A.S. Svintsitskyy, K.M. Revenok, G.A. Solovyeva, I.V. Korendovych

Bogomolets National Medical University, Kyiv

BARRETT'S ESOPHAGUS IN PATIENTS WITHOUT CLASSIC CLINICAL MANIFESTATIONS OF GASTROESOPHAGEAL REFLUX DISEASE

Summary

Barrett's esophagus (BE) is a complication of gastroesophageal reflux disease (GERD) that increases the risk of adenocarcinoma development. In patients with GERD symptoms, BE is diagnosed in 3-20%, however up to 40% of cases is revealed in patients without previous reflux symptoms. Our study showed that there are no significant differences and no clear correlation in complaints between patients with functional dyspepsia and BE. BE can be diagnosed in a significant percentage of asymptomatic patients and in patients without classic GERD complaints.

Keywords

Barrett's esophagus, gastroesophageal reflux disease, dyspepsia, esophagogastroduodenoscopy.

Introduction

Gastroesophageal reflux disease (GERD) is a consequence of antireflux barrier failure to protect the esophagus from frequent and volume gastroesophageal refluxate. Singly gastroesophageal reflux is not a disease but a physiological process. First definition of GERD was published in 2006, after the approval of Montreal Consensus. In accordance with this GERD is defined as «a condition that develops due to reflux of gastric contents, which causes «troublesome» symptoms and/or complications». The disease significantly impairs patients' quality of life. The incidence of GERD is almost identical for men and women, but the development of esophagitis and Barrett's esophagus (BE) is revealed more often in men. Although GERD is an extremely rare cause of death, this pathology is associated with the emergence of a significant number of complications, such as esophageal ulcers (5%), peptic strictures of the esophagus (4-20%) and Barrett's esophagus (8-20%) [21, 25].

BE is defined as a condition in which abnormal cylindrical epithelium, which is prone to malignancy, replaces stratified squamous one that normally covers the distal part of the esophagus [16]. The importance of BE diagnosis is that it increases the risk of adenocarcinoma development in future.

This pathology was named after the Australian surgeon Norman Barrett, who first drew attention to the presence of columnar epithelium in the esophagus and described this phenomenon [1].

The prevalence of BE in the population of Western Europe and the United States according to various studies is 0,9-10% [13, 19]. Interesting is the fact that BE is rare among African-Americans and Asians. Men of white race, aged 50-55 years are mostly affected [18]. BE is diagnosed in 3-20% of patients with GERD symptoms [7]. However up to 40% of esophageal adenocarcinoma cases are revealed in patients without previous reflux symptoms [23]. When analyzing data on the prevalence of BE due to the results of autopsy, it was found that the frequency is 16 times higher of clinically diagnosed ones [14].

Endoscopic evaluation of BE distinguishes long (when metaplastic epithelium extends over 3 cm above gastroesophageal junction) or short segment lesion (if metaplasia is less than 3 cm) of the esophagus [20]. Recently another classification, Prague C and M criteria, was proposed. It determines the circumference (C) and maximum length (M) of metaplasia [24].

Pathogenesis of BE is not studied yet. Progenitor cells that lead to Barrett's metaplasia are not known. According to one hypothesis metaplasia is the result of esophageal squamous epithelium damage in GERD, exposing multipotent stem cells of the basal layer to the gastric juice, which in its turn stimulates their differentiation into columnar cells [2]. Probably Cdx and BMP-4 genes, which are responsible for the differentiation of intestinal epithelial cells, play an important role in metaplasia development [22]. Recently the connection between BE and HLA-B7 was found as well [15]. Also, the study of telomere length in leukocytes revealed that shorter telomeres are associated with increased risk of esophageal adenocarcinoma (95% CI 1,35-8,78; p = 0,009) [9].

Risk factors for GERD, BE and esophageal adeno-

carcinoma development include obesity, *H.pylori,* smoking and alcohol consumption, delayed healing of the damaged epithelium of the esophagus, damage to the esophagus caused by bile acids and pancreatic enzymes reflux. Today there is a dramatic increase in the incidence of obesity in Europe and in the USA, which correlates with a similar increase in BE prevalence. In addition to increased intra-abdominal pressure, there are also increased levels of proproliferative hormones in serum such as insulin-like growth factor I (IGF I) and leptin, and reduced levels of antiproliferative hormone adiponectin, which may contribute to carcinogenesis in BE patients [8, 12]. The relationship between smoking and BE is amplified with increased number of cigarettes (about 20 pack-years) [3].

Objective. To assess the relationship between BE and dyspeptic symptoms.

