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Barrett’s esophagus: “All diseases are divine and all are human”

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ABSTRACT
Barrett’s esophagus (BE) is a controversial condition. The significance of this condition lies in its premalignant potential, so it is important that clinically applicable biomarkers be identified for early detection and targeted prevention. Dysplasia is currently used as main biomarker, but others most recently surveyed in cancer also include microRNAs. Classically, BE was considered to be an acquired disease related to pathological gastroesophageal acid and bile reflux. However, some cases are associated with genetic predisposition, representing an inherited, familial form of BE. The actual gene, or genes, involved in this condition have not yet been identified. Main therapeutic options include medical treatment and antireflux surgery. Both types of treatment are equally efficient in controlling symptoms and neither is able to cause the metaplastic segment to disappear, which is why the risk of malignancy remains. However, we may
use endoscopic radiofrequency to eradicate BE and replace it by the typical squamous epithelium of the esophagus. The currently accepted indications of radiofrequency in BE include low- and high-grade dysplasia, but not Barrett’s esophagus without dysplasia. In conclusion, BE may have two different presentations: environmental (“human”, reflux) or sporadic BE, which is the most common form, and genetic (“divine”, inherited) or familiar BE, less common but with a greater risk for malignancy. As they might be two different diseases, surveillance programs and treatments should also be different.


*Barrett’s esophagus: “All diseases are divine and all are human”*

*About sacred disease (De morbo sacro)*

*Hippocrates of Kos, 4th century b.C.*

**INTRODUCTION**

Barrett’s esophagus (BE) is a controversial condition. Esophagologists are not even able to agree on what BE actually is or is not. For American gastroenterologists (1), the current concept of BE rests on the endoscopic presence of metaplastic epithelium, and histological confirmation of goblet cells (incomplete intestinal metaplasia). However, for British gastroenterologists (2) the absence of goblet cells does not exclude a diagnosis of BE. In their opinion, even if biopsies do not reveal intestinal metaplasia, this does not mean it is not there: there may have been a sampling error and the biopsy may have been taken from areas other than the metaplastic segment with goblet cells. In this regard, it should be noted that even with correct protocols for taking biopsies (the Seattle protocol) only 5% of the whole metaplastic epithelium will be actually studied (3). Nevertheless, what they do all seem to agree on is that both congenital metaplasia islets in the cervical esophagus and microscopic cardial intestinal
metaplasia (without a visible endoscopic esophageal lesion) are not BE. The significance of this condition lies in its premalignant potential, since every year a small percentage (0.5%) of patients with BE will develop esophageal adenocarcinoma (ADC) (4). This risk for malignant progression varies from one patient to the next (5) according to some characteristics (male sex, genes, BE length, etc.), with the highest risk factor being the presence of low-grade dysplasia (6). The aim of the present study was to review the environmental and genetic causes of BE as well as the different treatment options currently available.

ENVIRONMENTAL ETIOLOGY: ACID AND BILE

“All diseases are human”

Classically, BE was deemed to be an acquired disease resulting from an increase in gastroesophageal reflux (GER), both acid and bile. In a previous study (7), we showed that acid reflux was significantly higher in patients with BE than in patients with esophagitis without BE (26.7% vs 15.4%). However, when dividing the whole esophagitis category into mild and severe subgroups, acid reflux rate in the latter was found to be similar to that of BE patients (26.7% vs 22.4%). Therefore, we concluded that some other factors in addition to reflux must be involved in the development of Barrett’s metaplasia.

For many years, bile has been considered to play an important role in the pathogenesis of Barrett’s metaplasia, as proven in experimental models (8) and using indirect methods of measurement in clinical studies. It was not until the appearance of the portable spectrophotometer known as Bilitec™ 2000 that the amount of bilirubin in the reflux content could be directly measured (9). Using this method along with 24-h pH monitoring we found that the percentage of bilirubin absorbance was significantly higher in patients with BE as compared to patients with gastroesophageal reflux disease (GERD) without BE (26.9% vs 4.6%) (10). Moreover, bile was shown to be involved in the progression of the metaplastic segment. In this respect, when comparing patients with and without low-grade dysplasia, the rate of bile reflux to the esophagus was higher in the former group (40.4% vs 19.5%). Thus we concluded that, when talking about BE in patients with GERD, bile is “the name of the game” (Fig. 1).
However, bile reflux alone cannot induce the development of BE, as we reported in patients with proven duodenogastroesophageal reflux following partial gastrectomy, who did not develop Barrett’s metaplasia since acid secretion had also been suppressed (11). In other words, the synergic actions of acid reflux and bile reflux are necessary to induce the metaplastic change.

In summary, we assumed that, in the absence of any esophageal reflux, the basal pluripotent cells of the esophageal mucosa would develop a squamous epithelium. When acid comes up from the stomach, the esophageal mucosa needs to be replaced by an epithelium resistant to acid such as gastric metaplasia. When bile is also present in the reflux content we hypothesized that the epithelium replacing the injured mucosa should be able to protect it from the biliopancreatic juice, which would lead to the development of intestinal metaplasia (Barrett’s esophagus).

