UDC 615.37+616-053.8+615.218.3+616.329-002+616.211-002.193
DOI: 10.56871/RBR.2025.30.88.010

EOSINOPHILIC ESOPHAGITIS AS A RARE COMPLICATION OF SUBLINGUAL ALLERGEN-SPECIFIC ALLERGEN IMMUNOTHERAPY. CLINICAL CASE

© Anna N. Kosova, Alexandra Yu. Pyrkh

Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation

Contact information: Anna N. Kosova — Assistant of the Department of Pathological Physiology with a Course of Immunopathology, pediatrician, allergologist-immunologist. E-mail: kosova@lahtaclinic.ru ORCID: https://orcid.org/0009-0005-5540-4066 SPIN: 8448-2479

For citation: Kosova AN, Pyrkh AYu. Eosinophilic esophagitis as a rare complication of sublingual allergen-specific allergen immunotherapy. Clinical case. Russian Biomedical Research. 2025;10(1):99–103. DOI: https://doi.org/10.56871/RBR.2025.30.88.010

Received: 23.01.2025 **Revised: 05.03.2025** **Accepted: 09.04.2025**

Abstract. Allergen-specific immunotherapy (ASIT) is the only disease-modifying method of allergy treatment that allows the development of long-term tolerance to an allergen. The therapy is that after confirmation of IgE-dependent sensitization to a particular allergen, the patient can receive treatment with a preparation of this allergen. The most common and effective ASIT for respiratory forms of allergy — rhinitis and bronchial asthma — is allergen therapy with pollen and house dust mite allergens. There is still insufficient data on the effectiveness of animal allergens. For vital indications, ASIT is performed with allergenic venoms of webworms and, in some countries, with food allergens. The duration of therapy is from 3 to 5 years, except for therapy with insect venoms and food allergens, when it is recommended to take the allergen for life to maintain tolerance. Tolerance itself is formed after 4–6 months from the start of treatment and is maintained for years. The safest in terms of anaphylactic reactions is sublingual allergen-specific immunotherapy (SLIT). However, cases of eosinophilic esophagitis (EoE), a rare complication of SLIT, have been described. The present case report describes the development of EoE in a 27-year-old man 4 weeks after starting SLIT with a tablet preparation of meadow grass allergens. The symptoms of EoE resolved rapidly within a few days of SLIT withdrawal. Possible options for continuing ASIT in the development of EoE and specifically in this patient are described.

Keywords: allergen immunotherapy (AIT), eosinophilic esophagitis (EoE), sublingual immunotherapy (SLIT), pollinosis

DOI: 10.56871/RBR.2025.30.88.010

ЭОЗИНОФИЛЬНЫЙ ЭЗОФАГИТ КАК РЕДКОЕ ОСЛОЖНЕНИЕ СУБЛИНГВАЛЬНОЙ АЛЛЕРГЕН-СПЕЦИФИЧЕСКОЙ ИММУНОТЕРАПИИ. КЛИНИЧЕСКИЙ СЛУЧАЙ

© Анна Николаевна Косова, Александра Юрьевна Пырх

Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, д. 2, Российская Федерация

Контактная информация: Анна Николаевна Косова — ассистент кафедры патологической физиологии с курсом иммунопатологии, врач-педиатр, аллерголог-иммунолог. E-mail: kosova@lahtaclinic.ru ORCID: https://orcid.org/0009-0005-5540-4066 SPIN: 8448-2479

Для цитирования: Косова А.Н., Пырх А.Ю. Эозинофильный эзофагит как редкое осложнение сублингвальной аллерген-специфической иммунотерапии. Клинический случай. Российские биомедицинские исследования. 2025;10(1):99–103.
DOI: https://doi.org/10.56871/RBR.2025.30.88.010

