Eozinofilni ezofagitis - potencijalna komplikacija sublingvalne terapije

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Eosinophilic esophagitis - a potential complication of sublingual immunotherapy

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Sažetak*

Uvod. Eozinofilni ezofagitis (EoE) predstavlja hroničnu, lokalnu imunološki posredovanu bolest sa simptomima disfunkcije jednjaka i histološkim znacima zapaljenja u kome prevlađuju eozinofili i zahteva trenutnu endoskopiju. Muški pol je glavni faktor rizika.

Prikaz slučaja. Predstavljamo slučaj pacijenta starog 25 godina sa istorijom alergijskog rinitisa, bronhijalne astme i povremenim smetnjama prilikom gutanja. Započeo je sublingvalnu imunoterapiju na polen ambrozije. Nakon šest nedelja osetio je žarenje u predelu jednjaka, bol u želucu i otežano gutanje. Šest dana nakon toga javio se Službi hitne medicinske pomoći jer mu se zalogaj čvrste hrane zaglavio u jednjaku. Histopatološki nalaz je ukazao na eozinofilni ezofagitis. Sublingvalna imunoterapija je obustavljena uz primenu terapije. Sada se dobro oseća.

Zaključak. Eozinofilni ezofagitis se najčešće dijagnostikuje u proleće i u jesen, 1-2 meseca nakon vrhunca sezone polena. Disfagija, odnosno otežano gutanje, bol u grudima, "lepljenje" hrane i opstrukcija su najčešći simptomi. Endoskopski nalazi su Šacijev (*Schatzki*) prsten, edemi, brazde, eksudat i striktore. Iz regiona sa endoskopskim abnormalnostima sluzokože uzima se šest biopsija; potreban nalaz za dijagnozu je infiltracija veća od 15 eozinofila u vidnom polju. Mogućnosti lečenja su inhibitori protonске pumpe - oralni disperzibilni prašak *budesonid* ili *flutikazon propionat*, eliminaciona dijeta i prekid započete sublingvalne imunoterapije. U proceni pacijenata sa disfagijom, porodični lekari treba da imaju na umu ovu osobenost pri nezi i praćenju pacijenata.

Ključne reči: Eozinofilni ezofagitis, disfagija, ukleštenje zalogaja, sublingvalna imunoterapija.

Abstract*

Introduction. Eosinophilic esophagitis (EoE) represents chronic, a local immune-mediated disease with symptoms of esophageal dysfunction and histologically eosinophil-predominant inflammation and requires immediate endoscopy. Male gender is a strong risk factor.

Case report. We presented a case of a 25-year-old young man with a history of allergic rhino-conjunctivitis, asthma, and intermittent severe feeding disturbance. The patient had begun sublingual immunotherapy therapy, containing specific soluble allergens for ambrosia. Six weeks after starting the ambrosia sublingual immunotherapy he developed burning epigastric pain, dysphagia, and odynophagia. Six days later, he was admitted to an emergency department due to choking on a solid of food. Esophageal histopathological findings were in favor of EoE. Sublingual immunotherapy was discontinued. He feels well now.

Conclusion. The majority of cases of Eosinophilic esophagitis are diagnosed in spring or fall, 1-2 months following the peak of pollen season. Dysphagia, chest pain, food sticking, and bolus obstruction are the most common symptoms. Endoscopic findings are Schatzki ring, edema, exudates, furrows, and strictures. Six biopsies should be taken from areas with endoscopic mucosal abnormalities, and infiltration of eosinophils (more than 15 eosinophils/HRI) (HRI – high resolution imaging) is necessary for the diagnosis confirmation. Treatment options are proton pump inhibitors – oral dispersible tablets of budesonide or fluticasone propionate, an elimination diet. Sublingual immunotherapy should be discontinued. Family physicians should be aware of this complication in evaluating patients with dysphagia.

Keywords: Eosinophilic esophagitis, dysphagia, food bolus impaction, sublingual immunotherapy.

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Uvod

Eozinofilne gastrointestinalne bolesti (EGID) se mogu podeliti na eozinofilni ezofagitis - *EoE* (*Eosinophilic esophagitis*) i eozinofilni gastroenteritis - *EGE* (*Eosinophilic gastroenteritis*), u zavisnosti od toga koji je deo gastrointestinalnog trakta zahvaćen. Za dijagnozu bolesti potrebno je prisustvo simptoma zahvaćenog dela gastrointestinalnog trakta i eozinofilna infiltracija¹.

