



An enigma of eosinophilic esophagitis

Enigma eozinofilnog ezofagitisa

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Abstract

Introduction. Eosinophilic esophagitis is a chronic immunogenic-antigen mediated disease of the esophagus, characterized by symptoms related to esophagus dysfunction, histologically defined by over 15 eosinophil counts seen in high-power microscopic field, without gastroesophageal reflux disease. In adults, the most common clinical manifestations are dysphagia, reflux, chest pain, regurgitation and bolus impaction. **Case report.** We presented the case of a female patient, hospitalized for a serious form of pancreatitis with complications, which required artificial ventilation and enteral feeding, after the initial esophagoscopy verified reflux esophagitis. Further treatment cured the primary illness, and peroral feeding was reintroduced. However, dysphagia with regurgitation occurred, and endoscopic and radiological tests verified esophagus stenosis, which histopathologically corresponded to erosive esophagitis. Two months of treatment by a double dosage of proton pump inhibitors led to no regression of disorders, and the repeated biopsies from the stenotic segments resulted in over 30 eosinophil counts in the high-power microscopic field, which histologically corresponds to eosinophilic esophagitis. Subsequent therapy included fluticasone 880 µg/day orally for a period of eight weeks, which led to complete regression of disorders, and endoscopic and histopathologic remission. **Conclusion.** In case of irresponsiveness to the conventional therapy by proton pump inhibitors, repeated esophagoscopy and histopathological analyses of esophagus mucosa biopsy can point to the diagnosis of eosinophilic esophagitis, and a good therapeutic response to topical corticosteroids can be regarded as the clinical confirmation of the diagnosis.

Key words:

eosinophilic esophagitis; diagnosis, differential; endoscopy, gastrointestinal; esophageal stenosis; biopsy; histological techniques; gastroesophageal reflux; treatment outcome.

Apstrakt

Uvod. Eozinofilni ezofagitis je hronična imunogena antigenom posredovana bolest jednjaka, koju karakterišu simptomi povezani sa disfunkcijom jednjaka, a histološki se definiše sa više od 15 eozinofila viđenih u mikroskopskom vidnom polju velikog povećanja, uz odsustvo gastroezofagealne refluksne bolesti. Kod odraslih osoba, najčešće kliničke manifestacije su disfagija, refluksni simptomi, retrosternalni bol, regurgitacija i zaglavljivanje (*impaction*) bolusa hrane. **Prikaz bolesnika.** Prikazana je bolesnica, hospitalizovana zbog teškog oblika pankreatitisa sa komplikacijama, koje su zahtevale veštačku ventilaciju i enteralnu ishranu putem nazojunalne sonde, kojoj je inicijalnom ezofagoskopijom verifikovan refluksni ezofagitis. U daljem toku, osnovno oboljenje je izlečeno i uvedena je peroralna ishrana. Međutim, došlo je do disfagije sa regurgitacijom, a endoskopski i radiološki verifikovana je stenoza jednjaka. Patohistološkom analizom utvrđeno je da se radilo o erozivnom ezofagitisu. Nakon dva meseca lečenja duplom dozom inhibitora protonске pumpe nije došlo do poboljšanja. Ponovljenim biopsijama sa stenotičnog segmenta prebrojano je preko 30 eozinofila u mikroskopskom vidnom polju velikog povećanja, što histološki odgovara eozinofilnom ezofagitisu. U terapiju je uveden flutikazon 880 µg dnevno oralno, u trajanju od osam nedelja, nakon čega je došlo do potpune regresije tegoba, kao i endoskopske i patohistološke remisije. **Zaključak.** U slučaju izostanka odgovora na konvencionalnu terapiju inhibitorima protonске pumpe, ponavljane ezofagoskopije i patohistološke analize biopata sluznice jednjaka mogu usmeriti dijagnozu u pravcu eozinofilnog ezofagitisa, a dobar terapijski odgovor na kortikosteroide za lokalnu primenu može se smatrati kliničkom potvrdom dijagnoze.

Ključne reči:

ezofagitis, eozinofilni; dijagnoza, diferencijalna; endoskopija, gastrointestinalna; jednjak, stenoza; biopsija; histološke tehnike; gastroezofagusni refluks; lečenje, ishod.

