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Duodenal Eosinophilia in Functional Dyspepsia

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Aim: to present observation of a patient diagnosed with functional dyspepsia based on current guidelines, and having increased eosinophil counts in the biopsy specimen of duodenal mucosa. To consider possible causes of duodenal eosinophilia in the light of present-day concepts.
Highlights. Patient K., 40 years old, complained of dyspeptic phenomena, the first appearance of which she had noted at the age of 18. The patient noted poor tolerance to canned and fermented foods, which provoked an increase in dyspepsia and sometimes caused watery diarrhea. The examination excluded "symptoms of concern". Successful antihelicobacter eradication therapy was carried out. Morphological examination of the stomach showed phenomena of mild chronic inflammation without intestinal metaplasia or glandular atrophy. A biopsy of the mucosa of the descending part of the duodenum showed a moderate increase in the levels of mononuclears and eosinophils in its *lamina propria* without penetration into the epithelium of the villi or formation of clusters. The patient suffers from pollinosis; sensitization to birch pollen was diagnosed by a skin prick test. However, she has no oral allergy symptoms, which does not allow linking duodenal eosinophilia to food allergy. Based on current guidelines, the patient was diagnosed with functional dyspepsia. In addition to dietary restrictions, treatment courses with a proton pump inhibitor, itopride, and S-methylmethionine sulfonium chloride, which has an antihistamine effect, were recommended for periods of worsening dyspepsia.
Conclusion. The clinical significance of duodenal eosinophilia and local histamine production in patients with a clinical diagnosis of functional dyspepsia deserves special attention. Triggering factors provoking the worsening of symptoms should be analyzed; in particular, a food diary and exclusion of food allergies are recommended. Histamine-neutralizing drugs may play a role in the treatment of FD with duodenal eosinophilia in the future.
Keywords: functional dyspepsia, duodenal eosinophilia, histamine, S-methylmethionine sulfonium chloride
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Дуоденальная эозинофилия при функциональной диспепсии

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Цель исследования: представить наблюдение пациентки, в биоптате двенадцатиперстной кишки которой установлено повышенное содержание эозинофилов, которой на основании современных рекомендаций был установлен диагноз функциональной диспепсии. Рассмотреть возможные причины дуоденальной эозинофилии в свете современных представлений.
Основные положения. Пациентка К. 40 лет обратилась с жалобами на диспепсические явления, первое появление которых отметила в 18-летнем возрасте. Пациентка отмечает плохую переносимость консервированной пищи и продуктов, приготовленных путем ферментирования, которые провоцировали нарастание диспепсии и иногда вызывали проявление водянистой диареи. В ходе обследования были исключены «симптомы тревоги». Проведена успешная эрадикационная антигеликобактерная терапия. При морфологическом исследовании желудка: явления слабовыраженного хронического воспаления без кишечной метаплазии и атрофии желез. В биоптате слизистой оболочки нисходящей части двенадцатиперстной кишки установлено умеренное повышение содержания мононуклеаров и эозинофилов в собственной пластинке без проникновения в эпителий ворсин и образования кластеров. Пациентка страдает поллинозом, с помощью кожного прик-теста установлена сенсибилизация к пыльце березы, однако дуоденальную эозинофилию мы не связываем с пищевой аллергией. На основании современных рекомендаций пациентке установлен диагноз функциональной диспепсии. Помимо диетических ограничений, в периоды нарастания диспепсии рекомендованы курсы лечения ингибитором протонной помпы, итопридом и S-метилметионинсульфония хлоридом, оказывающим антигистаминный эффект.
Заключение. Клиническое значение дуоденальной эозинофилии и местной продукции гистамина у пациентов с клиническим диагнозом «функциональная диспепсия» заслуживает особого внимания. Необходимо

провести анализ триггерных факторов, провоцирующих нарастание симптомов; в частности, рекомендуется ведение пищевого дневника и исключение пищевой аллергии. Определенное место в лечении ФД с дуоденальной эозинофилией в перспективе могут занять препараты, нейтрализующие действие гистамина.
Ключевые слова: функциональная диспепсия, дуоденальная эозинофилия, гистамин, S-метилметионинсульфония хлорид
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Background

Functional dyspepsia (FD) is a disease with a complex pathogenesis characterized by dysregulation along the gut- brain axis. The origin of FD symptoms is associated with the development of visceral hypersensitivity, tone and motility disorders (impaired gastric accommodation with redistribution of contents and increased load on the antrum, and delayed gastric emptying). According to the current ideas, one of the central roles in the pathogenesis of these disorders is assigned to increased intestinal permeability and low-grade inflammation with increased counts of T-helper 2 cells and eosinophils in lamina propria of the duodenum [1, 2].

