Eosinophilic oesophagitis *versus* reflux oesophagitis

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Abstract

Reflux oesophagitis (RO) is defined as the inflammation of the lower oesophagus due to damage caused by acid reflux from the stomach. Histopathologic features of acid reflux include epithelial hyperplasia, baloon cells, basal cell hyperplasia, papillary elongation, dilated intercellular spaces representing epithelial oedema, vascular congestion, and inflammatory cell infiltration comprising lymphocytes, neutrophils and eosinophils, most of which are non-specific. Eosinophils, on the other hand, are considered to be important in the differential diagnosis of RO and EoO which is a chronic inflammatory disorder characterized by eosinophil infiltration of the oesophageal mucosa associated with a history of atopy or allergy. A cut off value of more than 15 eosinophils per high power field is suggestive of EoO with a tendency of eosinophils to concentrate in the superficial parts of squamous mucosa just below the luminal surface where they tend to form eosinophilic microabsesses. Dense fibrosis is seen in up to one-third of the patients with EoO together with an increase in the number of eosinophils in the lamina propria. In patients with intermediate levels of eosinophil counts (7-15 eos/hpf) immunohistochemistry for eosinophil secretory products could prove useful as it highlights degranulated eosinophils. In conclusion, distinguishing EoO from RO requires a thorough clinical, endoscopic and histologic evaluation of the patient which can only be achieved when close communication between pathologist and gastroenterologist is established. (Acta gastroenterol. belg., **2011**, 74, **323-329**).

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 (e.g. radiotherapy or corrosives), and systemic inflammatory/immune disorders (e.g. Crohn's disease, collagen vascular disease) (1). However, oesohagitis 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). Atwood *et al.* (4), were first to describe EoO as a distinct entity and to provide comparisons between eosinophilic oesophagitis and reflux oesophagitis which, previously, was believed to be the only cause of tissue eosinophilia observed in oesophageal biopsies (4). It is important to distinguish eosinophilic oesophagitis from reflux disease in order to prevent patients from unnecessary therapeutic maneuvers used for reflux disease, such as long term proton pump inhibitor administration or surgical procedures like fundoplication.

This review, therefore, aims to focus on the distinction of EoO and RO, in terms of clinical presentation, pathogenesis, endoscopic findings, histopathologic features, treatment and prognosis.

Clinical presentation

RO is defined as the inflammation of the lower oesophagus due to damage caused by acid reflux resulting from lower oesophageal sphincter dysfunction (1), whereas EoO is a chronic inflammatory disorder characterized by eosinophil infiltration of the oesophageal mucosa associated with a history of atopy or allergy. Eosinophil infiltration of the oesophageal mucosa is the cardinal pathologic feature, although it may occur secondary to several unrelated diseases such as eosinophilic gastroenteritis, hypereosinophilic syndrome, drug exposure, parasitic and fungal infections, RO, oesophageal leiomyomatosis and scleroderma (5,6).

RO occurs at all ages and in both sexes, though there is a slight male predominance while EoO shows an age predilection of children and young adults also with a male predominance (1,7).

Clinically, RO may present either as nonerosive reflux disease (NERD) including patients with normal endoscopy with or without positive pH monitoring, as erosive reflux disease (ERD) including patients with positive endoscopy or as complicated RO comprising ulcers, strictures, hemorrhage, Barrett's oesophagus and adenocarcinoma (8,9). Typical symptoms are heartburn and regurgitation occuring more frequently after a fatty meal. Epigastric pain, chronic hoarseness and protracted hiccups are less frequently observed while there is a large group of asymptomatic patients (1,10). Though, similar symptoms may be seen, progressive dysphagia is the most common presenting symptom in adult patients with EoO. Dysphagia is typically described by the patients as intermittent and mostly induced with solid foods (11,12). Food impaction may also be the presenting symptom of

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Table 1. — **Clinical and endoscopic findings of EoO and RO**

	Eosinophilic oesophagitis	**Reflux oesophagitis**
Background	History of atopy / allergy	Obesity / GI motility disorders
Age Gender	Children and young adults Male predominance	All ages Slight male predominance
Symptoms	Dysphagia and food impaction	Regurgitation, epigastric pain
Endoscopy	White plaques, furrows, rings and strictures	Erythema, erosions and ulcers
Ph monitoring	Normal	Abnormal (hyperacidity)
Pattern of involvement	Proximal, mid and distal oesophagus	Distal oesophagus

EoO in adult patients (13), while children typically present with feeding refusal, food intolerance, vomiting, abdominal pain, and failure to thrive. Patients with EoO have normal pH monitoring and usually do not respond to acid suppression (8,14,15) (Table 1). According to the criteria of FIGERS (First International Gastrointestinal Eosinophil Research Symposium) (16) the diagnosis of EoO relies upon clinical and histological exclusion of RO and other causes of mucosal eosinophilia. Therefore, ambulatory pH monitoring, endoscopy and biopsy appear to be the most valuable procedures for the differential diagnosis of EoO and RO.

