Lecture N. 22

Barrett's Esophagus

In 1950, with an article published in the *British Journal of Surgery*, Norman Rupert Barrett described the first case of columnar metaplasia of the distal esophagus, concluding that the condition was a congenital abnormality owing to residual glandular epithelium that lines the esophagus during embryogenesis. In 1953, Allison and Johnston hypothesized the acquired onset of the disorder on the basis of its nearly constant association with gastroesophageal reflux pathologies.

Hence the definition of "Barrett's Esophagus" (BE): columnar metaplasia of the distal esophagus substituting normal squamous epithelium generally as the result of gastroesophageal reflux disease (GERD).

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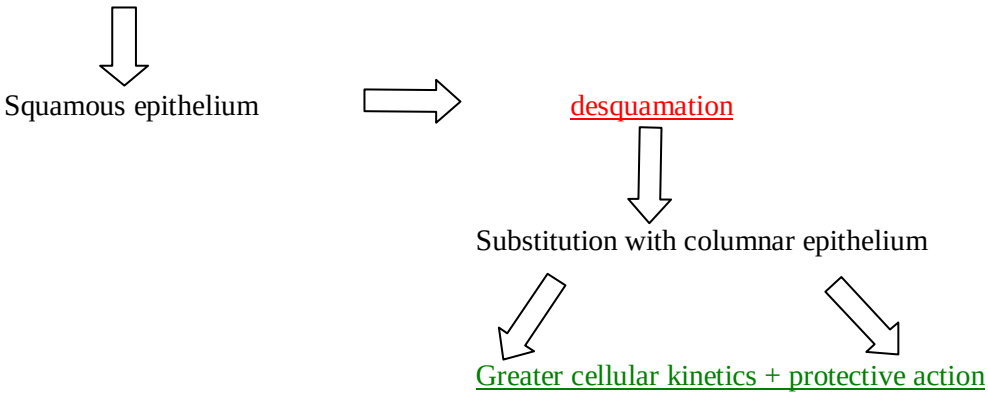
The pathophysiological course of BE would seem to begin with the destruction of the squamous epithelium of the distal esophagus where the harmful action of refluxate is stronger. The squamous lining would be replaced by columnar epithelium, whose cellular kinetics are 4-5 times faster than those of squamous epithelium. The stripped areas esophageal epithelium would thus be substituted by a lining that would offer greater resistance against the noxious damage.

The pathophysiological course of BE



This process would arise only in the presence of a persistent alteration of the esophagus' endoluminal environment and, as I will discuss later herein, also depending on the composition of the refluxate. When, on the other hand, the mucosal damage is the result of minor quantities and different compositions of refluxate, repair is normally achieved by the squamous epithelium.

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Numerous studies have over time investigated the **relationships between onset of BE and the composition of the refluxate**. Twenty-four hour pH monitoring has revealed some patterns of gastroesophageal reflux that are more often implicated in patients with BE. What was observed came as no particular surprise, namely the frequency of weakly acidic (e.g., pH < 3 - 2) refluxate in patients with metaplasia (Fig. 1).

What may not have been likewise obvious - but which is entirely comprehensible - was the important role of biliary acids present in gastroesophageal refluxate. Many Authors, in fact, have demonstrated that the esophagi of patients with BE show evidence more severe exposure to alkaline refluxate compared to the organs of subjects with esophagitis without metaplasia. Even radioisotopic techniques based on the use of biliary acids marked with radioactive isotopes (such as technectium-99) confirm that alkaline reflux occurs more frequently in patients with BE. This putatively occurs in the so-called "mixed refluxers", i.e., those subjects in whom the refluxate is mixture of acidic gastric and alkaline duodenal juices (Fig. 2). Under these circumstances damage to the esophageal mucosa would be greater given that the alkaline

component, particularly the biliary salts, would compromise the impermeability of the esophageal mucosa: the consequent weakening of the so-called mucosal barrier would induce the backflow of hydrogen ions thereby leading to serious mucosal damage. In duodenal-gastroesophageal reflux disease (D-GERD), the refluxate carries into the esophagus along with gastric acid secretion all of the components making up the endoduodenal secretion, namely the biliary acids and salts mentioned above, pancreatic enzymes and bicarbonates, lysolecithin, and so on. If we add to this picture the deficit in esophageal clearance present in these subjects, with the resulting stagnation of the refluxate in the terminal esophagus, the high degree of damage is fully comprehensible.

