CLINICAL AND PATHOPHYSIOLOGICAL CHARACTERISTICS OF SHORT-SEGMENT BARRETT'S ESOPHAGUS

By

**Salah El-Gamal, Ayman A. Eldesoky, Yahia Zakaria
Khaled R. Zalata *, and Moamer Mohamed.**

From

*Internal Medicine and *Pathology Departments
Faculty of Medicine, Mansoura University, Egypt*

ABSTRACT

Background : The histologic presence of intestinal metaplasia in the esophagus is a prerequisite for the diagnosis of Barrett's esophagus. Short-segment Barrett's esophagus is three times more frequent than long-segment Barrett's esophagus, with similar risk of dysplasia and adenocarcinoma. Our objective was to study the clinical and pathophysiological characteristics of short-segment Barrett's esophagus.

Patients and Methods : Demographic informations, data on tobacco and body mass index were recorded for all patients. Before upper gastrointestinal endoscopy and esophageal manometry, all patients completed a

validated gastroesophageal reflux disease questionnaire. The diagnosis of short-segment Barrett's esophagus was based on the presence of columnar-appearing mucosa in the distal 3cm of the esophagus, with confirmation by demonstration of intestinal metaplasia in biopsy specimens.

Results : The studied patients included group 1 (11 patients having short-segment Barrett's esophagus) and group 2 (29 patients suffering gastroesophageal reflux disease without Barrett's esophagus). In group 1, smoking was found in 4 patients, ulcerogenic drug intake in 4 patients, bad dietary habits in 6 patients and obesity in 5 patients. The relative risk for obesity (1.73), for drugs (1.5), for

smoking (1.33) and lastly for bad dietary habits (1.32). Similar endoscopic features were found in both studied groups, except for esophageal mass in one patient and esophageal bleeding in 5 patients of group I. Group I patients had goblet cells in 3 patients, dysplastic changes in 3 patients, and *Helicobacter pylori* in only two patients. Esophageal motility study proved lower esophageal wave amplitude in group 1 patients ($P < 0.02$) without significant differences in the lower esophageal sphincter manometric findings between the two studied groups.

Conclusion : Although obesity and ulcerogenic drugs carry a high risk for development of short-segment Barrett's esophagus in patients with gastroesophageal reflux disease, short-segment Barrett's esophagus cannot be diagnosed on the basis of symptoms, physical examination, or blood tests. So, endoscopic and histopathological examination of multiple lower esophageal biopsies from different sites are fundamental in all cases for accurate diagnosis of short-segment Barrett's esophagus. Furthermore, histologic grading of esophageal biop-

sies (metaplasia, dysplasia, and adenocarcinoma) could represent the cornerstone of management in those patients. In addition, the characteristic physiological changes of short-segment Barrett's esophagus in the form of greater impairment of peristaltic wave amplitude could be attributed to a higher esophageal acid exposure and a longer duration of illness.

Key Words : Barrett's esophagus, Gastroesophageal reflux, Endoscopy, Pathology, Motility.

INTRODUCTION

Barrett's esophagus (BE) is considered as a change of esophageal mucosa from normal squamous epithelium to columnar epithelium at any length. Skinner et al., (1983)¹ were among the first authors who restricted Barrett's esophagus to only those patients who had >3cm of columnar lining mucosa in the distal esophagus. This is all changed with the report of Spechler et al., (1994)² who observed that goblet cells were present at the gastro esophageal junction in 18% of subjects who had <3cm columnar lining esophageal mucosa. Such high prevalence of goblet cells,

a marker of specialized intestinal epithelium was considered as short-segment Barrett's esophagus (SSBE).

