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Endoscopic Classification of Esophagic Eosinophilia

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Abstract: Introduction: EoE (eosinophilic esophagitis) is an inflammatory condition characterized by a dense eosinophilic infiltrate in the esophageal epithelium. In Brazil, it remains a poorly diagnosed disease due to the lack of interaction between the clinician, the endoscopist, and the pathologist. The diagnosis is performed by histological study of esophageal biopsies, with at least fifteen eosinophils per high-power field (EOS/HPF). Some doubts remain with respect to patients with a clinical picture and symptoms compatible with the disease (EoE), but who have a lower number of eosinophils than established. The main objective of this study was to create an endoscopic classification for EsEo (esophageal eosinophilia), which pointed the way to the endoscopist towards the diagnosis. Methods: This study was a prospective, two-year study, at a gastrointestinal endoscopy center where all patients with endoscopic symptoms and/or endoscopic findings suggestive of EsEo were biopsied for histological examination of EOS/HPF. After the study and compilation of the results, a retrospective study was performed, based on a review of electronic medical records, where the same diagnosis was searched, although at a period when this classification was not adopted. Results: A total of 4,251 endoscopies were performed between September 2011 and September 2013. Two biopsies were performed, aimed at lesions, in 133 patients with clinical picture or imaging suggestive of EsEo. Eosinophils were found in 55 patients, corresponding to an incidence of 1.29% of the total population studied and 41.35% of the suspected cases of the disease. EoE was diagnosed in 24 patients during the period of this study. In the two-year retrospective study, only two cases of EoE were found. Conclusions: The results of this study demonstrate that the endoscopic standardization of esophageal lesions, suggestive of eosinophilia, in this case by classification, alerts the endoscopist for the diagnosis of EoE, prompting him to perform targeted biopsies. Further, it was observed that two samples of esophageal tissue were sufficient for the diagnosis. The relationship between the clinical picture, endoscopy, and histology was not evident in this study.

Key words: Endoscopic classification, eosinophilic esophagitis, esophageal eosinophilia, esophagus, eosinophils.

1. Introduction

EoE (eosinophilic esophagitis) is an inflammatory condition characterized by a dense eosinophilic infiltrate in the esophageal epithelium [1]. The disease has pathophysiological mechanisms similar to allergy, also known as allergic esophagitis, clinically evolving as a chronic disease, with periods of exacerbation and high gastrointestinal symptoms [2, 3].

This pathology is well known in the pediatric population, but only recently studied in adults and therefore still poorly diagnosed in this age group [1]. With the increase of the diagnosis the prevalence has been increasing, reaching 43 cases per 100,000 inhabitants [4]. It is the main cause of food impaction in young adults [5]. The preponderant age group ranges between 20 and 40 years [6] and is more frequent in men [2, 3]. There is a family and personal history of allergy in a considerable number of patients and the disease may have a familiar character in up to 10% of cases [7]. Some studies demonstrate the association of EoE with GERD (gastroesophageal reflux disease) in up to 40% of cases [8]. EoE may also be related with other inflammatory diseases, including the association between celiac disease [9] and other allergic diseases, such as asthma, allergic rhinitis, and atopic dermatitis [10].

The pathogenesis of EoE is still not fully understood, but it is known that differentiation of eosinophils from precursor cells in the bone marrow occurs from an antigenic, respiratory, or gastrointestinal stimulus [2]. Activation of eosinophils occurs in the tissues, which

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degranulate, releasing substances, such as histamine, causing inflammation of the tissues and the consequent symptomatology of EoE [11].

The normal esophageal mucosa is formed by stratified squamous epithelium, containing lymphocytes, dendritic cells, and stem cells, but no leukocytes, including eosinophils. There is still some variability in the histological concept of EoE. Some authors believe the disease is histologically characterized by more than 20 eosinophils per high-power field (EOS/HPF) [12]. Others suggest that the number of 15 EOS/HPF is sufficient [13, 14]. Some studies use a cut-off of 5 EOS/HPF [2].

