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Additional Endoscopic Corpus Biopsy May Increase Accuracy of Helicobacter Pylori Detection

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Abstract:

Background: *This study was designed to determine if it is important to add corpus biopsies to the routine antral ones for identification of H. pylori, especially in case of gastric atrophy and/or intestinalmetaplasia.*

Methods: *This is a prospective multicenter study including three hundred and twenty eight patients with gastritis from June 2014 through Dec.2015. Endoscopic mucosal biopsies from the gastric antrum and corpus were submitted to histological examination according to updated Sydney system for detection of H.pylori*.

Results: *In the study period, a total 328 consecutive patients underwent upper gastrointestinal endoscopy for different reasons. The mean age of the patients was 39±12 years; 183 (55.7%) were women. H pylori was found positive in 193 (58.8%) of the patients. Combined antral and corpus biopsies increased the result by 20.8% compared to antral biopsies alone and 4.5% compared to corpus biopsies alone. 20.8% of patients infected with H pylori would have been misdiagnosed if testing was based onantrum alone and not combined with corpus. Atrophy and intestinal metaplasia were found in 101(30.8%) and 17(5.2%) of our patients, respectively. Atrophic gastritis was significantly more often in the antrum than the corpus (29.2 VS 11.9%, respectively, p< 0.05). Patients with only positive corpus biopsies showed more incidences of both atrophy and intestinal metaplasia. Detection rates of H pylori decreased as more as atrophy increased regardless of biopsy site.*

Conclusion: *This study clarified that additional gastric corpus biopsy to the antral one increases the sensitivity to detect H pylori infection especially if associated with gastric atrophy*.

Keywords: *Gastric atrophy, Sydneysystem, H pylori and Gastritis*

1. INTRODUCTION

Helicobacter pylori (H. pylori) affect nearly half of the population among the world. It is one of the most frequent and persistent bacterial infections worldwide (1). It is responsible for many of the upper gastrointestinal tract diseases; chronic gastritis, gastrointestinal ulcers, mucosa associated lymphoid tissue lymphoma (MALT) and gastric cancer as well (*2*). Thus it has been known as "definitive biological carcinogen" by WHO in 1994 (*3*).

It is already documented that H pylori plays an important role in the promotion of atrophic gastritis. Severe degree of H pylori associated atrophic gastritis is suggested to be an important risk factor in development of gastric carcinoma. Therefore, it is presumed that eradication of H pylori from the stomach is linked to decrease the incidence of gastric cancer development (*4).*

There are various diagnostic tools to detect H pylori whether invasive (rapid urease test, histology or culture) or non invasive (urea breath test, serology or stool antigen)(5,6). Histological examination despite is invasive, is considered one of the most important diagnostic tests for H pylori infection because it also provides critical information related to the mucosa and presence of associated pathology (7,8).

H pylori can be seen in hematoxylin and eosin (H&E) stain as gram negative spiral bacteria with sensitivity and specificity as 69-93% and 87-90%, respectively (9). Accuracy can be increased up to 90-100% by using special stains such as modified Giemsa stain, Warthin-Starry silver stain, Genta stain and immune histochemicalstain(10).

H&E stain evaluate the degree of inflammation, atrophy and/or intestinal metaplasia (IM). It can also identify the H pylori in a high magnification field; however, it becomes difficult to see the H pylori when a low density of the organism and atrophic mucosal change are combined. As Giemsa stain is easy to use, inexpensive, and provides good results; it is the slandered method in many laboratories for H pylori detection(11).

Also, Uemura et al. reported that eradication of H.pylori decreases the incidence of recurrent gastric cancer in patients underwent endoscopic mucosal resection for early cancer stomach (12). It is widely recommended by many authors that eradication of H.pylori is mandatory in case of atrophic gastritis since the atrophy may reverse after successful eradication therapy(13,14). But, it's difficult and challenging the detection of H.pylori in case of atrophic gastritis (15). This study was designed to determine if it is important to add corpus biopsies to the routine antral ones for identification of H. pylori, especially in case of gastric atrophy and/or intestinal metaplasia

2. METHODS

2.1. Patients

Three hundred and twenty eight patientsof uninvestigated dyspepsia, whounderwent upper endoscopywere enrolled,(Mansura university hospital - Egypt,Benha University hospital – Egypt, HaferElbatin Central Hospital, KSA) from 2014 through 2015.Patients who received antibiotic or proton pump inhibitor treatment one month beforehand were excluded. All procedures in the study were performed in accordance with the institutional research board (IRB) committee in our institute.