BE is a consequence of chronic gastro-esophageal reflux disease (GERD).³ It is a metaplastic condition that occurs in about 12% of patients with GERD.⁴ However, the reason of why some patients with GERD develop BE and the others do not is unclear. It has been suggested that, gastro-esophageal acid reflux is more pronounced in patients without Barrett's epithelium. Furthermore, symptoms of GERD are common in adult populations as 25-65% of peoples experience symptoms of reflux at their lives and approximately 25% seek medical attentions for their symptoms.⁵ Because Barrett's epithelium may develop as a late sequence of chronic reflux esophagitis⁶, once-in-lifetime endoscopy for GERD patients is an adequate screening tool that may serve as a basis for a Barrett's esophagus surveillance program.⁷

The debate over SSBE is a matter of research. It is clearly associated with an increased risk of dysplasia or

cancer when compared to intestinal metaplasia of the cardia, and the cancer risk in this condition is similar to that with long-segment BE.⁸

AIM OF THE WORK

Study of the clinical and pathophysiological characteristics of patients with short-segment Barrett's esophagus.

PATIENTS AND METHODS

Patients :

The study included forty patients with gastroesophageal reflux disease with endoscopically suspected SSBE. The patients were selected from those subjected to upper gastrointestinal endoscopy in Mansoura Specialized Medical Hospital and in the Emergency Hospital. Patients with suspected long-segment Barrett's esophagus (>3cm columnar lining esophageal mucosa), esophageal varices, evidence of bleeding tendency, diabetes mellitus, renal failure, advanced liver disease and pregnant ladies were excluded.

Methods :

- Thorough history taking including age, sex occupation, special habits

(smoking, alcohol, dietary habits {excess fat, chocolate, coffee}), drug history (ulcerogenic drugs as NSAIDs and drugs decreasing LES pressure), reflux symptoms (heart burn, chest pain, regurgitation, water brash, nausea and vomiting). Lastly, symptoms of complications e.g. dysphagia, odynophagia, upper gastrointestinal bleeding, hoarseness of voice, bronchial asthma, and symptoms of recurrent upper respiratory tract infections were also recorded.

- Clinical examination including weight, height, body mass index, colour of the skin, chest examination with x-ray chest, and cardiac examination with ECG. Also, abdominal examination specially presence or absence of epigastric tenderness.
- Laboratory investigations including complete blood count, prothrombin time, serum creatinine, blood glucose, and some liver function tests (serum bilirubin, serum albumin, ALT, AST, ALP).
- Upper gastrointestinal endoscopy:

finding a segment of deep red mucosa suggestive of columnar epithelium in the form of circumferential sheet or irregular finger-like projections and islands which contrasts sharply with the pale glossy squamous epithelium, were interpreted as SSBE if extending for a distance less than 3cm from the esophagogastric junction. All patients with erosive esophagitis on the initial endoscopy underwent a second endoscopy to document healing and to rule-out underlying BE. Four quadrant biopsy specimens were taken from different sites within the segment of presumed SSBE.⁹

- Histopathological examination: all biopsy specimens were fixed in 10% formalin and embedded in paraffin. Next, the prepared slides were stained with Haematoxylin and Eosin. Additionally, special staining was done with Alcian blue at PH 2.5 to detect goblet cells.
- Motor functions of the lower esophageal sphincter (LES) and esophageal body were assessed by esophageal manometry using wa-

ter perfused 8 lumen manometric catheter connected to external pressure transducer (water infusion pump). The pressure is sensed by the transducer and converted to an electrical signal that is recorded by the computer (Phoenix Mk2 computerized system- Scotland).

RESULTS

According to the histopathological study of the biopsy specimens, our patients were subdivided into group 1 (included 11 GERD patients with SSBE, 8 male and 3 female with mean age 41.81 ± 15.94), and group 2 (included 29 GERD patients without SSBE, 15 males and 14 females with mean age 41.65 ± 12.95).

In group 1, smoking was found in 4 patients, intake of ulcerogenic drugs (NSAIDs) in 4 patients, bad dietary habits in 6 patients and obesity in 5 patients. However, in group 2, smoking, ulcerogenic drugs, bad dietary habits and obesity were found in 8, 7, 13, 13 patients respectively. The relative risk for development of SSBE in GERD patients was (1.73) for

obesity, (1.5) for ulcerogenic drugs, (1.33) for smoking and lastly (1.32) for bad dietary habits (table 1).

