

Study on metaplastic lesions in gastric cancerogenesis

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Introduction

Gastric cancer remains the second most frequent cause of cancer-related deaths and ranks 4th in cancer incidence worldwide [1-9]. Although mortality from gastric cancer has been declining in most countries, it still represents a major health problem throughout the world, accounting for 7.8% of cancers worldwide [10-13]. Areas where incidence is high at > 60 per 100,000 males include eastern Asia (Republic of Korea and Japan), eastern Europe and Central and Latin America [13-18]. The “intestinal” type of adenocarcinoma is relatively predominant in high - incidence regions of the world, whereas the “diffuse” type is relatively more common in low-incidence areas. The prognosis of GC varies depending on stages [3-7].

The 5-year survival rates for advanced gastric cancer are less than 20%. On the contrary, early gastric cancer (EGC) makes a good prognosis that the 5-year survival rates are over 90% to 95 % [6-12]. Therefore, it is important to individualize the management for high risk group of gastric cancer. The risk factors of gastric cancer are *Helicobacter pylori* infection, salt intake, smoking, alcohol, family history of gastric cancer and the main precursor lesions of the both atrophic gastritis (AG) and intestinal metaplasia (IM) [19-24]. *H. pylori* infection has been proved as the most important risk factor of AG and IM. So, AG is considered to be an ancestor to IM [13-30].

From this background, the aim of this review is to provide comprehensive information regarding the diagnosis and management of AG and IM and to establish strategies to prevent gastric cancer.

Atrophic gastritis and Metaplasia, as Precursor Lesions of the gastric mucosa

Chronic inflammation damages of inflamed cells triggers, a multistage carcinogenesis process [1-4,12-27]. These inflammatory cells contribute to cancer initiation, promotion and metastasis, by producing cytokines, reactive oxygen species and reactive nitrogen species [2,18-20,25-30]. Damages of cellular components result in increased mutations and altered functions of important enzymes and proteins in premalignant tissues, so contributing to the multistage of carcinogenesis process [4,5-10,16-19,29-33].

Thus, the eradication of *H. pylori* is the most important to prevent the progression (Figure 1). While dysplasia is a well recognized morphological marker of premalignant change in the gastric mucosa [1-6,18], the role of IM in the histogenesis of GC is still a matter of debate [21-26].

In most text books metaplasia is defined as “a change from one type of differentiated tissue to another, normally differentiated type”. The mechanisms of metaplastic transformation are still obscure.

Aim

In this chapter we focus on the heterogeneity of IM as indicated by morphological, histochemical, immunocytochemical and ultrastructural studies, providing the evidence for the IM - dysplasia - carcinoma sequence [7-10,11-16]. Based on a study of morphology, differentiation and mucin secretion, Jass and Filipe (1986) have identified three types of IM [2].

Materials and methods

During the period from 2013 to 2018, the 50 patients with autoimmune (A) Gastritis, (Figure 1), 50 patients with *Helicobacter pylori* + infectious (B) Gastritis, (Figure 2), as well as 20 patients in control group, had gastroscopy. Histopathological examination was done in

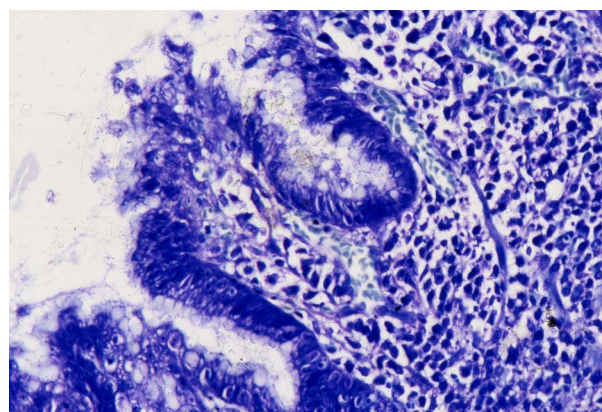


Figure 1. *Helicobacter pylori* B gastritis. Gimsa x 300.

