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Original Article

Helicobacter pylori, intestinal metaplasia, and the accuracy of biopsies in metaplastic gastric mucosa

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Abstract: The identification and eradication of Helicobacter Pylori (HP) is vital to prevent gastric cancer. After the detection of the HP colonization, accompanying histopathological findings belonging the gastric carcinogenesis should also be considered. According to the widely accepted proofs, although the presence of HP colonization initiates the sequential changes of carcinogenesis, the success rate of the histopathologic diagnosis of HP colonization in the mucosal areas with intestinal metaplasia is controversial. In this study we try to find out the incidence of HP colonization, the relation between HP colonization and gastric intestinal metaplasia (IM) and to describe mucosal pathologic changes. This prospective study was performed between August 2014 and September 2015 in endoscopy unit of Istanbul Traning and Research Hospital after obtaining ethical approve. In total, 201 Turkish patients were included into study. Demography, body mass index, endoscopic findings were enrolled. Fourquadrant biopsy was taken from each patient, including at least 3 pieces from each area. A total of 2412 biopsy material were investigated. All parameters were compared for each grouping method seperatly. No person has completely normal mucosal findings.Prevalence of HP colonization and IM were 82% and 31%. The rate of HP colonization was not significantly different in the areas with or without IM (P = 0.823). IM was detected in at least one biopsy area in 63 (31%) patients, and more common in older patients (P = 0.006). The rate of HP colonization and IM in cardia without simultaneous presence in the other sides of stomach were 3.5% and 2.5%, respectively. Routine biopsy from the cardia may not be required. HP colonization rate was not different between the areas with and without IM. Endoscopic biopsy is still the gold standard for diagnosis of HP colonization, even if IM exists.

Keywords: Gastric cancer, endoscopic biopsy, helicobacter pylori, intestinal metaplasia, dysplasia

Introduction

Helicobacter pylori (HP) is a microorganism living in human stomach for thousands of years [1]. Nowadays, it is well known that, HP initiates and promotes the sequential changes of the gastric mucosa from non-atrophic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, to carcinoma [2, 3]. As a result, it has been classified as a class I carcinogen by World Health Organization [4]. Although conflicted results have been reported in previous studies, HP eradication is the best approach to prevent HP induced gastric carcinogenesis especially in the early stage [5]. Of course, HP colonization should firstly be diagnosed before the eradication of it. Different diagnostic tests including endoscopic biopsy, confocal laser endomicroscopy, rapid urease test, breath urea test, stool antigen test, antibody detection in serum, and molecular methods have been proposed to detect the colonization or recurrance of HP [6, 7]. Histopathological diagonosis is the gold standart for correct diagnosis of HP colonization [7, 8]. After the detection of the HP colonization, accompanying histopathological findings belonging the gastric carcinogenesis should also be considered. Although the presence of HP colonization initiates the sequential changes of carcinogenesis, the success rate of the histopathologic diagnosis of HP colonization in the mucosal areas with intestinal metaplasia is controversial [9]. In this study, we aimed to define the gastric mucosal findings, to revealed common sides for HP colonization of adult Turkish population, to put forth the clinical features of patients with gastric intestinal metaplasia and the diagnostic accuracy of endoscopic biopsies for HP colonization in these patients.

Matreials and methods

The approval for this prospective study was taken from the Ethical Committee of Istanbul Training and Research Hospital (Date: 08/11/2013, Number: 368). Informed written consent was taken from each patient before the inclusion.

The patients admitted to the outpatient clinics between August 2014 and September 2015 with the compliants of epigastric and/or retrosternal burning, postprandial belching and/or bloating, and other dispeptic signs were undergone to upper gastrointestinal endoscopy. The patients were included to the study process consecutively. Exclusion criteria were as follows: Patients under the age of 18 years; patients with known hepatopancreticobiliary disease; history of upper gastrointestinal or hepatopancreaticobiliary surgery (including cholecystectomy); history of HP eradication treatment; use of a proton pump inhibitor or any other medication for gastritis or peptic ulcer in last three months; antibiotic use in last two weeks; detection of apparent ulcer, polyp, mass, or findings of bleeding.