The common endoscopic features of GERD are approximately similar among patients of both studied groups, except for esophageal mass in one patient and bleeding from the area of Barrett's epithelium in 5 patients in group 1 (table 2).

Histopathologically, group 1 patients had goblet cells in 3 patients, dysplastic changes in 3 patients, inflammatory cells infiltrations in 9 patients and *Helicobacter pylori* in only two patients (table 2).

No significant differences were found between GERD patients with or without Barrett's esophagus regarding any of the lower esophageal sphincter manometric parameters (table 3). However, group 1 patients had esophageal lower wave amplitude than group 2 patients ($P < 0.02$) but no differences in the duration of peristaltic contractions (table 4).

Table (1) History and clinical data of the studied patients:

Parameters	Group 1 (n=11)		Group 2 (n=29)		RR
	No	%	No	%	
Smoking	4	36.3	8	27.6	1.33
Dietary habits	6	54.5	13	44.8	1.32
Drugs	4	36.3	7	24.1	1.5
Obesity	5	45.5	13	44.8	1.73
Heart burn	4	36.3	18	62.1	-
Nausea and vomiting	3	27.3	9	31.1	-
Epigastric pain	6	54.5	12	41.4	-
Chest pain	4	36.3	5	17.2	-
Dysphagea	2	18.2	6	20.7	-

Table (2) Endoscopic and histopathological findings of the studied patients:

Findings	Group 1 (n=11)		Group 2 (n=29)	
	No	%	No	%
*Endoscopic				
-Reflux esophagitis	8	72.7	22	75.9
-Hiatus hernia	6	54.5	16	55.2
-Esophageal bleeding	5	45.4	0	0
-Esophageal mass	1	9.1	0	0
-Moniliasis	2	18.2	5	17.2
*Histopathological				
-Goblet cells	3	27.3	0	0
-Columnar epithelium	11	100	0	0
-Gastric cardiac cells	1	9.09	15	51.7
-Inflammation	9	81.8	21	72.4
-H. pylori	2	18.2	15	51.7
-Dysplasia	3	27.3	0	0

Table (3) LES manometric findings of the studied patients:

Parameters	Group 1 (n=11)		Group 2 (n=29)		P
	M	SD	M	SD	
Mean LES pressure	11.9	1.5	12.4	1.7	NS
Mean LES length	2.8	1.3	2.8	1.0	NS
LES relaxation reflex					
-complete	4 (36.3%)		9 (31.1%)		NS
-incomplete	7 (36.7%)		20 (68.9%)		NS

Table (4) Esophageal manometric findings of the studied patients:

	Group 1 (n=11)			Group 2 (n=29)		
	5cm	10cm	15cm	5cm	10cm	15cm
Distance above LES						
Mean amplitude	60.2 (37.1)	45.6 (21.2)	30.4 (16.2)	57 (33.2)	65.6 (26.3)	36.2 (20.1)
P-value				<0.05	<0.05	<0.02
Mean duration	3.38 (0.77)	3.2 (0.55)	3.25 (0.89)	3.65 (0.73)	3.33 (0.37)	3.22 (0.81)
P-value				NS	NS	NS

Figure (1): Endoscopic picture of the lower end of the esophagus showing irregular Z line with lower end esophagitis and superficial ulcers and bleeding involving most of circumference of the distal end of the esophagus.

Figure (2): Esophageal manometric study showing diminished amplitude of peristaltic contractions in the lower esophagus and complete relaxation of the lower esophageal sphincter in response to peristaltic contractions.

Figure (3): Section from lower esophageal endoscopic biopsy showing focal intestinal metaplasia with adjacent squamous epithelium (Magnification H & E X 40).

Figure (4): Section from lower esophageal endoscopic biopsy showing focal intestinal metaplasia with goblet cells (Magnification H & E X 400).