Kod polovine obolelih pacijenata mogu se otkriti i druge bolesti alergijskog porekla. Abnormalnosti koje ukazuju na alergijsku bronhijalnu astmu - alergijski rinitis i atopijski dermatitis mogu se ustanoviti tokom fizikalnog pregleda. Povišene serumske koncentracije ukupnog imunoglobulina *E* (*IgE*) često se mogu utvrditi, dok *IgE* protiv specifičnih alergena nisu pronađene uprkos intenzivnim istraživanjima².

Prikaz slučaja

Predstavljamo klinički slučaj mladog pacijenta starog 25 godina sa istorijom alergijskog rinokonjunktivitisa, alergijske bronhijalne astme i povremenih problema sa gutanjem hrane u smislu osećaja da zalogaj hrane sporo silazi niz jednjak. Specifični serumski *IgE* imunoglobulini su prepoznali ambroziju, travu, raž, lešnik, brezu i hrast kao glavne alergene. Porodična anamneza je bila pozitivna na polensku groznicu. Pacijent je započeo sublingvalnu imunoterapiju (*SLIT*) na polen ambrozije, jer je najviši nivo *IgE* ukazao na potrebu desenzibilizacije upravo na ovaj alergen. Nakon šest nedelja *SLIT* terapije u rastućim dozama i koncentracijama razblaženja, počeo je da oseća epigastrični bol, teškoće pri gutanju, "pečenje" iza grudne kosti praćeno bolom. Nekoliko dana potom, pri mesnom obroku došlo je do začepjenja zalogaja čvrste hrane u jednjaku, osećao je bolove u grudima i neprijatnost, te je bio prinuđen da se javi lekaru u Službi hitne medicinske pomoći. Zaglavljani zalogaj hrane je endoskopskim putem uklonjen i pacijentu je odmah bilo lakše. Gornja ezofagoendoskopija je pokazala slivne beličaste ekodate i uzdužne crvene brazde u proksimalnom i distalnom delu jednjaka. U drugom endoskopskom aktu je urađeno šest biopsija istaknutih ezofagealnih lezija. Patohistološki nalaz je pokazao predominantno eozinofilnu infiltraciju sa 44 eozinofila u vidnom polju, što je govorilo u prilog eozinofilnom ezofagitisu. Pacijentu je propisan inhibitor protonске pumpe *pantoprazol* u dozi 40 mg dva puta dnevno, tokom 8 nedelja, snažan inhibitor želudačne kiseline, *flutikazon propionat* u spreju (500 µg dva puta dnevno) i dugoročnu eliminacionu dijetu. Imunoterapija je prekinuta. Nakon četiri nedelja kliničke tegobe su u potpunosti prestale. Kontrolna endoskopija, četiri meseca nakon obustavljene sublingvalne imunoterapije i sprovedenog lečenja, pokazala je normalan lokalni ezofagealni nalaz a biopsija ezofagealne sluzokože pokazala je manje od 5 eozinofila u vidnom polju. Pacijent nije mogao da završi započetu imunoterapiju zbog razvoja eozinofilnog ezofagiti-

Introduction

Eosinophilic gastrointestinal diseases (EGIDs) are divided into eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EGE), depending on the involved part of the gastrointestinal tract. Important factors for diagnosing EGIDs are the presence of symptoms, possibly originating from the involved part of the gastrointestinal tract and dense eosinophil infiltration¹.

Since half of the affected patients are also affected by other allergic diseases, such as bronchial asthma, allergic rhinitis, and atopic dermatitis they shouldn't be overlooked in physical examination. An elevated immunoglobulin E (IgE) serum concentration is also frequently observed while IgE against a specific allergen has not been found even in intensive studies².

Case report

We presented a case of a 25-year-old young man with a history of allergic rhino-conjunctivitis, asthma, and intermittent severe feeding disturbance. Specific serum IgE identified Ambrosia Artemisiifolia, grass, rye, hazelnut, birch alder, and oak as major allergens. His family history was significant for pollinosis. The patient had begun SLIT (sublingual immunotherapy), containing specific soluble allergens for ambrosia. Six weeks after starting ambrosia SLIT he developed burning epigastric pain, dysphagia, and odynophagia. Several days later, he was admitted to an emergency department because of food sticking, bolus obstruction, retrosternal chest discomfort, and pain. The food that was stuck in his esophagus was endoscopically removed and the patient was instantly relieved. Upper endoscopy showed confluent whitish exudates and longitudinal red furrows in the proximal and distal esophagus. In the second endoscopic act, 6 biopsies were taken from these lesions and they revealed a predominantly eosinophilic inflammation with a peak infiltration of 44 eosinophils/HRI. Esophageal histopathological findings were in favor of EoE. He was treated with proton pump inhibitor pantoprazole 40 mg twice daily, for 8 weeks, a potent acid inhibitor that was responsive in combination with fluticasone propionat spray (500 µg, twice daily), and a long-lasting elimination diet. Hence, SLIT was discontinued. Clinical and histological findings resolved 4 weeks after SLIT withdrawal. Normal endoscopy findings were observed 4 months after SLIT discontinuation and EoE therapy. Esophageal tissue biopsy showed no more than 5 eosinophils/HRI in the examined biopsy samples. The patient could not complete the SLIT protocol due to the development of EoE. Endoscopy and biopsy after 3 months revealed complete resolution of EoE. On 12 month follow-up, the patient remained free of any esophageal symptoms.

