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Eosinophilic esophagitis: A clinicopathological review

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ABSTRACT

Eosinophilic esophagitis (EoE) is considered to be a chronic antigen-driven disease whereby food and/or aeroallergens induce a chronic inflammatory infiltrate in the esophagus, resulting in pathological hyperplasia of the epithelia and muscular layers, and fibrosis of the lamina propria (referred to collectively as remodelling) and the symptoms of dysphagia and food impaction. EoE shares features with other atopic conditions of asthma and atopic dermatitis, such as a TH2 cytokine milieu and a mixed inflammatory infiltrate of eosinophils, mast cells and lymphocytes. Relatively distinct features include the strong male predominance amongst adult patients, and the expression of the eosinophil chemokine eotaxin 3. Current first line treatments such as strict dietary modification and corticosteroids fail many patients. Looking forward, clarification of distinct genotype/phenotype associations, determining the reversibility of remodelling following treatment, and the development of new pharmacotherapies that target fibrotic pathways (as opposed to eosinophilic inflammation per se) or specifically improve barrier integrity appear relevant.

Contents

1. Introduction

Eosinophilic esophagitis (EoE) presents in adults as dysphagia and food impaction. The pathophysiological correlates of these symptoms are thought to comprise (1) acute narrowing of the esophageal lumen by inflammation and oedema, (2) fixed narrowing and limited distensibility of the lumen by remodelling and (3) dynamic and variable narrowing caused by muscular contraction or spasm (Fontillon & Lucendo, 2012; Liacouras et al., 1998; Read & Pandolfino, 2012). The relative contribution of these three pathological processes to the clinical syndrome is not known, although the focus of research and treatment relates to remodelling. (See Figs. 1 and 2) (See Tables 1 and 2.)

Eosinophilic esophagitis (EoE) is considered to be a chronic antigen-driven disease, whereby food and/or aeroallergens induce an eosinophilic infiltration in the esophagus (Mulder & Justinich, 2011). Remodelling refers to the structural changes caused by acute and chronic inflammation, namely epithelial hyperplasia, fibrosis of the lamina propria and muscular hypertrophy (smooth and longitudinal) of the esophagus resulting from an inflammatory infiltrate typical of a TH2-mediated milieu (Cheng et al., 2012). The mechanism of injury has been demonstrated using

Abbreviations: EoE, eosinophilic esophagitis; TSLP, thymic stromal lymphopoietin; IL (e.g. IL-3), interleukin; AD, atopic dermatitis; VCAM-1, vascular cell adhesion protein 1; APC, antigen presenting cell; MBP, major basic protein; TGF-β, transforming growth factor beta; ICAM, intracellular adhesion molecule; IFN, interferon; VEGF, vascular endothelial growth factor; EMT, epithelial mesenchymal transition.

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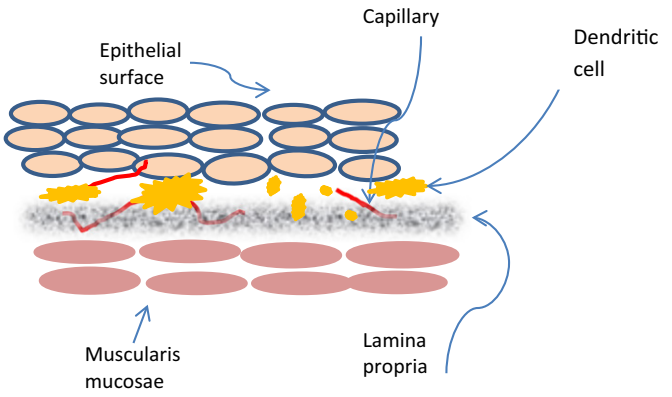

Fig. 1. Normal esophagus. Esophageal barrier function is maintained by an orderly arrangement of epithelial cells maintained by gap junction proteins. The muscularis is striated (upper 1/3 of the esophagus) and smooth (lower 2/3) of the esophagus. Antigen presentation may occur by dendritic cells or possibly epithelial cells.

animal models and in vivo human studies (before and after disease-modifying treatments) and may be conceptualised to involve cells (e.g., eosinophils, mast cells, epithelial cells and fibroblasts) cytokines (e.g., interleukins IL-4,5 and 13, and the chemokine eotaxin 3) and adhesion molecules (e.g., integrins and vascular cell adhesion protein 1 (VCAM-1))(Akei et al., 2005; Liacouras et al., 2011). The precise sequence of events and the dominant cellular signalling or adhesional molecules involved are not yet fully elucidated. Importantly, however, treatments such as topical corticosteroids and dietary modification may at least partially reverse the pathological changes in a significant number of patients, with resultant improvements in swallowing reported in some studies (Aceves et al., 2010; Lieberman et al., 2012). Other atopic conditions, such as asthma and atopic dermatitis (AD) manifest tissue remodelling, again typified by cellular infiltration and fibrosis, and the significant body of research in these fields provides valuable potential clues to the pathogenesis of EoE, and may direct future research (Boguniewicz & Leung, 2011; Royce et al., 2012). The role of epithelial barrier function, epithelial defence, and repair and bacterial colonisation (both crucial in the pathogenesis of AD) are neglected areas of research. The genetic and racial predilection of EoE as a disease predominantly