2.2. Study Protocol

All patients underwent upper gastrointestinal endoscopy and two standard gastric biopsies were taken from both antrum (2-3 cm from the pylorus both lesser and greater curvature) and corpus (8-10 cm from the cardia both lesser and greater curvature) for the histological examination (16).

2.3. Histological Examination

Endoscopic biopsies were processed as formalin fixed paraffin embedded tissues, cut into 3-µmthick sections, and then stained with H&E and modified Giemsa stain. These were scored semi-quantatively according to the updated Sydney classification (Fig 1) (16). The following features were evaluated on each slide, inflammatory activity, glandular atrophy and intestinal metaplasia. According to these histological criteria, there were four grades of atrophy; 0, none; 1, mild; 2, moderate and 3, severe.

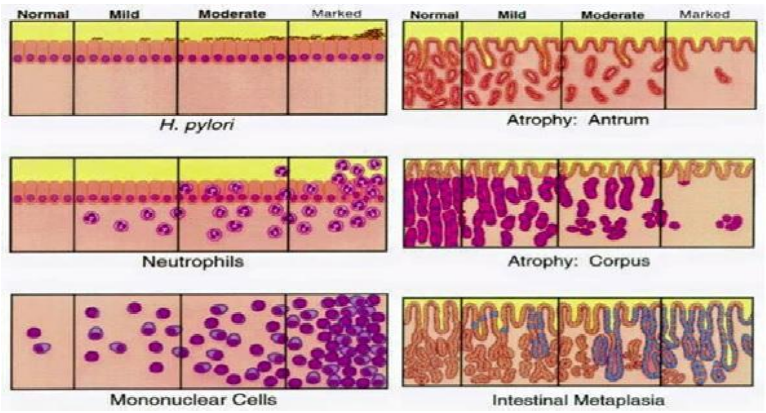

Fig1. *Sydney Classification for Gastric Biopsy (16)*

Presence of polymorphonuclear cell (PNC) infiltration in the specimen refers to activity of the H pylori infection. It is scored based on the density of inflammatory cells in both lamina propria and glandular epithelium (Fig 2). When gastric mucosa is replaced by intestinal epithelium (with goblet cells), it is diagnosed as gastric intestinal metaplasia that is also graded as showed above in Sydney system (Fig 3). Lymphocytes and plasma cell infiltration indicate chronic inflammation associated with H pylori infection (Fig 4). Glandular atrophy is defined as loss of gastric glands that fail to regenerate; the stromal space they previously occupied within the lamina propria is replaced by fibroblasts and extracellular matrix (Fig 5).