Introduction

Eosinophilic esophagitis (EoE) is a chronic immunogenic/antigen-mediated disease of the esophagus, clinically characterized by the symptoms of esophagus dysfunction, and histologically as predominantly eosinophil inflammatory infiltration, without gastroesophageal reflux disease (GERD)¹. Due to its clinical and pathophysiological features, it is often referred to as asthma of the esophagus in the literature². The precise etiology and pathophysiology of the disease is not entirely known, but it is assumed to be an allergic (Th2 mediated) disease. In healthy persons, due to constant exposure to foods, allergens and pathogens, eosinophils, which have protective function, are normally found within the whole digestive tract, except in the esophagus³. In EoE, Th2 lymphocytes mediated by IL-5, IL-13 and eotaxin 13 mobilize eosinophils in the mucosa of the esophagus. The activated eosinophils secrete proinflammatory and profibrotic mediators, causing damage to the local tissue and attracting other inflammatory cells (mastocytes and fibroblasts), thus increasing the inflammatory response and leading to the remodeling of the esophagus⁴. Histopathologically, EoE is defined by > 15 eosinophils seen in the high-power microscopic field (HPF) in at least one biopsy sample^{1,5}. The prevalence is as high as in 50 persons *per* 100,000 in some parts of the world; the disease usually affects males and is diagnosed between the ages 32 and 52. In adults, the most frequent clinical manifestations are dysphagia, reflux symptoms, retrosternal pain, regurgitation and bolus impaction, while the most common endoscopic findings include linear furrows, whitish exudate, vulnerable mucosa and fibrostenotic changes in the form of rings, strictures and stenosis of the esophagus^{1,2}. Besides the empirical treatment with the proton pump inhibitor (IPP), EoE is also treated with diet (elementary and elimination); medications (corticosteroids, immunomodulators, biological treatment); endoscopic dilatation (in esophageal strictures and stenosis, in cases of unsuccessful application of the above mentioned therapeutic modalities)^{6,7}.

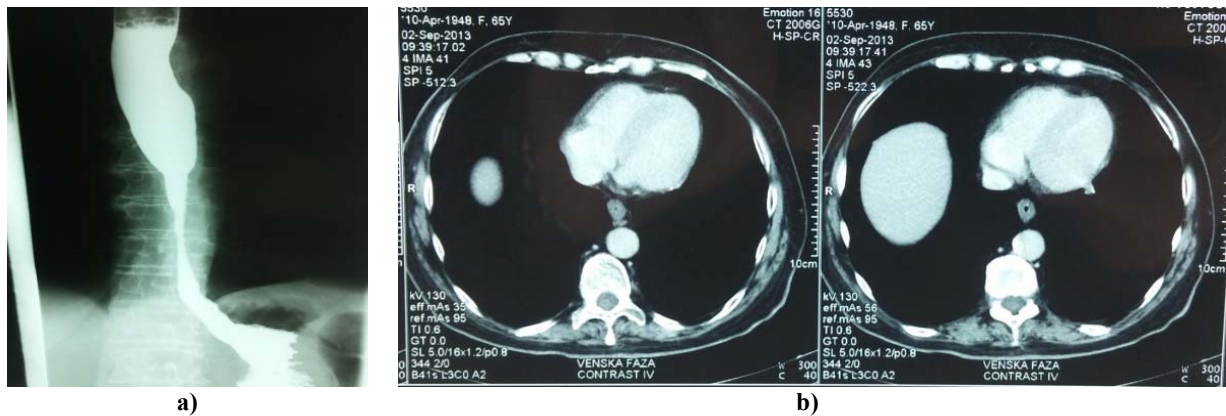
Case report

A 65-year-old female patient was hospitalized on June 17, 2013 at the Clinical Center of Vojvodina for acute biliary

pancreatitis. The patient reported previous history of type 2 diabetes mellitus and hypertension, and denied any allergic/atopic reactions and hazardous habits. Due to deteriorated respiration on the second day of hospitalization noninvasive ventilation was applied, and on the day 4 a nasojejunal triple lumen probe (NJS) was applied for the purpose of enteral feeding, after the first endoscopic examination confirmed the normal diameter of esophagus with no pathological changes in the mucosa. On the day 6, due to progressive deterioration the patient was intubated for controlled mechanical lung ventilation. On the same day the NJS was temporarily removed. On the day 9 the NJS was applied again, after the second endoscopy showed a number of erosive changes in the esophagus and gastric cardia, so IPP (pantoprazol 40 mg/12 h) was introduced in the therapy. Three weeks after hospitalization the NJS was removed, full liquid diet was introduced *per os*, and in the further course of the treatment acute necrotic pancreatitis and accompanying complications were healed. In the seventh week of hospitalization the patient suffered from dysphagia followed by regurgitation of solid foods. The third endoscopic examination at the 25th cm from the incisive revealed gradual stricture of the esophagus lumen up to the 32nd cm, where the lumen was circularly narrowed to 6 mm, aperistaltic and impenetrable for the endoscope, and proximally to the stenotic segment the epithelium was contact vulnerable (Figure 1). Biopsies taken for histopathology (HP), stained with the standard Hematoxylin and Eosin (HE), Periodic acid-Schiff (PAS) and Giemsa methods, consisted of necrotic detritus with an abundance of cells of inflammatory infiltrations built of lymphocytes, plasma cells and neutrophil granulocytes, containing desquamated squamous cells. The Roentgen examination (RTG) of the esophagus passage revealed a long benign stenosis of the distal esophagus, with mild dilatation of proximal parts of the thoracic esophagus, with sufficient passage with liquid barium (Figure 2a), while computed tomography (CT) of the thorax and abdomen revealed circular thickening of the esophagus wall 6 mm in diameter in the distal third (Figure 2b). Serological tests on cytomegalovirus (CMV) and herpes simplex virus (HSV) IgM and IgG excluded viral etiology of esophagitis. Three weeks following the onset of dysphagic disorders, and in the tenth week of hospitalization, the fourth upper endoscopy was performed, revealing unchanged morphological results. New



