Medicinski podmladak

Medical Youth

Mini review article

EOSINOPHILIC ESOPHAGITIS

EOZINOFILNI EZOFAGITIS

Jovan Jevtić[1], Radmila Janković[1]

[1] Univerzitet u Beogradu, Medicinski fakultet, Institut za patologiju „Dr Đorđe Joannović“, Beograd, Srbija

Correspondence: lordstark90@gmail.com

Abstract

Eosinophilic esophagitis (EoE) is an inflammatory disorder characterized by intraepithelial eosinophilic infiltration followed by esophageal dysfunction. Pathophysiological mechanism of EoE is still not well understood, with several factors that may contribute, such as host immunity, environmental and genetic factors. Modern diagnostic for EoE should include: esophageal dysfunction, esophageal biopsy with at least 15 eosinophils per high power field and absence of other pathology characterized by increased number of eosinophils. The most common presenting symptoms in adults are dysphagia, heartburn, food impaction and chest pain. Children are usually presented with nausea and vomiting, anorexia, heartburn, regurgitation, chest burn and abdominal pain. Endoscopically, patients with EoE are characterized by longitudinal furrows (vertical lines, darker than surrounding mucosa), esophageal trachealization (numerous transversal rings, as in trachea), exudate (white plaques), edema (decreased mucosal vascularization), strictures and crepe-paper mucosa (mucosal friability and tearing during endoscopy). Histological features of EoE could be separated into major and minor criteria. Major criteria include: intraepithelial infiltration by eosinophils (>15 eosinophils/HPF), eosinophilic microabscesses (≥4 eosinophils in a collection), eosinophils occupying outer layer of the squamous epithelium, epithelial sloughing and eosinophil degranulation. Minor criteria include: basal zone hyperplasia, lengthening of the epithelial papillae, intracellular edema and subepithelial fibrosis. In order to set adequate diagnosis, all other conditions related to increased number of eosinophils should be excluded. The most common and the most important differential is gastroesophageal reflux disease (GERD). Treatment of the EoE encompasses: proton pump inhibitors (PPI), corticosteroids (topical and systemic), elimination diet and esophageal dilation.

Keywords:
eosinophilic esophagitis,
eosinophils,
GERD,
pathology

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Sažetak

Eozinofilni ezofagitis (EoE) je inflamatorno stanje koje se karakteriše intraepitelnom eozinofilnom infiltracijom praćenom disfunkcijom jednjaka. Patofiziološki mehanizam EoE još nije dobro poznat. Postoji nekoliko faktora koji učestvuju u patogenezi, kao što su imunitet domaćina, faktori životne sredine i genetski faktori. Savremena dijagnostika EoE treba da obuhvati: kliničke manifestacije (disfunkcija jednjaka), biopsiju jednjaka sa najmanje 15 eozinofila po polju velikog uveličanja i odsustvo druge patologije koju karakteriše povećan broj eozinofila. Najčešći simptomi kod odraslih su disfagija, gorušica, zastoj hrane u jednjaku i bol u grudima. Kod dece se obično manifestuje mučninom i povraćanjem, anoreksijom, gorušicom, regurgitacijom, pečenjem u grudima i bolovima u stomaku. Endoskopski, pacijente sa EoE karakterišu uzdužne brazde (vertikalne linije, tamnije od okolne sluzokože), trahealizacija jednjaka (brojni transverzalni prstenovi, kao kod traheje), eksudat (beli plakovi), edem (smanjena vaskularizacija sluzokože), strikture i „*crepe-paper*" sluzokoža (krhkost sluzokože i kidanje tokom endoskopije). Histološke karakteristike EoE mogu se podeliti na major i minor kriterijume. Major kriterijumi uključuju: intraepitelnu infiltraciju eozinofilima (>15 eozinofila/HPF), eozinofilne mikroapscese (≥ 4 eozinofila u kolekciji), eozinofile koji zauzimaju spoljašnji sloj skvamoznog epitela, ljuštenje epitela i degranulaciju eozinofila. Minor kriterijumi uključuju: hiperplaziju bazalne zone epitela jednjaka, produženje epitelnih papila, intracelularni edem i subepitelnu fibrozu. Da bi se postavila adekvatna dijagnoza, treba isključiti sva ostala stanja povezana sa povećanim brojem eozinofila. Najčešća i najvažnija diferencijalna dijagnoza je gastroezofagusna refluksna bolest (GERB). Lečenje EoE obuhvata: inhibitore protonske pumpe (PPI), kortikosteroide (lokalne i sistemske), eliminacionu dijetu i dilataciju jednjaka.