Materials and Methods

283 patients that were referred to gastroenterologist were consecutively screened by clinical interview in the State Institution «Republican Clinical Hospital of the Ministry of Health of Ukraine» and Universal Clinic «Oberig». Inclusion criteria were the presence of complaints that were characteristic for dyspepsia, which occurred after a meal. Exclusion criterion was the presence of classic GERD symptoms: heartburn and regurgitation, which occurred after a meal. All patients underwent esophagogastroduodenoscopy (EGD) with NBI (narrow band imagining), chromoscopy, endoscopic scanning microscopy (×115), inversion in stomach, and précised biopsy with the next histological study of the material. Changes in esophagus were evaluated according to Prague C and M criteria and histological examination of biopsy samples. The presence of *H.pylori* was assessed using 2 methods: rapid urease test and morphological evaluation of tissue samples.

Statistical analysis was made by evaluation of significance between two groups on the basis of z-criterion. Odds ratio (OR) with 95% confidence intervals (CI) and validity criterion p with an error limit less than 5% (p<0,05) were estimated for all the characteristics. Statistical analysis of data was performed using Stata 11 software package.

Results and discussion

45 patients were enrolled into the study. 2 were excluded because of the refusal to participate. The average age of patients with BE was 37 ± 4 years. Among them: men - 29 (64,4%), women - 16 (35,6%). The control group was formed of 45 patients with clinically diagnosed functional dyspepsia according to the Rome III criteria (2006). The groups were comparable in age and sex ratio.

Esophageal metaplasia of gastric and intestinal type of varying degree was found in all patients of the study group. The use of NBI resulted in better visualization of esophageal and gastric mucosa. According to the research conducted by Japanese scientists, with the use of NBI and iodine chromoendoscopy the incidence of squamous islands detection (short segment BE) was increased to 75%, compared with white light endoscopy - 48% respectively [6].

28 (62,2%) patients of the study group complained of postprandial feeling of heaviness in the epigastrium, compared to the control group - 37 (82,2%) (OR 0,36; 95% CI 0,13-0,94; p = 0,04).

32 (71,1%) patients of the main group and 33 (73,3%) of the control one had moderate pain in the epigastric region and left upper quadrant, that in most cases decreased postprandial (OR 0,89; 95% CI 0,36-2,25; p = 0,80).

17 (37,7%) patients of the main group and 24 (53,3%) of the control one noted epigastric pain in the right upper quadrant that usually occurred within 20 minutes after a meal (OR 0,53; 95% CI 0,23-1,23; p = 0,14).

15 (33,3%) subjects of the main group and 20 (44,4%) of the control one were bothered by recurrent air belching (OR 0,63; 95% CI 0,27-1,47; p = 0,28).

8 (17,7%) of the study and 12 (26,6%) of the control group patients noted periodic morning sickness without vomiting claims (OR 0,59; 95% CI 0,22-1,63; p = 0,31).

1 (2,2%) patient of the main group had no complaints at all (EGD was performed according to preventive inspection program). There were no patients without complaints in the control group (0%) (OR 3,07; 95% CI 0,12-77,33; p = 0,49). The results are presented in the table.

Table. Comparison of complaints in patients of the study and the control groups

Complaints	Study group (n=45)		Control group (n=45)				
	n-value	*%*	*n-value*	*%*	*Odds ratio*	*95% CI*	*p-value*
Postprandial feeling of heaviness in the epigastrium	28	62,2	37	82,2	0,36	0,13-0,94	0,04
Moderate pain in the epigastric region and left upper quadrant	32	71,1	33	73,3	0,89	0,36-2,25	0,80
Epigastric pain in the right upper quadrant	17	37,7	24	53,3	0,53	0,23-1,23	0,14
Air belching	15	33,3	20	44,4	0,63	0,27-1,47	0,28
Periodic morning sickness	8	17,7	12	26,6	0,59	0,22-1,63	0,31
The absence of complains	1	2,2	0	0	3,07	0,12-77,33	0,49

Usually BE occurs in patients with symptoms of GERD or its complications. Patients complain of heartburn or acid regurgitation that lasts for at least a decade or more. In a prospective nonrandomized study of 35 patients with BE low-grade dysplasia, only 63% presented typical symptoms of GERD and in 15% of cases predominant symptom was not defined [5].

In a large prospective study of Pro-GERD (2004), that assessed risk factors for GERD for several years 6250 patients were recruited. BE was diagnosed in 11% of subjects with a long history of reflux [17]. In the open parallel group study on therapeutic/surgical management of GERD-LOTUS – which lasted for three years, BE was diagnosed in 10,8% of 412 patients with chronic reflux symptoms [11].

According to some authors, about 40% of patients with BE-associated esophageal adenocarcinoma have reflux symptoms. The frequency of occurrence and the intensity of symptoms is less in patients with uncomplicated BE than in those who have been diagnosed with esophagitis without BE. There is no clear correlation of symptoms with the onset or progression of BE. This may be due the changed the perception of pain. Therefore, in case of repeated gastroesophageal reflux or other factors that damage the lining of the esophagus, the symptoms did not occur at all or with minimal manifestations [5, 16].

