Eosinophilic Esophagitis
Pathophysiology and Definition

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KEYWORDS

- Eosinophilic esophagitis • Pathophysiology • PPI-REE
- Proton pump inhibitor responsive esophageal eosinophilia

KEY POINTS

- Eosinophilic esophagitis is an atopic, inflammatory condition of the esophagus characterized by eosinophlic infiltrate with subsequent fibrosis and reduced quality of life.
- Both genetics and the environment contribute to disease with risk identified in distant relatives, and external factors compound one's risk for disease.
- The pathophysiology results from complex interplay of many allergic and inflammatory cells including eosinophils, mast cells, basophils, and lymphocytes.
- Dense subepithelial fibrosis, mediated by TGF-β and associated cytokines, is a common complication of the disease.

OVERVIEW

Eosinophilic esophagitis (EoE) is an adaptive immune response to patient-specific antigens, mostly foods. EoE is not IgE-mediated and is instead likely mediated by Th2 lymphocytes (**Fig. 1**). The esophageal barrier function is impaired. The key cytokines and chemokines are thymic stromal lymphopoeitin (TSLP), interleukin (IL)-13, CCL26/eotaxin-3, and transforming growth factor-β1 (TGFB1). Chronic solid food dysphagia, the feared late complication, is caused by dense subepithelial fibrosis, likely induced by IL-13 and TGFB1.

DEFINITION

The current consensus criteria needed to define EoE require esophageal symptoms, an esophageal biopsy with 15 or more eosinophils in at least one high-power field

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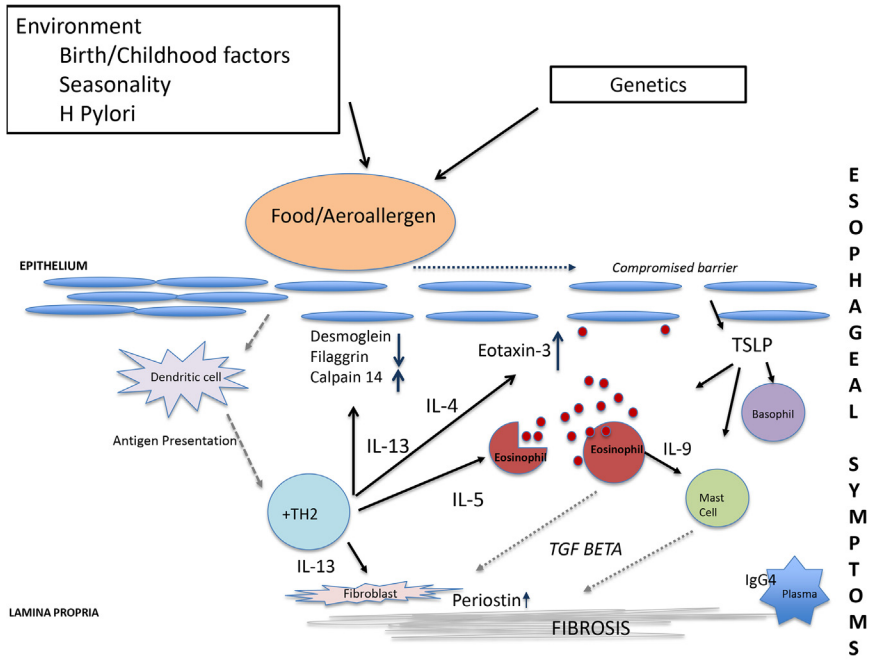

Fig. 1. The pathogenesis of EoE involves the complex interplay between genetics, a strong influence of environment, and antigenic stimuli from food or aeroallergens. The current paradigm suggests food and/or aeroallergen exposure with subsequent antigen presentation by dendritic cells and/or epithelium initiates disease. From antigen presentation, T cells are differentiated into Th2 cells secreting interleukin (IL)-4, IL-5, and IL-13. IL-4 and IL-13 are responsible for secretion of eotaxin-3 and upregulation of periostin in epithelial cells and fibroblasts. IL-13 has multiple effects including disruption of the epithelial barrier via actions on calpain, desmoglein, and filaggrin along with simulation of eosinophils. IL-5 is a key cytokine involved in eosinophil recruitment into the esophagus with a possible effect on mast cells. Eosinophils cytolyze releasing granule proteins toxic to epithelium. Eosinophils also release IL-9 aiding in proliferation and differentiation of mast cells. TSLP influences Th2 responses with specific influence on antigen presentation and basophil mobilization into esophageal tissue. TGF-β influences remodeling with subsequent fibrosis in the lamina propria. Plasma cells rich in IgG4 of unclear significance are found abundantly in the lamina propria. TGF, transforming growth factor; TSLP, thymic stromal lymphopoietin.

despite an 8-week or longer treatment with maximal dose proton pump inhibitor (PPI) therapy, and exclusion of other causes for esophageal eosinophilia (**Box 1**).[1]

Subsequent data challenge the exclusion of PPI-responsive patients from the definition of EoE; PPI-responsive patients can clinically and pathologically have essentially identical disease.[2] For example, the esophageal tissue transcriptomes are extremely similar.[3,4] In vitro studies show that PPIs directly block the IL-13/STAT6/eotaxin-3 signaling pathway, and, thus, response to PPI does not implicate acid reflux as causal to the disease.[5,6] PPI responders also respond to food elimination diets,[7] implying that the PPI responsive cases, like classically defined EoE, are induced by an aberrant food antigen–driven immune response. Clearly, PPI-responsive cases are extremely similar to EoE on a clinical and a molecular basis and probably should be considered together or as an extremely close disease variant.