These observations entail implications of a surgical pathology nature: the harmful action exerted by the alkaline component of mixed refluxate could annul the expected therapeutic effect on BE of treatment with inhibitors of gastric acid secretion compared to a greater protection afforded by surgical anti-reflux treatment.

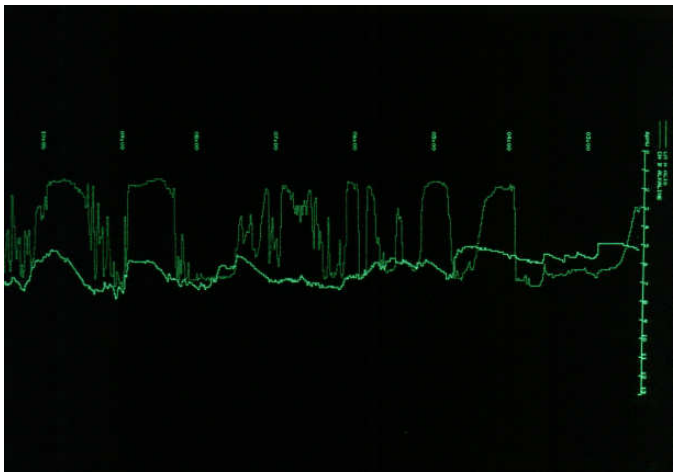

Fig. 1

Frequent, very low pH acidic refluxes

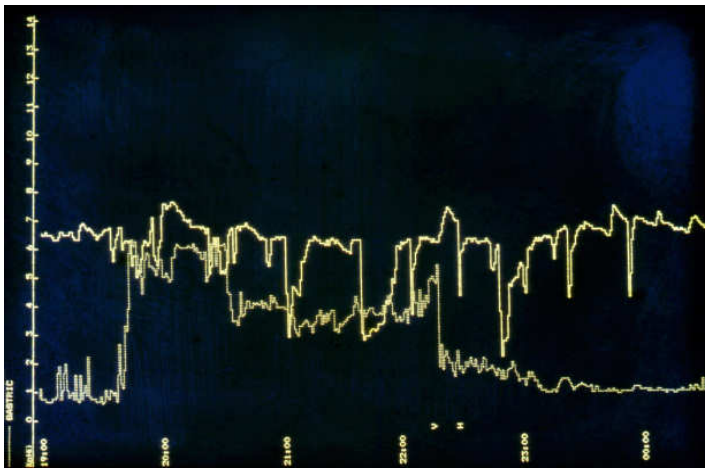

Fig. 2

Mixed and/or alkaline refluxes

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Reduction of PPI therapeutic activity
(proton pump inhibitors)

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Antireflux surgery

Endoscopic investigation is the primary standard diagnostic tool in patients with BE. In fact, it allows the accurate assessment of eventual lesions that refluxate causes to the esophageal wall. Generally speaking, the different degrees of severity in signs of esophagitis leading to BE can be summarized as follows:

Esophagitis
- hyperemic
- erosive
- ulcerating
- cicatricial stenotic
- Barrett's Esophagus

A hallmark feature by which BE is recognized is the raised z-line (gastroesophageal junction), which becomes quite irregular, displaying patches of reddish epithelial lining that at times are circumferential, but more often appear as flame-like tongues or islands of the same red color against the pearly-white backdrop of normal esophageal epithelium (Fig. 3 - 4).
Barrett's esophagus is classified as either long-segment (>3 cm) or short-segment (< 3 cm) depending on the extent of metaplastic columnar epithelium.