Pathogenesis

RO is a multifactorial disorder, with different abnormalities predominating in different patients. Predisposing factors include i) decreased oesophageal sphincter pressure, ii) diminished oesophageal clearance resulting from defective peristalsis, iii) delayed gastric emptying or abnormal gastric contractility iv) descreased salivary flow, and v) increased gastric acid production (1). Oesophageal dysmotility contributes to decreased clearance of the refluxed material, thereby leading to an increased mucosal contact time. The composition and length of time of mucosal contact of the reflux material determine the severity of the disease. A different pathogenetic mechanism is involved in EoO which seems to be linked to allergic responses to food or airborne allergens, but cases have also been reported in which patients have EoO without detectable food allergies by patch or prick skin testing (17-19). This indicates that EoO could also be associated with immune disregulation and these tests might not reflect hypersensitivity driven by discrete antigens (18,19). The mechanism is believed to be mediated through activation of Th2 lymphocytes leading to an increased production of proallergenic interleukins, especially, IL-4, IL-5 and IL13. While IL-5 promotes maturation of eosinophils and migration from the bone marrow into the circulating blood stream, IL-4 and IL-13 upregulate the production of Eotaxin 3 by the epithelium, a chemokine responsible for attracting the eosinophils into the oesophagus. As a result, mature eosinophils accumulate in the oesophagus, are activated and degranulate releasing multiple cytotoxic agents. Though, the mechanism of fibrogenesis is still unclear, IL-5, by inducing fibroblast-myofibroblast transdifferentiation, may be the critical molecule for tissue fibrosis as well as smooth muscle hyperplasia that leads to oesophageal stricture formation in EoO (18-21).

It has been speculated that RO can predispose individuals to develop EoO by causing acid injury to the epithelium which may become permeable to allergens. It may also attract eosinophils mainly to the distal part of the oesophagus, leading to mild tissue eosinophilia which is a frequent finding in RO (22). Alternatively, EoO could predispose to RO as a result of eosinophil secretory products, acute inflammation or fibrosis which can cause relaxation of the lower oesophageal sphincter (23). However, these speculative statements need further clarification through studies performed in large case series of EoO and RO.

Endoscopic findings

RO involves the most distal part of the oesophagus, and the gastrooesophageal junction, in particular. Even though most patients with RO have classic endoscopic findings of erythema, mucosal oedema, erosions, or ulcers, many patients with typical reflux symptoms have normal or nearly normal endoscopy (i.e. NERD) (1,9). In contrast to RO, EoO involves not only the distal oesophagus but mid and upper oesophagus are also frequently involved. Despite the lack of a pathognomonic endoscopic sign for EoO, red furrows, white exudates, crepe paper mucosa (i.e. fragile mucosa), corrugated rings, and severe stenosis are the most characteristic endoscopic findings (24,25). They seem to be related to the architectural changes resulting from chronic inflammation leading to fibrosis (19). Oeosphageal furrows may indicate active disease while white papules or plaques represent eosinophilic accumulations in the superficial mucosa (8,24,26). Endoscopic findings of EoO and RO are summarized in Table 1.

Histopathologic features

RO is associated with a variety of histologic features, spanning from changes secondary to acid injury to mucosal healing. Histopathologic features of acid reflux

are nonspecific and include epithelial hyperplasia, baloon cells, basal cell hyperplasia, papillary elongation, vascular congestion, inflammatory cell infiltration comprising lymphocytes, neutrophils and eosinophils, and dilated intercellular spaces representing epithelial oedema (3,9,27). Several investigators developed grading schemes for each of these histologic criteria in an attempt to correlate with disease severity and also to aid differential diagnosis (7,10,28).