Clinical observation

Patient K., 40 years old, complained of aching pain, feeling of distention in the epigastric region after a meal, burning in the epigastric region on an empty stomach, and frequent belching. Such symptoms first appeared at the age of 18 and were associated with psycho-emotional stress (university entrance). Since then, the patient noted poor tolerance to canned food, sauerkraut, red wine, cocoa, after consumption of which the pain in the epigastric region increased significantly, and episodes of watery stools would occur during the first 30–40 min after consumption of such products. She underwent esophagogastroduodenoscopy (EGDS) several times in previous years, which revealed signs of chronic antral gastritis without endoscopic signs of atrophy, with single hemorrhagic erosions. The patient was treated with proton pump inhibitors and antacids with a short-term effect. In 2016, a biopsy rapid urease test revealed *Helicobacter pylori* infection, after which a first-line eradication therapy (amoxicillin, clarithromycin, and rabeprazole) enhanced with bismuth salts was performed. A control study (^{13}C-urease breath test) showed a result indicating successful eradication. At follow-up, symptoms of dyspepsia persisted despite the consistent absence of signs of *H. pylori* infection at annual examination (fecal antigen test and ^{13}C-urease breath test). Due to the presence of atopic dermatitis, tests were conducted in 2019 to rule out celiac disease (due to a possible combination of these diseases). We evaluated the level of antibodies to gliadin IgG (found to be elevated up to 50 U/ml), tissue transglutaminase Ig A, G (not detected) and deamidated gliadin fragments Ig A, G (not detected). Biopsy of mucosa from the descending part of the duodenum was performed, which did not detect any significant changes in intestinal villi or crypts; moderate increase of mononuclear cells and eosinophils in lamina propria (no more than 25 in several neighboring fields of view under high magnification microscope) was found, without intrusion into villous epithelium or clustering (quantitative counting of eosinophils was not performed).

From her social history, it is known that the patient has higher education, works as a tour guide; no occupational hazards were noted. The patient does not smoke or drink alcohol. She eats irregularly; over the past few years she often consumed canned and excessively hot food. In the family history it is noteworthy that the patient's sister and maternal grandmother had stomach cancer at the age of 37 and 42 years, respectively, and that her aunt had colon cancer at the age of 50. The patient has suffered from atopic dermatitis since adolescence, with exacerbations provoked by psycho-emotional stress; trigger foods could not be identified. In addition, she suffers from pollinosis (allergic rhinitis and conjunctivitis); sensitization to birch pollen was determined by skin prick-test. Arterial hypertension has been diagnosed since the age of 35; the patient takes enalapril.

Physical examination of the patient at the visit: Overall health is satisfactory, consciousness is clear. Normosthenic body type. Body mass index is 26 kg/m^2. The skin is pink, clean, peripheral lymph nodes are not enlarged. No edemas. No abnormal changes in the respiratory system. The left border of relative cardiac dullness is 1 cm

medial to the left midclavicular line in the 5th intercostal space. The heart rate is 72 beats per minute, blood pressure is 130/90 mm Hg. The abdomen is soft on palpation, and tender in the epigastric region. On deep palpation, the sections of the large intestine are unaltered. The liver and spleen are not enlarged. No pathological changes in the excretory system revealed.

The leading syndrome in the disease pattern was that of dyspepsia. Further laboratory instrumental tests were performed in accordance with current clinical guidelines, which were aimed at detection of further "symptoms of concern" and exclusion of organic changes of the stomach and other diseases with similar symptoms [1]. Positive family history for malignant tumors required to exclude gastric cancer.

Clinical blood count: hemoglobin 140 g/l, erythrocytes 4.5×10^{12}/l, MCV 92 fl, color index 0.93; leukocytes 9.2×10^{9}/l, leukocytic formula unchanged, platelets 220×10^{9}/l, sedimentation rate 15 mm/h. No abnormalities were detected by biochemical blood tests. Fecal occult blood test was negative. Ultrasound examination of the abdominal organs did not reveal any significant abnormalities. The patient had the results of a recent colonoscopy testifying to the absence of pathological changes.

Esophagogastroduodenoscopy (12.2022): Gastric body mucosa is pale pink; antral mucosa is moderately focally hyperemic. Peristalsis was visible in all areas. The duodenal bulb is regular in shape, with pale pink mucosa; the postbulbar areas are unaltered. Biopsy rapid urease test for helicobacter infection with a fragment of antral mucosa was negative.