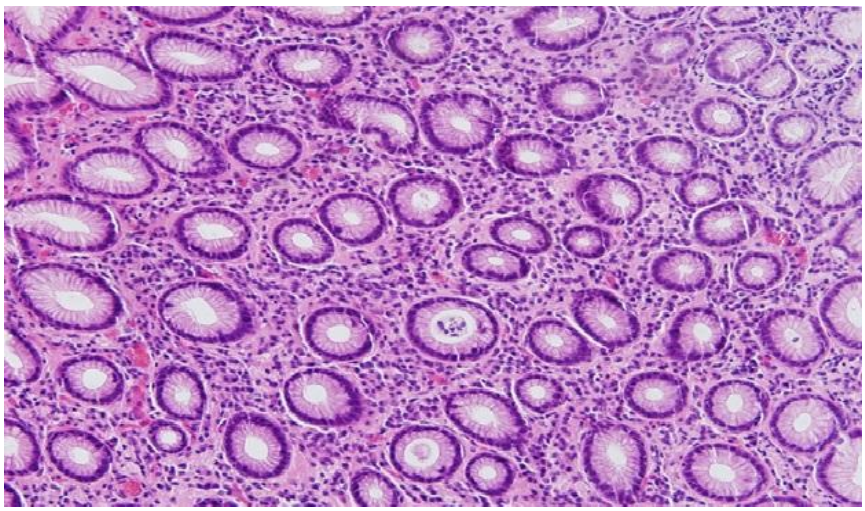

Fig2. *Antrum Biopsy Showed Moderate Activity (H&E X200)*

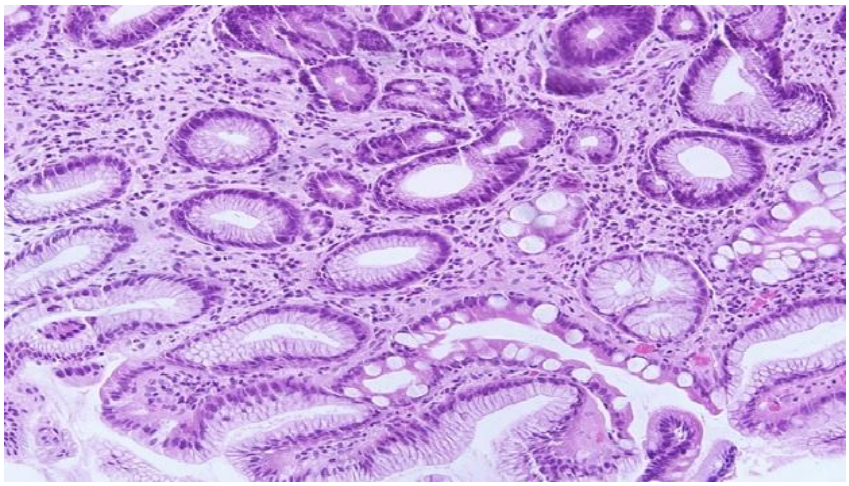

Fig3. *Gastric Biopsy Showed Intestinal Metaplasia (H&E X200)*

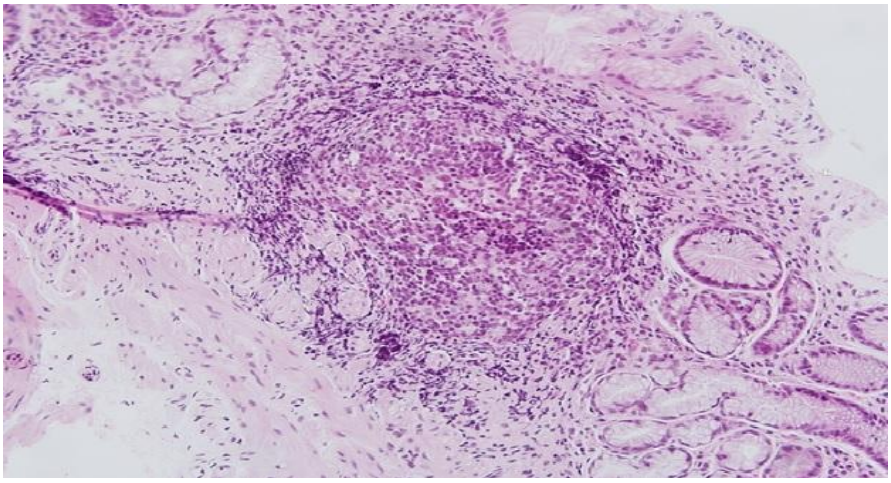

Fig4. *Gastric Biopsy Showed Severe Mononuclear Inflammation with Lymphocytes Follicle Formation (H&E X200)*

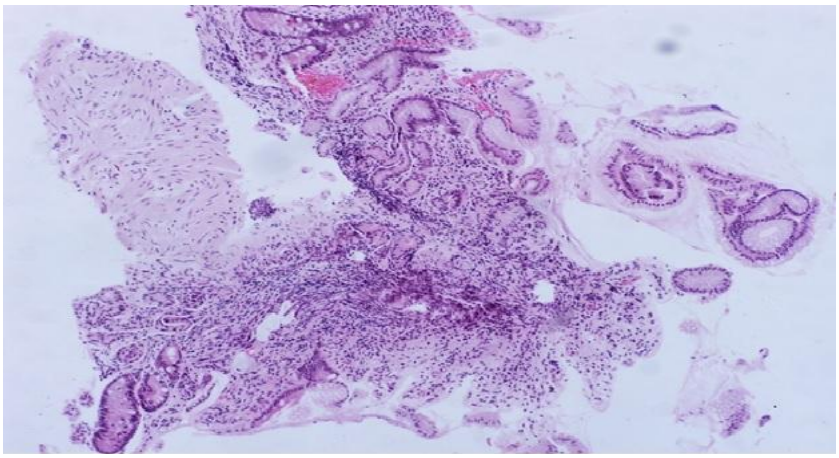

Fig5. *Gastric Biopsy Showed Marked Gastric Atrophy (H&E X100)*

2.4. Interpretation of Results

Criteria for positivity and negativity of H pylori were set:Patients were defined positive for H pylori if either one or both was positive with Giemsa stained slides. Patients were considered negative if all specimens were negative. The histological evidence of atrophy was identified when the gastric glands were found decreased in amount and/or widely separated(*17).*

2.5. Statistics

All data were collected prospectively in an excel file for statistic purposes. We used a student t-test to compare continuous or non parametric variables. While, categorical or parametric variables were compared using Chi-square test. P value less than 0.05 was considered statistically significant. We used the SPSS version 11.5 for statistical analysis (SPSS version 11.5) for windows; SPSS Inc, Chicago, IL, USA).

