Int J Clin Exp Pathol 2012;5(6):581-587
www.ijcep.com /ISSN: 1936-2625/IJCEP1206008

Original Article

An examination of the relationship between the endoscopic appearance of duodenitis and the histological findings in patients with epigastric pain

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Received June 20, 2012; Accepted July 19, 2012; Epub July 29, 2012; Published August 15, 2012

Abstract: The endoscopic appearance of duodenitis is a common finding in patients undergoing endoscopy because of epigastric pain however, the relationship of the visual findings to histology is poorly defined. We set out to ascertain if there was a correlation between the endoscopic and histological appearances of the duodenal mucosa. Consecutive patients with epigastric pain referred for diagnostic gastroduodenoscopy were studied. The visual appearances of 'duodenitis' (erythema, erosions and sub-epithelial haemorrhage) were reported independently by two endoscopists. Duodenal biopsies were taken and assessed for: neutrophil infiltrate, mononuclear infiltrate, gastric metaplasia, villous atrophy and a breach in the mucosa. *H pylori* status was determined. Of the 93 patients with endoscopic features of duodenitis an increase in histological markers of inflammation was found in 75 (81%). However, histological inflammation was absent or minimal in 68 (73%). Conversely, biopsies from normal-looking mucosa revealed histological evidence of inflammation in 26 (27%). For patients with the endoscopic features of duodenitis the positive & negative predictive value for neutrophilic infiltrate was 39% and 98% respectively. Biopsies from erosions confirmed a breach in the mucosa in only 2 of 40 patients. Neutrophilic infiltrate occurred with NSAI ingestion and infection with *H pylori*. The endoscopic appearance of the duodenal mucosa is unreliable in determining the presence of histological inflammation. The endoscopic appearance of 'erosions' is not usually associated with a mucosal breach.

Keywords: Duodenitis, endoscopy, histology

Introduction

Apparently inflamed duodenal mucosa is often seen at endoscopy in patients referred for investigation of epigastric pain, and the term 'duodenitis' frequently used. The visual features include erythema, erosions and petechial haemorrhage. The results of studies investigating whether the endoscopic changes represent histologically demonstrable inflammation have been variable, the correlations ranging from "poor" to "good" [1-13]. Duodenitis is often associated with the presence of Helicobacter pylori [13, 14]. Most of these studies were done prior to the discovery of Helicobacter pylori and control groups have not been included in more than half of these reports. The correlation between endoscopic and histological appearances of 'inflamed' looking gastric mucosa has been shown to be poor [4, 8, 9, 11, 12, 15]. A recent study has shown a poor relationship between symptoms of functional dyspepsia and histological duodenitis [14].

We set out to assess if there was any correlation between the endoscopic and histological appearances of the duodenal mucosa in patients referred for endoscopy to investigate epigastric pain. We used two control groups: biopsies from normal appearing mucosa adjacent to abnormal areas in patients with an endoscopic diagnosis of duodenitis and biop-

sies from patients whose endoscopic appearances were entirely normal. We also assessed the histology of duodenal erosions.

Methods

Consecutive patients over the age of 18 who were referred for diagnostic gastroduodenoscopy because of 'non-reflux' like epigastric pain, were asked to participate in the study. Patients were excluded if they had gastric or duodenal ulceration, prior gastric surgery, positive anti-tissue transglutaminase antibodies, were pregnant, taken a proton pump inhibitor or antibiotics within the previous two months. Written informed consent was obtained. Once the target recruitment of patients with normal-looking duodenal mucosa was reached, subsequent consented patients with normal looking duodenal mucosa were not recruited to the study.

A medical and a drug history was taken, and alcohol and tobacco consumption recorded. Gastroduodenoscopy was performed by experienced endoscopists (each having done a minimum of 2000 procedures) using either Olympus® or Fuji® endoscopy systems. A second experienced endoscopist, present in the examination room, recorded the endoscopic findings independently. Endoscopists were required to comment on the presence of 'duodenitis' (mucosal erythema, erosions and subepithelial haemorrhage) in both the first and second parts of the duodenum as well as any other pathology seen. Erosions were defined as apparent breaks in the mucosa covered in exudate, the latter, not washing off with a flush.

Biopsies were taken using 2.2mm Radial Jaw® biopsy forceps. Patients with the endoscopic appearance of duodenitis had two duodenal biopsies taken from visually abnormal mucosa and two from normal looking areas. 'Control' patients with normal endoscopic appearances of the duodenum had two duodenal biopsies taken. When erosions were present biopsies were also taken from across the lesion.

The specimens were prepared using standard techniques, fixed ensuring optical orientation. Each biopsy was examined at three levels (each level being 3 micrometers in thickness); twenty sections were cut and discarded between the first level and the second level, and between the second level and the third level. The sections were stained with haematoxylin and eosin.

