

Diagnosing oesophagitis in children : how discriminative is histology ?

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Abstract

Background and study aims : We set out to evaluate the discriminatory value of currently available histologic criteria in the differential diagnosis of reflux oesophagitis and eosinophilic oesophagitis in children.

Patients and Methods : We evaluated the oesophageal biopsies of 145 children and selected 28 demonstrative cases of clinically confirmed eosinophilic oesophagitis (n = 7), and reflux oesophagitis (n = 11) with a control group with normal histology (n = 10). Histological assessment was performed for the presence of papillary elongation, dilatation of intercellular spaces, basal cell hyperplasia and the number of intraepithelial eosinophils, lymphocytes and neutrophils.

Results : Among 28 children, there were 3 boys and 4 girls in eosinophilic oesophagitis group, 8 boys and 3 girls in reflux group, and 5 boys and 5 girls in normal group. The mean age was 10,4 years. Basal cell hyperplasia was observed in 12 cases while papillary elongation was found in 25, and dilated intercellular spaces were present in 20 cases. Lymphocyte and neutrophil counts were significantly higher in reflux group when compared to eosinophilic oesophagitis and normal group. Eosinophil counts were significantly higher in eosinophilic group.

Conclusions : Results of the present study suggest that, basal cell hyperplasia, papillary elongation, and dilated intercellular spaces all seem to be markers of oesophagitis regardless of the underlying pathology and etiology, thereby, highlighting their rather non-specific nature in the differential diagnosis of various types of oesophagitis. The additional information on inflammatory cell counts may help to distinguish reflux oesophagitis from other causes of oesophagitis including EoO. (*Acta gastroenterol. belg.*, 2013, 76, 300-305).

Key words : eosinophilic oesophagitis, reflux oesophagitis, histologic features.

Introduction

The term oesophagitis refers to any inflammatory condition that affects the oesophageal mucosa or wall. There is a wide variety of causes leading to oesophageal inflammation including infections (e.g. Herpes Simplex or Candida Albicans), exposure to physical or chemical agents and systemic inflammatory disorders (e.g. Crohn's disease, collagen vascular disease) (1). However, oesophagitis of these various etiologies often presents with overlapping histologic features such as epithelial hyperplasia, intraepithelial oedema, inflammatory cell infiltration comprising neutrophils, lymphocytes and eosinophils within the squamous epithelium, all representing reactive changes to injury (2, 3). These features make the distinction of the underlying disorder difficult, which is, particularly true for the two types of oesophagitis : reflux oesophagitis (RO) and eosinophilic oesophagitis (EoO). RO is the most common disease in adult patients referred

for upper endoscopy, with an incidence of 10 to 20% in the Western world (4, 5, 6).

EoO, on the other hand, is an emerging disease that has been more precisely defined by recent reviews and consensus studies (5). It was defined as a clinicopathologic entity, combining clinical data with i) relevant symptoms (distinct in the pediatric or adult populations, with mostly food impaction and dysphagia in adults and feeding intolerance, failure to thrive, and reflux symptoms in children), ii) esophageal biopsies showing ≥ 15 eosinophils/high-power field, and iii) exclusion of other diseases with overlapping features, especially RO (7). The pathologist, should, therefore, be aware of the histologic overlap between various types of oesophagitis, RO and EoO in particular, and should seek for clinical information as a definitive diagnosis will rarely be based solely on microscopic features (8).

We, therefore, set out to evaluate the discriminatory value of currently available histologic criteria in the differential diagnosis of reflux oesophagitis and eosinophilic oesophagitis in children.

Material and method

We retrospectively evaluated the oesophageal biopsies of 145 children who underwent upper gastrointestinal endoscopy for various gastrointestinal symptoms and selected 28 representative cases of clinically confirmed EoO (n = 7) (Table 1), and RO (n = 11) together with a control group comprising children with normal histology (n = 10). The mean age was 10,4 years with a range of 3 to 17 years. Histological assessment was performed by two pathologists together in a blinded manner and the presence of papillary elongation (PE) (Fig. 1), dilatation of intercellular spaces (DIS) (graded as mild : focal, occasional or sporadic small size intercellular spaces ; moderate : moderately spread and larger intercellular spaces ; marked : widespread and very large intercellular spaces) (Fig. 2), basal cell hyperplasia (BH) (graded as mild : 15-50% of epithelial thickness ; moderate : 50-75% of epithelial thickness ; marked : > 75% of epithelial

