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Eosinophilic Esophagitis: etiology, pathogenesis, diagnosis and treatment. Hypothesis

Abstract

Background: Eosinophilic esophagitis (EoE) and gastroesophageal reflux disease (GERD) are commonly regarded as distinct disorders. However, several clinical and histologic overlaps challenge this separation.

Aim: To analyze current inconsistencies in the understanding of GERD and EoE and to propose an alternative pathophysiological concept linking both conditions.

Methods: A critical review of literature and radiographic observations was conducted to evaluate the relationship between esophageal inflammation, acid hypersecretion, and allergic response.

Results: Current consensus definitions of GERD rely on symptom-based or instrumental criteria rather than histological confirmation, which may lead to diagnostic underestimation. Evidence suggests that EoE represents a histological variant of reflux esophagitis in individuals with allergic predisposition. The initiating event is hypersecretion of hydrochloric acid. Acid, penetrating the esophagus, disrupts mucosal integrity and induces an inflammatory response. The allergic component promotes fibrotic thickening of the esophageal wall, leading to narrowing, dysphagia, and sometimes formation of a Schatzki ring.

Conclusion: EoE may be interpreted as reflux esophagitis modified by allergic inflammation. Recognizing the shared pathogenesis of GERD and EoE could improve diagnostic accuracy and treatment strategies. There is reason to believe that the Schatzki ring is a manifestation of EoE. High reliability of radiographic examination using radiometric analysis of radiographs has been demonstrated.

Keywords: Eosinophilic esophagitis, gastroesophageal reflux disease, hypersecretion of hydrochloric acid, allergic inflammation, Schatzki ring, rigid antral gastritis

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Introduction

In modern literature, different histological types of esophagitis are considered as unrelated diseases. For example, eosinophilic esophagitis (EoE) is considered a special disease, not related to other problems of the digestive tract. There is a group of authors who devote their numerous articles to this problem. However, neither etiology nor the pathogenesis of EoE is known yet, because the authors are afraid to go beyond the established boundaries. For example, it is known that the use of PPIs leads to an improvement in the clinical picture and a decrease in eosinophils in biopsies. Nevertheless, the authors suggest that PPIs are better classified as a treatment for esophageal eosinophilia that may be due to EoE than as a diagnostic criterion.[1] In other words, they do not even consider the possibility that EoE may be a particular histological picture of GERD. Other authors devote their articles to lymphocytic esophagitis as a special disease.[2,3] However, in most patients with esophagitis, who did not undergo histological examination of the esophageal mucosa, esophagitis is diagnosed based on visual signs of inflammation (erosion, ulcers, stenosis) during endoscopic examination. Such findings are considered evidence of gastroesophageal reflux disease (GERD). It is known that endoscopic examination reveals only complications of GERD. In the so-called non-erosive form of GERD, the endoscopic picture of the pathology does not reveal.[4] To confirm the inflammatory process, some researchers recommend determining the width of the intercellular space, which increases with the inflammatory process.[5,6] Chandrasoma et al. believe that the appearance of cardiac epithelium over the lower esophageal sphincter (LES) occurs because of cardiac metaplasia of the squamous epithelium due to exposure to gastric juice. Cranial displacement of the plano-cylindrical junction (SCJ) is indicative of GERD.[7] Since different histologic patterns suggest different treatments, it would be logical to perform histologic examinations during routine endoscopy. However, neither Lyon consensus 2.0, nor the Chicago Classification 4 recommends doing this.[8,9] Practicing physicians, following the decisions of conferences, do not conduct endoscopic examinations even for so-called functional disorders of the digestive tract, if there is no suspicion of organic damage.[10,11]

Since esophagitis is an inflammation of the esophagus wall, it is obvious that the accurate diagnosis should be established by histological examination, especially in the presence of a specific reaction (eosinophilia, lymphocytosis). For practicing doctors, recommendations are needed on what stage treatment can be carried out without histological examination. However, for solving scientific problems, histological examination is a defining scientific document. The aim of this study is to determine whether EoE is a specific response of the body to GERD or a disease with other etiology and pathogenesis. To do this, we will begin with a comprehensive characterization of GERD.

On the reliability of clinical symptoms of GERD

A). It is known that the inflammatory process in the esophagus, caused by damage from aggressive gastrointestinal refluxate, can occur without clinical manifestations. For example, endoscopic examinations of individuals who consider themselves healthy revealed GERD in 16% among 6,683 health examinees.[12] Similar results were

obtained by Stål et al. who noted that "Histologic abnormalities are poorly related to acid reflux in healthy volunteers".[13] Shieh et al showed that after POEM, 41.9% had erosive esophagitis, but only 12% had GERD symptoms.[14] Often, GERD hides behind non-esophageal symptoms.[15] If we consider that endoscopic examination based on visual data determines only complications of GERD, it becomes obvious that the number of patients with GERD among individuals without clinical symptoms is significantly higher than shown above. This reliable data shows that the absence of clinical symptoms does not allow us to exclude GERD. Secondly, the absence of complaints in patients with reflux esophagitis can be explained by damage to sensitive nerve elements by hydrochloric acid and pepsin. Thirdly, endoscopic examination without histology does not allow GERD to be ruled out.

