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Chronic gastritis with intestinal metaplasia: clinico-statistical, histological and immunohistochemical study

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Abstract

Chronic gastritis has a high incidence in adults, causing progressive destruction of glandular structures, favoring the development of gastric atrophy. The association of chronic gastritis with intestinal type metaplasia of gastric mucosa has a poor outcome as intestinal metaplasia is regarded as a precancerous lesion. Metaplasia is common in patients with *Helicobacter pylori* infection and also heavy smokers. The aim of our study was to evaluate the relationship between chronic gastritis and intestinal metaplasia. The study was conducted on a total of 1218 patients, aged between 5 and 90 years, who presented for dyspeptic disorders in the period 2007–2010 and were examined clinically and endoscopically. During the gastroscopic examination, fragments of gastric mucosa were collected for the histopathological study and for highlighting the *H. pylori* infection. For the histopathological study, the Hematoxylin–Eosin and PAS–Alcian Blue stains were performed, while for the immunohistochemical study the anti-TAG72 and anti-PCNA antibodies were used. A diagnosis of gastritis was established in 615 patients, representing approximately 50.5% of all cases. Most cases with gastritis were found in people of middle age. Gastritis was present in almost all age groups, from teenagers to the elders. Of the 615 cases of gastritis, urease test was positive in 353 patients, representing approximately 57.40% of all patients with gastritis. Histopathological examination identified the presence of intestinal metaplasia in 61.60% of patients with chronic gastritis, mostly complete metaplasia. PCNA immunohistochemistry revealed that cell proliferation processes are intensified in intestinal metaplasia. This study highlights the importance of chronic gastritis, intestinal metaplasia, and *H. pylori* infection in the etiopathogeny of gastric cancer.

Keywords: intestinal metaplasia, chronic gastritis, goblet cells, atrophy, carcinogenesis.

Introduction

Chronic gastritis is characterized by inflammation of the gastric mucosa, with long-term evolution, characterized by progressive superficial and deep extension of the inflammatory process, eventually leading to destruction of glandular epithelium (atrophic gastritis) or of some components of the gastric wall (gastric atrophy). According to other authors [1], chronic gastritis has a high incidence in adults and the incidence increases with age.

Like any inflammatory lesion, chronic gastritis is characterized by a chronic inflammatory cell infiltrate located mainly in the chorion of the gastric mucosa, but sometimes also in the submucosa, consisting mainly of lymphocytes and plasma cells. The chronic inflammatory process affects the stomach and causes progressive destruction of glandular structures favoring the development of gastric atrophy [2].

The association of chronic gastritis with intestinal type metaplasia of gastric mucosa is an aggregate of histopathologic lesions that may have a poor outcome as intestinal metaplasia is regarded as a precancerous lesion that increases the risk of gastric cancer by six times [3].

Gastric mucosa metaplasia means the replacement of the lining epithelium and/or gastric glands with intestinal type epithelium glands similar to Lieberkühn glands [4]. Intestinal metaplasia is very common in adults, being detected in approximately one in four patients undergoing endoscopy. Prevalence of metaplasia is significantly

higher in patients infected with *Helicobacter pylori* and heavy smokers [4].

In our study, we evaluated the relationship between chronic gastritis and intestinal metaplasia.

Materials and Methods

The study was conducted on a total of 1218 patients, aged between 5 and 90 years, who presented for dyspeptic disorders at the "Rebirth" Gastroenterology Center in Craiova, in the period 2007–2010. They were examined both clinically and by gastroscopy. During the gastroscopic examination, fragments of gastric mucosa were collected for the histopathological study and for highlighting the *H. pylori* infection. Fragments of gastric mucosa were collected using standard endoscopic biopsy from five areas of the gastric wall, according to updated Sydney system. For the identification of *H. pylori* infection, the rapid urease test was performed immediately after gastroscopy, and for the histopathological and immunohistochemical studies gastric mucosa fragments were fixed in 10% neutral formalin solution and embedded in paraffin. For the histopathological study, the Hematoxylin–Eosin and PAS–Alcian Blue stains were performed, while for the immunohistochemical study the ABC/HRP (avidin biotinylated complex with peroxide) technique was used. Inhibition of endogenous peroxidase was performed by treating the histological samples for 30 minutes with 3% hydrogen peroxide, followed by washing with distilled water for 5 minutes. Antigen retrieval was carried out by heating in a microwave oven at 750 W, three cycles of 5 minutes each.

