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Chapter 1

The Role of Endoscopy and Biopsy in Evaluating Preneoplastic and Particular Gastric Lesions

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/52676

1. Introduction

Although incidence has declined in recent years, gastric cancer still represents the second most frequent cause of cancer-related mortality in the world [1]. The prognosis of stomach cancer is related to the stage of disease at the time of diagnosis, with a good prognosis associated with early gastric cancer [2]. Therefore, it is essential an early diagnosis of gastric carcinoma, at present only about 10-20% of cancers being diagnosed in an early phase [3]. A great interest has arisen in recent years in the detection and management of premalignant conditions and early gastric cancer because of the high cure rate achieved treating these lesions, compared with advanced gastric cancer. The well known multistep cascade of carcinogenesis developed by Correa [4] is represented by superficial gastritis followed by atrophic gastritis, intestinal metaplasia and increasing grades of dysplasia, leading to gastric adenocarcinoma. Surveillance of the premalignant lesions could determine an early detection of patients with disease progression, with the possibility of early therapeutic intervention and improved survival of these patients [5].

Diagnosis and localization of premalignant lesions and early gastric cancer is difficult because of the possible lack of evident gross endoscopic signs, even with the performance of multiple random biopsies [6]. Another problem with conventional white light endoscopic diagnosis of these lesions consists in finding the exact location of previously sampled sites for endoscopic or surgical treatment [7]. Recently developed new endoscopic techniques have surpassed some of these drawbacks and have an improved accuracy of diagnosing early cancers and precancerous lesions.

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2. Material and methods

In order to evaluate the role of endoscopy and biopsy in assessing preneoplastic gastric lesions, we prospectively included in our study 96 consecutive patients with dyspeptic symptoms, admitted at the Department of Gastroenterology of the County Emergency Hospital Timisoara, Romania, between April 2010 and March 2011. The patients with various conditions which prevented satisfactory endoscopic examination were excluded from the study. Previously, the patients were informed and given their written consent regarding the protocol and the maneuvers of intervention included in the study.

All the endoscopic investigations were performed by senior endoscopists, with a conventional endoscope of the type Olympus Exera 140 (Japan). According to the criteria of the Sydney system of endoscopic evaluation of the gastritis [8,9,10], we designed a protocol (completed for each case) including: location of lesions, endoscopic aspect at the antral and body level (normal, focal or diffuse erythematous gastritis, erosive gastritis, erosive-hemorrhagic gastritis, atrophic gastritis, petechial gastritis), maintaining of certain particular elements (hypertrophy of the folds, nodularity, etc.), the severity of gastritis on endoscopy (mild, moderate, and severe).

For each case 5 biopsies were taken and processed: two biopsies from the antral level (A1 = the small curvature; A2 = the large curvature), two biopsies from the gastric body (C1 = the small curvature; C2 = the large curvature) and a biopsy from the gastric angle (U). Moreover, all macroscopically visible lesions have been biopsied with specification of their location and clinical diagnosis.

Tissue fragments were processed in the same manner, with fixation in 4% formaldehyde, paraffin inclusion and stained with hematoxylin-eosin. For histological identification of H. pylori we utilized the Giemsa modified stain. Histochemical reactions AA-PAS pH 2.5 and HID-AA allowed to appreciate the profile of mucins on sections examined. Morphological investigation was performed by a pathologist with experience in digestive pathology.

Statistical analysis of data was performed in a computerized manner, on the folder created, with specialized programs: Epi Info 6.04, SPSS 10 and Open Epi. This analysis consisted of:

- calculating the arithmetic means and standard deviations, for the quantitative variables;
- calculating the frequencies and percentages for the qualitative variables;
- statistical comparison of percentages with the χ^2 (square Chi) test;
- statistical estimation of results was performed using the criteria of decision of statistical tests:
- $p<0.05$- significant differences
- $p<0.01$- very significant differences
- $p<0.001$- extremely significant differences.

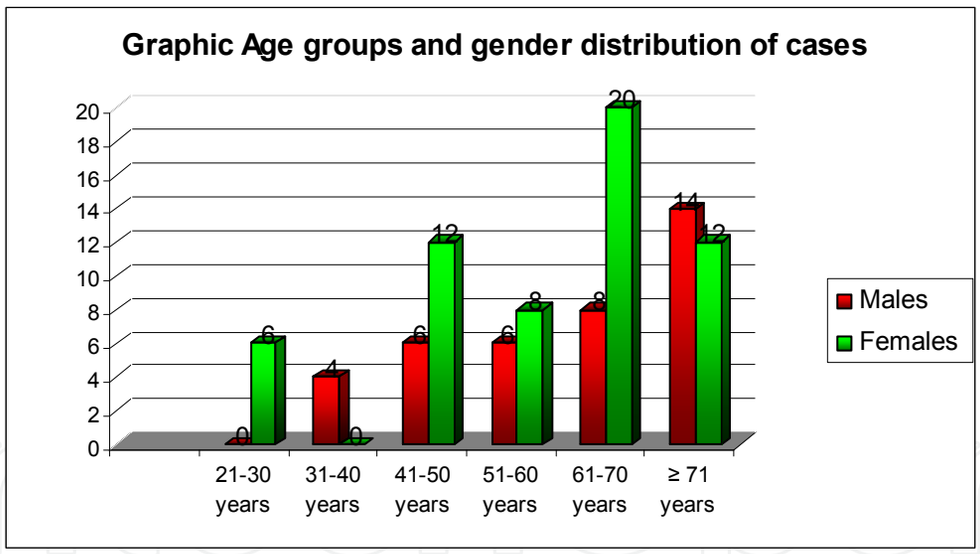
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3. Results

A total of 96 patients (58 females and 38 males) aged between 24 and 86 years (mean age 60.1±15.1 years) were included in the study. Age groups and gender distribution are shown in Table 1 and Graphic 1.