Duodenal biopsies were independently reported by two gastrointestinal histopathologists (with each over 24 years of experience) blinded to the endoscopic findings. Discrepancies in reporting were resolved by consensus. The biopsies were assessed for the four widely accepted criteria of duodenitis: neutrophil infiltrate, mononuclear (lymphocytes and plasma cell) infiltrate, gastric metaplasia and villous atrophy [16]. Inflammatory cells were assessed in the lamina propria and epithelial layer using an updated Sydney classification [16]. Gastric metaplasia was assessed according to method of Wyatt et al [17] and villous atrophy according to Blomquist et al [18]. Each of these features was scored: normal (0), mildly abnormal (1), moderately abnormal (2) and severely abnormal (3). A 'composite' histology score was constructed by simply adding the individual scores of each of the four histological parameters assessed.

Gastric antral and body biopsies were assessed for Helicobacter pylori by histology and by CLO test (Pronto dry, Medical Instruments France).

All patients underwent a C^{13} urea breath test (Aspire Health Care Ltd, London, UK).

To examine the relationship between endoscopic appearance and duodenal histology we compared three groups: biopsies from inflamed-looking mucosa in patients with endoscopic appearances of duodenitis (group 1), biopsies from adjacent normal-looking mucosa in patients with endoscopic appearances of duodenitis (group 2) and biopsies from patients without endoscopic signs of duodenitis (group 3).

Previous studies [1-5, 8, 9, 11] found histological evidence of duodenitis in 66% (Sd 20) of patients with endoscopicaly apparent changes and in 24% (Sd 19) of patients with visibly normal-looking duodenal mucosa. Power calculations suggest an incredibly small sample size of 5 patients in each group would be adequate (power=0.9, a=0.05) to show a difference between groups. However, in these studies histological changes were often minimal and of

Table 1. Endoscopic appearance of duodenitis in the first and second parts of the duodenum (n=93)

	Duodenal appearance		Difference
	First part	Second part	*p* value
Erythema (none, patchy, generalised)	19 : 71 : 3	66 : 25 : 2	<0.001
Erosions (none, <5, >5)	58 : 18 : 17	81 : 5 : 7	<0.001
Sub-epithelial haemorrhages (no/yes)	64 : 29	84 : 9	<0.001

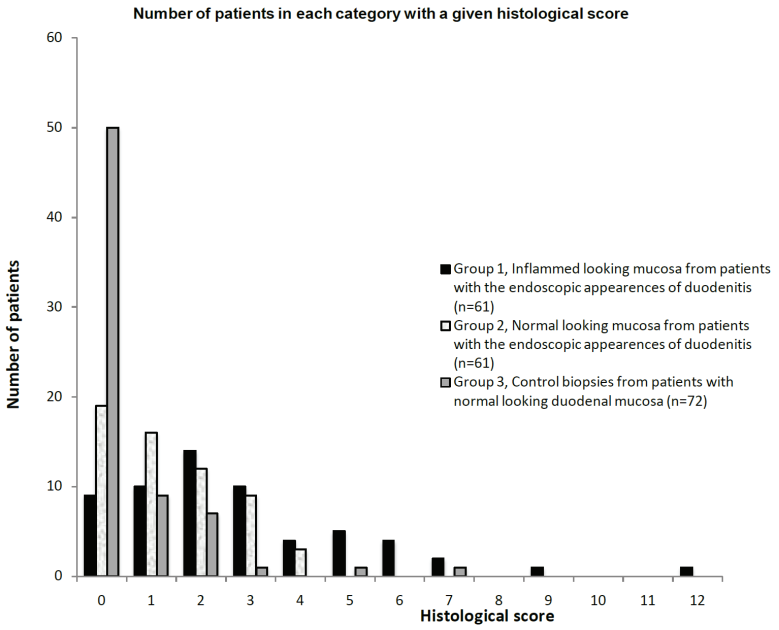

Figure 1. Number of patients in each category with a given histological score.

dubious clinical significance. Previous studies examined small numbers of patients (median 14 patients with apparent endoscopic appearances of duodenal inflammation, range 11-51). We decided to recruit 110 patients in each group to provide a clinically more meaningfully sized study.

Data were analysed blinded to group, using Stata 10 (StataCorp, College Station, Texas USA). Results were not normally distributed and therefore presented as medians and interquartile (IQ) ranges. Differences between groups were examined using Mann-Whitney U tests. Frequencies were examined using Fishers exact tests. Correlations between variables were assessed using Spearman's correlation method, the results presented as correlation coefficient r and p values. A p value of less than 0.05 was considered statistically significant.