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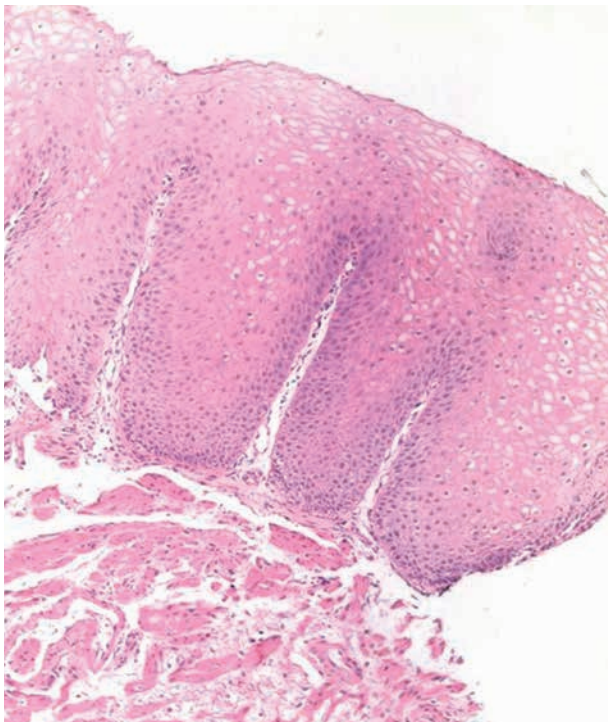


Fig. 1. — Severe papillary elongation > 75% of epithelial thickness (H&E ×200).

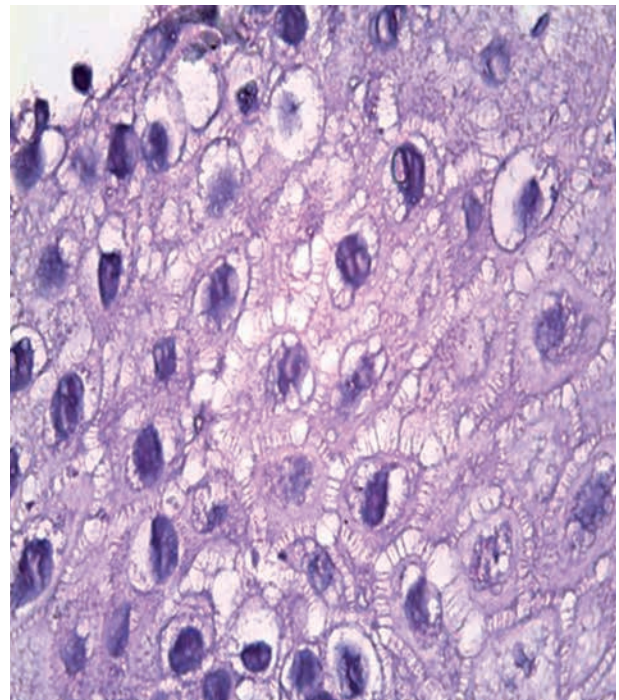


Fig. 2. — Dilated intercellular spaces between squamous cells in the form of bubbles and ladders (H&E ×400).

Table 1. — Demographic and clinical characteristics of EoO cases

Number	Gender	Age (years)	Symptoms	Associated allergic disease	Serum specific IgE	Serum total IgE level (Iu/mL)	Peripheral eosinophil percentage (%)
1	M	17	Abdominal pain	Anaphylaxis (cow's milk allergy)	Positive (cow's milk allergy)	92.7	6.1
2	M	6	Dysphagia	Asthma	Egg	197	10.5
3	F	13	GERD-like symptoms	None	Negative	NA	6.4
4*	F	10	NA	NA	NA	NA	NA
5*	M	10	NA	NA	NA	NA	NA
6	F	8	GERD-like symptoms	Asthma, allergic rinitis	NA	138	9.3
7	F	10	GERD-like symptoms	None	Negative	8.9	3.2

*Consultation cases.

thickness) (Fig. 3) was noted together with the number of intraepithelial eosinophils (Fig. 4), neutrophils and lymphocytes (Fig. 5) per high power field. Presence of necrosis/erosions, subepithelial inflammation and fibrosis were also recorded.