B). In 2006, the Montreal Consensus, using a modified Delphi process, adopted the following definition of GERD: - 'GERD was defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications".[16] From the point of view of a practicing physician, such a definition seems logical, since people without complaints do not seek medical help. However, from a scientific point of view, as shown above, it is not correct. Secondly, in a scientific definition of a disease, the etiology or pathogenesis of the disease is always recorded, and not the symptoms. A vote of selectively selected physicians led to a change in the name of the disease, which was previously defined as "GER", and began to be called "GERD". This implied that the reflux of aggressive gastric contents into the esophagus in the absence of symptoms is physiological, i.e., not requiring GERD treatment. Furthermore, based on this definition, individuals without symptoms began to be used as controls. As the above facts show, these two conclusions are mistaken.

C). In 1974 and 1976 DeMeester et al. published an articles proposing a normal range for esophageal pH monitoring. It was defined as pH < 4 for 4% of the 24 hours of monitoring 5 cm proximal to the LES. The authors examined 15 individuals who believed that they had no problems with their digestive system. Since then, this boundary has been called the "DeMeester score", and the proposed method of pH monitoring has long been considered the gold standard for diagnosing gastroesophageal reflux disease.[17,18] First, these studies contradicted the existing scientific facts that repeated reflux causes reflux esophagitis and cannot be physiological. Second, the assumption that acid and pepsin, being in the lumen of the esophagus for about an hour a day, may not damage the mucosa is contrary to common sense. Thirdly, the authors examined 15 people as the norm, considering them healthy, based on the absence of typical complaints. The same authors in other studies, they used endoscopic, manometric and radiographic studies, but for an unknown reason did not use them to determine the norm. As a result, 24-hour esophageal pH measurement has a false negative rate of 15% to 30%".[12,13,19] In addition, some patients have only atypical, including extraesophageal symptoms.[15]

Since 1999,[20] T.R. DeMeester, in collaboration with histologists, published numerous studies showing that GER begins with acid damage to the intra-abdominal portion of the LES. Cardiac epithelium, which occurs because of metaplasia of the esophageal squamous epithelium, appears over the LES at a later stage. They consider the recommendation not to perform histological examination during endoscopy to be erroneous, since timely detection of cardiac epithelium in the esophagus will allow treatment to begin at an early stage and avoid the development of Barrett's esophagus.[7,20,21] Thus, it has been proven that in the early stages of the disease, when acid enters only the intra-abdominal portion of the LES, it cannot be detected by pH monitoring in the esophagus. Secondly, this fact excludes the possibility of functional reflux. DeMeester, in collaboration with histologists, effectively ruled out the possibility of physiological reflux, which he had stated in previous articles. Thus, at various points in his career, DeMeester published mutually exclusive ideas, never once renouncing the false one. This error has become a cornerstone of modern gastroenterology.

From the above scientific data, it follows:

(a) The hypothesis about the high reliability of clinical symptoms in the diagnosis of GER is erroneous.

(b) pH monitoring, proposed based on the determining role of clinical symptoms, detects only severe forms of GER. Its use is dangerous, since about 30% of patients with GER are not diagnosed, which means they remain without treatment.

(c) The hypothesis based on pH monitoring, about the possibility of physiological reflux does not correspond to scientific facts.

(d) The Lyon Consensus 2.0 (2023) provides a modern definition of actionable GERD, where evidence from esophageal testing (prolonged wireless pH monitoring or catheter-based pH or pH-monitoring of antisecretory medication; pH-impedance monitoring) guides diagnosis and treatment.[22]

(e) All decisions determined by voting (Lyon Consensus 2.0, Rome IV criteria, Montreal definition GERD, Los Angeles classification GERD, and Chicago Classification version 4) are not based on reliable scientific facts and are therefore not scientific. Unlike scientific hypotheses, false hypotheses create chaos. In this chaos, the only obvious things are the forums participants' interest in advertising diagnostic equipment.

I will give a typical example. In the article by Gorgulu et al. presents the results of a study of Turkish patients who had their esophageal biopsies examined under high magnification.[5] Daniel Sifrim, who works in London, is listed as a co-author with the Turkish doctors. His role was critical revision and supervision. Patients who had typical GERD symptoms (heartburn and/or regurgitation), at least once a week were included. After taking the biopsies, high-resolution 36-channel solid-state esophageal manometry was performed to exclude motility disorders, except for pathologies associated with GERD. Then, 24-hour pH-multichannel monitoring of intraluminal esophageal impedance was carried out. The patients who had acid exposure time (AET) > 6% without erosion were classified as conclusive NERD patients according to Lyon Consensus. The patients who had typical GERD symptoms and AET < 4% without erosion were divided according to symptom association probability (SAP) and symptom index (SI). Patients who had both positive SAP (≥ 95%) and SI (≥ 50%) were classified as reflux hypersensitivity (RH). Patients who had both negative SAP (< 95%) and negative SI (< 50%) were classified as functional heartburn (FH). Healthy controls (HC) had normal upper gastrointestinal endoscopy (UGE), 24-hour pH-impedance monitoring and high-resolution manometry while having no gastrointestinal symptoms or surgical history. The authors found that only mild and severe ErosiveRD patients had increased mean intercellular spaces (IS) values compared to other groups. There was no significant difference between NERD, RH, FH, and HC. They would not recommend the practical use of mean IS length measurement for conclusive diagnostic purposes.

