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Diagnosis of reflux esophagitis in infants: histology of the distal esophagus must complement upper gastrointestinal endoscopy

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Abstract

Objective: The aim of this study was to validate the endoscopic findings against histologic features of the distal esophageal mucosa for the diagnosis of reflux esophagitis in infants.

Methods: The data records of 167 patients (88 M; 79F) aged 38-364 days, referred for investigation of reflux esophagitis, between January 1995 and December 2000 were retrospectively reviewed. The association between nominal (presence or absence of esophagitis) and ordinal (grades of esophagitis) variables was analyzed through a correlation between the results of endoscopic findings and histology.

Results: Endoscopy when compared with histologic analysis had a sensitivity of 45%; specificity of 71%; positive and negative predictive value of 89% and 21% respectively; and accuracy of 50%. Additionally, this study demonstrated that there was a poor correlation between endoscopic and histologic findings when endoscopy was normal or when endoscopic grade I esophagitis was observed (p = 0.10). Normal esophageal appearance failed to identify 79.2% of patients with histologic esophagitis. Conversely, amongst patients with endoscopic grade I esophagitis, 12.1% had normal histology.

Conclusions: We concluded that whilst endoscopy had a specificity of 71%, it did not attain an acceptable range of sensitivity (45%) to justify performing an endoscopy without biopsy, as many true cases of esophagitis would not be detected; and that the presence of grade I (non-erosive) esophagitis at endoscopy did not increase the value of the test in predicting histologic abnormality.

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Introduction

Reflux esophagitis (RE) is associated with an increase in esophageal exposure to acid. In infants it is difficult to diagnose RE based on clinical findings alone since they are unable to describe the classical symptoms observed in older children and adults – odynophagia and pyrosis. These patients may either present with irritability, refusal to eat, dysphagia and anemia, or may be asymptomatic.[1] In the majority of cases the initial investigation involves contrast radiography of the esophagus, stomach and duodenum. Incorrect interpretation of the findings from this diagnostic method may lead to unnecessary pharmacological treatment since the presence of reflux does not determine that there is pathological gastroesophageal reflux.

The esophageal mucosa responds to injury in a variety of ways and the macroscopic appearance of esophagitis will vary depending on the duration and severity of the disease.

A number of different grading systems for the endoscopic classification of reflux esophagitis have been proposed by different investigators.

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The Savary-Miller classification system and the more recently proposed Los Angeles classification, are widely used by adult endoscopists.[2-5] These classification systems have the disadvantage to diagnose the inflammatory process only when there is erosive esophagitis. They do not take into account less severe findings such as edema, hyperemia and friability and are less pertinent for pediatric patients in whom reflux esophagitis is rarely so severe.[1] Therefore a modified classification allowing subdivision of the less severe cases is more appropriate for pediatric use.

In an attempt to integrate these classification systems, a further method has been proposed that includes criteria such as erythema, friability and blurring of the mucosal junction.[6] In this classification system the endoscopic appearance of the esophagus is subdivided into 5 grades of severity (Table 1).

Endoscopic findings, while common among symptomatic adults with GER, are present in 60 to 80% of children, making biopsy necessary to confirm esophagitis, particularly during the initial phases of the inflammatory process, when the endoscopic appearance may be almost normal, in order to confirm esophagitis and grade its severity.[7]

The earliest histopathological abnormalities are basal cell hyperplasia, corresponding to 20% or more of the total mucosal thickness, and elongation of stromal papillae extending into the upper half of the epithelium.[8,9] The mechanism postulated is that superficial epithelial lesions result in stimulation of basal cells and consequently cause hyperplasia. The persistence of the inflammatory process particularly affecting the submucosa and muscular layer, may lead to stenosis due to edema, inflammatory cells and tissue fibrosis.

The European Society of Paediatric Gastroenterology, Hepatology and Nutrition, in a consensus document published in 1994 suggests the use of histological criteria for reflux esophagitis diagnosis, classifying it into 5 grades (Table 2).[1]

This study was performed with the objective of comparing the results of upper gastrointestinal endoscopy (UGIE) with the histological findings of the distal esophagus for the diagnosis of reflux esophagitis (RE) in infants.

Methods

This study was undertaken at the Pediatric Gastroenterology Unit of the Hospital Pequeno Príncipe and was approved by the Ethics Research Committee of the institution.

The medical records of 684 pediatric patients referred for UGIE and investigation of gastroesophageal reflux (GER) during the period between January 1995 and December 2000 were reviewed. Clinical information was obtained prior to the endoscopic procedure and recorded on the Endoscopy Unit database.