In EoO, biopsies show marked eosinophilic infiltrates at different levels of the oesophagus. However, the presence of an increased number of eosinophils in the oesophageal squamous epithelium is a nonspecific finding which may be seen in several disorders, including RO, infections, drugs and Crohn's disease (17,19). In order to distinguish EoO from other causes of mucosal eosinophilia, major and minor histologic criteria for the diagnosis of EoO have been described (29). Major features include epithelial eosinophilia > 15 eosinophils/hpf, "microabscesses" described as clustering of 4 or more eosinophils and superficial layering of eosinophils. Minor criteria include basal cell hyperplasia, papillary elongation, spongiosis (intercellular oedema) which is currently known as dilated intercellular spaces (DIS), and inflammatory cell infiltration (29,30).

Balloon cells

These are swallen, pale cells with pycnotic nuclei in the midzone of the epithelium (Fig. 1). They represent chemical damage to the epithelium and are found in two-thirds of RO patients. They can also bee seen in EoO, though less frequently (1).

Basal cell hyperplasia

The basal cell layer is composed of smaller cells with hyperchromatic nuclei and basophilic cytoplasm and is normally two-cell layer thick. Basal cell hyperplasia is defined as a basal cell layer with a thickness more than 15% of the total epithelial thickness (Fig. 2). It can be difficult however, to recognise the uppermost limit of the basal layer which is defined as the point where cells are distributed with a distance less than one epitelial cell nucleus (3). It is observed in 87% of EoO whereas only 11% of RO patients show this feature. Also the 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 in a previous study (7).

Papillary elongation

Elongation of the papillae of the lamina propria is defined as the length of papillae grow more than 50% of the epithelial thickness (Fig. 3). Its severity seems to correlate with the degree of reflux. It is crucial that both basal cell hyperplasia and papillary elongation are assessed in well-oriented specimens (1-3). Similar to basal cell hyerplasia, papillary elongation is more prominent in EoO compared to RO (7). In the absence of clinical information these features of epithelial hyperplasia are useful as they may ignite a search for eosinophils and aid the diagnosis.

Vascular congestion

Dilated and congested venules at the tips of the dermal papillae (Fig. 4) described as vascular lakes are seen in 83% of RO and 10% of non-RO patients (1). They are uncommon in EoO.

Inflammatory cell infiltration

Infiltration of lymphocytes, eosinophils and neutrophils are part of the response to chemical injury of acid reflux. Few lymphocytes and Langerhans cells can be found in the otherwise normal-looking oesophageal mucosa while they seem more prominent in patients with reflux. Intraepithelial lymphocytes are known as "squiggle cells" as their nuclei become curved and irregular (Fig. 5) when they reside between the epithelial cells (1,3). The lymphocytes are mostly $CD3^+$ $CD8^+$ cytotoxic T cells with no cut-off for normal limits and are of limited diagnostic value. Intraepithelial lymphocytes are present in both reflux and non-reflux oesophagitis, including EoO and therefore, are not considered as specific (3,25).

Neutrophils, when present are considered as suggestive of RO (Fig. 6), while they are uncommonly found in EoO. When neutrophils and ulcer are present in a biopsy, an alternative cause of oesophagitis rather than allergy should be considered (3). In this subgroup of patients, infections and pill oeosphagitis are the possible diagnostic entities (31).

Eosinophils, on the other hand, are considered to be important in the differential diagnosis of RO and EoO, and therefore possess a cut off value of more than 15 eosinophils per high power field (16). However, a strict consensus for the minimum number of eosinophils in oesophageal mucosa required to make a diagnosis of EoO is lacking. In a meta-analysis of the literature on EoO, the cut-off for eosinophils per hpf varied significantly in a large number of studies, ranging from 5 to 30 eosinophils/hpf (Fig. 7), with the most common being > 20/hpf (32,33). Despite the presence of eosinophils in RO, it is characterized by lower eosinophil counts in the oesophageal mucosa, usually 7 or fewer/hpf, though higher numbers can be observed in adult patients with RO, and in patients with other oesophageal diseases (34). There is also no standardized method for eosinophil counts which should be obtained from the most densely infiltrated area of the biopsy. More than 7 eosinophils/hpf as an avarage of all fields (35) or > 15/hpf of an avarege of 5 hpf (36) and > 20/hpf of a single hpf (37) are various methods reported by various investigators. Similarly, the normal range also varies in the literature due to the variation in the selection of normal controls.