Statistical analysis

Statistical analysis was performed by the SPSS 15 Statistical Package for Word. Numerical variables were shown as mean ± SD and the number of cases and per-

centages were used for nominal data. Spearman's rho test was used to determine the correlations between histologic parameters and inflammatory cell counts. A p value less than 0.05 was considered as significant.

Results

Among 145 children who underwent upper gastrointestinal endoscopy for various gastrointestinal complaints, 28 children comprising 7 (25%) with a diagnosis

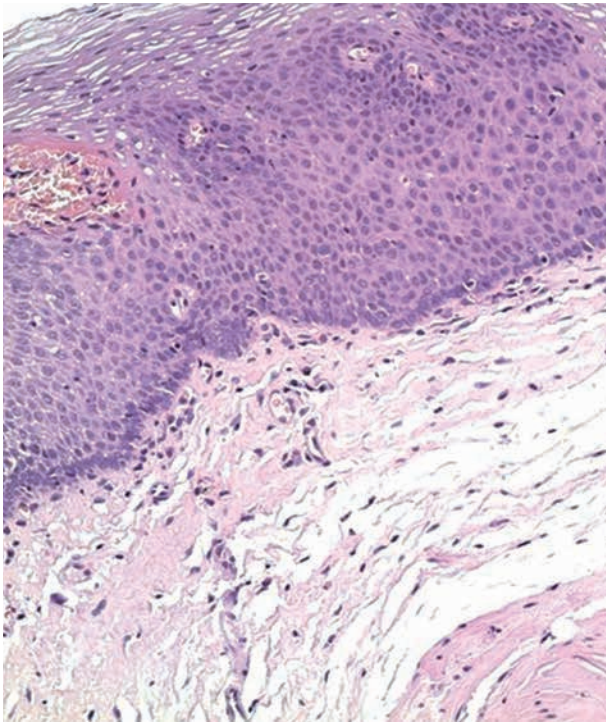


Fig. 3. — Severe basal cell hyperplasia > 50% of the epithelial thickness (H&E ×200).

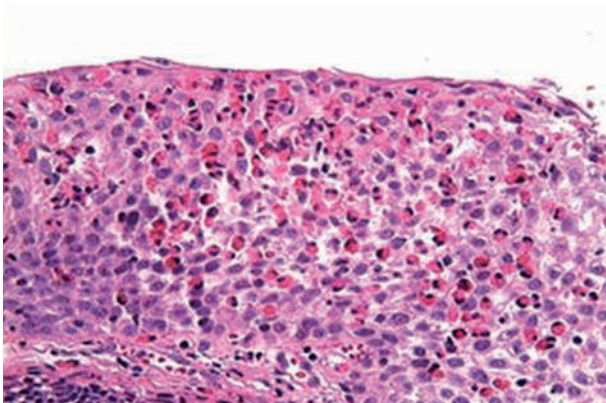


Fig. 4. — Marked intraepithelial eosinophilia and eosinophilic microabscesses (H&E ×200).

of EoO, 11 (39,3%) diagnosed as RO and 10 (35,7%) with normal oesophageal morphology were recruited to perform a comparison study. There were 3 boys and 4 girls in EoO group, 8 boys and 3 girls in RO group, and 5 boys and 5 girls in the normal group. No significant difference was observed between the three study groups in terms of age, gender, number of biopsy pieces, the presence of vascular congestion and intestinal metaplasia. Subepithelial inflammation was seen in one case in both EoO and RO groups while erosion and ulcer were observed in one RO case.

Overall, 12 cases showed BCH (7 severe and 5 mild), while 25 cases demonstrated PE (17 mild and 8 severe), and 20 cases presented with DIS (10 mild and 10 severe).