In this study, we used the anti-TAG72 and anti-PCNA antibodies (Table 1).

Table 1 – *Characteristics of primary antibodies used*

Antibody	Manufacturer	Host/Target	Clone	Isotype	Dilution	Antigen retrieval
Anti-TAG72	US Biological	Ms/Hm	9F171	IgG1k	1:1000	Sodium citrate, pH 6
Anti-PCNA	Dako	Ms/Hm	PC10	IgG2ak	1:50	Sodium citrate, pH 6

Results

Statistical analysis of patients with dyspeptic syndrome, clinically and endoscopically investigated at "Rebirth" Medical Center in Craiova, between 2007 and 2010, allowed us to note that of the total of 1218 patients with eso-gastro-duodenal pathology, a diagnosis of gastritis was established in 615 patients, representing approximately 50.5% of all cases. Most cases with gastritis were found in people of middle age, employed, especially between the age groups of 45–54 years and 55–64 years, where over 50% of people with dyspeptic syndrome were diagnosed with gastritis. It should also be noted that gastritis was present in almost all age groups, from teenagers to the elders (Figure 1).

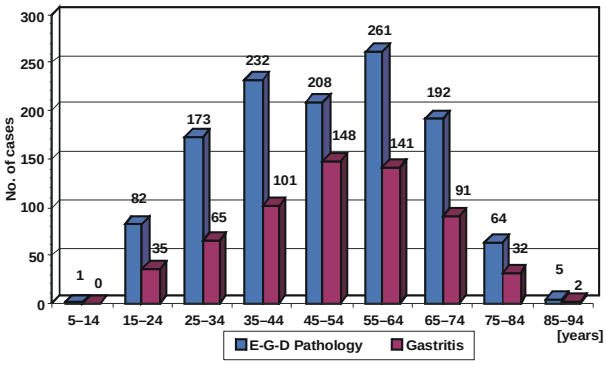

Figure 1 – *Distribution of cases with eso-gastro-duodenal (E-G-D) pathology as well as those with gastritis according to the patients' ages.*

According to the endoscopic appearance of gastritis, the most common forms were antral atrophic gastritis (185 cases, representing about 30% of gastritis cases), erythematous erosive gastritis (133 cases, representing approximately 21.62%), erythematous exudative gastritis (99 cases, representing about 16%), bile reflux gastritis (67 cases, representing about 11%), and papulopustular erosive gastritis (47 cases, representing about 7.64%).

In our study, we were particularly interested in the presence of *H. pylori* in patients with gastritis. Of the 615 cases of gastritis, urease test was positive in 353 patients, representing approximately 57.40% of all patients with gastritis (Figure 2).

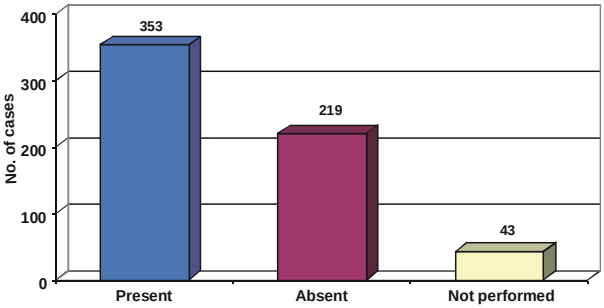

Figure 2 – *Distribution of cases according to the presence of H. pylori infection.*

In terms of bile reflux in the stomach, this situation was encountered in 77 patients, representing 12.53%.

Histopathological examination identified the presence of intestinal metaplasia in 61.60% of patients with chronic gastritis (Figure 3).