The analysis of the article by Gorgulu et al reveals many contradictions

A retrospective study of 149 patients who had typical GERD symptoms (heartburn and/or regurgitation) at least once a week were included. Fourteen of them had "normal UGE, 24-hour pH-impedance monitoring and high-resolution manometry while having no gastrointestinal symptoms".[5] Firstly, on what basis were patients with heartburn and/or regurgitation at least once a week assessed as having no gastrointestinal symptoms? Secondly, patients with typical GERD symptoms cannot be considered healthy and could not serve as a control group. It is known that endoscopic examination without histology does not reveal pathology in most patients with GERD (Nonerosive reflux disease). As shown above, the absence of pathological changes in pH monitoring does not allow GER to be excluded, since with an AET index of < 6%, GER is not diagnosed with more than 30% of patients. It follows that dilated intercellular spaces (DIS) in obvious patients were compared not with the control group, but with the same patients, and therefore no significant difference was obtained with all other so-called phenotypes. And since DIS, which indicates damage to the mucous membrane, was the same in patients with FH and RH as in typical GER, it follows from this that FH and RH are organic diseases (reflux esophagitis), and not functional disorders. Interestingly, in 14 articles published by Sifrim on DIS, including with Italian and Chinese doctors, where he also acted as a corrector, other equally important but more convincing signs of inflammation (impaired barrier integrity and immune cell infiltration, often combined with eosinophilic and lymphocytic infiltration) were not studied in biopsies. For 17 years (2007 - 2024), the reason for the study was articles about the feasibility of the DIS study for the accurate diagnosis of GERD. And most of the articles ended with an advertisement for HRM and pH monitoring.

The article states that after taking the biopsies, HRM was performed "with the exception of pathologies associated with GERD".[5] This statement contradicts the description of the "Material", since GERD was suspected in all patients. Therefore, in accordance with the recommendation of the Chicago Classification, HRM was not indicated in all cases. The contradictions described reveal the true purpose of this study, as well as all the other 13 articles by Daniel Sifrim. (1) The authors advertise equipment for HRM and impedance pH monitoring, claiming that instrumental methods are the only objective method for diagnosing GERD. To this end, they discriminate against histological examination as such, which is easiest to do by attacking DIS. Histological diagnostics that reveal esophagitis is very simple, cheap and impeccable in accuracy, especially using the method of determining the cardiac epithelium over the LES.[7] But its use will not only destroy the thriving industry of unnecessary equipment but also destroy all the false ideas that were based on pH monitoring. Therefore, all consensuses on GERD recommend not perform histological examination of the esophagus if there is no visual pathology during endoscopy.[7,22] (2) It is not clear why the authors of the article violated the Chicago Classification recommendation not to perform HRM in GERD. But it is important to understand why such a recommendation exists. I analyzed 29 radiographic studies of children diagnosed with esophageal achalasia (EA), including those using HRM. Radiographic evidence of true EA, but without histological confirmation, was detected in only one observation. In 4 cases, there was congenital stenosis at the level of the LES. In all other cases, the radiographic appearance, clinical symptoms, and anamnesis were consistent with reflux esophagitis, including stenosis at the level of the LES in 4 observations.[23] Since reflux esophagitis leads to significant changes in esophageal motility, knowledge of this pattern would destroy the doctrine of EA, which was adopted by vote in Chicago (Chicago Classification). Unreasonable substitution of the diagnosis of GER for EA led to an increase in the frequency of EA from 0.03 to 32.58 per 100,000 population (in one of the districts of Chicago) i.e. increased more than 1000 times.[24]

Pathological physiology of GERD

1. The current state of the problem. In an article by Sharma and Yadlapati on the pathophysiology of GERD, it is stated that: "GERD is a complex disease often based on a multifactorial pathogenesis".[25] Any disease unites patients based on a common cause (etiology) and stages of disease development (pathogenesis). The article by Sharma and Yadlapati does not describe physiology - neither normal nor pathological. It describes various characteristics of GERD, which are supposedly the cause of the disease, "development factors." At the same time, the results of using different equipment are cited as the boundaries between normal and pathological. For example, authors state that the presence of the acid pocket may predispose individuals to the development of GERD, although this phenomenon has been shown in those without GERD. Moreover, the presence of a hiatal hernia, have been associated with increased acid pocket size. And they conclude: - "As such, GERD should be approached as a disorder beyond acid".[25]