Age groups	Males (no. of cases; %)	Females (no. of cases; %)
21-30 years	0 (0%)	6 (10.35%)
31-40 years	4 (10.53%)	0 (0%)
41-50 years	6 (15.79%)	12 (20.69%)
51-60 years	6 (15.79%)	8 (13.79%)
61-70 years	8 (21.05%)	20 (34.48%)
≥ 71 years	14 (36.84%)	12 (20.69%)
Total patients	38 (100%)	58 (100%)

Table 1. Age groups and gender distribution of cases



Graphic 1. Distribution of cases according to age groups and gender

Gastric biopsies (480 samples) were taken and processed from these patients (two antral biopsies, two biopsies from the body, and one biopsy from the gastric angle for each case).

Atrophic gastritis, defined endoscopically by the appearance of submucosal vessels, giving rise to a mucosal vascular pattern similar to that found in the colon, sometimes associated with other features, e.g, mucosal discoloration, smoothness, or flattened rugal folds, constituted a rarely encountered entity in our study. In the cases studied we did not observe any

case of antral atrophic gastritis. In the gastric body, atrophic gastritis, was noted in 6 elderly patients (Tab 2).

Endoscopic aspect	Antrum No. of cases (%)	Body No. of cases (%)
Focal erythematous gastritis	12 (12.5 %)	0 (0%)
Diffuse erythematous gastritis	54 (56.1 %)	22 (23%)
Erosive gastritis	4 (4.2 %)	0 (0%)
Erosive-hemorrhagic gastritis	2 (2.1 %)	0 (0%)
Petechial gastritis	22 (23 %)	10 (10.4%)
Atrophic gastritis	0 (0 %)	6 (6.3%)
Normal aspect	2 (2.1 %)	58 (60.3%)

Table 2. Frequency of gastritis diagnosed endoscopically

For this lesion we noted a poor correlation between the conventional endoscopic investigation and histopathological examination (Tab. 3).

In accordance with the Sydney system, the morphological criteria of quantification applied to cases with gastric atrophy are the following:

- 0 = absent;
- 1 = mild (disappearance of less than 25% of glands);
- 2 = moderate (disappearance of 25 - 50% of glands);
- 3 = severe (disappearance of over 50% of glands);
- 4 = biopsy inappropriate for histopathological interpretation.

Age groups	Antral atrophy score (no. of cases; %)				Gastric body atrophy score (no. of cases; %)			
	0	1	2	3	0	1	2	3
21-30 years	6	-	-	-	6	-	-	-
31-40 years	2	-	2	-	2	-	2	-
41-50 years	10	2	6	-	8	4	6	-
51-60 years	8	-	6	-	8	2	4	-
61-70 years	20	4	4	-	18	2	8	-
≥ 71 years	4	4	16	2	2	6	14	4
Total patients	50 (52.1%)	10 (10.4%)	34 (35.4%)	2 (2.1%)	44 (45.8%)	14 (14.6%)	34 (35.4%)	4 (4.2%)

Table 3. Distribution of the histological score of atrophy identified histopathologically

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Atrophic chronic gastritis is characterized histopathologically by the numeric decrease in glandular structures of the gastric mucosa and development of new metaplastic glands lined by intestinal and/or pseudo-pyloric epithelium. We did not consider as real atrophy certain modifications of the gastric mucosa that produce a false reduction in gastric glands, such as the massive inflammatory infiltrate or the edema of the lamina propria.

From the total number of cases included in the study, we observed lesions of atrophic type in 46 antral biopsies (48%) and 52 gastric body biopsies (54.2%).

For antral location (Graphic 2) 10 cases with mild atrophy were noted (21.7%), 34 cases with moderate atrophy (74%) and 2 cases with severe atrophy (4.3% - Fig. 2). Glandular atrophy of gastric mucosa was observed much more frequently in patients with older ages (over 61 years). Biopsies noted with score 3 for atrophy pertain only to patients with ages ≥ 71 years.

Glandular atrophy was more frequently encountered in gastric body biopsies (but without significant differences compared with the antrum, p=0.386), being predominant in patients with average or old ages. Especially moderate and mild forms of atrophy were noted (14 cases with mild atrophy – 27%; 34 cases with moderate atrophy – 65.4% - Fig. 3; 4 cases with severe atrophy – 7.6%). All patients with severe glandular atrophy pertain to the age group ≥ 71 years.

