

Eosinophilic oesophagitis: an enigmatic, emerging disease

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ABSTRACT

Eosinophilic oesophagitis is a disease that has emerged in recent years. It is often associated with dysphagia and oesophageal food impaction in adults. The disease is characterised by infiltration of eosinophilic granulocytes into the oesophageal mucosa. This infiltrate may be responsible for the subtle peristaltic abnormalities that can be found in these patients. Endoscopic findings are usually absent or nonspecific, although a discrete circular ring pattern of the mucosa may be noticed. Occasionally, overt endoscopic abnormalities (such as exudative changes and shearing of the mucosa) can be found. The presence of at least 15 intraepithelial eosinophilic granulocytes per high-power field in random biopsies from the whole length of the oesophagus is considered to be diagnostic. Gastro-oesophageal reflux needs to be excluded as it may lead to eosinophilic infiltration as well. Adequate diagnosis is relevant for treatment and the prevention of unnecessary further investigations. The disease responds well to the ingestion of fluticasone propionate and its long-term prognosis is generally good. But when fluticasone is discontinued recurrent symptoms are common, and some cases are severe, needing treatment with systemic corticosteroids.

KEYWORDS

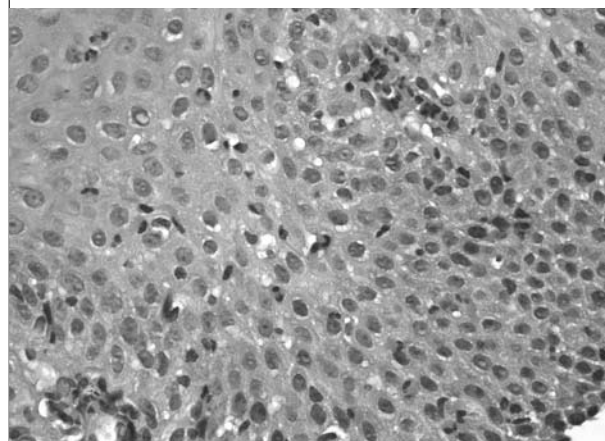
Eosinophilic oesophagitis, dysphagia, food impaction, intraepithelial eosinophilic granulocytes

CASE REPORT

A 50-year-old, previously healthy man presented to the emergency department because of complete obstruction of the oesophagus after eating meat. For several years he had

been visiting the emergency department occasionally with the same problem. Repeated upper gastrointestinal (GI) endoscopies had never shown any abnormalities. Between these events the patient suffered from mild dysphagia that could be managed by drinking water. The patient had not changed his diet nor suffered weight loss. Treatment with high-dose omeprazole did not improve his symptoms. Recent extensive evaluation including 24-hour ambulatory pH monitoring, manometry and barium X-ray of the oesophagus had revealed no abnormalities. Emergency endoscopy showed obstruction of the oesophagus due to an impacted food bolus. After endoscopic removal no mucosal abnormalities or stenosis were visible. Multiple biopsies were taken from the mucosa in the proximal and distal oesophagus. Histological examination showed a marked intraepithelial infiltration consisting of >20 intraepithelial eosinophilic granulocytes (IEGs)/high-power field (HPF) (figure 1). The diagnosis of eosinophilic oesophagitis (EO)

Figure 1. The oesophageal epithelium shows a prominent eosinophilic infiltrate (magnification inset: 400x)



was made. Treatment with fluticasone propionate (FP) ('spray-and-swallow') 250 µg twice daily was instigated which led to complete resolution of symptoms. After nine months the patient stopped his medication of his own accord. Six weeks later he presented to our emergency department again with food bolus obstruction. Since then, continuous fluticasone treatment has been given and he has remained free of symptoms for more than a year of follow-up. He did not develop oropharyngeal or oesophageal candidiasis.

EPIDEMIOLOGY

EO was first described by Dobbins *et al.* in 1977.¹ Between approximately 1985 and 1995 it was considered to be a rare disease, primarily affecting children and adolescents. After 1995, an increasing number of affected adults have been reported.² The annual incidence of EO has been estimated to be around 1:100,000 children in Ohio, with an increasing prevalence reported in Switzerland over the last decade.³ The prevalence was studied in a random sample of the Swedish population who underwent upper GI endoscopy for other reasons and about 1% of individuals met the histological criteria of EO.⁴ It is estimated that the prevalence of EO is around 1:2500 in children and 1:4000 in adults.⁵ The male-to-female ratio is approximately 3 to 1. More than 95% of reported cases are of the Caucasian race,^{2,6} although it remains unclear whether this reflects true racial difference or is due to selection bias.