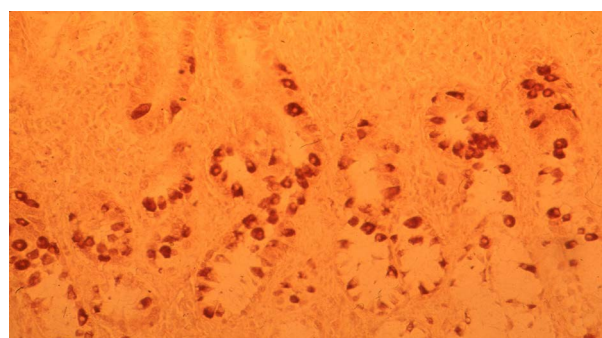


Figure 2. Autoimmune A gastritis: marked G-cell hyperplasia in antral mucosa. ABC x 300.

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endoscopic biopsies of gastric antral and corpus/fundic mucosa and fixed in 10% formaldehyde. Paraffin sections were stained with classic HE, histochemical AB - PAS, HID-AB, Giemsa, argentaffine Masson reaction for analysis of enterochromaffine (EC) and argyrophilic Sevier Munger method for the discover of argyrophilic enterochromafine-like (ECL) neuroendocrine cells. Immunohistochemical Avidine Biotin Complex (ABC) method, with antibody to Gastrin, has been applied for the detection of neuroendocrine Gastrin (G) cells. Basal Gastrin serum levels were examined by using Radio Immuno Assay (RIA) method.

Results

By analysis of endoscopically taken, processed and stained gastric biopsies, we are pointing out the following results:

Intestinal metaplasias, the most frequent preneoplastic lesions (Type I, II, III) of corpus/fundic localisation: in 86 % of patients is associated with autoimmune (A gastritis):

Type I (complete): The epithelium consists of mature absorptive and goblet cells, as well as Paneth cells (Figure. 3). Villi and straight crypts lined by mature absorptive and goblet cells. On Alcian Blue - PAS (AB-PAS) stain, the absorptive cells show a well formed brush border and are non - secreting. Goblet cells secrete sialomucin, as shown on HID -AB stain (Figure 4).

- EC cells: adenomatoid hyperplasia of argentaffine + cells, with black granules (Figure 5).

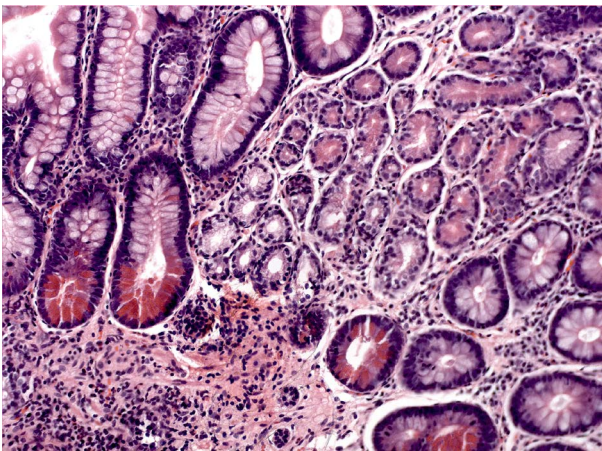


Figure 3. Intestinal metaplasia-complete type, with dominant Paneth cells (arrows) H&E x 200.

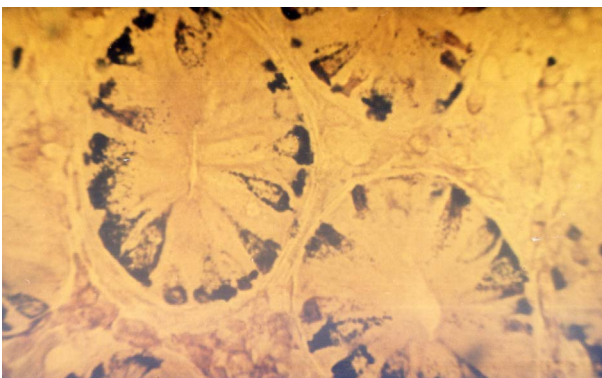


Figure 4. Intestinal metaplasia of neuroendocrine EC cells. Masson: Argentaffine reaction x 30.