3. RESULTS

Figure 6 shows the study flow chart for the whole study population. A total of 328 consecutive patients underwent an upper endoscopy procedure during the study period. The mean age of our patients was 39±12 years; 145(44.3%) were men. Upper gastrointestinal endoscopy was indicated for functional dyspepsia in 113(34.5%), epigastric pain in 118(35.9%) or heart burn in 97(29.6%) patients. Endoscopic diagnosis was peptic ulcer disease in 52 (15.9%), gastritis or duodenitis in 173(52.7%), or reflux esophagitis in 103(31.4%) patients. None of our patients were diagnosed with gastric carcinoma. Regardless of the biopsy site, a total of 656 biopsy specimens were received for histological evaluation (Table 1).

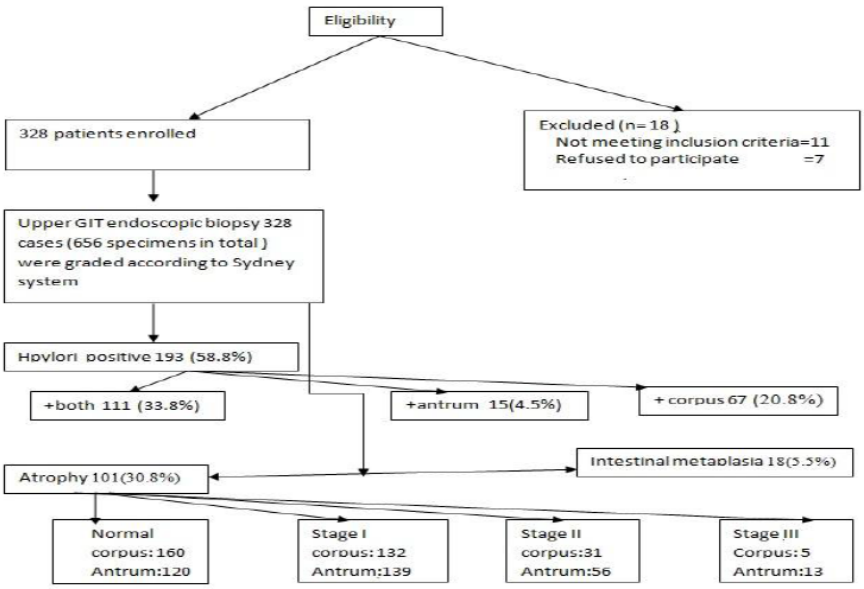

Fig6.*The patients' flowchart*

Table1. *Histology Outcomes by Patients' Characteristics*

Variables	N=328	Both+ve	both -ve	C+veonly	A+veonly
Gender					
-Male	215	63%	58%	62%	47%
-Female	113	37%	42%	38%	53%
Age in years	31±9	32±8	27±6	33±7	34±9.5
Endoscopic diagnosis					
-Peptic ulcer	87	33%	24%	26%	29%
-Gastritis/duodenitis	101	27%	29%	22%	16%
-GERD	63	29%	18%	31%	24%
-Normal	11%	13%	21%	31%	31%
Microscopic findings					
-Atrophy	101(30.8%)	43(38.7%)	19(14%)	2(13%)	37 (**55%**)
Corpus and antrum	34	19	-	-	13
Antrum only	62	24	15	-	23
Corpus only	5	-	4	-	1
-Intestinal metaplasia	18(5.5%)	6(5.4%)	5(3.7%)	-	7(**10%**)
Corpus and antrum	3	-	1	-	2
Antrum only	11	5	4	-	2
Corpus only	4	1	-		3

+ve;positive, -ve; negative, A; antrum, C; corpus

H pylori was found positive in 193 (58.8%) of the patients, (Fig 7). In 111 (33.8%) patients, both antral and corpus biopsies were identified positive for H pylori. Combined antral and corpus biopsies increased the result by 20.8% compared to antral biopsies alone and 4.5% compared to corpus biopsies alone. In all patients with positive H pylori, antral biopsies alone were positive in 15 out of 193 (7.7%) patients compared to corpus biopsies which were positive in 67 out of 193 (34.7%).