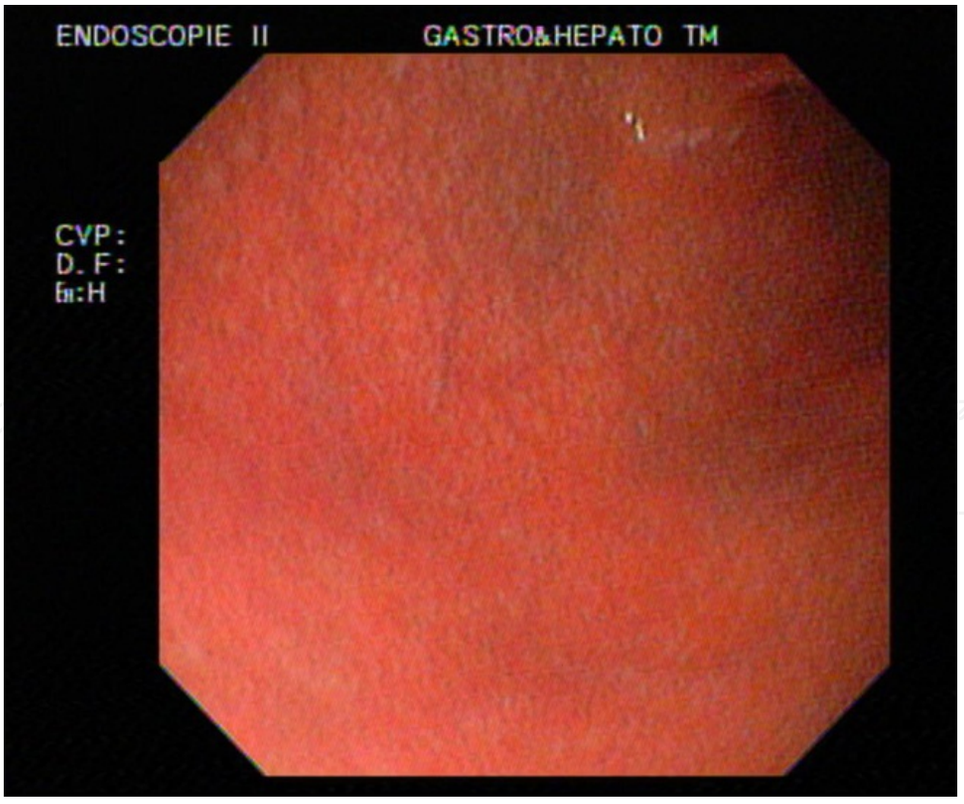


Figure 1. Congestive gastritis of gastric body, with mild atrophy of the mucosa

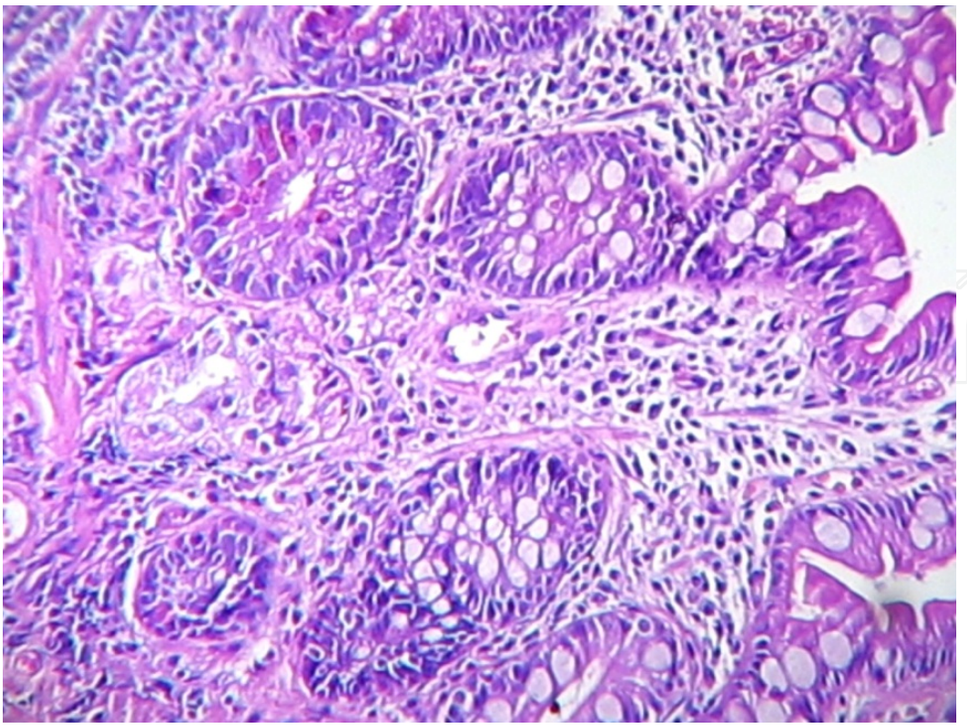


Figure 2. Antral chronic gastritis with severe atrophy and intestinal metaplasia. HE x 200.

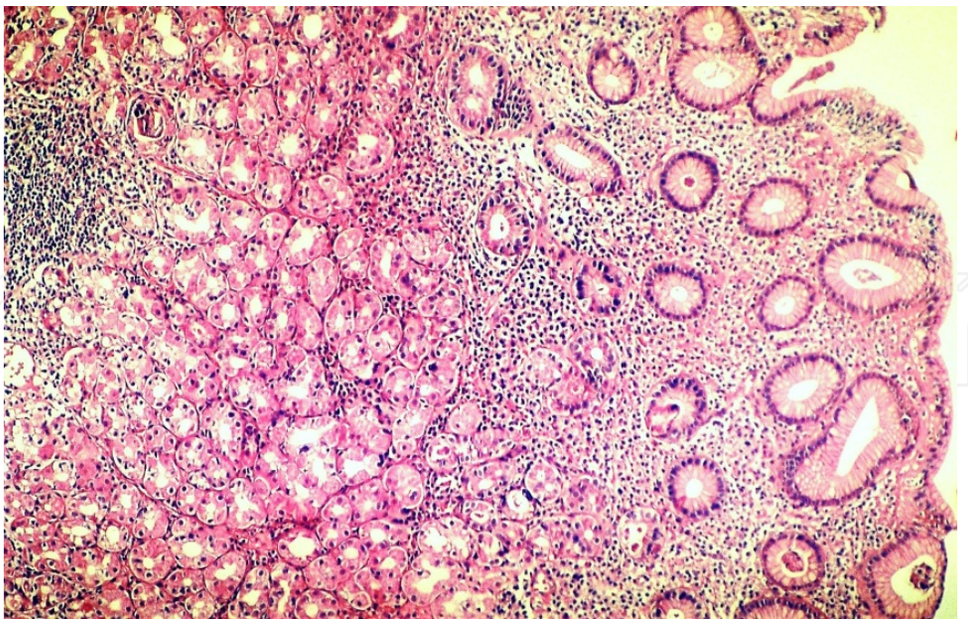
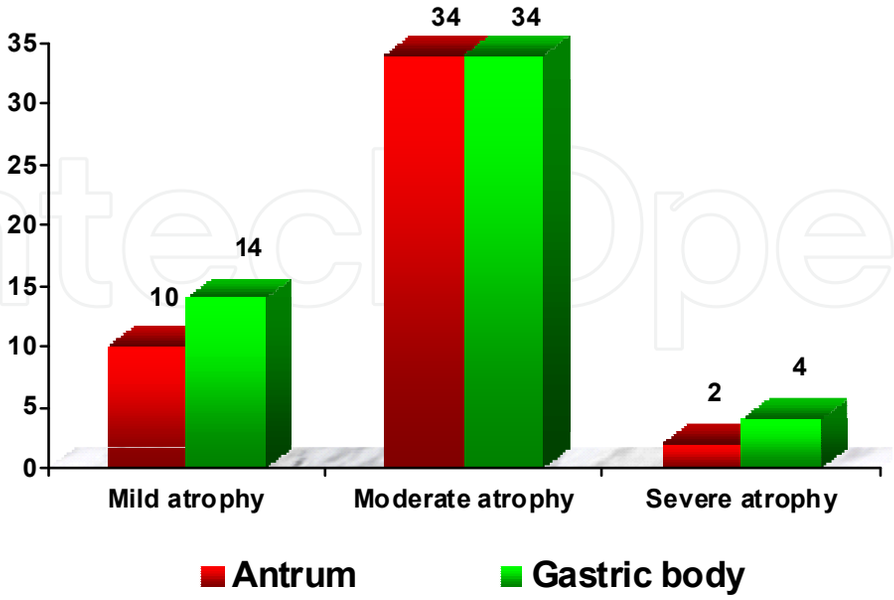