EoE is characterized by a varied spectrum of symptoms in adults, such as dysphagia, food impaction, vomiting, chest pain, nausea, heartburn, epigastric pain, sialorrhea, food intolerance, and difficulty in swallowing [15]. Respiratory symptoms such as cough, sinusitis, and pneumonia may also be present. In some situations, reflux symptoms may be present [16]. Often the diagnosis is performed only many years after the onset of these symptoms [17].

The diagnosis is performed through upper digestive endoscopy with analysis of the fragments of the esophageal mucosa obtained by biopsy [2]. Endoscopic findings are usually non-specific and similar to other diseases observed in the esophagus [18]. The endoscopic exam can be normal between 18% and 42% of the cases or exhibit alterations common to other pathologies [19, 20]. The most frequent endoscopic findings described in the literature include numerous esophageal mucosa alterations such as rings, transverse grooves, longitudinal erosions, edema, friability, whitish plaques, stenoses, polyps, among others [20, 21]. There are no pathognomonic signs of EoE. However, in symptomatic patients, the following endoscopic changes are suggestive of the disease: transverse rings (48%), longitudinal grooves (46%), stenoses (24%), and caliber of the esophagus (12%) [8]. It is critical that endoscopists are familiar with endoscopic observations, characteristic of this pathology, to avoid delays or errors in diagnosis [22].

Several therapeutic modalities have been studied and proposed for EoE. Corticosteroids, systemic [23] and topical, have been evaluated, demonstrating its efficiency both in remission of symptoms and in histological improvement [24]. Another therapeutic option includes diet [24, 25], which, according to some studies can lead to clinical and histological improvement in 75% to 98% of patients [25] through guidance of skin and serological tests [26]. In more extreme situations, endoscopic esophageal dilatation can be indicated, a procedure with considerable morbidity and restricted indications [27].

The number of studies on this pathology in adults is extremely reduced in Brazil, being limited to a few literature review works [2, 3]. There are no studies in the south of the country or in the South American continent. This justifies a more thorough investigation in a region of southern Brazil, the Alto Vale do Itajaí-SC, composed of 28 municipalities, with a population estimated at 300,000 inhabitants, populated predominantly by European descendants, who are epidemiologically more affected by this pathology [28].

2. Objective

This study aimed at demonstrating that the standardization of the endoscopic method through a classification system can significantly increase the diagnosis of EsEo (esophageal eosinophilia).

3. Materials and Methods

A classification for EsEo was initially developed based on the association of the clinical picture and endoscopic findings. The term esophageal eosinophilia was used with the following stratification: EsEo type 0 (Figs. 1 and 2)—absence of endoscopic lesions but with compatible clinical picture; EsEo type 1 (Figs. 3 and 4)—Longitudinal and/or circumferential stretch marks, with or without clinical picture; EsEo type 2 (Figs. 5 and 6).

EsEo type 0:

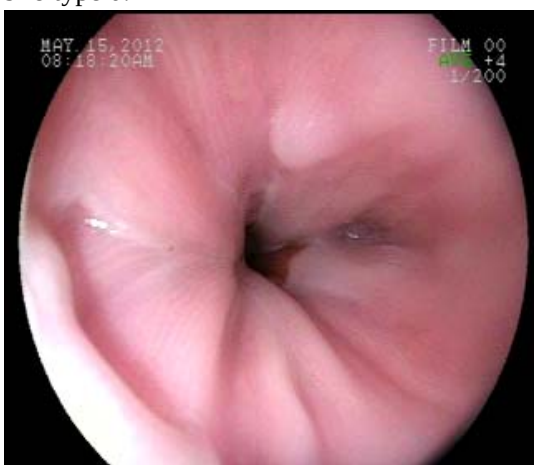

Fig. 1 20 EOS/HPF.