The study was approved by the Southwest Peninsula Local Research & Ethics Committee.

Results

Baseline characteristics

Of the 220 patients recruited, biopsies were inadequate for assessment in 30. Data were therefore analysed from 93 patients with and 97 without endoscopic evidence of duodenitis. Eighty-nine were female and 101 male, with a median age of 59 (19-93) years. There were no differences in age, sex, symptoms, NSAID use (including low dose aspirin), smoking, alcohol consumption or other endoscopic diagnosis between the two groups.

Abnormal endoscopic findings were more prevalent in the first part of the duodenum (**Table 1**). By far the commonest abnormality was patchy erythema.

Relationship between endoscopic and histological findings

Across all three groups the median 'composite' histology scores was 1 (0, 2). For group 1 the median score was 2 (1, 4), group 2 was 1 (0, 2) and in group 3 was 0 (0, 1) (**Figure 1**). The overlap was substantial with biopsies from endoscopicaly abnormal mucosa (group 1) being completely normal in 17 (18%) and graded between 1 and 3 in 51 (55%). Despite the substantial overlap between the three groups there were significant differences. Higher polymorphonuclear and mononuclear cell scores were found for group 1 than for group 2, and for group 2 than for group 3, the differences being more marked for polymorphonuclear infiltrate (**Table 2**). However, no less than 57 (61%) of the

Table 2. Relationship between the endoscopic appearance of duodenitis and the histological scoring

Endoscopic appearance	Histological findings					
	Neutrophilic infiltrate					
	Normal	Abnormal				*Intra-epithelial cells present*
		Mild	Moderate	Severe	Total	
Duodenitis	57	27	8	1	36	8
Duodenitis (normal mucosa)	83	10	0	0	10	2
Control	95	2	0	0	2	0
Duodenitis vs Duodenitis (normal mucosa) p<0.001 *Duodenitis vs Control = p<0.001, Duodenitis (normal mucosa) vs Control p=0.03*						
	Monocytic infiltrate					
	Normal	Abnormal				*Intra-epithelial cells present*
		Mild	Moderate	Severe	Total	
Duodenitis	36	42	13	2	57	14
Duodenitis (normal mucosa)	61	31	1	0	32	3
Control	80	13	3	1	17	4
Duodenitis vs Duodenitis (normal mucosa) p<0.001 *Duodenitis vs Control 1 p<0.001, Duodenitis (normal mucosa) vs Control p=0.002*						
	Gastric metaplasia					
	Normal	Abnormal				
		Mild	Moderate	Severe	Total	
Duodenitis	55	23	11	4	38	
Duodenitis (normal mucosa)	67	20	6	0	26	
Control	85	8	3	1	12	
Duodenitis vs Control p<0.001, Duodenitis (normal mucosa) vs Control p=0.015						
	Villus atrophy					
	Normal	Abnormal				
		Mild	Moderate	Severe	Total	
Duodenitis	46	36	7	4	47	
Duodenitis (normal mucosa)	62	24	7	0	31	
Control	89	8	0	0	8	
Duodenitis vs Control p<0.001, Duodenitis vs Duodenitis (normal mucosa) p=0.028, Duodenitis (normal mucosa) vs Control p<0.001						

93 comprising Group 1 scored 0 for polymorphs. Overall, polymorphonuclear infiltrate correlated with monocytes (r=0.28, p<0.0001), gastric metaplasia (r=0.32, p<0.0001) and villous atrophy (r=0.36, p<0.0001).

For patients with the endoscopic appearance of duodenitis (**Table 3**) the proportion of patients with supportive histological changes (positive predictive value) was poor (39-61%), while, negative predictive values were good (82-98%). The proportion of patients with histological changes who had endoscopic changes of duodenitis (sensitivity) was generally good (76-95%), especially for neutrophilic infiltrate, while the proportion of patients with no histological changes who had normal endoscopic appearances (specificity) was only moderate (61-69%).

Intra-epithelial neutrophils and lymphocytes were uncommonly seen (**Table 2**), but were more common in biopsies from areas of endoscopically apparent duodenitis (neutrophils p<0.001; lymphocytes p<0.001).

