Eosinophilic oesophagitis – a brief review

Eozinofilni ezofagitis – kratek pregled

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Izvleček

Eozinofilni ezofagitis je bil prvič opisan leta 1992. Čeprav je nekaj področij v patofiziologiji še nejasnih, pa je precej že pojasnjenega. Število otrok in mladostnikov s to boleznijo stalno narašča. Diagnoza temelji na kliničnih, endoskopskih in histoloških značilnostih. Čeprav je biopsija požiralnika pomembna, ne more pojasniti vseh dejavnikov, ki privedejo do pojava znakov in simptomov. Kljub objavljenim soglasjem in smernicam je jasno, da so za obravnavo bolnikov s to boleznijo potrebna nova diagnostična orodja in načini zdravljenja. V pregledu so obravnavane nekatere pomembne morfološke, diagnostične in terapevtske značilnosti.

Abstract

Eosinophilic oesophagitis was first described in 1992. Although there are some areas unclear in the pathophysiology, much has been unveiled. An increasing number of children and adolescents have this entity. Diagnosis relies on clinical, endoscopic and histological features. Biopsies of the oesophagus, although important, may not show all the events that lead to signs and symptoms. Although there have been consensus and guidelines published, it is clear that new diagnostic tools and therapeutic modalities are needed to address patients affected by this condition. Some relevant features of morphology, diagnosis and treatment are reviewed.

Eosinophilic oesophagitis (EoE) was first described only 20 years ago. The number of publications both in Paediatric and Adult Gastroenterology has risen continuously. The incidence in paediatric patients seems to be variable according to geographic locations, although it is not entirely clear whether this reflects a true difference in epidemiology or just parallels the availability of centres with facilities for paediatric endoscopy. A recent review of published reports concludes that the incidence ranges from 1.6 (Denmark) to 8.0 (UK) per 100.000 and from 0.7 to 10 per 100.000 in the USA.[1] Despite increased knowledge about pathophysiology and clinical features this is still an intriguing disease. A large consensus has been reached about the main features required for diagnosis, based on a high number of eosinophils in multiple biopsies of the oesophagus at different levels despite previous treatment with proton pump inhibitors (PPI's). International consensus publications have addressed the clinical and histological findings that should be used to make a firm diagnosis of EoE.[2,3] Clearly, the isolated identification of eosinophils in the oesophageal mucosa, albeit beyond normal pattern, may be insufficient to establish the diagnosis not only because gastroesophageal reflux may be a cause of mucosal eosinophilia, but also because some cases of marked eosinophilic infiltration in the oesophagus may respond to PPI treatment.[4] This latter has been classified as PPI-responsive oesophageal eosinophilia and it is not yet clear if it is a subtype of EoE or a different entity. Therefore, it is currently recommended that patients with typical clinical or endoscopic features consistent with EoE should be treated with PPIs and re-evaluated 8 weeks later for the persistence of eosinophilic infiltration.