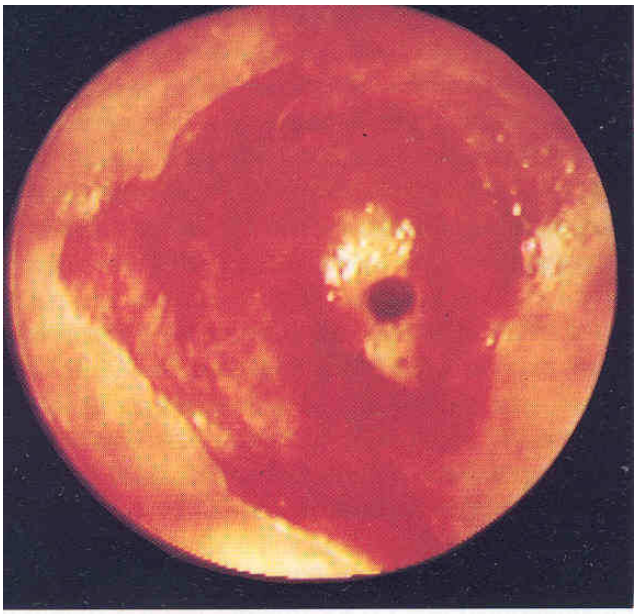

Fig. 3

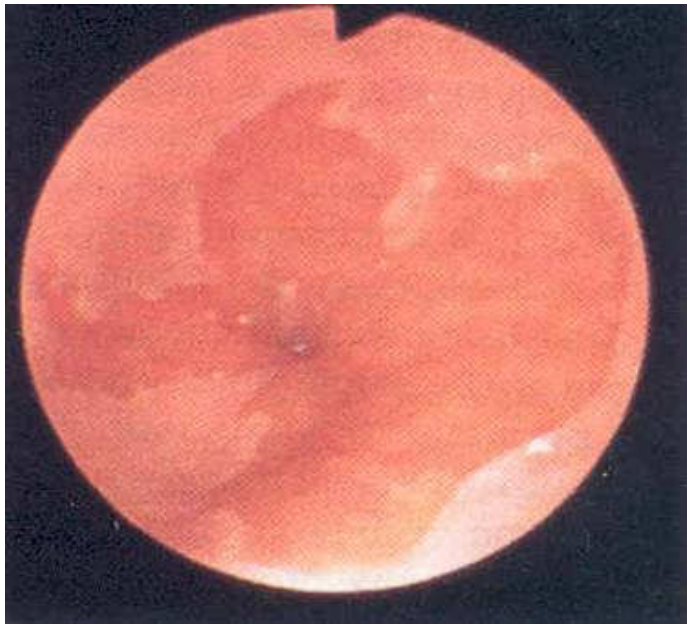

Fig. 4

While endoscopy cannot always reliably detect or rule out the presence of BE, especially if signs of severe esophagitis coexist, **histology** represents the gold standard for the diagnosis of the disease. In truth, expert endoscopist can admirably conjecture on the diagnosis or at least the suspected diagnosis of BE; however, it is only the comparison of endoscopic and histologic findings that can establish the disorder with certainty. Here as nowhere else does the close collaboration between endoscopist and pathologist become pivotal.

Histomorphology distinguishes three types of metaplastic columnar epithelium that may be present alone or in combination:

1. Specialized intestinal
2. gastric fundic
3. gastric cardial or junctional

Of these, specialized intestinal metaplasia is the most frequently detected type and the one which more than the others is subject to dysplasia and neoplastic transformation. This is why, as we will see below, it demands more attention and care in the taking and handling of biopsies and often requires consultation among pathologists to accurately interpret histomorphological features.

Intestinal metaplasia presents with a villiform and epithelial surface made up of calyciform cells (goblet cells) and columnar cells. Below the surface, glands similar to crypts lined with cuboidal seromucous cells can be observed, with enterochromaffin cells and rare endocrine cells containing somatostatin and gastrin. The lamina propria may present a varying degree of congestion, edema and features of chronic inflammation represented by infiltration of plasma cells, lymphocytes, granulocytes that are often eosinophilic, mast cells and histiocytes at times showing signs of fibrosis (Fig. 6). These inflammatory features are proportional to the degree of damage caused by gastroesophageal reflux.