37 (82,2%) patients of the main group were infected with *H.pylori*. In the control group, infection was detected in 41 (90,2%) patient (OR 0,45; 95% CI 0,13-1,62; p = 0,22).

Although opinions about the involvement of *H.pylori* in the development of BE and esophageal adenocarcinoma differ, most studies did not confirm the role of bacteria. According to the XXIV Meeting of the International Working Group on Helicobacter pylori and Related Bacteria in Chronic Digestive Inflammation and Gastric Cancer (Dublin, Ireland, 2011) and Management of Helicobacter pylori infection – the Maastricht IV / Florence Consensus Report, *H.pylori* has no effect on the severity, frequency of symptoms and the effectiveness of therapy for GERD, and epidemiological studies demonstrate a negative association between the prevalence of *H.pylori*, GERD and esophageal adenocarcinoma [10]. Several studies have shown that *H.pylori* infection may protect against neoplasia and BE, perhaps by reducing the secretion of gastric acid in the presence of bacteria and atrophic gastritis [4].

In 5 (11,2%) patients of the study group erosive esophageal mucosa defects were found, that were assessed due to the Los Angeles Classification of Gastroesophageal Reflux Disease: 4 patients – LA-A, 1 patient – LA-B.

Conclusions

Significant differences in complaints between two groups were not found (p>0,05).

BE was diagnosed in a significant percentage of asymptomatic patients and in patients without classic GERD symptoms. According to the data, there is no clear correlation between the presence of dyspeptic complaints and BE.

The presence of a large number of diagnosed BE cases may be explained by the use of modern technologies, EGD with NBI-chromoscopy, endoscopic scanning microscopy (×115), and inversion in the stomach.

The absence of GERD symptoms does not guarantee the absence of metaplastic changes in the esophagus. Both metaplasia and dysplasia are considered to be precancerous conditions. But on this stage it is still possible to prevent the development of cancer by removing these cells. Although to correctly identify the affected areas is rather problematic. They can be missed during endoscopic examination of the patient, or by taking biopsy samples from unaffected parts of the esophagus. As a result – an untimely made diagnosis and annual increase in prevalence and incidence of adenocarcinoma.

References

1. *Barrett N.R. Chronic peptic ulcer of the oesophagus and "oesophagitis" / N.R.Barrett // Br. J. Surg. - 1950. - Vol. 38. - P. 175-182.*
2. *Bone marrow progenitor cells contribute to esophageal regeneration and metaplasia in a rat model of Barrett's esophagus / G.Sarosi, G.Brown, K.Jaiswal [et al.] // Dis. Esophagus. - 2008. - Vol. 21. - P. 43-50.*
3. *Cigarette smoking increases risk of Barrett's esophagus: an analysis of the Barrett's and Esophageal Adenocarcinoma Consortium / M.B.Cook, N.J.Shaheen, L.A.Anderson [et al.] // Gastroenterology. - 2012. - Vol. 142. - P. 744-753.*
4. *Delaney B. Helicobacter pylori and gastro-oesophageal reflux disease / B.Delaney, K.McColl // Aliment. Pharmacol. Ther. - 2005. - Vol. 22. - P.32-40.*
5. *Efficacy of Nissen fundoplication versus medical therapy in the regression of low-grade dysplasia in patients with Barrett esophagus: a prospective study / M.Rossi, M.Barreca, N.de Bortoli [et al.] // Ann. Surg. - 2006. - Vol. 243. - P. 58-63.*
6. *Endoscopic characteristics of short-segment Barrett's esophagus, focusing on squamous islands and mucosal folds / N.Ishimura, Y.Amano, J.D.Sollano [et al.] // J. Gastroenterol. Hepatol. - 2012. - Vol. 27. - P. 82-87.*
7. *Gerson L.B. Prevalence of Barrett's esophagus in asymptomatic individuals / L.B.Gerson, K.Shetler, G.Triadafilopoulos // Gastroenterology. - 2002. - Vol. 123. - P. 461-467.*
8. *Hampel H. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications / H.Hampel, N.S.Abraham, H.B.El-Serag // Ann. Intern. Med. - 2005. - Vol. 143. - P. 199-211.*
9. *Leukocyte telomere length predicts cancer risk in Barrett's esophagus cancer / R.A.Risques, T.L.Vaughan, X.Li [et al.] // Epidemiol. Biomarkers. Prev. - 2007. - Vol. 16. - P. 2649-2655.*
10. *Management of Helicobacter pylori infection - the Maastricht IV/ Florence Consensus Report / P.Malfertheiner, F.Megraud, C.A.O'Morain [et al.] // Gut. - 2012. - Vol.61. - P. 646-664.*