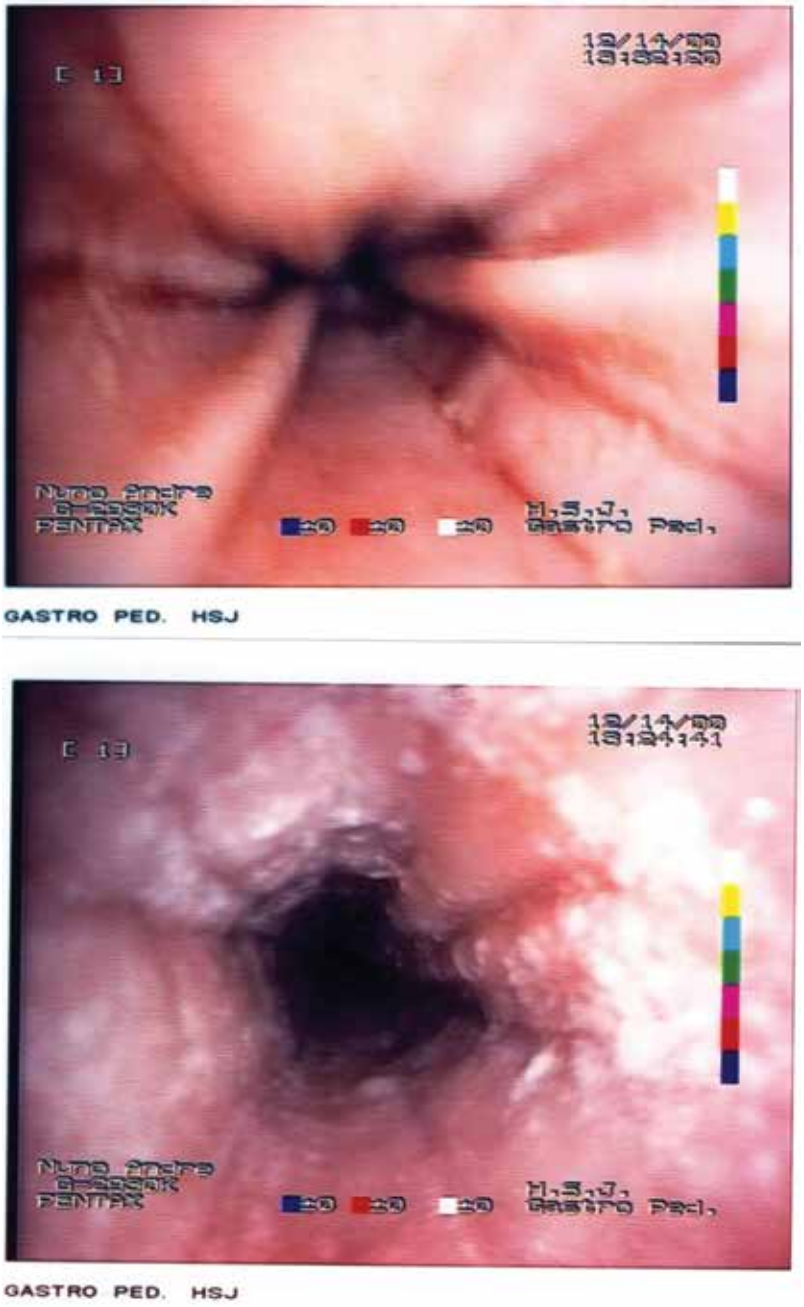


Figure 1: Oedema of the oesophageal wall and white spots corresponding to eosinophilic submucosal abscesses.

Diagnostic features

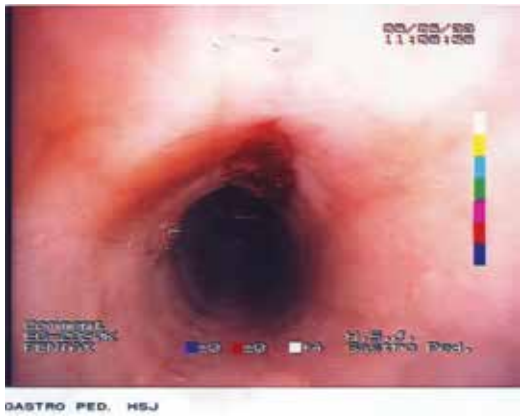
The usual signs and symptoms that are suggestive of EoE depend on age groups. Adults and adolescents usually present with dysphagia, food impaction or chest pain. Children may have similar features, but more unspecific complaints may occur.[5] Failure to thrive, vomiting and abdominal pain are not uncommon is children and may even represent a larger proportion than the usual features from older age groups. Therefore, multiple biopsies (at different levels) should be taken at endoscopy. There are endoscopic signs very typical of EoE: mucosal tears, longitudinal furrows and rings giving the appearance of trachea-like pattern (fig 1–3). However these features may be absent in some patients, so diagnosis requires a detailed clinical and histologic assessment. Furthermore, eosinophilic infiltration is restricted to the oesophagus, which is different from eosinophilic gastroenteropathy that affects other segments of the GI tract. Thus, it is appropriate to take biopsy samples from the stomach and duodenum for differential diagnosis.