Figure 3. Chronic gastritis of the gastric body with moderate atrophy. HE x 100.

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Graphic 2. Histological evaluation of gastric atrophy

Intestinal metaplasia (IM) represents the replacement of the surface and glandular gastric epithelium by one composed of cells of the intestinal type (small or large intestine).

In conventional endoscopy, modifications such as nodules of yellow and white-nacreous color, aspect like fish scales or diffuse granular are suggestive for intestinal metaplasia of gastric mucosa. Such lesions were evident in 7 patients (4 males and 3 females) with ages between 54 and 76 years, with location in the gastric body.

In histopathological examination, preparations stained through usual morphological methods do not allow for the certainty diagnosis, nor do they allow for classification of intestinal metaplasia. For these reasons we used histochemical stain methods which give exact information on the composition of the mucus synthesized by the modified glands, respectively the neutral mucins, sialo- and sulfomucins.

Among histochemical methods recommended by the specialty literature, we used staining methods PAS-AA at pH 2.5 and reaction with colloidal iron diamine-AA (HID-AA).

Type I intestinal metaplasia (complete) is characterized by relatively normal glandular architecture, with straight crypts and glands lined by absorbing cells which do not secrete mucus and goblet cells with flattened nuclei and with widened apical pole, these two cellular types being encountered in approximately equal proportions. Occasionally, at the base of the glands one can observe Paneth cells. We identified this form of intestinal metaplasia with the PAS-AA stain, due to the presence of blue sialomucins in goblet cells (Fig. 4). Reaction with paraphenyldiamine is negative.

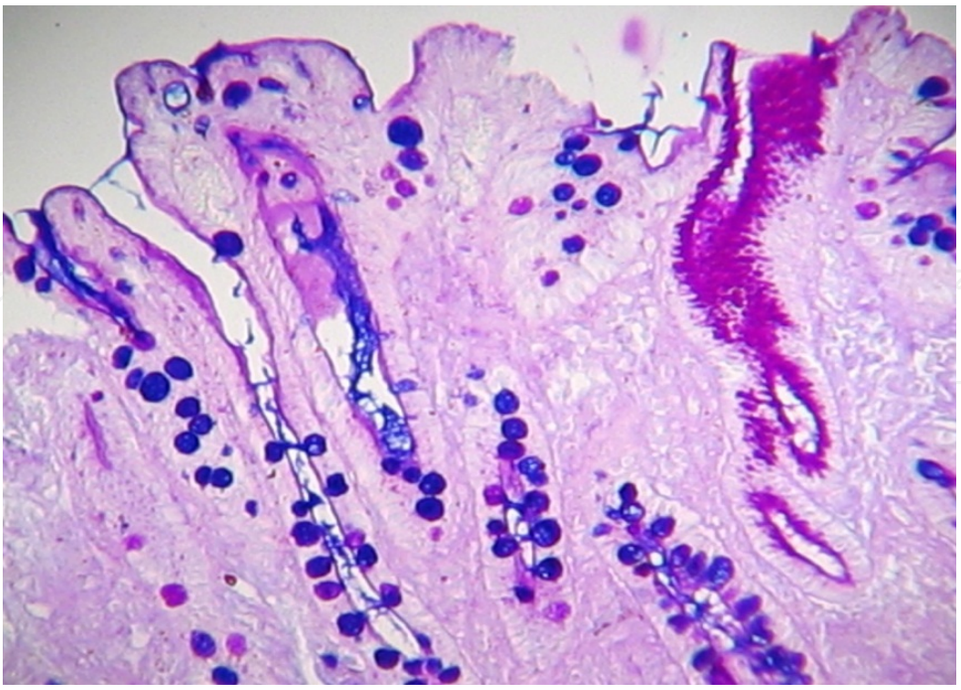


Figure 4. Type I intestinal metaplasia. AA-PAS x 200.

Type II intestinal metaplasia presents slight architectural modifications, with elongated and tortuous crypts, with focal areas of foveolar hyperplasia and columnar cells in variable number, which contain a mixture of neutral mucines and sialomucins, but not sulfomucins. The proportion of the goblet cells is greater than in type I. PAS-AA positive reaction is translated by mixed areas, PAS-positive and alcyanophil, representing neutral and acid mucines. The positive material is located in the apical portion of epithelial cells, in the lumen of some glands and in goblet cells (Fig. 5).

Type III of intestinal metaplasia is characterized morphologically by important glandular distortions, with ramified glands, lined with columnar cells which secrete sulfomucins and goblet cells secreting sialomucins. PAS reaction is negative, but the HID-AA reaction appears intensely positive, through both dyeing solutions. The positive substrate appears in goblet cells (blue), in the apical portion of columnar cells and in the lumen of metaplastic glands (dark brown) (Fig. 6 and Fig. 7).