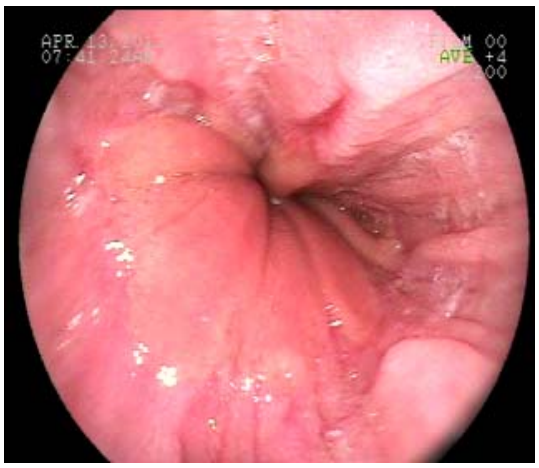

Fig. 2 15 EOS/HPF image GERD.

EsEo type 1:

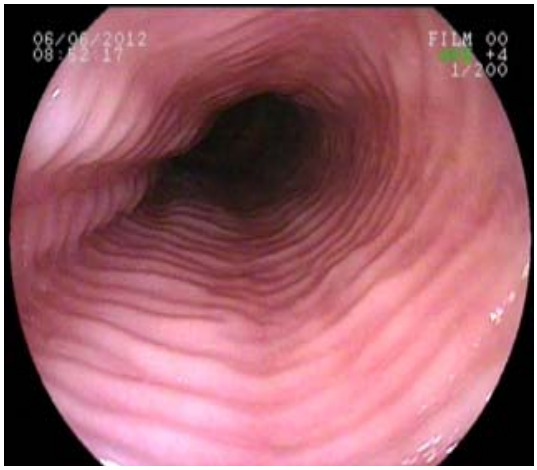

Fig. 3 16 EOS/HPF.

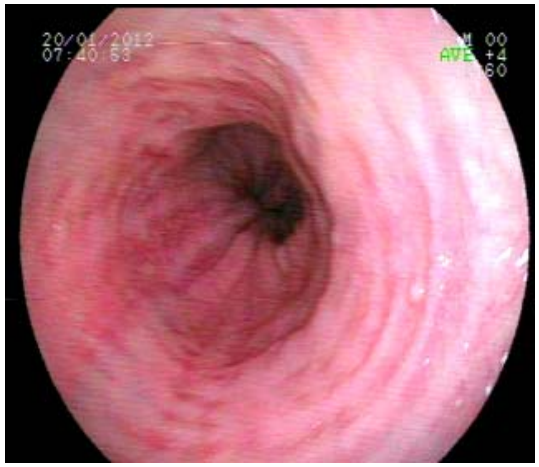

Fig. 4 25 EOS/HPF.

EsEo type 2:

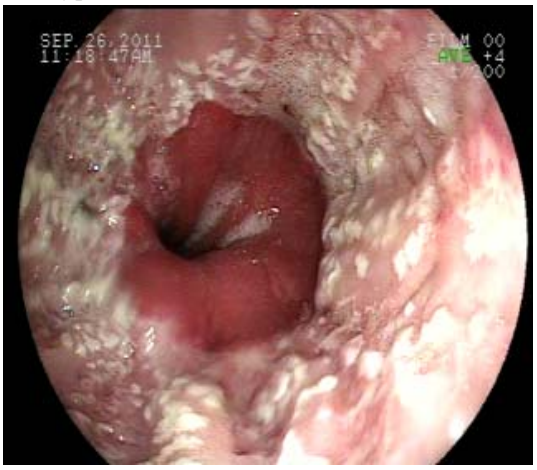

Fig. 5 20 EOS/HPF.

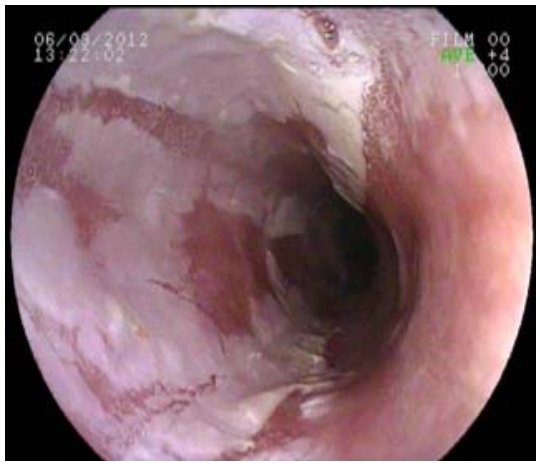

Fig. 6 35 EOS/HPF.