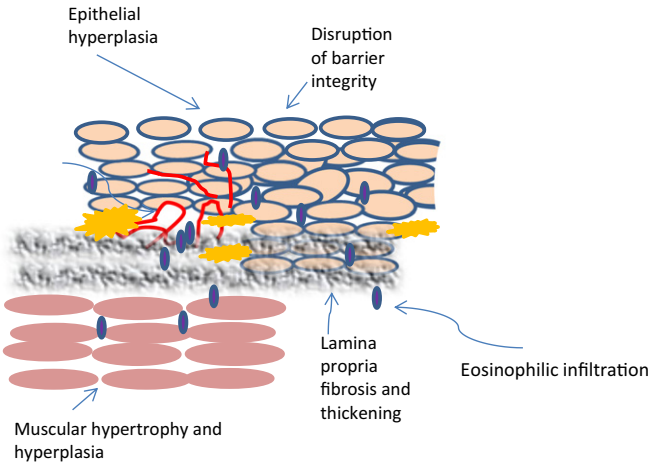

Fig. 2. Eosinophilic esophagitis. Epithelial barrier integrity is disrupted, allowing greater contact between antigens and dendritic cells. The epithelial layer is thickened and disorderly, and an inflammatory infiltrate rich in eosinophils extends throughout all layers, and may contribute to dysmotility. Angiogenesis is present; the esophagus is friable and bleeds easily at endoscopy. The lamina propria is thickened and fibrotic. The clinical sequelae of the pathological changes are dysphagia and food bolus obstruction due to luminal narrowing, limited distensibility and disturbance of peristalsis.

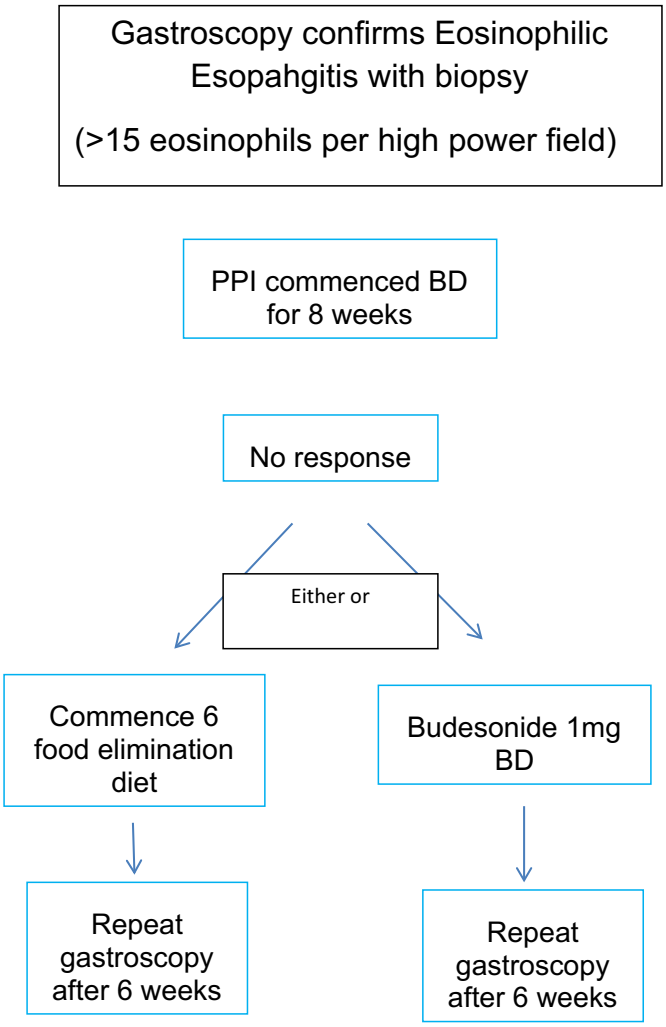

Fig. 3. There are significant shortcomings in the current treatment options.

of white male Caucasians also deserves careful consideration (Spergel et al., 2009).

The natural history of EoE in the era of disease-modifying treatments (elimination diets and corticosteroids), and the clinicopathological correlations between remodelling, acute inflammation and esophageal dysmotility remain to be determined (Dellon et al., 2013; Gonsalves et al., 2012). The clinical and research tools that determine symptoms (such as dysphagia scores) and esophageal function (manometry) and structure (endoscopic biopsy) have limitations. Improvements in technical utilisation (such as measuring esophageal distensibility instead

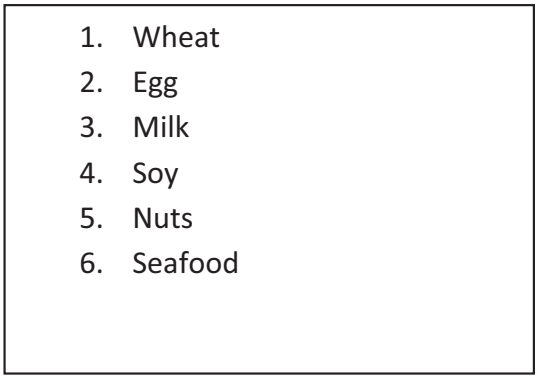

Fig. 4. The 6 food elimination diet.