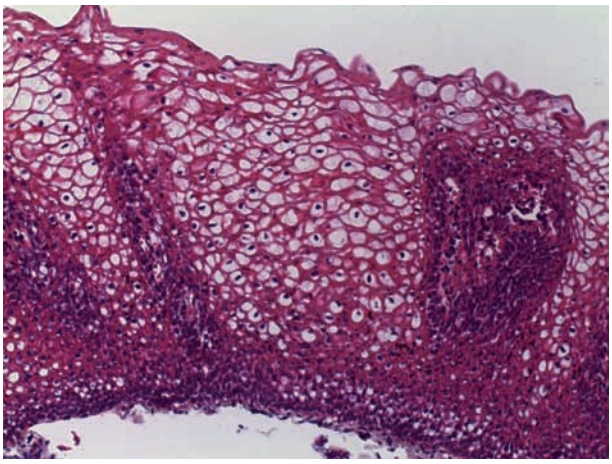

Fig. 1. — Balloon cells with pale staining cytoplasm in the midzone of the epithelium (H&E ; ×200).

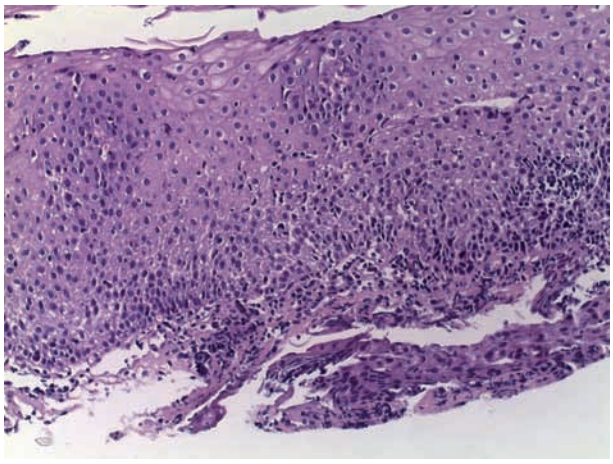

Fig. 2. — Basal cell hyperplasia > 50% of the epithelial thickness (H&E ; ×200).

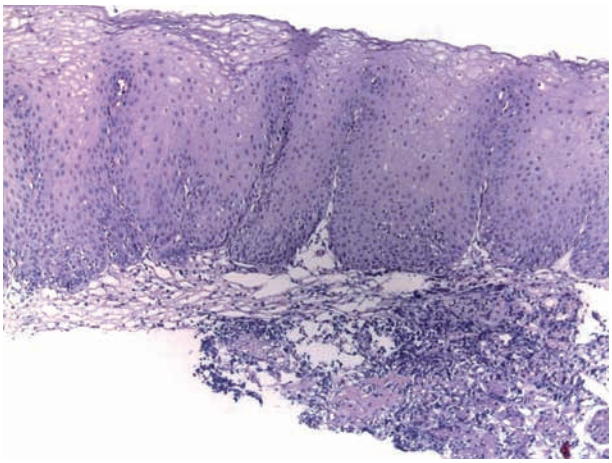

Fig. 3. — Papillary elongation > 75% of the epithelial thickness (H&E ; ×100).

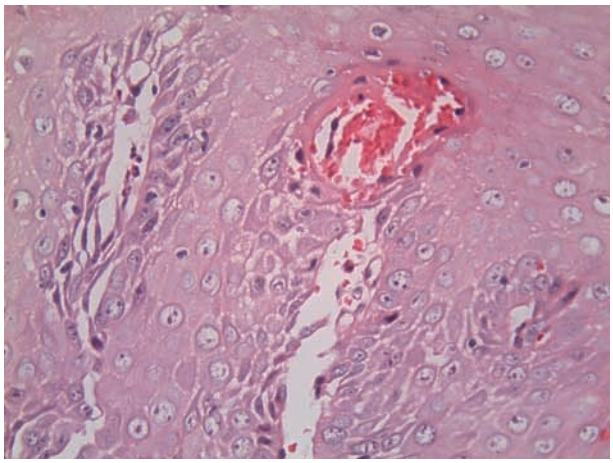

Fig. 4. — Congested venule at te tip of the papilla (H&E ; ×400).

