

Gastric Mucosa In Nonulcer Dyspepsia: A Histopathological Study Of Nigerian Patients

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Abstract

Background/Objectives:

A large group of patients seen by gastroenterologists in clinical practice present with chronic or recurrent symptoms that continue to defy explanation, despite structural and biochemical studies. Nonulcer dyspepsia is one of such conditions and the Rome diagnostic criteria have simplified its definition by the use of symptom-based diagnosis. The objective of this study was to examine the pattern of gastric mucosal histopathological alterations in patients with nonulcer dyspepsia as defined by the Rome II criteria.

Methods:

Consecutive patients who had upper gastrointestinal endoscopy for typical dyspeptic symptoms during an eighteen month period in whom no endoscopic abnormality was found had gastric mucosal biopsies. The specimens were processed and examined histologically using the Sydney schema.

Results:

There were 152 patients with dyspepsia who had upper gastrointestinal endoscopy. Seventy five (49.3%) had no endoscopic abnormality in the upper gastrointestinal tract. Out of these, 53 patients (70.7%) had one or more indices of gastritis in varying grades of severity while the remaining 22(29.3%) had histologically normal gastric mucosa. Mucosal inflammation was more common in female patients than their male counterparts ($p=0.00497$).

Conclusion:

Nonulcer dyspepsia accounts for nearly half of cases of dyspepsia in Nigerian patients. A high degree of gastric mucosal inflammation is seen in these patients. There is need for controlled studies to determine the implication of this finding.

INTRODUCTION

Dyspepsia means a chronic or recurrent discomfort or pain centered in the upper abdomen, often related to meals (1). In nonulcer dyspepsia, the upper digestive tract produces symptoms such as pain or discomfort in the upper abdomen but tests fail to reveal an ulcer or any other organic cause. In the Western world, it accounts for about 60% of cases of dyspepsia (2,3,4,5). In developing countries such as Nigeria, nonulcer dyspepsia accounts for 30 – 40% of patients undergoing upper gastrointestinal endoscopy(6,7,8,9,10).

For many years it remained a diagnosis of exclusion after so many tests have been carried out. The year 1988 witnessed a paradigmatic shift from this approach to the use of symptom-based diagnosis (11) in what is today known as

Rome I. This was revised in 1992 to give the Rome II criteria (12) which gained currency and formed the basis of entry into numerous research studies on functional gut disorders. The Rome II criteria were further modified in the recently released Rome III document.

Following the discovery of *Helicobacter pylori* in 1983(13) and in an attempt to remove confusion in the diagnosis of various forms of gastritis the Sydney classification was introduced in 1990(14,15) and updated in Houston, Texas in 1994(16). The histological division of this classification utilizes graded variables. These include chronic inflammation, polymorphonuclear neutrophil activity, glandular atrophy, intestinal metaplasia and *Helicobacter pylori* density. Each of these variables is scored semi-

quantitatively on an ordinal scale ranging from 0 to 3 representing absent, mild, moderate and marked. Therefore a maximum of 15 can be scored for the 5 variables. Published studies on gastric mucosal changes in patients with nonulcer dyspepsia were carried out mainly on Caucasians^(17,18). Furthermore the Sydney system was not applied in the histological description of gastric mucosal changes in those studies. Grading of morphological variables and reproducibility make the Sydney system a very useful research tool. The aim of this study was to determine the pattern of gastric mucosal histopathological findings in Nigerian patients with nonulcer dyspepsia using the updated Sydney schema.

PATIENTS AND METHODS

This was a cross sectional study of consecutive patients with dyspeptic symptoms referred to the gastroenterology clinic of the University of Nigeria Teaching Hospital (UNTH), Enugu, Nigeria from December 2003 to June 2005. Detailed history was obtained from each patient and complete physical examination conducted with special emphasis on the gastrointestinal system.