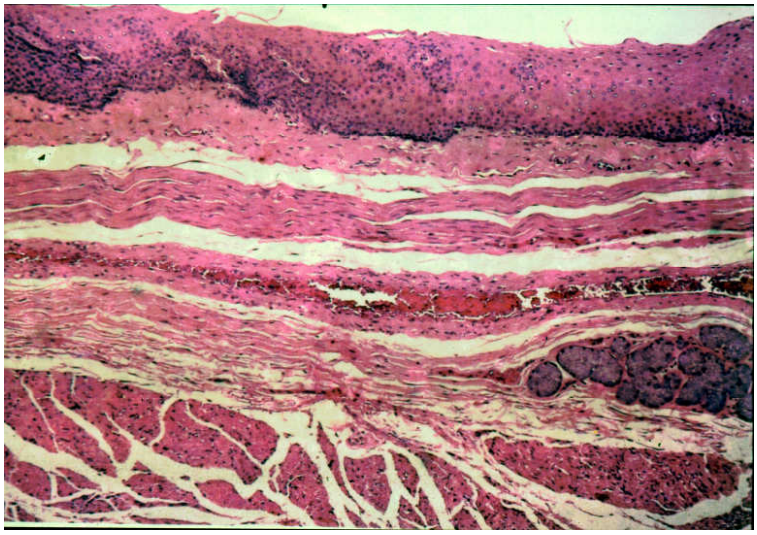

Fig. 5 - Squamous epithelium in a normal esophagus

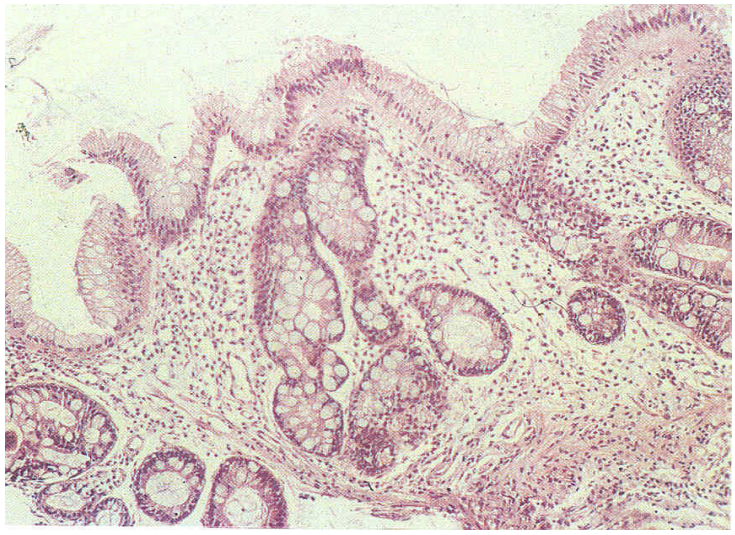

Fig. 6 - Intestinal type metaplasia in BE (1)

Gastric-fundic metaplasia displays an architecture similar to that of the gastric fundic-corporal mucosa: a foveolar surface with a superficial mucous-secreting epithelium and glands composed of principal and parietal cells; endocrine cells are rare. Abundant connective lamina propria separates glands from one another, thereby giving the mucosa an atrophic semblance. Gastric-cardial or junctional metaplasia is characterized by a gastric foveolar-like structure with superficial columnar epithelium and cardial mucosal glands. The combination of these metaplastic manifestations or cases with histopathological features so diversified and hardly characteristic as to lead some authors to defining them "undetermined" are not uncommon.

The difficulties that pathologists may encounter in establishing an exact diagnosis and, above all (as we will see further on), in identifying possible elements of neoplastic risk, thus become clear. As such, multiple biopsies must be taken from the metaplastic areas; moreover, as advised by numerous authors, the diagnosis should be scrutinized by more than one specialist.

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Columnar metaplasia, particularly intestinal, of the esophagus, poses the risk of esophageal adenocarcinoma (EAC). The prevalence of EAC in subjects in whom diagnosis of BE is made for the first time ranges according to different statistical surveys from between 5-6% up to 15% and beyond. Numerous Authors opine that the risk of cancer in BE is from 20 to 350 times greater than in normal esophagus. Compared to the general population, subjects with BE have a 30 to 125 times higher risk of developing EAC, with an incidence rate equal to a case of cancer every 150 patients per year. Bearing in mind that the prevalence of BE in the Western world is estimated at 22 cases/100,000 in endoscopic cohorts, but that autoptic reviews raise this figure 17-fold to 326/100,00, it's obvious that BE is considered a precancerous lesion. On the other hand, these findings parallel the increase in cardial/terminal esophagus adenocarcinoma and the increased frequency of GERD seen in Western populations, thus suggesting a pathogenic connection among the three conditions (GERD > BE > EAC).

There are multiple hypotheses regarding the passage between BE and EAC, but most authors agree on one conviction: the step preceding neoplastic transformation is putatively represented by the onset of dysplasia in the columnar epithelium. Indeed, the presence of epithelial dysplasia is frequent (83 - 100%) in the columnar epithelium surrounding EAC, thus modifying the sequence: metaplasia > dysplasia > EAC. The literature describes a frequency of dysplasia in 5 - 10% of BE patients, prevalently in the specialized intestinal form.

