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Association between endoscopic findings and histopathological confirmation in patients with suspicion of eosinophilic esophagitis

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ABSTRACT – **Background** – The diagnosis of eosinophilic esophagitis (EoE) is performed by the detection of 15 or more eosinophils per field in an esophageal biopsy sample, but the endoscopic findings alone are not validated for a diagnosis of the disease. **Objective** – To evaluate the association between the endoscopic findings and histopathological diagnosis in patients with suspected EoE in endoscopy. **Methods** – A retrospective study of 24 patients with suspicion of EoE during endoscopy was held. The information was collected from databases of Endoscopy and Pathology services of the *Hospital Universitário Walter Cantídio*, *Universidade Federal do Ceará*, from March 2012 to April 2018. The patients were divided into a group with positive biopsy (>15 Eosinophils/field, N=8) and a group with negative biopsy (<15 Eosinophils/field, N=16), and the endoscopic findings were compared between the two groups. **Results** – From a total of 24 patients, 79.1% had longitudinal grooves, 20.8% white exudates, 33.3% mucosal pallor or loss of vascularity and 45.8% had more than one endoscopic finding. There was a significant difference (P<0.05) in the evaluation of the finding of mucosal pallor or decreased vasculature alone among the groups. The positive predictive value and negative predictive value of the presence of more than one endoscopic findings for the diagnosis of EoE was 54% and 84%, respectively. **Conclusion** – There was a low association between the presence of endoscopic findings and histopathological confirmation of the disease, which indicates that endoscopic findings alone are not reliable for the diagnosis of EoE.

HEADINGS – Eosinophilic esophagitis. Esophageal diseases. Eosinophils.

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease characterized by esophageal dysfunction and marked esophageal eosinophilic infiltrate. Currently, the disease is the most prevalent cause of chronic esophagitis after gastroesophageal reflux disease (GERD) and the main cause of dysphagia and food impaction in children and young adults[1,2].

EoE is more common in males and can affect all age groups, with peak prevalence in adults between 30 and 50 years. The incidence (1 to 20 new cases per 100,000 inhabitants per year) and the prevalence (13 to 49 cases per 100,000 inhabitants per year) of the disease vary widely in North America and in Europe and has increased dramatically over the years[2,3].

The most common symptoms in the adult population are dysphagia (70%-80%) and food impaction (33%-54%). Other associated symptoms are heartburn, regurgitation, chest discomfort and exercise-induced chest pain[2,4].

Because it is a relatively new recognized disease, diagnostic criteria have undergone constant changes, being the target of significant controversy in recent years. According to the recent guideline of the United European Gastroenterology (UEG), the diagnosis of EoE is based on the presence of eosinophils, 15 or more per high-power field in at least one fragment of the esophageal mucosa obtained by biopsy[2]. This cutoff point displayed a sensitivity of 100% and a specificity of 96% for the diagnosis in a recent study, allowing one to safely differentiate EoE and GERD[5].

The endoscopic findings of the EoE include esophageal rings, stenoses, longitudinal grooves, white plates or exudates and pallor or decreased vasculature. Although the endoscopic findings display high levels of specificity, low sensitivity and variable predictive values suggest that these findings alone are inadequate for the diagnosis of EoE[1].

In this study, the objective was to evaluate the association between the endoscopic findings and histopathological diagnosis in patients with suspected EoE in endoscopy

METHODS

This was a retrospective study with analysis of information collected from databases of the Endoscopy and Pathology services of the *Hospital Universitário Walter Cantídio*, Universidade Federal do Ceará (HUWC), from March 2012 to April 2018. The patients with an endoscopic diagnosis suggestive of EoE and submitted to biopsies (minimum of four) of the distal, middle or proximal esophagus for eosinophil count were selected for the study. In our endoscopy

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unit, the protocol is to take at least four biopsies of the esophagus, in patients with suspected EoE. Experienced pathologists evaluated and confirmed the presence and count, or absence of eosinophils in the samples. A biopsy was considered positive for the diagnosis of EoE when presenting 15 or more eosinophils per high-power field. Patients who had corticosteroids or immunosuppressants during endoscopic examination were excluded from the study. All patients were at least one week without proton pump inhibitor therapy. Gender, age and endoscopic and anatomopathological findings were evaluated. The GraphPad Prism statistical program and the Fisher's exact test were used for statistical evaluation. This study was approved by the Human Research Ethics Committee of HUWC (Protocol: 45868215.7.0000.5045).

A comparative analysis was performed between patients with negative biopsy with those with positive biopsy for EoE regarding gender and age, and endoscopic characteristics, presence of longitudinal grooves, white exudates, mucosal pallor or decreased vasculature and the presence of more than one endoscopic finding.