Поступила: 23.01.2025 **Одобрена: 05.03.2025** **Принята к печати: 09.04.2025**

Резюме. Аллерген-специфическая иммунотерапия (АСИТ) — единственный болезнь-модифицирующий метод лечения аллергии, который позволяет выработать долгосрочную толерантность к аллергену. Терапия заключается в том, что после подтверждения IgE-зависимой сенсибилизации к конкретному аллергену пациент может получать лечение препаратом этого аллергена. Терапия может проводиться препаратами для сублингвального применения либо подкожными инъекциями. Наиболее распространена и эффективна АСИТ при респираторных формах аллергии — рините и бронхиальной астме аллергенами пыльцы и клещей домашней пыли. Об эффективности применения аллергенов животных данных пока недостаточно. По жизненным показаниям проводится АСИТ ядами перепончатокрылых, и в некоторых странах — пищевыми аллергенами. Длительность терапии — от 3 до 5 лет, за исключением терапии ядами насекомых и аллергенами пищи, когда аллерген рекомендуется принимать пожизненно для поддержания толерантности. Сама толерантность формируется уже через 4–6 месяцев от начала лечения и сохраняется годами. Наиболее безопасная в плане развития анафилактических реакций — сублингвальная аллерген-специфическая иммунотерапия (СЛИТ). Тем не менее описаны случаи развития редкого осложнения СЛИТ — эозинофильного эзофагита (ЭоЭ). В данном клиническом случае приводится пример развития ЭоЭ у 27-летнего мужчины через 4 недели от старта СЛИТ таблетированным препаратом аллергенов луговых трав. Симптомы ЭоЭ быстро разрешились в течение нескольких дней после отмены СЛИТ. Описаны возможные варианты продолжения АСИТ при развитии ЭоЭ и конкретно у этого пациента.

Ключевые слова: аллерген-специфическая иммунотерапия (АСИТ), эозинофильный эзофагит (ЭоЭ), сублингвальная иммунотерапия (СЛИТ), поллиноз

INTRODUCTION

Allergen-specific immunotherapy (ASIT) is the only disease-modifying method of allergy treatment that allows the development of long-term tolerance to an allergen. The essence of therapy is that after confirmation of IgE-dependent sensitization to a particular allergen, the patient can be treated with a preparation of this allergen. The formation of tolerance is based on the induction of allergen-specific T-regulatory cells (T-reg), which, with the help of suppressor cytokines, modulate the specific T- and B-cell response [1]. This leads to increased production of specific IgG4, blocking the action of IgE, functional restriction of mast cells, basophils and eosinophils and the formation of long-term tolerance to the allergen. Therapy can be carried out with sublingual drugs or subcutaneous injections. Each method has its own advantages and disadvantages. The most common and effective ASIT for respiratory forms of allergy — rhinitis and bronchial asthma caused by pollen and house dust mite allergens. There is still insufficient data on the effectiveness of animal allergens. For vital indications, ASIT is performed with venoms of webworms and, in some countries, with food allergens. The duration of therapy is 3 to 5 years, with the exception of insect venom and food allergen therapy, where it is recommended to take the allergen for life to maintain tolerance. Tolerance is formed in 4–6 months from the beginning of treatment and lasts for years. The method is more than 100 years old, its founders — Leonard Noon and John Freeman — first published the results of their work — therapy of hay fever by subcutaneous injections of aqueous pollen extracts — in The Lancet in 1911 [2]. Over the years, the ASIT methodology has been improved, and effective and standardized preparations with a high safety profile have appeared.

(СЛSublingual allergen-specific immunotherapy (SLIT) is the safest in terms of systemic allergic reactions (there is no cases requiring epinephrine administration have been reported) and is often the method of choice [3]. However, cases of eosinophilic esophagitis (EoE), a rare complication of SLIT, have been described [4–6].

Typical adverse reactions when using SLIT are localized (burning under the tongue) and moderate aggravation of allergic rhinoconjunctivitis at the beginning of therapy. These phenomena are successfully controlled with antihistamines and, if necessary, topical steroids without discontinuation of ASIT. These symptoms usually disappear within 2–4 weeks.

Eosinophilic esophagitis is a rare (less than 1% of cases according to the ASIT product instructions) complication of sublingual allergen-specific immunotherapy. EoE is a chronic, immune/antigen-mediated esophageal disease clinically characterized by symptoms associated with esophageal dysfunction and histologically by eosinophil-dominated inflammation [7–13].