The prevalence of intestinal metaplasia identified histopathologically at the antral level was of 20.8% (20 cases), and at the level of the gastric body of 25% (24 cases – Tab. 3) (p=0.492). At the antral level we noted 18 cases with focal distribution (score given 1 and 2) and only two cases with diffuse distribution (score 3) interesting almost entirely the gastric glandular epithelium. Following the extension of intestinal metaplasia according to patients' age, we observed the great frequency of types II and III in patients over 61 years old. For gastric body biopsies we did not encountered intestinal metaplasias with score 3, but 18 cases of metaplasias with score 1 and 6 cases with score 2 were identified. These metaplastic transformations occur more frequently in older patients, but also in patients from the age groups 31-40 years and 41-50 years (Tab 4).

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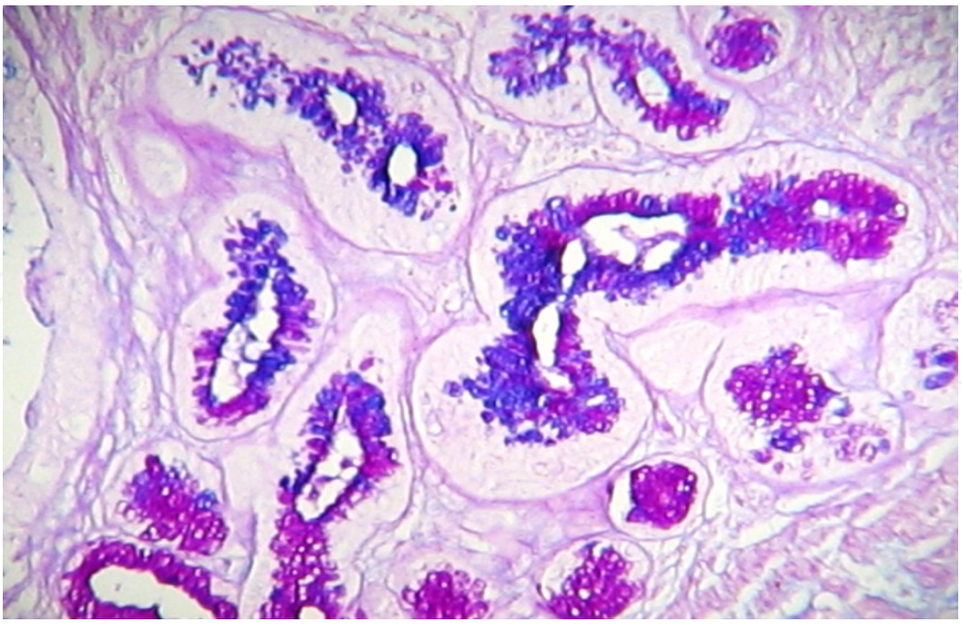


Figure 5. Type II intestinal metaplasia. AA-PAS x 200.

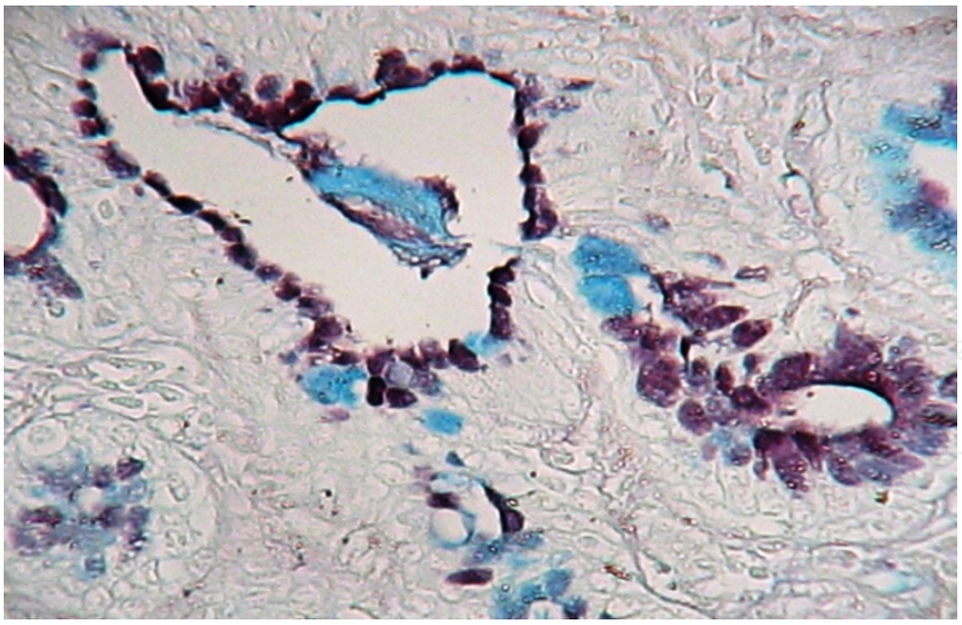


Figure 6. Type III intestinal metaplasia. HID-AA x 400.

