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# Heterotopic Gastric Mucosa in the Proximal Esophagus (Inlet Patch): Endoscopic Prevalence, Clinico-pathological Characteristics and Its Association with *Helicobacter pylori*

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## Abstract

**Objective** To determine the prevalence of the inlet patch (IP), its clinico-pathological features, and its association with *Helicobacter pylori*.

**Materials and Methods** A prospective observational study was performed on 1,889 patients referred for esophagogastroduodenoscopy for various reasons, primarily for the evaluation of dyspepsia. All patients were enquired about the presence of symptoms and carefully examined for the presence of IP during upper gastrointestinal (GI) endoscopy. Biopsies were taken from the patients who had IP.

**Statistical Analysis** All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 13.0 software for Windows XP. Categorical variables were compared using the chi-squared test or Fisher's exact test and continuous variables were compared using Student's *t*-test and univariate analysis. A *P*-value of less than 0.05 was considered to be statistically significant.

**Results** Inlet patches were found in 34 of 1,889 patients (1.8%). *H. pylori* was identified in 23.52% of patients (8/34) with IP. Gastric *H. pylori* infection was positive in all (08/08) patients who had IP. Colonization of *H. pylori* was more common in antral type mucosa (6/8). *H. pylori* positivity in the IP correlated with globus sensation symptom in our study, 87.5% of patients with IP and *H. pylori* positive had globus sensation.

**Conclusion** The prevalence of IP seems to be underestimated. *H. pylori* colonization of the IP is common and it positively correlates with globus sensation and is closely related to the *H. pylori* density in the stomach. Though preneoplasia within IP is rare, which does not support the recommendation to regularly obtain biopsies for histopathology, it might be beneficial in a subset of patients with persistent globus sensation.

**Keywords**

- cervical heterotopic gastric mucosa
- globus sensation
- *Helicobacter pylori*
- inlet patch

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## Introduction

Islands of heterotopic gastric mucosa are found throughout the gastrointestinal tract, the most common site being the cervical esophagus. IP is not always an acquired condition; several studies suggest an embryologic origin. During normal embryonic development, the squamous cell epithelium of the esophagus is replaced by columnar epithelium starting from the mid esophagus to the cervical esophagus. However, persistent columnar-lined areas that result from incomplete squamous epithelialization can further differentiate into an inlet patch (IP).[1]

Patients with cervical heterotopic gastric mucosa (CHGM) have various laryngeal and oropharyngeal symptoms, ranging from asymptomatic to protracted symptoms such as globus sensation and chronic cough due to acid secretion from the IP.[2–5] The usual complaint in patients with globus sensation or globus pharyngeus is the sensation of a ball or lump in the throat, generally not accompanied by dysphagia. Globus sensation is felt medially deep in the throat during dry swallowing (empty swallow), and almost never while drinking or eating. It is not painful, and there is no obstruction of food.[3,4] *Helicobacter pylori* (*H. pylori*) produces chronic inflammation in the CHGM (as in non-ulcer dyspepsia). *H. pylori* infection plays a role in altered gastric perception in non-ulcer dyspepsia. *H. pylori* in CHGM may cause altered cervical perception such as globus sensation.

In this prospective study, we aimed to determine the association between *H. pylori* and globus sensation in patients with CHGM. Some experts recommend taking biopsies from IP to detect neoplastic or preneoplastic alterations[6–8] or advise follow-up examinations.[8,9] Before such recommendations can be generalized, more data on the prevalence of preneoplastic alterations in IP are needed.

## Materials and Methods

**Subjects:** A prospective observational study was performed on 1,889 patients referred for esophagogastroduodenoscopy for various reasons, primarily for the evaluation of dyspepsia between October 2019 and February 2021 at our hospitals (Kilpauk Medical college; Government Peripheral Hospital, Anna Nagar; Royapettah Government Hospital).

All patients were enquired about the presence of symptoms of globus sensation (lump in the throat), hoarseness, sore throat, frequent clearing of the throat, cough, dysphagia were questioned prior to endoscopy.

Informed consent was obtained from all subjects and the study was approved by the ethical review committee of Kilpauk Medical College.