RESULTS

Patients

A total of 21009 high digestive endoscopies were performed in the Endoscopy Sector of the HUWC from March 2012 to April 2018. Of these patients, 31 had an endoscopic diagnosis suggestive of EoE, and seven patients were excluded from the analysis, since during the endoscopic examination they were using corticosteroids or immunosuppressants. Thus, 24 patients fulfilled the inclusion criteria for correlation of the endoscopic findings suggestive of EoE and the histological confirmation of the disease. Of these patients, 8 (33.3%) had histological confirmation of EoE (FIGURE 1).

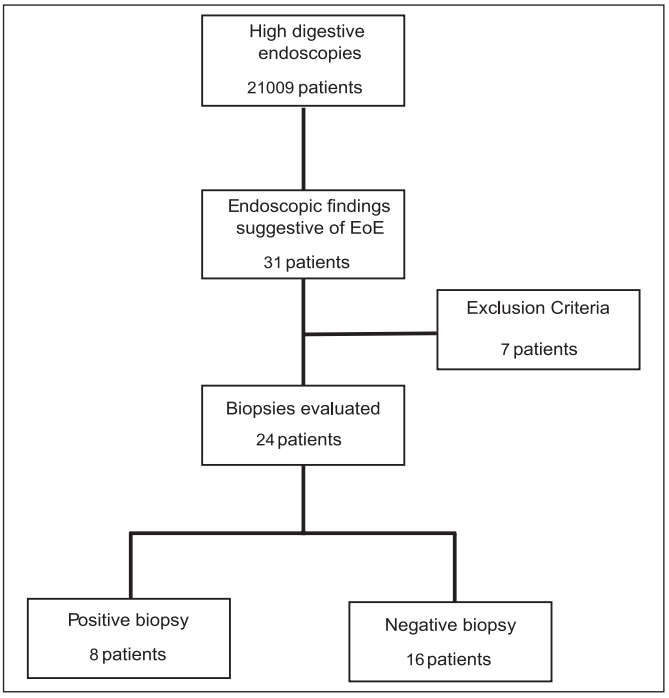

FIGURE 1. Patients allocated in the study from the database of the endoscopy sector, with a suggestive diagnosis of eosinophilic esophagitis, excluded patients, being assessed according to the presence (positive) or absence (negative) of histological criteria for eosinophilic esophagitis.

Epidemiological and endoscopic characteristics

TABLE 1 shows that of the 24 patients included in the study, 58.3% were female and 54.1% were aged <50 years. With regard to the endoscopic findings, 79.1% displayed the presence of longitudinal grooves, 20.8% white exudates, 33.3% mucosal pallor or loss of vascularity and 45.8% had more than one endoscopic findings. None of the patients in the sample presented esophageal rings.

TABLE 1. Patients with endoscopic findings suggestive of eosinophilic esophagitis.

Characteristics	Numbers (%)
Female	14 (58.3%)
Aged <50 years	13 (54.1%)
Longitudinal grooves	19 (79.1%)
White exudates	5 (20.8%)
Mucosal pallor	8 (33.3%)
>1 endoscopic findings	11 (45.8%)

Endoscopic and histological correlation

Of the patients with negative biopsy, 62.5% were female, 37.5% aged less than 50 years, 68.7% had longitudinal grooves, 25% white exudates, 18.7% pallor or loss of vascularity and 31.2% had the presence of more than one endoscopic findings (TABLE 2).

Of patients with positive biopsy, 50% were female, 87.5% aged less than 50 years, 100% displayed longitudinal grooves, 12.5% white exudates, 62.5% mucosal pallor or loss of vascularity and 75% had more than one endoscopic finding (TABLE 2).

The comparative analysis of epidemiological data (TABLE 2) revealed a significant difference (P<0.05) in the evaluation of age less than 50 years between the groups with positive and negative biopsy. The comparative analysis of the endoscopic data (TABLE 2) revealed a significant difference in the finding of pallor or decreased vasculature, alone, however there was no significant difference (P>0.05) in the sole finding of longitudinal grooves and white exudates. In relation to the presence of more than one endoscopic finding, we found a statistical result very close to the cutoff point (P=0.055) to be considered significant for the diagnosis of EoE (TABLE 2). The presence of more than one endoscopic finding in patients with positive biopsy for EoE displayed no correlation with the amount of eosinophils found in samples (FIGURE 2).

TABLE 2. Comparison of the characteristics of patients with negative and positive biopsy.

Characteristics	Positive biopsy	Negative biopsy	*P**
Female	10 (62.5%)	4 (50%)	0.438
Aged <50 years	6 (37.5%)	7 (87.5%)	0.027
Longitudinal grooves	11 (68.7%)	8 (100%)	0.102
White exudates	4 (25%)	1 (12.5%)	0.445
Mucosal pallor	3 (18.7%)	5 (62.5%)	0.047
>1 endoscopic findings	5 (31.2%)	6 (75%)	0.055

* Fisher's test.

