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Original Research Paper

Gastroenterology

COMMON AND INFREQUENT COMORBIDITIES OF EOSINOPHILIC ESOPHAGITIS

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ABSTRACT **Background.** Eosinophilic esophagitis (EoE) is characterized by dysphagia and food impactions in adults, gastroesophageal reflux disease (GERD) symptoms-like in children, and ≥15 eosinophils per high power field. Patients have a disease burden due to chronic symptoms and the comorbidities associated. Minor comorbidities in EoE have not been adequately studied in the literature. For this reason, this study aims to investigate the prevalence of atopy, autoimmune, infectious, genetic diseases, and minor others. **Methods.** A prospective observational study in patients evaluated in a multidisciplinary EoE unit. **Results.** The most frequent comorbidities were atopic, but the autoimmune and infectious were minorities. In conclusion, in EoE, we must carry out an anamnesis and exhaustive review of the clinical history for the early diagnosis of comorbidities. In patients with atopy, infectious esophagitis, and autoimmune diseases, we will ask about symptoms of GERD or swallowing disorders due to the risk of associated EoE.

KEYWORDS : Comorbidities; atopic; autoimmune; infectious

Eosinophilic esophagitis (EoE) is a clinicopathological disease characterized by esophageal symptoms, such as dysphagia and food impactions in adults gastroesophageal reflux disease (GERD) symptoms-like in children and ≥15 eosinophils per high power field in the esophagus after exclusion of other eosinophilic disorders (1,2). EoE has increasing worldwide prevalence in children and young adults. (3)

The prevalence of EoE continues to increase in parallel with atopic diseases. Allergic rhinitis is the most common comorbidity (4) Patients carry a considerable disease burden due to chronic symptoms and the comorbidities associated with EoE. The incidence and prevalence of EoE and inflammatory bowel disease (IBD) are rising similarly. Co-occurrence of both disorders in the same patient has been increasingly reported (5,6) Minor comorbidities in EoE have not been adequately studied in the literature, and not because they are less prevalent, they are less important. For this reason, the objectives of this study are: To study in patients with EoE the prevalence of autoimmune, infectious, rare genetic diseases, and others.

METHODS

Observational prospective Unicenter study included consecutive patients evaluated in a multidisciplinary EoE unit from January 2012 to December 215, and later, they were assessed on Allergology service for five years. All included patients gave their written consent to participate in the study. The study was designed according to the principles of the Helsinki Declaration and was approved by the center's Ethics Committee.

Patients of this study were adults and children (> 8 yrs old) and, according to current guidelines, received a diagnosis of EoE by symptoms of esophageal dysfunction (SED) and esophageal inflammation > 15 eosinophils per high power field (Eos/HPF).

We performed a systematized study protocol for all patients, including demographic data (age, gender, and personal history). We ask questions in the anamnesis about the diseases that they had suffered and review t of the electronic medical history to confirm the disorders of each patient - atopic, autoimmune /connective tissue (AI/CT), infectious, genetic, psychiatric, rhinosinusitis with nasal polyposis (RSwPs), intolerances, immunoglobulin deficiency, and obesity-. We recorded patients' symptoms and performed an upper gastrointestinal endoscopy with esophageal, gastric, and duodenal biopsies.

An anesthetist monitored all endoscopic procedures under conscious sedation with a 9 mm high-definition flexible endoscope of 9 mm caliber (GIF-H180, Olympus Medical Systems, Ale) and Exera II image processor (Olympus Medical Systems, Ale).

Biopsy specimens were taken with a conventional needle clamp (Radial JawTM 4 Boston Scientific. Proparck, Costa Rica) from the proximal and distal third of the esophagus, taking at least three samples in each section. Two additional biopsies from the antrum and duodenum were taken in all patients.

Biopsy samples were fixed with formalin 4% and embedded in paraffin for further staining with hematoxylin and eosin. Samples were examined under a Nikon® Eclipse 80i optical microscope (Nikon, Tokyo, Japan) with an HPF (x400) of 0.24 mm2. Samples were also stained with PAS to exclude the presence of fungi.Statistical study: Qualitative and quantitative variables will be expressed as absolute frequencies and percentages.

RESULTS

Table 1. Atopic, autoimmune, and infectious comorbidities in Eosinophilic Esophagitis (EoE)

comorbidities	ABSOLUTE FREQUENCIES	percentages
Atopic		
Rinoconjunctivits	258	67%
bronchial asthma	65	22%
Food allergy Anaphylaxis	122 33	29% 8.5%
Atopic Dermatitis	42	11%
Autoimmune		
Mellitus diabetes Hypothyroidism Hyperthyroidism	3 14 2	0.8% 3.6% 0,52%
cutaneous lupus Psoriasis rheumatoid Arthritis	1 1 1	0.26% 0.26% 0.26

IBD (INFLAMMATOR Y BOWEL diseases): Crohn disease ULCERATIVE COLITIS Celiac Disease	3 1 2 8	0.8% 0.26% 0.52% 2.1%
INfeCTioUS fungi (Cándida Albicans) virus (HERPES simplex virus)	10 7 3	2.6% 1.8% 0.8%