Patients aged less than 12 months old, with symptoms suggestive of reflux esophagitis including irritability, regurgitation, refusal to eat and poor weight gain and who had undergone an upper gastrointestinal endoscopy with esophageal biopsy were included. Patients were excluded of the study if they had been using peptic acid inhibitors or neutralizers, if they had neuromuscular diseases resulting in developmental disorders, if they had congenital abnormalities, caustic lesions or had had previous surgery of the esophagus. One hundred and sixty-seven patients met these criteria.

The methods used for the investigations are described below.

Upper gastrointestinal endoscopy was performed using a forward viewing Olympus® videoendoscope, model CV-E, (Olympus Optical Co. Ltd., Tokyo, Japan), and grasp biopsies were taken using a Wilson-Cook® elliptical biopsy forceps (Wilson-Cook Medical Inc., Winston-Salem, USA). The procedure was performed under general anesthesia performed by an anesthetist, with the patient fasting for 6 hours. The endoscopic findings of the esophagus were classified according to the Tytgat grading system. (Table 1).[6]

At the end of the endoscopic procedure two fragments were collected from the distal esophagus, at least 2 cm above the gastroesophageal mucosal junction, using biopsy forceps that remove samples sized between 2 and 2.5 mm. Biopsy specimens were carefully removed from the forceps and oriented on filter paper and immersed in 10% formalin. The specimens were submitted to routine histological processing, embedded in paraffin and sectioned perpendicular to the mucosal surface. Slices of 5 to 6 µm thickness were mounted on slides and then stained with hematoxylin & eosin (HE).

Table 1 - Grading of Reflux Esophagitis (Tytgat classification system)

Grade 0	No evidence of reflux-induced damage, sharply delineated squamocolumnar mucosal junction (SCMJ).
Grade I	Mild, patchy, or diffuse erythema at the level of the SCMJ; slight blurring of the SCMJ; minor friability; loss of shininess of the distal squamous mucosa. There is no apparent break in the mucosa.
Grade II	One or more discrete superficial erosions seen as red dots or streaks with or without adherent whitish exudate.
Grade III	Confluent but non-circumferential erosions seen as defects that merge either longitudinally or laterally. There may be additional exudate covering the erosive defects or slough formation. Less than 50% of the overall mucosal surface of the distal 5 cm is involved.
Grade IV	Circumferential erosions or exudative lesions at the level of the SCMJ, regardless of the extent along the distal esophagus.
Grade V	Deep ulceration anywhere along the esophagus, with various degrees of stricturing.

Histological analysis of the biopsy samples was performed using a conventional binocular optical microscope from Zeiss® (Carl Zeiss Group, Oberkochen, Germany). The findings were classified according to Knuff & Leape as recommended by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (Table 2). With the intention of simplifying the comparison between the two methods, hyperplasia of basal cells, lengthening of the papillae and dilation of intraepithelial vessels were grouped and defined as grade 1, without dividing this into three further categories.

Table 2 - Histological classification of the reflux esophagitis (based on Knuff & Leape)

0	Normal
I A	Basal zone hyperplasia
I B	Elongated stromal papillae
I C	Vascular ingrowth
II	Polymorphonuclear cells in the epithelium, lamina propria or both
III	Polymorphs with epithelial defect
IV	Ulceration
V	Abnormal columnar epithelium

There was only one observer for each diagnosis method. The endoscopist knew the clinical details of the patient and the pathologist was not informed of the endoscopic diagnosis.

Data obtained from the database were analyzed using a Microsoft Excel® (Microsoft Corporation, Redmond, USA) spreadsheet and SPSS 10.0 for Windows® (SPSS Inc., Chicago, USA).

Associations between nominal variables (presence or absence of esophagitis) and among ordinal variables (grades of esophagitis) were analyzed after tables had been produced and divided into two parts:

- comparison between the results of the upper gastrointestinal endoscopy (UGIE) and histology.
- independent analysis between results: Normal and grade I UGIE versus Normal and grade I Histology in 112 patients; and grades I and II UGIE *versus* grades I and II histology in 60 patients.

The diagnostic value of endoscopy as a predictor of esophagitis using the test values of sensitivity, specificity, accuracy, positive and negative predictive values, and positive and negative likelihood ratios (LR+ and LR-) was calculated. Statistical analysis was performed using the chi-squared and Fisher's exact tests and significance was set at $p < 0.05$. The Fisher's exact test was used when at least one expected frequency in the contingency tables was less than 5.

