

# Eosinophilic oesophagitis – a common disease, newly recognised

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**ABSTRACT – Eosinophilic oesophagitis is a clinico-pathologic diagnosis that describes patients with dysphagia (intermittent or continuous), food bolus obstruction or regurgitation, where endoscopy and biopsy reveals high concentrations of eosinophils in the lining of the oesophagus. At endoscopy, the presence of rings (trachealisation), furrows, micro-abscesses and strictures may be noted, but sometimes the appearance is normal. Hence biopsy is essential in every patient with dysphagia. The condition, recognised 25 years ago as a separate disease entity, not related to gastro-oesophageal reflux, is now becoming common. It is important for all general physicians to recognise this and make an accurate diagnosis in order to give specific treatment. This may involve topical steroids, leukotriene D4 antagonists, dietary exclusions and dilatations.**

**KEY WORDS: Dysphagia, eosinophilic oesophagitis, inflammation, eosinophilia, oesophageal**

## Introduction

Although first described 20 years ago, eosinophilic oesophagitis (EoE) has only recently been recognised as a relatively common disease. It is variable in presentation, with dysphagia the predominant symptom in adults, and regurgitation and failure to thrive in children, although both clinical patterns are because of its obstructive effect on oesophageal function.

Before 1993, only a few single case reports described eosinophils in the oesophagus and they did not describe the circumstances of the disease that is now recognised as EoE. One such case report had found eosinophils in achalasia<sup>1</sup> and another oesophageal involvement in eosinophilic gastroenteritis.<sup>2</sup> Small numbers of eosinophils are present in the mixed inflammatory reaction to gastrooesophageal reflux disease. The realisation that EoE is a disease of dysphagia in atopic individuals and not related to gastrooesophageal reflux came from two case series that emerged during 1993–1994 of patients with a distinct clinicopathologic pattern of presentation. The first of these came from the USA and described 13 patients with high densities of eosinophils in the epithelium. All patients had undergone pH monitoring that demonstrated the lack of pathologic acid reflux in 12 of 13 patients.<sup>3</sup> This original series also identified that half of the patients had either bronchial asthma or atopy. A similar series came from Switzerland<sup>4</sup> and

described 10 patients without evidence of gastrooesophageal reflux disease. A paediatric series emerged in 1995 describing eight children with biopsy-proven oesophageal eosinophilia.<sup>5</sup> Although pH studies were not a feature in this paper, the patients had not responded to acid suppression therapy. These studies established that EoE was a disease entity in its own right, characterised by distinct clinicopathologic criteria.

## Symptom presentation

Patients with EoE typically have dysphagia that is intermittent and of variable severity and frequency. It is a common presentation of acute bolus obstruction, and patients are acutely aware of this risk, which modifies their social behaviour and what they choose to eat. Patients are prolonged chewers, slow to eat and the last to finish a meal. Eating out in social company can be stressful, with their reaction to bolus obstruction causing a degree of alarm as they writh and heave to clear the blockage. For some, the obstruction clears in minutes, others in hours and, for some, emergency presentation to hospital becomes necessary. EoE is now the most common underlying cause of emergency admission to hospital with food bolus obstruction.<sup>6</sup>

The pattern of presentation in children is one of regurgitation and vomiting. For the very young, it is not clear whether they feel bolus obstruction or food sticking. The pattern of regurgitation can be linked with aspiration pneumonia and failure to thrive. Although differences in the pattern of presentation exist between childhood and adults, all of the symptoms can occur at any age. Although four times more common in males than in females, this condition can present at any age and in either sex. When severe, the dysphagia can be present with every meal, and can be associated with chest pain. A family history is present in up to 10% of cases.

A major current problem with EoE is the frequent incorrect labelling of the patient as having gastrooesophageal reflux disease (GORD). It might be that a significant number of patients with proton pump inhibitors (PPI) might have EoE.<sup>7</sup> Although regarded as highly effective therapy of GORD, PPIs are effective in <80% of patients. The reason behind this failure might be that the patient does not have reflux but instead has EoE. Adolescents with EoE are often initially labelled as having eating disorders, which can cause major difficulties for them until their eventual diagnosis. To diagnose EoE requires endoscopy, biopsy and good pathology reporting – therefore, it is often missed.

The natural history of EoE was described in 2003 by Alex Straumann<sup>8</sup> and demonstrated that EoE is a chronic disorder, with few complete remissions, and requiring considerable healthcare utilisation. Early papers describing a symptomatic

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treatment (montelukast, a leukotriene D4 antagonist, commonly used for the treatment of asthma<sup>9</sup>, and a swallowed topical steroid<sup>10</sup>) were published in 2003. The common use of treatments that otherwise were suitable for bronchial asthma gave rise to the term ‘asthma of the gullet’, a reasonable but not widely accepted alternative name for this condition.