Other minority comorbidities in eosinophilic esophagitis	ABSOLUTE FREQUENCIES	percentages
• oCCUPATIONAL COMORBIDITIES	4	1%
rhinoconjunctivitis AND	3	0.8%
ASTHMA TO:	1	0.1%
• TTTTTAT FLOUR		
• egg proteins		
• Chronic Rhinosinusitis with nasal Polyposis	3	0.8%
• lactose intolerance	1	0.26%
• Non-celiac gluten intolerance	1	0.26%
• OBESITY	5	1.3%
• IMMUNOGLOBULIN DEFICIT	5	1.3%
• NEOPLASMS (0 Esophagus, 3 Breast, 2 Colon, and Essential thrombocythemia)	1	0.26%
• Eosinophilic granulomatosis con poliangeitis		

DISCUSSION

EoE and other atopic diseases are characterized by a TH2 predominant inflammation and are frequently associated with multiple comorbid in the patients (7,8). Currently, TH2 inflammation is an underestimated global health problem of increasing prevalence (8) It has been suggested that EoE may concur with gastrointestinal (GI)and AI/CT conditions (9 Shahetalin first described the association between celiac disease (CD) and EoE. In 2016 Petersonet al. reported that patients with EoE were 8.7 times more likely to be diagnosed with CD than the controls. Similarly, subjects with IBD were nearly four times more likely to be diagnosed with unaffected controls. This same group reported higher rates of AI/CT diseases in patients with EoE, including multiple sclerosis, systemic sclerosis, and Hashimoto's thyroiditis.

A study detected an increased prevalence of EoE in children with CT diseases (Marfan syndrome and Ehlers-Danlos syndrome) and children with autism spectrum disorder (ASD). They also had an increased risk of pollen food allergy syndrome, anaphylaxis, and autoimmune and psych comorbidities compared with of Pennsylvania population (10). Comparing the results of this study with ours, the percentages of atopic comorbidities are similar (with some difference of no more than 5%) except for asthma, which is much more frequent in our patients (Table 1). The majority of EoE in adult and pediatric patients with CD ranges from 3.2% to 10.7%, based on American, Italian, and Australian studies. However, the prevalence of CD in patients with EoE is less well delineated. In a large cohort of adults with EoE, the majority of CD was 2% (similar to ours, 2,1%). The prevalence of Pennsylvania CD is 0.11%, significantly lower than the estimated prevalence in the United States (0.54%). Regarding AI diseases, in general, our frequency is much lower. The frequency of IBD is similar to ours. The frequency of psoriasis is lower, and the frequency of thyroid diseases is higher in our environment (10) Risk factors leading to the development of Candida esophagitis (CE) in immunocompetent patients have not been fully elucidated. In a study with more than 80,000 patients, the prevalence of CE was 1.7% in all patients, 9.8% in HIV-infected patients, and 1.6% in HIV-uninfected patients. The majority of CE from 2002-2003 to 2012-2014 tended to increase in HIV-uninfected patients. Risk analysis revealed that increasing age, HIV infection, and corticosteroid use, particularly at higher doses, were independently associated with EC.

PPI drugs can facilitate this infection by raising PH, and they could favor the growth of this fungus. The prevalence of CE in our patients with EoE was 1.8%. The concurrence of EoE and CE is poorly described in the literature; we have only found one case published in 1998 by Brito EM et al. In our series of patients with EoE, the most common symptom was mild dysphagia; our patients attributed this symptom to a previous diagnosis of EoE/GERD. In a study, they have abdominal pain (12).

The EoE and the herpetic esophagitis (HE) can coexist, or one of the two precedes the other in more or less time. Different theories have been postulated depending on the time sequence, and the treatment followed for EoE. On the one hand, when HE appears in cases of EoE already diagnosed and untreated, it is believed that the absence of treatment can cause an alteration in the integrity of the mucosa of the esophagus and favor the invasion of viral agents. On the other hand, in cases in which HE precedes EoE, it is believed that the infection may act as a trigger by generating an immune response and his development, or even that EoE already existed and was not initially diagnosed, which supports the first theory (13).

The prevalence of Helicobacter Pylori (HP) infection in our patients is half that of the general population. However, in 2021, 50% of the Spanish population suffered from this infection (14). The claim that H.P protects against EoE is quite incomplete and controversial. Therefore, more mechanistic studies are needed to elucidate a possible association (15,16). EoE is not considered a premalignant disease. There appears to be no association between esophageal cancer and EoE (17). A case of EoE has been described as part of an intrathoracic paraspinal ganglioneuroblastoma. After surgical removal of the tumor, all upper gastrointestinal symptoms I resolved. A control esophageal biopsy 4 weeks after tumor resection was routine. The authors do not mention whether there was a subsequent follow-up to confirm your remission (18).

In conclusion, it is justified for patients with EoE to carry out a complete anamnesis by apparatus and exhaustive review of the clinical history for the early diagnosis of comorbidities that can contribute to worsening patients' quality of life. Also, in patients with Infectious esophagitis, AI/CT, atopic, and rare disorders, we ask about SED due to the risk of associated EoE.

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