sa. Tokom 12 meseci njegovog praćenja zbog prikazane bolesti, nisu se ponovo ispoljili ezofagealni simptomi.

Diskusija

Eozinofilni ezofagitis je hronična imunološka i antigenom posredovana kliničko-patološka bolest. Dijagnostički kriterijumi zahtevaju odgovarajuće kliničke i histološke karakteristike. Lekari bi trebalo da razmotre eozinofilni ezofagitis kod adolescenata i odraslih kada se pacijenti najviše žale na otežano gutanje koje prijavljuje 60%-100% pacijenata³. Najspeцифичнији i indikativni simptom eozinofilnog ezofagitisa je osećaj "lepljenja" hrane tokom gutanja. Ponekad je to samo osećaj da se hrana sporo kreće niz jednjak, drugi pacijenti osećaju kao da se hrana neko vreme zadrži iza grudne kosti a kod nekih zadržavanje zalogaja traje dugo. Povremeno, prvi simptomi zahtevaju medicinsku pomoć kada se zalogaj zaglavi satima, te je pacijent primoran da se javi Odeljenju za hitne slučajeve.

Akutna opstrukcija bolusom hrane predstavlja uznemirujuću smetnju za pacijenta i zahteva trenutnu hitnu medicinsku pomoć. Nijedna određena terapija nije efikasna osim organizovanja endoskopije za uklanjanje zalogaja. To može uključivati ekstrakciju bolusa u manjim komadima, eventualno korišćenje tubusa za zaštitu disajnih puteva ili potiskivanje bolusa u stomak. Poslednju strategiju treba preduzeti nežno i u slučajevima gde lumen ezofagusa omogućava prolazak bolusa i endoskopa. Rizik od perforacije kod ovih postupaka postoji, ali su retki⁴.

Porodična istorija atopijskog poremećaja nalazi se kod više od 50% pacijenata sa *EoE*. Razjašnjavanje simptoma disfagije može biti osetljiv zadatak, jer su mnogi pacijenti godinama nesvesno razvijali kompenzatorna ponašanja u ishrani kako bi simptome sveli na minimum. Specifična ponašanja kao znak za ocenjivanje efikasnosti, uključuju sledeće: spori obroci, prekomerno žvakanje hrane, uzimanje obilne količine tečnosti nakon svakog zalogaja, ponovljeno gutanje radi olakšavanja prolaska zalogaja niz jednjak, izbegavanje hrane koju otežano guta ili drobljenje, odnosno izbegavanje tableta⁴.

Većina slučajeva *EoE* se dijagnostikuje u proleće ili ujesen, otprilike 1-2 meseca nakon vrhunca sezone polena. Patogeneza *EoE* tek treba da bude potpuno razjašnjena, uzimajući u obzir kako genetske faktore, tako i faktore okoline. Pokazalo se da pacijenti izloženi kućnim ljubimcima u ranom životnom dobu, koji žive u razvijenim zemljama ili rođeni carskim rezom, imaju veći rizik za razvoj *EoE*⁵.

Sublingvalna imunoterapija (SLIT)

Svetska zdravstvena organizacija je odobrila *SLIT* kao lek za alergijske poremećaje kod odraslih 1998. a za decu 2001⁶ godine. Eozinofilni gastrointestinalni poremećaji su potvrđeni kod nekih pacijenata koji su podvrgnuti *SLIT* terapiji⁷.

Discussion

Eosinophilic esophagitis is a chronic immune and antigen-mediated clinicopathologic disease. Diagnostic criteria require both the appropriate clinical and histologic features. Practitioners should consider EoE in adolescents and adults when the predominant complaint is esophageal dysphagia reported by 60% to 100% of patients³. The most specific and indicative symptom of eosinophilic esophagitis is a feeling of food sticking in the chest after swallowing. Sometimes it is just a feeling of the food moving slowly, in other patients it feels as if food sticks for a while, and in some, the sticking of a food bolus continues for a longer time. Occasionally, the first time symptom is brought to medical attention when a food bolus gets stuck for hours and the patient presents to the emergency department.