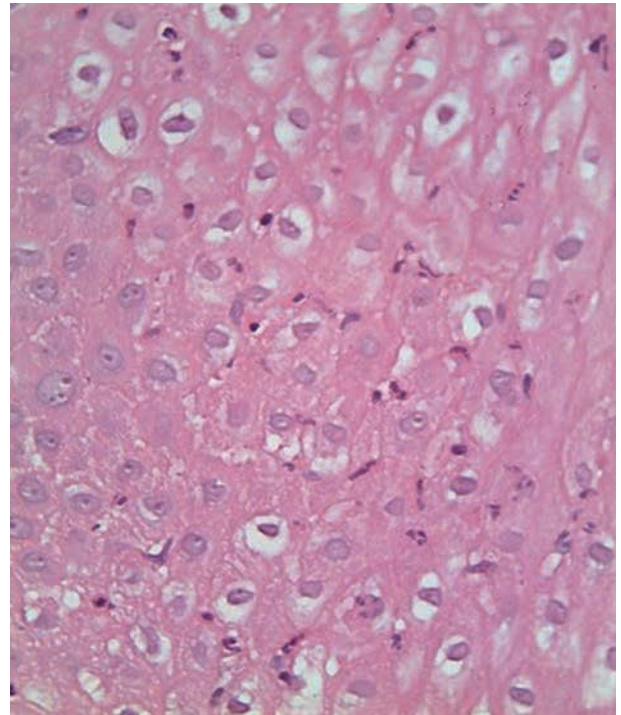


Fig. 5. — Neutrophils and lymphocytes in the squamous epithelium (H&E ×200).

When the three study groups were evaluated, both the frequency and severity of BCH were significantly higher in EoO group than RO group, ($n = 7$; 100%, all with severe BCH, and $n = 5$; 45.5%, all with mild BCH, respectively) while none of the cases in normal group showed BCH. Similarly, PE was more frequently observed in RO group (100%) 6 of which were mild and 5 were severe, followed by EoO (85,7%) 3 of which were mild and 3 were severe, and normal group (80%) 8 of which were mild. DIS was more common in RO group (100%) 3 of which were mild and 8 were severe compared to the EoO (57,1%) group, 2 of which were mild and 2 were severe, and normal group (50%) all 5 of which were mild. No statistical significance was reached for any of the above parameters studied. The distribution of histological parameters is summarized in Table 2.

Inflammatory cell counts were determined for lymphocytes ($14,17 \pm 17,54$; median 7,5), neutrophils ($1,5 \pm 4,84$; median 0) and eosinophils ($8,35 \pm 19,45$; median 0) in all cases included in the study.

RO group had the highest number of lymphocytes ($26 \pm 21,47$) followed by EoO ($12,42 \pm 10,89$) and normal groups ($2,4 \pm 2,27$) and there were significant differences between normal and RO ($p < 0,05$), and EoO ($p < 0,01$), and also between EoO and RO ($p < 0,001$). Neutrophils were present only in RO group ($3,81 \pm 7,31$) while EoO and normal group showed no neutrophils ($p < 0,05$). Eosinophil counts were significantly higher in EoO ($29,71 \pm 30,9$) group in comparison to both RO ($2,36 \pm 4,56$) and normal group which showed no eosinophils ($p < 0,01$). Eosinophilic microabscesses were found

Table 2. — Histologic features in the study groups

Histologic Diagnosis	BCH				PE				DIS			
	Absent	Present			Absent	Present			Absent	Present		
		M	Mod	S		M	Mod	S		M	Mod	S
Normal	10 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (20%)	8 (80%)	0 (0%)	0 (0%)	5 (50%)	5 (50%)	0 (0%)	0 (0%)
RO	6 (54,5%)	5 (45,5%)	0 (0%)	0 (0%)	0 (0%)	6 (54,5%)	0 (0%)	5 (45,5%)	0 (0%)	3 (27,3%)	0 (0%)	8 (72,8%)
EoO	0 (0%)	0 (0%)	0 (0%)	7 (100%)	1 (14,3%)	3 (42,9%)	0 (0%)	3 (42,9%)	3 (42,9%)	2 (28,6%)	0 (0%)	2 (28,6%)

RO ; reflux oesophagitis, EoO ; eosinophilic oesophagitis, BCH ; basal cell hyperplasia, PE ; papiller elongation, DIS ; dilated intercellular spaces, M ; mild, Mod ; moderate, S ; severe.

Table 3. — Inflammatory cell populations in study groups

Histologic Diagnosis		Lymphocyte	Neutrophil	Eosinophil
Normal	Mean	2,4000	0,000	0,000
	Std-D	2,270	0,000	0,000
	Median	2,000	0,000	0,000
RO	Mean	26,000	3,818	2,363
	Std-D	21,470	7,318	4,566
	Median	18,000	1,000	0,000
EoO	Mean	12,428	0,000	29,71
	Std-D	10,891	0,000	30,9
	Median	9,000	0,000	25

RO; reflux oesophagitis, EoO; eosinophilic oesophagitis.

in all cases of EoO. Inflammatory cell populations in each group are summarized in Table 3.