In view of the endoscopic signs of chronic gastritis and positive family history for gastric cancer, biopsies were taken from the antrum (2 samples), gastric angle (1 sample), and gastric body (2 samples — from the lesser and greater curvature) in accordance with the latest guidelines on gastritis diagnosis [2]. Morphological examination revealed phenomena of mild chronic inflammation without intestinal metaplasia or glandular atrophy (stage I grade 0 according to OLGA (Operative Link for Gastritis Assessment) and stage 0 according to OLGIM (Operative Link for Gastritis — Intestinal Metaplasia), Figure 1).

In this case, considering the development of gastric cancer in close relatives at a young age, a thorough control of *Helicobacter pylori* infection is of fundamental importance. For this purpose, an additional ^{13}C-urease breath test with the highest accuracy was performed and the result obtained indicated the absence of infection (2.06 DOB, ‰).

The patient did not have a tumor, peptic ulcer, or helicobacter gastritis, no evidence of taking medications or other factors which could have caused an autonomous lesion of gastric mucosa; also, no organic lesions of internal organs (liver or biliary tract, pancreas, or colon) which could have triggered the development of the described symptoms were detected. The clinical presentation corresponded to mixed-type FD. More than six months had passed since successful eradication of *Helicobacter pylori*, and, as the symptoms persisted, we could rightfully assume the presence of this disease [1].

The patient was recommended a diet with restricted intake of salt and foods made by fermentation or preservation, as well as regular meals. During periods of worsening dyspepsia, the patient was treated with proton pump inhibitor in a standard dose, itopride, and S-methylmethionine sulfonium chloride (Gastrarex) for 1 month three to four times a year. These measures had a positive effect: the frequency and severity of exacerbations decreased significantly, and for the last 2–3 years the patient felt quite satisfactory; her working ability improved, she no longer had episodes of watery stools after eating the "trigger" foods.

Discussion

In this case, the diagnosis of FD was made according to current guidelines, which imply reliable exclusion of organic diseases with similar symptoms [3, 4]. Taking into account the burdened familial history, special attention was paid to the exclusion of precancerous gastric lesions (atrophy and metaplasia), and close monitoring of *H. pylori* infection status.

The patient suffered from atopic gastritis and pollinosis (allergy to birch pollen antigen). A biopsy of her duodenum showed low-grade inflammation with increased eosinophil counts in the lamina propria. Legitimate question arises about the possible association of these phenomena.

According to present-day ideas, duodenal disorders play the major role in the impairment of gastric tone and motility, and visceral hypersensitivity in FD [1, 2]. Biopsy of duodenal mucosa is not part of the obligatory examination plan in PD [3, 4]. If endoscopic signs of duodenitis are present, a biopsy is performed to assess the severity of inflammation and the nature of the lesion [3, 4]. The state of villi and Brunner's glands, the presence of metaplasia areas, the