Acute food bolus obstruction is a highly distressing disturbance to a patient and requires immediate attendance at an emergency department. No particular therapy is effective other than arranging an endoscopy to remove the food bolus. This may involve the extraction of the bolus piecemeal, possibly using an over tube for airway protection, or pushing the bolus into the stomach. The latter strategy should only be undertaken gently and where there is a lumen available to allow passage of the bolus and the endoscope. There is a risk of perforation with these maneuvers but this has been rarely reported⁴.

A family history of an atopic disorder is found in more than 50% of patients with EoE. Elucidating symptoms of dysphagia can be a subtle task, as many patients have subconsciously developed compensatory eating behaviors over years to minimize symptoms. Specific behaviors to assess include the following: eating slowly, excessive food chewing, lubrication of food boluses or drinking a copious amount of liquid after each bite, repeated swallows to facilitate food bolus passage, avoidance of troublesome foods, or crushing or avoiding pills⁴.

The majority of cases of EoE are newly diagnosed in spring or fall, approximately 1-2 months following the peak of pollen seasons. The pathogenesis of EoE has yet to be completely elucidated, with both genetic and environmental factors considered to be involved. Patients with exposure to pet animals in early life, living in a developed country, or delivered by cesarean section were shown to have a higher risk for developing EoE⁵.

Sublingual immunotherapy (SLIT)

SLIT was approved by the World Health Organization as a treatment for allergic disorders in adults in 1998 and children in 2001⁶. Eosinophilic gastrointestinal disorders (EGIDs) have been documented in some of the patients undergoing SLIT⁷.

Mehanizam uključen u upalu jednjaka nakon *SLIT* terapije može biti povezan sa hroničnom antigenom izloženosti atopijskog pacijenta. Postepeno unošenje većih koncentracija alergena sa ciljem ublažavanja reakcije preosetljivosti, može prouzrokovati hroničnu stimulaciju imunog sistema⁸. Sistematski pregled literature sa meta-analizom 2014. godine pokazao je da je ukupna prevalencija *EoE* nakon sublingvalne imunoterapije čak 2,7%⁹.

Epidemiologija

Incidencija eozinofilnog ezofagitisa je povećana i trenutno varira od 1 do 20 novih slučajeva na 100.000 stanovnika godišnje. Muški pol je snažan faktor rizika za *EoE*, kod dece i kod odraslih.

Rinitis, bronhijalna astma i ekcem su znatno češći kod pacijenata sa *EoE* u poređenju sa opštom populacijom. Međutim, još uvek istraživanja nisu dokazala da atopija predisponira razvoju *EoE*. Eozinofilni ezofagitis predstavlja poseban oblik alergije na hranu. Dokazano je da su alergije na hranu posredovane imunoglobulinom *E* česte kod pacijenata sa *EoE*. Kod starije dece i odraslih sa *EoE* otežano gutanje čvrste hrane, zaglavljivanje hrane u jednjaku i bol u grudima koji nije direktno povezan sa gutanjem, najčešće su prijavljeni simptomi¹⁰.

Dijagnostika

Dijagnoza *EoE* se postavlja na osnovu simptoma, endoskopskih abnormalnosti i rezultata histološkog pregleda (Tabela 1). Najtipičniji simptomi koji su prijavile obolele osobe je disfagija, koju pacijenti izražavaju na različite načine, poput zaglavljivanja hrane, zadavljivanja, teškog gutanja, poprečivanja zalogaja i drugih sličnih¹¹.

Tabela 1. Uobičajene tegobe pacijenata

Table 1. Common patient symptoms

Uobičajeni simptomi pacijenata sa eozinofilnim ezofagitisom <i>Common symptoms associated with eosinophilic esophagitis</i>	
Adolescenti i odrasle osobe <i>Adolescents and Adults</i>	Deca <i>Children</i>
Otežano gutanje čvrste hrane/ <i>Solid food dysphagia</i> Začepjenja bolusima hrane/ <i>Food bolus impaction</i> Gorušica/ <i>Heartburn</i> Bol u grudima/ <i>Chest pain</i>	Mučnina i povraćanje/ <i>Nausea and vomiting</i> Regurgitacija/ <i>Regurgitation</i> Gorušica/ <i>Heartburn</i> Abdominalni bol/ <i>Abdominal pain</i> Bol u grudima/ <i>Chest pain</i> Anoreksija/odbijanje hrane/slabo napredovanje <i>Anorexia/feeding refusal/failure to thrive</i>

The mechanism engaged in esophageal inflammation following *SLIT* might be related to chronic antigenic exposure in an atopic patient. The gradual entrance of the culprit allergen while attenuating the immediate-type hypersensitivity reactions can cause a chronic stimulation of the immune system⁸. A systematic review with meta-analysis in 2014 overall found the prevalence of *EoE* after *SLIT* to be as high as 2.7%⁹.