Demography, body mass index, gross endoscopic findings were also enrolled. Four quadrant biopsy, including prepyloric antrum, incisura angularis, greater curvature of corpus, and kardia, was performed with cold endoscopic forceps in all patients. Three spicemen at least were taken in each area. All spicemens were fixed in formalin immediately, then underwent histopathological examination. Standart Hematoxylin & Eosin and Giemsa staining were used in histopathologicl examination. Explored histopathological findings in each area included the colonization of HP, presence of inflammatory findings including neutrophil activation, nonatrophic gastritis, intestinal metaplasia, dysplasia, and intramucosal carcinoma, and graded according to the modified Sydney classification [10]. Grade 3 intestinal metaplasia was accepted as low grade dysplasia.

The clinical features of the presence of intestinal metaplasia and the relation between HP colonization and intestinal metaplasia were evaluated seperately. To put forth the clinical features, the patients were divided into the IM+ (intestinal metaplasia present) and IM- (intestinal metaplasia absent) according to the presence of intestinal metaplasia at least in one biopsy area. To evaluate the relation between HP colonization and intestinal metaplasia, each biopsy area considered seperately. Hence, "201 patients x 4 qaudrant biopsy = 804 spicemen area" were divided into two groups according to presence of intestinal metaplasia in each spicemen area, bIM+ (biopsy area intestinal metaplasia present) and bIM- (biopsy area intestinal metaplasia absent). Then, all parameters were compared for each grouping method seperately.

The SPSS 20.0 (SPSS Inc, IBM Corporation, Armonk, NY, USA) software was used for statistical analysis. Normally distrubuted continuous variables were expressed as mean (SD) and compared by using a t-test. Nominal data were expressed as case numbers and percentages, and were compared using Fisher's exact test. All tests were two-sided. A value of $P<0.05$ was accepted as statistically significant.

Results

In total, 201 patients were included into the study, 89 males and 112 females. Mean age was 46.8±14.7 years, mean body mass index was 25.1±5.2 kg/m^2. Overall prevalence of HP colonization and intestinal metaplasia were 82% and 31%, respectively. When we considered each biopsy area seperately, there was completely normal mucosal findings in only 18 areas (2.2%). No person has completely normal mucosal findings.

In gross endoscopic evaluation, normal gastric mucosa was reported in 32 cases (16%). Of them, HP colonization was seen in 27 patients (84%), intestinal metaplasia in at least one biopsy area was demonstrated in 6 patients (25%), but, there were inflammatory findings (gastritis) in all of these patients in at least one biopsy area. In 63 patients (31%) intestinal metaplasia was detected in at least one biopsy area. Dysplasia was seen in only 4 patients (2%) (2 in kardia, 2 in incisura angularis).

The rate of HP colonization to cardia was 56%. However, isolated colonization to cardia was diagnosed in only 7 patients (3.5%), in one of which intestinal metaplasia was accompanying to the HP colonization. Likewise, the rate of intestinal metaplasia in cardia was 9%, but it

Table 1. The relation between HP colonization and histopathological findings

Cardia			Histopathological Findings				
	HP Colonization	(n, %)	Normaln (n, %)	Non-atrophic Gastritis (n, %)	Atrophic Gastritis (n, %)	Intestinal Metaplasia (n, %)	Dysplasia (n, %)
	Yes	112 (56)	0	99 (88)	2 (2)	10 (9)	1 (1)
	HP+	*48 (24)*	0	42 (88)	1 (2)	5 (10)	1 (1)
	HP++	*55 (27)*	0	48 (87)	0	0	0
	HP+++	*9 (5)*	0	9 (100)	0	0	0
	No	89 (44)	8 (9)	70 (79)	3 (3)	8 (8)	1 (1)
Overall			8 (4)	169 (85)	5 (2)	18 (9)	2 (1)
Korpus-Incisura Angularis			Histopathological Findings				
	HP Colonization	(n, %)	Normal (n, %)	Non-atrophic Gastritis (n, %)	Atrophic Gastritis (n, %)	Intestinal Metaplasia (n, %)	Dysplasia (n, %)
	Yes	121 (60)	2 (2)	94 (78)	5 (4)	13 (11)	1(1)
	HP+	*41 (20)*	2 (5)	33(27)	0	6 (5)	0
	HP++	*72 (36)*	0	61 (50)	5 (4)	5 (4)	1 (1)
	HP+++	*8 (4)*	0	6 (5)	0	2 (2)	0
	No	80 (40)	2 (3)	62 (51)	1 (1)	14 (18)	1 (1)
Overall			4 (2)	156 (78)	6 (3)	27 (13)	2 (1)