Histological evaluation may show an increased number (≥ 15/hpf) of eosinophils in the mucosa, eosinophilic microabscesses, surface layering of eosinophils, extracellular eosinophil granules, basal cell hyperplasia, dilated intercellular spaces, and fibrosis of the lamina propria (Figure 4).[2] Pathologists should be encouraged to report all histological features and to evaluate areas with the highest density of eosinophilic infiltration. The term "high power field" may correspond to different surface areas in microscopy and this adds some bias into the interpretation of cell counts alone. A publication of a case of marked variability within the surgically resected oesophagus of a patient with EoE shows that histological diagnosis based solely on endoscopic biopsy specimens may underestimate the cellular mechanisms leading to EoE.[6] Actually, there is accumulated evidence that various processes may be very active in deeper layers of the oesophageal wall that may be relevant for both pathogenesis and therapeutic implications.[7]

Morphologic alterations

EoE pathogenesis is complex and not fully understood. Eosinophilic infiltration of the epithelium alone does not explain all the features of the disease. Other factors such as T-cell recruitment, response to inhaled allergens and mast cells certainly play a role in the production of cytokines like IL-5, IL-13 and chemokine eotaxin-3 that are important for eosinophilic recruitment and response.

Apart from the abundant infiltration of eosinophils in the mucosa, patients with EoE showed various abnormalities in the



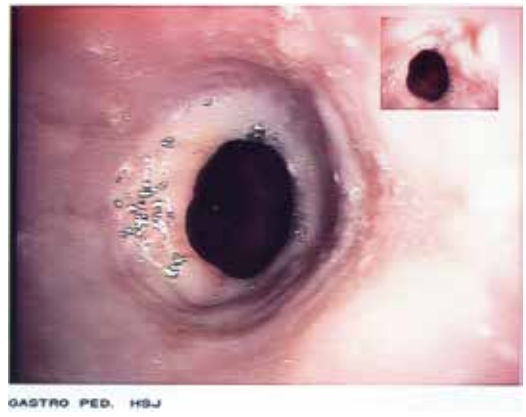


Figure 2 (left): Longitudinal tear after contact with endoscope. **Figure 3 (right):** Rings giving the trachea-like appearance.

oesophagus, such as mast cell infiltration,[8] subepithelial fibrosis,[9] angiogenic remodelling[10] and thickening of oesophageal mucosa and submucosa.[11] These features show that this is a transmural disorder and may account for the dysmotility and inflammation.

Allergy tests

There has been considerable evidence that food may be the triggering factor for oesophageal abnormalities in most patients with EoE, and it is well demonstrated that food elimination or even amino acid based formula lead to an improvement of symptoms.[12,13] Seasonal variations and experimental models have also revealed that other sources of atopy may play a relevant role in many patients.[14,15] Therefore, allergy tests have been used in the investigation of patients with EoE.[16] However, there is no consensus yet about the value of these tests, with one report showing that performing tests only identified half of the patients that responded to milk eviction.[17] Utility and significance of the detection of specific IgE to foods or aeroallergens remain unclear.[18] However, there is some evidence that the combined use of skin prick-tests (SPT) and atopy patch tests (APT) may provide relevant indication about the food to be avoided.[19]

Treatment

The accumulated evidence of a food-related allergic condition has led to dietary restrictions, but also the use of corticosteroids and more recently anti-IL5 monoclonal antibodies. The selection of foods to avoid may be done in 3 different ways: (a) empiric, with avoidance of the foods more frequently causing EoE (dairy, soy, eggs, wheat, peanuts, fish/shellfish), usually called Six-Food Elimination Diet (SFED),[12]; (b) targeted, with avoidance of the foods identified by suggestive history of food triggers and results of specific IgEs, SPT and APT[20]; and (c) amino acid based formula that removes all whole or partially digested proteins[13,21]. Multiple food elimination diets may improve symptoms with a tendency of requiring a larger number of foods to be avoided at a young age.[19] Although the targeted elimination diet may be tried, results have also been variable. However, given the nutritional risk of multiple food restriction, close supervision must be kept on the dietary balance. Comparison of the 3 dietary approaches showed that elemental diet provided the best results.[22] The duration of the elimination diet has not been clearly established and studies have used 4 to 8 weeks.[23] If elemental diet is used then the duration to obtain remission may be shortened (4 weeks). The ESPGHAN working group recommends 4–8 weeks of elimination diet (position paper in press). Clinical and histologic remission should be documented after this treatment. Following remission, careful reintroduction of eliminated foods should be performed with close monitoring of symptoms by endoscopic and histologic evaluation. A study in adults showed that reintroduction of foods led to relapse of symptoms and endoscopic lesions; allergy tests were poor predictors of the foods causing reaction.[24]