Epidemiology

The incidence of eosinophilic esophagitis has increased and currently varies widely from 1 to 20 new cases per 100.000 inhabitants per year. Male gender is a strong risk factor for *EoE* both in children and adults. Rhinitis, asthma, and eczema are significantly more common in *EoE* patients compared to the general population. However, it remains unproven that atopy predisposes to *EoE*. Eosinophilic esophagitis is a distinct form of food allergy. Immunoglobulin *E* (*IgE*) mediated food allergies are common in *EoE* patients. In older children and adults with *EoE* solid food dysphagia, food impaction and non-swallowing associated chest pain are the most commonly reported symptoms¹⁰.

Diagnostic procedures

Diagnosis of *EoE* is made based on symptoms, endoscopic abnormalities, and histological examination results (Table 1). The most typical symptoms reported by affected individuals is dysphagia, expressed by a patient with a variety of wording, such as obstruction, impaction, difficult ingestion, oppression, and such¹¹.

Endoskopski nalazi su edem, prstenovi, eksudativne brazde, striktore, jednjak poput krep-papira (krhko tkivo) i jednjak uskog prečnika. Normalni nalazi na endoskopiji se retko javljaju. Šacijev (*Schatzki*) prsten je povremeno prisutan. Potrebno je uraditi šest biopsija sa više mesta bilo da se uzimaju iz područja sa jasnom endoskopskom abnormalnošću, ili dve na gornjem kraju, dve u sredini i dve na donjem kraju jednjaka. Endoskopski nalazi su korisni za dijagnozu. Pacijenti sa *EoE* pokazuju razne abnormalnosti koje se mogu otkriti standardnim endoskopskim pregledom belim svetlom sa uzdužnim brazdama, prstenovima i belim plakovima koji se najčešće primećuju, posebno kod mladića sa nekom vrstom alergije¹².

Za potvrdu dijagnoze *EoE* neophodna je histopatološka identifikacija guste eozinofilne infiltracije u ezofagealnim epitelnim slojevima sa više od 15 eozinofila u vidnom polju. Preporuka je uzeti najmanje 5 uzoraka biopsije za histološki pregled za analizu eozinofilne infiltracije^{13,14}. Ispituju se mogućnosti sakupljanja ezofagealnih epitelih fragmenata citološkim sunđerom i fotohemijском detekcijom eozinofilne peroksidaze *Raman* spektroskopijom, manje invazivnim histopatološkim metodima¹⁵.

Terapija

Izbor lečenja *EoE* pacijenata su inhibitori protonске kiseline, lokalna kortikosteroidna terapija i eliminaciona dijeta¹⁴. Odrasli pacijenti koji postižu kliničku i histološku remisiju terapijom inhibitorima protonске pumpe, deo su kontinuuma *EoE*, a ne odvojen entitet. Responderi i nonresponderi na ovu terapiju pokazuju preklapajuće fenotipske, genetske i mehaničke karakteristike¹⁰. Kortikosteroid lokalnog dejstva – *budesonide*, postao je dostupan pacijentima sa eozinofilnim ezofagitisom u obliku disperzione tablete koja se topi u ustima i uzima se nakon jela ili pića kako bi se zadržala na površini jednjaka. Optimalno vreme večernje doze je pred spavanje, nakon što je pacijent opraо zube i ne uzima više sredstava za ispiranje usta ili tečnost. Osoba koja spava manje proizvodi pljuvačku i ređe guta, što omogućava *budesonidu* mnogo duže delovanje na ezofagealnom epitelu, nego uzimanje tokom dana sa naknadnim pićem i obrocima¹⁶.

Koliko je autorima poznato, do sada takav oblik leka nije dostupan na srpskom tržištu, tako da se sa uspehom primenjuje oblik koji je predviđen za inhalacionu upotrebu.