EsEo type 3:

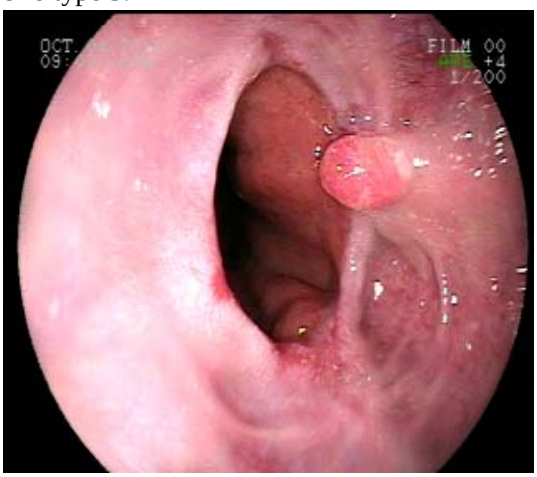

Fig. 7 30 EOS/HPF/stenosis + polyp.

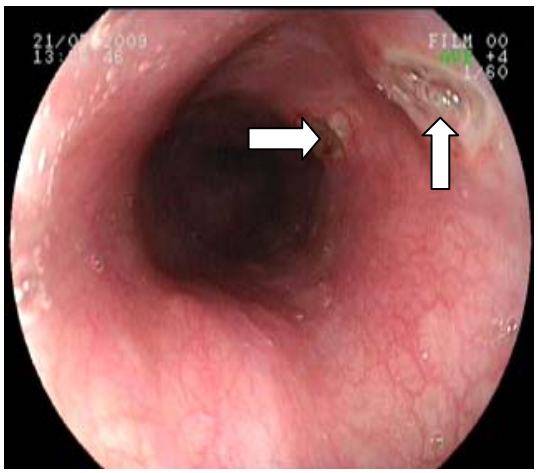

Fig. 8 20 EOS/HPF/ulcer.

Esophageal lesion with whitish areas in lumps or plaques, with or without clinical picture; EsEo type 3 (Figs. 7 and 8)—Complex esophageal lesions suspected of eosinophilic esophagitis with stenosis, polyps or ulcers. The study involved the performance of upper digestive endoscopies, in a period of two years, always by the same endoscopist (the author), with two esophageal tissue biopsies, in exams with findings suggesting EsEo or with compatible clinical picture. The endoscopies were all performed in the same clinic and the slides examined in the same laboratory, by the same pathologist. These patients received an informed consent form, with information about the examination, disease, the study, and the possibility of future contact for consultations, treatment, questionnaires or new examinations. Patients who accepted to participate in the study and exhibited a clinical picture or endoscopic image suggestive of esophageal eosinophilia were submitted to a questionnaire about their age, sex, ethnicity, eating habits, symptoms, morbid family and personal history.

Next, slides with 1 to 4 EOS/HPF were selected and named Group A (GA), slides with 5 to 14 EOS/HPF were called Group B (GB) and slides containing 15 or more EOS/HPF were named Group C (GC), to search for a clinical, endoscopic, and histological correlation. This division was chosen by the fact that up to 4 EOS/HPF can be found in the GERD. With 15 EOS/HPF or more, the eosinophilic esophagitis diagnosis is confirmed. However, patients who are between 5 and 14 EOS/HPF are without confirmation of the diagnosis of EoE.

4. Results

A total of 4,251 endoscopies were performed from September 2011 to September 2013. Biopsies were carried out in 133 patients with clinical picture or imaging suggestive of EsEo. In 55 patients, eosinophils were found in a large-scale field survey, representing an incidence of 1.29% of the total population studied and 41.35% of the suspected cases of the disease.

