ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN-POLONIA
VOL. LXI, N1, 7 SECTIO D 2006

Chair and Department of Gastroenterology, Medical University of Lublin

BEATA KASZTELAN-SZCZERBIŃSKA, MARIA SŁOMKA, KRZYSZTOF CELIŃSKI, HALINA CICHOŻ-LACH, AGNIESZKA MĄDRO

Barrett's esophagus – present knowledge

Barrett's esophagus (BE) was first described by Norman Barrett in 1950. The definition of this pathology has been dynamically changing throughout the last two decades. Initially only the presence of columnar epithelium in the esophagus was stressed. At present BE is diagnosed when intestinal metaplasia (i.e. the presence of minimum 2 goblet cells) is observed in columnar epithelium of the esophagus. Barrett's epithelium increases the risk of esophageal adenocarcinoma about 30–50 times compared to the healthy population; however, esophageal cancer will develop in only 3–7% of these patients. The recent studies demonstrate that annual carcinoma incidence in patients with BE is 0.5–1% (7, 21, 24). In the majority of BE patients cancer remains undetected and adenocarcinoma arising from it is diagnosed in its advanced stage when first clinical symptoms – dysphagia, weight loss – develop and when it is too late for radical treatment. The analysis of epidemiological data of the last two decades have revealed that the incidence of BE-associated adenocarcinoma has been increasingly growing in USA and Western Europe (21). In Poland, carcinoma of the esophagus is the 13th malignant neoplasm in men and 33rd in women. Nevertheless, an increase in adenocarcinoma incidence in our country is not so rapid (19).

PATHOGENESIS OF BARRETT'S ESOPHAGUS

Barrett's esophagus is a complication of gastroesophageal reflux disease. It develops in about 10% of patients with clinically diagnosed BE (7, 21). It results from chronic exposure of the stratified squamous epithelium to gastric acid and bile reflux, which damages the normal esophageal epithelium and leads to inflammation. Due to long-time exposure to aggressive effects of the above factors, the injured epithelium does not regenerate and is replaced by a new abnormal epithelium called Barrett's epithelium. This epithelium contains goblet cells and produces mucus, similarly to the gastric epithelium. Therefore, its occurence in the esophagus is likely to be a protective response of the organism to chronic irritation of this region caused by gastro-esophageal reflux. To date it remains unclear why Barrett's epithelium develops only in some patients with esophageal reflux disease (15).

At present a hypothesis about the role of free radical processes in the pathogenesis of reflux disease and BE arouses much interest. Elevated levels of reactive oxygen species (ROS) were noted in the esophageal wall in esophagitis and BE. Moreover, a positive correlation between these levels and inflammation severity was observed. However, it has not been explicitly demonstrated that free radical scavengers may prevent the progression of BE to adenocarcinoma (8).The results of studies carried out by Piazuelo et al. (17) on the animal model seem to support the above. Furthermore, Carlson et al. (3) associate adverse effects of gastro-esophageal reflux with free radical processes. Hydrochloric acid is supposed to induce oxidative damage of DNA via lipid peroxidation–then the cell cycle is stopped in G1 or G2 phase in order to remove the abnormal genetic material. However, if additionally the mutation of gene p53 occurs, the control of the cell cycle is lost and instead of apoptosis the neoplastic progression of cell lesions develops.

Intensive discussions are also focused on the role of nitrogen oxide (NO) in the pathogenesis of BE and adenocarcinoma. In the esophageal lumen the concentration of dietary nitrites is high. In the region of entering the stomach nitrites are converted into NO which is likely to be involved in neoplasia of the oesophago-gastric junction and gastric cardia. The studies conducted by Suzuki et

al. (22) demonstrated high levels of nitrites in the saliva and proximal esophagus and their rapid decrease by 98% after entering the BE segment which was exposed to gastric acid reflux. The results of monitoring pH and NO concentration within Barrett's epithelium showed that gastric acid reflux into the BE segment immediately resulted in an extremely high No level in the esophageal lumen. Such an exposure of BE may potentially trigger neoplastic progression, therefore further studies about the effects of NO synthesis inhibitors are planned.