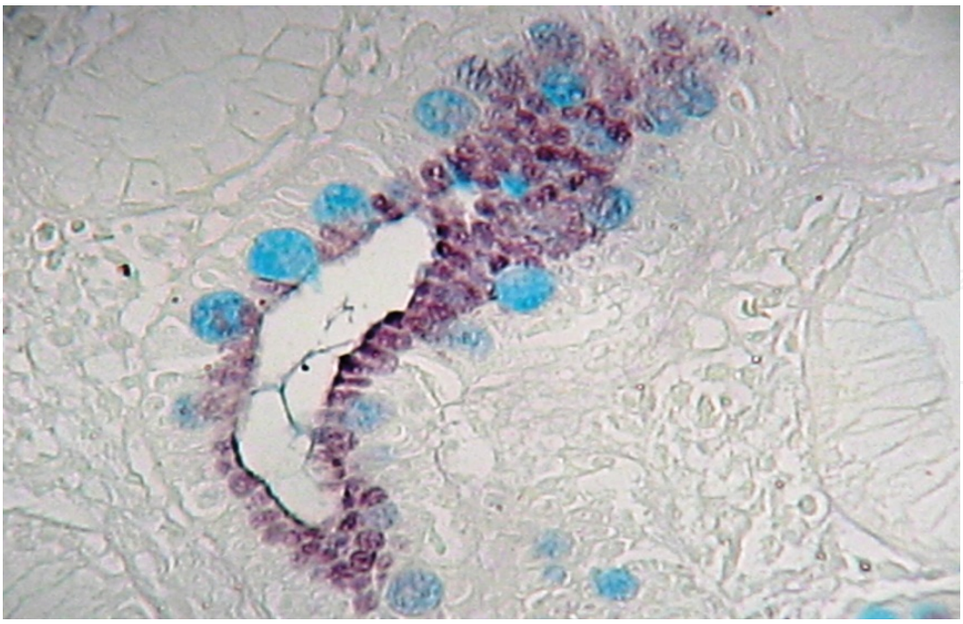


Figure 7. Secretion of sulfomucins (brown) and sialomucins (blue) from intestinal metaplasia type III. HID-AA x 400.

In accordance with the Sydney system, the morphological criteria of quantification applied to cases with intestinal metaplasia are the following:

- 0 = absent;
- 1 = mild (intestinal metaplasia in a focus of 1-4 glands);
- 2 =moderate (intestinal metaplasia in separate foci, but limited as extension);
- 3 = severe (intestinal metaplasia in over 50% from the gastric epithelium);
- 4 = biopsy inappropriate for histopathological interpretation.

Age groups	IM – antral biopsies (no. cases; %)				IM – gastric body biopsies (no. cases; %)			
	0	1	2	3	0	1	2	3
21-30 years	6	-		-	6	-	-	-
31-40 years	4	-	-	-	2	-	2	-
41-50 years	18	-	-	-	16	2	-	-
51-60 years	10	4	-	-	12	2	-	-
61-70 years	24	2	-	2	24	2	2	-
≥ 71 years	14	10	2	-	12	12	2	-
Total patients	76 (79.2%)	16 (16.6%)	2 (2.1%)	2 (2.1%)	72 (75%)	18 (18.7%)	6 (6.3%)	0 (0%)

IM –intestinal metaplasia

Table 4. Distribution of the histological score given to intestinal metaplasia

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For both locations, type I intestinal metaplasia was the most frequent encountered type (11.4% for antral biopsies and 15.6% for gastric body biopsies). The distribution of the three types of intestinal metaplasia at the antrum and gastric body level, respectively, did not differ significantly (p=0.560). Type II of intestinal metaplasia presented a relatively uniform distribution in all age groups (Tab. 5).

Age groups	IM – antral biopsies			IM – gastric body biopsies		
	I	II	III	I	II	III
21-30 years	-	-	-	-	-	-
31-40 years	-	-	-	-	1	1
41-50 years	-		-	1	1	-
51-60 years	3	1	-	1	1	-
61-70 years	-	3	1	3	-	1
≥ 71 years	8	2	2	10	1	3
Total patients	11 (11.4%)	6 (6.25%)	3 (3.1%)	15 (15.6%)	4 (4.2%)	5 (5.2%)

Table 5. Types of intestinal metaplasia

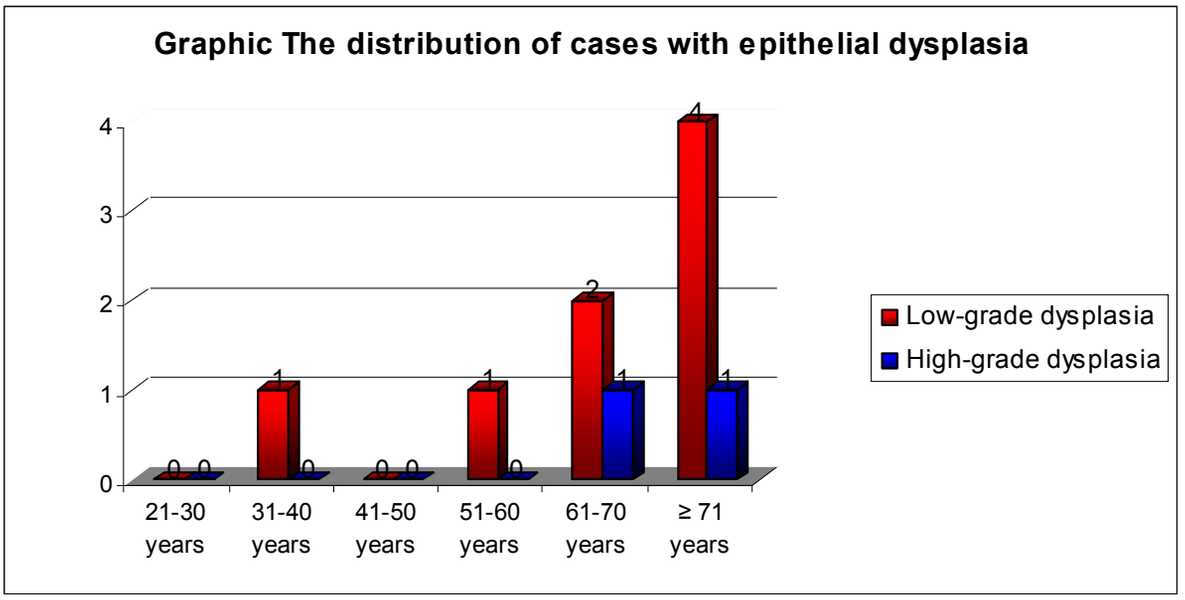
In our study we evaluated the incidence and types of **epithelial dysplasia** encountered in patients with dyspeptic symptoms. In accordance with the Vienna classification, dysplastic modifications were divided in low-grade dysplasia and high-grade dysplasia.

Histopathological examination of the 96 cases showed dysplastic lesions in 10 patients, prevalence being of 10.4%.

