Histological Characteristics Associated with Intestinal Metaplasia of Stomach in Symptomatic Patients Undergoing Upper GI Endoscopy

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Abstract

Objectives: This study was done to determine the histological characteristics associated with intestinal metaplasia in epithelial gastric biopsy specimens of symptomatic patients undergoing upper GI endoscopy at a tertiary care setup in Pakistan. Materials and methods: A total of 87 endoscopic biopsies were studied prospectively taken from patients presenting with dyspepsia. Descriptive statistics and chi-square test were used for data analysis. Results: Intestinal metaplasia was found in 27.5% (24) specimens. H. pylori active gastritis was found in 79.3% (69) specimens. Among specimens with gastritis, mild, moderate and severe gastritis were present in 59.7% (43), 23.6% (17) and 16.6% (12) biopsies respectively. Metaplasia was invariably associated with H. pylori active gastritis (100%; p<0.05). Chances of having metaplasia significantly increased with moderate to severe gastritis as compared to mild gastritis (p<0.05). Depth of epithelial infiltration and germinal centre formation were not associated with metaplasia (p>0.05). Conclusions: Intestinal metaplasia was found in 27% of biopsy specimens in patients with dyspepsia which is quite high (more than 1/4th). Higher grade of gastritis was associated with higher chances of developing intestinal metaplasia in stomach. It was invariably associated with H. pylori. We suggest that pathologists should categorically look for focuses of intestinal metaplasia in biopsy specimens with moderate to severe gastritis and H. pylori irrespective of the depth of epithelial infiltration or germinal centre formation as it is a precursor for future risk of developing gastric carcinoma.

Keywords: Intestinal metaplasia, Gastritis, Endoscopy, Histopathology, H.pylori, Gastric carcinoma.

Introduction

Endoscopy is considered the gold standard in the work-up of a number of diseases of the GI (Gastrointestinal) tract. Gross visual picture of the tract during endoscopy is further complemented by studying the histopathology of suspected lesions on biopsy [1]. Over the years, it has been realized that endoscopic appearances of the GI tract reported by expert GI interventionalist can suggest the most likely diagnosis but in no way is pathognomic [2]. Definitive diagnosis needs histopathological confirmation in the context of a good history, thorough physical examination and endoscopic appearances [3].

Despite this, a number of cases end up without a definitive diagnosis based merely on histopathology unless there is a consensus dialogue between the clinician, endoscopist, radiologist and histopathologist [4] A number of these cases end up in malignancy and are diagnosed in late stages with poor chances of cure [5] An early clue to this catastrophic outcome is intestinal metaplasia that can help devise follow up plan for individual patients in the context of age, gender, ethnicity, history, examination and laboratory work up [6].

In this regard, histopathological findings commonly associated with intestinal metaplasia can help categorize patients needing meticulous search for findings of metaplasia. This might aid in selection of patients requiring future follow up endoscopies and biopsies to screen for early
development of gastric carcinoma. By following such a method, we might be able to diagnose stomach cancer in its early stages and thus improve patient outcomes.

Following this hypothesis, we devised this study to determine the histological characteristics associated with intestinal metaplasia in epithelial gastric biopsy specimens of symptomatic patients undergoing upper GI endoscopy at a tertiary care setup in Pakistan.

Methods

The study was approved by hospital ethical committee and carried out according to international ethical standards of the responsible committee on human experimentation and with the latest version of Helsinki Declaration of 1975. All patients underwent a detailed history taking and physical examination and all relevant investigations were performed.

A total of 87 patients were registered in the study over a period of 12 months. Both male and female individuals ≥ 18 years of age who were referred for endoscopy to our unit with dyspepsia were included in the study. All patients were assessed for fitness by a consultant physician before the procedure and prepared.

Endoscopic biopsies were taken from gastric antrum, corpus and cardia of dyspeptic patients in a prospective analysis. For endoscopy, flexible video-endoscope, Olympus 140 endoscope system was used along with standard punch biopsy forceps.

All procedures were performed and documented under supervision of consultant gastroenterologist. Strict aseptic measures were taken for all. Biopsies were performed and samples were collected in sterile bottles containing 10% neutral formalin. Biopsies were processed and stained routinely with Haematoxylin and Eosin (H and E). All biopsy specimens were studied and reported by consultant histopathologist. Following parameters were studied and recorded on histopathology:

- Presence/absence of gastritis and grade i-e-, mild, moderate or severe,
- Presence/absence of metaplasia with type i-e-, complete/incomplete
- Helicobacter pylori (H. pylori) status i-e-, present/absent
- Depth of inflammatory cellular infiltration of epithelium in case of gastritis
- Presence/absence of germinal centre formation.

