Research Article

Endoscopic early detection of premalignant changes in stomach with mucosal biopsy in patients with symptomatology of acid peptic disease

Ajay A. Gujar¹*, Geeta A. Gujar²

¹Department of Surgery, D Y Patil Medical College, Nerul, Navi Mumbai, Maharashtra, India
²Department of Research, Amruta Surgical Home, Mumbai, Maharashtra, India

Received: 15 December 2015
Revised: 06 January 2016
Accepted: 11 January 2016

*Correspondence:
Dr. Ajay A. Gujar,
E-mail: drgujars@yahoo.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Stomach cancer is the second-most common cancer among men and third-most among females in Asia and worldwide. The symptoms and sign of the stomach cancer are often reported late when the disease is already in advanced stages and 5-year survival is less than 30% in developed countries and around 20% in developing countries. Early detection of cancer stomach is still remains challenge to the gastroenterologist.

Methods: This study was done to detect early premalignant changes by upper GI scopy and histopathological examinations of mucosal biopsies in patients with symptoms of acid peptic disease not responding to any type of medications. 200 patients above 20 years of age with acid peptic disease symptoms selected for upper GI scopy and histopathology with follow up from 6 months to two years to detect whether premalignant lesion changes to malignancy.

Results: Different types of inflammatory lesions of gastric mucosa detected endoscopically and on histopathology in our study. In 7 patients premalignant changes were detected and 7 patients already had gross malignancies in stomach. Out of the total number of biopsies included in the study, we observed lesions of atrophic type in 4 antral biopsies (2.25%) and 3 biopsies of the gastric body (1.69%). All were grade 1 as per Sydney classification.

Conclusions: Upper endoscopy with histopathology has excellent output to detect early premalignant changes in stomach mucosa, though it is long way to continue this study to correlate both.

Keywords: Endoscopic biopsy, Premalignant lesions of stomach cancer, Gastritis, Atrophic gastritis

INTRODUCTION

Stomach cancers tend to develop slowly over many years. Before a true cancer develops, pre-cancerous changes often occur in the inner lining (mucosa) of the stomach. These early changes rarely cause symptoms and therefore often go undetected. Cancers starting in different sections of the stomach may cause different symptoms and tend to have different outcomes.

In Indian scenario most of the patients carried away with acid peptic disease symptoms with inadequate treatment and knowledge. Therefore detecting premalignant conditions are bit difficult. Most of the patients of stomach cancer in India present with advance stage.

Although incidence has declined in recent years, gastric cancer still represents the second most frequent cause of cancer-related mortality in the world.¹ The prognosis of stomach cancer is related to the stage of disease at the time of diagnosis, with a good prognosis associated with early gastric cancer.² Therefore, it is essential an early diagnosis of gastric carcinoma, at present only about 10-20% of cancers being diagnosed in an early phase.² Most gastroenterologist developed interest in detecting...
premalignant lesions and follow up of such patients regularly.

The well-known multistep cascade of carcinogenesis developed by Correa is represented by superficial gastritis followed by atrophic gastritis, intestinal metaplasia and increasing grades of dysplasia, leading to gastric adenocarcinoma. Surveillance of the premalignant lesions could determine an early detection of patients with disease progression, with the possibility of early therapeutic intervention and improved survival of these patients.

Diagnosis and localization of premalignant lesions and early gastric cancer is difficult because of the possible lack of evident gross endoscopic signs, even with the performance of multiple random biopsies. Another problem with conventional white light endoscopic diagnosis of these lesions consists in finding the exact location of previously sampled sites for endoscopic or surgical treatment. Recently developed new endoscopic techniques have surpassed some of these drawbacks and have an improved accuracy of diagnosing early cancers and precancerous lesions.

Stomach cancer is more common in men than in women. There is a sharp increase in stomach cancer rates in people over the age of 50. Most people diagnosed with stomach cancer are between their late 60s and 80s.

Infection with Helicobacter pylori (H. pylori) bacteria, people with diets that have large amounts of smoked foods, salted fish and meat, and pickled vegetables, use of tobacco and smoking, overweight, previous stomach ulcer surgeries and resection of stomach, people with pernicious anemia have an increased risk of stomach cancer.

Menetrier disease (hypertrophic gastropathy), people with type A blood have a higher risk of getting stomach cancer, some inherited conditions may raise a person’s risk of stomach cancer. Hereditary diffuse gastric cancer. This inherited syndrome greatly increases the risk of developing stomach cancer.