Of these, 21 presented 1 to 4 EOS/HPF, called (GA); 10 patients exhibited between 5 and 14 EOS/HPF, named (GB), and 24 patients showed 15 or more EOS/HPF, named (GC); amounting to the 55 patients included in the study.

Forty-three (78.18%) patients were male and 12 (21.81%) were female; age ranged between 17 and 73 years with a mean of 39.70 years.

All the patients included in the research were of European origin (Italians, Germans, and Polish).

The most frequent symptoms (Fig. 9) were heartburn (33) 60%, food impaction (27), chest pain (18), hiccups (3), vomiting (2), and nausea (1). No predominance of specific symptoms in any type of lesion was observed.

In 19 cases (42.42%) there was a report of associated

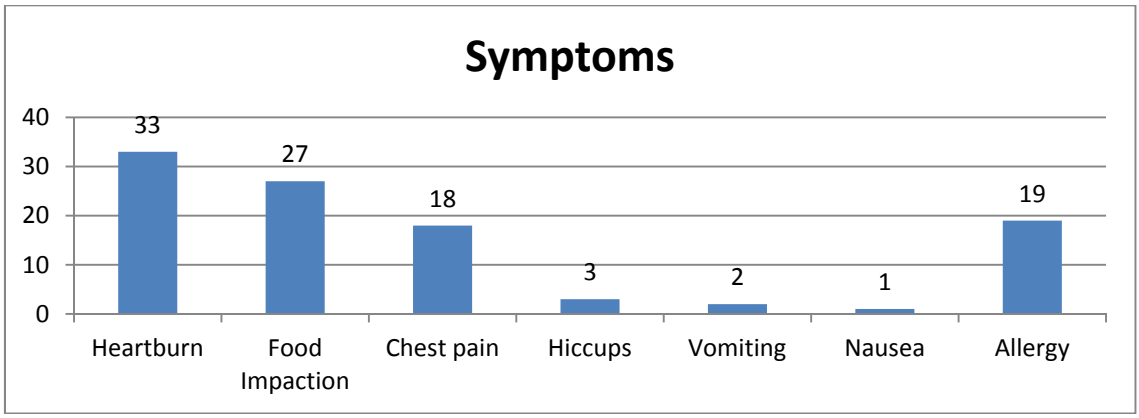

Fig. 9 Symptoms.

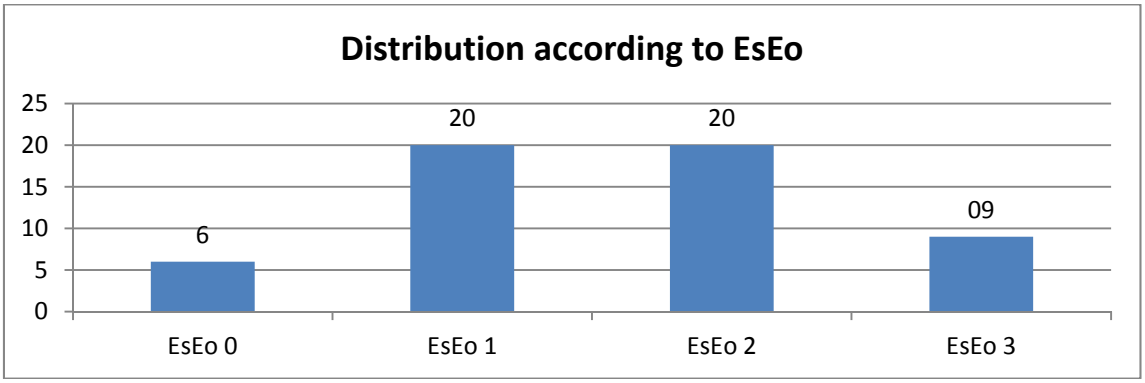

Fig. 10 Patient distribution according to EsEo.