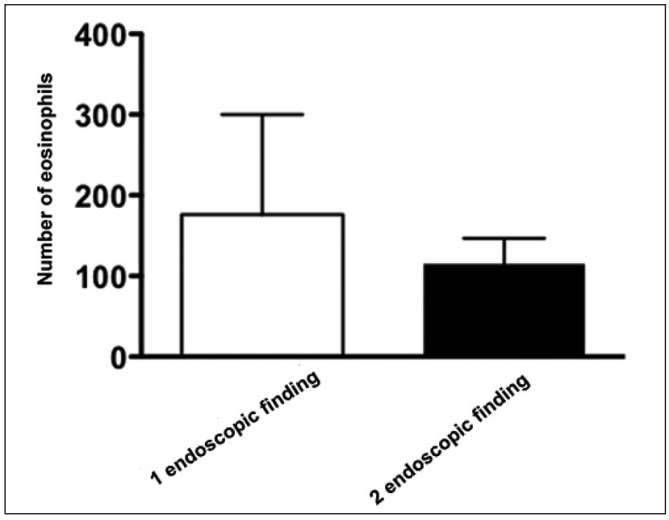

FIGURE 2. Comparison between the number of eosinophils and the amount of endoscopic findings in biopsies positive for eosinophilic esophagitis.

The statistical evaluation of the endoscopic findings revealed that the finding of longitudinal grooves presented a sensitivity of 100%, specificity of 31%, positive predictive value (PPV) of 42% and negative predictive value (NPV) of 100%. The presence of more than one endoscopic finding presented a sensitivity of 75%, specificity of 68%, PPV of 54% and NPV of 84% (TABLE 3).

TABLE 3. Sensitivity, specificity, positive predictive value and negative predictive value of endoscopic findings suggestive of eosinophilic esophagitis.

	Endoscopic findings			
	Longitudinal grooves	White exudates	Mucosal pallor	>1 endoscopic findings
Sensitivity	1.00	0.12	0.63	0.75
(95 IC)	(0.63–1.00)	(0.00–0.52)	(0.24–0.91)	(0.34–0.96)
Specificity	0.31	0.75	0.81	0.68
(95 IC)	(0.11–0.59)	(0.47–0.92)	(0.54–0.96)	(0.41–0.88)
VPP	0.42	0.20	0.63	0.54
(95 IC)	(0.20–0.67)	(0.00–0.71)	(0.24–0.91)	(0.23–0.83)
VPN	1.00	0.63	0.81	0.84
(95 IC)	(0.48–1.00)	(0.38–0.83)	(0.54–0.96)	(0.54–0.98)

(95 IC): 95% confidence interval.

DISCUSSION

EoE is an emerging disease with increasing prevalence and incidence in recent decades[3]. Upper gastrointestinal endoscopy has a fundamental role in its diagnosis, because this examination enables esophageal biopsies for eosinophil count and one can visualize the findings suggestive of the disease.

Our study identified 31 patients with findings suggestive of EoE, which corresponds to 0.15% of the examinations performed during the study period; seven patients were excluded from the sample, limiting the analysis to 24 patients. The low prevalence of EoE cases detected in our endoscopy service may be associated with the low prevalence of this condition in the country. However, we cannot discard the possibility of other factors being involved, as it is a retrospective study. Of these patients, 33.8% had histological confirmation of the disease. Prospective studies have found values of 38% and 29.4%, similar to our data[6,7].

The majority of patients in our sample were females aged less than 50 years. In the comparative analysis between the groups studied, a significant association with the diagnosis of EoE was observed in the group of patients aged less than 50 years. Studies in adults have reported that the peak incidence occurs between 30 and 50 years[8,9]. With regard to gender, the literature shows a higher prevalence in males[3]. Despite the higher prevalence of females in our study, we observed an equality (1:1) in the analysis of the group with positive biopsy, however with no statistical significance. Another possible explanation is that women are more likely to seek health care[10]. In our study, the finding of longitudinal grooves was the most prevalent, similar to that described in the literature with an average prevalence of 66.7%[11].

In the comparative analysis, only the finding of mucosal pallor or loss of decreased vasculature presented significant statistical value for the diagnosis. It is worth noting that the presence of more than one finding had a statistical result very close to the 95% (P=0.055) to be considered significant. A possible explanation for this might be the small number of patients in our sample that hindered the statistical analysis. In agreement with published data, we observed the presence of more than one endoscopic findings for EoE in 75% of the sample with positive biopsy. Prospective studies have shown that the histological diagnosis of EoE seems to increase in frequency with increased number of endoscopic findings. Prasad GA et al. and Lee KM et al. found a sensitivity of 66% and 85.7%, respectively[6,7]. Another relevant fact is that patients with esophageal rings were not identified in our sample. We believe that this is due to the fact that there is no emergency unit in the HUWC, which means that patients with more severe and evolutionary changes that evolve with esophageal stenosis seek other services.