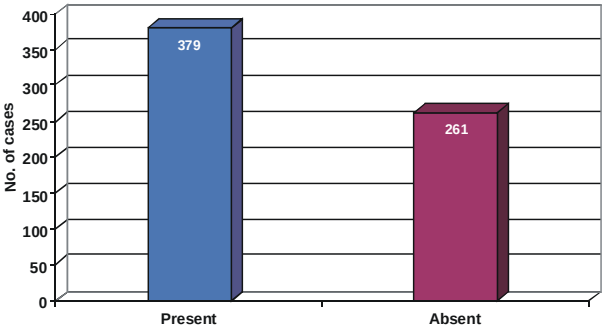

Figure 3 – *Distribution of cases according to the presence of intestinal metaplasia.*

Most cases showed the histological form of complete metaplasia (Figures 4 and 5), consisting of goblet cells and ciliated cells of intestinal type. The most obvious form of intestinal metaplasia was that with goblet cell

proliferation, while the presence of Paneth cells was more rare. The transition from gastric type epithelium to the intestinal type was sometimes sudden, and sometimes by a "transition zone" with cells of various sizes giving a pseudostratified aspect of the surface epithelium. The PAS–Alcian Blue staining allowed for an easier identification of areas with isolated intestinal metaplasia since goblet cells with as intestinal metaplasia were Alcian-positive, while the rest of the gastric epithelium remained PAS-positive (Figures 6 and 7).

The assessment of cell proliferation was performed by using the anti-PCNA antibody. Chronic gastritis showed a reduction of the area of cell proliferation correlated with the severity of the lesion. Thus, severe atrophic gastritis revealed a weak reactivity for PCNA both in terms of intensity and in extent. Even in gastritis associated with erosion of the surface epithelium, where the intensity of the reparative processes should be increased, the reaction to PCNA was reduced. In chronic gastritis associated with intestinal metaplasia, the reaction to proliferating cell nuclear antigen (PCNA) was diffuse, with moderate intensity, larger extent, and present in both the bottom of gastric crypts and the gastric surface epithelium, showing that cell proliferation processes are intensified in intestinal metaplasia (Figures 8 and 9).

The reaction to the anti-TAG72 antibody revealed very interesting data concerning the identification of goblet cell intestinal metaplasia, which is difficult to differentiate when these cells are isolated (Figures 10 and 11).

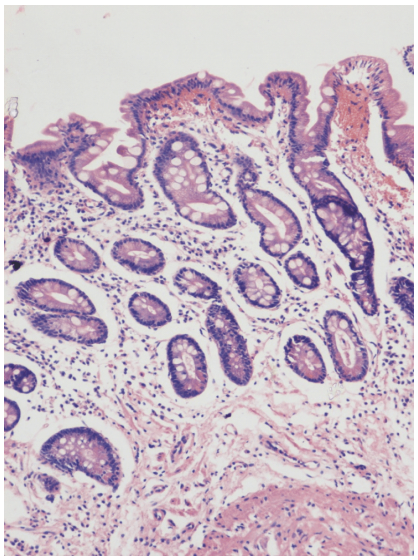

Figure 4 – ***Chronic gastritis with complete intestinal metaplasia (HE stain, ×100).***

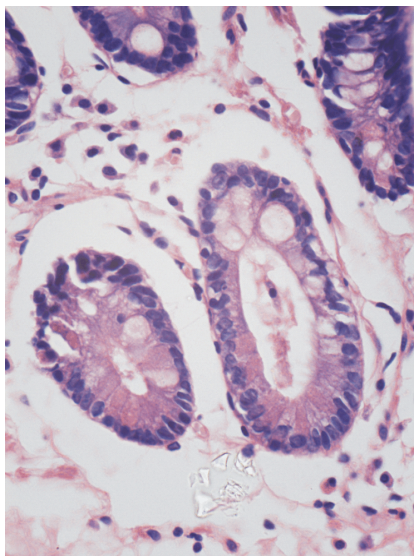

Figure 5 – ***Paneth cells at the bottom of foveolae (HE stain, ×200).***

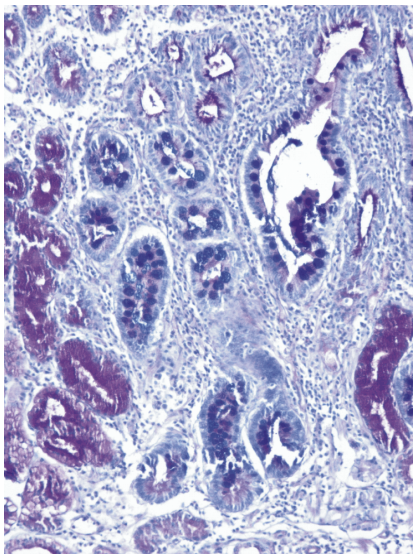

Figure 6 – ***Chronic gastritis with area of intestinal metaplasia and numerous Alcian+ goblet cells; gastric epithelial cells remained PAS+ (PAS–Alcian Blue stain, ×100).***