When the correlation between inflammatory cell counts and other histologic parameters was assessed (Table 4), a positive correlation between BCH and lymphocyte counts ($r = 0,437$; $p < 0,05$), and eosinophil counts ($r = 0,389$; $p < 0,05$) was observed. Presence of PE and high lymphocyte ($r = 0,448$; $p < 0,05$), neutrophil ($r = 0,409$; $p < 0,05$) and eosinophil ($r = 0,550$; $p < 0,01$) counts showed significant correlation while the presence of DIS correlated with high lymphocyte ($r = 0,497$; $p < 0,01$), and neutrophil counts ($r = 0,386$; $p < 0,05$) but not with eosinophil counts.

Discussion

In both EoO and RO, histologic evaluation provides diagnostic clues, allows assessment of the severity of disease, monitors response to therapy, and predicts possible complications. Biopsy and histology are mandatory for a diagnosis of EoO, even when the mucosa appears healthy on endoscopy. On similar grounds, RO, particularly in the form of NERD, requires histologic evaluation to improve the sensitivity of endoscopy in detecting the so-called microscopic oesophagitis (9). Besides, based on the findings of a recent study by Takubo *et al.* (10) a set

of histologic changes that were invariably defined reflux associated found to be nonspecific. To define a set of histologic change through sampling is necessary and endoscopists should have taken multiple biopsies from sites that have different endoscopic appearance.

The present study is designed to assess the discriminatory value of currently available histologic criteria in the differential diagnosis of RO and EoO in children. The results showed that papillary elongation and dilated intercellular spaces, though more frequently observed in reflux oesophagitis, failed to be discriminative for the three study groups while basal cell hyperplasia was found only in cases with both types of oesophagitis, thus discriminating them from the normal group. Inflammatory cell counts, on the other hand, proved to be more discriminatory as high lymphocyte and neutrophil counts were significantly associated with reflux oesophagitis and high eosinophil counts were related to eosinophilic oesophagitis. Due to the small number of cases in each group, however, it was not possible to determine a cut-off for each inflammatory cell type in relation to a specific diagnostic category.

Although, the threshold for eosinophil numbers required for the diagnosis of EoO vary widely in the literature, a peak eosinophil count of more than 15 per HPF has been indicated by the American Gastroenterological

Table 4. — Correlation of histologic features and inflammatory cell populations

Histologic features		Lymphocyte	Neutrophil	Eosinophil
BCH	R	0,437	0,041	0,389
	P	< 0,05	> 0,05	< 0,05
PE	R	0,448	0,409	0,550
	P	< 0,05	< 0,05	< 0,01
DIS	R	0,497	0,386	0,298
	P	< 0,01	< 0,05	> 0,05

BCH; basal cell hyperplasia, PE; papiller elongation, DIS; dilated intercellular spaces.

P; p values.

R; r values.

Association consensus recommendations for the diagnosis of EoO. Preferential localization of the eosinophilic infiltrate in the superficial oesophageal epithelium and formation of eosinophilic microabscesses, defined as clusters of 4 or more eosinophils, are considered as diagnostic histologic findings of EoO (7). In contrast, RO is usually characterized by lower intramucosal eosinophils, usually 7 or fewer for per HPF (11) a strong correlation is observed between the number of intraepithelial eosinophils and the endoscopic or histologic severity of the lesions (12). The current view is that, a peak eosinophil count of greater than 15 per HPF (especially during PPI therapy), or of less than 5 per HPF should be interpreted as “consistent with” EE or GERD, respectively (13). It should be emphasized, however, that large numbers of eosinophils (> 20 per HPF) may occasionally be present in adult patients with RO and in patients with other oesophageal disorders such as “pill oesophagitis” (12-15).

In the present study, the mean eosinophil count was 8 for all study groups, while a mean of 30 eosinophils together with eosinophilic microabscesses was observed in EoO, and two eosinophils in RO. No eosinophils were present in the normal group. There were three cases of EoO in the present study which presented with a peak eosinophil count of 7, 11, and 12 per high power field, respectively. They all showed eosinophilic microabscesses. Our findings, suggest that, even in the absence of high eosinophil counts other accompanying features of EoO in a biopsy in the correct clinical setting (14,16-18) can be considered as diagnostic.