Low-grade dysplasia, observed in 8 patients (Tab. 6, Graphic 3), is characterized by glandular architecture mostly preserved, sometimes with the presence of pseudovilli, cystic dilated glands or slightly irregular glands, with discrete intraluminal papillary projections or serrated aspect. Glandular structures are lined with high, crowded cells, with or without mucous vacuoles at the apical pole. The nuclei appear elongated and pseudostratified, discretely pleomorphic, being situated in the lower half of the cytoplasm (Fig. 8 and Fig. 9). Mitotic activity is discrete.

Age groups	Gastric epithelial dysplasia	
	Low-grade dysplasia	High-grade dysplasia
21-30 years	-	-
31-40 years	1	-
41-50 years	-	-
51-60 years	1	-
61-70 years	2	1
≥ 71 years	4	1
Total patients	8 (8.33%)	2 (2.1%)

Table 6. Epithelial dysplasia in the cases studied



Graphic 3. The distribution of cases with epithelial dysplasia

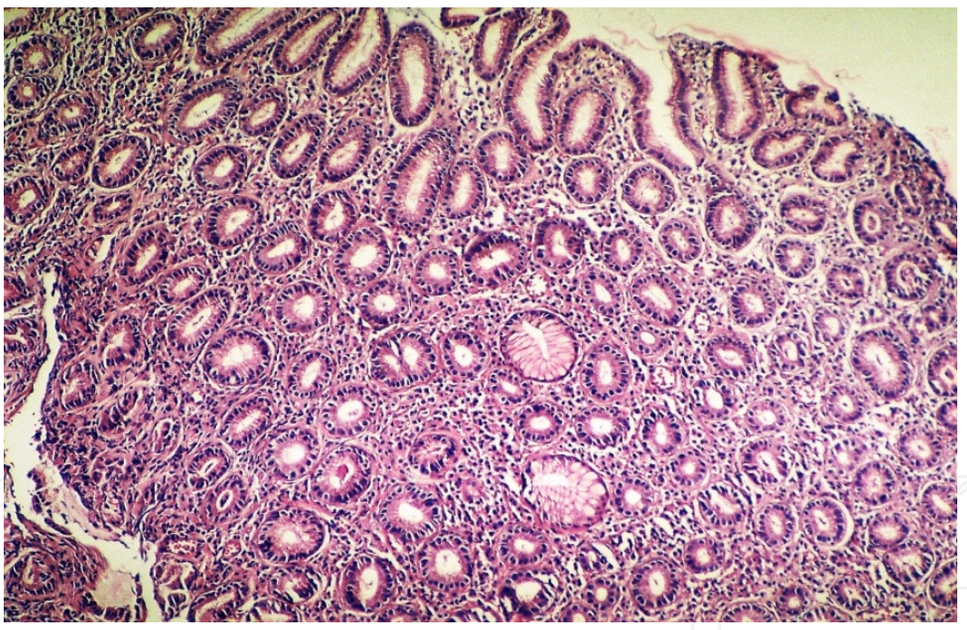


Figure 8. Low-grade epithelial dysplasia. HE x 100.

In all cases, dysplastic lesions were diagnosed histopathologically in the biopsies taken from the antrum. From an endoscopic point of view, patients presented more frequently aspects of antral diffuse erythematous gastritis (in 7 cases). In the case of a 66 year-old patient, the antral mucosa did not show macroscopic modifications which were visible with conventional gastroscopy. Epithelial dysplasia is observed mostly in patients in age groups 51-60 years, 61-70 years, and ≥ 71 years. In the cases studied we noted low-grade dysplastic lesions in a young patient, of age 36.

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Only in 2 patients we noted high-grade dysplastic modifications. High-grade epithelial dysplasia is characterized histopathologically by highly distorted glandular architecture, with crowded, irregular and ramified glands, with frequent papillary intraluminal projections, lined with stratified epithelium, with crowded, pleomorphic nuclei overlapping, with intense mitotic activity, losing of normal polarity, nuclei that touch the apical pole of the cell. In the neoplastic epithelium, goblet cells and Paneth cells are absent (Fig. 10).

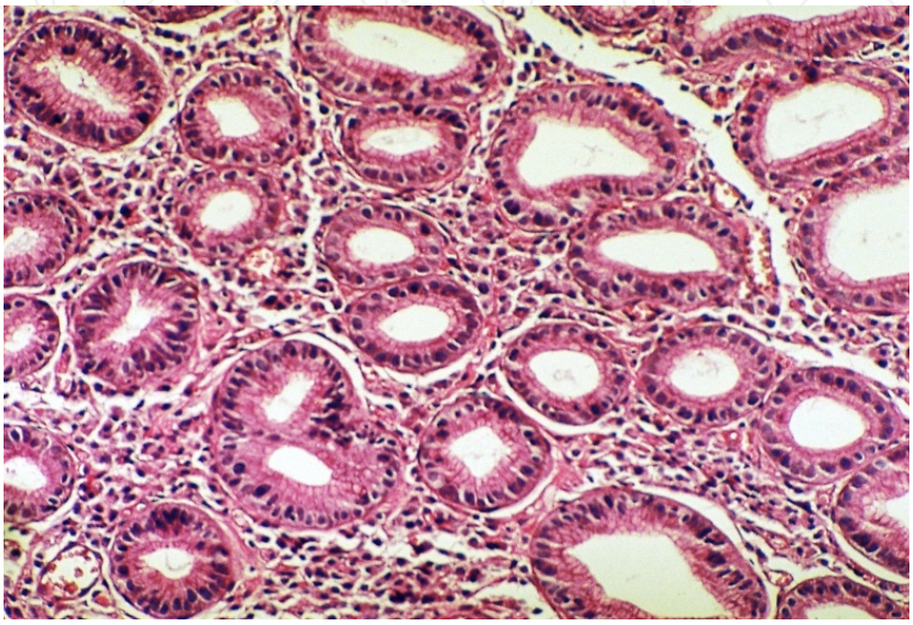


Figure 9. Low-grade epithelial dysplasia (detail). HE x 200.