DISCUSSION

Barrett's esophagus is a metaplastic condition in which columnar epithelium is usually accompanied by variety of cells such as goblet cells, gastric and intestinal columnar cells, intermediate cells, Paneth cells and endocrine cells.¹⁰ The presence of goblet cells is the most useful feature for diagnosis of BE. However, the exact site of goblet cells is not that critical because the metaplastic changes denote an increased risk of neoplasia.⁴

Esophageal adenocarcinoma develops on a background of Barrett's esophagus. A number of risk factors have been linked to both conditions, including gastroesophageal reflux and smoking. There is an indication for a role of smoking in inducing DNA damage in esophageal mucosa.¹¹ Regarding the studied group 1, smoking was found in 4 patients, ulcerogenic drugs in 4 patients, bad dietary habits in 5 patients and obesity (BMI>30 kg/m²) in 5 patients. So, the findings of this study could be a considered as a new addition clarifying some of the risk factors (obesity, ulcerogenic drugs, smoking and bad

dietary habits; RR=1.73, 1.5, 1.33, 1.32 respectively) that could be incriminated in the pathogenesis of SSBE in GERD patients.

Symptoms of GERD (including heart burn, nausea and vomiting, epigastric pain, chest pain and dysphagia) are among the most common symptoms in patients with upper gastrointestinal diseases. Because many patients do not seek care for symptoms of GERD and many physicians do not specifically ask about them, these symptoms are usually underestimated.¹² In this study the clinical features of GERD are similar in the two studied groups. So these features could be considered of little significance and can not be used in distinguishing GERD patients with SSBE from those without BE. One exception is the heart burn which is less common in SSBE patients as the columnar epithelium may serve a protective function in guarding against symptoms of acid reflux.¹³ On the other hand, longer duration in years of chest pain and severe or very severe dysphasia were the symptoms characteristic of GERD associated with longer lengths of Barrette's mucosa.¹⁴

In our study, esophageal bleeding from the Barrett's epithelium and esophageal mass lesion were found to be more frequent in patients with SSBE patients. These complications could be explained by being the severe end spectrum of chronic GERD and subsequently SSBE.¹⁵ With the exceeding large number of patients with GERD, however, it appears cost effective to perform endoscopy for each patient with reflux.¹³ Upper gastrointestinal endoscopy and multiple mucosal biopsies from the lower esophagus are mandatory for columnar lined esophagus in the following patients with GERD; patients with a stricture, severe esophagitis or esophageal ulcer, patients with GERD and a reticular pattern of pseudomembrane found on barium esophagogram, patients with a long history (>10 years) of persistent reflux symptoms, patients with dysphagia, patients with bleeding due to severe lower end esophagitis and patients with reflux symptoms who are at increased risk for Barrett's metaplasia (e.g. with scleroderma, white men ...etc).¹⁶

SSBE could be suspected at en-

doscopy but the correlation between the endoscopist's prediction and the presence of specialized intestinal metaplasia is about 25%.¹⁷ Our study proved histopathologically the presence of SSBE in nearly one fourth of the studied patients. These results are in agreement with what is previously reported that, Although endoscopy is important to predict SSBE, yet, it is of little value in confirmation of intestinal metaplasia. But, with greater experience, an endoscopist is more likely to diagnose SSBE. This may be due to more accurate procurement of adequate tissue samples, which thereby results in a greater yield of histopathologic diagnosis.¹⁸

In spite of following the protocol of 4 quadrant biopsy technique during conduction of this study, goblet cells were found in only less than one third of GERD patients with SSBE. This could be due to sampling (the patient had BE but biopsy had missed the areas of intestinal metaplasia) and this suggestion is based on previous study that reported similar prevalence of dysplasia in patients with Barrett's esophagus (long-, short- segment