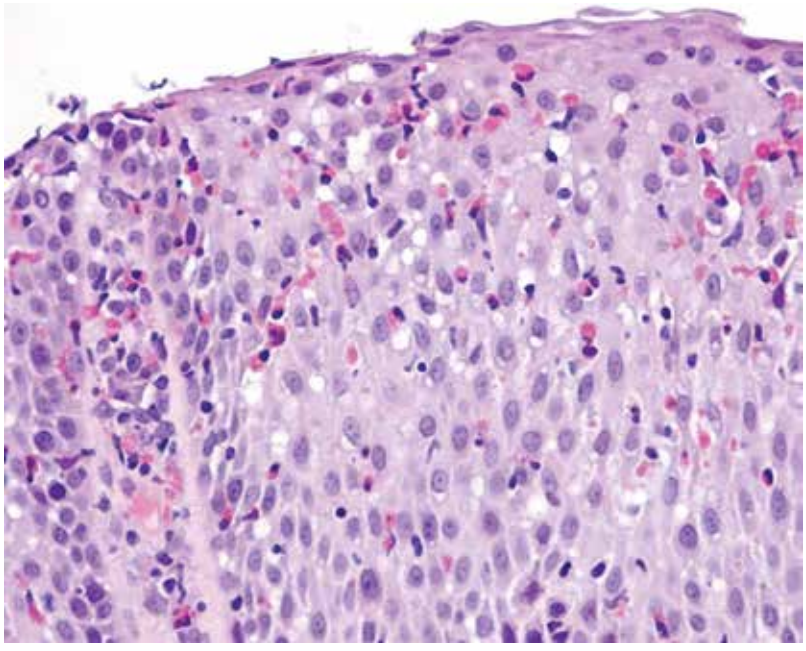


Figure 4: Biopsy specimen showing marked eosinophilic infiltration (courtesy of Prof. Fátima Carneiro).

Although dietary treatment seems to be a logical option in an allergic condition, this may not be feasible in many patients, either due to compliance or the capacity to identify a single trigger for the inflammation. Therefore, pharmacological treatment is often needed, consisting mostly of topical steroids. These have shown to be effective using aerosol fluticasone or budesonide swallowed instead of inhaled. This method provides therapeutic effect in most patients but clearly a part of the drug ends up in the respiratory tract. A viscous syrup was proposed for delivering the steroid into the digestive tract.[25-27] Although a diet or topical steroids have shown to relieve the clinical manifestations and histologic signs, relapse often occurs after discontinuation of treatment. A study evaluating the benefit of long--term use of budesonide showed that low--dose was better than placebo.[28] However, the long-term strategy and endpoints for the treatment of asymptomatic patients is still under debate. Oral systemic steroids should be reserved for severe forms of disease that do not respond to diet or topical steroids. In case of stenosis of the oesophagus, which is uncommon in the paediatric population, endoscopic dilation may be performed following a course of steroids.

Recently monoclonal antibodies were developed against IL-5 (mepolizumab and reslizumab) and clinical trials showed a moderate effect.[29,30] This limited effect is not surprising given the multiple pathways involved in the pathogenesis of the disease.

New diagnostic methods and improved knowledge of the pathogenic mechanisms taking place below the epithelial layer of the oesophagus may help us to better understand this emerging disease and provide better therapeutic tools to control it.

The long-term prognosis of paediatric patients with EoE has not been clearly established yet. In adult symptomatic patients there is an increased risk of stenosis, which may also occur in untreated children. At present, there is no clear indication that the risk of malignancy is increased but careful follow up of patients and patient registries may bring new information about this emerging condition.