Over the past 5 years, there has been a dramatic increase in the frequency of diagnosis of EoE, with international guidelines being published in 2007<sup>11</sup> in the USA, and a recent update of the guidelines in 2011.<sup>12</sup> There are now more than 1,000 articles describing oesophageal eosinophilia, or EoE in the PUBMED database. EoE has become a topic of major interest at national and international gastroenterology meetings, and it is now important for both the general physician in primary care, and general secondary-care physicians to be aware of this condition and how to diagnose it. Estimates of true disease frequency are difficult. In 2009, Prasad *et al.* showed the rapidity of this increase in diagnosis in the USA<sup>13</sup> and estimates of true incidence range from 15 to 45/100,000 population. This is similar to the UK prevalence of inflammatory bowel disease.<sup>14</sup>

### Endoscopic appearance

EoE should be suspected on the medical history of the patient, with the pattern and chronicity of dysphagia being the key symptom. All patients with dysphagia warrant endoscopy and biopsy. However, it is useful for the endoscopist also to be aware of the characteristic features of EoE.<sup>15,16</sup> These include tram track lesions along the length of the oesophageal body (ie linear furrows that are not ulcerated and distinct from the linear ulcers seen in GORD). In some patients, nodularity is present and, in others, submucosal rings appear (trachealisation). The combination of trachealisation, furrows and nodularity can cause a cobblestone appearance. In some patients, distinct white exudates occur, where eosinophils are bursting in clumps from the mucosa into the lumen. These micro-abscesses might look endoscopically like *Candida*. Dellon<sup>16</sup> showed the variable pattern of EoE on endoscopy, indicating that, in children, rings are less frequent, but generalised inflammation is more frequent.

Lastly, the oesophagus in EoE might appear normal; therefore, the maxim ‘in dysphagia biopsy the oesophagus even it looks normal’ has become the standard teaching. Biopsies should be taken in pairs each from the lower, mid and upper third of the oesophagus, to ensure diagnostic sensitivity as the disease is patchy in nature.

### Complications

Complications of EoE include stricture, perforation and malnutrition.<sup>12</sup> Strictures occur in approximately 10% of patients. It is often hard to know when the stricture first occurred. Most patients have had symptoms for years before they present. A recent case report<sup>17</sup> underlines the diagnostic difficulties experienced in relation to apparent reflux in a young man who, at 17 years of age, presented to this author with a more than 10-year

history of dysphagia. His dysphagia was severe, and he had never in his memory been able to swallow solid food. He grew strong on a diet based entirely on liquid food supplements. At the age of 12 years, a surgeon had ordered a barium swallow and, although it showed classic trachealisation and pH monitoring demonstrated no pathological reflux, the patient was still operated on. A Nissen fundoplication was performed for presumed reflux. No improvement occurred. At 17 years old, having symptoms of dysphagia with every meal, the young man presented to this author. The diagnosis was obvious at endoscopy, showing a stricture with a 3-mm lumen. Biopsy confirmed EoE and, after a single dilatation and subsequent maintenance with topical steroids, he has eaten normally.

Straumann *et al.*<sup>18</sup> described perforation of this condition when the emergency assessment was done using rigid endoscopy, which is popular with ENT specialists. Flexible endoscopy should be performed and the obstructed bolus broken up before attempts to move it. Spontaneous perforation of the oesophagus in EoE occurs as a result of straining and retching with food bolus obstruction.<sup>19</sup> These perforations are not like the original Boorhaave massive tears, but seem to be a partial tear, with escape of gas and creation of surgical emphysema and mediastinitis. These partial perforations are managed conservatively with antibiotics, intravenous nutrition and, occasionally, removable occlusion stents.

### Diagnostic criteria

The diagnosis is a clinicopathologic one, identifying high concentrations of eosinophils (>15 eosinophils per high power field<sup>3,11,12</sup> in patients with characteristic history of dysphagia or other oesophageal obstructive phenomena. The biopsy should be taken while the patient is taking PPIs, to reduce the overdiagnosis of EoE in reflux injury. In addition to counting the maximum eosinophils per high power field, the pathologist should be asked to identify surface congregation, micro-abscess and background markers of inflammation, such as hyperplasia of the basal zone. The size of the high power field should also be standardised to aid consistency<sup>11</sup> at a field size of 0.035 mm<sup>2</sup>.

### Aetiology

EoE is an antigen-driven oesophageal reaction that is more similar to focal allergy than to autoimmunity. Increased markers of hyperplasia (Ki67) and interleukin (IL)-13-mediated down-regulation of cyclooxygenase (Cox)-2 receptors occurs,<sup>20</sup> indicating again a pattern of atopy rather than of luminal irritation of acid reflux. Correlation with aeroallergens has been described, with relatively weak association with different seasons. The difficulty with therapy might relate to failure to treat the underlying cause, or because the pathogenesis of subepithelial fibrosis has already become established. Submucosal fibrosis and remodelling occurs in EoE<sup>21</sup> and medical or dietary therapies might fail to reverse this. Angiogenic remodelling<sup>22</sup> activated by vascular endothelial growth factor (VEGF) A, VEGFR2,

angiotensin and IL-13 might occur. The cellular and molecular mediators of EoE include cytokines (Eotaxin-3), mast cell activators and periostin. Immunology studies show that the reactivity of eosinophilic inflammation depends on T helper type 2 (Th-2) cells through an IL-13 mediated reaction. Affected squamous epithelium becomes rich in CD8 and CD1a lymphocytes, and mast cells express IL-5 and IL-13 receptors. Despite this growth in understanding of the immune basis of this condition, effective therapies targeted at these reactions have yet to prove effective.<sup>23</sup>