A family history of stomach cancer, people with first-degree relatives (parents, siblings, or children) and hypertrophic, inflammatory, adenomatous polyps.

Epstein-Barr virus (EBV) infection Epstein-Barr virus causes infectious mononucleosis (also called mono). Almost all adults have been infected with this virus at some time in their lives, usually as children or teens. EBV has been linked to some forms of lymphoma.

The signs and symptoms of stomach cancer can include:

- Vague discomfort in the abdomen, usually above the navel
- A sense of fullness in the upper abdomen after eating a small meal
- Heartburn or indigestion
- Nausea
- Vomiting, with or without blood
- Swelling or fluid build-up in the abdomen
- Low red blood cell count (anemia)

**Endoscopy, biopsy and immunohistochemistry**

Upper endoscopy (also called esophagogastro-duodenoscopy or EGD) with biopsy is the main test used to find stomach cancer. It may be used when someone has certain risk factors or when signs and symptoms of disease are present.

If a sample contains adenocarcinoma cells, it may be tested to see if it has too much of a growth-promoting protein called HER2/neu (often just shortened to HER2). The HER2/neu gene instructs the cells to make this protein. Tumors with increased levels of HER2/neu are called HER2-positive. Stomach cancers that are HER2-positive can be treated with drugs that target the HER2/neu protein, such as trastuzumab (Herceptin®).

Fluorescent in situ hybridization (FISH) method used for HER2 receptor confirmation.

**METHODS**

200 cases of upper abdominal discomfort have been studied. Patients selected were all above 20 years of age. The study was divided into investigations including upper GIscopy and subsequent histopathological report. Follow up of patients was done from 6 months to 2 years.

Those patients of acid peptic disease who were treated inadequately were studied for response with single drug 12 weeks complete therapy and life style modification. The mean age of the patient was 45.78 years.

All patients had CBC and USG abdomen before endoscopy. Upper endoscopy done with a Olympus Exera CV-180 scope. Biopsies were taken from suspected inflamed area and sent for histopathology and if required for immunohistochemistry. All patient’s mucosal tissue also examined for Helicobacter pylori organisms.

For each case 5 biopsies were taken and processed: two biopsies from the antral level (A1 = the small curvature; A2 = the large curvature), two biopsies from the gastric body (C1 = the small curvature; C2 = the large curvature) and a biopsy from the gastric angle (U). Moreover, all macroscopically visible lesions have been biopsied with specification of their location and clinical diagnosis.
RESULTS

Out of 200 patients who subjected to upper GI scopy with subsequent mucosal biopsy 123 (61%) were males and 77 (39%) were females.

<table>
<thead>
<tr>
<th>Age Group in years</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-30</td>
<td>25</td>
<td>08</td>
</tr>
<tr>
<td>31-40</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>41-50</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>51-60</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>61-70</td>
<td>15</td>
<td>06</td>
</tr>
<tr>
<td>71-80</td>
<td>05</td>
<td>04</td>
</tr>
<tr>
<td>Above 80</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>Total</td>
<td>123</td>
<td>77</td>
</tr>
</tbody>
</table>

Table 1: Age and gender percentage.

Out of 200 patients 178 patients had inflammation. Out of 178 biopsies, 7 were adenocarcinoma and remaining 171 were showing different types of changes in mucosa on histopathology reporting.

<table>
<thead>
<tr>
<th>Number of males with inflammation</th>
<th>Number of females with inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td>68</td>
</tr>
</tbody>
</table>

Table 2: Number of inflammation.

Out of 123 male patients who underwent scopy 105 patients (52.5%) were having gastritis and duodenitis with minimal to moderate loss of rugosity of mucosa at antrum, 13(4%) patients had normal study, 5 (2.5%) were gross malignancy of stomach which later confirmed the diagnosis of adenocarcinoma.

<table>
<thead>
<tr>
<th>Inflammation of mucosa (gastritis)</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross malignancy</td>
<td>05</td>
</tr>
<tr>
<td>Normal study</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>123</td>
</tr>
</tbody>
</table>

Table 3: Endoscopic distribution of mucosal involvement in males.

Out of 77 female patients who underwent scopy 66 (33%) were having inflammatory changes in mucosa, 9 (4.5%) patients had normal study, 2 (1%) were gross malignancy which later confirmed by HP as an adenocarcinoma.