The pathogenesis is based on genetically determined disruption of esophageal epithelial function, which leads to failure of its barrier function and development of Th2 inflammation. The triggers are mainly food allergens. Much less frequent are cases of provocation by aeroallergens — seasonal exacerbations of EoE in patients with allergic rhinitis against the background of flowering of significant plants. SLIT with pollen allergens can also be a trigger and, as a rule, it is a contraindication for continuing SLIT [3, 4].

EoE was previously classified as an allergic disease with a mixed mechanism: type I, IgE-dependent, and type IV, delayed-type hypersensitivity. Modern classification categorizes EoE as type IVb allergic reactions, which are based on Th2 inflammation. Th2 produce a variety of cytokines — interleukin-4 (IL-4), IL-5, IL-9, IL-13, IL-31 and eotaxins I-III. IL-4 and IL-13 play a key role in inducing a switch of B-lymphocytes to synthesize IgE. IL-13 is also responsible for tissue remodeling involved in chronic inflammation. IL-5 ensures the recruitment of eosinophils from the bone marrow and their persistence in the focus of inflammation. Degranulation of eosinophils and release of their endogenous proteases contributes to further tissue damage, inflammation chronization, and aggravation of the defect in the barrier function of the epithelium [14].

EoE was previously considered a rare disease. However, nowadays, there is an increasing number of publications and a growing incidence, which is probably due to the introduction of knowledge into practice and continued study of this pathology.

The first publications on esophageal eosinophilia appeared in the 70s of the XX century. In the Russian Federation, recommendations on the diagnosis and treatment of EoE were first published in 2013 [9].

CLINICAL CASE

A 27-year-old male patient with seasonal allergic rhinitis and conjunctivitis, sensitization to meadow grasses. His complaints have been present for several years, with clinical manifestations increasing in dynamics. Sensitization to meadow grasses was confirmed by prick tests.

The first course of SLIT was started in February 2022. According to the drug instructions, the patient swallowed saliva after dissolving the tablet. In the first week of therapy, a moderate local reaction (burning of the mucous membrane under the tongue) was noted, which is common with SLIT and expected at the initial stages of therapy. Against the background of antihistamines, these symptoms decreased and later did not bother even without medication support.

Approximately one month after the start of therapy, the patient first developed symptoms of dysphagia, which he did not pay attention to and did not connect with SLIT. The patient did not report his symptoms until 2 weeks later, as they became daily and there was a very intense pain when swallowing,

according to the patient, “to the point of tears”. There were also complaints of intermittent nasopharyngeal discomfort, a feeling of shortness of breath, and an intractable cough lasting up to several minutes after meals, mostly during the day.

EoE was clinically suspected, and immediately after the patient reported the side effect of the drug SLIT was interrupted, leading to a rapid resolution of the clinical picture. The patient was examined by an otorhinolaryngologist (ENT), no pathology from the ENT organs was found.

In the next few days, an endoscopic examination (esophagogastroduodenoscopy — EGDS) was performed. Due to the short time of SLIT administration, the macroscopic picture was not convincing and was regarded only as a suspicion of EoE. Histologic examination of six biopsy specimens of esophageal mucosa revealed up to 50 eosinophils in the field of view at ×400 magnification with acceptable values for esophagus up to 15, which confirmed the diagnosis of EoE.

Since after the drug withdrawal the symptoms of dysphagia completely resolved within 1–2 days, drug therapy for esophagitis was not prescribed. On re-endoscopy performed 10 months later, a normal mucosal picture was observed. The biopsy showed no evidence of esophagitis.

Despite the development of a serious complication of SLIT, the patient was determined to continue ASIT in the next season (each season SLIT with pollen allergens begins 4 months before the onset of flowering and lasts until the end of flowering), because the symptoms of pollinosis severely impaired the quality of life. The possibility of continuing SLIT against the background of standard therapy of EoE (proton pump inhibitors (PPIs), budesonide or fluticasone) was considered, which would not exclude a possible exacerbation. The possibility of continuing SLIT “under cover” with Dupilumab for the treatment of EoE was considered. However, given the normal results of repeat endoscopy with biopsy, receipt of this therapy within the framework of compulsory medical insurance was excluded. Switching to subcutaneous immunotherapy (SCIT) was also undesirable due to the lack of standardized drugs for SCIT.