The text implies that not GERD did cause the formation of the acid pocket, impaired esophageal clearance, hiatal hernia, or transient lower esophageal sphincter relaxation, but rather that these listed factors led to GERD. This statement is based on the false assumption that all these factors are observed in patients with GERD and also without GERD, i.e., in whom an AET <4%. However, as shown above, pH monitoring has significant methodological flaws and cannot be applied in practice. Thus, the acid pocket, impaired esophageal clearance, hiatal hernia, or transient lower esophageal sphincter relaxation are the results of GERD pathogenesis, not its cause. The authors further state that "In regard to symptom presentation, gastric acid increases sensitivity to reflux and thus enhances the perception of reflux symptoms".[25] This irresponsible statement substantiates the presence of functional heartburn, as well as other supposedly functional diseases, in cases where the clinical picture of GERD is detected in patients with AET < 4%.[25-27] The authors ignore the evidence above that 16% of people who considered themselves healthy had gastroscopic signs of GERD.[12] In 41.9% of patients after POEM with erosive esophagitis, there were no clinical manifestations. This indicates that refluxate damages nerve endings, which leads to impaired sensitivity, i.e., esophageal hyposensitivity.[14] The use of diagnostic equipment has replaced physiology and common sense. Based on pH monitoring, a distinction is made between gastric belching (GB) and supragastric belching (SGB). Belching less than 13 times a day is considered a physiological norm. It is believed that if a person swallows air, belching is the only way to eliminate it.[28] A survey of people of various ages shows that only 25% of children and young adults belch, but it is always accompanied by GERD symptoms. This suggests that air enters the intestines and is utilized there. Repeated belching is a symptom of GERD.[29] This analysis prompts us to briefly discuss the etiology and pathogenesis of GERD.

2. Etiology and pathogenesis of GERD from a scientific point of view. The overproduction of acid and the associated illnesses have a lifetime prevalence of 25-35% in the United States.[30] Hypersecretion of hydrochloric acid leads to damage to the upper gastrointestinal tract. During the use of drugs that suppress hydrochloric acid secretion, gastric and duodenal ulcers became extremely rare. The esophageal wall, unlike the stomach and duodenum, lacks such strong

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protection. Therefore, the symptoms of hypersecretion manifest primarily as reflux esophagitis. This is the tip of the iceberg, because erosions, deep changes in the wall, and dyskinesia of the stomach and duodenum leave their mark on the symptoms of GERD. Normally, the esophagogastric junction ensures one-way movement of the bolus. It allows the bolus to pass from the esophagus into the stomach and prevents its reverse movement. The final peristaltic wave, in accordance with the law of the intestine creates high pressure above the LES, which not only causes the LES to open but also exceeds gastric pressure, which is higher at rest than in the esophagus.[31] After the final peristaltic wave injects the bolus into the stomach, the LES contracts. The increased gastric pressure causes a reflex increase in LES tone, and the higher pressure leads to simultaneous contraction of the upper esophageal sphincter (UES) and the LES. This physiological pattern is the basis for radiographic examination, which allows one to determine the length of the contracted LES, the width and walls of the esophagus, including the ampulla, and the functional sphincters that appear during inflammation in the esophagus.[32]

The disease begins with acid penetration into the intra-abdominal portion of the LES. At this stage, the acid has not yet penetrated the esophagus and therefore cannot be detected by pH monitoring. Secondly, this indicates that functional reflux cannot occur. The acid disrupts the function of the LES, causing the intra-abdominal portion of the LES to open, leading to a shortening of the functional portion of the LES. Acid and pepsin also damage the esophageal wall, leading to lumen dilation and weakening of the final peristaltic wave. To maintain high pressure in the dilated and weakened peristaltic wave, the sphincter begins to function, closing this wave proximally (the proximal sphincter, PS). This allows this wave (ampulla) to create a threshold pressure for LES opening that is higher than the gastric pressure (Figure 1).

GERD is a chronic, progressive process. During ontogenesis, the LES shortens and the esophagus, particularly the ampulla, dilates. To determine the severity of the pathological process, I calculate the reflux index (RI), which is the ratio of the ampulla width to the LES length. Normally, increased gastric pressure does not impede LES contraction, and barium passes through the dilated LES. Since reflex LES dilation occurs because of contraction of longitudinal, spirally oriented muscles attached to the esophagus and to the stomach, the LES length during opening decreases relative to the age norm (Figure 1b).

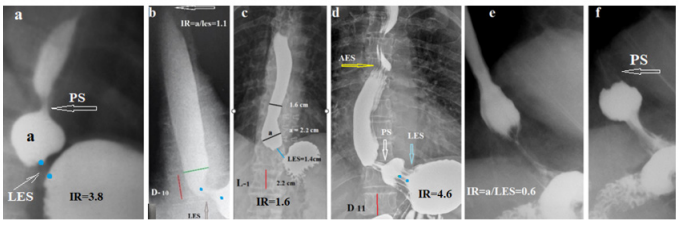

Figure 1 Esophageal and EGJ radiographs were taken with the patient supine during barium ingestion under high gastric pressure.[3]

(a) An 8-year-old child with GERD shows a marked shortening of the LES (0.9 cm) and a wide ampulla (4.2 cm). The area of esophageal contraction above the ampulla is the proximal sphincter (PS), whose contraction allows the ampulla to generate high pressure to inject bolus into the stomach. It also contracts during reflux from the stomach, preventing chyme from refluxing into the proximal esophagus. If the PS cannot withstand the pressure and opens during ampulla contraction, the pressure in the ampulla drops, and chyme from the stomach penetrates through the open LES into the esophagus. This is the transient lower esophageal sphincter relaxation mechanism, which is observed only in GERD. IR=3.8

(b) A 48-year-old man (a volunteer I know) with no gastrointestinal problems. The LES has opened despite high gastric pressure, indicating a strong peristaltic wave. The area of contraction of the wave is shown by the arrow. The length of the dilated LES is equal to the height D10, i.e., 2 cm, which is less than the minimum normal value (3.2 cm). All smooth muscle sphincters shorten during opening. ID=1.1 - significantly less than in patients with GERD.