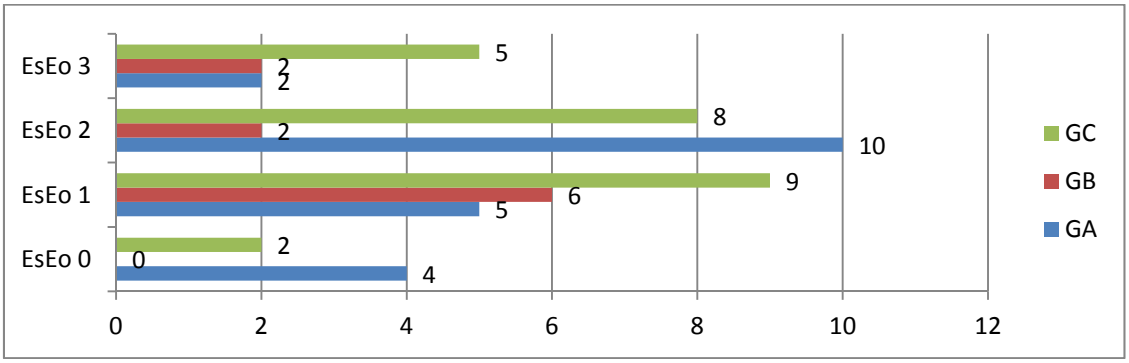

Fig. 11 Correlation between EsEo and eosinophilia.

allergic disease, such as asthma, rhinitis, skin, or food allergy. In one case, there was association with psoriasis, one case with achalasia, and six cases with esophageal moniliasis.

Of the six cases of moniliasis, five were EsEo 2, one EsEo 3, four belonged to GA and two to GC.

Regarding heartburn, it was observed that 100% of the GA patients presented the symptom, against 60% of GB and 41.66% of GC.

According to the classification proposed in this study we found six patients with EsEo 0, twenty with EsEo 1, twenty with EsEo 2 and nine with EsEo 3 (Fig. 10).

In the analysis of the different EsEo by group, the following distribution was observed: in GA, four cases of EsEo 0, five of EsEo 1, ten of EsEs 2, and two of EsEo 3; in GB zero cases of EsEo 0, six of EsEo 1, two of EsEo 2 and two of EsEo 3; in GC two cases of EsEo

0, nine of EsEo 1, eight of EsEo 2 and five of EsEo 3 (Fig. 11).

In the retrospective review of medical records, in a period of 24 months prior to the study, from August 2009 to August 2013, a high digestive endoscopy was performed in 4,332 patients, and the diagnosis of eosinophilic esophagitis was performed in only two patients, with 17 and 22 EOS/HPF respectively.

5. Discussion

This study was performed over 2 years and involved 4,251 patients underwent endoscopy. Of these, 133 underwent biopsies, and eosinophils were found in 55. In 24 patients 15 or more EOS/HPF were detected, and, therefore, diagnosed with EoE. A study carried out at a Canadian research center, over a 10-year period, found 94 cases with more than 15 EOS/HPF [29]. A large multi-center study performed in the United States over 4 years determined that the prevalence of EoE in that period was 56.7 per 100,000 inhabitants [30]. A Swiss study in 2011 detected a prevalence of 43 cases of EoE per one hundred thousand inhabitants [31].

The fact that there is a classification, based on symptoms and endoscopic aspects, alerts the endoscopist to the possibility of the existence of the disease in cases that would not normally be perceived. This situation is evident when we have a patient with classic symptoms of EoE, but with normal endoscopy (Fig. 1). In this case, based on the classification, EsEo 0, the endoscopist would be authorized to perform esophageal biopsies, thus allowing diagnosis. This fact is repeated when we have a typical endoscopic image of reflux, but with typical symptoms of EoE, as in Fig. 2, where the histological study demonstrated 15 EOS/HPF.