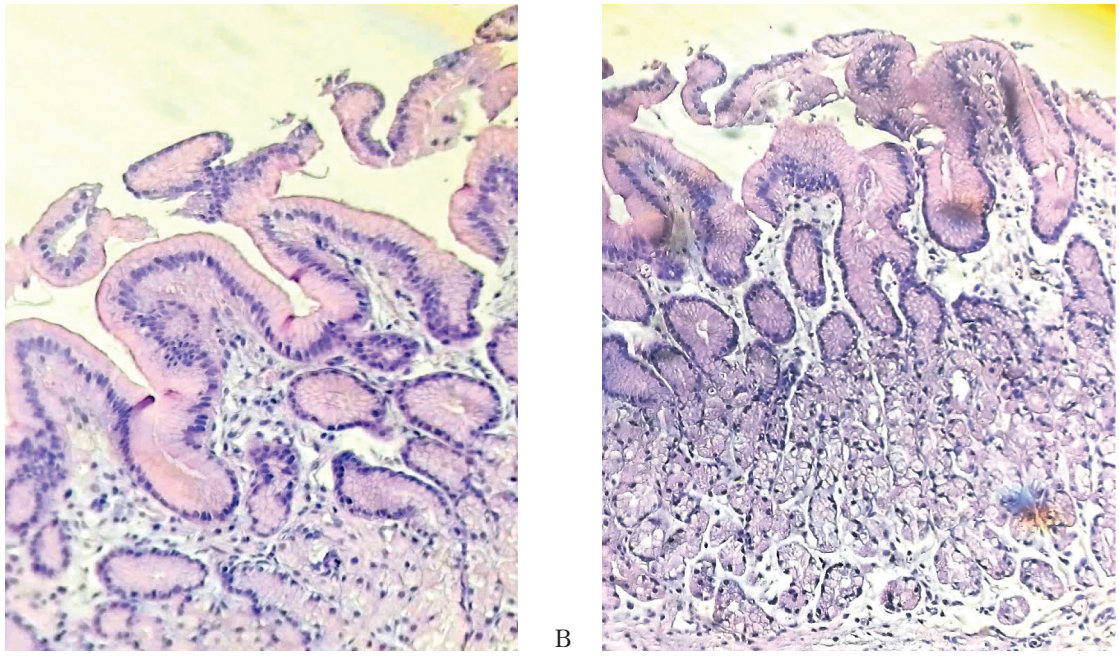

Fig. Biopsy of gastric body mucosa (A) and antral mucosa (B). No signs of atrophy or intestinal epithelial metaplasia

Рис. Биоптат слизистой оболочки тела (А) и антрального отдела (Б) желудка. Отсутствуют признаки атрофии и кишечной метаплазии эпителия

counts and composition of immunocompetent cells in the lamina propria (eosinophils, neutrophils, lymphoid clusters or follicles) are assessed; the count of intraepithelial lymphocytes per 100 villous enterocytes is an important parameter. The severity of duodenal inflammation is often assessed descriptively (as "low-grade", "moderate", or "active"), but scoring systems have also been proposed [5].

Duodenal eosinophilia is considered a characteristic feature of FD [1]. The number of eosinophils in the lamina propria is counted in adjacent nonoverlapping fields of view at high microscope resolution (≤15 is suggested as normal). Detection of ≥30 eosinophils per field of view at high microscope magnification in ≥3 adjacent fields of view, especially in clusters, supports the diagnosis of "eosinophilic duodenitis" [6, 7].

In FD, there is a slight increase in the eosinophil count in the lamina propria of the duodenum (10–40 % more than in healthy individuals). The cause of immune activation is increased mucosal permeability due to the influence of intraluminal (hydrochloric acid, food components, impaired microbiota) and endogenous factors (genetic predisposition and stress). Excessive penetration of antigens into mucosal lamina propria provokes activation of T-helper type 2 cells and migration of eosinophils under the influence of eotaxins (CC-ligands-11, -24, -26, RANTES molecule, interleukin-5, tryptase) [1, 2]. Eosinophils and mastocytes attracted by them are in a state of activation characterized by increased degranulation. Eosinophils secrete a number of molecules with anti-inflammatory effects, but at the same time, through the production of major basic protein, eosinophil peroxidase, eosinophilic cationic protein, and corticotropin-releasing hormone, they stimulate mast cell degranulation. In this respect, the action of eosinophils is concomitant with the effect of T-helper 2 cells on mastocytes, which is realized by means of interleukins -4, -5, -13. Lack of a clear association of the density of eosinophils in the duodenal mucosa and the degree of their degranulation with intestinal permeability can be explained by imperfect methods for assessing these parameters [8].

A meta-analysis of 22 case-control studies involving 1108 patients with FD and 893 control patients without dyspepsia showed an association of clinical manifestations with the signs of low-active inflammation in the duodenum and elevated eosinophil counts, although the authors noted heterogeneity in the data. In FD, the duodenal

lamina propria showed a significant increase in eosinophils (pooled standardized mean difference, 1.29; 95 % CI 0.85–1.73; $p = 0.0001$) and mast cells (pooled standardized mean difference, 2.11; 95 % CI 1.14–3.07; $p = 0.0001$). The degree of eosinophil degranulation in FD was significantly elevated (odds ratio 3.78; 95 % CI 6.76–4.48; $p = 0.0001$). In FD, the development of which could be associated with a past gastrointestinal infection ("postinfectious FD"), eosinophil counts were particularly high (pooled standardized mean difference 3.91; 95 % CI 1.32–6.51; $p = 0.001$ compared with controls without dyspepsia and 1.42; 95 % CI 0.88–1.96; p = 0.001 compared with the FD group without association with a past infection). There were no significant differences in eosinophil counts depending on the clinical subtype of FD (epigastric pain syndrome or postprandial distress syndrome) [9].