### Esophagogastroduodenoscopy

After an overnight fast, a routine esophagogastroduodenoscopy was performed using a standard white light endoscope. During the procedure when slowly withdrawing the scope, the esophagus was carefully examined for the presence of the IP. Inlet patch was defined as the presence of salmon-red mucosa with well-defined margins within the surrounding grayish pearl-colored esophageal mucosa within the first 3 cm from the UES. As per the literature, IPs are generally found between the first 3 cm and the upper esophageal sphincter, on the lateral or posterior wall and sometimes encroaching on the upper sphincter.[10]

Biopsies were taken from the patients who had IPs. A minimum of two biopsies were obtained from the IP and antral gastric mucosa. Histological slides were stained with hematoxylin–eosin and a modified Giemsa stain (2%) to detect *H. pylori*. In cases with doubtful *H. pylori* status, Warthin–Starry stain was used in addition. Detection of goblet cells led to the diagnosis of intestinal metaplasia.

### Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 13.0 software for Windows XP. Categorical variables were compared using the chi-squared test or Fisher's exact test, and continuous variables were compared using Student's *t*-test and univariate analysis. A *p*-value of less than 0.05 was considered to be statistically significant.

## Results

### Prevalence, Demographic Characteristics

Inlet patches were found in 34 of 1,889 patients. The endoscopic prevalence of IP was determined to be 1.8%. The female/male ratio was 1.25 in 34 patients with patches and 0.75 in those without. There was no significant difference between the mean age of the patients with CHGM with and without *H. pylori* ($p > 0.05$). Female patients with IPs had higher colonization of *H. pylori* than male patients ($p < 0.05$). Demographic characteristics of the patients with and without patches are shown in ►**Table 1**.

### Histological Characteristics

In the IP, fundic type mucosa was the most common histologic type (22/34), followed by antral type of mucosa (10/34). Two specimens of the inlet patch contained only foveolar epithelium. Intestinal metaplasia was found in three patients

**Table 1** Demographic characteristics of the patients with and without inlet patch

| | With IP | Without IP | Level of statistical significance |
|---|---|---|---|
| Number | 34 | 1855 | |
| Gender | | | |
| Female | 18 (52.9%) | 766 (40.55%) | $p = 0.09$ |
| Male | 16 (47.1%) | 1,089 (59.44%) | |
| Age | | | |
| Age range (y) | 17–62 | 18–80 | $p = 0.44$ |
| Mean age (±SE) | 37.29 ± 1.85 | 47.9 ± 0.3 | |

Abbreviation: IP, inlet patch.

 

**Table 2** Histological characteristics of patients with inlet patch

| Histological characteristics | Number | Percentage |
|---|---|---|
| Type of mucosal pattern | | |
| Fundic type mucosa | 22/34 | 64.75 |
| Antral type mucosa | 10/34 | 29.41 |
| Foveolar epithelium | 02/34 | 5.88 |
| Intestinal metaplasia | 03 (2 fundic type, 1 antral type) | |
| Dysplasia | 00 | |

**Table 3** Comparison of the H.pylori (+ve) and H.pylori (−ve) patients with inlet patch

| | HP + (8/34) | HP − (26/34) | *p*-Value |
|---|---|---|---|
| Age (y) | 35.6 ± 2.3 | 37.3 ± 3.2 | 0.09 |
| Female *n* (%) | 5 (62.5%)* | 12 (46.1%) | < 0.05 |
| Male *n* (%) | 3 (37.5%) | 14 (53.8%) | 0.10 |
| Fundic type | 02 (25%) | 7 (26.9%) | 0.08 |
| Antral type | 06 (75%)* | 11 (42.3%) | < 0.05 |
| Intestinal metaplasia | – | | |
| Foveolar epithelium | – | | |

Abbreviation: HP, *Helicobacter pylori*.
*$p < 0.05$.

