Digestive and Liver Disease 45 (2013) 871–878

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review article

Eosinophilic oesophagitis: From physiopathology to treatment

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ARTICLE INFO

Article history:
Received 17 January 2013
Accepted 25 February 2013
Available online 30 March 2013

Keywords:
Diagnosis
Eosinophilic oesophagitis
Treatment

ABSTRACT

Eosinophilic oesophagitis is a chronic inflammatory disease characterized by eosinophilic infiltration of the oesophageal mucosa. Food and aero-allergens are involved in its pathogenesis. Dysphagia and food impaction are the dominant symptoms in adult with eosinophilic oesophagitis. However, a wide range of symptoms has been noticed such as chest pain or gastro-oesophageal reflux disease-like symptoms. Upper gastro-intestinal endoscopy and oesophageal biopsies are crucial for the diagnosis of eosinophilic oesophagitis. Endoscopy might be normal or reveal typical patterns such as rings, furrows, exudates, oedema, and stricture. Two to four biopsies should be performed both in the distal and in the proximal oesophagus, and 15 eosinophils per high power field within the oesophageal epithelium are the minimal threshold to diagnose eosinophilic oesophagitis. Allergy testing is recommended, although its impact to orient treatment remains to be demonstrated. Eosinophilic oesophagitis treatment includes medical treatment, diet and endoscopic dilation. Proton pump inhibitors are the first-line therapy as some eosinophilic oesophagitis phenotypes respond well to proton pump inhibitors. Topical viscous corticosteroids or diet elimination are the treatment of choice. There is no clear evidence in the literature to prefer one to the other. Finally endoscopic dilation should be considered in case of persistent symptomatic stenosis despite medical therapy.

1. Introduction

Eosinophilic infiltration of the oesophagus was first described in adults with dysphagia in the 1990s [1]. It was recognized as being different from gastro-oesophageal reflux disease (GERD). A recent international consensus defined eosinophilic oesophagitis (EoE) as "a chronic, immune/antigene-mediated disease characterized clinically by symptoms related to oesophageal dysfunction and histologically by eosinophil-predominant inflammation".

Since the first description, EoE incidence has dramatically increased [2,3]. The prevalence is estimated around 43–55 per 100,000 inhabitants in Western countries. A recent study based on long-term follow-up tends to prove that there is a true increase of incidence and not only a better recognition by both gastroenterologists and pathologists [3].

Eosinophilic oesophagitis seems to be more frequent in young adult males even if it may affect individuals at any age. Thus, age is a predictive factor of EoE in patients with dysphagia. Among outpatients who underwent endoscopy for dysphagia at the Mayo Clinic in Rochester, age younger than 47 years was an independent predictive factor of EoE (odds ratio 0.94, 95% confidence interval 0.90–0.98, $p = 0.01$) [4]. In Olten county in Switzerland, the incidence of EoE was lower in women than men (relative risk = 0.585, 95% confidence interval 0.331–1.034, $p = 0.065$) [3]. In this population the sex ratio female/female was 3:1.

The aims of this review were to give a general update of this newly recognized entity including pathophysiology, clinical presentation, diagnostic modalities and treatment.

2. Physiopathology

Eosinophilic oesophagitis is characterized by an eosinophil infiltration within the oesophageal epithelium, and T-helper 2 (Th2)-type immune responses, which are typical of other atopic conditions. The inflammatory response is restricted to the oesophagus and does not involve the stomach and the duodenum.

2.1. Inflammatory process of oesophageal epithelium

In EoE, the oesophageal epithelium is infiltrated not only by eosinophils but also by T-cells, B cells and mast cells [5]. Increased

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1590-8658/$36.00
http://dx.doi.org/10.1016/j.dld.2013.02.015

numbers of denditric cells have also been observed in oesophageal epithelium of patients with EoE.

Increased levels of cytokines such as IL-4, IL-5, IL-9 and IL-13 have been noticed in oesophageal mucosa of patients with EoE [6,7]. These cytokines activate eosinophils, mast cells and B cells.

Oesophageal epithelium cells may be involved in this inflammatory process as well. They express TNF-α and eotaxin-3 that are responsible for the recruitment of eosinophils in the oesophagus. The crucial role of eotaxin-3 was demonstrated in a murine model as mice deficient in the eotaxin receptor were protected from experimental EoE. Finally, eosinophils also produce thymic stromal lymphoprotein (TSLP), a cytokine promoting Th2 differentiation.

This inflammatory process is summarized in Fig. 1. It induces an oesophageal remodelling which leads to oesophageal dysfunction and bolus impaction. Deposition of extracellular matrix proteins is associated with subepithelial fibrosis [8,9]. Eosinophils may contribute to EoE pathogenesis by secreting tumour growth factor (TGF) β1 and eosinophil granulations. TGFβ1 is a cytokine involved in epithelial growth, fibrosis and tissue remodelling and has been identified in EoE. Some eosinophil granulations (eosinophil cationic protein, eosinophil peroxidase for example) may have cytotoxic effects explaining epithelial cells death observed in EoE.

2.2. Allergy

The concept of food allergens as a primary trigger of EoE was introduced first in a paediatric cohort by Kelly et al. [10]. Since then, it has become increasingly clear that there was an allergic predisposition in the EoE population. A link has been described between atopy and EoE [11,12]. Allergic disorders (rhinitis, asthma, atopic dermatitis) are encountered in up to 70% of adults with EoE [12].