PATHOGENESIS

The cause of this disease is not known. In health the oesophagus has no eosinophils.⁷ The recruitment of eosinophils is observed in a variety of inflammatory or infectious conditions and exposure to food and aeroallergens.^{8,9}

The presence of intraepithelial eosinophilic granulocytes in the oesophageal mucosa – as anywhere in the digestive tract – may be a nonspecific phenomenon. It can be caused by any irritating agent, noticeably acid or non-acid refluxate, non-steroidal anti-inflammatory drugs or food stasis due to oesophageal motility disorders such as achalasia and systemic sclerosis.⁷ Furthermore, eosinophilic infiltration of the oesophageal mucosa has also been found in asymptomatic subjects. Whether these findings represent 'early' EO and may progress to symptomatic EO or are incidental findings is not known.¹⁰ We do know that during an allergic response, tissue injury, or infection eosinophils can be major effector cells and are able to release chemokines, lipid mediators, cytokines, and cytotoxic secretory products.⁷

Although eosinophils seem to play a major role in EO it is not the only critical contributor. A combination of environmental exposure, allergen sensitisation, eosinophils and other cells, molecules released and genetic predisposition, all interplay in EO pathogenesis.¹¹

Most studies characterising the allergic phenotype have been performed in children.⁶

The high prevalence of atopic constitution among patients with EO and the good response of EO to elimination or elemental diets reinforce the link between the disease and the allergic aetiology.¹¹⁻¹⁴ The presence of food sensitisation and the response to elimination diets insinuate an immunoglobulin (Ig)E-dependent mechanism. Although, as only a minority of EO patients present with food anaphylaxis, it indicates a distinct mechanism. As such, a local oesophageal population of allergen specific IgE producing B cells is possible.¹¹ Or there may be a mixed IgE- and non-IgE-mediated reaction. On the basis of allergy testing results EO is thought to be a polygenic allergic disorder.¹⁵ Intriguingly patients with EO have sometimes reported seasonal variations in symptoms and oesophageal IEG levels,^{16,17} suggesting it is not only a food but also an aeroallergen hypersensitivity.

Furthermore EO seems also to be associated with Th2-type immune responses and local or systemic Th2 cytokine overproduction.¹¹ American investigators showed that not only food but also environmental allergens induced a significantly higher production of specific Th2 cytokines (IL-5 and IL-13) by peripheral blood mononuclear cells (PBMCs) in patients with EO compared with healthy controls.¹⁸

Animal models have linked EO and allergic diseases and assess the sensitisation pathways that could occur in human EO.¹¹ Experimental models can be induced in mice by sensitisation or exposure, as well as by administration or overexpression of specific Th2 cytokines.^{11,19,20} The experimental models demonstrate an intimate connection between the development of eosinophilic inflammation in the respiratory tract, skin and oesophagus, not only to external allergic triggers but also to intrinsic Th2 cytokines.^{11,21,22}

A genetic predisposition for EO has been reported in children. An abnormal gene encoding for eotaxin-3, a key promoter of eosinophil attraction and inflammation, was found in nearly half of the children with EO.²³

Of note, allergy and genetics do not explain all patients with EO. In adults the prevalence of atopy is much smaller and no genetic association has been established.²⁴

Just like the aetiology, the development of dysphagia in EO remains a mystery. An important hypothesis on this field is the role of oesophageal dysmotility. Certain biologically active components, produced by IEGs, may induce motility disorders,⁹ although there is no strong evidence and the