There are studies confirming the possibility of continuing SLIT if saliva is spit out after sublingual exposure to the drug [5]. Before resuming SLIT, the patient underwent endoscopic examination with biopsy, which showed the absence of eosinophilic inflammation in the esophagus. Therapy was continued. With this method of SLIT, the patient in 2023 successfully completed the entire first preseasonal-seasonal course of therapy without side effects and with positive results in the form of reduction of pollinosis symptoms. The treatment is currently ongoing (the 2nd course out of the required three), indicating that continuation of SLIT is possible and effective.

CONCLUSION

This example demonstrates that in case of EoE development on the background of SLIT, continuation of SLIT with the causative allergen is possible. For successful continuation of therapy, certain conditions must be met: achievement of complete remission of EoE before returning to SLIT, saliva spitting after sublingual exposure to the allergen.

In our case, the continuation of SLIT was carried out after a year, which was dictated by the peculiarities of SLIT with pollen allergens — a preseasonal-seasonal protocol, when treatment begins 4 months before flowering and continues throughout the flowering period. This long interval ensured complete remission of EoE in the patient. A repeat endoscopy with biopsy was performed immediately before the planned continuation of SLIT.

In case of using SLIT with year-round protocol it is necessary to be guided by the terms of standard remission of EoE. In most cases, repeated esophageal endoscopy with biopsy after 2 months of elimination of the causative allergen reveals complete resolution of esophageal eosinophilia [8].

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

The manufacturer was informed about the complication that had arisen.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие пациента на публикацию медицинских данных.

Компании-производителю о возникшем осложнении было сообщено.

REFERENCES

1. EAACI Allergen Immunotherapy User's GuidePediatr Allergy Immunol. 2020;31(Suppl 25):1–101. DOI: 10.1111/pai.13189.
2. Noon L., CantabB.C. , Eng F.R.C.S. Prophylactic inoculation against hay fever The Lancet. 1911:180(4580).
3. De Filippo M., Votto M. et al. Safety of allergen-specific immunotherapy in children. Pediatr Allergy Immunol. 2022;33(Suppl 27):27–30.
4. What Is the Relationship Between Eosinophilic Esophagitis (EoE) and Aeroallergens? Implications for Allergen Immunotherapy. Maureen Egan, Dan Atkins. Review. Curr Allergy Asthma Rep. 2018;18(8):43.
5. A case series of sublingual immunotherapy-induced eosinophilic esophagitis: stop or spit. Yasuhiro Fujiwara, Fumio Tanaka et al. Clin J Gastroenterol. 2021;14(6):1607–1611.
6. Votto M., De Filippo M., Caminiti L. et al. Rewiew. Eosinophilic gastrointestinal disorders and allergen immunotherapy: Lights and shadows. Pediatr Allergy Immunol. 2021;32(5):814–823. DOI: 10/1111/pai.13458.
7. Liacouras C.A., Furuta G.T., Hirano I., Atkins D., Attwood S.E., Bonis P.A., Burks A.W., Chehade M., Collins M.H., Dellon E.S., Dohil R., Falk G.W., Gonsalves N., Gupta S.K., Katzka D.A., Lucendo A.J., Markowitz J.E., Noel R.J., Odze R.D., Putnam P.E., Richter J.E., Romero Y., Ruchelli E., Sampson H.A., Schoepfer A., Shaheen N.J., Sicherer S.H., Spechler S., Spergel J.M., Straumann A., Wershil B.K., Rothenberg M.E., Aceves S.S. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128(1):3.
8. Wright B.L., Spergel J.M. Eosinophilic Esophagitis. MOC: Difficult Cases. J Allergy Clin Immunol Pract. 2018;6(5):1799–1801.
9. Kaibysheva V.O., Mikhaleva L.M., Nikonov E.L., Shapovaliants S.G. Epidemiology, etiology and pathogenesis of eosinophilic esophagitis. Latest data. Dokazatel'naya gastroenterologiya. 2019;8(2):50–72. (In Russian).
10. Updated international consensus diagnostic criteria for eosinophilic esophagitis: Proceedings of the AGREE conference. Gastroenterology. 2018;155(4):1022–1033.e10. DOI: 10.1053/j.gastro.2018.07.009.
11. Listopadova A.P., Novikova V.P., Zamyatina Yu.E. i dr. Comparison of morphological features of chronic esophagitis with the level of cytokines and neuropeptides in children with concomitant allergic diseases. Meditsina: teoriya i praktika. 2019;4(1):164–171. (In Russian).
12. Namazova-Baranova L.S., Alekseeva A.A., Altunin V.V. i dr. Allergy in children. Moscow: Pediatr; 2011. (In Russian). EDN: QMMLXP.
13. Nasyrov R.A., Uspensky Yu.P., Fominykh Yu.A., Kalinina E.Yu., Gnutov A.A. Morphological features of the esophagus in norm and in pathology. Universitetskiy terapevticheskiy vestnik. 2022;4(3):4–13. (In Russian).
14. Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: an EAACI position paper. Allergy. 2023;78(11):2851–2874.