Many authors emphasize the variability of eosinophil counts depending on the area of residence and dietary habits. The degree of peptic aggression, the presence of dysbiosis or excessive bacterial growth in the upper small intestine, recent infections and parasitosis are important; therefore, duodenal mucosal biopsy is used for differential diagnosis rather than to confirm the diagnosis of FD [1–4]. Assessment of degranulation requires rather complicated techniques, the informative value of which is unclear.

The variety of functions of eosinophils in the intestine, their influence on immunity reactions, repair and fibrosis, have prompted a more in-depth research of the mechanisms influencing the attraction and functional activity of these cells. Recent years' studies have shown a critical relationship between the state of intestinal eosinophils and the microbiome. By influencing chemokine production and eosinophil activity, intestinal microorganisms can determine gut tissue remodeling and the degree of sensitization to food antigens [5]. A target of research is the interaction of eosinophils with the cells of the nervous system. In the duodenum, eosinophils are located in close proximity to the submucosal plexus neurons, and in FD, the degree of their activation is related to the remodeling of fibrils [10]. Eosinophils are activated under the influence of neurotransmitters — acetylcholine and substance P. In turn, eosinophils have been described to influence the production of serotonin and substance P by dorsal spinal ganglion cells, which indicates their role as a kind of mobile "sensors" of the nervous system [1].

Symptoms of functional disorders of the digestive organs and excessive bacterial growth in the intestine (pain in the epigastric region, attacks of watery diarrhea as a reaction to meals) have a certain similarity to the manifestations of so-called "histamine intolerance" and are often provoked by the consumption of foods rich in biogenic amines (canned foods, wine, dishes prepared by fermentation, long-stored fish and meat, etc.). [11]. Excessive histamine release by mastocytes, which is supported by eosinophils and the action of intraluminal stimuli, contributes to the maintenance of visceral hypersensitivity and motor disorders. In the small intestinal mucosa, histamine is neutralized by histaminase, which limits the damaging effect of this biogenic amine and its entry into the blood. Inside of cells, histamine methylation and neutralization are performed by histamine-N-methyltransferase. Polymorphism of genes of these enzymes underlies individual susceptibility to histamine action [11]. Four types of histamine receptors (histamine receptor, HR) — H1R, H2R, H3R and H4R — have been described. The genes encoding the structure of HR are subject to alternative splicing, and their activity can vary depending on environmental conditions. Histamine stimulates the secretion of hydrochloric acid, increases the inflammatory response and the contraction of smooth muscle cells. On immunocompetent cells, in the intestinal epithelium and neuroendocrine cells, H4R is predominantly represented [12]. Performing a number of important homeostatic functions, histamine plays a crucial role in the activation of the interleukin-18/interleukin-18 receptor axis and can increase the permeability of the mucosal barrier. When eosinophils are stimulated with H4R, their reactivity increases significantly.

Increased intestinal permeability and duodenal inflammation in FD cannot be considered separately from the changes in the microbiome [13]. The "bacterial load" on duodenal mucosa is related to the severity of postprandial symptoms. An important aspect of the influence of microorganisms is their ability to produce histamine, which is particularly characteristic of Gram-negative and some lactic acid bacteria. In this regard, their contribution to the development of symptoms may be similar to eosinophil and mastocyte degranulation. The increased count of *Porphyromonas* in duodenal mucosa correlates with the severity of FD symptoms and eosinophil density [14].

In a certain proportion of patients diagnosed with FD, the contribution of hypersensitivity reactions to the pathogenesis of symptoms cannot be completely excluded. According to a population-based study, bronchial asthma, food allergies, pollen and animal allergies, psoriasis, and rheumatoid arthritis were statistically significantly associated with FD and irritable bowel syndrome. Bronchial asthma (OR = 1.32; 95 % CI 1.04–1.68, P = 0.025), food allergies (OR = 1.78; 95 % CI 1.28–2.49, P = 0.001) may be considered independent predictors of FD [10]. The likelihood of a combination with atopic disease is particularly high in patients with two or more functional disorders [15, 16].