Ključne reči:
eozinofilni ezofagitis,
eozinofili,
GERB,
patologija

Introduction

Eosinophilic esophagitis (EoE) is an inflammatory disorder characterized by intraepithelial eosinophilic infiltration followed by esophageal dysfunction. It affects both adults and children with prevalence of 7.0/100.000/year and 5.1/100.000/year respectively (1).

Pathogenesis of eosinophilic esophagitis

Pathophysiological mechanism of EoE is still not well understood, there are several factors that may contribute, such as host immunity, environmental and genetic factors. It is antigen driven condition mediated by adaptive immune system, T helper type 2 (Th2) lymphocytes involving interleukin (IL)-4, IL-5, IL-13 and chemoattractant eotaxin-3 (CCL26). In addition to its role in attraction of the eosinophils, some of the cytokines (IL-5, IL-13) contribute to tissue remodeling of the esophagus (2).

Diagnosis of eosinophilic esophagitis

Based on A Working Group on proton pump inhibitors responsive esophageal eosinophilia (PPI-REE) (AGREE) conference from 2018, modern diagnostic for EoE should include: 1) esophageal dysfunction; 2) esophageal biopsy with at least 15 eosinophils per high power field and 3) absence of other pathology characterized by increased number of eosinophils (3).

Diagnostic procedure for EoE starts with anamnesis and presenting symptoms. It affects all age groups, and symptoms may be quite different between children and adults (4). The most common presenting symptoms in adults are dysphagia, heartburn, food impaction and chest pain (5-7). Children are usually presented with nausea and vomiting, anorexia, heartburn, regurgitation, chest burn and abdominal pain (8). Due to aforementioned symptoms and struggling with swallowing, patients with EoE develop different strategies in order to facilitate swallowing, such as prolonged chewing, drinking water after every bite, picking and avoiding specific food (9). Atopy related comorbidities are usually associated with EoE, with prevalence from 20% to 80% (10). Prevalence of asthma, allergic rhinitis and other allergic conditions are much higher in children with EoE compared to children in general population (11). Also, some connective tissue diseases characterized by hypermobility can be associated with EoE, especially Ehlers-Danlos syndrome, joint hypermobility syndrome and Marfan like syndrome (12). Laboratory analysis showed increased level of immunoglobulin E and periphery blood eosinophilia, especially in pediatric population (13).

Endoscopy with biopsy sampling for histopathological analysis is mandatory for a diagnosis of EoE. Endoscopically, patients with EoE are characterized by longitudinal furrows (vertical lines, darker than surrounding mucosa), esophageal trachealization (numerous transversal rings, as in trachea), exudate (white plaques), edema (decreased mucosal vascularization), strictures and crepe-paper mucosa (mucosal friability and tearing during endoscopy (**table 1**) (**figure 1**) (14).

Those aforementioned endoscopic features in patients with EoE are not specific and could be related to

other esophageal pathology as well (15). It is recommended to take six samples of the esophagus during endoscopy, biopsying proximal and distal part of the esophagus (16, 17). Up to 25% of patients with EoE may have normal endoscopic features, especially children (18).

Histological features of EoE could be separated into major and minor criteria. Major criteria include: intraepithelial infiltration by eosinophils (> 15 eosinophils/HPF), eosinophilic microabscesses (≥ 4 eosinophils in a collection), eosinophils occupying outer layer of the squamous epithelium, epithelial sloughing and eosinophil degranulation (**figure 2**) (**figure 3**) (19). Minor criteria include: basal zone hyperplasia, lengthening of the epithelial papillae, intracellular edema and subepithelial fibrosis (**table 2**) (**figure 4**) (19).