Table 2. Comparison of the patients with and without intestinal metaplasia*

	Intestinal Metaplasia or Dysplasia		
	IM+	IM-	*p* value
Number of cases (n)	63 (31%)	138 (69%)	
Gender (Male/Female)	28/35	61/77	1.000
Age (years)	51±13	45±15	*0.006*
BMI (kg/m^2)	26.6±2.6	25.6±4.3	0.157
Endoscopists' diagnosis**			
Normal	10 (16%)	24 (18%)	0.850
Antral Gastritis	18 (29%)	36 (26%)	0.733
Pangastritis	31 (49%)	71 (52%)	0.879
Atrophic Gastritis	4 (6%)	5 (4%)	0.456
HP Colonization	53 (84%)	111 (80%)	0.695

*In terms of number of patient with intestinal metaplasia or dysplasia in at least one sample. **The dignosis reported by the endoscopist according to the visual features of the gastric mucosa. HP: Helicobacter pylori, IM: intestinal metaplasia.

was 2.5% (5 cases), when the multiple localizations were excluded. The detailed analysis is shown in **Table 1**.

The unique significant difference was obtained in the age, that the patients with intestinal metaplasia was seen in older patients (P = 0.006). The details are shown in **Table 2**.

The rate of HP colonization was not significantly different in the areas with or without intestinal metaplasia (P = 0.823). The relation between intestinal metaplasia and HP colonization is summarized in **Table 3**. The colonization of HP in metaplastic mucosa seen in **Figure 1**.

Discussion

HP is a gram-negative proteobacterium with the shape like helical-rod with flagellea [11]. Although it has been found in every population worldwide, the incidence varies with living environment, occupation, and geographic region. The recently reported prevalence in North Europe and North America was less than 40%, while it was over 70% in East Asia, Africa, and Middle East region with some exception like Indonesia and Saudi Arabia with approximately 25% of prevalence [2, 12-14]. The reported prevalence of HP has been much more for Turkey in previous studies. For instance, in a very large population based study performed among adults by screening with ^{13}C-Urea breath test, the reported prevalence of HP was 82%. [15]. HP colonization rate in gastric mucosa increases with age. According to the results of two recent studies from Turkey, it was 45% for pre-school and school aged children [16], while it was 75% between the ages of 13 and 18 [17]. In the current study, the prevelance of HP colo-

Table 3. Relation between intestinal metaplasia and HP colonization*

	Intestinal Metaplasia or Dysplasia		
	bIM+	bIM-	*p* value
Kardia	19 (9%)	182 (91%)	1.000
HP Colonization	11 (58%)	101 (55%)	
Corpus-Incisura Angularis	29 (14%)	172 (86%)	0.219
HP Colonization	14 (48%)	107 (62%)	
Corpus-Greater Curvature	13 (6%)	188 (94%)	0.251
HP Colonization	5 (38%)	107 (57%)	
Antrum	33 (16%)	168 (84%)	0.312
HP Colonization	25 (75%)	110 (65%)	
Overall	94 (12%)	710 (88%)	0.823
HP Colonization	55 (59%)	425 (60%)	

*Each biopsy region were considered seperately. HP: Helicobacter pylori. bIM+: biopsy area with intestinal metaplasia, bIM-: biopsy area without intestinal metaplasia.