In murine model, oesophageal eosinophilia was inducible by allergens [13]. IL-13 and IL-5 were also found to be crucial for the disease development [14]. As a consequence these experimental data support the concept that EoE represents an allergic disease in which T cells and eosinophils play key pathogenic roles.

In humans, relevant allergens have been identified for EoE. In children EoE seems clearly to be a food antigen-driven disease. In contrast aero-allergen sensitization has mainly been observed in adults [6]. Seasonal exacerbations of EoE in spring and summer are in favour of a potential role of aero-allergens. Elevated IgE serum levels have been observed in EoE. They were specific to food and/or aero-allergens. Positive skin prick test have also been noticed. Finally based on elimination diet and reintroduction test, wheat and milk were the most common allergens in a cohort of 50 adults (60% and 50% respectively) [15]. However, skin-prick testing predicted only 13% of food association in this cohort.

2.3. Genetics

Different studies have suggested genetic inheritability in EoE [6,16]. Sibling recurrence risk ratio was estimated around 80 in EoE [17]. Genome-wide analysis has identified a susceptibility locus on chromosome 5q22 [18]. Thymic stromal lymphoprotein (TSLP) gene is located on this locus. A genetic variant in the TSLP receptor gene located on the pseudoautosomal region of the X-chromosome was also linked with EoE in males [19]. Finally variations in TGF-β and filaggrin genes have been also observed in EoE [19] as well as exotoxin-3 gene polymorphism [20].

2.4. Relation between GERD and eosinophilia

It is well-known that GERD may induce microscopic oesophagitis and eosinophilic infiltration [21,22]. This histological feature can be reversed by proton pump inhibitors (PPIs) therapy [23]. Some data suggested that PPIs might also be effective to treat oesophageal eosinophilia in absence of identified acid reflux [24]. Thus, a subgroup of patients has been recently recognized: this was named "PPI responsive oesophageal eosinophilia" by the latest consensus meeting [19]. These patients exhibit a typical EoE symptom presentation. GERD has been excluded and these patients demonstrate a clinical and pathological response to PPIs. Different hypotheses have been raised to explain this phenotype [19]. Healing of a disrupted epithelial barrier may prevent further immune activation. Eosinophil longevity may decrease on PPIs or PPIs may have some anti-inflammatory properties. In vitro, PPIs might inhibit eotaxin-3 expression by oesophageal cells [25].

Table 1
Clinical features of eosinophilic oesophagitis in children and adults.

Gastrointestinal symptoms	Atypical symptoms
Dysphagia (adolescents and adults)	Chest pain
Food impaction (adolescents and adults)	Rhinitis
Heartburn	Asthma
Regurgitations	Hoarseness
Abdominal pain	Croup, cough
Feeding disorders (paediatric < 2 years)	Rhinosinusitis
Failure to thrive (paediatric < 2 years)	Atopic dermatitis
	Sleep disorders breathing

3. Clinical presentation

Patients with EoE may present with a wide range of symptoms including dysphagia, food impaction, heartburn and chest pain. The clinical presentation may be very different according to the age of onset [19,26,27] (Table 1).

In adults, intermittent dysphagia for solids is the most typical symptom of EoE (ranging from 25 to 100%) with long-lasting food impaction representing the most frequent and severe presentation of dysphagia [19,27]. In fact, it has been observed that 35–50% of adults experienced at least one episode of food impaction requiring emergent evaluation and endoscopic bolus removal during the natural history of their disease [28,29]. It is not uncommon that patients modify their chewing habits (i.e. eating food more slowly and washing down solid food with liquids), thereby making the clinical manifestations of EoE less evident and leading to delayed diagnosis [30]. A minority of patients complain also of retrosternal pain that may occur spontaneously or after ingestion of alcohol, acidic liquids or foods, particularly when food consistency is dry or rough and/or when patients eat too fast. Other symptoms such as nausea, vomiting or abdominal pain as well as diarrhoea and weight loss can also occur [30–32].

In children younger than 2 years of age, feeding disorders (refusal to eat, chewing problems, choking after liquids or solids ingestion) and failure to thrive are dominant symptoms, while up to the age of 12, vomiting, nausea, abdominal pain, water brash, heartburn and regurgitation (GERD-like symptoms) are the most common symptoms (ranging from 5 to 82%) [19,31–34]. Dysphagia, food impaction, chest pain and diarrhoea were also reported and their frequency usually increases with age [30–32].

Finally, patients with EoE may also complain of additional atypical GERD symptoms such as asthma, hoarseness, cough, croup, rhino-sinusitis, others ear-nose-throat (ENT) symptoms and sleep-disordered breathing (ranging from 10 to 25%) [35,36].

No symptom in isolation is specific for the diagnosis of EoE. Regardless of age, if a patient develops GERD-like symptoms and does not respond to pharmacological or surgical treatment, EoE should be strongly suspected [19].

Finally EoE might be revealed by oesophageal complications such as spontaneous perforation [19]. Perforation might be transmural (Boerhaave's syndrome) [37] or partial as intramural tears or deep lacerations on endoscopy. These complications are rare and