There was no association between the number of endoscopic findings and the amount of eosinophils in the samples. In agreement with our finding, a study conducted by Mateus RF et al. found no correlation of endoscopy findings and the intensity of the eosinophilic infiltration[12].

The endoscopic findings display low sensitivity and high specificity in the diagnosis of EoE[1,2,11]. The findings of white exudates/pallor and decreased vasculature in our sample displayed greater specificity (75% and 81%, respectively), however when alone presented low sensitivity (12% and 63%, respectively). When we grouped in the presence of more than one endoscopic finding we observed a greater balance between the specificity (68%) and sensitivity (75%), suggesting that we should always evaluate the endoscopic findings as a whole and not in an isolated way. A systematic review performed by Kim HP et al. showed that the sensitivity of the endoscopic findings varies between 15 and 48% and the specificity varies between 90% and 95%[1]. We believe that the difference between our results and those reported in the current literature is due to the small number of patients in the sample and the exclusion of patients with a diagnosis of EoE with normal endoscopy.

With regard to the predictive values found in this study, longitudinal grooves presented a PPV of 42% and an NPV of 100%.

A result similar was found by Achem SR et al., who reported a PPV of 42% and an NPV of 94%[13]. White exudates showed a PPV of 20% and an NPV of 63%. Dellon et al. found a PPV of 43% and an NPV of 63%[14]. Pallor or decreased vasculature presented a PPV of 63% and anNPV of 81%. A systematic review showed a great variability in the literature in the predictive values for each endoscopy finding, with longitudinal grooves having a PPV ranging from 17% to 100% and an NPV between 37% and 97%, white exudates PPV ranged between 12% and 100%, and the NPV between 24% and 95% and pallor or decreased vasculature having a PPV ranging from 20% and 83%, and the NPV between 29% and 97%[1].

We can conclude that there was a low association between the presence of endoscopic findings and histopathological confirmation of the disease, which indicates that endoscopic findings alone are not reliable for the diagnosis of EoE. More studies with a large number of patients are need to confirm or not our findings.

Authors' contribution

Barbosa JPC: implementation of research, data gathering and drafting of the text. Tavares PRV: endoscopic data collection. Aguiar PMF: histopathological data collection and review of pathology data. Franco LM: histopathological data collection and review of pathology data. Nobre-e-Souza MA: drafting the text and critical review. Souza MHLP: implementation of research, drafting the text, statistical analysis and critical review.

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RESUMO – **Contexto** – O diagnóstico da esofagite eosinofílica é realizado através da detecção, em amostra de biópsia esofágica, de 15 ou mais eosinófilos por campo, sendo que os achados endoscópicos isolados não são validados para o diagnóstico da doença. **Objetivo** – Avaliar a associação entre os achados endoscópicos com o diagnóstico histopatológico em pacientes com suspeita de esofagite eosinofílica na endoscopia. **Métodos** – Estudo retrospectivo de 24 pacientes com suspeita de esofagite eosinofílica durante endoscopia digestiva alta. As informações foram colhidas de bancos de dados dos serviços de Endoscopia e Patologia do Hospital Universitário Walter Cantídio da Universidade Federal do Ceará, no período de março de 2012 a abril de 2018. Os pacientes foram divididos em grupo com biópsia positiva (>15 eosinófilos/campo, N=8) e grupo com biópsia negativa (<15 eosinófilos/campo, N=16), sendo comparados os achados endoscópicos entre os dois grupos. **Resultados** – Do total de 24 pacientes, 79,1% tinham a presença de sulcos longitudinais, 20,8% exsudatos brancos, 33,3% palidez de mucosa ou perda da vascularização e 45,8% apresentaram mais de um achado endoscópico. Houve diferença significativa (P<0,05) na avaliação do achado de palidez ou perda da vascularização, isoladamente, entre os grupos. O valor preditivo positivo e valor preditivo negativo da presença de mais de um achado endoscópico para o diagnóstico de esofagite eosinofílica foi de 54% e 84%, respectivamente. **Conclusão** – Houve uma baixa associação entre a presença de achados endoscópicos e a confirmação histopatológica da doença, o que faz com que os achados endoscópicos isolados não sejam confiáveis para o diagnóstico de esofagite eosinofílica.

DESCRITORES – Esofagite eosinofílica. Doenças do esôfago. Eosinófilos.

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