Results

There were 88 (52.7%) boys and 79 (47.3%) girls. Age ranged from 38 to 364 days with a mean of 190.1 days, median of 169 days and standard deviation of 91.99 days.

Symptoms included irritability (100%), regurgitation (95.8%), refusal to eat (25.7%), poor weight gain (10.8%) and respiratory manifestations (3%).

Upper gastrointestinal endoscopy was normal in 96 (57.5%) cases. Grade I esophagitis was observed in 66 patients, grade II esophagitis in 4 (2.4%) and grade III esophagitis in 1 (0.6%) case.

Histology was normal in 28 patients (16.8%), revealed grade I esophagitis in 86 (51.5%), grade II esophagitis in 45 (26.9%) and grade III esophagitis in eight cases (4.8%).

The endoscopic findings were compared with histological features. Microscopic abnormalities compatible with esophagitis were observed in 76 (79.2%) of the 96 patients with normal endoscopy. Conversely, eight (11.3%) of the 71 patients with endoscopic abnormalities presented with normal histology.

Upper gastrointestinal endoscopy presented a sensitivity of 45% and specificity of 71%; a positive predictive value of 89% and a negative predictive value of 21%, with an accuracy of 50%.

The positive predictive value expresses the probability (post-test) of esophagitis occurring when the test result is positive. The negative predictive value expresses the probability that the patient does not have esophagitis when endoscopy is normal. Accuracy represents the proportion of tests giving the correct result.

The positive likelihood ratio (LR+) was 1.59 and the negative likelihood ratio (LR-) was 0.77. These tests express the probability that a given diagnostic examination will result in the confirmation of the disease when its result is positive, or conversely, in the disease being ruled out if the result is negative. In other words, the factor by which the pretest probability is multiplied when the test is positive or negative.

A comparison of the endoscopic and histological findings, according to grade of esophagitis is shown in Table 3.

When analyzing the groups with normal endoscopies and grade I esophagitis (n = 112) and comparing them with those whose histology was normal and had grade I esophagitis, it was observed that: 65 (58%) patients exhibited normal endoscopies and 47 (42%), grade I esophagitis; while 28 (25%) had normal histology and 84 (75%), grade I esophagitis. Of the 65 patients with normal UGIE, 45 (69%) presented grade I esophagitis at histology. Conversely, of the 47 patients with grade I esophagitis in UGIE, eight (17%) had no histological abnormalities (Table 4).

When analyzing the groups (n = 60) with grade I and II esophagitis at UGIE compared with those classified at grades I and II by histology, it was observed that 56 (93.3%) patients exhibited grade I and grade II UGIE

Table 3 - Summary of the endoscopic and histological diagnosis according to the grade of esophagitis

Endoscopy	Histology				
	Normal	**Grade I**	**Grade II**	**Grade III**	**Total**
Normal	20 (20.8%)	45 (46.9%)	26 (27.1%)	5 (5.2%)	96
Grade I	8 (12.1%)	39 (59.1%)	17 (25.8%)	2 (3.0%)	66
Grade II	0	2 (50.0%)	2 (50.0%)	0	4
Grade III	0	0	0	1 (100%)	1
Total	28	86	45	8	

Table 4 - Comparison between normal and grade I UGIE versus normal and grade I Histology (n = 112)

Endoscopy	Histology		
	Normal	**Grade I esophagitis**	**Total**
Normal	20	45	65
Grade I esophagitis	8	39	47*
Total	28	84	112

* p = 0.10

(6.7%), with 41 (68.3%) exhibiting grade I esophagitis and 19 (31.7%) grade II esophagitis at histology. In this group, 56 patients with grade I UGIE, 17 (30.4%) presented grade II esophagitis at histology. Conversely, two (50%) of the four patients with grade II esophagitis at UGIE had grade I histological findings (Table 5).

Table 5 - Comparison between grade I and grade II UGIE versus grade I and grade II Histology (n = 60)

Endoscopy	Histology		
	Grade I esophagitis	**Grade I esophagitis**	**Total**
Grade I esophagitis	39	17	56
Grade II esophagitis	2	2	4*
Total	41	19	60

*p = 0.58

Discussion

In this study, patients aged than 1 year were selected due to the fact that clinical and pathophysiological features are similar for this age group when compared with older children and adults. The population studied was obtained by referral from pediatricians concerned with the persistent nature of symptoms suggestive of esophagitis.