Lečenje *EoE* se preporučuje i u ranim inflamatornim fazama ne samo zbog ublažavanja simptoma, već i zbog sprečavanja fibroze jednjaka. Prva opcija lečenja za *EoE* treba da bude primena inhibitora protonске pumpe, jer približno 60% slučajeva *EoE* može uspešno tako da se leči. Inhibitori protonске pumpe ublažavaju refluks iako nema dokaza da je refluks uključen u patogenezu eozinofilnog ezofagitisa, primećeno je poboljšanje kod nekih pacijenata. Suzbijanje želučane kiseline smanjuje vreme izlaganja kiselinu u krajnjem

Endoscopic findings are edema, rings, exudative furrows, strictures, crêpe paper esophagus (tissue fragility), and narrow caliber esophagus. Normal findings on endoscopy occur in the minority. *Schatzki* ring is occasionally present. Six biopsies should be performed from multiple sites, either taken from areas of clear endoscopic abnormality or two at the upper, two in the middle, and two at the lower end of the esophagus. Endoscopic findings are useful for diagnosis. Patients with *EoE* show various abnormalities that can be detected by a standard white light endoscopic examination with longitudinal furrows, rings, and white plaque (the most frequently observed), especially in young males with some type of allergy¹².

For confirmation of *EoE* diagnosis, histopathological identification of dense eosinophil infiltration in esophageal epithelial layers greater than 15 eosinophils/HPF is necessary. At least 5 biopsy samples for pathological examination are reported to be necessary for sensitive detection of dense eosinophil infiltration^{13,14}. The possible roles of esophageal epithelial fragments collected with the Cytosponge procedure and photochemical detection of eosinophil peroxidase by *Raman* spectroscopy, less invasive histopathological methods have been investigated¹⁵.

Therapy

Three useful options for treating *EoE* patients are acid inhibitors, oral topical corticosteroids, and an elimination diet¹⁴. Adult patients achieving clinical and histological remission on proton pump inhibitors (PPI) therapy are part of the *EoE* continuum, rather than a separate entity. Responders and non-responders to PPI therapy show overlapping phenotypic, genetic, and mechanistic features¹⁰. Approved topical steroid *budesonide* has become available for patients with eosinophilic esophagitis. This treatment is a dispersible tablet held in the mouth on the tongue, taken at a time when there is no plan to eat or drink anything that might wash it away from the surface of the esophagus. The optimal timing of a dose is the last thing at night after the patient has brushed his/her teeth and is not taking any further mouth wash or fluids. A person who is asleep makes less saliva and swallows less often, making the *budesonide* available to the esophageal epithelium for much longer than taking it during the day with subsequent drinks and meals¹⁶.

To our knowledge, such a form of corticosteroid is not yet available in Serbia but we use inhalation forms with a great deal of success.

Starting the treatment of *EoE* is recommended in the early inflammatory phases of the disease, not only to ease the patient's symptoms but to prevent esophageal fibrosis. The first treatment option should be PPIs because approximately 60% of the cases of *EoE* could be successfully treated that way. Proton pump inhibitors have two potential methods of action. By reducing the acidity of stomach fluids, if reflux

delu jednjaka, što se smatra smanjenjem oštećenja jednjaka izazvanog izlaganjem kiseline. *Attwood SE* je utvrdio da kod manjeg broja pacijenata inhibitori protonske pumpe mogu smanjiti upalu epitela jednjaka direktnim efektom na put eotaksin-3-eozinofila¹⁶. Kod novootkrivenih pacijenata, koji ranije nisu koristili inhibitore protonske pumpe, poželjno je započeti ovu terapiju u punoj dozi (*omeprazol ili pantoprazol 40 mg* dva puta dnevno) i nakon 12 nedelja izvršiti proveru simptoma, endoskopiju i biopsiju, kako bi se procenila dalja terapija održavanja ili prešlo na lokalne steroide. Naš pacijent je zadovoljavajuće odgovorio na terapiju jer je po prvi put koristio ovu grupu lekova.

Prema međunarodnom konsenzusu, inhibitori protonske pumpe ne mogu se koristiti u dijagnostičke svrhe. Pacijenti koji reaguju na inhibitore protonske pumpe imaju slične odlike eozinofilnog ezofagitisa, kao i oni koji ne reaguju na ovu grupu lekova¹⁷. Primećena je relativna vrednost pomenute vrste terapije, jer je 23% pacijenata koji su osam nedelja koristili inhibitore protonske pumpe reagovalo smirivanjem tegoba. U kombinaciji sa ishranom, stopa odgovora je u početku bila 69%, da bi nakon devet meseci pala na 55%. Upotrebom samo *budesonida* dat je odgovor kod 92% obolelih¹⁸.

Kod pacijenata otpornih na lokalnu steroidnu terapiju i dijetu, može se razmotriti dilatacija jednjaka. Budući da osnovna patogeneza eozinofilnog ezofagitisa podrazumeva preoblikovanje zida jednjaka fibrozom, najefikasniji način lečenja striktura ili rezistentne bolesti je dilatacija¹⁹. Metod dilatacije nije dobro proučen, ali poštovanje smernica Britanskog udruženja za gastroenterologiju (*British Society of Gastroenterology*) za terapijsku dilataciju jednjaka je rutinska intervencija većine Odeljenja za gastroenterologiju²⁰.