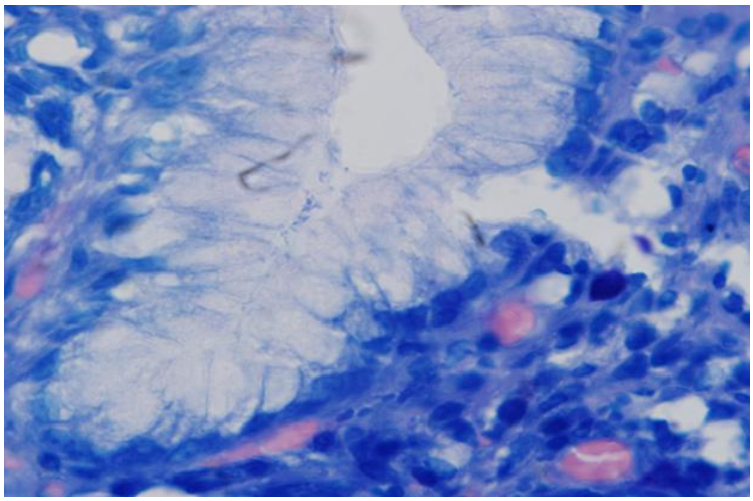

Fig7. *Gastric Biopsy Showed H Pylori Bacterai With in Lumen of Glands (Giemsa Stain With Oil)*

In endoscopic diagnosis, atrophy was found in 101(30.8%) of our patients. Atrophic gastritis was significantly more often in the antrum than the corpus (29.2 vs. 11.9%, respectively, $p< 0.05$). Intestinal metaplasia was identified in 17(5.2%) of the patients and antrum was more often than the corpus (4 vs 2% of all patients, respectively). Patients with only positive corpus biopsies showed more incidences of both atrophy and intestinal metaplasia compared with the other possible outcomes, 55 vs. 24.5% for atrophy and 10 vs. 4.6% for metaplasia.(Table 1,2)

Table2. *Histopathological Classification of Submitted Biopsies According to Sydney System*

Sites –based biopsy	Score / Variables	Activity	Mononuclear inflammation	Metaplasia	Atrophy
	Normal(0)	128	17o	321	289
	Mild (1)	104	74	7	31

Corpus	Moderate (2)	64	54	0	7
	Severe (3)	32	30	0	1
Total		**328**	**328**	**328**	**328**
Antrum	Normal(0)	150	182	315	232
	Mild (1)	86	84	7	69
	Moderate (2)	66	44	6	27
	Severe (3)	26	38	0	5
Total		**328**	**328**	**328**	**328**

In biopsies with atrophic gastritis, detection of H. pylori in the antrum specimens was inversely correlated with the degree of atrophy. The H pylori positivity in antrum biopsies decreased from 40% within score (0-1) to 18.5% within score (2-3) compared to corpus biopsies (54.6 to 37.5%, respectively). Positivity of H pylori was found significantly more often in the corpus biopsies than in the antrum regardless the degree of atrophy or metaplasia. (Table 3)

Table3. *The Sensitivity of Biopsy-Based Test (Histology Giemsa Stain) According to Grade of Mucosal Atrophy*

Positive H pylori				
	Total	0-1 atrophy	2-3 atrophy	
Antrum Corpus	126(38.5%) 178(54%) **P<0.05**	121/301 (40%) 175/320(54.6%) **P<0.05**	5/27(18.5%) 3/8 (37.5%) **P<0.05**	**p<0.05** p<0.05
Atrophy -Antral biopsies -Corpus biopsies -Combined	 126/193(**65%**) 178/193(**92.2%**) 193/193(**100%**) **P<0.05**	 121/193(**62.6%**) 175/193(**90.6%**) 189/193(**97.9%**) **P<0.05**	 5/193(2.6%) 3/193(1.5%) 4/193(2%)	

Our results showed that, regardless the gastric biopsy location, as the degree of atrophy increased the prevalence of H pylori infection decreased. Sensitivity of corpus biopsies alone to diagnose H pylori was found significantly higher than the antrum biopsies alonewithin the same Sydney's score of atrophy (sensitivity of antrum biopsies alone, 65% compared to 92.5% in corpus alone or 100% if combination of both). Prevalence rate of H pylori infection between normal and mild atrophy and moderate or severe atrophy were also evaluated. (Table 3)