<table>
<thead>
<tr>
<th>Inflammation of mucosa (gastritis)</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross malignancy</td>
<td>02</td>
</tr>
<tr>
<td>Normal study</td>
<td>09</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
</tr>
</tbody>
</table>

Table 4: Endoscopic distribution of mucosal involvement in females.

Chronic active gastritis was encountered in 4 cases (2.34%). strongly associated with the presence of Helicobacter pylori organisms, where H. pylori seen in 3 (60%) biopsies out of 5 cases of chronic active gastritis. Atrophy was present in 7 (4.06%) biopsies, whereas intestinal metaplasia in 1(0.58%) cases. Dysplasia found only in 1 case (0.58%). Precancerous lesions were 7 biopsies out of 171, as gross malignancy were already present in remaining 7 cases. Remaining cases with other mucosal changes are shown in Table 7.

In accordance with the Sydney system, the morphological criteria of quantification applied to cases with gastric atrophy are the following:

- 0 = absent
- 1 = mild (disappearance of less than 25% of glands)
- 2 = moderate (disappearance of 25 - 50% of glands)
- 3 = severe (disappearance of over 50% of glands)
- 4 = biopsy inappropriate for histopathological interpretation.

Table 5: Histopathology distribution.

<table>
<thead>
<tr>
<th>Different types of gastritis</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>007</td>
</tr>
<tr>
<td>Total</td>
<td>178</td>
</tr>
</tbody>
</table>

Table 6: Histological Sydney score.

<table>
<thead>
<tr>
<th>No. of cases antrum (score)</th>
<th>No. of cases body (score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (1)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Table 7: Frequency of endoscopic diagnosis of type of gastritis.

<table>
<thead>
<tr>
<th>Endoscopic Aspect</th>
<th>Antrum No. of cases (%)</th>
<th>Body No. of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal erythema</td>
<td>22 (12.35%)</td>
<td>04 (2.25%)</td>
</tr>
<tr>
<td>Diffuse erythema</td>
<td>92 (51.68%)</td>
<td>19 (10.68%)</td>
</tr>
<tr>
<td>Erosive gastritis</td>
<td>20 (11.24%)</td>
<td>10 (5.6%)</td>
</tr>
<tr>
<td>Erosive hemorrhagic</td>
<td>02 (1.12%)</td>
<td>00 (0%)</td>
</tr>
<tr>
<td>Atrophic</td>
<td>04 (2.25%)</td>
<td>03 (1.69%)</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>01 (0.56%)</td>
<td>00 (0%)</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>01 (0.56%)</td>
<td>00 (0%)</td>
</tr>
</tbody>
</table>

Above findings suggestive of antrum involvement is more i.e. (79.77%) compare to body of stomach (20.23%).
In accordance with the Sydney system, the morphological criteria of quantification applied to cases with gastric atrophy are the following:

Total 7 patients detected with gross malignancy in this study. Out of these 7 patients 6 had anemia lower than 10gm%. And that was the main cause to induce them for endoscopy.

Relation of etiological factors with inflammation.

Out of 178 patients who had positive endoscopy findings,

- 102 patients had habit of daily non vegetarian food and spicy food.
- 108 patients had habit of alcohol drinking.
- 72 patients had NSAIDS.
- 72 male patients had habit of tobacco.
- 14 patients had family history of gastrointestinal cancers.

Out of 178 biopsies, 7 were adenocarcinoma and remaining 171 were showing inflammatory changes in mucosa.

All precancerous 7 lesions were detected in males age group of above 55years at antrum. All gross 7 adenocarcinoma were found in age group above 52 years with 5male (3 in distal and 2 in fundus of stomach) and 2 female patients (both in body of stomach).

Out of 7 adenocarcinoma 6 patients successfully operated for radical gastrectomies. One patient had metastasis in liver.

All 171 patients asked to follow up, but only 121 patients followed up with 12 weeks regular treatment and maintenance dose of omeprazole 20mg. 125 patients responded well to treatments and symptomatically they were cured.

Only 18 patients Helicobacter pylori were positive treated with 14 days course of H. pylori kit (amoxicillin 750 mg,

Figure 1: Endoscopic findings of atrophic gastritis.

Figure 2: Histopathology showing atrophic gastritis with intestinal metaplasia.