References

1. Soon IS, Butzner JD, Kaplan GG, Debruyn JC. Incidence and prevalence of eosinophilic esophagitis in children. J Pediatr Gastroenterol Nutr 2013; 57(1): 72–80.
2. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011; 128(1): 3–20.
3. Papadopoulou A, Koletzko S, Heuschkel R, Dias JA, Allen KJ, Murch S et al. Management Guidelines of Eosinophilic Esophagitis (EoE) in Childhood: A Position Paper of the Eosinophilic Esophagitis Working Group and the Gastroenterology Committee of ESPGHAN. J Pediatr Gastroenterol Nutr. In press 2013.
4. Dohil R, Newbury RO, Aceves S. Transient PPI responsive esophageal eosinophilia may be a clinical sub-phenotype of pediatric eosinophilic esophagitis. Dig Dis Sci 2012; 57(5): 1413–1419.
5. Dellon ES, Gibbs WB, Fritchie KJ, Rubinas TC, Wilson LA, Woosley JT et al. Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2009; 7(12): 1305–1313.
6. Saffari H, Peterson KA, Fang JC, Teman C, Gleich GJ, Pease LF, III. Patchy eosinophil distributions in an esophagectomy specimen from a patient with eosinophilic esophagitis: Implications for endoscopic biopsy. J Allergy Clin Immunol 2012; 130(3): 798–800.
7. Murch S, Allen KJ, Chong SKF, Dias JA, Papadopoulou A, ESPGHAN WG on EoE. Potential for

improving therapy and defining new research targets in eosinophilic oesophagitis based on understanding of immunopathogenesis. J Pediatr Gastroenterol Nutr. In press 2013.
8. Kirsch R, Bokhary R, Marcon MA, Cutz E. Activated mucosal mast cells differentiate eosinophilic (allergic) esophagitis from gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr 2007; 44(1): 20–26.
9. Aceves SS, Newbury RO, Dohil R, Schwimmer J, Bastian JF. Distinguishing eosinophilic esophagitis in pediatric patients: clinical, endoscopic, and histologic features of an emerging disorder. J Clin Gastroenterol 2007; 41(3): 252–256.
10. Persad R, Huynh HQ, Hao L, Ha JR, Sergi C, Srivastava R et al. Angiogenic remodeling in pediatric EoE is associated with increased levels of VEGF-A, angiogenin, IL-8, and activation of the TNF-alpha-NFkappaB pathway. J Pediatr Gastroenterol Nutr 2012; 55(3): 251–260.
11. Fox VL, Nurko S, Teitelbaum JE, Badizadegan K, Furuta GT. High-resolution EUS in children with eosinophilic "allergic" esophagitis. Gastrointest Endosc 2003; 57(1): 30–36.
12. Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clin Gastroenterol Hepatol 2006; 4(9): 1097–1102.
13. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol 2003; 98(4): 777–782.
14. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. J Clin Invest 2001; 107(1): 83–90.
15. Magnusson J, Lin XP, Dahlman-Hoglund A, Hanson LL, Telemo E, Magnusson O et al. Seasonal intestinal inflammation in patients with birch pollen allergy. J Allergy Clin Immunol 2003; 112(1): 45–50.
16. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. J Allergy Clin Immunol 2002; 109(2): 363–368.
17. van Rhijn BD, Verheij J, Smout AJ, Bredenoord AJ. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. Neurogastroenterol Motil 2013; 25(1): 47–52.
18. Straumann A, Aceves SS, Blanchard C, Collins MH, Furuta GT, Hirano I et al. Pediatric and adult eosinophilic esophagitis: similarities and differences. Allergy 2012; 67(4): 477–490.
19. Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol 2012; 130(2): 461–467.
20. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology 2007; 133(4): 1342–1363.
21. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology 1995; 109(5): 1503–1512.
22. Henderson CJ, Abonia JP, King EC, Putnam PE, Collins MH, Franciosi JP et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. J Allergy Clin Immunol 2012; 129(6): 1570–1578.
23. Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. Ann Allergy Asthma Immunol 2005; 95(4): 336–343.
24. Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology 2012; 142(7): 1451–1459.
25. Aceves SS, Bastian JF, Newbury RO, Dohil R. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. Am J Gastroenterol 2007; 102(10): 2271–2279.
26. Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. Gastroenterology 2010; 139(2): 418–429.
27. Dellon ES, Sheikh A, Speck O, Woodward K, Whitlow AB, Hores JM et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. Gastroenterology 2012; 143(2): 321–324.
28. Straumann A, Conus S, Degen L, Frei C, Bussmann C, Beglinger C et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2011; 9(5): 400–409.
29. Assa'ad AH, Gupta SK, Collins MH, Thomson M, Heath AT, Smith DA et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterology 2011; 141(5): 1593–1604.
30. Spergel JM, Rothenberg ME, Collins MH, Furuta GT, Markowitz JE, Fuchs G, III et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol 2012; 129(2): 456–63, 463.