4. DISCUSSION

In the clinical setting, it is desirable to find a rapid and cost-effective method for detection of H pylori. There are many methods for detection of H pylori infection (*18).* Endoscopic mucosal biopsy and histopathology are considered a valuable diagnostic tool for H pylori detection. As well as, it provides a proper evaluation of gastric mucosal changes that have been attributed to chronic H pylori infection i.e. glandular atrophy and/or intestinal metaplasia. It is still widely used as a main diagnostic method in suspicious patients with upper gastrointestinal symptoms or in highly prevalent areas (*7).*We reported in our study that193 (58.8%) have been detected to have H pylori. 111(38.8%) patients, both antral and corpus biopsies were identified positive for H pylori. 30.8% of our patients had atrophy in the antrum and/ or corpus or both. Intestinal metaplasia was identified in17 (5.2%) patients

There is always a debate about the best location of gastric mucosal biopsy that can yield more sensitive detection of H pylori especially in presence of atrophic gastritis (18).In our work; we found that the frequency of H pylori detection in case of gastritis without atrophy or metaplasia was higher with additional corpus biopsy compared with only antrum-based biopsy.

According toZhang et al (3), and Arimendi-Marillo et al (19), H pylori detection rates were significantly varying depending on the site of the gastric biopsy taken, ranging from 30 % at the antrum lesser curvature to 100% at the corpus greater curvature. Their results were almost comparable to ours in showing that the sensitivity of *H. pylori* detection was 92.2% at corpus while it was 65% at antrum, suggesting that corpus biopsy should be evaluated to detect *H. pylori* infection. Hazell *et al* (20) also found that it is necessary to evaluate combined biopsies from antrum and corpus. However, other authors reported that antrum biopsy is sufficient to diagnose H pylori gastritis without and morphological changes (21,22)

Our results showed that, regardless the gastric biopsy location, as the degree of atrophy increased the prevalence of H pylori infection decreased. Sensitivity of corpus biopsies alone to diagnose H pylori was found significantly higher than the antrum biopsies alone within the same Sydney's score of atrophy (sensitivity of antrum biopsies alone, 65% compared to 92.5% in corpus alone or 100% if combination of both). Prevalence rate of H pylori infection between normal and mild atrophy and moderate or severe atrophy were also evaluated.

In this study, we found up to 20% of patients with H pylori would be misdiagnosed if H pylori status was based on only antral biopsies. We noticed in our study that patients with only positive corpus biopsies showed more incidences of atrophy and intestinal metaplasia compared with the other possible outcomes. This is explained by the fact that detection of H pylri inversely correlate with the presence of atrophy and as shown from our results that the antrum was the predominant site for atrophy. Therefore, antrum based biopsy only in case of atrophic gastritis yields to more false negative results(*23).*This finding was in concordance with others (15,24-27).This study clarified that the sensitivity of H pylori detection is decreased in cases of antral atrophic gastritis more than corpus one in the same time as inversely correlated with degree of atrophy.

Our study is not without limitations, the overall number of patients enrolled in the study is not that large number. We did not use urease CLO testor culture test to confirm the diagnosis because these tests are not available in our institutions where the histological examination for H pylori is the routine. Our study was not designed to study the incidence of H pylori infection; it was merely designed to determine the benefit of testing H pylori from two separate gastric sites. So we recommend for another future study to recruit more number of patients. We are currently working on those patients with atrophy and / or intestinal metaplasia to find if their atrophy is reversible after giving the eradication therapy.

5. CONCLUSION

H pylori associated atrophic gastritis decreases sensitivity of detection rates of H pylori. Atrophic changes are predominantly affect antrum first. Adding corpus biopsy to the routine antrum biopsy during endoscopy is recommended for proper evaluation of H pylori infection case of gastric atrophy and to avoid false negative diagnosis.

AUTHOR'S CONTRIBUTION: Mohamed AbdEllatif, Ahmed Mohamed Husien, Ahmed Shawqy, Ahmed AbdelghafarSaleh, Hosam El-Ghadban, Ashraf Abbas, Mohamed Abdel Aziz Amerand Rania Shahin contribute equally in this study.

DISCLOSURE: Drs Mohamed AbdEllatif, Ahmed Mohamed Husien, Ahmed Shawqy, Ahmed AbdelghafarSaleh, Hosam El-Ghadban, Ashraf Abbas, Mohamed Abdel Aziz Amer and Rania Shahin have no conflicts of interest or financial ties to disclose.

ETHICAL STATEMENT: All patients included in this study gave informed written consent after a full explanation of the procedure. All procedures in the study were performed in accordance with the institutional research board (IRB) committee in our institute.

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