This is not the only condition characterized by

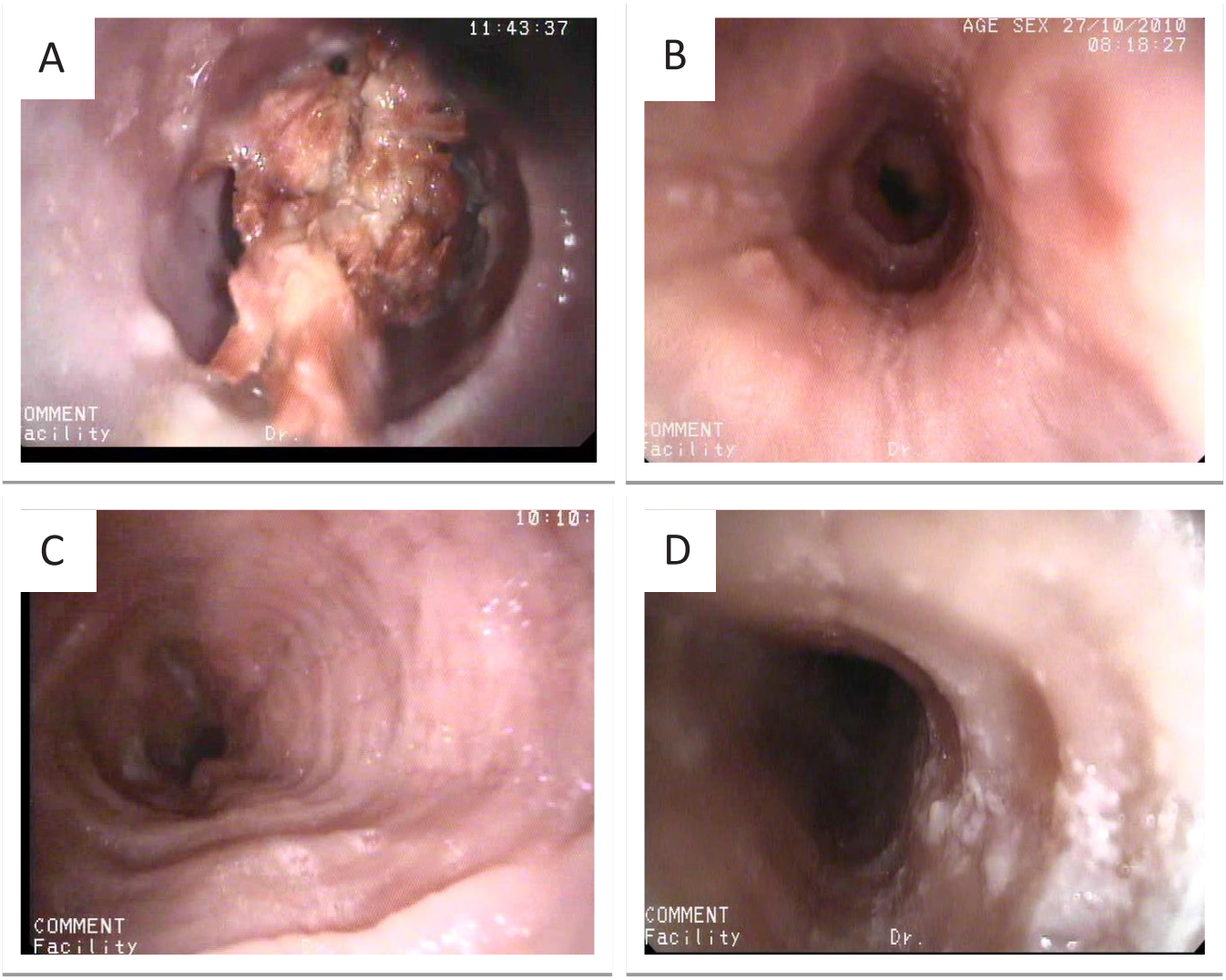

Figure 1. A - Food impaction; B - Longitudinal furrows; C - Esophageal trachealization; D - White exudate.