ЛИТЕРАТУРА

1. EAACI Allergen Immunotherapy User's GuidePediatr Allergy Immunol. 2020;31(Suppl 25):1–101. DOI: 10.1111/pai.13189.
2. Noon L., CantabB.C. , Eng F.R.C.S. Prophylactic inoculation against hay fever The Lancet. 1911:180(4580).
3. De Filippo M., Votto M. et al. Safety of allergen-specific immunotherapy in children. Pediatr Allergy Immunol. 2022;33(Suppl 27):27–30.
4. What Is the Relationship Between Eosinophilic Esophagitis (EoE) and Aeroallergens? Implications for Allergen Immunotherapy. Maureen Egan, Dan Atkins. Review. Curr Allergy Asthma Rep. 2018;18(8):43.
5. A case series of sublingual immunotherapy-induced eosinophilic esophagitis: stop or spit. Yasuhiro Fujiwara, Fumio Tanaka et al. Clin J Gastroenterol. 2021;14(6):1607–1611.
6. Votto M., De Filippo M., Caminiti L. et al. Rewiew. Eosinophilic gastrointestinal disorders and allergen immunotherapy: Lights and shadows. Pediatr Allergy Immunol. 2021;32(5):814–823. DOI: 10/1111/pai.13458.
7. Liacouras C.A., Furuta G.T., Hirano I., Atkins D., Attwood S.E., Bonis P.A., Burks A.W., Chehade M., Collins M.H., Dellon E.S., Dohil R., Falk G.W., Gonsalves N., Gupta S.K., Katzka D.A., Lucendo A.J., Markowitz J.E., Noel R.J., Odze R.D., Putnam P.E., Richter J.E., Romero Y., Ruchelli E., Sampson H.A., Schoepfer A., Shaheen N.J., Sicherer S.H., Spechler S., Spergel J.M., Straumann A., Wershil B.K., Rothenberg M.E., Aceves S.S. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128(1):3.
8. Wright B.L., Spergel J.M. Eosinophilic Esophagitis. MOC: Difficult Cases. J Allergy Clin Immunol Pract. 2018;6(5):1799–1801.
9. Кайбышева В.О., Михалева Л.М., Никонов Е.Л., Шаповальянц С.Г. Эпидемиология, этиология и патогенез эозинофильного эзофагита. Новейшие данные. Доказательная гастроэнтерология. 2019;8(2):50–72.
10. Updated international consensus diagnostic criteria for eosinophilic esophagitis: Proceedings of the AGREE conference. Gastroenterology. 2018;155(4):1022–1033.e10. DOI: 10.1053/j.gastro.2018.07.009.
11. Листопадова А.П., Новикова В.П., Замятина Ю.Е. и др. Сопоставления морфологических особенностей хронического эзофагита с уровнем цитокинов и нейропептидов у детей с сопутствующими аллергическими заболеваниями. Медицина: теория и практика. 2019;4(1):164–171.
12. Намазова-Баранова Л.С., Алексеева А.А., Алтунин В.В. и др. Аллергия у детей. М.: Педиатр; 2011. EDN: QMMLXP.
13. Насыров Р.А., Успенский Ю.П., Фоминых Ю.А., Калинина Е.Ю., Гнутов А.А. Морфологические особенности пищевода в норме и при патологии. Университетский терапевтический вестник. 2022;4(3):4–13.
14. Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: an EAACI position paper. Allergy. 2023;78(11):2851–2874.