Clinical Implications and Pathogenesis of Esophageal Remodeling in Eosinophilic Esophagitis

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KEYWORDS

• Eosinophilic esophagitis • Remodeling • Fibrosis • Gastroesophageal reflux disease • Dysphagia • Endoscopy • Esophagitis

KEY POINTS

- Remodeling changes in eosinophilic esophagitis include epithelial basal zone hyperplasia, lamina propria fibrosis, expansion of the muscularis propria, and increased vascularity.
- Esophageal inflammation in eosinophilic esophagitis drives the remodeling process with mediators that include IL-5, IL-13, TGFβ1, mast cells, fibroblasts, and eosinophils.
- Recent studies have provided increasing evidence that the primary symptoms of esophageal dysfunction in children and adults as well as clinical complications of eosinophilic esophagitis are consequences of esophageal remodeling and fibrostenosis.
- Esophageal remodeling in eosinophilic esophagitis can be demonstrated using widely available tests, such as histopathology, barium esophagram, upper endoscopy, and endoscopic ultrasonography.
- Clinical trials need to account for the presence and reversibility of esophageal remodeling to fully elucidate the potential benefits and limitations of therapeutic interventions.

INTRODUCTION

Since the initial case descriptions 2 decades ago, eosinophilic esophagitis (EoE) has emerged as an important clinical entity with steadily rising prevalence.[1] In children, EoE is an increasingly recognized etiology for feeding disorders and manifests with poor weight gain, anorexia, vomiting, regurgitation, abdominal pain, and dysphagia. In adult patients, EoE is one of the most common causes of dysphagia. An increasing

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number of studies have shown that the primary symptoms in children and adults, as well as clinical complications of EoE, are consequences of esophageal remodeling and fibrostenosis. This article focuses on the current understanding of the pathogenesis, clinical detection, and therapeutic implications of esophageal remodeling in EoE.

DEFINITION OF ESOPHAGEAL REMODELING

The concept of eosinophil-associated tissue remodeling stems from diseases such as the hypereosinophilic syndrome and asthma. Remodeling can be defined as tissue changes in target organs that result in end organ dysfunction. Remodeling is associated with histologic alterations, such as fibrosis and angiogenesis, which are caused by changes in cellular function, phenotype, and products. Remodeling itself may not be a pathogenic process, as it could be considered to represent a protective mechanism akin to wound healing. However, when remodeling is not controlled, presumably due to unbridled inflammation, there are negative consequences for organ function. Indeed, the natural history of untreated EoE is to progress to stricture formation, at least in adults.[2,3]

In EoE, remodeling changes are seen histologically in both the epithelium and subepithelium (**Fig. 1**). Epithelial changes include basal zone hyperplasia and increased length of the vascular papillae. The papillae are intrusions of the subepithelium into the epithelial space and, as such, are likely a further reflection of subepithelial expansion. Subepithelial changes include lamina propria fibrosis with increased collagen deposition and thickness and increased vascularity with vascular activation. Muscularis remodeling changes include smooth muscle hypertrophy and hyperplasia. Together these tissue changes are the likely mechanisms for the esophageal

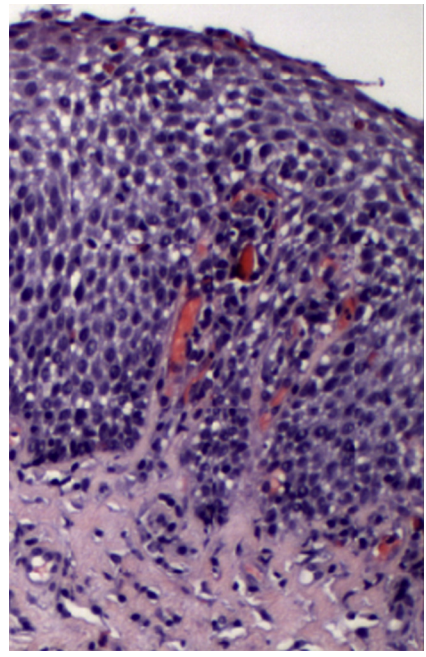

Fig. 1. Histopathology of remodeling changes in EoE. The squamous epithelium shows basal zone hyperplasia and LP shows increased collagen density in EoE. (original magnification ×400)