Regarding EsEo, the study found 21 patients with 1 to 4 EOS/HPF and 10 patients with 5 to 14 EOS/HPF. The Consensus of the American College of Gastroenterology states that the presence of any number of eosinophils in the esophagus is abnormal and its cause should be determined [32]. In a Chinese study, where biopsies were performed on 1,021 random endoscopies, eosinophils were found in 67 patients (6.6%) and in only 4 (0.4%) the diagnosis of EoE was confirmed [33].

It was observed that 43 (78.18%) patients were male and 12 (21.81%) were female; age ranged between 17 and 73 years with a mean of 39.70 years and all patients included in the study were of European origin (Italians, Germans and Polish). These data are consistent with a study carried out at Mayo Clinic, which included 477 adults with esophageal eosinophilia. This study showed that the majority of the patients were males, with ages ranging between 40 and 50 years old, and Caucasians [34].

The most frequent symptom was heartburn (33) observed in 60% of the cases, being associated with GERD or having GERD as a predisposing factor. This relationship is demonstrated in the literature [35]. The other symptoms reported in the study included food impaction (27), chest pain (18), hiccups (3), vomiting (2), and nausea (1) [36].

In 19 cases (42.42%) there was a report of associated allergic disease, such as asthma, rhinitis, skin, or food allergy. Some studies reported up to 80% association with atopy [37]. In one case, there was association with psoriasis (no previous reports in the literature could be found), one case with achalasia [38] and six cases with esophageal moniliasis, which has been described as a differential diagnosis [39] or complication of treatment [40] and not as a concomitant disease. However, in this study four cases of moniliasis with less than 5 EOS/HPF (GA) and two with more than 15 EOS/HPF (GC), were found. We believe that in cases of GA moniliasis, eosinophilia may have been triggered by fungal infection. However, in the cases of GC we believe these could be associated diseases.

In the analysis of the different EsEo by group the following distribution was observed: in GA, four cases of EsEo 0, five of EsEo 1, ten of EsEo 2 and two of EsEo 3; in GB, zero cases of EsEo 0, six of EsEo 1, two of EsEo 2 and two of EsEo 3; in GC, two of EsEo 0,

nine of EsEo 1, eight of EsEo 2 and five of EsEo 3. From these data, it can be observed that a greater number of normal tests (EsEo 0) were found in group A, with less eosinophils (1-4 EOS/HPF). It is also evident that in group C, with more eosinophils (15 EOS/HPF or more), there was a higher incidence of complex cases (EsEo 3). This relationship was not clear in a study by Hirano et al. [41] who could not establish a relationship between the endoscopic findings and histological changes. This study shows that endoscopic findings alone are not enough to confirm the diagnosis of EsEo, since seventeen patients exhibited some endoscopic alteration, although histology demonstrated less than five EOS/HPF. This situation is similar to other published studies where authors state that endoscopic findings are not reliable to define the diagnosis and treatment [42, 43].

The study also showed that histology is not always an accurate parameter when compared with the endoscopic and/or clinical findings. In Group A, 23.80% of patients with typical symptoms such as food impaction and chest pain upon swallowing were identified. Further, 80.95% of the patients exhibited some endoscopic alterations compatible with EsEo 1, 2 or 3. It is possible that some patients who actually have EoE, for some reason, at the moment of the examination did not present enough EOS/HPF to confirm the diagnosis. In other cases, it is noted that patients with exuberant eosinophilia had a normal endoscopic exam. Some studies already demonstrated these situations of occasional disagreement between the clinical picture, endoscopy, and histology with respect to EoE [44, 45].

6. Conclusions

The results of this study demonstrate that endoscopic standardization of esophageal lesions, suggestive of eosinophilia, in this case by classification, alerts the endoscopist for the diagnosis of EsEo, prompting him to perform targeted biopsies. This fact promoted a significant increase in the diagnosis of the disease relative to a previous period, when this classification was not yet adopted.

Positive histological findings for the disease with only two biopsies targeting endoscopic lesions suggest that this number of biopsies may be adequate. However, this fact should be further evaluated with comparative studies between two or more samples.

The relationship between clinical picture, endoscopy, and histology was not evident in this study.

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