DISCUSSION

Precancerous lesions were encountered with significant frequency in patients with endoscopic chronic gastritis. Based on these findings, it is proposed that it is a rational approach to get biopsies from patients with endoscopic chronic gastritis, which can allow us to detect precancerous lesions thus providing opportunity to primary chemo preventive strategies along with life style changes and initial steps of gastric carcinogenic cascade.

For the endoscopists, evaluation the presence or absence of gastritis based on the endoscopic aspect of the gastric mucosa represents a common practice. Throughout the years, the concept of “endoscopic gastritis” has gained credibility, its existence being recognized by the Sydney System of classifying gastritis.8-10 Numerous studies followed the concordance between endoscopy and histopathological exam regarding the diagnosis of gastritis. The results of these works are contradictory, most of them supporting a low degree of concordance. However, the significant correlation between the gastroscopic and histopathological aspects in severe forms of gastritis are mentioned, and exclusion of active gastritis in case of a normal endoscopic aspect.11

Epidemiological and clinicopathological studies have proved that the extent, the intensity and the distribution of gastric atrophy and inflammation are closely correlated with the incidence of gastric cancer.12,13 Presently, the idea is accepted that only histopathological examination of gastric mucosa can correctly assess the risk of neoplastic progression of a gastric lesion, through identifying the modifications called preneoplastic:
atrophic gastritis, intestinal metaplasia, epithelial dysplasia.\textsuperscript{14}

Following the studies performed by Siurala M. in Finland and Estonia \textsuperscript{15}, Correa P. in Columbia and numerous Japanese authors \textsuperscript{4}, initially separate entities such as superficial chronic gastritis, atrophy, metaplasia, dysplasia and carcinoma were integrated in a hypothetical sequence, called “the cascade of Correa.”\textsuperscript{16} This hypothesis of gastric carcinogenesis, presented in 1984, was lacking the triggering etiologic element. The discovery in the same year of \textit{H. pylori} placed the infection of gastric mucosa with this bacterium on the first step of the carcinogenesis cascade.\textsuperscript{17,18}

Histopathological lesions regarded as preneoplastic are represented by chronic atrophic gastritis, intestinal metaplasia and dysplasia. In their evolution, these entities can be regarded as a pyramid with a very wide base, composed of the population infected with \textit{H. pylori}. A segment of this population (greater in the developing countries, compared with industrialized countries) will present the evolution of lesions towards atrophic gastritis, with or without intestinal metaplasia. Only a small part of the population will develop lesions of dysplasia and possibly gastric adenocarcinoma. In the cascade of carcinogenesis, the closer a lesion is of neoplasia, the greater is its risk to progress towards gastric carcinoma.\textsuperscript{14} Thus, chronic gastritis is a remote and uncertain precursor of gastric cancer, which constitutes rather a predisposing condition. High-grade dysplasia is a true neoplastic lesion.\textsuperscript{19,20}

Gastric atrophy is defined as a numeric reduction of the self glandular structures of the gastric mucosa.\textsuperscript{21,22} This definition, purely morphological, implies a disappearance of glands characteristic for an area of the gastric mucosa, for instance specialized glands from the gastric body, and their replacement either with extracellular matrix, fibroblasts or collagen, or by intestinal type or pseudopyloric glands. These modifications imply the alteration of physiological mechanisms, for instance, anomalies of the secretion of mucus and acid.

Atrophic lesion is defined by the presence of atrophy areas in the gastric mucosa. The most frequent causes are the long-term infection with \textit{H. pylori} and autoimmune gastritis. In the actualized Sydney system, the term of “atrophic gastritis” is used to differentiate this entity by the “non-atrophic gastritis” or simply “gastritis”, a lesion with severity expressed in the antrum and identified in most patients infected with \textit{H. pylori}.

Atrophic gastritis is characterized by the numeric decrease or disappearance of typical gastric glands, the expansion of antral type mucosa in the gastric body (antralization or pseudopyloric metaplasia) and areas of intestinal metaplasia. This entity presents a significant epidemiologic risk for the gastric adenocarcinoma, the prognostic implications being determined by the extent and distribution of atrophic areas.\textsuperscript{14,16,23,24}

Studies from literature have shown that the presence of atrophic gastritis has an annual incidence of progression to gastric cancer of approximately 0.5–1\%. and that the extent of atrophic gastritis within the stomach correlates with the risk of progression to carcinoma.\textsuperscript{25-28}