Fig. 1 – Esophagoscopy at the 25th cm from the incisive revealed gradual stricture of the esophagus lumen up to the 32nd cm, where the lumen is circularly narrowed to 6 mm, and the epithelium is contact vulnerable.



**Fig. 2 – a) X-ray of the esophagus passage, revealed a long benign stenosis of the distal esophagus, with mild dilatation of proximal parts of the thoracic esophagus;
b) Chest computed tomography (CT) revealed circular thickening of the esophagus wall 6 mm in diameter in the distal third.**

biopsies were taken for HP, consisting of the pieces of necrotic and granular tissue originating from ulceration, pervaded by a number of neutrophil granulocytes, which corresponds to reflux esophagitis. Eleven weeks after hospitalization, following clinical, laboratory and radiological regression of necrotic acute pancreatitis, the patient was released from the hospital for home care, with recommendation of full liquid diet and double dosage of IPP. Ten weeks after the onset of dysphagic disorders, and 14 weeks after the introduction of IPP, the fifth upper endoscopy was performed, morphologically unchanged in comparison to the previous one, and the biopsies taken for HP analysis showed pieces of granulation and necrotic tissue originating from ulceration with the areas of fresh bleeding, with a lesser piece of tissue, pervaded by mixed inflammatory infiltrate abundant in eosinophilic granulocytes (over 30/HPF), which corresponded to

EoE (Figure 3). Alongside IPP, topical corticosteroid fluticasone was introduced with the dosage of 880 µg/day, divided into two doses for 8 weeks, together with elimination diet. Six weeks after the introduction of topical corticosteroid therapy, the patient came to control examination, denying dysphagia or regurgitation and stating to be tolerant to solid foods. Five months after the diagnosis of esophagus stenosis, sixth upper endoscopy was performed, showing passable esophagus of normal morphology and mucosa (Figure 4). Ten months after the onset of dysphagia, and nine months after the introduction of topical corticosteroid in the therapy for the duration of two months, the seventh endoscopy was performed, showing normal morphological results of the esophagus, stomach and duodenum, while the biopsies of the esophagus taken for HP analysis had no elements of eosinophilic esophagitis, erosions or ulceration (Figure 5).

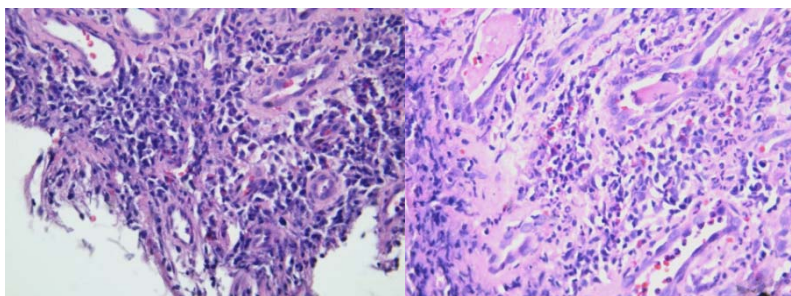


Fig. 3 – Piece of tissue, pervaded by mixed inflammatory infiltrate abundant in eosinophilic granulocytes (over 30/high-power microscopic field), which corresponds to eosinophilic esophagitis (HE, ×400).



Fig. 4 – Esophagoscopy 5 months after the diagnosis of esophagus stenosis, and 2 months after the therapy, showing the passable esophagus of normal morphology and mucosa.