INCLUSION CRITERIA

- The inclusion criteria conformed with the Rome II diagnostic criteria for functional gastrointestinal disorders (12).
- Persistent or recurrent pain or discomfort centered in the upper abdomen of at least 12 weeks (which need not be consecutive) in the preceding 12 months.
- Pain or discomfort not relieved by defecation or associated with onset of change in stool frequency or stool form.
- No evidence of organic disease from the history, physical examination or laboratory tests that is likely to explain the symptoms.
- No evidence of any mucosal lesion in the oesophagus, stomach or duodenum at upper gastrointestinal endoscopy.

EXCLUSION CRITERIA

- Patients whose symptoms were predominantly heart burn and/or regurgitation.
- Patients whose dyspepsia had been investigated

previously by radiology, endoscopy or other tests and specific diagnosis established.

- Patients who had used nonsteroidal anti-inflammatory drugs (NSAIDs) in the last 2 weeks prior to endoscopy.
- Attempt at *Helicobacter pylori* eradication or acid suppressive therapy in the last 2 weeks prior to endoscopy.
- Patients with symptoms suggestive of irritable bowel syndrome i.e., lower abdominal pain or altered bowel habit.

Upper gastrointestinal endoscopy was performed on each patient after over night fast for 12 hours. Systematic examination of the oesophagus, stomach, duodenal cap and 2nd portion of the duodenum was carried out using a forward viewing Fujinon gastroscope UGI – FP7 seven series. All the endoscopic examinations were performed by one endoscopist. Patients in whom no endoscopic lesion was found in the oesophagus, stomach, duodenal cap and 2nd portion of the duodenum were further evaluated by obtaining two gastric antral biopsy specimens and two specimens from the body of the stomach. The specimens were properly labeled, fixed in 10% buffered formalin, processed using paraffin embedding technique, sectioned at 4 micrometer perpendicular to the mucosal surface and stained with hematoxylin and eosin (H & E) as well as with Giemsa. The same pathologist examined all the materials. The histopathological parameters were graded using the Sydney system. Where there was a difference in grading between the antral specimen and that of the body of the stomach, the specimen with higher score was used.

RESULTS

One hundred and fifty two (152) patients had upper gastrointestinal endoscopy during the study period. Seventy five (75) of them had no endoscopic abnormality in the upper gastrointestinal tract (49.3%) and they actually constituted the study population. They consisted of 38 males (50.7%) and 37 females (49.3%). Their ages ranged between 14 years and 83 years (mean = 44.03 ± 14.96). The mean age of the male patients was 42.87±15.72 years while that of the female patients was 44.63±14.71 years. The difference between them was not statistically significant (p=0.609)

Histological examination of the biopsy specimens showed that 22 patients had normal mucosa (29.3%) and 53 had

abnormal mucosa (70.7%). The 22 patients who had normal gastric mucosa consisted of 14 males and 8 females, thus a greater proportion of male patients had normal gastric mucosa ($p=0.0129$). The 53 patients in whom varying degrees of mucosal abnormalities were found consisted of 24 males and 29 females indicating that mucosal abnormality was more common in the female patients and the difference was statistically significant ($p=0.00497$). Analysis of the graded morphological variables in the 53 patients with abnormal mucosa is shown in Table 1.

Figure 1

Table 1: Morphological Variables in Patients with Nonulcer Dyspepsia

| Variable | Grade | | | | Total |
|------------------------------------|----------|----------|--------------|------------|-----------|
| | 0 (None) | 1 (Mild) | 2 (Moderate) | 3 (Marked) | |
| Chronic inflammation | 25 | 22 | 24 | 4 | 50(66.7%) |
| Neutrophilic Activity | 48 | 9 | 12 | 6 | 27(36%) |
| Glandular Atrophy | 43 | 9 | 17 | 6 | 32(42.7%) |
| Intestinal Metaplasia | 69 | 6 | 2 | 5 | 6(8%) |
| <i>Helicobacter pylori</i> Density | 47 | 13 | 10 | 1 | 28(37.3%) |

Chronic inflammation (figure 1) was present in 50 patients (66.7%), neutrophilic activity in 27 patients (36%) and glandular atrophy (figure 2) in 32 patients (42.7%).

