Eosinophilic oesophagitis and food allergy

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Abstract

Eosinophilic oesophagitis (EoE) is an allergic condition of the oesophagus. It is a clinicopathological diagnosis, in which intermittent dysphagia and/or food impaction in adults occur in the presence of severe eosinophilic infiltration of the oesophagus. In children, symptoms can be less well defined, with feeding refusal, vomiting and failure to thrive. Symptoms of reflux, often described by both adult and paediatric patients are typically unresponsive to acid suppression treatment. Patients tend to have a history of atopy, and both food and aero-allergens are implicated in EoE pathophysiology. EoE is defined as ≥15 eosinophils/HPF in oesophageal biopsies. Its prevalence is reported at 4 per 1000 adult population, but its incidence is increasing and it is commoner in males. Although current guidelines require acid reflux to be excluded before making a diagnosis of EoE, the two conditions can overlap. Clinical awareness is necessary for the condition to be diagnosed, by ensuring oesophageal biopsies are taken when patients present with symptoms suggestive of EoE even if the oesophagus looks normal. The main treatment options include dietary therapy with elimination or exclusion diets in children, and topical or systemic corticosteroids, with or without concurrent use of PPIs in adults. Endoscopic dilatation of identified strictures is less commonly needed; there is a high risk of perforation associated with this.

Keywords Dysphagia; elimination/exclusion diet; eosinophilic oesophagitis; food allergy; food bolus obstruction; topical inhaled steroids

Introduction

Eosinophilic oesophagitis (EoE) is a chronic, immune/antigen-mediated condition of the oesophagus. It is a clinicopathological diagnosis, in which symptoms of oesophageal dysfunction, most often dysphagia and food impaction in adults, occur in the presence of eosinophil-predominant inflammation of the oesophagus. In children, symptoms are less well defined with feeding refusal, vomiting and failure to thrive. Symptoms of reflux, often described by both adult and paediatric patients are typically unresponsive to acid suppression treatment.[1,2] Patients tend to have a history of atopy and both food and aero-allergens are implicated in EoE pathophysiology.[3]

The prevalence of EoE is reported at 4 per 1000 population. Although increasing awareness of the condition is probably contributing to increased reporting of the condition, there appears to have been a genuine rise in the prevalence of EoE.[4] The main treatment options include dietary therapy, and topical or systemic corticosteroids.[5,6]

Diagnosis

In patients with clinical symptoms suggestive of EoE, oesophageal eosinophilia of over 20 eosinophils per high powered field (eos/HPF) has historically been taken as consistent with the diagnosis.[7] Consensus guidelines, first published in 2007 and updated in 2011,[8,9] required the presence of 15 or more eosinophils in 1 HPF, in the presence of symptoms of oesophageal dysfunction that did not respond to proton pump inhibitors (PPIs) or occurred in the presence of normal pH monitoring of the oesophagus. More recent clinical guidelines by the American College of Gastroenterology (ACG) in 2013, require clinical symptoms of oesophageal dysfunction in the presence of 15 or more eosinophils in 1 HPF on histology. Histology rather than symptoms alone is given more emphasis: mucosal eosinophilia must be isolated to the oesophagus, and must persist after a trial of proton-pump inhibitors (PPIs).[8,10] Exclusion of other causes of eosinophilia is also required (Table 1). A response to treatment with dietary exclusion and/or corticosteroids supports but is not required for the diagnosis.

The updated guidelines also introduce PPI-responsive oesophageal eosinophilia as a distinct condition from eosinophilic oesophagitis.[9,10] In these cases, symptoms and oesophageal eosinophilia respond to PPIs. This should not be assumed to be related to gastro-oesophageal reflux (GORD) and should be actively investigated, including use of ambulatory 24-hour pH studies.

Presentation

Adults present primarily with symptoms of intermittent dysphagia (81–93%) and/or food bolus obstruction (55–62%).[2] More than one-third of patients presenting with food bolus impaction may have underlying eosinophilic oesophagitis[11] with other common causes for food impaction, including GORD, oesophageal stricture and Schatzki rings. Of all cases of dysphagia 10–12% have been attributed to underlying EoE.[12] Men are most commonly affected (4M:1F), with age at diagnosis usually younger than 45 years, and highest prevalence at age 20–39 years.[2,13] Symptoms of heartburn, atypical chest pain, and odynophagia may also be reported. These generally tend to be unresponsive to high-dose PPIs. Rarely, oesophageal perforation has been reported.[14] Although symptoms do not tend to deteriorate over time, most patients report a significant impact on their quality of life.[15]

Children present with symptoms of reflux unresponsive to acid suppression but also with non-specific symptoms of failure to thrive, food avoidance, abdominal pain, nausea and vomiting.