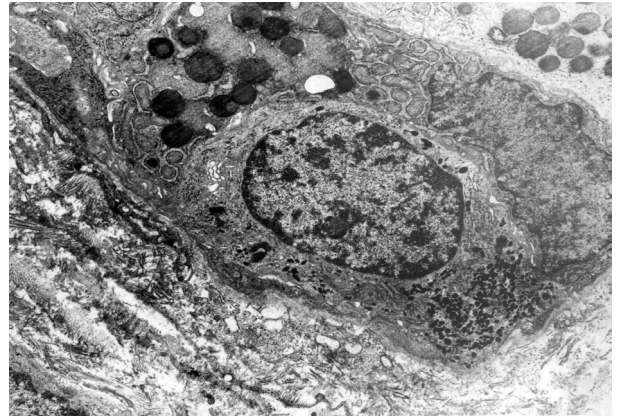


Figure 5. Complete IM: Endocrine EC-cell: Opened type Ultrastructural pattern.

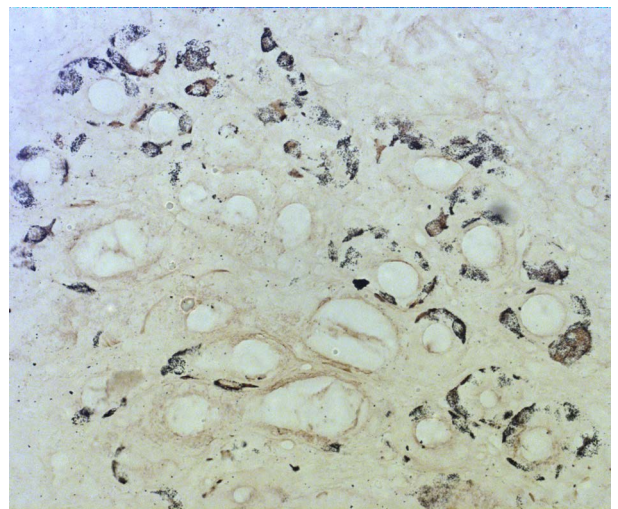


Figure 6a. ECL-cell hyperplasia, induced by hypergastrinemia. Sevier - Munger 200



Figure 6b. Blackberry pattern of ECL cells. Sevier-Munger x 400

- Ultrastructural pattern: Gastric EC (closed) type has become Intestinal (opened) type (Figure 6a,b).
- Hyperplasia antral G cells (Figure 7) and metaplasia Corpus G cell inside of pyloric metaplastic fields) (Figure 8), associated with achlorhydria and hypergastrinaemia.
- Basal serum levels of Gastrin (Figure 9).
- Linear and blackberry ECL cell hyperplasia in fundic mucosa, associated with achlorhydria and hypergastrinaemia (Figures 10 and 11a,b).