Figure 2

Figure 1: Antral biopsy showing moderate chronic inflammation and moderate glandular atrophy.

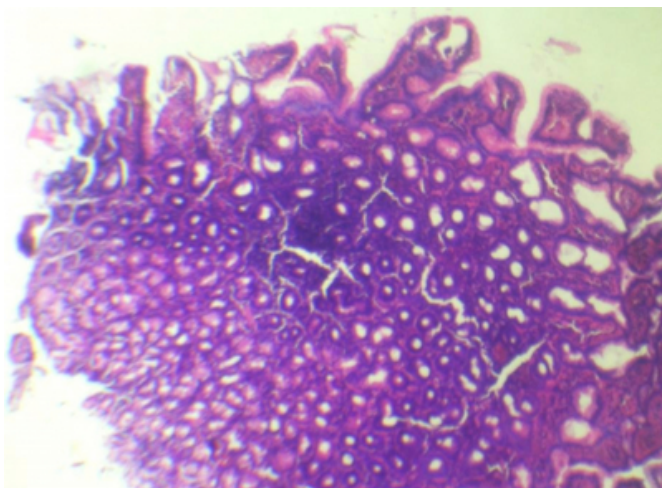
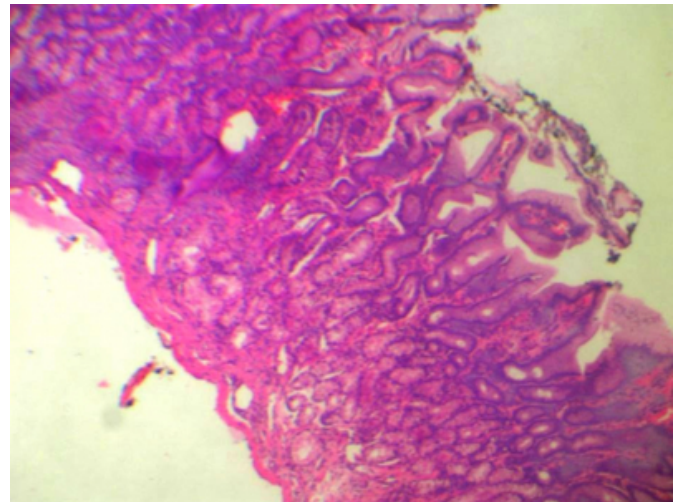


Figure 3

Figure 2: Antral biopsy showing moderate glandular atrophy only without chronic inflammation.



The mean ages of patients with glandular atrophy and those without this abnormality were 41.5 ± 15.65 years and 45.86 ± 14.77 years respectively. The difference was not statistically significant ($p=0.2216$). Intestinal metaplasia was present in 6 patients (8%) and *Helicobacter pylori* was detected in 28 patients (37.3%). The total score for all the patients is shown in table 2.

Figure 4

Table 2: Summary of Histological Findings in Patients With Nonulcer Dyspepsia (n= 75)

| Sydney Score | Number of Patients | Percentage |
|--------------|--------------------|------------|
| Zero | 22 | 29.0 |
| <5 | 26 | 34.7 |
| 5 – 10 | 25 | 33.3 |
| >10 | 2 | 2.7 |
| Total | 75 | 100 |

DISCUSSION

Dyspepsia is among the most common complaints evaluated by both the general practitioner and gastroenterologist. In North America about 60% of patients with dyspepsia have nonulcer dyspepsia (2,3,4,5). In this study nearly half of patients with dyspepsia (49.3%) who had upper gastrointestinal endoscopy had nonulcer dyspepsia, occurring equally in both sexes. This is different from what was observed in some studies carried out in the developed world in which female patients were more commonly affected (19,20).