CRITERIA OF DIAGNOSIS AND DIVISION OF BARRETT'S ESOPHAGUS

The diagnosis of BE is based on two main examinations: endoscopy of the upper digestive tract and histopathological evaluation of esophageal biopsy specimens. The diagnostic criteria include: 1) in gastroscopy the Z line does not coincide with the upper border of gastric folds, 2) in the distal esophageal specimens the columnar epithelium is present with intestinal metaplasia within it (minimum 2 goblet cells); when additionally dysplasia occurs, there is a risk of neoplastic transformation (7, 19, 21). One should be aware that accurate diagnosis of this pathology is strongly associated with proper cooperation between the physician conducting endoscopy and pathomorphologist evaluating the material as well as their accuracy. BE is divided according to the distance between the Z line joining the two epithelia and the upper border of gastric folds. The distance is measured on the endoscopic corpus in relation to the ? line. The following kinds of BE are distinguished: a) classical BE – when the distance between the Z line and upper border of gastric folds is at least 3cm; b) short BE – when the above distance is shorter than 3 cm (7, 20, 21).

PROTOCOL OF DIAGNOSTIC BIOPSY IN BE

It should be remembered that once BE has been diagnosed the only possible objective evaluation of the risk of dysplasia and adenocarcinoma is regular endoscopic surveillance supplemented by numerous biopsy specimens for histopathological examination. The directives of the American College of Gastroenterology define the rules of conducting diagnostic biopsies in patients with the diagnosis of BE to obtain good quantity and quality of specimens(19, 20). The strategy includes: 1) collection of specimens from the whole length of BE, every 1–2 cm, starting 1 cm below the esophago-gastric junction and ending 1 cm above the Z line; 2) collection of 4 specimens from every level; 3) collection of additional specimens from every suspicious focal lesion; 4) collection of specimens with the biggest available forceps.

The optimal time of collection is the period in which the inflammation features are absent (when they are present the patient is treated with proton pump inhibitors and the examination is repeated since the inflammatory process may be accompanied by the picture of cellular atypia). Moreover, proper surveillance involves close cooperation with the histopathologist – an expert in BE diagnosis.

METHODS IMPROVING DIAGNOSTIC EFFECTIVENESS IN BE

The majority of dysplastic regions in BE remain macroscopically invisible during standard endoscopic diagnostic procedures. The identification of dysplastic regions is likely to be hindered by concomitant inflammatory lesions and/or earlier ablation therapy. Therefore new methods are being searched for to increase the diagnostic effectiveness. The recent reports (2, 6, 21) reveal the usefulness of the following methods: 1) magnification endoscopy – possible magnification of the randomly chosen area of the mucosa using smaller visual field; 2) high resolution endoscopy – increases contrast within the elements of mucosa without any change in visual field; 3) chromoendoscopy – endoscopic evaluation after staining the mucosa surface (methylene blue, indigo carmine) accentuating the difference in the mucosa structure when dysplasia or intestinal metaplasia is present; 4) laser-induced tissue fluorescence – autofluorescence of the tissue due to laser stimulation of endogenous molecules accumulated in dysplastic regions (NADH, FAD, porphyrins); 5) photodynamic diagnostics – after administering the substances accumulating in the dysplastic region (e.g. 5-amino-laevulinic acid) and illuminating the tissue with the laser, the characteriscic fluorescence is observed; 6) optical coherence tomography – reflection of infrared

light from tissue microstructures enables us to obtain the image of the mucosa section and to visualize its individual layers; 7) immunological staining of esophageal specimens for cytokeratins CK7, CK20 (structural proteins of the cell cytoplasm)–BE is characterized by strong epithelium staining for CK7 and poor one for CK20 (9).

Since there are only few conducted and published studies concerning the effects of the above-mentioned diagnostic techniques in BE patients their objective evaluation is impossible and therefore their use in routine medical practice is limited. Moreover, the reports published in 2003 demonstrating that methylene blue and light waves may damage epithelial cell DNA and increase the risk of neoplasia (16) suggest that they should be used with caution.

BIOMARKERS FOR IDENTIFICATION OF PATIENTS WITH HIGHER RISK OF PROGRESSION TO ADENOCARCINOMA IN BARRETT'S EPITHELIUM

For many years the risk of carcinoma in BE patients has been determined exclusively on the basis of the grade of dysplasia in the esophageal epithelium. However, some relevant reservations were expressed concerning the accuracy and repeatability of histopathological evaluation due to the fact that pathologists differently interpreted the progression of dysplastic lesions. This suggested that additional biomarkers deciding about the risk of carcinoma should be used. To date many studies have been published evaluationg over 60 biomarkers (18) among which only a few may raise hope and interest of gastroenterologists. These include: 1) mutations of suppressor genes p16 and p53, 2) cell tetraploidy and aneuploidy – abnormalities of cell DNA determined with flow cytometry, 3) hyperexpression of cyclooxygenase-2 – decreases apoptosis, induces angiogenesis, favours metastases, 4) longer segment of Barrett's epithelium.