precise role in EO remains far from elucidated. Technological advances such as high-resolution manometry and combined manometry with impedance may provide new insight into the more subtle motility abnormalities.²⁵ It must also be noted that it remains uncertain whether the eosinophilic infiltration of the mucosa is the primary cause of dysmotility or the result of mucosal irritation by food stasis and impaction.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The single most common presenting symptom of EO is intermittent or persistent mild dysphagia occasionally leading to food impaction, which occurs in more than 90 and 60% of cases, respectively.^{2,6} These symptoms do not lead to weight loss.²⁶ Endoscopic abnormalities may be absent or inconspicuous. But when present, typical findings are a fine ring pattern, vertical furrows, white spots or mucosal fragility.^{2,8,27-30} Recently a prospective study showed that the prevalence of EO in patients with solid food dysphagia and a normal-appearing oesophagus is approximately 10%.³ And only one third of the patients with EO had any of the typical findings. It was also observed that when one of the typical findings was present, EO was only histologically present in 38% of the cases.³ So the endoscopic findings are nonspecific and have been reported in other oesophageal diseases, such as gastro-oesophageal reflux disease (GERD), achalasia and other motility disorders.⁶ Especially GERD is an important differential diagnosis and should be excluded after a thorough work-up to justify a diagnosis of true EO.^{13,31,32} Occasionally, impressive endoscopic findings have been described consisting of white exudates, a small calibre oesophagus and a Schatzki's ring.^{2,6,30} It is unclear whether these patients, usually suffering from severe symptoms, represent a distinct subgroup of EO.

Obviously, the frequently observed obstruction of a normal-appearing oesophagus by well-chewed food can only be due to an underlying motility disorder. Although standard oesophageal motility studies have failed to demonstrate abnormalities in a large proportion of patients with EO, 24-hour manometry is able to demonstrate oesophageal dysmotility in patients with EO.³³ Because manometric alterations can be intermittent or remain undetected by the usual measurement techniques, the true incidence of dysmotility in EO may be underestimated.³⁴

The diagnosis of EO is made when suggestive symptoms and, if present, endoscopic findings are supported by biopsy specimens demonstrating an abnormal accumulation of IEGs. Although the exact number of IEGs/HPF required for diagnosis remains a matter of debate, most experts believe that the presence of more than 15 IEGs/HPF in the oesophageal squamous epithelium with concurrent symptoms establishes the diagnosis of EO.^{6,32}

In 2007 medical experts made consensus recommendations for the diagnosis of EO.⁶ They stated that intraepithelial eosinophils should be counted in the most intensely inflamed HPF of the biopsy (x400) to generate a peak count. They concluded that a peak count of 15 IEGs/HPF is an absolute minimum number to make the diagnosis of EO. If all HPFs are counted, the mean eosinophil number may be less than 15 because of focal inflammation in the biopsy specimens, but at least one HPF must contain at least 15 IEGs.⁶

The distribution of histological abnormalities may be patchy and therefore the amount of IEGs may vary throughout the length of the oesophagus.³⁵ Therefore, it is recommended to take multiple biopsies from the entire length of the oesophagus. Furthermore, the presence of IEGs in the distal oesophagus only may be suggestive of reflux disease rather than EO,^{1,8} suggesting that it would be prudent to collect biopsies at this level in a separate container.

As previously stated, the differential diagnosis primarily includes GERD, which should be excluded properly. Most authors suggest that a trial with a high-dose proton-pump inhibitor, without effect on symptoms of the oesophagus, is required to exclude GERD. It is unknown whether non-acid GERD (demonstrable with the use of impedance monitoring²⁶) plays a role in EO.³⁶ At present no recommendations can be given with regards to the value of impedance monitoring in the work-up of these patients.

As achalasia is part of the differential diagnosis of EO, oesophageal manometry is mandatory, although strong supporting literature is lacking and consensus recommendations currently see no diagnostic value in patients with EO.⁶ Eosinophilic infiltration of the oesophagus in the setting of a generalised eosinophilic gastroenteritis has been reported and some have advocated taking jejunal biopsies to rule out this condition.³¹ Eosinophilic gastroenteritis, however, has quite a different clinical manifestation and contrary to EO includes abdominal pain, nausea, vomiting, and diarrhoea.³⁷ For this reason, we have not adopted this policy in our patients.

Finally, hypereosinophilic syndrome must be ruled out, especially, when there are extra-gastrointestinal manifestations and splenomegaly, cutaneous, respiratory, neurological or cardiac findings are present. Missing this diagnosis can have important implications, as cardiac and neurological involvement can be life-threatening.³⁸

TREATMENT AND PROGNOSIS

The mainstay of treatment consists of topical steroid ingestion.