Lečenje EoE preporučuje se već u ranim fazama bolesti, ne samo za olakšavanje simptoma disfagije, već i za sprečavanje ezofagealne fibroze. Prva opcija u lečenju EoE treba da budu potentni inhibitori lučenja kiseline jer približno 60% EoE slučajeva može biti uspešno lečeno upotrebom inhibitora protonske pumpe (IPP). Terapijski efekat IPP na EoE uglavnom zavisi od njihove sposobnosti da spreče lučenje kiseline. Sprečavanje lučenja želudačne kiseline smanjuje vreme izlaganja dejstvu kiseline u distalnom delu ezofagusa. Smatra se da ovo umanjuje oštećenje ezofagusa uzrokovano dejstvom kiseline.

Normalizacija povećane propustljivosti ezofagealnog epitela sprečava nesmetan ulazak hrane i antigena u tkivo jednjaka, takođe, suzbija alergijske reakcije u jednjaku, što redukuje EoE. Široko korišćeni protokol primene IPP pre procene efekata je period od 2 do 3 meseca u dvostruko standardnoj dozi. *Flutikazon* u dozi od 400 mg - 800 mg dnevno u dve podeljene doze široko se koristi kao lokalni glukokortikoid za kontrolu aktivnosti EoE bolesti u Japanu. Najvažniji patogenetski faktori povezani sa EoE su prehrambeni alergeni, zatim alergeni iz okoline poput polena i gljivičnih antigena.

happens, the symptoms may be reduced. However, there is no evidence that acid reflux is involved in the pathogenesis of eosinophilic esophagitis, and the improvement seen in some patients is not related to the presence or absence of acid in the lumen of the esophagus. *Attwood* has identified that in a minority of patients, proton pump inhibitors can reduce the inflammatory drivers in the esophageal epithelium by a direct effect on the eotaxin-3-eosinophil pathway¹⁶. In a newly diagnosed patient, naive to proton pump inhibitors it might be worth starting a course of full dose proton pump inhibitor (such as omeprazole or pantoprazol 40 mg, twice daily) and performing a standardized symptom check, endoscopy, and biopsy at 12 weeks, in order to guide long-term maintenance with a proton pump inhibitor or switch to topical steroid. Our patient's response to therapy was satisfactory because it was his first time using this sort of drug.

It is now agreed, by international consensus, proton pump inhibitors should not be used in the diagnostic process of eosinophilic esophagitis, and patients responding to proton pump inhibitors have an otherwise similar phenotype of eosinophilic esophagitis to those who do not respond to proton pump inhibitors¹⁷. The relative value of each type of therapy has been observed and it was found that 23% of patients who completed 8 weeks of proton pump inhibitor course were responsive, and when combined with diet, the response rate rose to 69% initially but dropped to 55% at 9 months. Budesonide alone produced a 92% response¹⁸.

Patients resistant to topical steroids or dietary therapy should be considered for dilatation. Since the underlying pathogenesis of eosinophilic esophagitis involves remodeling of the esophageal wall with fibrosis, the single most effective treatment for strictures or resistant disease is dilatation¹⁹. The method of dilatation is not well studied but following the *British Society of Gastroenterology* guidelines for esophageal therapeutic dilatation is a straightforward process that is well within the capability of most Gastroenterology departments²⁰.

Treatment of EoE is recommended even in the early inflammatory stages not only for relieving dysphagia symptoms but also for preventing esophageal fibrosis. The first treatment option to be attempted for EoE should be the administration of a potent acid inhibitor as approximately 60% of EoE cases can be successfully treated with the administration of a proton pump inhibitor (PPI). The therapeutic effect of PPI administration on EoE is mainly dependent on its acid-suppressing effect. Gastric acid suppression decreases the time of acid exposure in the distal esophagus, which is thought to decrease esophageal damage caused by acid exposure. Normalization of augmented esophageal epithelial permeability will inhibit easy entry of food and environmental antigens in esophageal tissue, and also suppress allergic reactions in the esophagus, with resulting resolution of EoE. The widely used administration protocol before evaluation of the effects of a PPI is a 2-3 month period at double standard dose. Fluticasone at a dose of 400 mg to 800 mg/day in 2 divided

Dijeta sa ishranom lišenom antigenih proteina dovodi do remisije u preko 70% slučajeva *EoE*²¹. Zabeleženo je da otkrivanje i uklanjanje alergena iz hrane, na osnovu testova kožnih proba, nije efikasno za odabir namirnica koje će se eliminisati²². Umesto toga, potpuno uklanjanje šest vrsta hrane (mleka, pšenice, jaja, soje, orašastih plodova i morskih plodova) pokazalo je da uzrokuje remisiju kod skoro 70% pacijenata sa *EoE*²³. Kada je organska striktura jednjaka uzrok disfagije, dilatacija ezofagealnim balonom smatra se odgovarajućim lečenjem, ali ne i za druge uzroke disfagije. Za lekara opšte medicine je važno da identifikuje i pošalje pacijenata sa *EoE* na više nivoa zdravstvene zaštite.