Some important information for defining the way of surveillance of BE patients may be provided by genetic examinations. The signals of increased carcinoma risk in BE patients are genetic disorders within p16 and p53 leading to dysfunction of these suppressor genes. Mutations of p16 are the earliest disorders known so far developing in the metaplasia-Barrett's dysplasia sequence. They were demonstrated in over 85% of BE cases.The observations show that the number of mutations of this gene increases with an increase in the length of Barrett's epithelium segment – which led to a hypothesis stressing the importance of mutations of this gene in the expansion of Barrett's cells along the esophagus. Moreover, this gene is likely to be involved in the development and spread of additional gene mutations (11, 18). P 53, on the other hand, is the first discovered gene which controls the cell cycle. Its role is to prevent the divisions of cells with genetic errors, which in turn prevents subsequent expansion and evolution of abnormal cell clones. The abnormalities of this gene were found in 95% of patients with carcinoma arising from BE (11, 18). Mutations of the above-mentioned genes are the first and earliest signals of increased neoplasia risk in BE patients.

Great diagnostic hopes are also associated with flow cytometry evaluation of biopsy specimens as everything indicates that this method is more objective than histopathological examinations. One of the large studies assessing the usefulness of flow cytometry showed 94% uniformity of interpretation of cell DNA contents in various laboratories. The method enables us to define the percentage of cells in different cell cycle phases on the basis of DNA content. Normally in the biopsy from Barrett's epithelium the majority of cells remain in G0/G1 phase and have diploid DNA content. The patients in whom flow cytomewtry histograms reveal an increase in cell fraction with tetraploidy over 6% and aneupliody of cell population have higher risk of the development of dysplasia and progression to adenocarcinoma. The cell disorders in Barrett's epithelium are detected by flow cytometry before the development of dysplasia and adeno-carcinoma when histopathological findings remain negative. This allows to distinguish the group of patients requiring endoscopic surveillance at shorter intervals (7, 11, 18, 21).

SURVEILLANCE AND TREATMENT OF PATIENTS WITH BARRETT'S ESOPHAGUS ACCORDING TO THE GRADE OF DYSPLASIA

Patients with the diagnosis of BE should be under endoscopic and histopathological surveillance at intervals depending on the presence and grade of dysplasia (4, 7, 19). The need of follow-ups in such patients is favoured by the fact that the grade of adenocarcinoma of the

esophagus detected during such examinations is lower than in the cases in which carcinoma is detected when clinical symptoms are already found, which obviously increases the chances of effective treatment. Even one abnormal cell found outside the basilar membrane (in lamina propria) is enough to diagnose carcinoma. On the basis of clinical data the following management is recommended: 1) lack of dysplasia – confirmed in 2 successive gastroscopies with biopsy specimens collected according to the surveillance protocol → gastroscopy every 3 years; 2) low-grade dysplasia – confirmed in 2 gastroscopies with biopsy specimens collected according to the surveillance protocol→ gastroscopy every 6 months through one year, then every year; 3) high-grade dysplasia – should be confirmed by 2 histopathology experts, biopsy every 1cm and individualization of management recommended: endoscopic surveillance every 3 months or esophagectomy or ablation therapy.

TREATMENT OF BARRETT'S ESOPHAGUS

The detection of BE does not necessitate specific treatment and the goals of therapy are identical as those in reflux disease: healing of the inflammatory lesions of the mucosa and maintaining its normal condition. Current therapy of reflux disease and BE aims mainly at the reduction of exposure of the esophagus to gastric acid (21).