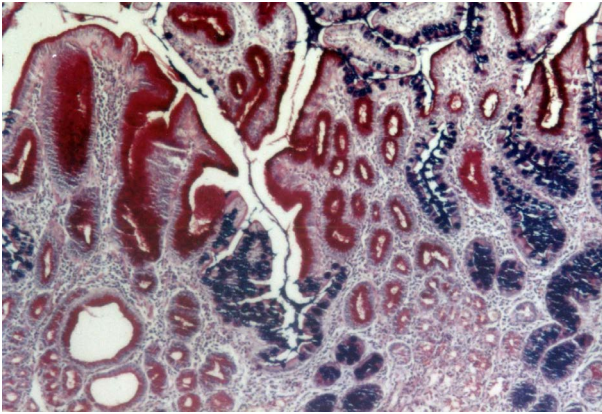


Figure 7. Gastritis with mixed: pyloric and intestinal metaplasia. AB-PAS x 200

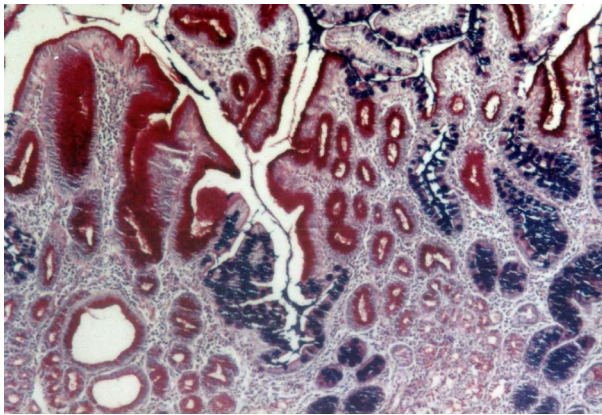


Figure 8. Combined pyloric (red) – intestinal (blue) metaplasia. AB – PAS x 200

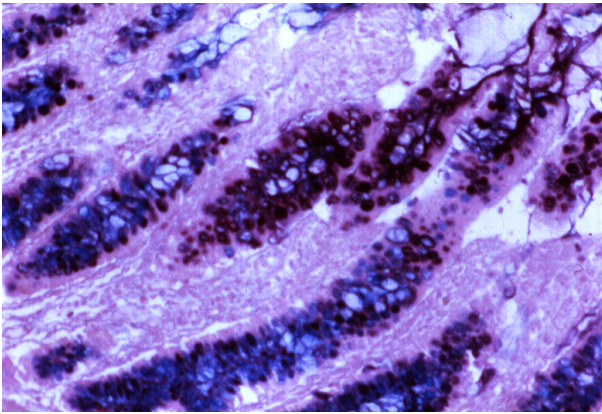


Figure 9. Intestinal incomplete metaplasia with predominant sialomucin (blue stain). HID-AB x 300

Type II (incomplete): the crypts are elongated and tortuous. The epithelium is characteriyed by few or absent absorptive cells and the presence of columnar mucous cells in various stage of differentiation (Figure 12); the goblet cells secrete sialo- and occasionally sulphomucins (Figure 13). Paneth cells are rarely observed.

Type III (incomplete): distortion of glandular architecture is more pronounced and cell atypia and loss of differentiation is more marked than in type II. (Figure 14). Columnar cells secrete predominantly sulphomucins, and goblet cells contain sialo- and/ or sulphomucins (Figures 15, 16 and 17). Paneth cells are usually absent. The highest value of cell heights being seen in type III. The presence of sulphomucin

in goblet cells can be seen in any IM type, therefore is not a criteria for a type III IM [2].

Forms of transition, both in terms of morphology and mucin profiles between these three principal variants are also noted, suggesting that IM heterogeneity and may reflect the stages in a dynamic process in which one form evolves to another, or regress [2]. The incomplete types remain unchanged and correspond to known types II and III. Sulphomucin + incomplete type (type III) is significantly associated with intestinal gastric carcinoma, whereas the sulphomucin negative incomplete type (type II) is more frequently seen in benign conditions [2]. By Jarvi and Lauren classification, gastric carcinomas are subclassified into tumours

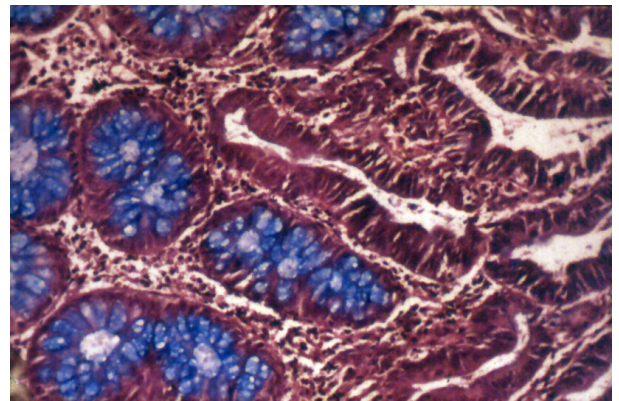


Figure 10. Intestinal incomplete metaplasia, surrounded by adenocarcinoma without mucin. Type II. HID – AB x 300.