Histological examination of the gastric mucosal biopsies of these patients showed a high degree of inflammation which occurred in 70.7% of them. It is interesting to note that the female patients with nonulcer dyspepsia showed a higher degree of gastric mucosal inflammation than their male counterparts ($p=0.00497$). The reason for this observation is not clear but one possible explanation is the fact that females tend to be immunologically stronger than males and therefore are able to mount inflammatory response to various infective and non infective agents that may come in contact with the gastric mucosa. Such infective agents include *Helicobacter pylori* which were detected in 37.3% of patients.

The implication of gastric mucosal inflammation in patients with nonulcer dyspepsia is also not clear because of lack of comparison with an appropriate control group made up of healthy subjects. Upper gastrointestinal endoscopy can hardly be justified ethically in normal individuals and consequently there is a general rarity of studies on gastric mucosa in healthy people. One study carried out on healthy volunteers made up of mainly hospital staff in Netherlands (21) showed that 64% had normal gastric mucosa. This contrasts sharply with the finding in this study in which only 29.3% of patients with nonulcer dyspepsia had normal mucosa. This calls for controlled studies in Nigerian patients who obviously live in an environment characterized by a high prevalence of *Helicobacter pylori* infection.

The role of *Helicobacter pylori* infection in the pathogenesis of nonulcer dyspepsia remains unresolved. Although some investigators have found a higher prevalence of *Helicobacter pylori* infection in patients with nonulcer dyspepsia, study results have not been consistent (22,23). The fact that dyspepsia occurs after intentional *Helicobacter pylori* infection supports involvement of this pathogen (24). However treatment results have been inconsistent and the role of *Helicobacter pylori* infection in nonulcer dyspepsia remains controversial (25,26). The role of gastric mucosal inflammation unrelated to *Helicobacter pylori* infection in nonulcer dyspepsia as demonstrated in this study also remains to be elucidated.

Chronic inflammation, evidenced by mononuclear cellular infiltrate in the lamina propria of gastric mucosa was present in 66.7% of our patients with nonulcer dyspepsia. This was the commonest morphological alteration and its prevalence was significantly higher than that of *Helicobacter pylori* infection (37.3%). One possible explanation is the fact that

there may be other causes of inflammation apart from *Helicobacter pylori*. It is also possible that patients who were *Helicobacter pylori* negative had ingested acid suppressant drug and/or antibiotics which are known to suppress the organism. It is a well known fact that chronic inflammatory cells are slow to disappear after eradication of *Helicobacter pylori* and may take a year or more to fall to normal levels (27,28,29). Virtually all the patients in this study had taken acid suppressant drug(s) before presentation. Although a wash off period of two weeks was applied as an inclusion criterion, this is probably inadequate, the standard being one month (30).

Neutrophilic activity was present in 36% of our patients with nonulcer dyspepsia. This contrasts with the observation by Atkins et al (31) that a normal endoscopy excludes active gastritis. When the Sydney system is used in the histological examination of the gastric mucosa of patients with endoscopically normal mucosa, significant neutrophilic activity may be seen as this study shows. This again underscores the age long lack of concordance between endoscopy and histology with regard to the diagnosis of gastritis (18, 21,31). The discordance becomes more apparent when the Sydney schema is applied.

Glandular atrophy was present in as many as 42.7%. Since this variable is known to be age dependent, a comparison was made between the mean age of patients with glandular atrophy and that of patients without atrophy and the difference was not statistically significant. This suggests that the atrophy may have arisen from a prolonged inflammatory process. The presence of intestinal metaplasia in 8% of the patients lends credence to this thinking. Extensive atrophy in the antral mucosa which may be associated with intestinal metaplasia carries an increased risk of gastric malignancy (32).

In conclusion, nonulcer dyspepsia is a very common problem encountered in gastroenterological practice in Nigeria, occurring in about half of patients with dyspepsia. Patients with this condition have a high degree of gastric mucosal inflammation. The clinical implication of these inflammatory changes needs to be defined in controlled studies.

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