Crying, irritability and other manifestations of pain in infants with esophagitis may also be symptoms of a wide variety of diseases including infections, food allergies or neurological disorders, and difficulties with diagnosis are due to the inability of the patients to describe pain. It is important to consider the diagnosis of reflux esophagitis when infants present these clinical symptoms with the objective of avoiding complications due to chronic inflammation or insufficient caloric intake.

Until recently RE was seen as an uncommon condition among infants. This impression may have resulted from lack of histological assessment and reliance on endoscopic findings.[10]

One of the main objectives of diagnostic methods is to maintain simplicity. As this was a retrospective study, special techniques (dissection microscope) were not used by the pathologist and technicians, although the precautions concerning biopsy samples were always taken by the investigator.

Upper gastrointestinal endoscopy allows clear observation of the mucosa, but it is impossible to determine to what extent the normal appearance is not merely the result of increased salivary and mucous production, local compensatory anti-inflammatory mediators, or even of altered esophageal motility, increasing the clearance and rapidly relieving the organ of persistent reflux of gastric contents. These defense mechanisms may be enough to maintain normal mucosa appearance, but not to block the sensitivity of the organ, thus explaining why highly symptomatic individuals may present normal endoscopic findings.[11]

The systems for grading endoscopy and histological findings were established independently and were intended to reflect the intensity of abnormalities. The different classification systems used to grade reflux esophagitis have their advantages and disadvantages, since there is controversy over criteria for assessing the injury. While the Los Angeles classification offers a better description of injury to the mucosa, intra-observer and inter-observer variation is significant, particularly among less experienced endoscopists.[12] These findings are comparable with those observed when a classification that takes milder alterations such as edema, hyperemia and mucosa friability into account is used to define esophagitis.[13] The endoscopic grading of esophagitis according to the Los Angeles criteria has not yet been evaluated in children and may possibly provide more uniform definitions of severity when applied to more severe esophagitis.[14] Other findings, such as the presence of vertical lines, also correlate with histological findings in children.[15] In this study, the Tytgat classification system which describes the mild alterations observed with non-erosive esophagitis, was used.[6]

There is controversy over the value of erythema, edema and friability in the distal esophagus for diagnosing esophagitis. Grade I esophagitis was the most common from both the endoscopic (39.5%) and histological (51.5%) points of view. Agreement between endoscopic and histological diagnoses was weak and predominated at the more severe grades.[10] This analysis, however, was adversely affected by the fact that there were few cases of grade II (n = 4) and grade III (n = 1) esophagitis at endoscopy.

Little is known about the changes occurring in infants with GERD, where the duration of exposure may be only months and not years, and severe abnormalities are not often found. Normal UGIE findings or the absence of macroscopic damage does not rule out the presence of histological esophagitis.[16] In such cases esophagitis would be restricted to minimal alterations and would not be severe. Because there is a poor correlation between endoscopic and histological findings, biopsy is recommended whenever UGIE is performed since it can be obtained easily and without significant risks.[17] Microscopic examination of esophageal biopsies can allow for a certain amount of grading and can help to define the intensity of RE more precisely than can the endoscopic classification. Furthermore, recognition that children with normal endoscopies may have eosinophilic esophagitis and histological reflux esophagitis has motivated pediatric gastroenterologists to perform biopsies even in the absence of macroscopic findings.[18]

This study has demonstrated that the endoscopic findings were not associated with histological esophagitis when UGIE was normal or in grade I esophagitis. A normal endoscopic appearance failed to identify 79.2% of the patients with histological RE. These findings call the attention to the difficulties in the endoscopic diagnosis of esophagitis, especially when there are no macroscopic alterations observed or when mild changes are identified. Upper gastrointestinal endoscopy must therefore be complemented by histology of the distal esophagus when evaluating infants with suspected reflux esophagitis.

The crucial question is: what is the importance of non-erosive esophagitis? What is the risk of an infant with minimal histological abnormalities or eosinophilic and neutrophilic intraepithelial infiltrates of developing long-term complications? This question is very difficult to be answered and would require long-term follow-up, with endoscopic control of treated and untreated patients and normal controls. The clinical relevance of minimal esophagitis has not been established and it is not clear whether treatment would be different in the presence or absence of microscopic esophagitis.

For uniformity it is important that all endoscopists at a given pediatric endoscopy unit always adopt the same classification, whichever it may be, since all have their pros and cons.[19] Finally, biopsies are essential for confirming or ruling out RE as the cause of symptoms and possibly for excluding other diseases.

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