In the clinical observation under consideration, there was a combination of atopic dermatitis and pollinosis with hypersensitivity to the birch pollen antigen and duodenal eosinophilia. In 70 % of patients with sensitization to the main antigen of birch pollen (Betula verrucosa, Bet v 1) a cross-allergic reaction to a number of vegetables, fruits and greens is observed, which is usually limited to the oral cavity and nose. Because of the rapid degradation of this allergen when heated and in the acidic environment of the stomach, the allergen often does not reach the duodenum, and intestinal symptoms develop very rarely. For this reason, an elimination diet for allergy to birch pollen antigens with the exclusion of a fairly wide range of fruits, berries, carrots and celery is not always justified. A food diary is recommended to establish a cause-and-effect relationship. In the case described, the patient had no oral allergy symptoms and no clear increase in symptoms when consuming foods containing Bet v 1. In recent years, another important component contained in the pollen of birch and other plants (Bet v 2, a protein of the profilin family) has been isolated; one of the papers showed that when specific IgEs to Bet v 1 and profilin are detected, not only oral but also intestinal allergy manifestations are significantly more frequent [17]. The high prevalence of atopy in the population makes it relevant to study its possible contribution to the pathogenesis of dyspepsia corresponding to the diagnosis of FD. The study of this issue is complicated not only by the wide variability of clinical manifestations of sensitization and its laboratory markers, but also by the fact that eosinophilia is often caused not by IgE-mediated hypersensitivity reactions [18].

Proton pump inhibitors remain the first-line drugs in the treatment of FD in any of its clinical variants. With their antisecretory effect, they help to restore the integrity of the mucosal barrier and indirectly produce an anti-inflammatory effect with a decrease in the count of eosinophils in the duodenum. Interestingly, it is the "anti-eosinophil" effect of proton pump inhibitors that has been shown to be most associated with clinical efficacy in FD. In patients with refractory symptoms of FD, persisting against the background of the administration of these drugs for more than a month, signs of inflammation with eosinophilia in duodenal lamina propria also persist [19]. "Traditional" prokinetics, herbal medicines of combined action, and neuromodulators, effective in a considerable part of patients, nevertheless are characterized by a limited spectrum of action in treatment of functional disorders.

The complexity of pathophysiological mechanisms of FD necessitates the search for new therapeutic targets; the use of antihistamine drugs, probiotics, "intestinal" antibiotics seems to be a promising direction [20]. The problem of treatment of frequently relapsing and refractory forms of FD remains relevant. New antisecretory agents (potassium-competitive proton pump blockers), agents improving gastric accommodation (acotiamide, azapyrone), stimulating restoration of barrier properties of mucous membrane, central and peripheral neuromodulators are studied. Indirect confirmation of the role of dysbiosis in the upper parts of the small intestine in the development of FD is the effectiveness of rifaximin, and some probiotic strains (*Lactobacillus gasseri* OLL2716, *Bacillus coagulans* MY01, *Bacillus subtilis* MY02, etc.) [21].

The efficacy of antihistamines and antileukotrienes in the treatment of FD in pediatric practice has aroused particular interest in the possibility of using such drugs in adults. Some studies have reported the efficacy of H1R blockade and combined H1R and H2R blockade with ranitidine and loratadine. Patients with FD who responded to such treatment had higher initial eosinophil levels in duodenal mucosa [22, 23].

The aspect of maintaining the integrity of the epithelial barrier, which prevents exposure to aggressive factors, is important. Mucin production is an important component of the pre-epithelial protection; mucin with insufficient sulfation is less hydrated and susceptible to bacterial degradation. Natural sulfur donors that support mucin production include methionine, cysteine, and foods rich in the most bioavailable source of sulfur, methylmethionine sulfonium (S-methylmethionine, or vitamin U). Examples of such foods are white cabbage, asparagus, egg

yolk, milk, herbs, and carrots. The necessity to limit the intake of many of these foods in gastrointestinal diseases prevents adequate intake of vitamin U. Gastrarex containing 300 mg of methylmethionine sulfonium per capsule is used as a source of this substance. Acting as a donor of methyl groups in the processes of protein synthesis and antioxidant protection, Gastrarex stimulates regeneration of gastric and duodenal epithelium, and as a donor of sulfur it supports mucin production. Another important effect of methylmethionine sulfonium is methylation of histamine and its conversion into its inactive form — methylhistamine, which helps to reduce secretion of hydrochloric acid and regression of inflammation. Due to the combination of these effects, Gastrarex can help to reduce the severity of dyspeptic symptoms [24–26]. Gastrarex is safe to use, which allows this drug to be recommended as an adjunct to the current treatments for FD and gastritis.

Conclusion

The clinical significance of duodenal eosinophilia and local histamine production in patients with a clinical diagnosis of FD deserves special attention; a complicating factor is the lack of clear criteria for normality and the difficulty in assessing functional cell activity. In cases where FD is combined with atopic diseases, the presence of possible signs of food allergy should be evaluated, including the use of a food diary. One promising aspect of FD treatment may be the use of agents that neutralize the effects of histamine.

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