Endoscopy

Linear furrows, oesophageal rings (trachealization of the oesophagus), mucosal fragility, white papules or strictures may be present on endoscopy. However, up to 42% of cases may have a normal endoscopy, and a high level of suspicion is needed by

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Differential diagnoses of oesophageal eosinophilia

- Gastro-oesophageal reflux disease and PPI-responsive oesophageal eosinophilia (see text)
- Inflammatory bowel disease
- Drug hypersensitivity reactions
- Parasitic infections
- Malignancy
- Connective tissue diseases
- Churg–Strauss syndrome
- Systemic lupus erythematosus
- Eosinophilic gastroenteritis (may necessitate gastric and duodenal biopsies to exclude this if there is clinical suspicion)
- Hypereosinophilic syndrome
- Graft versus host disease
- Food allergies

Table 1

the endoscopist to ensure that oesophageal biopsies are taken even in the presence of a normal oesophagus, especially in the younger population. EoE tends to be patchy and eosinophilic infiltration in the lower oesophagus can occur in reflux, so it is recommended that two to four biopsies are obtained from both the proximal and distal oesophagus to improve yield. As eosinophilic gastroenteritis or other differential diagnoses need to be excluded, gastric antrum and duodenal biopsies should also be taken.[8,10]

Histopathology

Eosinophils are seen under normal conditions in the remainder of the gastrointestinal tract but they are usually absent from the normal oesophagus. Aggregation of eosinophils is seen in gastro-oesophageal reflux although generally in lower number (usually up to 6–10 eos/HPF) than in EoE. The two conditions cannot be distinguished on histological criteria alone and correlation between symptoms and histologic findings is paramount.[16,17] Other features often present in EoE include extensive basal cell hyperplasia, dilatation of intracellular spaces, superficial layering of eosinophils, eosinophil degranulation and eosinophil clustering to form microabscesses.[13,16]

However, it may be that reflux and EoE can co-exist, especially in adults, in whom GORD is a common condition.[18,19] Spechler has speculated that four possibilities may exist: high numbers of eosinophils in the oesophagus can indeed exist in GORD; GORD can occur in patients with EoE by chance; EoE may predispose to or exacerbate GORD; or GORD may predispose to or exacerbate EoE.[20] It is unclear whether PPI-responsive oesophageal eosinophilia represents a subset of GORD, EoE or a distinct condition (Figures 1 and 2).

Pathophysiology

Patients with eosinophilic oesophagitis often have a history of allergic disease (asthma, allergic rhinitis, eczema) and sensitization to allergens, demonstrated by positive RAST testing or prick skin testing (PST), and may have elevated serum IgE and peripheral eosinophilia. Especially in the paediatric population, EoE appears to be directly linked to an immunological response to food allergens. A mixture of IgE (type I) and cell-mediated (type IV) hypersensitivity responses is involved.[21]

In active EoE, defects in desmosomal and tight junction adhesion proteins result in disrupted oesophageal mucosal integrity. It is unclear whether this is due to non-specific inflammation or whether there is a predisposition in patients with EoE. Loss of the oesophageal mucosal barrier function allows allergens to breach the oesophageal epithelium and trigger an inflammatory response. This appears to be driven by type 2 T-helper cells with increased expression of interleukin (IL)-5, IL-13 and tumour necrosis factor α, and accumulation of IgE receptor-rich eosinophils and mast cells. IL-5 is a specific eosinophil differentiation and survival factor, generated in chronic allergic conditions. Induction of eotaxin 3 facilitates eosinophilic migration to the oesophagus. There is no correlation between the number of eosinophils and the severity of endoscopic findings, suggesting that eosinophil aggregation alone is not the cause of epithelial damage.[22] Eosinophil aggregation and degranulation with release of chemo-active agents are the cause of tissue damage. These agents include major basic protein (MBP), an antagonist at muscarinic M_2 receptors that increases smooth muscle reactivity. Chronic inflammation results in increased collagen deposition, leading to progressive subepithelial fibrosis and remodelling, and eventually to oesophageal wall stricturing.[23]

Available endoscopic ultrasound findings report thickening of the oesophageal wall,[11,24,25] while dynamic studies using concurrent high-frequency intraluminal ultrasound and manometry suggest that asynchrony between oesophageal circular and longitudinal muscle may be one of the mechanisms of early dysphagia in patients with EoE. Available manometric studies have shown inconsistent and variable oesophageal dysmotility findings, including normal manometry, non-specific oesophageal motor disorder, hyperkinetic peristalsis and diffuse oesophageal spasm, or aperistaltic waves. High-resolution manometry and impedance, which may pick up more subtle manometric and functional changes, are pending.

Treatment

Food allergens and dietary modifications

Early research in the topic has been done in the paediatric population. Children commonly have food allergies and are better at tolerating available treatment options that include elemental or exclusion diets. More recently, evidence has been accumulating to support a role for early dietary intervention in adults too.

Dietary interventions include:

- amino acid-based elemental diet[26]
- specific food elimination guided by identified food allergens using skin-prick and patch testing[21]
- empirical six-food elimination diet (SFED) for six weeks, based on known common food allergens, namely cow's milk, egg, soy, wheat, peanut, and seafood.[27,28]

Studies looking into the effectiveness of various therapies in the treatment of EoE in the paediatric population have illustrated the effectiveness of dietary modifications, which have a more favourable adverse–effect profile than corticosteroids. Awareness of nutritional and calorific needs, and supervision of their