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Original Article

Pathology Section

# Intestinal Metaplasia in Barrett's Oesophagus: A Clinicopathological Study

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## ABSTRACT

**Introduction:** The incidence of Oesophageal Adenocarcinoma (EAC) has increased at a faster rate than any other cancer in the developed nations. Despite advances in treatment, five year survival rate for EAC is <15%. Till date, Barrett's Oesophagus (BE) is the only known precursor of EAC increasing its risk by greater than 30 to 60 fold. Most important risk factor for development of dysplasia and EAC is specialised Intestinal Metaplasia (IM) in BE.

**Aim:** To find the association between clinical, endoscopic and histopathological features and presence of IM in patients with endoscopically suspected BE.

**Materials and Methods:** This was an institution based descriptive study with a cross-sectional design conducted in the Departments of Pathology and Surgery, in a tertiary care centre of North Bengal for four years (2017-2021), among patients attending Surgery and Medicine Outpatient Department (OPDs) or Inpatient Department (IPDs), suspected on clinical basis and subsequent endoscopic detection of BE utilising Prague criteria. Periodic Acid-Schiff (PAS) and Alcian Blue (pH 2.5) stains were used to detect complete or incomplete IM and results were analysed using appropriate statistical software.

**Results:** Among 120 cases included in the study, 72 (60%) had Short Segment Barrett's Oesophagus (SSBE) and 48 (40%) Long Segment Barrett's Oesophagus (LSBE). Hiatal hernia was significantly more frequent in LSBE patients (32 out of 48) compared to patients with SSBE (24 out of 72). The associations of tobacco and alcohol abuse with microscopically proven BE were statistically significant with p-values of 0.005 and 0.004, respectively. The association of IM with the increasing length of Columnar Lined Oesophagus (CLE) was statistically significant (p-value=0.004).

**Conclusion:** Tobacco and alcohol abuse, presence of hiatal hernia (particularly in LSBE patients) were significantly associated with BE. Increasing length of CLE is more commonly associated with IM. Incomplete IM was observed more commonly in LSBE cases whereas complete IM was detected more frequently in cases diagnosed as SSBE by endoscopy.


**Keywords:** Columnar lined oesophagus, Endoscopy, Oesophageal adenocarcinoma

## INTRODUCTION

The EAC are persistent gastroesophageal reflux induced cancers. Globally, the number of deaths due to EAC is approximately half the number of deaths from breast cancer and one-third the deaths from colorectal cancer. The mechanism of carcinogenesis is believed to pass through columnar metaplasia, IM in the columnar epithelium, and an increasing degree of dysplasia to adenocarcinoma [1]. As per the Montreal Workshop consensus, histologically proven metaplastic columnar epithelium with qualifier about the existence or absence of IM is designated as BE [2]. Risk and incidence rate of EAC in patients with BE is 30 to 60 times and over 100 times that of the general population, respectively. Most important risk factor for development of dysplasia and EAC is specialised IM in BE [3]. Evidence also suggests increased association of EAC related mutations with IM [4-6]. Endoscopic biopsy and histomorphological study are the screening methods available for diagnosing BE, the definitive precursor of EAC.

But despite such global concerns, there are few studies in India [7-11] and to the best of our knowledge no study involving sub-Himalayan North Bengal population, pertaining to BE and its clinicopathological aspects, thus inspiring this study to fill up the lacuna. The clinical, endoscopic and pathological findings were studied in patients with endoscopically suspected BE. Presence of IM was also detected using special stains.

## MATERIALS AND METHODS

The present study was an institution based descriptive study with cross-sectional design conducted in the Departments of Pathology and Surgery in a Tertiary Care Centre of Sub-Himalayan North Bengal Region over a period of four years (2017-2021), among patients attending Surgery and Medicine OPDs or IPDs and suspected to have BE on a clinical basis and subsequent endoscopy. The study was performed after obtaining prior approval from the Institutional Ethics Committee (IEC) (NBMC/IEC 2016-17/03, dt. 12/11/16).