Data for all the procedures was collected and processed using SPSS version 16 (SPSS Inc. USA). Simple descriptive statistics were used for data analysis. Mean ± SD was calculated for numerical and frequency and percentage for categorical variables. Chi-square test was used and p value was calculated with a significance value less than 0.05.

Results

Males and females constituted 56.3% (49) and 43.6% (38) of the entire cohort respectively. Mean age for the entire cohort was 48.0 ± 15.5 years. The youngest patient was 18 years old and the oldest patient was 80 years old. The peak incidence of gastritis as well as intestinal metaplasia was in the 5th followed by 4th decade of life. Intestinal metaplasia was found in 27.5% (24) specimens. Complete metaplasia was present in 37.5% (9) specimens and incomplete in 62.5% (15). Male to female ratio for metaplasia was 1.4:1.

Gastritis was seen in 82.7% (72) biopsies while evidence of H. pylori active gastritis was found in 79.3% (69) specimens. Intestinal metaplasia was found in 27.5% (24) specimens. Among those with intestinal metaplasia, 87.5% (21) had mononuclear and polymorphic cellular infiltration up to the level of lamina propria while only 12.5% (3) had infiltration up to submucosa/beyond mucosa. Germinal centre formation was seen in 16.6% (4) of those with metaplasia.

Among specimens with gastritis, mild, moderate and severe gastritis were present in 59.7% (43), 23.6% (17) and 16.6% (12) biopsies respectively. Metaplasia was invariably associated with H. pylori active gastritis (100%; p<0.05). Chances of having metaplasia significantly increased with moderate to severe gastritis as compared to mild gastritis (p<0.05). Depth of epithelial
infiltration and germinal centre formation were not associated with metaplasia \((p>0.05)\) (Table 1).

### Table 1: Association of histopathological findings with intestinal metaplasia

<table>
<thead>
<tr>
<th>Category</th>
<th>Intestinal metaplasia % (n)</th>
<th>No intestinal metaplasia % (n)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28.5 (14)</td>
<td>71.5 (35)</td>
<td>0.34</td>
</tr>
<tr>
<td>Female</td>
<td>26.3 (10)</td>
<td>73.6 (28)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>48.38 ± 13.9</td>
<td>47.7 ± 16.3</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Gastritis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33.3 (24)</td>
<td>66.6 (48)</td>
<td>0.02*</td>
</tr>
<tr>
<td>No</td>
<td>0 (0)</td>
<td>100 (15)</td>
<td></td>
</tr>
<tr>
<td><strong>H. pylori active gastritis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34.7 (24)</td>
<td>65.2 (45)</td>
<td>0.01*</td>
</tr>
<tr>
<td>No</td>
<td>0 (0)</td>
<td>100 (18)</td>
<td></td>
</tr>
<tr>
<td><strong>Depth of epithelial infiltration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited to mucosa</td>
<td>27.6 (21)</td>
<td>72.3 (55)</td>
<td>0.46</td>
</tr>
<tr>
<td>Beyond mucosa</td>
<td>27.2 (3)</td>
<td>72.7 (8)</td>
<td></td>
</tr>
<tr>
<td><strong>Germinal centre</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>66.6 (4)</td>
<td>33.3 (2)</td>
<td>0.32</td>
</tr>
<tr>
<td>Absent</td>
<td>24.6 (20)</td>
<td>75.3 (61)</td>
<td></td>
</tr>
<tr>
<td><strong>Severity of gastritis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>9.3 (4)</td>
<td>90.6 (39)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Moderate</td>
<td>52.9 (9)</td>
<td>47.0 (8)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>91.6 (11)</td>
<td>8.3 (1)</td>
<td></td>
</tr>
</tbody>
</table>

![Figure 1: Endoscopic view of gastric lesions with dyspepsia and histopathological findings in intestinal metaplasia:](image)

1A: Schematic diagram of gastric lining on endoscopy showing inflamed, red lesions suggestive of gastritis, 1B: Endoscopic view of stomach while taking full thickness mucosal biopsy (patient 16), 1C: Microscopic view of stomach lining (H & E stain; 40X) showing intestinal metaplasia with intestinal type mucosal lining having goblet cells (arrowheads) and deep cell infiltrates (arrow) (patient 32), 1D: Microscopic view of stomach lining, magnified view (H & E stain; 100X) showing intestinal metaplasia with goblet cells in mucosal lining (arrow) (patient 45).
Discussion
Gastroscopically hypertrophic or chronic gastritis was thought to be characterized by a veracious appearance of the gastric mucosa which Benedict and Mallory considered to be represented microscopically by an exaggeration of the chronic inflammatory infiltrate normally found in nearly every stomach. An inflammatory band occupying a third or more of the width of the gastric mucosa was considered pathologic except in the antrum where such a band was regarded as disease only if it involved at least half the width of the mucosa (Figure 1) [6, 7].

