

# Association Between Gastric Lymphoid Follicles (Precursor Of MALT Lymphomas) And *H. pylori* Infection At A Referral Hospital In Iran

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Homayoon Bashiri<sup>1,2</sup>  
Abbas Esmailzadeh<sup>3</sup>  
Hassan Vossoughinia<sup>3</sup>  
Kamran Ghaffarzadegan<sup>4</sup>  
Hamid Reza Raziei<sup>5</sup>  
Arezoo Bozorgomid<sup>1</sup>

<sup>1</sup>Infectious Diseases Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran; <sup>2</sup>Department of Internal Medicine, Faculty of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran; <sup>3</sup>Gastroenterology and Hematology Department, Faculty of Medicine, Ghaem Hospital, Mashhad, Iran; <sup>4</sup>Pathology Department, Education and Research Department, Razavi Hospital, Mashhad, Iran; <sup>5</sup>Department of Oncology and Radiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

**Purpose:** Mucosa-associated lymphoid tissue (MALT) is the most common endoscopic finding in *Helicobacter pylori* positive patients that can progress to MALT lymphoma after a prolonged antigenic contact. This study was aimed to evaluate the prevalence of lymphoid follicles and aggregates (precursors of MALT lymphomas) in gastric mucosal biopsies and their correlation with *H. pylori* infection.

**Patients and methods:** In this study, 100 patients who had undergone an upper gastrointestinal endoscopy were enrolled. Five biopsy specimens were taken each patient through screening endoscopy and histopathological changes were evaluated and graded using the Wotherspoon System. The clinical background and *H. pylori* infection status were also investigated.

**Results:** Among the 100 cases in our series, 79 patients (79%) showed evidence of MALT in at least one biopsy specimen taken from the stomach and 21 cases (21%) had no evidence of MALT. *H. pylori* infection was detected in 74 (74%) patients. Lymphoid follicles were detected more frequently in *H. pylori*-positive patients (59%) compared to *H. pylori*-negative cases (3%) ( $P < 0.001$ ).

**Conclusion:** The frequency of lymphoid follicles and aggregates in gastric mucosal is associated with *H. pylori* infection. Further community-based studies in larger sample sizes using a combination of microscopic methods and PCR assay are required for effective monitoring of *H. pylori* infection.

**Keywords:** gastritis, *Helicobacter pylori*, lymphoid aggregate, lymphoid follicle

## Introduction

*Helicobacter pylori* (*H. pylori*) is a spiral, gram-negative bacterium that causes chronic gastritis, peptic ulcer disease and is associated with the development of gastric cancer.<sup>1</sup> Its prevalence is about 4.4 billion individuals in worldwide, affecting more than half of the world's population.<sup>2</sup> Chronic infection of the stomach by *H. pylori* is being increasingly recognized as a precursor of mucosa-associated lymphoid tissue (MALT) lymphoma.<sup>3</sup> Gastric cancer is the fifth most common cancer. It is that estimated about one million new cases and 783,000 related deaths occur every year.<sup>4</sup> Gastric MALT lymphoma accounts for only 1-6% of all gastric malignancies and about 50% of primary gastric lymphomas.<sup>5</sup>

*H. pylori* infection serves as an antigenic driver that can activate innate immune system. As a result of this phenomenon, the immune and gastric epithelial cells respond by the secretion antimicrobial peptides and cytokines (pro- and anti-inflammatory).<sup>6</sup> Immune response accelerates the formation of lymphoid follicles in the gastric

Correspondence: Arezoo Bozorgomid  
Infectious Diseases Research Center,  
Kermanshah University of Medical  
Sciences, Kermanshah, Iran  
Tel +98 918 872 8269  
Email arezooboorgomid@yahoo.com

mucosa.<sup>6</sup> This statement is supported by the fact that about 75% of low-grade gastric MALT lymphoma can be improved by eradication of *H. pylori* infection with antibiotic therapy.<sup>7</sup>

Mucosa-associated lymphoid tissue (MALT) lymphoma is defined as an extranodal low-grade marginal zone B cell lymphomas.<sup>8</sup> Although the stomach is the most common site of MALT lymphomas, it in healthy individuals does not have organized or diffuses lymphoid tissue.<sup>9</sup> Symptoms associated with gastric MALT lymphoma are generally non-specific and signs including dyspepsia, vague epigastric pain, bloating and heartburn; anemia, melena as well as hematemesis are common in this disease.<sup>10</sup> The clinical diagnosis of gastric MALT lymphoma depends largely on clinical symptoms, endoscopic examination and histopathologic finding of gastric biopsy tissue.<sup>10</sup>

Studies have shown that the incidence of gastric cancer in Iran, unlike developed countries, has increased over the past 30 years.<sup>11,12</sup> This study was designed to determine the prevalence of gastric lymphoid follicles and aggregates (precursors of MALT lymphomas) in gastric mucosal biopsies and evaluate its correlation with *H. pylori* infection.