**Table 4** Comparison of symptoms between patients with and without inlet patch and H.pylori co-infection

| | IP + (34) | IP – (1855) | HP + (8/34) | HP – (26/34) |
|---|---|---|---|---|
| Globus sensation | 18 (52.9%) * | 75 (4.04%) | 7 (87.5%) * | 11 (38.4%) |
| | * $p < 0.05$ | | * $p < 0.05$ | |

Abbreviations: HP, *Helicobacter pylori*; IP, inlet patch.

with IP(two in fundic type and one in antral type). None of the patient with IP had dysplasia. Histological characteristics of patients with IPs are shown in ►**Table 2**.

### Association of IP with *H. pylori*

*H. pylori* was identified in 23.52% of patients (8/34) with IP. Gastric *H. pylori* infection was positive in all (08/08) of these patients. Colonization of *H. pylori* was more common in antral type mucosa (6/8). Female patients with IP had higher colonization of *H. pylori* than male patients ($p < 0.05$). Comparison of the *H. pylori* (+ ve) and *H. pylori* (−ve) patients with IP are shown in ►**Table 3**.

### Symptomatic Characteristics

In our study, globus sensation was present in 18/34 patients with IP and 75/1,855 patients without IP ($p < 0.05$). Globus sensation symptom was significantly associated with *H. pylori* infection ($p < 0.05$). Among patients with IP and *H. pylori* infection, 87.5% of patients had globus sensation (7/8), compared with only 38.4% of patients with IP and without *H. pylori* infection. Comparison of symptoms between patients with and without IP and *H. pylori* infection co-infection are shown in ►**Table 4**.

### Clinico-pathologic Classification

Clinico-pathologic classification was performed according to the classification reported by von Rahden et al[2] in patients with CHGM (►**Table 5**). Asymptomatic carriers of esophageal CHGM were classified as CHGM I. Also, 7/34 patients were classified with CHGM I in our study. Symptomatic individuals with esophageal CHGM complaining of globus sensation, cough, hoarseness or "extra esophageal manifestations" were classified as CHGM II without morphologic changes. Next, 27/34 patients were classified with CHGM II. Patients with additional morphologic changes (IP complications) were classified as CHGM III. If dysplasia was present, this was classified as CHGM IV. If the diagnosis was invasive cancer and originated within the IP, this was classified as CHGM V. None of the patients belonged to CHGM category 3, category 4, or category 5.

## Discussion

The usual endoscopic appearance of CHGM is a salmon rose-colored mucosal patch with a sharp border or edge in the upper esophagus. The patches vary in diameter from 1 to 20 mm or more. Inlet patches are recognized endoscopically as one or two patches mostly in the lateral walls between the level of the cartilage and the fifth tracheal ring and are seen as sharply demarcated, salmon rose-colored oval or round patches.

The prevalence of CHGM varied between 0.29% and 2.27% in one prospective study.[7] Akbayir et al[6] reported a prevalence of 1.67% and Tang et al[11] reported a prevalence of 1.1%. In our

**Table 5** Clinico-pathologic classification according to the classification reported by von Rahden et al

| | Number (%) | Symptoms/findings |
|---|---|---|
| CHGM 1 | 7/34 (20.58) | Asymptomatic |
| CHGM 2 | 27/34 (79.41) | Globus sensation, cough, hoarseness |
| CHGM 3 | 0 | |
| CHGM 4 | 0 | |
| CHGM 5 | 0 | |

Abbreviation: CHGM, cervical heterotopic gastric mucosa.

 

prospective study, over a period of 17 months, 34 cases (1.8%) of CHGM were documented and confirmed by histology.

Microscopically, gastric mucosa containing either cardiac, antral, or potentially acid-secreting fundic mucosa can be found. In general, CHGM is uniform of the fundic type, containing both parietal and chief cells. Less frequently, histopathologic examination of CHGM shows an "antral pattern," defined by the absence of chief cells and only a few parietal cells.[2,11,12] In our series, fundic type mucosa was found in 22 of 34 (64.75%) patients examined histologically. There are controversial reports regarding the type of mucosa reported in IP.