Papillary elongation and basal cell hyperplasia have both been shown to correlate with the duration of exposure to acid secretions (19,20). Dilated intercellular spaces correspond to enlargement of the intercellular spaces resulting from a break in the epithelial barrier and, as such, are probably early findings of erosions (21,22,23). Dilated intercellular spaces are also found in EoO, in *Candida* infections, and in up to 30% of healthy controls, suggestive of constant chemical irritation of the oesophageal epithelium by luminal contents (22). Supporting this data, we also observed DIS in the normal group as well as in patients with, EoO and RO. Antonioli *et al.* showed that basal cell hyperplasia in EoO was correlated with the density of intraepithelial eosinophil and mast cell infiltra-

tion, at least in children, and occupied more than 50% of the epithelial thickness (24). In another study, basal cell hyperplasia was observed in 87% of EoO whereas only 11% of RO patients showed this feature. Also, the degree of severity of basal cell hyperplasia was shown to be higher in EoO exceeding 75% of the epithelial thickness while less severe hyperplasia was observed in RO (25). Similarly, in the present study, all patients in EoO group showed severe BCH whereas only half of the patients in RO group presented with mild basal cell hyperplasia. In a previous study, basal cell hyperplasia, papillary lengthening, and dilatation of intercellular spaces correlated with eosinophil degranulation, which may be related to biopsy processing (25,26). Though, basal cell hyperplasia proved to be discriminatory between oesophagitis and normal groups, papillary elongation and dilated intercellular spaces seemed to be almost always present in RO while they did not vary between EoO and the normal group, in the present study. The severity of all the above parameters, except for BCH, however, was higher in RO group compared to EoO and the normal group, suggesting that some degree of chemical irritation occurs in the lower oesophagus of asymptomatic individuals represented by mild degrees of histologic changes, thereby highlighting the importance of histologic grading in the evaluation of these parameters.

While more lymphocytes were observed in biopsies with histologic evidence of oesophagitis, RO in particular, their numbers were not statistically different from normal controls in previous publications (24,28-30). Neutrophils, when present however, are considered as suggestive of RO, while they are uncommonly found in EoO (26,31). In the present study, similar to the previous publications, neutrophil counts were higher in RO than in EoO in the same manner as lymphocyte counts. There was a positive correlation between the morphologic criteria and lymphocyte, neutrophil, and eosinophil counts. Interestingly, the normal group included in the study, also showed similar morphologic findings, except basal cell hyperplasia, in a less severe manner compared to EoO and RO. Intraepithelial lymphocytes were also observed in the normal group with much lower numbers than EoO and, RO, in particular, suggesting that a cut-off for intraepithelial lymphocytes is necessary to distinguish

microscopic oesophagitis cases from cases with normal histology. The presence of neutrophils, on the other hand, should always be considered as pathologic.

In our study the mean age of the cases was 10,4 years with a range of 3 to 17 years and there was not any younger child than three years. The pathology in the younger children, such as < 1 years, may however be different and DIS can be the only feature in younger children with GERD and non-erosive oesophagitis, irrespective of the amount of acid exposure as measured by pH monitoring (32). Additionally, it is known that eosinophilic infiltrates involve both the distal and proximal segments of the oesophagus with some indications of a more proximal involvement. In this retrospective study the oesophageal biopsies were taken from the distal oesophagus using standard biopsy technique. Thus, histological findings in the unevaluated proximal oesophagus might have had an influence on the results, especially on the group that microscopically considered as normal from the distal oesophageal biopsies.

According to the results of the present study, basal cell hyperplasia, papillary elongation, and dilated intercellular spaces all seem to be markers of oesophagitis regardless of the underlying pathology and etiology, thereby, suggesting their rather nonspecific nature in the differential diagnosis of various forms of oesophagitis. The additional information on inflammatory cell counts may help to distinguish reflux oesophagitis from other causes of oesophagitis including EoO. However, the definitive diagnosis of EoO relies upon clinical and histological exclusion of RO and other causes of mucosal eosinophilia. Therefore, biopsy findings should be supported by the patients' history and clinical symptoms, ambulatory pH monitoring, and endoscopy for the differential diagnosis of EoO and RO and biopsy. Moreover, the pathology report should include the peak eosinophil count for EoO, together with a description of other histologic criteria, whether present or absent and a note of "in the right clinical setting" should also be added when no clinical information is provided.

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