients T_H2-associated eotaxins and interleukins activate eosinophils to release granule products and growth factors that propagate inflammation and cause tissue damage. Continual and recurrent dysregulated repair leads to tissue remodeling with subsequent fibrosis and end-organ dysfunction. The reversibility, natural history, and clinical consequences of eosinophil-associated remodeling have been largely debated, especially in human disease, in which the paucity of tissue for repeated analysis has been a rate-limiting factor in our understanding. The availability of adequate surrogate markers in patients with disorders such as asthma has obviated any clinical requirement for direct tissue assessment.

In contrast, eosinophilic esophagitis (EoE), a relatively recently described antigen-driven disease of increasing worldwide prevalence, by its definition requires microscopic esophageal tissue evaluation for its diagnosis and management.² This necessity for repeated histologic analysis allows EoE to function as a new model for studying allergic, eosinophil-associated remodeling over time. Although asthmatic airway remodeling has been hypothesized to begin in early childhood, the ability to study airway tissue in children remains elusive. EoE, on the other hand, affords the potential to monitor the genesis and evolution of remodeling in young children.¹ However, despite readily available esophageal tissue, remodeling analysis in patients with EoE still has its challenges. Esophageal biopsy specimens are small, approximately 3 mm. Although the esophageal epithelium is uniformly available from all biopsy specimens, only the minority of biopsy specimens contain adequate subepithelial lamina propria (LP) and muscularis mucosa for analysis. Because a large number of remodeling events, including fibrosis and angiogenesis, occur in the LP, this can generally only be studied in a subset of patients with EoE. Whether this required selection of biopsy

specimens that have adequate LP introduces a phenotypic patient bias into studies of esophageal remodeling is unclear. In addition, whether any or all subepithelial findings are adequately reflected by epithelial changes remains to be systematically evaluated. Nonetheless, we have had multiple insights into esophageal remodeling from the current EoE literature. Human and animal model studies of EoE demonstrate that esophageal remodeling includes subepithelial fibrosis, angiogenesis, smooth muscle hypertrophy, and dysfunction; occurs both in children and adults; requires eosinophils, eotaxin-3, IL-5, and IL-13 for its pathogenesis; and involves eosinophil- and mast cell-derived TGF- β 1.³⁻¹⁰

In this issue of the *Journal*, Lucendo et al¹¹ report their findings in 10 adult patients treated for 1 year with topical esophageal fluticasone propionate. Using large-volume forceps, the investigators were able to overcome the problem of having only a subset of patients whose biopsy specimens contain adequate subepithelial tissue. All 10 consecutive patients' biopsy specimens had LP and muscularis mucosa, allowing a nonbiased approach to those patients who could be evaluated for fibrotic changes. The adult patients with EoE in their cohort had a relatively severe phenotype with prolonged symptoms (mean, >5 years), with 40% having esophageal rings or stricture indicative of decreased esophageal caliber, 60% having dysphagia, and 80% having food impactions. Patients with EoE were treated with a nonthickened, swallowed liquid formulation of fluticasone for which efficacy and safety have not been documented in prior clinical trials and that might not have the same mucosal penetration, adherence, or transit-time properties of a thickened suspension or particulate.

Similar to prior studies in adults and children, IL-5⁹ and fibroblast growth factor 9¹² levels were increased in patients with EoE compared with levels seen in the control groups, who had normal esophageal histology or gastroesophageal reflux disease. Unlike other reports, there were increased levels of CCL-18, a factor associated with M2 macrophages and fibrous diseases. After esophageal fluticasone treatment, the overall group showed significant decreases in CCL-18 levels. In contrast, the effects on the overall fibrosis score and mRNA levels of IL-5, fibroblast growth factor 9, and TGF- β 1 were less striking, and a degree of subepithelial eosinophilia persisted despite epithelial eosinophil resolution. As such, although CCL18 levels were significantly decreased, its potential contribution to esophageal fibrosis is complicated by the lack of a corresponding significant decrease in LP fibrosis. TGF- β 1 and IL-5 mRNA levels correlated to one another, and like fibrosis, neither was significantly reduced after therapy. This is in contrast to shorter-duration studies in children and adults in whom the resolution of epithelial eosinophilia after topical corticosteroids is accompanied by improvements in fibrosis, TGF- β 1 (levels of which are increased at baseline), phosphorylated Smad2/3 protein, and vascular activation.^{6,13} These disparate results could stem from an incomplete fluticasone penetration into the LP, the use of deeper biopsies with proportionally more

From the Division of Allergy, Immunology, University of California, San Diego, and Rady Children's Hospital, San Diego.

Supported by National Institutes of Health/National Institute of Allergy and Infectious Diseases grant R01AI092135, the Department of Defense, and the International Gastrointestinal Eosinophil Researchers.

Disclosure of potential conflict of interest: S. Aceves is a co-inventor of oral viscous budesonide, funded by UCSD/Meritage Pharma; has received research support from GlaxoSmithKline; and is an AAAAI Committee Member.

Received for publication September 15, 2011; accepted for publication September 26, 2011.