**Inclusion criteria:** Only endoscopically suspected BE cases with proper informed consent was included in the study.

**Exclusion criteria:** EAC diagnosed cases were excluded from the study.

### Study Procedure

All relevant clinical data of patients undergoing upper Gastrointestinal (GI) endoscopy for Gastroesophageal Reflux Disease (GERD) was collected from surgery/medicine OPD/IPDs. After endoscopy, if BE was suspected using Prague C&M criteria (C-circumferential and M-maximal extent of CLE in cm. from gastroesophageal junction) [1], then endoscopic and histopathologic findings were recorded. Haematoxylin and Eosin (H&E) stained slides were studied under the microscope and examined for columnar metaplasia. The presence of *Helicobacter pylori (H. pylori)* infection was detected by rapid urease test.

Histological typing of the metaplastic epithelium was done subsequently. All the slides were treated with PAS and Alcian Blue (pH 2.5) stains and examined to detect the presence of foveolar cells containing neutral mucin, and acidic goblet cells containing sialomucin and sulfomucin. IM was further categorised into incomplete or complete. Presence of goblet cells with negative Alcian Blue (pH 2.5)-PAS stain in columnar-type cells was defined as Complete IM. Incomplete IM or Specialised Columnar Epithelium

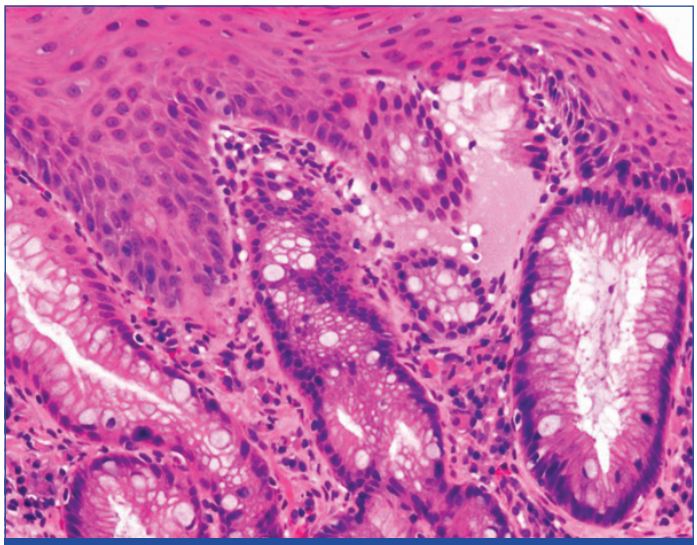
(SCE) was diagnosed by the presence of goblet cells, with Alcian Blue (pH 2.5)-PAS stain positive acidic mucins in goblet and adjacent columnar-appearing cells. Microscopic oesophagitis/GERD was defined as lamina propria papillae extending into the upper third of the oesophageal stratified squamous mucosa with basal cell hyperplasia with or without the infiltration of inflammatory cells. Other histological findings were examined if present, like dysplasia (low grade, high grade and indefinite for dysplasia) of intestinal and gastric type, EAC or any other heterotopic tissue. The final histopathological observation was based on consensus reached following judgement and scrutiny separately by three senior faculty members of the Department of Pathology.

## STATISTICAL ANALYSIS

The outcome was tabulated and analysed using appropriate statistical software (SPSS version 24.0, IBM, USA). Paired t-test, Independent sample t-test and Chi-square test were used to calculate p-value. A p-value <0.05 was considered to be statistically significant.

## RESULTS

Among the study population of 120 cases, 72 patients had microscopically confirmed BE [Table/Fig-1]. The rest 48 cases were diagnosed histopathologically to have reflux oesophagitis/GERD. Of the 120 cases, 80 (66.7%) were male and 40 (33.3%) were female, with a mean age of 58.13 years. Patients aged ≥60 years were 64 (53.4%), whereas 56 patients (46.7%) belonged to the age group of 50-59 years. Among these 72 patients with microscopically confirmed BE, 64 (88.9%) cases revealed IM.