Superficial gastritis has been diagnosed gastroscopically by the presence of increased reddening, edema and adherent secretion. Microscopically an infiltrate of polymorphonuclear neutrophils is seen in the interstitial tissue of the upper portion of the gastric mucosa [8]. Atrophic gastritis or gastric atrophy is seen gastroscopically as a pale, thin mucosa with visible blood vessels. Histologically, there is intestinal metaplasia and a variable degree of chronic inflammatory infiltrate and loss of the glandular portion of the mucosa (Figure 1) [8, 9].

The present study consisted of a total of 87 gastric biopsies out of which 24 (27.5%) cases had intestinal metaplasia. The frequency was almost double of that noted by Khan and colleagues in 2001 i.e., 27% versus 12%. They suggested repeat endoscopy and biopsy in such cases because of the increased risk of malignancy [10]. Most of the intestinal metaplasia in our study was incomplete with moderate to severe gastritis having inflammatory cellular infiltrates up to lamina propria without germinal center formation (Table 1). However, only those with moderate to severe gastritis had higher chances of developing metaplasia (p<0.05) irrespective of the depth of epithelial invasion or germinal centre formation (p>0.05) (Table 1).

A study by Haroon et al. concluded that frequency of precancerous lesions in endoscopic gastric biopsies of patients with chronic gastritis in Karachi was markedly high. Most common lesion was chronic active gastritis and precancerous lesions were frequent in these lesions [11].

In an international study by Lee and colleagues, old age and dysplasia were independent risk factors for gastric cancer. As compared with the risk in the general population, the standardized incidence ratio of gastric cancer among patients with gastric intestinal metaplasia was 2.5. Standardized incidence ratio was only 2.0 in the non-dysplasia subgroup, but was up to 35.2 in the high-grade dysplasia subgroup. They concluded that gastric intestinal metaplasia is an important risk factor for gastric cancer, but surveillance should be arranged only for those at an especially high risk [12].

*Helicobacter pylori* is the most common cause of non erosive non- specific gastritis. In our study, gastritis was seen in 82.7% (72) biopsies while evidence of *H. pylori* active gastritis was found in 79.3% (69) specimens. Metaplasia was invariably associated with *H. pylori* active gastritis (100%; p<0.05). In a study by Fareed et al. correlation coefficient of *H. pylori* density and neutrophil activity was 0.542, 0.644 and 0.729 for antrum, corpus and cardia respectively (p=0.00); while the correlation coefficient of mononuclear cell infiltrate with *H. pylori* density was 0.173, 0.245 and 0.326 for antrum, corpus and cardia respectively (p=0.03, 0.00, 0.00).

They concluded that neutrophil activity shows a direct association with *H. pylori* density [13] In 2007, Arif and associates reported that a significant number of *H. pylori* were found in patients of carcinoma of stomach. Both intestinal and diffuse types of gastric carcinoma showed strong association with *H. pylori* and chronic gastritis was the background lesion while intestinal metaplasia indicated long term infection [14]. Contrary to this, a local study by Bukhari et al. advocated that significant gastric lesions were seen in biopsies positive for *H. pylori* as compared to *H. pylori* free gastritis. However dysplasia and malignancies were non significantly associated with *H. pylori* bearing biopsies versus *H. pylori* negative ones [15].
Concluding from above, we suggest that pathologist should categorically look for focuses of intestinal metaplasia in biopsy specimens with moderate to severe gastritis and *H. pylori* irrespective of the depth of epithelial infiltration or germinal centre formation as it is a precursor for future risk of developing gastric carcinoma. The above mentioned association of histopathological findings with intestinal metaplasia can help categorize patients needing meticulous search for findings of metaplasia and development of carcinoma.

Such a categorization might help to further improve the histopathological classification of gastritis and intestinal metaplasia. This might aid in selection of patients requiring future follow up endoscopies and biopsies to screen for early development of gastric carcinoma. By following such a method, we might be able to diagnose stomach cancer in its early stages and thus improve patient outcomes.

**Conclusion**

Intestinal metaplasia was found in 27% of biopsy specimens in patients with dyspepsia which is quite high (more than 1/4th). Higher grade of gastritis was associated with higher chances of developing intestinal metaplasia in stomach irrespective of the depth of epithelial invasion by inflammatory cells and germinal centre formation. It was invariably associated with *H. pylori*. We suggest that pathologists should categorically look for focuses of intestinal metaplasia in biopsy specimens with moderate to severe gastritis and *H. pylori* irrespective of the depth of epithelial infiltration or germinal centre formation as it is a precursor for future risk of developing gastric carcinoma.

**References**