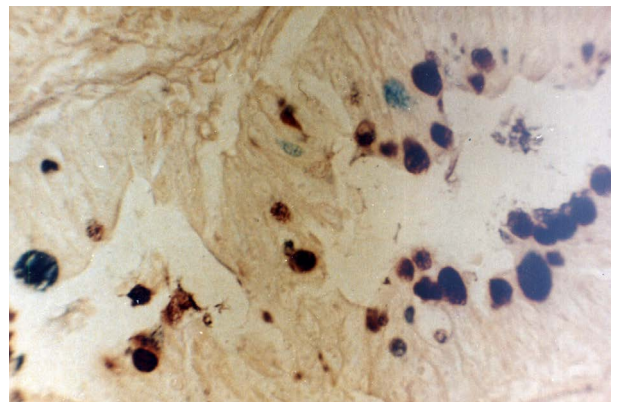


Figure 11a. Enterocolic metaplasia with sulphomucin – Type III. HID AB x 300

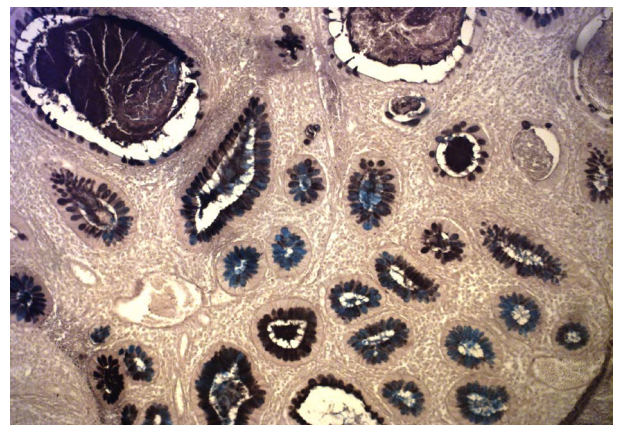


Figure 11b. B Gastritis: Enterocolic metaplasia (Type III) with Sulphomucin. HID-AB x 300

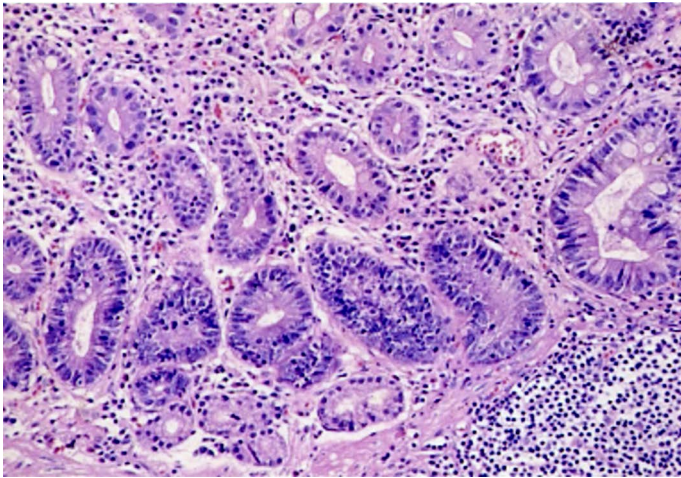


Figure 12. Dysplastic intestinal metaplasia. HE x 200

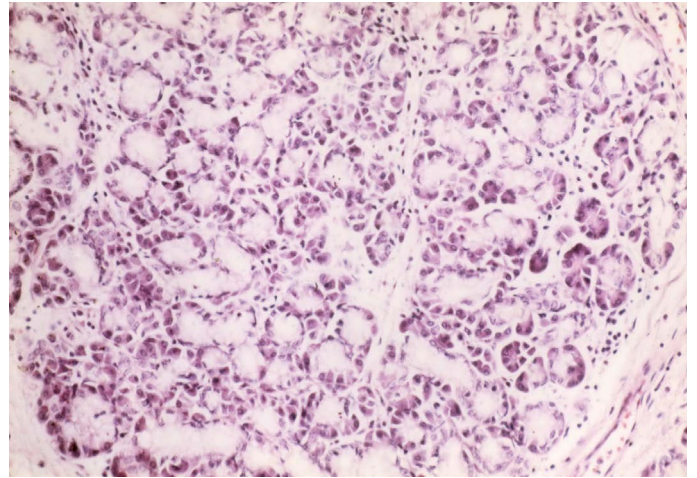


Figure 15. Exocrine lobular pancreatic structures in gastric antral mucosa. HE x 300