**GENETIC ETIOLOGY: FAMILIAL BARRETT’S ESOPHAGUS**

“All diseases are divine”

Cases are reported in the literature of patients with BE or BE-ADC in the same family. This condition is known as “familial BE”. In 2008 we published a paper about several members of a Spanish family affected by BE over three generations (12). The history of this family began with one 50-year-old patient who had esophageal ADC on Barrett’s metaplasia. When asked about his family history, the patient reported that his father, three maternal uncles, four brothers and two nephews had been diagnosed with BE, some of them having died from an advanced esophageal ADC. The two youngest brothers underwent a Nissen fundoplication after severe acid and bile reflux rates were found in association with their BE. For several years they underwent a surveillance program that included endoscopy and biopsies as well as functional tests in order to confirm the success of surgery. When they were 50 years old (the same age as their brother), both were diagnosed with in situ ADC on BE, and then operated on (Ivor-Lewis transthoracic esophagectomy). Both of them are alive and disease-free after more than five years of follow-up (Fig. 2).

As has been reported by other authors, patients with familial BE, with or without ADC, are younger than those without a family history (13). Furthermore, the rate of
malignancy in familial Barrett’s esophagus is higher than the 0.5% reported in the literature for non-familial BE, which may indicate that in the former group the condition may be more aggressive.

According to some authors, nearly 7% of patients with BE have a positive family history (14), which suggests a genetic predisposition that would be inherited with a dominant autosomal pattern with incomplete penetration. However, the actual gene or genes involved in this inherited predisposition remain to be identified. Only some studies have identified shared genetic regions on chromosomes 2, 4, 12, and 15 (15). Recently, Fecteau et al. (16) reported an uncharacterized gene as potential genetic predisposing factor in familial BE. By using high-throughput sequencing in affected individuals from a large multigenerational family, they performed whole exome sequencing (WES) on DNA from peripheral lymphocytes, and identified a germline mutation (S631G) at a highly conserved serine residue in the uncharacterized gene VSIG10L that segregated in affected members. The expression of the normal VSIG10L gene contributes to the normal differentiation of the esophagus with a squamous epithelium. In contrast, the mutated S631G variant disrupts cell organization and squamous epithelial maturity, which could contribute to the progression of BE to ADC.

We are also studying six families with BE using WES. The variables found were filtered using statistical and biological criteria, and mutations in 66 genes were obtained. These genes include EGFR, estrogen receptor (ESR1), platelet-derived growth factor B (PDGFB), ADAM9, and WNT, all of them involved in tumor progression. Mutations in seven of these genes have already been validated (EGFGR, KMT2D, NELL2, AKAP8, ESR1, CD86, DNAJC13), and experiments are in progress to validate the remaining ones (unpublished data).

MARKERS OF MALIGNANCY: MICRO-RNA

“From the office to the laboratory”, translational research

IMIB (Murcian Institute of Biosanitary Research), Spain

Dysplasia is currently used as the main biomarker to identify BE patients at high risk of developing esophageal ADC. However, the frequency of surveillance endoscopies to assess the progression of BE to ADC is being debated because of their cost. Therefore,
it is critical for the control and treatment of this malignancy that clinically applicable biomarkers for early detection and targeted prevention be identified. Indeed, great interest surrounds the identification of early molecular changes contributing to the pathogenesis of BE and its progression to ADC. Among the molecular biomarkers most recently surveyed regarding cancer are microRNAs. MicroRNAs are a class of small (16-29 nucleotides) noncoding segments of RNA that alter gene expression by targeting messenger RNA (mRNA) degradation. MicroRNA expression profiles in BE and EAC were first reported by Feber et al. (17), who demonstrated that microRNA expression patterns discriminated between tissue types. Since then, different reports have described altered microRNA expression in BE and ADC. Among all the differentially expressed microRNAs identified, we were particularly interested in finding microRNAs as specific biomarkers responsible for the carcinogenesis associated with BE. Accordingly, we used 23 shared microRNAs for further validation by qRT-PCR using samples from the BE patients in our long-term study who developed EAC. MicroRNAs -192, 194, 196a, and 196b showed a significantly higher expression in the BE samples from patients who progressed to EAC as compared with those who did not (18). These data suggested that such microRNAs might be useful biomarkers to predict the progression of the disease, and should be further evaluated in clinical trials of BE progression in a large-scale study (Fig. 3).