Dysplasia is defined as epithelial modifications of different degrees, architectural disorder and cytological atypia. Suspicion or prediction of the neoplastic nature of the lesion is possible above all if these latter features are diffuse and accentuated. The foremost problem in interpreting these signs is distinguishing

the dysplasia from reactive or repair modifications induced by the inflammatory stimulus, as occurs with esophagitis, thereby making discrimination anything but straightforward. In such cases, the term

"indefinite diagnosis of dysplasia" is often used. This explains the need, above and beyond multiple biopsies, to resort to the consultation of different experts in order to establish consensus on diagnosis.

Epithelial dysplasia is commonly classified as either low grade (LGD), that is, mild, or high grade (HGD), i.e., moderate to severe. This second category also includes *in situ* carcinoma. This classification is the result of work by Schmidt and coworkers (8), and it is, for a number of reasons, more convincing than the more recent Vienna classification - 2000 (7), which uses the term "non-invasive neoplasia" to label the above-mentioned low- and high-grade forms: many authors find Schmidt and coworkers' guidelines easier to apply.

Low-grade dysplasia is recognized by dilated and stratified glands, with nuclear dysmorphology characterized by hyperchromatism, elongated so-called "pencil" forms, overcrowding and stratification.

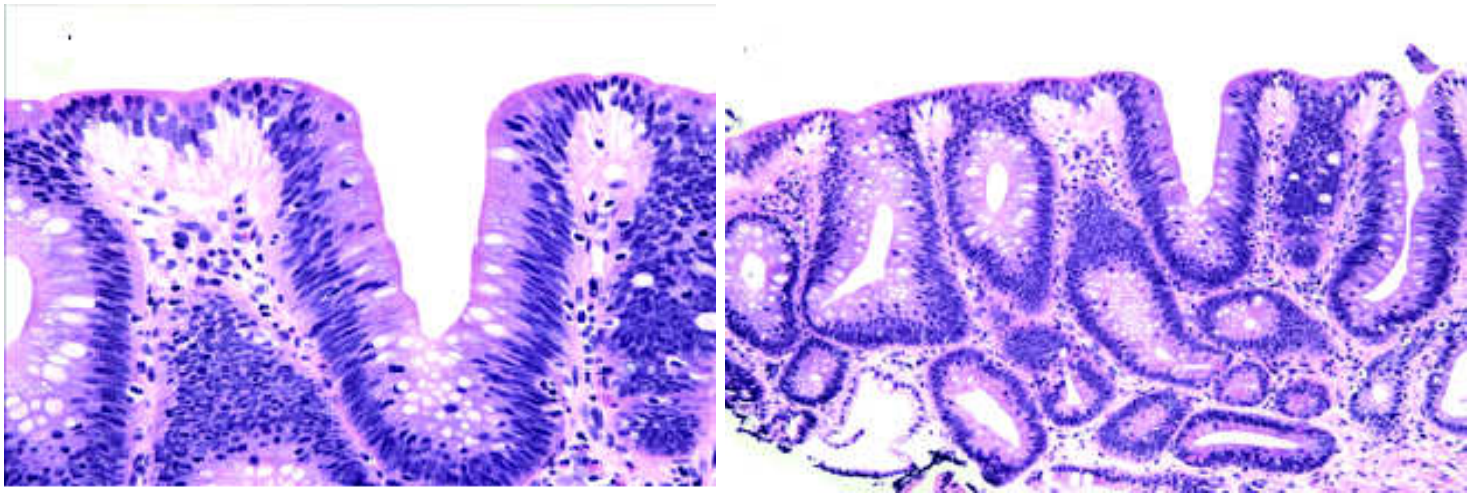

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Fig. 7 - Low-grade dysplasia (LGD) (2)

The same features described above for LGD are amplified in HGD, i.e., glandular structures are more complex, overcrowding of nuclei is exasperated with stratification and increased nuclear pleomorphism, and the nuclear polarity that was conserved in the previous form is lost. When these anomalies become increasingly intensified and the general architecture even more distorted, *in situ* carcinoma develops.