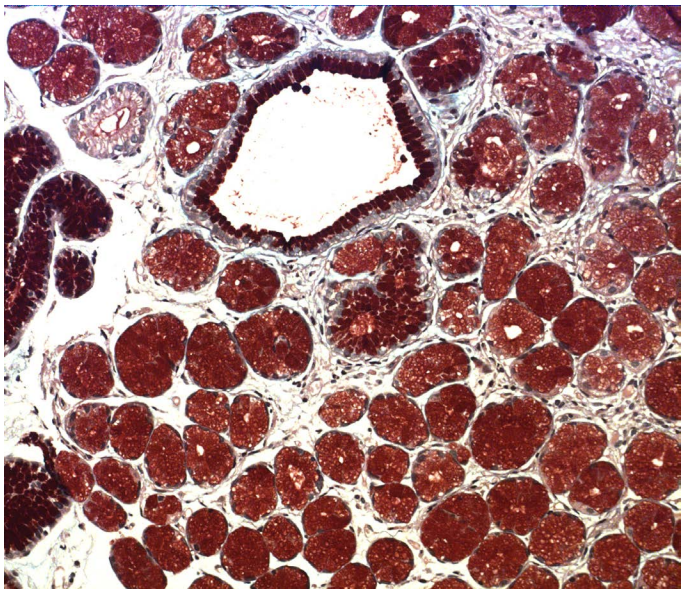


Figure 13. Predominant pyloric metaplasia with hipersecretio the neutral mucin AB-PAS x 300 neutral mucin