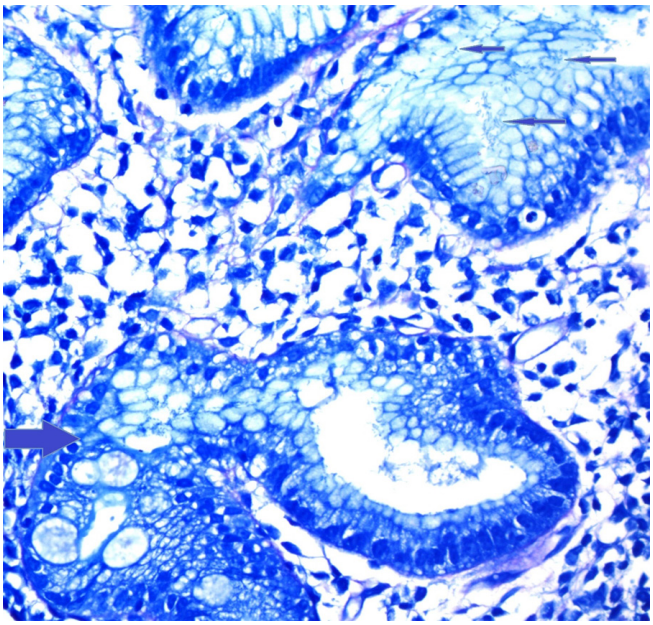

Figure 1. Histopathological view of gastric mucosa. Small arrows indicate colonizations of Helicobacter Pylori. Big arrow indicates area of intestinal metaplasia. Giemsa ×40.

nization was 81.5% that was very compatible with previous result, despite the difference in screening method. It is another remarkable point that, participants in the present study were composed of patients admitted to outpatient clinic with some compliants.

The clinical importance of HP colonization is, as widely known, the relation with gastric carcinogenesis [2, 18, 19]. The side and number of the biopsies were in close relation with the diagnostic success [7, 20]. To decrease the false negative results in HP diagnosis, 3- or 5-sided biopsies were recommended by the guideline for endoscopic mucosal sampling American Society for Gastrointestinal Endoscopy (ASGE) [20]. However, two-side biopsy including at least two specimen from antrum and corpus have also been recently recommended with a considerable success rate [8, 21]. Routine biopsy from cardia is controversial. According to the results of presented study, HP was more commonly colonized to the distal gastric mucosa. Although HP colonization to the cardia was seen in 56% of our cases, the rate of only cardia colonization was 3.5%. In addition, the rate of intestinal metaplasia in the mucosa of cardia was 2.5%, when the multiple localizations were excluded. As a result, we believe that routine biopsy from cardia during upper gastrointestinal endoscopy may not be required for the diagnosis of HP or intestinal metaplasia, despite the recommendation of ASGE [20].

In the present study, the prevelance of intestinal metaplasia was 31%. This result is a little bit more than the result of the worldwide population which is approximately 25% [5]. When it was compared, the prevelance of HP colonization was not different between the patients with and without intestinal metaplasia. In addition, body mass index and the diagnosis of endoscopist according to the external view of gastric mucosa were also not different between these patients. However, the presence of intestinal metaplasia was in significant relation with increasing age. Likewise, in a population based study from Oregon-USA, a strong age-associated increase in the prevalence of intestinal metaplasia was reported in 2013 [22]. In another study with very large case number from China, the results were similar [23]. However, in contrast to our results, this disorder was more common in men according to the same studies and the others [22-24].

An interesting point in this issue is impaired HP colonization in the area of intestinal metaplasia

[9]. As clearly known, HP selectively lives in gastric mucosa [2]. Hence, the impairment of HP colonizaiton in the areas with intestinal metaplasia is predictable. Based on this hypothesis, Galiatsatos et al. [9] queried the efficacy of histopathological examination for the diagnosis of HP colonization in patients with known intestinal metaplasia. The results of the current study revealed that the rate of HP colonization was not differs whether intestinal metaplasia was present or not. Based on the histological findings, although the gastric mucosa with intestinal metaplasia looks like the intestinal mucosa, it would still have the features of gastric mucosa according to the grade of metaplasia. Therefore, HP colonization can be diagnosed with the similar success rate by histologic examination, even if intestinal metaplasia exists.

According to our opinion, the major limitation of this study is the relatively less number of cases, despite the prospective nature of the study. However, we believe that the reported results are in success to answer the targeted questions.

In conclusion, the rate of HP colonization and intestinal metaplasia in cardia without simultaneous presence in the other sides of stomach were 3.5% and 2.5%, respectively. Therefore, routine biopsy from the cardia may not be required, despite the recommendation of ASGE [20]. HP colonization rate was not different between the areas with and without intestinal metaplasia. Endoscopic biopsy is still the gold standard for diagnosis of HP colonization, even if intestinal metaplasi exists.

Disclosure of conflict of interest

None.

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