The oxyntic mucosa cell type is most commonly reported[11] but cardiac, antral, and mixed types (both oxyntic and antral) have also been detected.[13]

*H. pylori* is a well-known pathogenic microorganism responsible for chronic inflammation. Ectopic gastric mucosa of the IP is an ideal location for *H. pylori* colonization.[13] Borhan–Manesh et al[14] found *H. pylori* in the IP in 35% of patients in a subset with gastric *H. pylori*. Among our 34 patients with inflamed IPs, 8 were positive for *H. pylori* (23.52%), and all these 8 patients also had *H. pylori* in the antrum. Co-infection with *H. pylori* in the IP and gastric antrum has also been reported by others.[13] *H. pylori* colonization of heterotopic gastric mucosa in the upper esophagus is common and is closely related to the *H. pylori* density in the stomach. The fact that *H. pylori* was not found in all cases suggests that another event such as reflux may be required for *H. pylori* to colonize heterotopic mucosa[13]. Because the infection by *H. pylori* is through the oral route, IP may be an important site of *H. pylori* infection in the upper gastrointestinal tract because of its more proximal location. The IP may function as reservoirs for *H. pylori*. Inlet patch colonization by *H. pylori* can occur during the ingestion of food, and the presence of gastric *H. pylori* may play a role in the development of IPs. We believe that the elimination of *H. pylori* in both the IP and antrum is very important in the treatment of patients with coinfection.

In this study, the female/male ratio in the *H. pylori* (+ve) CHGM group was higher than that in the *H. pylori* (−ve) CHGM group. Females had higher IP colonization with *H. pylori* than males ($p < 0.05$). Epidemiological studies on the general population show a male preponderance in the infection rate by *H. pylori*[15]; Although there are controversial reports representing comparable rates. In our study, we found that female patients with IPs had higher colonization of *H. pylori* than male patients. Similar results were seen in a study done by Alagozlu et al.[16] The mechanism of *H. pylori* colonization in female IP is unclear.

A clinicopathological classification of CHGM as proposed by von Rahden et al[2] was performed on all 34 patients, 7 patients were classified as CHGM 1 and 27 patients were classified as CHGM 2. Theoretically, laryngeal and oropharyngeal symptoms should be common due to acid secretion from the IP. Several studies have reported cases of esophageal IP presenting with various laryngeal and oropharyngeal symptoms, ranging from asymptomatic to protracted symptoms such as chronic cough and globus sensation.[5,17–19] In addition, CHGM can cause stricture, ulcer, perforation, web or polyp in the esophagus because of the its capability to secrete acid.[20,21] None of our patients with IPs had any local complications.

The usual complaint in GS is that of a ball or lump in the throat generally not accompanied by dysphagia. This sensation is often more pronounced when taking an "empty swallow." In our study, seven of eight patients with *H. pylori* in cervical IPs had globus sensation. A study[16] done by Hakan et al showed similar results.

*H. pylori* infection plays a role in causing symptoms in patients fulfilling the criteria for non-ulcer dyspepsia. There is an agreement that *H. pylori* infection causes changes in gastric physiology. In addition, *H. pylori* infection plays a role in altered gastric perception in non-ulcer dyspepsia. We speculate that the disturbances in globus sensation are like non-ulcer dyspepsia. *H. pylori* produces chronic inflammation in the CHGM (as in non-ulcer dyspepsia). It could be speculated that globus sensation is non-ulcer dyspepsia of CHGM. *H. pylori* is a potential cause of GS in patients with CHGM.

One case report, in particular, found that *H. pylori* eradication was able to ameliorate the extragastric symptoms associated with CHGM and resulted in beneficial histopathological changes.[22] However, this report was limited by the fact that the patient had both gastric and esophageal IP *H. pylori* colonization. Thus, it is impossible to determine if the improvement in globus sensation and heartburn are due exclusively to the eradication of *H. pylori* or to the proton pump inhibitor (PPI) that is commonly included in the treatment as well.

However, there was no significant difference in the improvement in globus symptoms in patients who received only PPI treatment.[23] Additional studies are needed to understand the fundamental mechanisms leading to globus sensation in CHGM. These patients might benefit from *H. pylori* eradication therapy to alleviate this potentially aggravating factor. Based on these important findings, we expect to see more studies on IP in the near future.

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Conflict of Interest
None declared.

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