Histology of erosions and petechial haemorrhages

Forty patients had duodenal erosions, which were accompanied by erythema in 34. Biopsies from across the erosions revealed a break in the mucosa in 2. In other cases the histology showed a similar spectrum to that found in

Table 3. The sensitivity, specificity, positive and negative predictive values for biopsies taken from patients with the endoscopic appearance of duodenitis demonstrating histological change

			Predictive Value	
Histological abnormality	Sensitivity	Specificity	Positive	Negative
Neutrophils	95%	63%	39%	98%
Monocytic cells	77%	69%	61%	82%
Metaplasia	76%	61%	41%	88%
Crypt villi ratio	85%	66%	51%	92%
Total Score* (0 vs >0)	74%	80%	81%	73%
Total Score* (≤3 vs >3)	93%	58%	27%	98%

**Each of these features was scored: normal (0), mildly abnormal (1), moderately abnormal (2) and severely abnormal (3). A 'composite' histology score was constructed by simple adding the individual scores of each of the four histological parameters assessed.*

areas of erythema, ranging from normal to severely abnormal.

Petechial haemorrhages were seen in 23 patients, always accompanying erythema and/or erosions. No specific histological features were noted.

Relationship between duodenitis and non-steroidal anti-inflammatory use and H pylori infection

The endoscopic appearances of 'duodenitis' were associated with ingestion of non-steroidal anti-inflammatory consumption $p<0.05$ (principally low dose aspirin intake) but not infection with *H pylori*. Histological change was associated with infection with *H pylori* $p<0.01$ and weakly (neutrophilic infiltrate only) with NSAI ingestion $p<0.05$, but not the combination of both.

Characterisation of endoscopic duodenitis and other findings

Ten endoscopists took part in the study performing a median of 17 (4, 39) procedures each. Agreement between endoscopists was high (erythema 95%, subepithelial haemorrhage 100%, erosions 100%, contact bleeding 93% and normal mucosal 100%).

Other endoscopic findings such as gastric polyps, oesophagitis or antral "erosions" were no more common in those patients with duodenitis than those without.

Discussion

In patients undergoing upper gastrointestinal endoscopy for investigation of epigastric pain the accepted histological features of duodenal inflammation including neutrophil infiltrate, the hallmark of active duodenitis [16], were increased in areas of apparent duodenal inflammation at endoscopy. However, the absence of significant histological inflammation in more than half of our patients with an endoscopic diagnosis of duodenitis and the presence of histological inflammation in a number of patients with normal-looking mucosa, led us to conclude that the endoscopic appearance alone is unreliable for its diagnosis. Similar conclusions have been reached for gastric mucosa [15]. Toukan et al [11] (in a study comprising 31 patients with endoscopic duodenitis and 32 controls) had results broadly similar to ours and suggested the conventionally used endoscopic features of duodenitis might be due to changes in mucosal vasculature rather than inflammatory states.

Our findings relating to the individual histological features of duodenitis are in line with others studies in which controls were included [7, 11]. In each of these areas apparent duodenal inflammation at endoscopy has shown increased polymorphonuclear infiltrate compared with normal looking mucosa, but the overlap with controls has been substantial. For mononuclear cells the difference has been less or absent. It is now well established that gastric metaplasia and villous atrophy are the result of

active duodenitis and therefore correlate well with the polymorphonuclear infiltrate [10, 17].

We are unaware of any previous studies of the histology of "duodenal erosions". They are generally regarded as a superficial break containing exudate in the mucosa. The latter results have a characteristic white appearance. It is therefore surprising that we were only able to confirm the mucosal break histologically in two of 40 patients. We have previously failed to find histological evidence for a break in mucosa in the majority of patients with gastric erosions [19]. There also was no histological suggestion that the lesions looking like erosions were lymphangiectatic. We cannot therefore confirm the generally held view regarding the nature of apparent duodenal erosions.

Unsurprisingly infection with *H pylori* was associated with histological inflammation. Other studies have found histological duodenitis often associated with *H pylori* (75-82%) [13, 14], although the ability for *H pylori* to cause inflammation may be strain specific [20]. Whilst histological inflammation was seen with NSAI ingestion, changes were not marked. NSAI ingestion along with *H pylori* infection is considered a risk for duodenal ulceration [21]. It was unexpected that significant inflammation was not seen in the group with *H pylori* positive and taking NSAID. Although others have suggested that NSAID intake may be protective against *H pylori* induced duodenitis [21].

In conclusion, histological duodenitis is a common finding at diagnostic endoscopy, characterised by inflammatory infiltrate, gastric metaplasia and villous atrophy. However, if a diagnosis is based solely on conventionally accepted endoscopic features it would be overdiagnosed. Terms such as duodenitis or duodenopathy [22] imply duodenal pathology is present. We therefore suggest the term duodenitis is reserved for histologically proven cases. Similarly the use of the term "erosions" would appear inappropriate in that we could rarely demonstrate evidence of a true break in the mucosa in this study.

Acknowledgments

The study was designed by SL & SW, recruitment was by SL, WS, AA, NP. Histology assessed by RW, AS & NR. Analysis and manuscript preparation by SL, SC, WS, AA & SW.

Conflicts on interest statement

None declared

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