**[Table/Fig-1]:** Barrett's oesophagus (H&E 40X).

Out of 120 patients, 64 (53.3%) were obese, 76 (63.3%) were tobacco abuser and 48 (40%) alcoholic. Eighty four (70%) patients were residents of urban areas whereas 36 (30%) patients were from rural and semi-urban areas. All of the urban patients with BE in the present study were alcoholic and obese. All the 120 cases studied, had reflux symptoms like heartburn, retrosternal pain, epigastric pain and odynophagia. The mean duration of symptoms was 7.03 years. All patients were on proton pump inhibitors for varying durations (mean 3.8 years). Out of 120 patients in the present study, 44 were reported to have GERD and/or oesophagitis on histopathology amounting to 36.67% of the study population. Out of 72 patients having histologically confirmed BE, 36 (50%) had been associated with microscopic evidence of GERD and/or oesophagitis.

Among the 72 cases microscopically proved to have BE, 60 (83.4%) patients had history of tobacco abuse and 44 (61.2%) patients were alcoholic. Whereas out of 48 patients whose oesophageal biopsies were negative for BE, only 16 (33.4%) had tobacco abuse history and 04 (8.4%) patients were detected as alcoholic. Hence, in the present study, the associations of microscopically proven BE with tobacco and alcohol abuse were found to be statistically significant with p-values of 0.005 and 0.004, respectively [Table/Fig-2].

| Parameters | BE present (72) | BE absent (48) |
|---|---|---|
| Tobacco user | 60 | 16 |
| Alcoholic | 44 | 4 |
| Non tobacco user | 12 | 32 |
| Non alcoholic | 28 | 44 |

**[Table/Fig-2]:** Association of microscopically confirmed BE with tobacco and alcohol abuse.

In the present study, hiatal hernia was detected by endoscopy in 56 (46.67%) patients. All these 56 patients with hiatal hernia were in the microscopically confirmed BE group. Hiatal hernia was not detected in any of the patients who were negative for microscopic evidence of BE. The association of microscopically proven BE with hiatal hernia was found to be statistically significant (p-value=0.001) [Table/Fig-3].

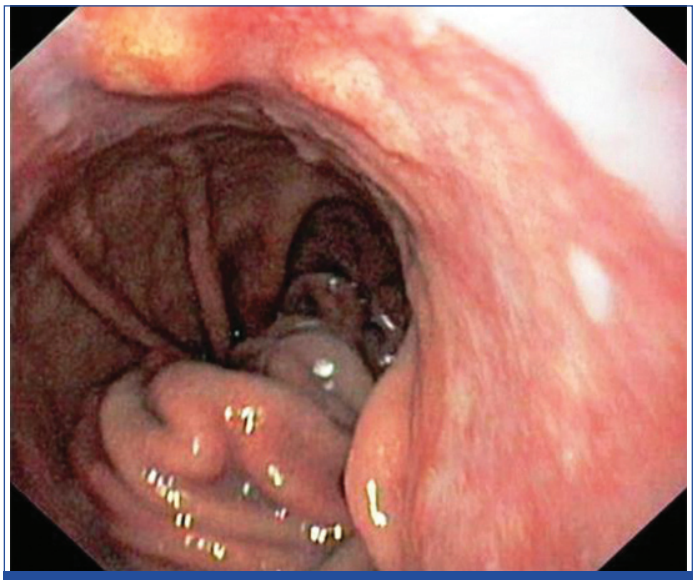
| Parameters | BE present (72) | BE absent (48) |
|---|---|---|
| Hiatal hernia present | 56 | 0 |
| *H. pylori* present | 0 | 12 |
| Hiatal hernia absent | 16 | 48 |
| *H. pylori* absent | 72 | 36 |