However, when increased, they are very useful in the diagnosis, especially, in biopsies where orientation is poor (33). There is a tendency of eosinophils to concentrate in the squamous mucosa just below the luminal surface forming clusters called "eosinophilic microabscesses" which is a diagnostic feature for EoO (28,38). Dense fibrosis is seen in up to one-third of the patients with EoO together with an increase in the number of eosinophils in the lamina propria (1,39). It is patients with intermediate levels of eosinophil counts (7-20 eos/hpf) that often cause difficulty in the differential diagnosis (25). Immunohistochemistry for eosinophil secretory products could prove useful in the diagnosis of these patients as it highlights degranulated eosinophils as well (30). Multiple endoscopic biopsies from upper, mid, and lower oesophagus are crucial for a definite diagnosis in EoO. It is equally important, however, to note that the recommendations regarding eosinophil counts are only meaningful in the correct clinical context. Therefore, close communication between pathologist and gastroenterologist should be established before a diagnosis is made.

Dilated intercellular spaces (DIS)

DIS is considered as an early sign of RO while it is constantly observed in EoO (40) with a prevelance varying between 67% to 94% in RO (3,40). The first descripton of this feature was made on electron microscopy and was characterized by irregular intercellular spaces more than 0.47 microns between cells (Fig. 8) resulting from oedema stretching or detaching the desmosomes (41). It is believed that the loss of tight junctions between squamous cells, results in increased paracellular permeability that facilitates acid leakage through the mucosa and cause direct contact with terminal dendritic processes of underlying sensory neurons in the epithelium (42). DIS in the bubble form is defined as irregular round dilata-

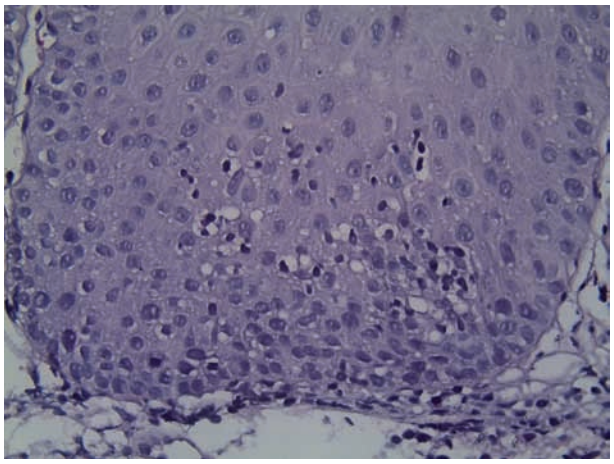

Fig. 5. — Lymphocytic infiltration in the squamous epithelium (H&E ; ×400).

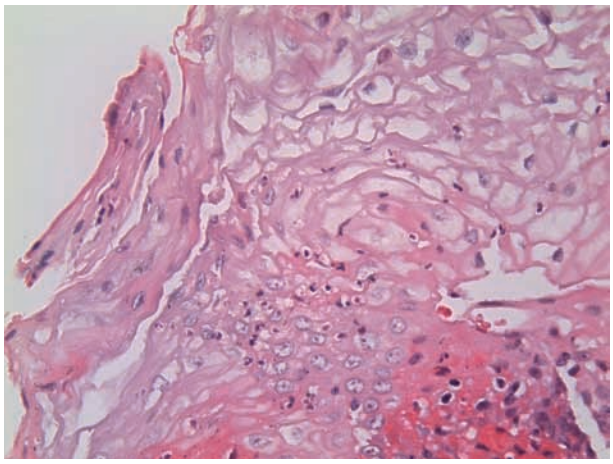

Fig. 6. — Neutrophils in the squamous epithelium (H&E ; ×400).

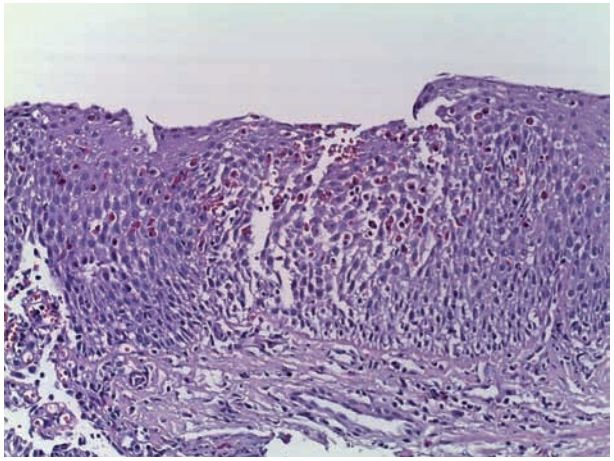

Fig. 7. — Numerous eosinophils in the squamous epithelium showing basal cell hyperplasia (H&E ; ×200).