Pharmacotherapy. In order to suppress chronic esophagitis large doses of proton pump inhibitors (PPIs) are used. It should be stressed that treatment should also involve the BE patients without complaints as they are found to have hidden occilt and chronic reflux disease. The recent studies reveal that cyclooxygenase-2 (COX-2) is involved in esophageal carcinogenesis. The BE patients show hyperexpression of COX-2. This led to the studies evaluating the role of COX-2 inhibitors in the therapy of reflux disease of the esophagus. The currently conducted randomized study AspECT is to involve 900 patients , aged 45–70 with the diagnosis of classical Barrett's esophagus (≥3 cm). The aim of the study is to determine the optimal dose of proton pump inhibitors (esomeprasol 20 mg vs. 80 mg/day) and the effects of therapy combined with aspirin (300 mg/day). Endoscopic evaluation is performed after 2, 4, 6 and 8 years (11). The results of other studies, both in animal and human models, suggest that the use of selective COX-2 inhibitors decreases the release of prostaglandin E2 and cell proliferation in BE patients. PPIs decrease the exposure of distal esophagus to gastric acid and bile – this effect together with the suppression of reflux disease symptoms is likely to decrease COX-2 expression and the release of inflammation mediators. Therefore the therapy with COX-2 inhibitors combined with the treatment inhibiting gastric acid secretion may be a promising kind of chemoprevention of dysplasia and adenocarcinoma of the esophagus (7, 11, 21).

Surgical treatment. An alternative treatment of reflux disease in patients with BE may be antireflux surgery. Unfortunately, meta-analyses and epidemiological studies demonstrate similar adenocarcinoma prevalence in patients undergoing pharmacological and surgical treatment (0.5% vs. 0.4%) (4). Furthermore, not all patients undergo surgical procedures as they carry some risk. The results of Nissen fundoplication, the procedure most frequently used in BE are not satisfying: 20% of patients with persistent symptoms of reflux disease, 21% with recurrent hernias, 19% with abnormal pH of the esophagus, 8% requiring reoperation (10). An alternative to classical surgical procedures are new endoscopic techniques approved by FDA: Strett's procedure (application of radiowave-frequency energy) (5) and Endocinch (endoscopic suture) (13).

Endoscopic ablation therapy. The risk of esophageal carcinoma increases when the histopathological examination demonstrates high-grade dysplasia and therefore many experts recommend to eradicate these regions by esophagectomy or endoscopic ablation. The latter is an attractive alternative to surgical resection due to its lower mortality (13). Moreover, this procedure is better than pharmacological treatment or antireflux surgery as it destroys Barrett's epithelium! Many ablation techniques are used, the most popular ones include: 1) thermal ablation: multipolar electrocoagulation, laser, argon plasmic coagulation (APC) (7, 21); 2) photodynamic therapy (14); 3) mucozectomy – enables local therapy providing large tissue samples for

histopathology, which is an additional advantage of this intervention (12).

Enthusiasm for ablation of Barrett's epithelium with features of dysplasia was quenched when intestinal metaplasia and adenocarcinoma were found under a new, macroscopically normal stratified squamous epithelium (23). Although the BE patients without dysplasia and even those with low-grade dysplasia should not be treated by the methods of endoscopic ablation except for the examination protocol, the initial observations show that these methods may be potentially important in the treatment of patients with high-grade dysplasia and early adenocarcinoma of the esophagus (12, 14).

One should be aware that the therapy should not stop the surveillance of patients and after ablation of Barrett's epithelium the orientation points may be destroyed, which makes such a surveillance more difficult. In order to assess the effectiveness of ablation techniques in BE patients further detailed studies covering at least the 5-year surveillance period are needed to be carried out in highly experienced centres.