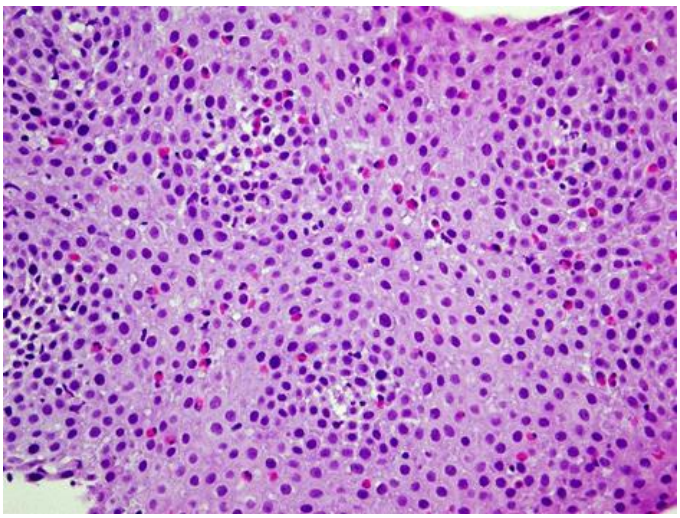

Figure 2. Intraepithelial infiltration by eosinophils.

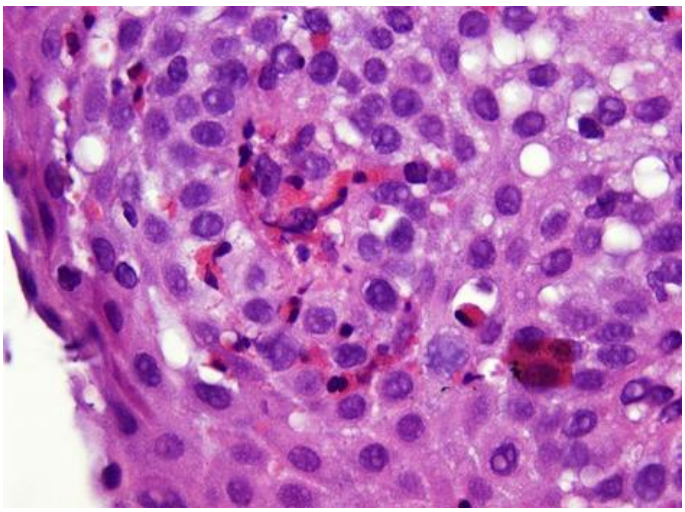

Figure 3. Eosinophlic microabscess.

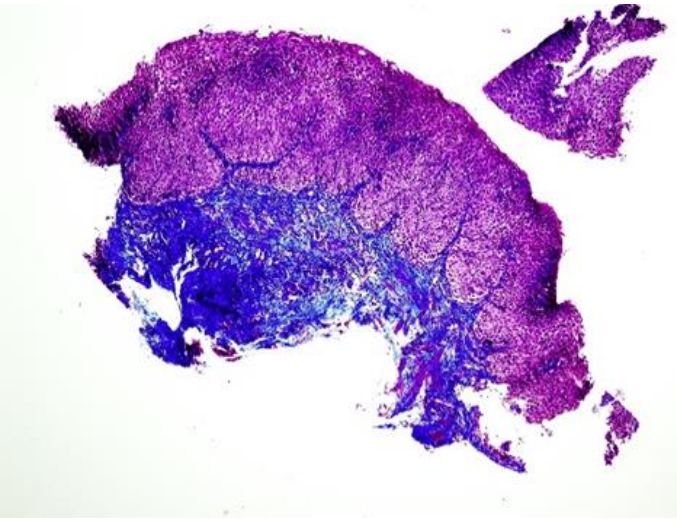

Figure 4. Subepithelial fibrosis (Masson trichrome stain).