(c) A 78-year-old woman regularly taking PPIs with a history of occasional belching, heartburn past heartburn and a 2-cm hiatal hernia on gastroscopy. ID=1.6, indicating mild GERD.

(d) A 71-year-old female patient with a long history of GERD and lactose intolerance. She frequently regurgitates food eaten the previous day. Gastroscopy reveals a large hiatal hernia. Radiograph shows a wide hiatus. Free reflux is present at rest. The PS and sphincter at the level of the aortic narrowing of the esophagus (aorto-esophageal sphincter - AES) are also visible. IR=4.6 indicates severe GERD.

(e) **(e-f)** A patient with a narrow, rigid esophagus and a narrow ampulla. The LES is not shortened, but its lumen contains traces of barium, indicating an inflammatory process. (f) During contraction of the PS, the contracting ampulla created high pressure and opened the LES. ID=0.6 confirms the diagnosis of eosinophilic esophagitis.

Eosinophilic esophagitis (EoE)

EoE represents a chronic, local immune-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. EoE manifested by dysphagia, intermitted food impactions and symptoms like gastroesophageal reflux disease, that predominantly affects young adults.[1,33-36] The diagnosis of EoE is established by an esophageal biopsy demonstrating at least 15 eosinophils per high-power field in the absence of other conditions associated with esophageal eosinophilia such as gastroesophageal reflux disease or achalasia.[1] Current therapies include proton pump inhibitors; topical steroid preparations, such as fluticasone and budesonide and dietary. Proton pump inhibitor therapy is associated with a histologic response, defined as less than 15 eosinophils per high-power field on endoscopic biopsy, in 41.7% of patients, while placebo was associated with a 13.3% response rate.[1] The authors avoid deciding why PPIs have a therapeutic effect. They suggest that PPIs are better classified as a treatment for esophageal eosinophilia that may be due to EoE than as a diagnostic criterion.[1] Instrumental research proponents have taken EoE beyond their interests, since histological examination is a decisive diagnostic method, unlike GERD, in which it allegedly has no advantage over pH monitoring. However, an analysis of the literature reveals many contradictions in the theoretical opposition of EoE and GERD.

Eosinophilic gastrointestinal diseases (EGIDs) comprise a group of chronic, inflammatory diseases of the gastrointestinal (GI) tract, that are characterized, clinically, by symptoms related to the dysfunction of the involved segment(s) of the GI tract, and histologically, by dense eosinophilic inflammation, in the absence of an identifiable secondary cause. The group of EGIDs comprises EoE, eosinophilic gastritis, eosinophilic gastroenteritis, and eosinophilic

colitis. Eosinophilic infiltration can be found in several parts of the digestive tract in one patient.[37] Mahendra et al showed that duodenal eosinophilia was associated with symptomatic erosive GERD.[38]

1. Literary analysis indicates that EoE is associated with GERD. It is well known that GERD and EoE may be accompanied by eosinophilia in mucosal biopsies. Therefore, the question of a possible connection between these diseases has repeatedly arisen.[34] Monnerat and Lemme, using pH monitoring, found pathological reflux in 25% of patients with EoE.[35] Pesce et al. found that Higher esophageal acid exposure time and lower baseline impedance values were significantly associated with eosinophilic infiltration ($P < .05$ and $P < .01$, respectively).[39] Frazzoni et al. using impedance-pH monitoring, concluded that reflux plays a role in the pathogenesis of EoE.[40] Surprisingly, all authors believe that pH monitoring cannot predict whether PPI treatment will be effective, as if pH monitoring is used for such predictions in other conditions. If pH monitoring is the main diagnostic method for GERD, then why can't it be considered a diagnostic method for EoE? We should not be confused by the low percentage of reflux detection (25%), because it is known that pH monitoring detects only severe forms of GERD. It is highly likely that in 75% of patients with an AET <4%, hydrochloric acid and pepsin, which break down dietary proteins, constantly enter the esophagus, remaining there for less than 1 hour per day. However, this is more than enough to cause reflux esophagitis, i.e., GERD. Thus, in the above articles the difference between EoE and GERD is only in the size of the eosinophilic infiltrate, which determines the more severe clinical picture in EoE. Eosinophilia is an allergic reaction to inflammation. Normally, i.e., in healthy people, there are no inflammatory cells, including eosinophils, on the wall of the esophagus.[41] Eosinophils arise during an inflammatory reaction, the more so, the more severe the allergy. This means that the limit of the norm is the absence of eosinophils. There are no limits to pathology. The limit of "at least 15 eosinophils per high-power field" was proposed empirically, since dysphagia is more common under these conditions. However, not always, and especially after PPI treatment. Secondly, even with greater eosinophilia, typical symptoms are not always detected. It is not surprising that a higher barrier (>35 eo/HPF) is phenotypically indistinguishable from EoE patients.[42]

2. **PPI use is effective in the treatment of EoE** PPI treatment for EoE has a positive effect, alleviating symptoms and reducing the number of eosinophils. Its effect reaches 33 to 70%,[34,35,40,42] almost the same as for GERD. To rule out reflux as a cause of EoE, 66 doctors (2018) in the proceedings of the AGREE conference stated that gastric acid inhibition is not the only important effect of PPIs, hinting, but without evidence, at the possibility of an anti-inflammatory effect of PPIs. However, what "may be" but has no scientific evidence should not be considered.