and intestinal metaplasia of the cardia).¹⁹

Thus, most biopsies from short segments of columnar appearing mucosa in the lower esophagus failed to reveal intestinal metaplasia, and repeated upper endoscopy with biopsy from the velvety-like redness must be warranted in patients with tongues of columnar mucosa in the distal esophagus. Of interest in this study is the presence of dysplastic changes in about one third of group 1 patients, including two cases without goblet cells. So, screening of chronic GERD patients with SSBE for the precancerous dysplastic changes in areas of intestinal metaplasia could be recommended even in the absence of goblet cells. On the other hand, recognized complications of Barrett's esophagus, such as ulceration, stricture, high-grade dysplasia, and adenocarcinoma, were previously reported as uncommon complications in SSBE.²⁰ The possible explanation for the relatively high prevalence of dysplasia in this study could be attributed to the small number of the included patients in addition to the relatively long duration of GERD symptoms

and fairly advanced disease.

Helicobacter pylori (*H. Pylori*) infection evident in esophageal biopsy specimens was found in only two patients in group 1 and 15 patients in group 2. This finding is in agreement with what is previously reported that, *H. pylori* infection appears to be uncommon in patients with BE.²¹ The low prevalence of *H. pylori* infection in the studied GERD patients could be attributed to repeated *H. pylori* eradication therapy among such chronic symptomatic patients. We asking for further studies that could address the possible impacts of *H. pylori* either on the pathophysiology or on the characterization of symptoms in GERD patients with or without SSBE.

A long history of GERD is more commonly associated with presence of dysphagia, delayed esophageal transit, severe esophagitis, presence of Barrett's esophagus, and impaired esophageal motility.²² In our study, no statistical differences were found between GERD patients with and without SSBE regarding LES pressure, length or reflex sphincter relaxation in response to esophageal peris-

talsis. On the other hand, the greater impairment of peristaltic wave amplitude found in group 1 patients could be attributed to a higher esophageal acid exposure and a longer duration of illness.²³⁻²⁴ Apart from impaired lower esophageal peristaltic wave amplitude in patients with SSBE, it is not surprising to find nearly similar other esophageal motility parameters in both studied groups as SSBE is considered as one of the serious complications of chronic severe GERD.

We can conclude that, although obesity and ulcerogenic drugs carry a high risk for development of SSBE in patients with GERD, SSBE cannot be diagnosed on the basis of symptoms, physical examination, or blood tests. So, endoscopic and histopathological examination of multiple lower esophageal biopsies from different sites are fundamental in all cases for accurate diagnosis of SSBE. Furthermore, histologic grading of esophageal biopsies (metaplasia, dysplasia, and adenocarcinoma) could represent the cornerstone of management in those patients. In addition, the characteristic physiological changes of

SSBE (greater impairment of peristaltic wave amplitude) could be attributed to a higher esophageal acid exposure and a longer duration of illness.

REFERENCES

- 1-Skinner DB, Walther KM, Ridell RH. (1983) : Barrett's esophagus: comparison of benign and malignant cases. *Ann Surg*; 198: 554-66.
- 2-Spechler SJ, Zeroogain JM, Antonioli DA, et al. (1994) : Prevalence of metaplasia at the gastro esophageal junction. *Lancet*; 344: 1533-6.
- 3-Spechler SJ and Goyla RK. (1996) : The columnar lined esophagus, intestinal metaplasia and Norman Barrett. *Gastroenterology*; 110: 614-21.
- 4-Winters CJ, Spurling TJ, Chobanian SJ, et al. (1987) : Barrett's esophagus: a prevalent, occult complication of gastro esophageal reflux disease. *Gastroenterology*; 92: 118-24.