Zaključak

Naš prikaz slučaja sugerise da sublingvalna imunoterapija može biti *okidač* za razvoj eozinofilnog ezofagitisa kod predisponiranih osoba. U proceni pacijenata sa disfagijom lekari primarne zdravstvene zaštite treba da uzmu u obzir ovu potencijalnu i klinički značajnu komplikaciju pri lečenju i praćenju pacijenata.

- Disfagija ili opstrukcija bolusom u prisustvu velikog broja eozinofila u sluznici jednjaka je poseban entitet koji se naziva eozinofilni ezofagitis, koji je u porastu.
- Svim pacijentima s disfagijom treba da se uradi biopsija jednjaka uzeta sa više mesta, čak i kada je endoskopski nalaz normalan.
- Endoskopija obično pokazuje tipično linearne brazde, prstenove, edeme, mikro apsece, krhkost tkiva i striktore.
- Eozinofilni ezofagitis je češći kod muškaraca, u zapadnih populacija i javlja se u svim uzrastima.
- Prezentacija kod male dece može uključivati regurgitaciju, povraćanje i odbijanje hrane kod starije dece i adolescenata slična odraslima s pretežnom disfagijom, ređe bolovima u grudima i bolom prilikom gutanja.
- Iako se smatra da je povezan s antigenima hrane i da se češće javlja kod atopičnih osoba, patogeneza je neizvesna, može biti posredovana *IgG₄*.
- Alergijsko testiranje je vrlo nepouzđano u definisanju terapije za eozinofilni ezofagitis.
- Terapijske mogućnosti uključuju lekove - lokalna steroidna terapija u obliku disperzivnog *budezonida* ili *flutikazon propionate*, inhibitori protonske pumpe, empirijsku dijetu i endoskopsku dilataciju jednjaka.

doses is widely used as a topical glucocorticoid for control of *EoE* disease activity in Japanese adults. Food allergens have been reported to be the most important pathogenetic factors related to *EoE*, followed by environmental allergens such as pollen and fungal antigens.

Complete replacement of the diet with an amino acid elemental diet devoid of antigenic proteins resulted in remission in over 70% of cases of *EoE*²¹. On the other hand, detection and elimination of food allergens based on skin patch or prick tests have been reported to not be effective for selecting foods to be eliminated²². Rather empirical elimination of 6 types of foods was reported to be successful, with complete elimination of milk, wheat, egg, soy, nuts and tree nuts, and seafood. It led to remission in nearly 70% of patients with *EoE*²³. When an organic esophageal stricture, formed in cases of *EoE*, is the cause of dysphagia, esophageal balloon dilatation is considered to be an appropriate treatment, though not for other causes. For the primary care provider, the identification and referral of patients with suspected *EoE* are indispensable.

Conclusion

Our case report suggests that pollen SLIT could be a *trigger* for *EoE* in predisposed individuals. Family physicians should be aware of this potential and clinically relevant complication of SLIT when evaluating patients with dysphagia and consider it in patient care and follow-up.

- Dysphagia or food bolus obstruction in the presence of high density esophageal mucosal eosinophilia is a distinct disease called eosinophilic esophagitis, with an increasing frequency.
- All patients with dysphagia should have biopsies of the esophagus taken from multiple sites (six) even if the endoscopic appearances are normal.
- Endoscopy usually shows typical features in eosinophilic esophagitis that may include linear furrows, rings, edema, microabscesses, tissue fragility, and strictures.
- Eosinophilic esophagitis is more common in men and western population and occurs at all ages.
- Presentation in young children may involve regurgitation, vomiting, and food refusal but in older children and adolescents the presentation becomes similar to adults with predominant dysphagia, and less common chest pain and odynophagia.
- Although considered to be related to food antigens, and more common in atopic individuals, the pathogenesis is uncertain, does not involve IgE but may be *IgG₄* mediated.
- Allergy testing is very unreliable in defining therapy for eosinophilic esophagitis.
- Therapeutic options include drugs (oral steroid therapy using dispersible budesonide or fluticazon propionate proton pump inhibitors), empiric elimination diets, or therapeutic endoscopic dilatation.

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