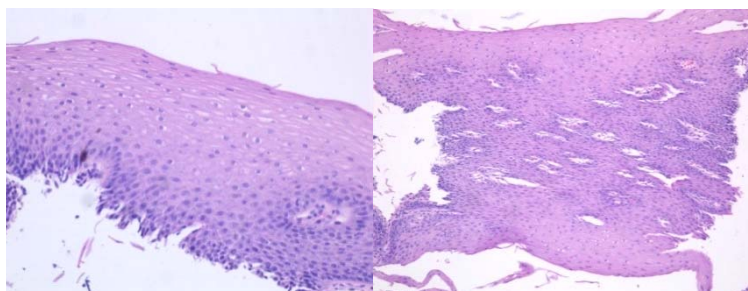


Fig. 5 – Histopathology (HP) analysis 2 months after the therapy, showing no elements of eosinophilic esophagitis, erosions or ulceration (HE, ×200).

A year after the onset of dysphagic disorder the patient was in good general condition, without dysphagia, tolerant to liquid, full liquid and solid foods. Pancreatitis was entirely cured and elective cholecystectomy planned.

Discussion

We presented the case of a female patient with esophageal clinical symptomatology, with chronologically different endoscopic and pathohistological changes of the esophagus mucosa, with the final diagnosis of EoE and excellent response to the application of topical corticosteroids. Following the consensus (FIGERS, 2007), EoE is a clinical-histological entity that excludes GERD as the cause of esophageal eosinophilia, either for the lack of response to therapies involving high dosage of IPP or the negative results of pH-matter^{5, 8}. However, a complex interrelation between EoE, GERD and esophageal eosinophilia has been recognized. In some patients both EoE and GERD have been found, described as the entity of esophageal eosinophilia responsive to the IPP therapy (PPI-REE)^{5, 8}. GERD may lead to esophageal eosinophilia, which is histologically most commonly characterized by counts lower than 10 eosinophils in HPF. Patients with GERD, not responsive to IPP therapy are regarded as resistant cases. A possible reason for GERD resistance could be EoE³. The efficacy of IPP in curing some cases of EoE is well-known, as well as the potential role of hydrochloric acid in the pathogenesis of EoE⁶. However, although there is overlapping between these two diseases, the interrelation between EoE and GERD remains controversial and is a motivation for further research. In the patient presented in this paper, the etiology of EoE is not entirely clear. Although allergologic tests were not performed, it cannot be positively claimed that food is the cause of EoE, since she received hypoallergenic enteral feeding while in the critical condition. Nutritional allergens, especially those from soya, milk, eggs, cereals, nuts and seafoods are a far more common cause of EoE in pediatric age⁹. Aeroallergens, as another possible cause of EoE, are less probable in the areas of intensive care units, as well as in the conditions of artificial ventilation, although they are not negligible. Attention should be paid to *Aspergillus*, as a potential aeroallergen that can be found in ventilation systems. It has been shown in animal and human research studies that this fungus may cause the infiltration of the esophagus with eosinophils¹⁰⁻¹². In the case presented

here the first endoscopic examinations revealed reflux esophagitis, yet the application of the full dosage of IPP led to the esophageal stenosis accompanied with dysphagia, which remained irresponsive to the extended double dosage of IPP for over two months. In the study by Foroutan et al.¹³ EoE is described in patients with refractory GERD, and it is concluded that out of 66 patients, 33.3% had endoscopic esophagitis, but that all of them had a previous history of atopy or allergy. Fujiwara et al.¹⁴ studied the endoscopic results resembling EoE in patients with erosive esophagitis, and they concluded that there were many overlapping and common features of the two diseases, which may point to common pathogenic mechanisms. The question that arises here is whether the HP result in this case is isolated located eosinophilia, caused by GERD and reflux of hydrochloric acid above the esophagogastric (EG) junction. Abe et al.¹⁵ describe the cases of isolated esophageal eosinophilia, in 90% above the EG juncture, which is exposed to acid reflux, which indicates that isolated EoE might be a subtype of GERD. Since in the patient presented here there was no clinical nor endoscopic improvement at double dosage and extended therapy with IPP, it was probably not a case of PPI-responsive esophageal eosinophilia. Lastly, the extended usage of NJS should not be disregarded, which could have been another potential cause of esophagitis, eosinophil infiltration and esophagus stenosis. Still, this possibility is less likely, considering the fact that modern feeding probes are made of hypoallergenic materials based on silicon or polyurethane. No similar cases have been reported in the literature.

Conclusion

The patient presented in this paper leads to the conclusion that despite the latest findings, eosinophilic infiltration of the esophagus is still an intriguing and complex clinical problem. Although there are common features of eosinophilic esophagitis and gastroesophageal reflux disease, their interrelation remains controversial. In case of irresponsiveness to the conventional therapy with proton pump inhibitors, repeated esophagoscopies and HP analyses of esophagus mucosa can direct the diagnosis towards eosinophilic esophagitis, and the good therapeutical response to topical corticosteroids can be taken as the clinical confirmation of the diagnosis.

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