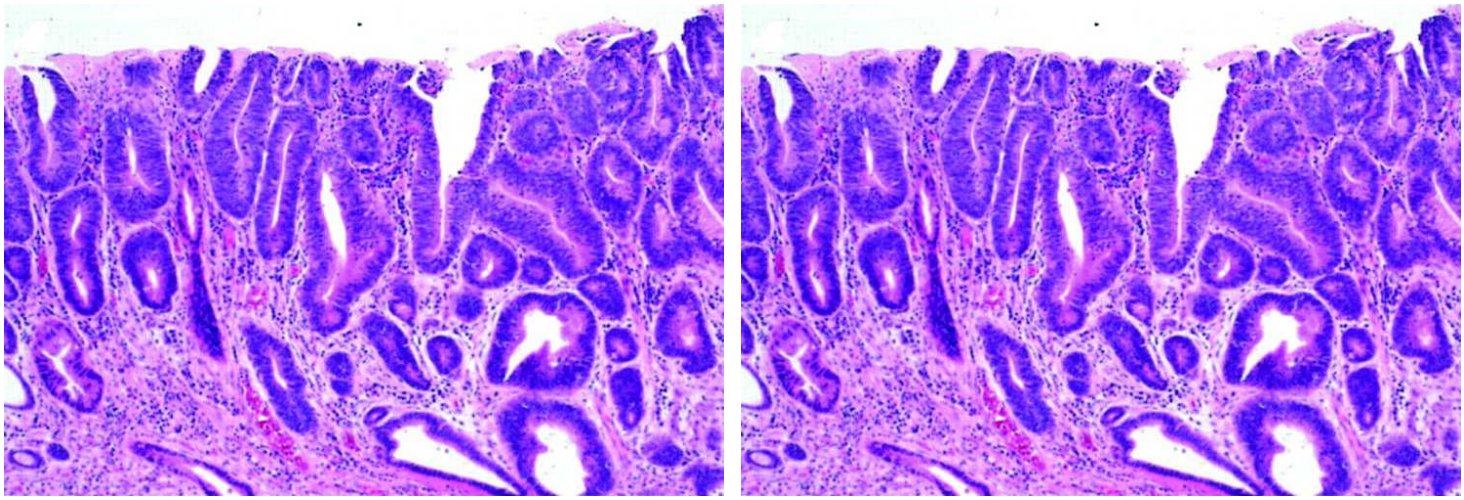

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Fig. 8 - High-grade dysplasia (LGD) (2)

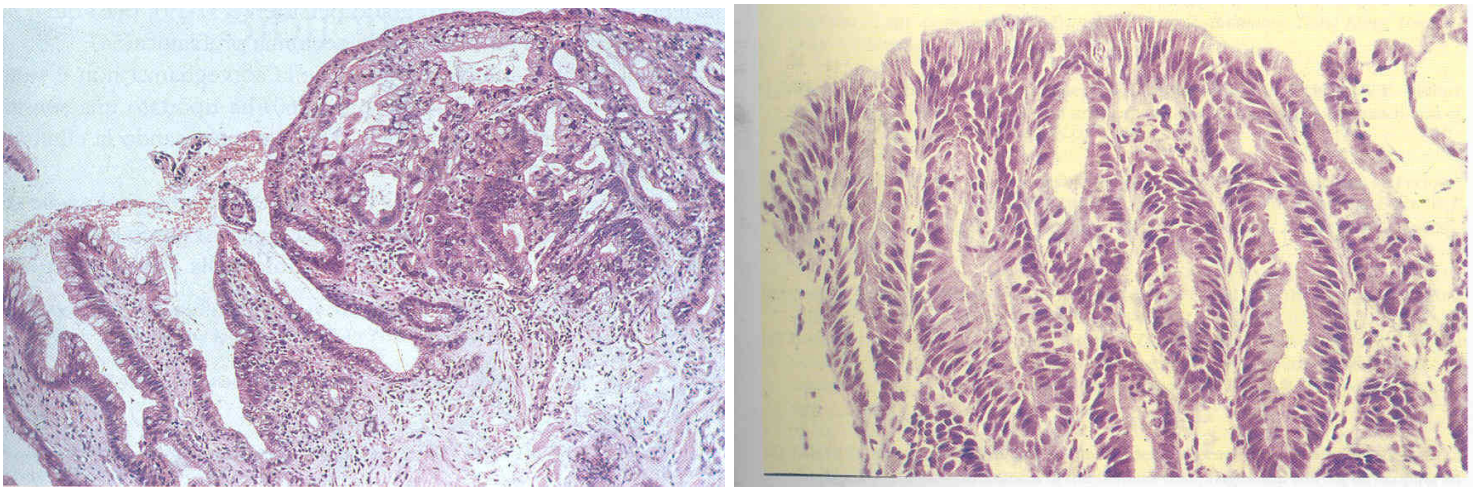

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Fig. 9 - a: LGD - b: HGD (1)