The literature concerning EO is dominated by paediatric studies. Two randomised controlled trials concerning the use of FP in children were carried out.^{39,40}

American investigators assigned 36 children randomly to oral FP or placebo for three months. Histological remission was observed significantly more frequently in the fluticasone group (50 vs 9%). Clinically, vomiting improved significantly in FP responders, but other clinical symptoms did not reach a significant improvement with FP treatment.³⁹ Another American research group from Indianapolis treated 80 children with either FP or systemic corticosteroids and demonstrated a greater degree of histological improvement but no significant difference in clinical remission rates.⁴⁰ In adult patients only case series have been published. The investigators treated 21 patients with 220 µg FP, swallowed twice a day for six weeks: all patients experienced symptomatic relief.⁴¹ Remedios *et al.* confirmed the symptomatic effectiveness of FP in 19 adult patients with concurrent significant histological improvement.²⁸

Although topical corticosteroids have been proven to be effective, all studies, including a recently published prospective study,⁴² show a high relapse rate after stopping treatment (as in our case). This highlights the need for maintenance treatment. As long-term treatment is needed in EO, systemic corticosteroid use is precluded by its long-term side effects including cataract, growth retardation in children, osteoporosis and adrenal suppression. Using oral FP, these systemic effects can be minimised, thus enhancing compliance.²⁸ Acute and severe exacerbations of EO, however, can still be treated with systemic corticosteroids.²²

It must be noted that before high-dose inhaled FP can be fully implemented as maintenance treatment for EO it is important for future trials to further investigate the use of possible systemic side effects. And continuing evaluations of dose and duration of therapy are needed. Proposed mechanisms through which corticosteroids influence EO are inhibition of pro-inflammatory mediators, down-regulation of chemotactic factors and induction of apoptosis.⁹

Other proposed treatments are exclusion diets, elementary diets, gastric acid suppression, and stabilisers of eosinophilic trafficking and activation.

The selective elimination of foods with demonstrable allergic effects in the patient under consideration has been reported as an effective strategy in individual patients. In children, the use of an elemental diet has also been shown to be effective.^{14,43} However, the long-term implementation of such therapy is hampered by nutritional deprivation, psychological problems, unnecessary food aversion and loss of quality of life.

As mentioned earlier, a trial of high-dose proton pump inhibitor therapy is justified to exclude acid GERD as part of the differential diagnosis of EO, but as gastric acid plays no part in the pathogenesis of true EO, long-term treatment with proton-pump inhibitors is not effective.⁶

Treatments that target eosinophilic trafficking and activation have been assessed in pilot studies. A case series using the leukotriene inhibitor montelukast showed symptomatic but no histological improvement and unfortunately a quick relapse after therapy cessation.⁴⁴ Mepolizumab, a humanised monoclonal antibody directed against IL-5, was infused intravenously once a month in one patient with EO unresponsive to topical and oral steroid therapy. Mepolizumab produced symptomatic, endoscopic, and histological improvement.⁴⁵ Following this initial success, ongoing placebo-controlled trials have been set up to further analyse the use of mepolizumab in EO.

Therapies focussing at controlling a suggested allergy component of EO, using antihistamines and cromolyn – a mast cell stabiliser and also an inhibitor of eosinophil mediator release and T-cell function – showed limited success in case reports.^{13,46}

Recently there have been promising results in case reports concerning the use of purine analogues – azathioprine (AZA) and 6-mercaptopurine – showing clinical and histological response. Two of the three studied patients experienced relapses after ceasing AZA therapy.⁴⁷

Finally, EO, although chronic, does not appear to limit life expectancy and no associated oesophageal malignancies have ever been reported.^{6,48}

CONCLUSION

EO is a mucosal inflammatory disorder, most likely leading to oesophageal dysmotility with an unclear pathogenesis which is increasingly recognised in children but also in adults. The diagnosis should be considered in patients with unexplained dysphagia, especially when there are no or only subtle endoscopic abnormalities of the oesophagus. Histological biopsies of normal appearing mucosa throughout the length of the oesophagus are pivotal in establishing the diagnosis. Absence of endoscopic signs of GERD and a negative PPI trial of the oesophagus are prerequisites for making a definite diagnosis of EO. The use of FP aerosol is the most successful long-term treatment, with minimal side effects. With such treatment the long-term prognosis seems good.

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