## Materials And Methods

This cross-sectional study was conducted in 100 consecutive patients admitted to Imam Reza Hospital (a referral center affiliated with Kermanshah University of Medical Sciences) Kermanshah, Iran for endoscopic screening. Five biopsy specimens were taken from each patient through endoscopy (1 from incisura angularis, 2 from antrum, lesser and greater curvature and 2 from cardia, lesser and greater curvature). Biopsy specimens were fixed in 10% formalin and embedded in paraffin. Then, 4- $\mu$ m paraffin sections were stained with hematoxylin and eosin and Giemsa. All the available slides were evaluated for the presence of lymphoid aggregates, lymphoid follicles and other pathological changes in gastric mucosa by two pathologists, independently. The Wotherspoon scoring system was used for scoring gastric lymphoid infiltrates. Based on the histological scoring system of the Wotherspoon, a score of 2 or less is categorized as benign gastritis and a score of 3 or 4 represents suspicious MALT lymphoma cases.<sup>13</sup>

To detect the presence of *H. pylori*, all biopsy specimens were evaluated by rapid urease test and Gram staining. Patients were considered positive for *H. pylori* if it was detected on histological and/or bacteriological examination. Exclusion criteria were a history of *H. pylori* eradication, a history of consumption of proton pump

inhibitors (PPIs), H2-receptor blockers or antibiotics within 2 weeks prior to endoscopy and a history of gastric surgery or gastric neoplasms.

Associations between categorical variables were evaluated with Chi-squared test and Fisher's exact test. The  $P < 0.05$  was considered as statistically significant.

## Results

This study was conducted in 40 men and 60 women aged 22–62 years old (median: 49 years). The distribution of biopsy specimens according to the histological score in each gastric region is summarized in Table 1. Seventy-nine patients (79%) showed evidence the presence of MALT in at least one biopsy specimen taken from the stomach and 21 cases (21%) had no evidence of MALT.

Overall, *H. pylori* was detected in 74 (74%) patients. The relationship between mucosa-associated lymphoid tissue and *H. pylori* infection is shown in Table 2, indicating that 71% of the patients with mucosa-associated lymphoid tissue had *H. pylori* infection as opposed to 8% of them who did not ( $P < 0.001$ ). Additionally, lymphoid follicles were detected more frequently in *H. pylori*-positive patients (59%) compared to *H. pylori*-negative cases (3%) (Table 3).

## Discussion

This study evaluated the prevalence of lymphoid follicles and aggregates (precursors of MALT lymphomas) in gastric mucosal biopsies and correlates them with *H. pylori* infection at a referral hospital in the western part of Iran.

**Table 1** Frequency Of Graded Histological Variables In Patients Admitted To Imam Reza Hospital, Kermanshah, Iran

Localization	Grade		
	0 (Normal)	I (Chronic Active Gastritis)	2 (Chronic Active Gastritis With Florid Lymphoid Follicles Formation)
Antrum			
Lesser curvature	33	40	27
Greater curvature	31	41	28
Angulus	34	32	34
Cardia			
Lesser curvature	39	38	23
Greater curvature	33	40	27

**Table 2** The Distribution Of *Helicobacter pylori* According To Presence Lymphoid Follicles And Lymphoid Aggregate

	Lymphoid Follicles And Lymphoid Aggregate, n (%)		P-value
	Positive	Negative	
<i>H. pylori</i> (+)	71 (71)	3 (3)	0.0001*
<i>H. pylori</i> (-)	8 (8)	18 (18)	
Total	79 (79)	21 (21)	

Note: \*P < 0.01 is statistically significant.

**Table 3** Histological Grading Of All Biopsies In Relation To The Presence Of *Helicobacter pylori*

	Grade, n (%)			P-value
	0	1	2	
<i>H. pylori</i> (+)	3 (3)	12 (12)	59 (59)	0.0001*
<i>H. pylori</i> (-)	18 (18)	5 (5)	3 (3)	
Total	21 (21)	17 (17)	62 (62)	

Note: \*P < 0.01 is statistically significant.