The two forms of atrophic gastritis are represented by corporal autoimmune and by multifocal atrophic gastritis, the later being more common, associated with \textit{H. pylori} infection, and with lesions of metaplasia. The presence of infection has been associated with an approximately 10-fold increased risk of atrophic gastritis development. There has been demonstrated an important regional variation in the prevalence of atrophic gastritis in \textit{H. pylori} infected individuals, with an increase of about 3-fold in Asia, in comparison with Western countries.\textsuperscript{29,30}

The pathophysiology associated with the increased risk of gastric cancer in patients with gastric atrophy may be related to achlorhydria, which predisposes to gastric bacterial overgrowth, accumulation of N-nitroso compounds, and diminished ascorbate secretion into the gastric lumen. Moreover, low acid output determines increased serum gastrin levels that may contribute to abnormal cell growth and increased risk of neoplastic progression.\textsuperscript{31}

In our study, the endoscopic aspect of atrophic gastritis was rarely encountered. Some authors signal the reduced percentage of atrophic gastritis cases diagnosed endoscopically, the lesions being obvious only for the severe forms as intensity.\textsuperscript{32} In the cases studied we did not observe any case of antral atrophic gastritis. In the gastric body, atrophic gastritis, was noted in 6 elderly patients.

For this lesion we noted a poor correlation between the conventional endoscopic investigation and histopathological examination. Out of the total number of biopsies included in the study, we observed lesions of atrophic type in 4 antral biopsies (2.25\%) and 3 biopsies of the gastric body (1.69\%). All were grade 1 as per Sydney classification.

In a recent study it is shown that most gastric carcinomas of intestinal type develop on the background of a wide terrain of atrophic gastritis, with small dispersed areas of intestinal metaplasia, which progresses proximally towards the large gastric curvature.\textsuperscript{33}

Intestinal metaplasia represents the replacement of the gastric lining and glandular epithelium by one composed of cells of the intestinal type (small or large intestine).

The most used classification is the one proposed by Jass and Filipe, which includes 3 types of intestinal metaplasias:
• Type I intestinal metaplasia (the complete type or of small intestine type)
• Type II intestinal metaplasia (the incomplete type or enterocolic type)
• Type III of intestinal metaplasia (the incomplete type or colonic type)

Only 1 patient (0.58%) out of 178 biopsies had type 1 intestinal metaplasia in our study.

**Dysplasia**

Gastric epithelial dysplasia occurs when the cells of the stomach lining (mucosa) become abnormal. These abnormal cells may eventually progress to adenocarcinoma, the most common type of stomach cancer. Gastric epithelial dysplasia can be divided into 2 types:

*Low-grade dysplasia*

The abnormal cells are changing and growing slowly. It has a low risk of progressing to cancer. It may change back to normal (regress).

*High-grade dysplasia*

The abnormal cells are changing and growing very quickly.

Cells are very abnormal, fast growing and aggressive. It has a high risk of progressing to cancer.

Only 1 case (0.58%) of low grade dysplasia was detected in this study.

**CONCLUSIONS**

Precancerous lesions were encountered with significant frequency in patients with chronic gastritis. Based on these findings, it is proposed that it is a rational approach to get biopsies from patients with endoscopic gastritis, which can allow us to detect precancerous lesions thus providing opportunity to apply chemo-preventive strategies along with lifestyle changes and initial steps of the gastric carcinogenic cascade.

In this study of 200 patients we found 178 patients with positive endoscopic findings of which 7 had adenocarcinoma and 7 had premalignant changes in gastric mucosa. We continue to do more biopsies in patients with endoscopic inflammatory changes for early detection of premalignant lesions and early carcinoma.

For the diagnoses of atrophy we noted a poor correlation between the conventional endoscopic investigation and histopathological examination. The use of modern endoscopic techniques may help identifying gastric precancerous lesions. Among our study group, we found atrophic gastritis, intestinal metaplasia and dysplasia, emphasizing the importance of performing multiple biopsies for an accurate histopathological diagnosis of gastritis.

**ACKNOWLEDGEMENTS**

1. American cancer society
2. The role of endoscopy and biopsy in evaluating preneoplastic and particular gastric lesion. Daniela Lazar, Sorina Taban, Sorin Ursoniu.

**Funding: No funding sources**

**Conflict of interest: None declared**

**Ethical approval: The study was approved by the Institutional Ethics Committee**

**REFERENCES**

6. Gastric Carcinoma- New Insights into Current Management.
12. Kaur G, Raj M. A study of the concordance between endoscopic gastritis and histological gastritis in an area with a low background prevalence of