11. *Medical or surgical management of GERD patients with Barrett's esophagus: the LOTUS trial 3-year experience / S.E.Attwood, L.Lundell, J.G.Hatlebakk [et al.] // Gastrointest. Surg. - 2008. - Vol. 12. - P. 1646-1654.*
12. *Obesity increases oesophageal acid exposure / H.B.El-Serag, G.A.Ergun, J.Pandolfino [et al.] // Gut. - 2007. - Vol. 56. - P. 749-755.*
13. *Prevalence of Barrett's esophagus in the general population: an endoscopic study / J.Ronkainen, P.Aro, T.Storskrubb [et al.] // Gastroenterology. - 2005. - Vol. 129. - P. 1825-1831.*
14. *Prevalence of columnar-lined (Barrett`s) esophagus. Comparision of population - based clinical and autopsy findings / A.J.Cameron, A.R.Zinsmeister, D.J.Ballard [et al.] // Gastroenterology. - 1990. - Vol. 99. - P. 918-922.*
15. *Rajendra S. Human leucocyte antigen determinants of susceptibility to Barrett's oesophagus in Asians - a preliminary study / S.Rajendra, R.Ackroyd // Aliment. Pharmacol. Ther. - 2005. - Vol. 21. - P. 1377-1383.*
16. *Rao M. Natural history of Barrett's esophagus / M.Rao, S.E.Attwood // World J. Gastroenterol. - 2012. - Vol. 18. - P. 3483-3491.*
17. *Risk factors of gastroesophageal reflux disease: methodology and first epidemiological results of the ProGERD study / M.Kulig, M.Nocon, M.Vieth [et al.] // J. Clin. Epidemiol. - 2004. - Vol. 57. - P. 580-589.*
18. *Sampliner R.E. Epidemiology, pathophysiology and treatment of Barrett's esophagus: reducing mortality from esophageal adenocarcinoma / R.E.Sampliner // Med. Clin. North Am. - 2005. - Vol. 89. - P. 293-312.*
19. *Screening for Barrett's esophagus in colonoscopy patients with and without heartburn / D.K.Rex, O.W.Cummings, M.Shaw [et al.] // Gastroenterology. - 2003. - Vol. 125. - P. 1670-1677.*
20. *Sharma P. Short segment Barrett's esophagus. The need for standardization of the definition and of endoscopic criteria / P.Sharma, T.G.Morales, R.E.Sampliner // Am. J. Gastroenterol. - 1998. - Vol. 93. - P. 1033-1036.*
21. *Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management / Edited by M.Feldman, L.S.Friedman, L.J.Brandt. - 9th ed. - Saunders, 2010. - 2480 p.*
22. *Souza R.F. Acid, bile and CDX: The ABCs of making Barrett's metaplasia / R.F.Souza, K.Krishnan, S.J. Spechler // Am. J. Physiol. Gastrointest. Liver. Physiol. - 2008. - Vol. 295. - P. 211-218.*
23. *Spechler S.J. Barrett's esophagus. Prevalence of Barrett's esophagus in asymptomatic individuals / S.J.Spechler // N. Engl. J. Med. - 2002. - Vol. 346. - P. 836-842.*
24. *The development and validation of an endoscopic grading system for Barrett's esophagus: The Prague C & M criteria / P.Sharma, J.Dent, D.Armstrong [et al.] // Gastroenterology. - 2006. - Vol. 131. - P. 1392-1399.*
25. *The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus / N.Vakil, S.V.van Zanten, P.Kahrilas [et al.] // Am. J. Gastroenterol. - 2006. - Vol. 101. - P. 1900-1943.*

СТРАВОХІД БАРРЕТТА В ПАЦІЄНТІВ БЕЗ КЛАСИЧНИХ КЛІНІЧНИХ ПРОЯВІВ ГАСТРОЕЗОФАГЕАЛЬНОЇ РЕФЛЮКСНОЇ ХВОРОБИ

А.С. Свінціцький, К.М. Ревенок, Г.А. Соловйова, І.В. Корендович

Резюме

Стравохід Барретта (СБ) є ускладненням гастроезофагеальної рефлюксної хвороби (ГЕРХ), що збільшує ризик розвитку аденокарциноми. СБ діагностується в 3-20% пацієнтів із симптомами ГЕРХ, проте до 40% випадків виявляються в безсимптомних хворих. Дане дослідження не виявило істотних відмінностей та чіткої кореляції між наявністю диспепсичних скарг у пацієнтів із функціональною диспепсією та СБ. СБ може бути діагностований у значного відсотка безсимптомних хворих та в осіб без класичних симптомів ГЕРХ.

Ключові слова: стравохід Барретта, гастроезофагеальна рефлюксна хвороба, диспепсія, езофагогастродуоденоскопія.