Corresponding author: Seema S. Aceves, MD, PhD, Division of Allergy, Immunology, University of California, San Diego, 9500 Gilman Dr, MC 0635, La Jolla, CA 92093. E-mail: saceves@ucsd.edu or saceves@rchsd.org.

J Allergy Clin Immunol 2011;128:1047-9.

0091-6749/\$36.00

© 2011 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2011.09.026

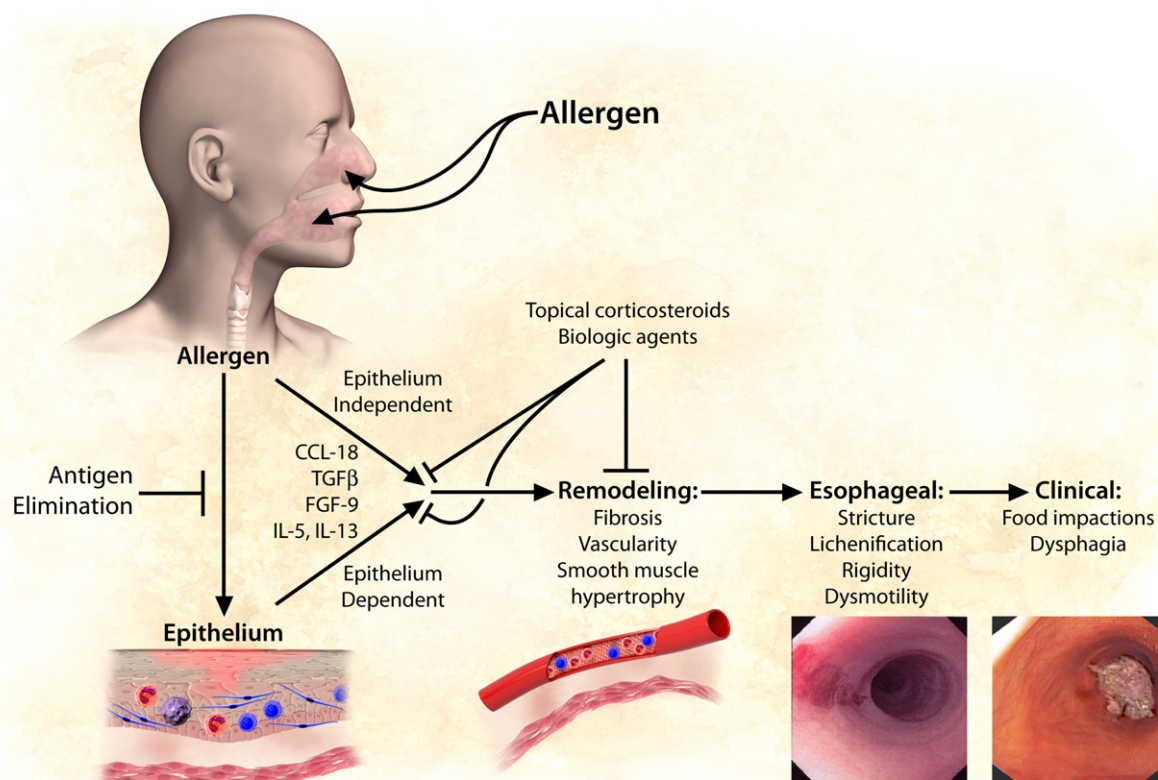


FIG 1. Potential pathogenesis and effects of tissue remodeling in patients with EoE. Antigen (food allergen or aeroallergen) drives epithelial inflammation and production of chemokines, interleukins, and growth factors, causing LP and smooth muscle remodeling through mechanisms that could be both dependent and independent of epithelial inflammation and that could create a positive feedback loop. LP remodeling, in turn, causes the abnormalities visible on endoscopy and esophageal dysfunction, which result in clinical symptoms and complications. Topical steroids, biologic agents, and antigen elimination might be able to alter the course to remodeling. *FGF-9*, Fibroblast growth factor 9.

subepithelial tissue, the analysis of transcript versus protein levels, an overall variability that is missed in other studies caused by a lack of unbiased LP procurement, and/or the use of a distinct TGF- β 1-independent fibrotic pathway in a subset of adults.

In patients with diseases such as idiopathic pulmonary fibrosis, there are accumulating data that epithelial injury is a substantive force for orchestrating fibrosis.¹⁴ Consistent with this hypothesis, there is alignment of epithelial healing and subepithelial inflammation in children whereby only patients with epithelial EoE resolution have improved LP findings and children with epithelial nonresponsive EoE have persistent LP fibrosis and inflammation.¹³ However, the cohort of Lucendo et al¹¹ has a subset of adult patients with epithelial eosinophil resolution, symptom improvements, and endoscopic normalization who show continued fibrosis and profibrotic gene expression after therapy. A few patients have progressive fibrosis despite apparent disease resolution in the epithelium. The propagation of fibrosis in these patients might be guided by LP signals that function independently from the epithelium and that are unable to limit the fibrotic cascade. These findings might also point to differences in the mechanisms of pediatric versus adult fibrosis.