**[Table/Fig-3]:** Association of microscopically confirmed BE with hiatal hernia and *H. pylori*.

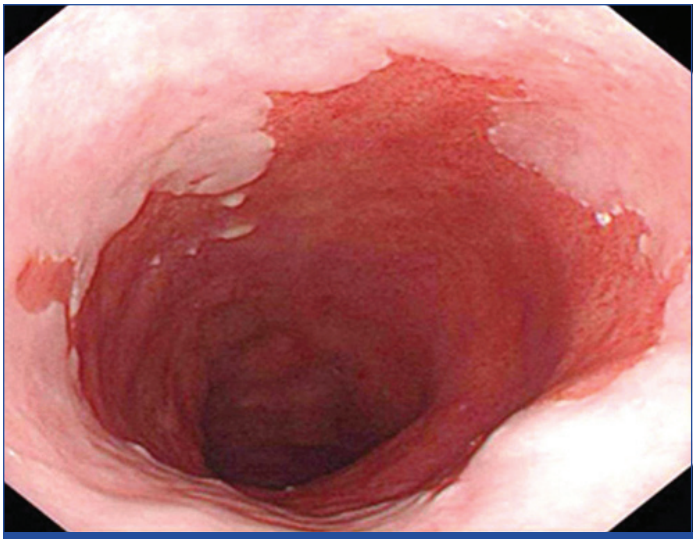
Of the 120 patients with endoscopically suspected BE, 72 (60%) had SSBE [Table/Fig-4-6] whereas the rest 48 (40%) were diagnosed with LSBE [Table/Fig-5] on endoscopy. Out of 48 LSBE patients, 32 (66.7%) cases were diagnosed by endoscopy to have hiatal hernia whereas out of 72 SSBE patients, hiatal hernia was detected in 24 (33.4%) cases. Hence, hiatal hernia was found to be significantly more frequent in LSBE patients compared to those with SSBE.

| Characteristic | IM | | Total N (%) | p-value |
|---|---|---|---|---|
| | Yes n (%) | No n (%) | | |
| LSBE | 44 (91.7) | 4 (8.3) | 48 (100) | 0.004 |
| SSBE | 28 (38.9) | 44 (61.1) | 72 (100) | |
| Total patient BE | 72 (60) | 48 (40) | 120 (100) | |

**[Table/Fig-4]:** Presence of IM in endoscopically suspected BE.



**[Table/Fig-5]:** Long Segment Barrett's Oesophagus (LSBE) with hiatal hernia-endoscopy.



**[Table/Fig-6]:** Short Segment Barrett's Oesophagus (SSBE)-endoscopy.

The presence of *H. pylori* infection obtained by rapid urease test was positive in 12 patients (10%) and negative in 108 patients (90%) out of the 120 endoscopically suspected BE. Among the 72 cases of microscopically proven BE, none was detected positive for *H. pylori*. Whereas out of the 48 patients where microscopically no evidence of BE was found, 12 cases were urease test positive. The association of microscopically proven BE with absence of *H. pylori* was found to be statistically significant (p-value=0.025) [Table/Fig-2].

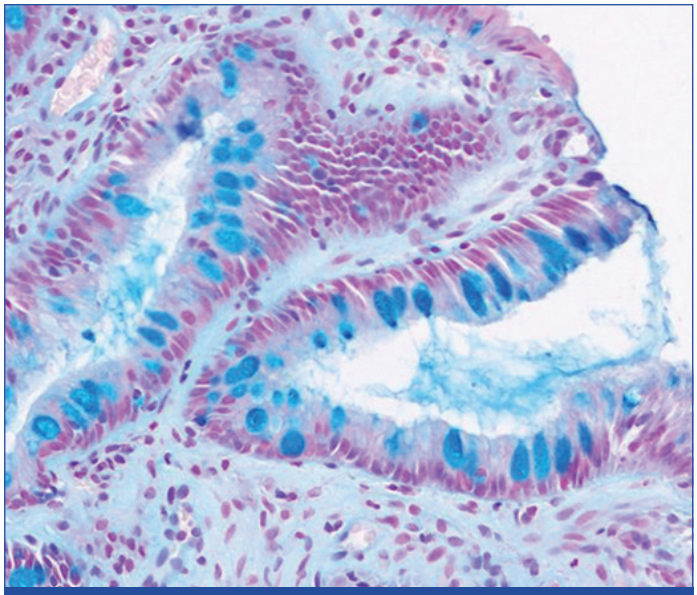
Out of 72 patients diagnosed endoscopically as SSBE, 28 (38.9%) cases were found to have histologically confirmed IM; whereas 44 (91.7%) out of 48 patients with endoscopic diagnosis of LSBE had histologically confirmed IM. The association of IM with the increasing length of CLE was statistically significant (p-value=0.004) [Table/Fig-4].