MALT lymphomas are non-Hodgkins B-cell neoplasms derived from lymphoid aggregates in the lamina propria.<sup>8</sup> According to previous reports, lymphoid follicles and aggregates in the gastric mucosa are a specific the immune response to *H. pylori*.<sup>14</sup> This organism serves as an antigenic driver that can activate the immune system and accelerate lymphoid follicles proliferation in the gastric mucosa.<sup>6</sup>

In the present study, the prevalence of *H. pylori* infection was 74%. The prevalence of *H. pylori* ranges from 15.1% to 87.7% in previous publications depending on the socioeconomic status, hygiene and sanitary conditions.<sup>15</sup> Improvements in these factors lead to a decrease in the prevalence of *H. pylori* and consequently in the peptic ulcer disease. The host immune response, especially the functionality of cytotoxic T-cells (killer T-cells), plays a key role in the outcome of *H. pylori* infection.<sup>14</sup> Although half of the world's population is infected with this bacterium, only about 3% of all *H. pylori* infected subjects present with gastric adenocarcinoma.<sup>16</sup> Some reports have described that *H. pylori* cagA-positive strains have enhanced pathogenicity by stimulating cell transformation.<sup>17</sup>

Iran is one of the largest developing countries in the Middle East with highly diverse dietary factors, lifestyle preferences, socioeconomic and hygiene conditions. According to the 2012 Census results, Iran has a population of 80.28 million and about one-third of the population lives

below the national poverty line.<sup>18</sup> In a study conducted by Solimany et al, findings indicated a growing rate of gastric malignancy incidence in Kermanshah Province, where we carried out this study.<sup>19</sup> The clinical diagnosis of gastric MALT lymphoma depends largely on clinical symptoms, endoscopic examination and histopathologic finding of gastric biopsy tissue.<sup>10</sup> Countries with high incidence of gastric cancer, such as Japan and South Korea, have implemented gastric cancer screening programs using endoscopy for several decades.<sup>20,21</sup> During the last years, endoscopy has been widely used as a part of health screening. However, few studies have reported some side effects for endoscopic screening, such as infections, false-positive results, and overdiagnosis.<sup>22</sup> Although upper gastrointestinal endoscopy is an invasive procedure, further evaluation of the impact of endoscopic screening is needed regarding the balance of cost and mortality reduction.

Fakhro et al found that the prevalence of lymphoid follicles and aggregates was 31.4% and 24.5% in gastric biopsy specimens in patients with dyspepsia, respectively.<sup>23</sup> Also, authors reported that the odds ratio of developing lymphoid follicles in *H. pylori*-positive patients compared to *H. pylori*-negative cases was 11:1. Kalebi et al found that the prevalence of lymphoid follicles was 11% among adult patients seen at a referral hospital in Kenya and all these patients had *H. pylori* infection.<sup>24</sup> Garg et al also reported that there are lymphoid aggregates and lymphoid follicles in 25% and 19% of subjects, respectively.<sup>25</sup> In our study, prevalence of lymphoid follicles and aggregates in gastric mucosa in patients with *H. pylori* infection was 62% and 38%, respectively and lymphoid follicles were detected more frequently in *H. pylori*-positive patients (59%) compared to *H. pylori*-negative cases (3%) (P<0.001). The differences in prevalence can be explained by differences in the number and site of biopsy specimens, methods of *H. pylori* detection, and study populations. Furthermore, the bacterial load in biopsy specimens is generally low and irregular.<sup>26</sup> It appears that prevalence of lymphoid follicles and aggregates in oxyntic mucosa (14.8–44.0%) is lower than antral mucosa.<sup>27</sup>

Previous studies showed that *H. pylori* is associated with an increased risk of gastric adenocarcinomas.<sup>28,29</sup> Persistent inflammation of the stomach by *H. pylori* leads to the transition from normal mucosa to chronic superficial gastritis which may then progress to atrophic gastritis and intestinal metaplasia, and eventually to dysplasia and adenocarcinoma.<sup>28,29</sup> There is no evidence to support the association between atrophic gastritis and gastric lymphoma.<sup>30</sup> Although both gastric adenocarcinomas and MALT lymphomas occur as a

consequence of chronic gastric inflammation, differentiating them from each other is important because the prognosis and treatment options differ.

## Conclusion

Our findings showed that the formation of gastric lymphoid follicles and aggregates significantly correlated with *H. pylori* infection. Early diagnosis and eradication of *H. pylori* infection in suspicious MALT lymphomas detected via histopathological evaluation will improve the patient's quality of life and possibly prevent gastric cancer. Further community-based studies in larger sample sizes using a combination of microscopic methods and PCR assay are required for effective monitoring of *H. pylori* infection.

## Ethics Approval And Consent To Participate

All the participants provided written informed consent prior to the study and this study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Mashhad University of Medical Sciences Ethics Committee (8103907).

## Data Sharing Statement

The data sets used and/or analyzed during this study are available from the corresponding author on reasonable request and were received permission for use by the Mashhad University of Medical Sciences Ethics Committee.

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## Disclosure

The authors report no conflicts of interest in this work.

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