3. **Histological studies support the role of chemical trauma to the esophagus in the etiology of EoE**.

Some authors argue that EoE is a chronic allergic disease associated with type 2 inflammation and epithelial barrier dysfunction. For example, Rank et al, in an experiment on mice, discovered disrupted epithelial integrity was noted in (detergent) SDS-treated esophageal organoids. They showed increased esophageal width, increased IL-33 protein expression, basal zone hyperplasia, CD4+ cell infiltration, and esophageal eosinophilia.[43] The impaired barrier may develop as result of acid injury, from trauma, or infection. In this circumstance, food or aeroallergens may then contact the damaged epithelium and sensitized microenvironment in the esophageal mucosa, leading to activation of type 2 inflammatory pathway.[41] A study by Markey et al. revealed a previously unappreciated role for miR-155 in mediating epithelial barrier dysfunction in esophageal inflammation in EoE.[44] In a review article by Lei et al. it is argued that diagnosis of EoE can be difficult because it often overlaps clinically and histologically with GERD.[45]

4. **The radiographic picture of EoE indicates damage to the LES.** In the available literature, I found 10 cases of radiographic examination in patients with EoE, where the radiograph, in addition to the esophagus, captured the esophagogastric junction. All authors drew attention to the narrow width of the esophagus and the presence of erosions. Meanwhile, in all cases, I discovered the pathological function of the lower esophageal sphincter (LES). Figure 2 shows the most demonstrative radiographs.

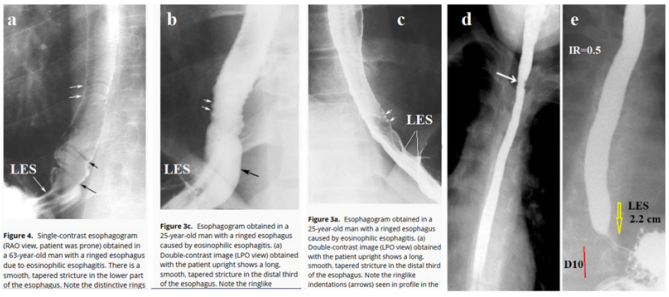

Figure 2 Radiographs of patients with EoE. (a-b-c) from the article by Zimmerman et al [46] with parts from figure captions. (a) In a 68-year-old patient, I have shown a short, wide, and folded LES. (b) In a 25-year-old patient, a wide, gaping LES is visible. (c) In the same patient, in another projection, it is visible that the LES is significantly shorter than normal. (d-e). From the article by Al-Hussaini et al.[47] (d) Barium esophagogram in a 15-year-old patient shows a stricture at 3 cm below upper esophageal sphincter, long-segment narrow caliber in middle and lower esophagus. (e) In the same patient after three sessions of the esophageal dilation (up to size 11 mm) the LES length is 2.2 cm. IR=0.5.

Barium swallow study is frequently normal in pediatric EoE except for narrow-caliber esophagus.[47] In adults at barium studies in seven patients (50%), the strictures contained multiple fixed ringlike indentations that produced a ringed esophagus. The ringlike indentations appeared as multiple, fixed, closely spaced, concentric rings traversing the stricture. Ten (77%) had hiatal hernias and nine (69%) had reflux during X-ray examination.[46] The analysis of radiographs found in published articles confirms the hypothesis that EoE is provoked by reflux of gastric refluxate into the esophagus. This follows from the understanding that reflux on X-ray examination is convincing evidence of impaired LES function, i.e., GERD. Secondly, what the authors call hiatal hernia is actually a phrenic ampulla, which occurs only with GERD. Thus, radiographic studies confirm the other evidence listed above that EoE is a special histological form of GERD.

EoE is a cause of Schatzki ring

Schatzki first reported a ring-like structure at the esophagogastric mucosal junction in 1953. There is still no uniform agreement as to its exact location, etiology, or clinical importance. Johnson et al. found Schatzki ring (SR) in 15% to 18% of 22,368 patients having routine upper gastrointestinal examinations.[48] SR is commonly associated with hianal hernia (96%), EoE (40%) and GERD (40%).[49] Sarbinowska et al. found the increase in TGF-β1 and MBP concentrations, which indicates the inflammatory and probably fibrostenotic pathogenesis of SR. Obtained results do not allow for an unequivocal classification of SR as a complication typical only for GERD or EoE.[50] The relationship

between the localization of SR and the width of the esophagus and the state of the LES is shown in Figure 3. I have selected typical cases SR where peptic stenosis could be excluded.

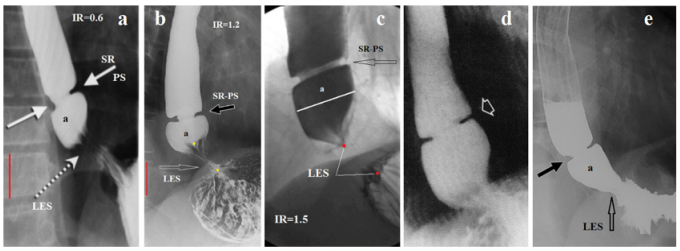

Figure 3 Radiographs of patients with SR.