Among the 72 microscopically diagnosed BE cases, total 64 (88.9%) patients were detected to have IM. Out of these 64 cases incomplete IM was detected in 40 patients, whereas complete IM was detected in 24 patients. Among the 40 patients diagnosed with Incomplete IM, endoscopic detection of LSBE and SSBE were in 36 and 04 patients, respectively. In case of complete IM, out of 24 patients, endoscopic LSBE and SSBE were in 04 and 20 cases, respectively [Table/Fig-7].

| Characteristic | Incomplete IM, n (%) | Complete IM, n (%) | Without IM (%) | Total (%) |
|---|---|---|---|---|
| LSBE | 36 (75.0) | 04 (8.3) | 08 (16.7) | 48 (100) |
| SSBE | 04 (5.5) | 20 (27.8) | 48 (66.7) | 72 (100) |

**[Table/Fig-7]:** Incomplete and complete metaplasia in BE.

Out of 48 LSBE patients in the present study, 16 (33.4%) had dysplasia including four Indeterminate for Dysplasia (IDP) (8.4%), four High-grade Dysplasia (HDP) (8.4%) and eight Low-grade Dysplasia (LDP) (16.7%), whereas out of 18 SSBE patients, 8 (44.4%) had IDP. Microscopically, incomplete metaplasia is shown in [Table/Fig-8].



**[Table/Fig-8]:** Incomplete intestinal metaplasia. Alcian Blue (pH 2.5) 40X.

## DISCUSSION

In the present study, the patients with endoscopically suspected BE mostly belonged to the sixth decade (36.67%) with a mean age of 58.13 years. Abrams JA et al., and Edelstein ZR et al., also demonstrated that BE was usually detected during the sixth decade of life or later [12,13]. Gashi Z et al., performed an epidemiological study in relation to BE on 58 patients and showed that the mean age was 50.4±2.4 (SD) years and the most populated group was 50-59 years which corroborates well with those of the present study [14]. The gender distribution of the present study shows that male patients constituted 66.7% of patients and females constituted the rest. Yachimski P et al., showed that M:F ratio for BE was approximately 2:1 [15]. Gashi Z et al., also found that males (60%) were significantly more affected [14].

Obesity was associated in 53.4% of patients in the present study. In the published literature, GERD, BE and EAC have all been associated with obesity. It is thought to be due to increased GE sphincter gradient [16], intraabdominal pressure [17] and increased incidence of hiatal hernia in obese patients [18]. A retrospective case-control study showed a direct relationship between mean visceral adipose tissue and BE [19]. A similar correlation between BMI and BE was found in a study by Stein DJ et al., [20]. In the present study, 63.3% of the patients were tobacco abusers and 40% were alcoholics. In microscopically proven BE, 83.3% were tobacco abusers (p-value 0.005) and 61.1% were alcoholics (p-value 0.004). Ronkainen J et al., and Kim JH et al., had found both alcohol and smoking to be significant risk factors but others have shown no significant importance of the same [21,22]. Robertson CS et al., Eloubeidi MA et al., and Ritenbaugh C et al., found no such association [23-25].

Hiatal hernia distorts the anatomy that normally protects against reflux by reducing LES tone and decreasing the peristaltic activity [7]. In the present study, out of 48 LSBE, 32 (66.7%) had hiatal hernia. Out of 72 SSBE patients, 24 (33.3%) had hiatal hernia. Thus, hiatal hernia was more related to LSBE patients. In microscopically proven BE, 77.8% cases were diagnosed by endoscopy to have hiatal hernia (p-value=0.001). Westhoff B et al., showed that in 50 patients with GERD who developed BE, 63% had hiatal hernia [8]. Gashi Z et al., found that all the LSBE patients in their study had hiatal hernia whereas 35% of SSBE had the same [14].

Out of 120 patients in the present study, 44 (36.67%) of cases were detected to have GERD and/or oesophagitis on histopathology. Of the 72 patients having histologically confirmed BE, 50% were associated with microscopic evidence of GERD and/or oesophagitis. Shaheen N and Ransohoff DF reported that BE was strongly associated with reflux symptoms. They also concluded that 5-15% of patients with long term reflux symptoms will have BE of some length with varying duration of time [26].