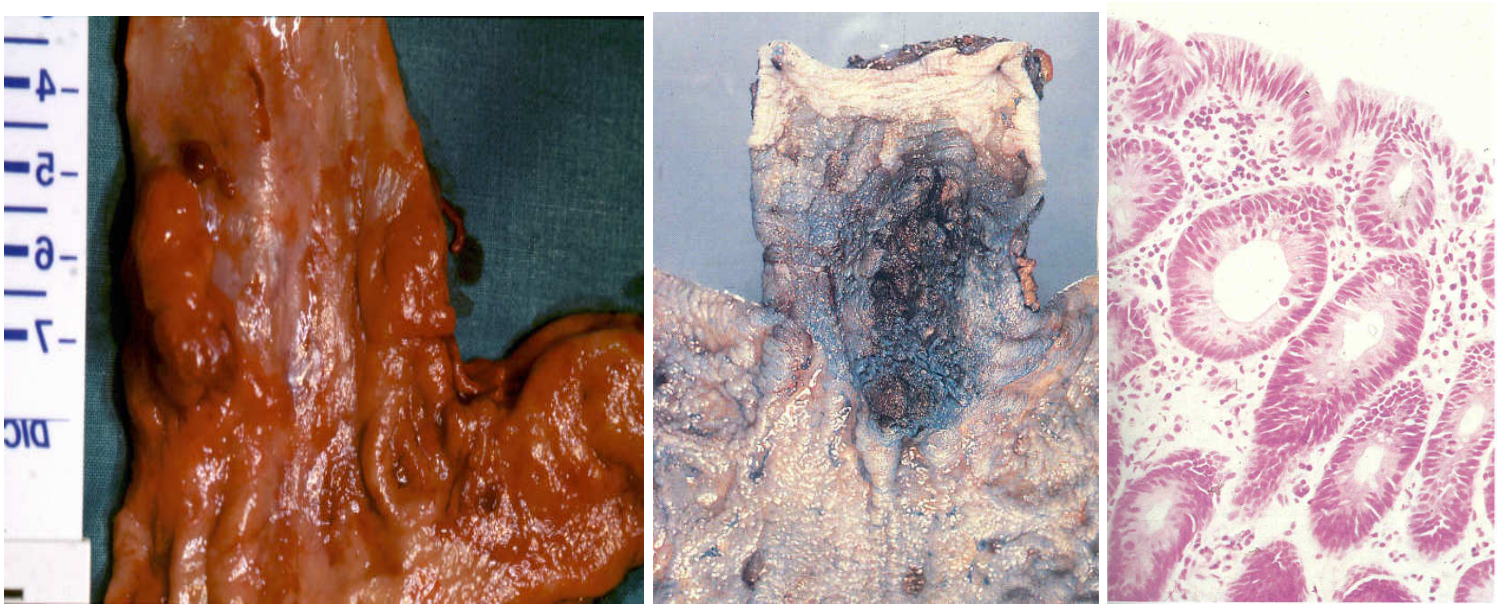

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Fig. 10 - a) EAC in Barrett's esophagus; b) EAC in intestinal metaplasia in Alcian blue; c) EAC in intestinal metaplasia (1)

While the diagnosis of LGD may often not meet with consensus among pathologists, the interpretation of HGD - given the unmistakable proof found in manifestations - are shared in nearly 85% of cases.

Nevertheless, establishing the diagnosis of dysplasia and its related evolutionary potential exclusively on histological findings not the correct approach, precisely because of the already-mentioned high veriation rate in pathologists' interpretations. Such circumstances highlight the need for more sensitive biomarkers able to discriminate the processes of neoplastic progression.

Numerous experimental studies have revealed processes of genomic instability with frequent modifications in DNA content in the cell population already in the metaplastic phase during carcinogenesis in BE.