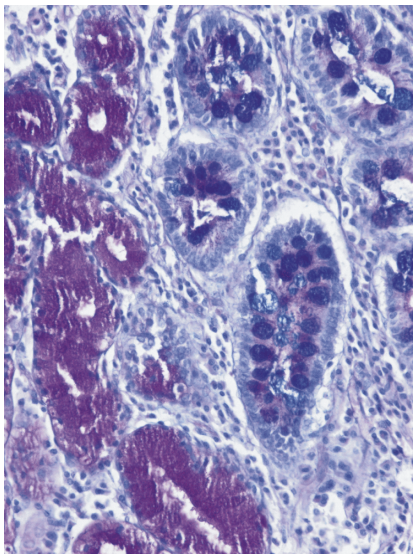

Figure 7 – ***Detail from the previous image (PAS–Alcian Blue stain, ×200).***

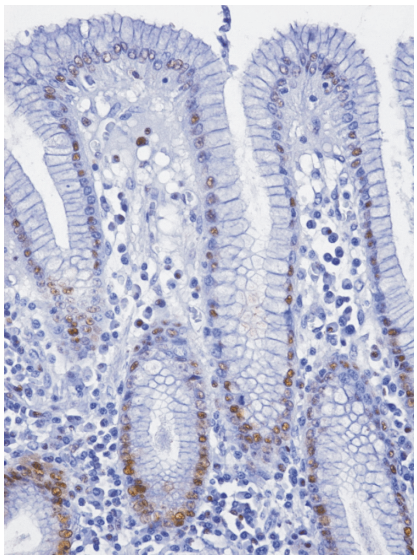

Figure 8 – ***Gastric mucosa with normal PCNA-positive reaction at the bottom of gastric crypts and gland neck (PCNA immunohisto-chemistry, ×200).***

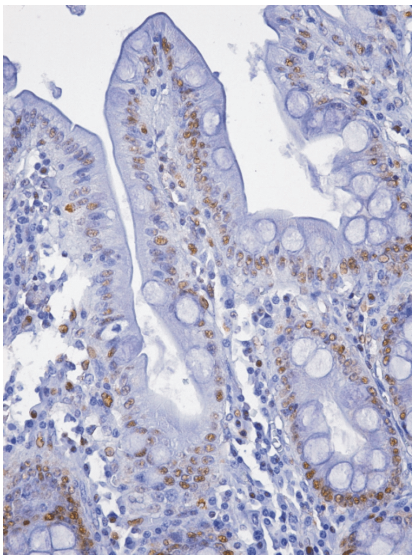

Figure 9 – ***Atrophic gastric mucosa with complete intestinal metaplasia and increased reactivity for PCNA (PCNA immunohistochemistry, ×200).***

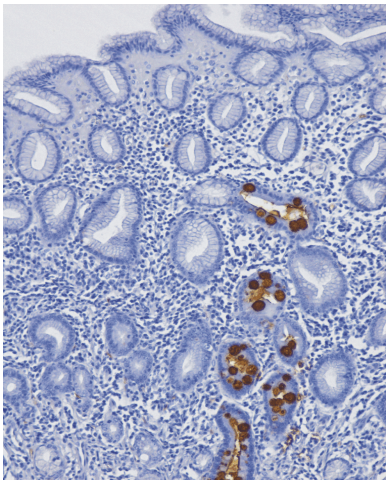

Figure 10 – ***Isolated intestinal metaplasia with TAG+ goblet cells (TAG72 immunohistochemistry, ×100).***

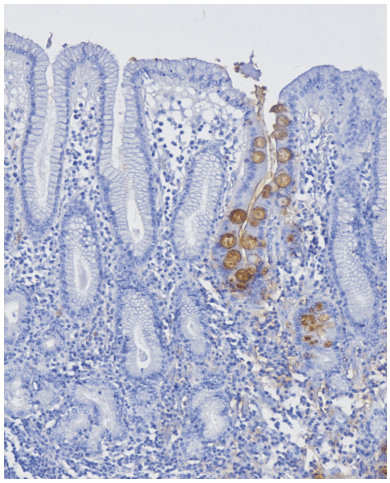

Figure 11 – ***Complete foveolar intestinal metaplasia with numerous and intense TAG72-positive goblet cells (TAG72 immunohistochemistry, ×100).***