Table 1. Endoscopic features of eosinophilic esophagitis

1. Longitudinal furrows
2. Esophageal trachealization
3. Exudate
4. Edema
5. Strictures
6. Crepe-paper mucosa

Table 2. Major and minor pathohistological diagnostic criteria for eosinophilic esophagitis

Major
1. Intraepithelial infiltration by eosinophils (> 15/HPF)
2. Eosinophilic microabscesses (≥ 4 eosinophils in a collection)
3. Eosinophils occupying outer layer of the squamous epithelium
4. Epithelial sloughing
5. Eosinophil degranulation
Minor
1. Basal zone hyperplasia
2. Lengthening of the epithelial papillae
3. Intracellular edema
4. Subepithelial fibrosis

Table 3. Differential diagnosis of eosinophilic esophagitis

1. Gastroesophageal reflux disease
2. Pill esophagitis
3. Hypereosinophilic syndrome
4. Drug hypersensitivity
5. Crohn's disease
6. Achalasia
7. Infections
8. Connective tissue diseases

eosinophilic infiltration. In order to set adequate diagnosis, all other conditions related to increased number of eosinophils should be excluded. The most common and the most important differential is gastroesophageal reflux disease (GERD). It is of great importance to bear in mind that EoE affects all parts of the esophagus (proximal, middle and distal) in contrast to GERD, usually affecting lower third of the esophagus since numerous other histological features overlap between those two entities. Other less common conditions related to increased eosinophilia are the following: pill esophagitis, hypereosinophilic syndrome, drug hypersensitivity, Crohn's disease, achalasia, infections, connective tissue diseases (**table 3**) (18, 20, 21).

Treatment of eosinophilic esophagitis

Treatment of the EoE encompasses: 1) proton pump inhibitors (PPI); 2) corticosteroids (topical and systemic); 3) elimination diet and 4) esophageal dilation.

The first line therapy for EoE is PPI who achieve their effect on EoE independently of gastric acid secretion. By reducing inflammatory cytokine expression, the PPI have antioxidative and immunosuppressive effect (22). There is no difference in efficacy between different PPIs (23). Therapeutic goal in patient with EoE is to decrease total number of eosinophils per HPF (< 15) (Muir, 2021). Study of Rank and collaborators showed efficacy of PPI administration represented by decreased number of eosinophils per HPF (< 15) in 41.7% patients with EoE (24).

Topical steroids are a potent treatment option showing efficacy in 80% of patients. In case of topical steroids treatment failure, systemic steroids may be applied. Considering numeorus side effects, systemic steroids should be applied solely in severe cases such as severe dysphagia and prolonged usage is not recommended (20).

Elimination diet is based on three principles: 1) elemental diet (ED); avoiding intake of intact proteins (ingestion of amino acids); 2) empirically based diet and 3) diet based on allergic tests.

Elemental diet (ED) is a balanced liquid form of nutrition composed of amino acids, fats, sugar, vitamins etc. Rank and collaborators showed huge clinical improvement and decreasing in number of eosinophils (< 15) in 93.6% of patients underwent elemental diet (24). Despite its efficacy, this way of treatment has numeorus disadvantages. It is expensive, usually not of satisfactory taste and requires huge amount of formula to accomplish daily need (25).

Empirically based diet represents restriction of the most common food associated with EoE such as dairy, egg, legumes, wheat, nuts and seafood (26). It is less effective than ED showing improvement in 67.9% patients with EoE, but it is more tolerable and some of the food can be returned to nutrition (24).

Diet based on allergic tests is not standardized and

it is the least effective, showing improvement in 50.8% patients with EoE.

Endoscopic dilation showed great clinical improvement in 95% of patients with strictures due to EoE. It is relatively safe procedure with low rate of complications (27).

Conclusion

Although a rare condition, the incidence of EoE is increasing. Today, EoE represents one of the most important factors of the esophageal morbidity. Considering clinical presentation it is of great importance to diagnose and treat EoE in order to improve quality of life and prevent complications.

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