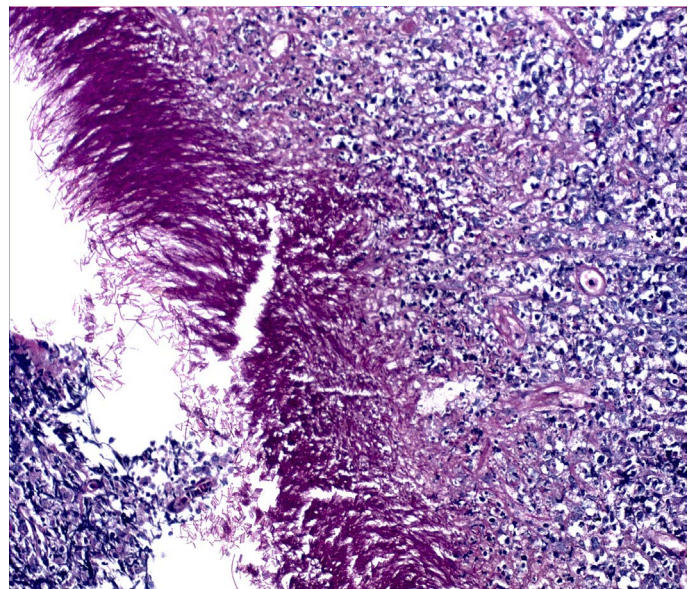


Figure 16. Mucotic gastritis. PAS + hyphae

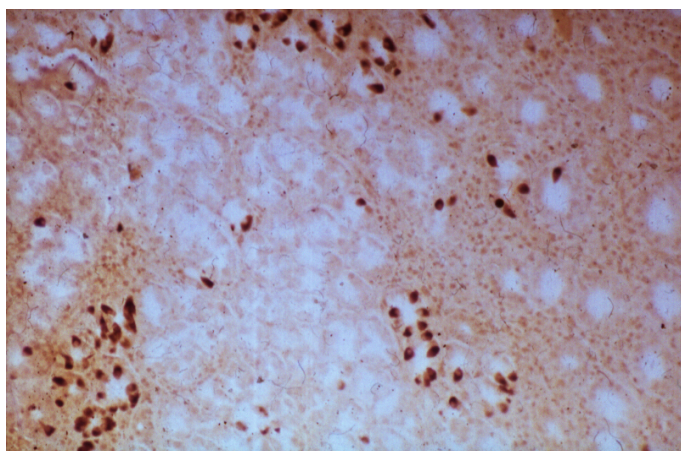


Figure 14. A gastritis: pyloric metaplasia with gastrin cells. PAP x 200

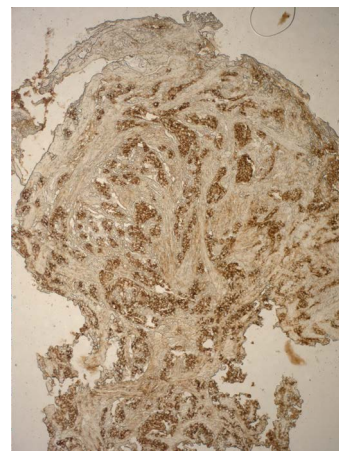


Figure 17. ECL- cell carcinoid: strong chromogranine A + reaction in neuroendocrine cells. ABC x 200

with intestinal, gastric and mixed differentiation, by using gastric markers (mucins MUC5AC, MUC6), intestinal markers (MUC2), transcription factors (CDX2, CD10) and others, representing new challenge for the researchers in the future [1,10].

Rare metaplasias in gastric mucosa

Less known the role of Pyloric, and rarer Pancreatic as well as Ciliar metaplasia in the gastric mucosa, requests detailed studied in the future. Except wrong definition that pancreatic acinar metaplasia represents the nodules of normal pancreatic tissue up to 1 cm in gastric or intestinal mucosa. Sometimes these islands presented in submucosa or in muscularis propria, mixing in this way the process of "metaplasia" with hamartomatous "pancreas aberrans" [32,33].

Discussion

Mucin histochemistry

Normal mucinous gastric cells secrete neutral mucins. The goblet cells of the complete and incomplete IM secrete acid mucins. In complete IM this includes N- and O-acylated sialomucin and small amounts of sulphomucins. The columnar cells of complete IM resemble intestinal enterocytes and therefore do not secrete mucus. The columnar cells of incomplete IM secrete mainly neutral mucins or sulphomucins [10,16]. There is generally an agreement that a variant of IM secreting a sulphomucins shows a selective association with gastric carcinoma, particularly the intestinal type [8,10,11,15,18-20].

Sulphomucins are secreted also by gastric dysplasia and gastric carcinoma. Some authors have adopted the term "colonic" metaplasia to describe the sulphomucin digesting secreting variant of IM [18,19]. The secretion of sulphomucin may not so much indicate early neoplastic transformation, but rarely reflects cellular adaptation to a carcinogenic microenvironment [30-37]. However, the secretion of sulphomucin may represent an important cytoprotective mechanism. Secretion of sulphomucin may be linked in several ways to gastric carcinogenesis. Finally, neoplastic clones which are protected by the secretion of sulphomucin, may be better able to resist gastric acid.

Metaplasia

Metaplasia may be important signal of a potentially cancerogenic environment. In the stomach, metaplasia itself may undergo malignant transformation [1-7]. The first step involves chronic superficial gastritis, reversible lesion, induced by a variety irritant. Atrophy or loss of parietal cell mass leads to hypochlorhydria and this allows the growth of bacteria which contain nitrate reductases which transform dietary nitrate to nitrite, a very active molecule which with the appropriate substrates may form N-nitroso compounds in situ. Nitrate is ubiquitous in foods; most diets contain more than adequate amounts to enter in the reactions.

Conclusions

- Gastric cancer is still a major cause of death in our republic.
- *H. pylori* infection triggers a multistep inflammation from chronic gastritis, atrophic gastritis, IM and finally to gastric cancer.
- As the infection of *H. pylori* is the most important risk factor of AG and IM, it is important to perform *H. pylori* eradication to prevent the progression to gastric cancer.
- However, side effects induced by eradication *H. pylori* therapy, are both mycotic gastritis and ECL- cell type I carcinoid of the corpus/fundic localisation, requesting further researches.

The proposed protocol

The protocol has been in progress since 1981 in a multicentric study (Filipe *et al.*). The essential points are:

1. Sampling of various regions and multiple biopsies.
2. Two levels cut from each biopsy.
3. H and E and Alcian blue + PAS stain in each case. If incomplete IM is present, further HID-AB stain is requested.
4. Report to the clinician to include IM types and advice for follow up according to protocol. A close relationship with the endoscopist is important as clinical as well as histological parameters will determine management.

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