These findings underpin ongoing investigation into the events lying at the base of progression and into the identification of possible early molecular markers that allow assessing the stages of progression.

As a result of these efforts two markers have been distinguished, p53 and Ki-67, that would seem to meet this need, since their accumulation is associable to the degree of neoplastic progression. Below are the data reported in a recent study on the subject (3):

	p53	Ki-67
G1: Normal esophageal squamous epithelium	7%	21.3 ± 19.5%
G2: Esophagitis	37.5%	38.8 ± 24%
G3: Columnar epithelium with unspecialized metaplasia	30%	37.7 ± 26.3%
G4: Columnar epithelium with intestinal metaplasia	62.5%	52.8 ± 24.6%
G5: Adenocarcinoma	71.4 %	57.1 ± 25.1%

As for p53, other works (4) have shown it to behave similarly in both the LGD and HGD phases. An analogous trend in the transition from dysplasia to adenocarcinoma also seems to exist for the Her-2/neu protein (also known as ErbB-2) (5, 6).

The risk of carcinoma developing in BE through the above-mentioned stages must therefore be carefully assessed. To this end, the standard means is endoscopic monitoring. This generally entails taking a biopsy every 2 cm of metaplastic areas; every 1 cm in case of dysplasia, particularly HGD. Some other tools are helpful in establishing the diagnosis: Methylene blue is able to stain metaplastic epithelium, but not dysplastic areas that are otherwise undistinguishable from non-dysplastic areas; some authors also advocate the use of a chromophore, such as 5-aminolevulinic acid, which has a greater uptake in neoplastic areas that are then recognized under laser stimulation.

The frequency with which endoscopic and bioptic surveillance should be performed is still the subject of debate. A number of strategies have been proposed in the literature. When dealing with BE without dysplasia, examination is recommended every 24 months in case of “low-risk” subjects, i.e., those with gastric-fundic metaplasia; this interval is reduced to 12 months in cases of intestinal metaplasia, inasmuch as these patients are considered to be “high-risk”. In the presence of dysplasia there is even more disagreement: from six to 12 months for LGD, also in relation to possible yet unlikely modifications secondary to pharmacological therapies. The above-mentioned results yielded by molecular diagnostics should make criteria deriving from BE endoscopic-bioptic surveillance more reliable.

The management of patients with Barrett’s esophagus is not simple, nor - as could be expected from what we’ve illustrated above - are proposed strategies shared by all. The truth of the matter is that our notions about this complication of reflux disease, especially about the degree of neoplastic risk it carries, are not always adequate, despite targeted investigations on the subject. At present, therefore, the prognostic orientation and therapeutic criteria are fundamentally based on the extension of the metaplastic area (short and long BE) and on the degree of dysplasia. Choice of treatment is thus made according to endoscopic findings and biopsy.

Discussion surrounds the possibility of whether BE without dysplasia may regress after medical and/or surgical treatment of reflux disease; or whether the evolution of LGD may come to a halt (regress?) after treatment. Even if we admit such possibilities, we are still faced with the undeniable need for monitoring over time, all the more frequently the more pronounced signs of risk are. The alterations present in HGD (cytological atypia, varying degrees and combinations of epithelial disorder and architecture, etc.) are increasingly interpreted as being equivalent to carcinoma in situ and, in any event situations reflecting a high neoplastic risk.

In short, the treatment of Barrett’s esophagus must be conditioned by the above evidence. First-line care may be conservative, as long as the need for efficacious surgical therapy of the reflux disease is borne clearly in mind. Options after this include:

- post-surgical endoscopic and biopsy monitoring;
- endoscopic ablation

The methods tested for this latter are as follows:

- Thermal
  - Laser
  - Mono/bipolar electrocoagulation
  - Argon plasma coagulation

- Chemical
  - Photodynamic therapy

- Mechanical
  - Ultrasound-guided aspiration
  - Endoscopic mucosectomy

These procedures may be adopted in selected patients, above all if they are included in a controlled trial. They often require repeated applications, and are not free from undesired events. Results appear, however, to be conflicting for many reasons, chief of which is the incomplete ablation of the metaplastic-dysplastic area.

When BE takes on the manifest signs of high neoplastic risk, namely high-grade dysplasia, it becomes clear that the patient must undergo resective surgery, which may range from partial resection of the esophagus and recanalization with an interposed loop to total esophagectomy.

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