Interestingly, patient age, but not symptom duration, was directly associated with the severity of fibrosis. This brings up 2 important points about EoE. First, it suggests that active disease

duration can be associated with progressive fibrosis, an observation that is supported by limited pediatric data. Second, it suggests that symptom activity does not accurately reflect fibrotic severity or endoscopic appearance. Patients with chronic EoE likely have compensatory behaviors that mask symptom severity. As such, there is a pressing need for new modalities to assess the potential clinical consequences of remodeling, including validated symptom-scoring tools and a systematic assessment of esophageal dysmotility and rigidity¹⁵ in adults and children.

The most severe consequence of EoE is stricture formation.² Currently, the natural history, phenotypes, genotypes, and gene-environment interactions that predispose to severe fibrosis remain unclear. However, unlike in asthmatic patients, in whom there are no clear data that inhaled corticosteroids reverse remodeling, current EoE data show that remodeling features can be reversed in a subset of patients.^{6,13} Whereas in asthmatic patients the age of remodeling onset is unclear,¹ EoE studies show us that children less than 2 years old can have remodeling and that long-standing EoE in children can be associated with higher numbers of TGF- β 1⁺ cells (unpublished data).¹⁴ On the molecular level, remodeling in patients with EoE implicates antigen induction of subepithelial inflammation and fibrovascular changes, which are postulated to lead to clinical sequelae, such as strictures, dysmotility, and dysphagia (Fig 1). We hope that the removal of antigens and/or

treatment with biologic agents, topical corticosteroids, or both can halt the fibroinflammatory cascade and intervene in the natural history and clinical complications related to remodeling in patients with EoE. If this is the case, then earlier aggressive therapy to control epithelial and subepithelial inflammation, especially in children during a “developmental window of opportunity,”¹ might be indicated. Future pediatric and adult studies that systematically evaluate remodeling in the context of clinical EoE features will be paramount in providing an understanding of the mechanisms and true clinical sequelae of what lies beneath the surface in patients with EoE.

I thank Drs Glenn Furuta and David Broide for critical reading.

REFERENCES

1. Al-Muhsen S, Johnson JR, Hamid Q. Remodeling in asthma. *J Allergy Clin Immunol* 2011;128:451-62.
2. 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.
3. Aceves SS, Newbury RO, Dohil R, Bastian JF, Broide DH. Esophageal remodeling in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2007;119:206-12.
4. Fox VL. Eosinophilic esophagitis: endoscopic findings. *Gastrointest Endosc Clin N Am* 2008;18:45-57.
5. Nurko S, Rosen R, Furuta GT. Esophageal dysmotility in children with eosinophilic esophagitis: a study using prolonged esophageal manometry. *Am J Gastroenterol* 2009;104:3050-7.
6. Straumann A, Conus S, Degen L, Felder S, Kummer M, Engel H, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology* 2010;139:1526-37.
7. 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;116:536-47.
8. Zuo L, Fulkerson PC, Finkelman FD, Mingler M, Fischetti CA, Blanchard C, et al. IL-13 induces esophageal remodeling and gene expression by an eosinophil-independent, IL-13R alpha 2-inhibited pathway. *J Immunol* 2010;185:660.
9. Mishra A, Wang M, Pemmaraju VR, Collins MH, Fulkerson PC, Abonia JP, et al. Esophageal remodeling develops as a consequence of tissue specific IL-5-induced eosinophilia. *Gastroenterology* 2008;134:204-14.
10. Aceves SS, Chen D, Newbury RO, Dohil R, Bastian J, Broide DH. Mast cells infiltrate the esophageal smooth muscle in eosinophilic esophagitis, express TGFβ1, and increase esophageal smooth muscle contraction. *J Allergy Clin Immunol* 2010;126:1198-204.
11. Lucendo AJ, Arias A, De Rezende LC, Yagüe-Compadre JL, Mota-Huertas T, González-Castillo S, et al. Subepithelial collagen deposition, profibrogenic cytokine gene expression, and changes after prolonged fluticasone propionate treatment in adult eosinophilic esophagitis: a prospective study. *J Allergy Clin Immunol* 2011;128:1037-46.
12. Mulder DJ, Pacheco I, Hurlbut DJ, Mak N, Furuta GT, MacLeod RJ, et al. FGF9-induced proliferative response to eosinophilic inflammation in oesophagitis. *Gut* 2009;58:166-73.
13. Aceves SS, Newbury RO, Chen D, Dohil R, Mueller J, Hoffman H, et al. Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. *Allergy* 2010;65:109-16.
14. Hardie WD, Hagood JS, Dave V, Perl AK, Whitsett JA, Korfhagen TR, et al. Signaling pathways in the epithelial origins of pulmonary fibrosis. *Cell Cycle* 2010;9:2769-76.
15. Kwiatek MA, Hirano I, Kahrilas PJ, Rothe J, Luger D, Pandolfino JE. Mechanical properties of the esophagus in eosinophilic esophagitis. *Gastroenterology* 2011;140:82-90.