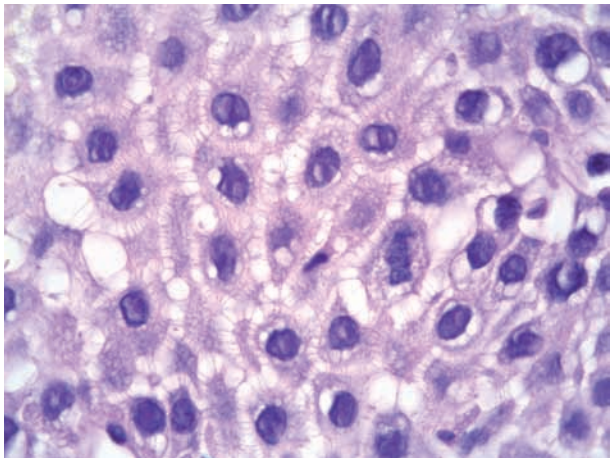

Fig. 8. — Dilated intercellular spaces in the form of bubles and ladders between squamous cells (H&E ; ×400).

tions whereas the ladder form is defined as diffuse widening of intercellular spaces (9). Table 2 summarizes histopathologic features of EoO and RO.

There are very few studies that systematically compare the clinical, endocopic, and histologic characteristics of patients with EoO to patients with RO. Aceves *et al.* (11), compared children with EoO to those with a milder degree of tissue eosinophilia (non-EoO patients) and found that histologicaly EoO patients were more likely to have basal cell hyperplasia, more eosinophils and degranulated eosinophils. More recently, Müeller *et al.* (28), demonstrated that eosinophil infiltration (54.8 vs 9.1/hpf), degranulation as well as epithelial hyperplasia and presence of DIS were significantly more commonly observed in EoO in comparison to RO. A significant increase in the mast cell counts was found in the same study both on H&E and on immunohistochemically stained slides (28). In parallel with other studies on smaller case series (43,44), the authors have concluded that the differential diagnosis of EoO and RO could not be based on eosinophil counts alone and that secondary changes in the epithelium should also be evaluated (8,28).

Treatment and prognosis

Prognosis of RO depends on the degree of LES pressures as well as early diagnosis which enables to prevent complications. Changing the lifestyle of the patients is crucial to increase the effect of medical therapy including proton pump inhibitors while endoscopic/surgical procedures are reserved for cases unresponsive to more conservative measures (1). The prognosis is surprisingly good in EoO when prompt treatment is given. Therapy includes dietary elimination of allergic foods together with steroid administration. In addition gastric acid should be neutralized even in patients without accompanying reflux disease. When untreated, chronic scarring

Table 2. — **Histologic features of EoO ad RO**

Histologic features	**Eosinophilic oesophagitis**	**Reflux oesophagitis**
Epithelial hyperplasia	marked	moderate
Basal cell hyperplasia	marked (> 50% of epithelial thickness)	mild – moderate (> 30-50% of epithelial thickness)
Papillary elongation	marked (> 75% of epithelial thickness)	moderate (> 50% of epithelial thickness)
DIS	marked	marked
Balloon cells	rare	common
Vascular lakes	rare	common
Lymphocytes	common	common
Neutrophils	very rare	common
Eosinophils	> 15-20/HPF in clusters	0-7/HPF scattered

and oesophageal stricture formation could develop as the disease progresses (26).

Conclusions

The differential diagnosis of EoE and RO is a difficult task for the pathologist. Multiple biopsies and good orientation are critical for correct interpretation of features such as basal cell hyperplasia, papillary elongation while inflammatory cells, and in particular eosinophils, should be counted in areas where they are most numerous. When in doubt, eosinophilic "microabscesses" in the superficial sqamous epithelium should be searched for. It should be noted however, that, the diagnosis, especially in cases where histopathology is less discriminatory, relies upon good clinicopathologic correlation.

Prospects for future research

Histologic assessment of oesophageal biopsies is currently the most reliable procedure for distinguishing eosinophilic oesophagitis from reflux oesophagitis. Therefore, studies using endoscopy with a defined protocol and extensive biopsies obtained from disease control subjects as well as subjects with NERD will help to determine the optimal cutoffs for every histopathologic criterion used in the diagnosis. It is possible that new biomarkers capable of differentiating EoO from RO will emerge from these studies.

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