Discussion

Gastritis is the most common stomach disorder and, because of its polymorphism, it is very difficult to make an accurate characterization of this disease. According to some authors [2], chronic inflammation of gastric mucosa is observed at all ages, with a higher frequency between 20 and 35 years. Clinical and statistical data we obtained showed that gastritis was present in over 50% of patients having an upper gastrointestinal distress, which is a very high percentage. The fact is that the evaluation of gastritis incidence in the general population is difficult to determine because the diagnosis of gastritis is often established only superficially based on subjective complaints, and another part of the patients are showing reduced clinical signs of gastritis although gastric mucosal lesions observed at endoscopy and histopathology confirmed, may be quite advanced.

Our study showed that lesions of gastritis can be found at any age but the maximum incidence was seen in people aged between 45 and 64 years. We believe that the data we obtained are more realistic because at this age etiopathogenic factors act more intensively. Thus, certain fried foods, some canned food and meat, spicy foods, alcohol, coffee and tobacco abuse underlying histological and physiological changes of gastric mucosa are more common in these age groups. Many of the drugs with irritating effect on the stomach, as salicylates, aminophenazone, anti-neuralgics, preparations of reserpin, cortisones, indocide, phenylbutazone, etc., were used by adults included in the study group.

In our study, most cases of chronic gastritis were of atrophic type. Gastric atrophy is considered the final stage of chronic gastritis and as a precancerous condition [5–7]. Most cases of gastric atrophy are associated with *H. pylori* infection, bacteria regarded as an important cause of chronic atrophic gastritis [8, 9]. Correa P postulates that carcinogenesis occurs as a progression from chronic gastritis to gastric atrophy and intestinal metaplasia, then dysplasia, and ultimately to cancer [7]. We believe that as chronic gastritis progresses, morphological changes of gastric glandular elements, among which gastric metaplasia is the most common, can occur. Intestinal metaplasia represents the conversion of gastric glands to a form similar to small bowel mucosal glands containing goblet cells, absorbing cells and Paneth cells. This transformation of the mucosa is a risk factor leading to the development of intestinal-type gastric cancer [10].

It seems that intestinal metaplasia is the most frequent and most common change of the gastric mucosa. Although the Sydney system of examination of the gastric mucosa is used a lot worldwide, a large-scale study in Houston showed that intestinal metaplasia was diagnosed in less then 50% in patients with chronic gastritis [11].

Numerous studies have shown that *H. pylori* infection is the most common identifiable cause of gastritis in children and adults [12]. Although *H. pylori* infection is usually acquired during childhood, there is little information regarding the prevalence of atrophy or intestinal metaplasia in the stomach of the child. Gastric mucosal atrophy in children is either rare or unrecognized, and when identified, it was not well characterized [13, 14].

In our study, using urease assay, *H. pylori* was identified at a rate of 57.40% of cases of cases with gastritis, which leads us to believe that this bacterial infection in the population of Romania is very high. Numerous studies show that *H. pylori* infection varies from country to country. However, it is estimated that 60% of the world population is infected with the organism [15]. Generally, infection is correlated with social and economic conditions [16]. Infection incidence rates in countries with developing economies reach an impressive rate: 80–90% [17, 18].

It is well established that chronic inflammation induced by *H. pylori* may lead to loss of normal gastric mucosal architecture, with destruction of gastric glands and replacement by fibrosis of subepithelial connective tissue. This process of gastric atrophy and intestinal metaplasia occurs in approximately half of patients with *H. pylori* infection, especially in patients with severe inflammation [19].

Zhang C *et al.* (2005) suggest that *H. pylori* seems to be the most important risk factor for development of glandular atrophy and intestinal metaplasia, but not the only risk [20]. Other identified risk factors include cigarette smoking, bile reflux, use of NSAIDs, salt, autoimmune gastritis and not yet recognized genetic factors [21–23].

Conclusions

Chronic gastritis was clinically and endoscopically diagnosed in more than 50% of patients with dyspepsia, and intestinal metaplasia was identified in more than 60% of patients with chronic gastritis.

H. pylori infection was identified in 57% of patients with chronic gastritis, highlighting the importance of bacterium in the pathogenesis of gastric lesions.

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