(a) The red line shows the height of D10, the true value of which is 2 cm. The width of the ampulla (a) is 1.9 cm, and the distance from the ampulla to the stomach is 3 cm with longitudinal folds—this is the length of the LES. The width of the esophagus above the SR is 1.4 cm. The reflux index (IR) is equal to the ratio of the width of the ampulla to the length of the LES. It is equal to 0.6

There is a concept, which has no logical explanation, that a dilation in the lower part of the esophagus up to 2 cm wide is an ampulla, and more than 2 cm is a hiatal hernia. The concept of a hiatal or sliding hernia, which is observed only in the horizontal position, suggests that the LES is displaced into the chest due to shortening of the esophagus. As an analysis of such studies shows, the authors mistake shortening of the LES in patients with GERD for shortening of the esophagus.[7,31,32] Longitudinal folds in the LES are evidence of an inflammatory process and are not related to the stomach.[7] This radiograph shows that the SR is in the usual location of the PS. Secondly, the narrow lumen of the esophagus and ampulla suggests EoE.

(b, c, d, e) In the presented radiographs, the fibrous ring is in the place of the PS.

(d, e) These radiographs, in contrast to the previous images, reveal dilation of the hiatal canal and insufficiency (gaping) of the LES, which indicates a severe form of GERD.

Analysis of SR radiographs suggests that the rigid ring is an altered PS due to GERD, with a predominantly allergic reaction leading to fibrotic changes.

Hypothesis of the pathogenesis of EoE

The above analysis shows that all patients with EoE have GERD. If we discard assumptions that have no scientific evidence, as well as statements that contradict known scientific facts, then the pathophysiology of EoE is as follows. Eosinophilic esophagitis is a reflux esophagitis in individuals with an allergic reaction to various allergens. Hypersecretion of hydrochloric acid disrupts the integrity of the esophageal mucosa and causes an inflammatory reaction. The trigger for hypersecretion is lactose in patients with lactose intolerance. In EE and GERD, an increase in the number of eosinophils, basal cell hyperplasia, intercellular edema, and elongation of epithelial papillae are observed. There is no absolute histological criterion allowing distinction between EoE and GERD, and cutoff values for numbers of eosinophils vary according to studies and authors.[51] Elimination of foods that cause allergies from the diet leads to a decrease in eosinophilia and clinical improvement in more than 75% of patients.[52] Clinical and histological improvement after refusal to foods containing lactose is explained by the cessation of lactose intake.[24] Esophageal narrowing that leads to dysphagia does not occur suddenly, but is the culmination of a process that began long before dysphagia and was manifested by GERD symptoms. Since hypersecretion of hydrochloric acid affects all parts of the digestive tract, it can lead to eosinophilic infiltration of other parts and cause a violation of their functions (Figure 4).[1,37,38]

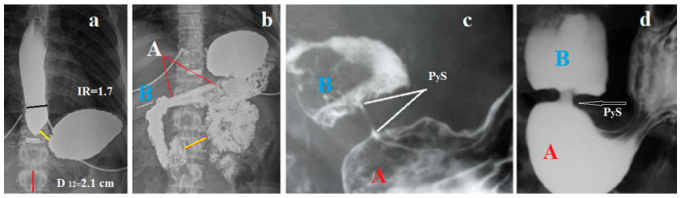

Figure 4 (a-b) Radiographs of a 19-year-old girl with heartburn and abdominal pain, overweight. Recently, she lost 20 kg due to vomiting after eating. She has an allergy to bird feathers. **(a)** During high pressure in the stomach, the LES contracted. A shortened LES (yellow) and dilated esophagus (black) indicate GERD (IR = 1.7). **(b)** After 5 minutes, a sharp narrowing of the antral part of the stomach (A) with straightened contours, a thickened wall, and a narrow passage is determined. The bulb of the duodenum (B) is deformed. Contraction of the Ochsner sphincter is determined in the third part of the duodenum (yellow line), indicating hypersecretion of hydrochloric acid [24]. Radiographs **(c-d)** show a normal picture of the bulb (B) and a wide antrum of the stomach (A) with clear walls and deep peristalsis. The opening of the pyloric sphincter (PyS) is accompanied by its shortening. All smooth muscle sphincters behave this way.

The above case demonstrates that hypersecretion of hydrochloric acid damages not only the esophagus (GERD) but also the stomach and duodenum. Rigid antral gastritis is detected in the stomach, the narrowing of which is like the changes in the esophageal wall seen in EoE. Given the patient's allergies, the most likely diagnosis is eosinophilic antral gastritis.