**Treatment: PPIs vs Nissen fundoplication**

*Barrett’s esophagus. Now what?* (19)

The treatment of BE is controversial and aims not only to control symptoms but also to prevent BE from progressing to dysplasia and ADC. Primary therapeutic options include medical treatment for life and antireflux surgery. Both types of treatment are equally efficient in controlling symptoms, and neither is able to cause the metaplastic segment to disappear. The question is whether the premalignant potential of BE may be different according to the treatment given. Spechler SJ et al. (20), in a randomized controlled trial, questioned the advantages of surgical treatment in preventing the development of adenocarcinoma.
In this regard, more than 30 years ago we started a randomized prospective study comparing medical treatment with omeprazole (40 mg/day) and surgical treatment using Nissen fundoplication. The results have been published twice previously (21,22), and presented at many national and international medical conferences. The latest data published (22) included a total of 146 patients diagnosed with BE from the period 1982-2000. All of them were evaluated for inclusion in this prospective study, 43 with medical treatment and 58 with antireflux surgery. Median follow-up was five years (range, 1-18) in the medical treatment group, and six years (range, 1-18) in the surgical treatment group. High-grade dysplasia developed in two out of 43 patients (5%) in the medical treatment group, and in two of 58 patients (3%) in the surgical treatment group. In the latter case both patients presented with clinical and pH-metric recurrence. There was no case of malignancy after successful antireflux surgery. The main conclusion was that there were no statistically significant differences between medical and surgical treatment in preventing BE from progressing to dysplasia and adenocarcinoma. However, when surgery was successful (85% in our series) the risk of progression to dysplasia and adenocarcinoma was significantly lower than in patients under medical treatment, perhaps because surgery totally suppresses acid and biliopancreatic reflux to the esophagus (Fig. 4). These results are similar to those published in a meta-analysis in 2016 (23).

However, some cases of malignant progression have been observed during the further follow-up of patients with successful surgery (that is, with absence of acid and bile reflux repeatedly checked using functional tests such as 24-h pH monitoring and Bilitec study). In 2012, we once again analyzed the results of 161 patients (75 receiving medical treatment and 86 undergoing surgery, with a mean follow-up period of 13 years). Seven patients in the medical group (9.3%) and five in the surgical group (5.8%) had malignant progression, with only two of them having had unsuccessful surgery. The other three patients that developed esophageal ADC since our last paper (22) had some relatives with BE and/or esophageal ADC, which means they had familial BE (unpublished data).

Recently we had to terminate our study because of patient randomization difficulties (many potential subjects present with previous information obtained through the
internet, and refuse to be assigned to one arm or another at random). In addition, the option of treatment with radiofrequency made it impossible to continue with the study.

As a result of our findings, we wonder how is it possible that patients with absence of acid and bile reflux, as measured with objective tests, go on to develop malignant progression.

As an English proverb says, perhaps “it is too late to shut the stable door after the horse has bolted”. In other words, once histological, molecular, and genetic changes have begun and BE develops, progression does not depend on antireflux treatment.

**ABLATION OF BE: RADIOFREQUENCY**

“A hammer looking for a nail” or the future of Barrett’s esophagus?

Neither proton-pump inhibitors (PPIs) nor antireflux surgery are able to induce the regression of the metaplastic epithelium, which is why the risk of malignancy remains in spite of reflux suppression, as was mentioned previously. Therefore, the only way to eliminate this risk is by removing Barrett’s esophagus. Several endoscopic methods have been used with this aim for many years: laser irradiation, multipolar electrocoagulation, argon plasma coagulation, or photodynamic therapy. The results obtained with these techniques, with notable risks and complications, have not been good enough for any of them to become the gold standard in the treatment of BE.

More recently, the use of endoscopic radiofrequency (RF) has led to a revolution in the treatment of BE. Its aim is to eradicate BE and replace it by the typical squamous epithelium of the esophagus. Since its introduction in 2006, its use has been widespread in most units specialized in esophageal disorders around the world, with many studies reporting BE eradication in 95% of patients (24). The currently accepted indications of RF for BE include low- and high-grade dysplasia, but not Barrett’s esophagus without dysplasia.

The next question is: which treatment is better to prevent BE from recurring after metaplastic epithelium eradication? PPIs or antireflux surgery? Currently, we are carrying out a prospective study comparing both options after RF by using immunohistochemical techniques for measuring cell proliferation and apoptosis.
CONCLUSIONS

The genetic changes that promote cancer can be inherited from our ancestors or can also be acquired during a person’s life as a result of DNA errors, which occur due to exposure to physical, chemical, and radioactive factors. It is known that 75-80% of tumors are caused by external (that is, environmental) factors and are therefore preventable (25).

BE has always been considered as an acquired disease related to acid and bile reflux. Perhaps chronic exposure to these substances may induce genetic changes, which may promote the development of cancer in the metaplastic epithelium.

In summary, BE may have two different presentations: environmental (“human”, reflux) and sporadic BE, the most common form, and genetic (“divine”, inherited) or familial BE, less common but with a greater risk for malignancy.

As they may be two different diseases, the question now is: should surveillance programs and treatments be also different?

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