The generation of dysphagia in EoE might be multifactorial.<sup>24</sup> Dyskinesia of the longitudinal and circular muscle can occur, also measured by endoscopic ultrasound scans. In some patients, submucosal fibrosis might not be visible but it prevents distensibility of the oesophagus when a large bolus arrives. This can be measured using balloon devices to assess compliance (eg Endoflip),<sup>25</sup> which is useful in determining the potential value and site of oesophageal dilatation.

## Investigation

Investigation of EoE with oesophageal manometry and 24-h pH testing is useful. It excludes achalasia and other named motility disorders as the cause of the symptom of dysphagia. The 24-h pH test is useful if it demonstrates the complete lack of acid reflux, which would help clarify the reason for failure of PPI therapy. Occasionally, (approximately 10%) patients do have pathological acid reflux, and a small proportion of patients with EoE can be managed with just PPI medication.

## Therapy

Treatment of EoE can be categorised under three headings – diet, drugs and dilatation. Diets are commonly used in children but less so in adults. Complete exclusion of all foreign protein is achieved with elemental diets, but these often require enteral feeding tubes (usually nasogastric, followed after some weeks by restoration of normal dietary constituents one at a time<sup>26</sup>). Such an approach requires intensive involvement of dieticians with an interest in EoE and is unwise in units without such support because of the potential for malnutrition. An alternative dietary strategy is the six-food elimination diet,<sup>27</sup> where the potentially common drivers of allergy, such as wheat, milk, soya, nuts, egg and shellfish, are excluded. Although acceptable to some, when tried in adults few patients could continue with this diet for more than 12 months. The use of allergy testing, particularly skin-prick testing, is not accurate, with 67% of patients with reaction to reintroduced foods after elimination diets having had negative skin tests to these foods.

Drug treatment is most effective with topical steroids.<sup>28</sup> These can reverse the subepithelial fibrosis and remodelling and they commonly reduce the density of eosinophil count in the mucosa. In my view, the primary aim of therapy should be good symptom control, maintenance of nutrition and restoration of a normal

quality of life. Topical steroids are easy to administer using fluticasone inhaler 250 microgram given as two or three sprays to the back of the throat and swallowed, last thing at night and after breakfast in the morning. The aim is to leave the topical steroid on the oesophageal mucosa for as long as possible without washing it off. *Candida* can occur in 10–20% in long-term treatment and is easy to treat with nystatin. The degree of symptom improvement with topical steroids can be dramatic. Oral budesonide (in a viscous solution) is sometimes preferred because, particularly with children, the dosing is more reliable. Although efficacious in controlled trials, recent studies have raised concerns about significant long-term systemic absorption. Given that EoE is a chronic disease, it is important for therapies to have minimal long-term adverse effects. Oral steroids are no better than topical steroids and should be avoided because of long-term adverse effects.

An alternative drug therapy is montelukast, the leukotriene D4 antagonist.<sup>9</sup> Initial studies demonstrated symptom improvement, used on its own or in conjunction with topical steroids. Doses of 10 mg twice daily are effective, and the dose response curve might extend to higher doses. Adverse effects are few. As mentioned above, some patients have a PPI-responsive EoE, but they are not common, because the presentation of patients for diagnosis often starts with persistent symptoms already treated with a PPI.

Dilatation is valuable in patients with obvious stricture, or with measured reduced compliance on Endoflip test. The complication of perforation with careful dilatation seems relatively rare<sup>14,29</sup> and should be <1%. When strictures are present, it is often the only way to get adequate improvement to allow a solid diet and patients often get prolonged symptom benefit over >1 year. It is normal practice to use a maintenance medical therapy as above after such dilatation.

## Future aspects

One of the major hurdles currently is the lack of a measure of disease severity. Variability in symptoms, eosinophil count, endoscopic appearance and the poor correlation of each to the other have created a difficult field for the development of good patient-reported outcomes or objective outcomes of disease severity for drug testing and long-term management. The endoscopic features have recently been standardised<sup>30</sup> and the combination of this with standardised symptom questionnaires and health-related quality-of-life studies will be important instruments in the future.

## Summary

EoE is a distinct clinical entity characterised by dysphagia, with variable presentation that is more common in young men, and asthmatics, that has typical endoscopic features but demands a structured biopsy protocol for diagnosis. Treatment with topical steroids, leukotriene antagonists and dilatation is effective. Dietary exclusion is popular in paediatric practice.

Immunotherapy has not been successful in clinical trials. The rapid increase in recognition now makes EoE a relatively common condition that all primary- and secondary-care physicians need to be aware of.

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