Discussion

EoE was first described as an entity distinct from GERD in 1993 by Attwood and colleagues who observed increased intraepithelial esophageal eosinophils (>20 eos/hpf, mean of 56 eos/hpf) and squamous epithelial hyperplasia in 12 adults with dysphagia in the absence of GERD (that is, with normal findings on endoscopy and 24 h pH testing).[53] American Gastroenterological Association Institute and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition defined EoE in 2007 as a clinic-pathological disorder characterized by esophageal symptoms, biopsies showing >15 eos/hpf and the absence of pathological GERD as shown by normal pH testing or lack of response to high-dose PPI treatment. This definition implied that GERD and EoE were mutually exclusive conditions.[54] The 2011 consensus definition has no such preclusion.[55] In terms of the condition of the esophageal wall, EoE and GERD differ from each other and require different treatment. Thirty years have passed since 1993. During this time, physicians dedicated to the study of EoE met twice for conferences. But instead of publishing the discussion materials, as is customary in the scientific world, they published the "arithmetic mean" of their opinions—consensus statements. This may be why it has only recently been found that these two conditions are very similar in clinical manifestations, histological findings, and radiological findings. They allegedly often coexist, and therefore, in many cases, there are serious diagnostic difficulties.[56-58] No authors do not recommend using the pH test, which was the main differential diagnostic method between EoE and GERD in the article by Attwood et al.[53] This is because the "physiological reflux" is seen in as many as 25% of patients with documented erosive esophagitis.[57] The recommendation not to use pH monitoring is justified because physiological reflux is a fiction used to promote the equipment. For example, studies using the preparation of human esophageal mucosa

have found that acid stimulates the release of platelet activating factor (PAF), a phospholipid that can attract and activate eosinophils.[57] This means that the penetration of aggressive gastric chyme into the esophagus with pH <4 in < 3.2% in 24 hours also damages the esophagus, since there is no physiological reflux.[27,32]

The widespread promotion of pH monitoring has distorted many ideas about GERD. For example, a review article by Dellon states that "The motility may be altered in these (EoE) patients, and they may have issues with clearing of physiological normal reflux.[56] This phrase confirms that the patient with EoE had reflux, i.e., GERD. In another case, the authors diagnosed EoE, not GERD, in a patient with a 1 cm hiatal hernia. However, as demonstrated above, the presence of a hernia is evidence in favor of GERD. Therefore, this case should also be considered a GERD. The clinical picture also confirms the presence of reflux in EoE, because studies reporting heartburn as a common symptom of EoE.[57] The most accurate diagnostic sign of GERD is damage to the LES, which, on radiographic examination, is shortened relative to the minimum age-appropriate limit. Shortening of the LES was also found in EoE. Thus, after adjusting clinical symptoms, radiographic, and endoscopic data, we found a near-complete, if not complete, overlap between EoE and GERD. At the same time, all authors claim that: - "At the present time, an adequate biomarker to distinguish these entities is lacking".[56-59] Dietary intervention studies provide significant information regarding the pathogenesis of GERD and EoE. For example, in pediatric patients with refractory GERD who had failed prior medical and surgical treatments directed at GERD found that treatment with an elemental formula resulted in marked reduction in intraepithelial esophageal eosinophils and improvement in symptomatology, introducing the concept that a food-protein-induced, allergic mechanism was responsible for the pathogenesis of EoE.[56] Kliewer et al. compared the effectiveness of a milk elimination nutrition program (1FED) with a 4-ingredient elimination nutrition program (4FED), including milk. Although 4FED moderately improved symptoms compared with 1FED, the histologic, endoscopic, QoL, and transcriptomic outcomes were similar in both groups. They concluded that 1FED is a reasonable first-choice therapy for pediatric EoE, given its effects, tolerability, and relative simplicity.[59] These studies show that EoE and GERD respond similarly to milk exclusion. However, there is no evidence that milk protein is the chemical element that causes pathology. My research has shown that in patients with lactose intolerance, eliminating lactose-containing dairy products from the diet leads to a significant improvement in symptoms of both GERD and EoE.[60] This is because undigested lactose causes an increase in mast cells in the small intestinal mucosa, which leads to hypersecretion of hydrochloric acid.[24] The exclusion of all products containing lactose enhances the therapeutic effect of the diet. This is especially important for patients over 50 years of age, because the older the patient, the less lactose quantity causes an exacerbation of acid-related problems.

This study supports the hypothesis that EoE is not a simple combination of two diseases with different etiologies and pathogenesis. It is not EoE leading to the development of GERD, but rather primary GERD complicated by an eosinophilic infiltrate resulting from an allergic reaction. This hypothesis allows for the diagnosis of EoE based on the combination of dysphagia and reflux symptoms in the presence of allergies. Radiographic examination confirms the diagnosis in the presence of esophageal stenosis and shortening of the LES. Treatment of EoE involves treating GERD[60] and allergies.

Conclusion

Based on the literature review, I have come to the following understanding of the pathophysiology of EoE. Eosinophilic esophagitis is reflux-esophagitis in individuals with an allergic reaction to various allergens. The trigger is hypersecretion of hydrochloric acid, which disrupts the integrity of the esophageal mucosa and causes an inflammatory reaction. The allergic component leads to fibrous thickening of the esophageal wall, narrowing of the lumen, and may be accompanied by dysphagia. In some patients, fibrous changes occur in the proximal sphincter, which in GERD closes the proximal esophageal ampulla. This is how the Schatzki ring develops. It is hypothesized that eosinophilic gastritis manifests as rigid antral gastritis. Radiographic examinations with high intragastric pressure have high diagnostic accuracy. Understanding the etiology and pathogenesis of eosinophilic esophagitis is important for choosing effective treatment.

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