REFERENCES

1. Barrett N.R.: Chronic peptic ulcer of the oesophagus and "oesophagitis". Br. J. Surg., 38, 175, 1950.
2. Bruno M.J.: Magnification endoscopy, high resolution endoscopy, and chromoscopy; towards a better optical diagnosis. Gut, 52, iv 7, 2003.
3. Carlson N. et al.: Acid suppression therapy may not alter malignant progression in Barrett's metaplasia showing p53 protein accumulation. Am. J. Gastroenterol., 97, 1340, 2002.
4. Corley D.A. et al.: Surveillance and survival in Barrett's adenocarcinomas: a population-based study. Gastroenterology, 122, 633, 2002.
5. Corley D.A. et al.: Improvement of gastroesophageal reflux symptoms after radiofrequency energy: a randomized, sham-controlled trial. Am. J. Gastroenterol., 98, 1921, 2003.
6. Egger K. et al.: Biopsy surveillance is still necessary in patients with Barrett's oesophagus despite new endoscopic imaging techniques. Gut, 52, 18, 2003.
7. Falk G.: Barrett's esophagus. Gastroenterology, 122, 1569, 2002.
8. Farhadi A. et al.: Reactive oxygen species: are they involved in pathogenesis of GERD, Barrett's esophagus, and the latter's progression toward esophageal cancer? Am. J. Gastroenterol., 97, 22, 2002.
9. Flucke U. et al.: Immunoreactivity of cytokeratins (CK7, CK20) and mucin peptide core antigens (MUC1, MUC2, MUC5AC) in adenocarcinomas, normal and metaplastic tissues of the disatal oesophagus, oesophago-gastric junction and proximal stomach. Histopathology, 43, 127, 2003.
10. Hofstetter W.L. et al.: Long-term outcome of antireflux surgery in patients with Barrett's esophagus. Ann. Surg., 234, 532, 2001.
11. Jankowski J., Sharma P.: Review article: approaches to Barrett's oesophagus treatment- the role of proton pump inhibitors and other interventions. Aliment Pharmacol. Ther., 19, 54, 2004.
12. Lambert R.: Endoscopic mucosectomy: an alternative treatment for superficial esophageal cancer. Recent Results in Cancer Research, 155, 183, 2000.
13. Machmood Z. et al.: Endocinch therapy for gastro- oesophageal reflux disease: a one year prospective follow up. Gut, 52, 34, 2003.
14. May A. et al.: Local endoscopic therapy for intraepithelial high- grade neoplasia and early adenocarcinoma in Barrett's oesophagus: acute-phase and intermediate results of a new treatment approach. Eur. J. Gastroenterol. Hepatol,, 14, 1085, 2002.
15. Menges M. et al.: Increased acid and bile reflux in Barrett's esophagus compared to reflux esophagitis, and effect of proton pump inhibitor therapy. Am. J. Gastroenterol., 96, 331, 2001.
16. Olliver J.R. et al.: Chromoendoscopy with methylene blue and associated DNA damage in Barrett's oesophagus. Lancet, 362, 373, 2003.

17. Piazuelo E. et al.: Superoxide anion dismutase prevents the development of adenocarcinoma in a rat model of Barrett's esophagus. Gastroenterology, 124, A- 32, 2003.
18. Reid B.J. et al.: Biomarkers in Barrett's esophagus. Gastrointest Endosc Clin. N. Am., 13, 369, 2003.
19. Rosołowski M. et al.: Rak przełyku - ciągle aktualny problem diagnostyczno-terapeutyczny, Gastroenterologia Polska, 11, 51, 2004.
20. Sampliner R.E.: Updated guidelines for the diagnosis, surveillance, and therapy of Barrett's esophagus. Am. J. Gastroenterol., 97, 1888, 2002.
21. Slehria S., Sharma P.: Barrett's esophagus. Curr. Opin. Gastroenterol., 19, 387, 2003
22. Suzuki H. et al.: In Barrett's esophagus, acid reflux generates high luminal concentrations of nitric oxide derived from dietary nitrate. Gastroenterology, 124, A - 31, 2003.
23. Van Laethem J.L. et al.: Intramucosal adenocarcinoma arising under squamos re-epithelialisation of Barrett's esophagus. Gut, 46, 574, 2000.
24. Ye W. et. al.: Risk of adenocarcinoma of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. Gastroenterology, 121, 1286, 2001.

SUMMARY

Our article presents up-to-date information about diagnosis and treatment of Barrett's oesophagus. The majority of displastic areas of Barrett's oesophagus (BE) are not visible on standard endoscopy. During last years, efforts have therefore been made to improve the diagnostic sensitivity and specificity. The risk of cancer development and the need for careful monitoring of patients with BE can be evaluated on the basis of many biomarkers (p16 and p53 mutations, the amount of cells DNA, cyclooxygenase- 2 overexpression, the length of BE segment). Data of the safety and efficacy of the new pharmacologic and endoscopic approaches in patients with BE have been recently published.

Przełyk Baretta – stan wiedzy

Artykuł przedstawia stan wiedzy na temat diagnostyki i leczenia przełyku Barretta. Większość obszarów dysplazji w przełyku Barretta (BE) pozostaje makroskopowo niewidoczna podczas standardowej diagnostyki endoskopowej. W ciągu ostatnich kilku lat opracowano nowe metody, które poprawiają skuteczność diagnostyczną. Ryzyko rozwoju raka i potrzebę ściślejszego nadzoru pacjentów z rozpoznanym BE można ocenić na podstawie biomarkerów (mutacji p16 i p53; ilości DNA w komórkach, nadekspresji cyklooksygenazy- 2, długości odcinka z nabłonkiem Barretta). W ostatnim okresie opublikowano również doniesienia na temat bezpieczeństwa i skuteczności zastosowania nowych metod leczenia farmakologicznego i endoskopowego pacjentów z BE.