- 5-Zentilin P, Reglioni S, Savarino V. (2003) : Pathophysiological characteristics of long- and short-segment Barrett's oesophagus. Scand J Gastroenterol Suppl.;(239):40-3.
- 6-Iascone C, De Meester TR, Little AG, et al. (1983) : Barrett's esophagus: functional assessment, proposed pathogenesis and surgical therapy. Arch Surg; 33: 801-10.
- 7-Hartmann D, Kudis V, Jakobs R, Riemann JF, Schilling D. (2006) : Course of erosive gastroesophageal reflux disease (GERD); a prospective examination under therapeutic daily life conditions with a mean follow-up of 6.5 years. J Gastroenterol. Oct;44(10):1039-42.
- 8-Falk GW. (2001) : Gastro esophageal reflux disease and Barrett's esophagus. Endoscopy; 33(2): 109-18.
- 9-Westhoff B, Brotze S, Weston A, McElhinney C, Cherian R, Mayo MS, Smith HJ, Sharma P. (2005) : The frequency of Barrett's esophagus in high-risk patients with chronic GERD. Gastrointest Endosc. Feb;61(2):226-31.
- 10-Krishnamurthy S and Dayal Y. (1995) : Pancreatic metaplasia in Barrett's esophagus. Am J Surg Pathol; 19: 1172-80.
- 11-Olliver JR, Hardie LJ, Gong Y, Dexter S, Chalmers D, Harris KM, Wild CP. (2005): Risk factors, DNA damage, and disease progression in Barrett's esophagus. Cancer Epidemiol Biomarkers Prev. Mar;14(3):620-5.
- 12-Shaheen N, Provenzale D. (2003) : The epidemiology of gastroesophageal reflux disease. Am J Med Sci. Nov;326(5):264-73.
- 13-Brandt MG, Darling GE, Miller L.

exposure and motility in patients with Barrett's esophagus. *Can J Surg.* Feb;47 (1):47-51.

14-Dickman R, Kim JL, Camargo L, Green SB, Sampliner RE, Garewal HS, Fass R. (2006) : Correlation of gastroesophageal reflux disease symptoms characteristics with long-segment Barrett's esophagus. *Dis Esophagus.*; 19(5):360-5.

15-Smid SD and Blackshaw LA. (2000) : Neuromuscular function of the human lower esophageal sphincter in reflux disease and Barrett's esophagus. *Gut* 2000; 46: 872-876.

16-Katzaka DA. (1995) : Columnar-lined (Barrett) esophagus. In: Haubrich WS, Schaffer F, Berk JE (Eds): *Gastroenterology*. Philadelphia, WB Saunders, P 468.

17-Eloubeidi MA and Provenzal D. (1999) : Does this patient

have Barrett's esophagus? The utility of predicting Barrett's esophagus at the index endoscopy. *American Journal of Gastroenterology*; 49: 4.

18-Padda S, Ramirez FC. (2001) : Accuracy in the diagnosis of short-segment Barrett's esophagus: the role of endoscopic experience. *Gastrointest Endosc.* Nov;54 (5):605-8.

19-Csendes A, Smok G, Burdiles P, Quesada F, Huertas C, Rojas J, Korn O. (2000) : Prevalence of Barrett's esophagus by endoscopy and histologic studies: a prospective evaluation of 306 control subjects and 376 patients with symptoms of gastroesophageal reflux. *Dis Esophagus.*; 13(1):5-11.

20-Donahue D, Navab F. (1997) : Significance of short-segment Barrett's esophagus. *J Clin Gastroenterol.* Sep;25(2):480-4.

- 21-Navab F. (2000) :** Barrett' esophagus: clinical implications. Med scope Gastroenterology; 1:16.
- 22-Chrysos E, Prokopakis G, Athanasakis E, Pechlivanides G, Tsiaoussis J, Mantides A, Xynos E. (2003) :** Factors affecting esophageal motility in gastro esophageal reflux disease. Arch Surg. Mar; 138(3):241-6.
- 23-Oberg S, DeMeester TR, Peters JH, Hagen JA, Nigro JJ, DeMeester SR, Theisen J, Campos GM, Crookes PF (1999) :** The extent of Barrett's esophagus depends on the status of the lower esophageal sphincter and the degree of esophageal acid exposure. J Thorac Cardiovasc Surg. 1999 Mar;117(3):572.
- 24-Byrne PJ, Mulligan ED, O'Riordan J, Keeling PW, Reynolds JV. (2003) :** Impaired visceral sensitivity to acid reflux in patients with Barrett's esophagus. The role of esophageal motility. Dis Esophagus.; 16(3):199-203.