*H. pylori* is supposed to have a protective role against BE. But it is a risk factor for peptic ulcer disease and gastritis. *H. pylori* decreases gastric reflux disease through the activity of urease [27]. Gashi Z et al., reported a lower prevalence of *H. pylori* infection among patients with BE (15.5%) as compared to GERD and control patients [14]. Blot W et al., reported a reduced risk of EAC and BE among individuals infected with *H. pylori* in particular of CagA type [9]. The results of the present study were in concordance with that of the published studies.

Of the 120 patients with endoscopic BE, 48 (40%) patients were reported as LSBE and 72 (60%) as SSBE. Gashi Z et al., in their study found that out of 58 patients, 35 (60.3%) patients had SSBE and 23 (39.7%) patients had LSBE which is almost similar to the present study [14]. According to Rastogi A and Sharma P observed prevalence of SSBE was higher than that of LSBE. The demographics and the symptom profile of patients evaluated in their study varied significantly from those of the present study [28].

Of the 48 patients with LSBE in the present study, 44 (91.7%) patients had IM, while 04 (8.4%) patients were negative for IM. On the other hand, out of 72 SSBE patients, 28 (38.9%) had IM and the rest 44 (61.2%) were negative for IM. This finding was statistically significant having a p-value of 0.004, which demonstrates that IM was more prevalent in LSBE cases in the present study. In relation to LSBE, 36 (75%) patients had incomplete IM and 04 (8.33%) had complete IM and the rest 08 (16.7%) had no IM. In case of SSBE, only 04 (5.6%) patients had incomplete IM, 20 (27.8%) had complete IM and rest 48 (66.7%) patients had either Indeterminate for Barrett's (IDB) (55.6%) or IDP (11.2%). In the IDP group, 04 patients (5.6%) had IM. Spechler SJ et al., noted that the frequency of finding specialised IM increased from 15% of patients with no CLE visible in the oesophagus to 90% of patients with greater than 3 cm of oesophageal CLE [10]. In another study by Eloubeidi MA and Provenzale D IM increased from 25% of patients with less than 3 cm of CLE to 50% in patients with 3-5 cm of CLE and to >65% in patients with greater than 5 cm of CLE [24]. Gashi Z et al., showed that 91.3% of patients with LSBE had microscopically confirmed IM while 45.7% of patients with SSBE had confirmed IM [14]. All these findings are at par with those of the present study.

In a study on North Indians, by Wani IR et al., reported that prevalence of specialised IM was more in LSBE cases [29]. The predominant form of IM in BE was incomplete IM which corroborates with findings of the present study [30]. Incomplete IM was less differentiated and therefore more likely to be a precursor of dysplasia. In practice, incomplete and complete IM may exist adjacent to each other and their identification may purely be a result of sampling. Hence, subtypes of IM are not generally mentioned in pathology reports [31]. As suggested by de Meester SR, a practical approach may be to consider that patients with LSBE nearly always have or will develop IM and these patients should be considered to have microscopically confirmed BE along with shorter length CLE who show IM on histopathology [32].

### Limitation(s)

Considering the magnitude of problem of BE, the sample size of this present study was a limitation. Prospective short and long-term follow-up of the cases detected with BE would have allowed comment regarding natural outcome of such cases in this particular study population. This study, not being a population based study; the actual burden of disease, especially in asymptomatic patients could not be assessed. Ancillary Immunohistochemistry or molecular studies were also warranted for subcellular level observations and establishing scientific rationale behind the associations observed in this study.

## CONCLUSION(S)

The present study revealed that microscopically confirmed BE was more common in endoscopically detected LSBE than in SSBE cases. The association of BE with alcohol and tobacco abuse, hiatal hernia and absence of *H. pylori* infection was statistically significant. IM was detected more in LSBE than SSBE having a significant statistical association. Incomplete IM was observed more commonly in LSBE cases whereas complete IM was detected more frequently in cases diagnosed as SSBE by endoscopy.

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