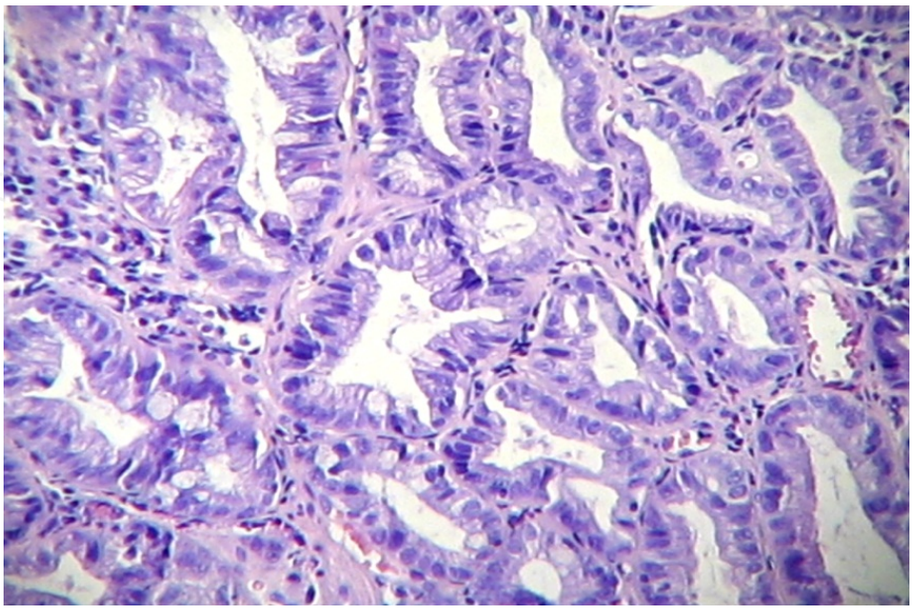


Figure 10. High-grade epithelial dysplasia. HE x 200.

These 2 patients were males of 64 and 75 years, respectively. In the case of the 75-year old patient, pangastritis obvious endoscopically was characterized through aspects of focal erythematous gastritis of the antrum with mild intensity and petechial gastritis of the gastric body, of severe intensity. For the second patient, gastroscopy showed only aspects of erythematous diffuse antral gastritis with moderate intensity. In both patients, infection with H. pylori proved to be negative histopathologically.

From **the particular lesions** observed, we mention the case of a 79-year old patient who presented in endoscopic investigation a nodular aspect of the mucosa of the antrum and gastric body, on the background of a petechial antral gastritis with mild intensity (Fig. 11). Histopathologically a particular form of pangastritis was diagnosed, granulomatous gastritis with non-necrotizing granulomas consisting of epitheloid cells and multinuclear cells, surrounded by lymphocytes, accompanied by a rich inflammatory lymphoplasmocytic infiltrate and atrophic modifications of the mucosa (Fig. 12 and Fig. 13). Lesions were more intense on the large curvature, for antral biopsy as well as for the biopsy taken from the gastric body. Anamnestic data and other investigations performed excluded a possible sarcoidosis or an idiopathic granulomatous gastritis, diagnostic conclusion being that of gastric Crohn's disease.

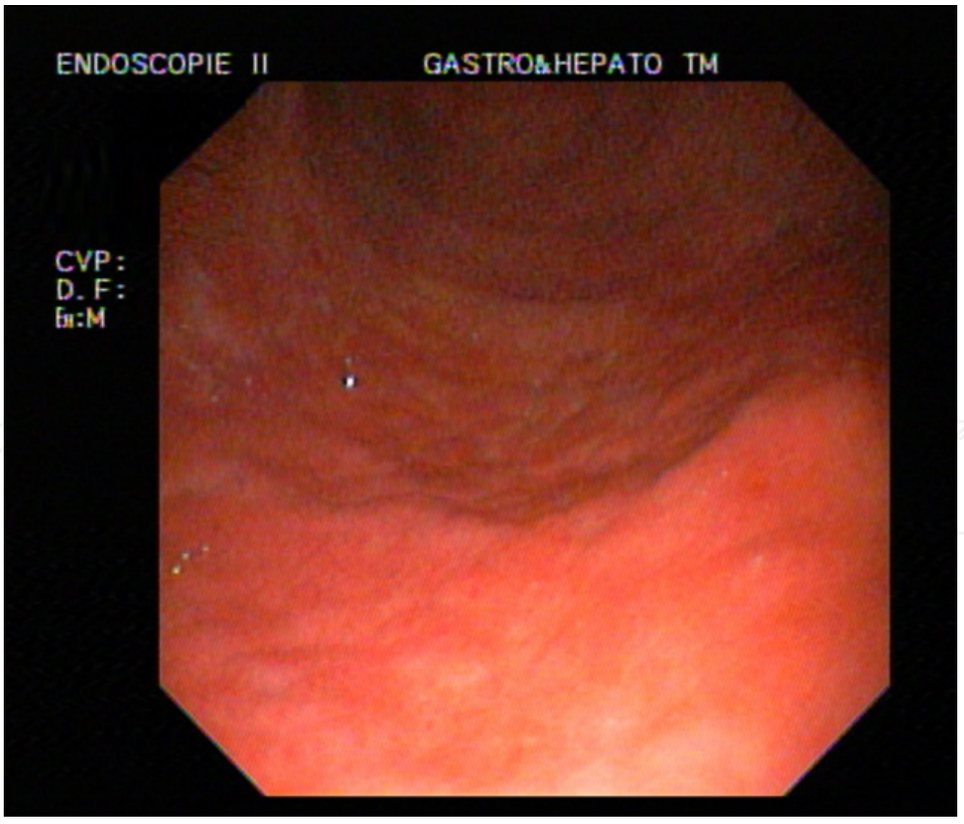


Figure 11. Congestive gastritis of the gastric body, at the large curvature, with nodular aspect.

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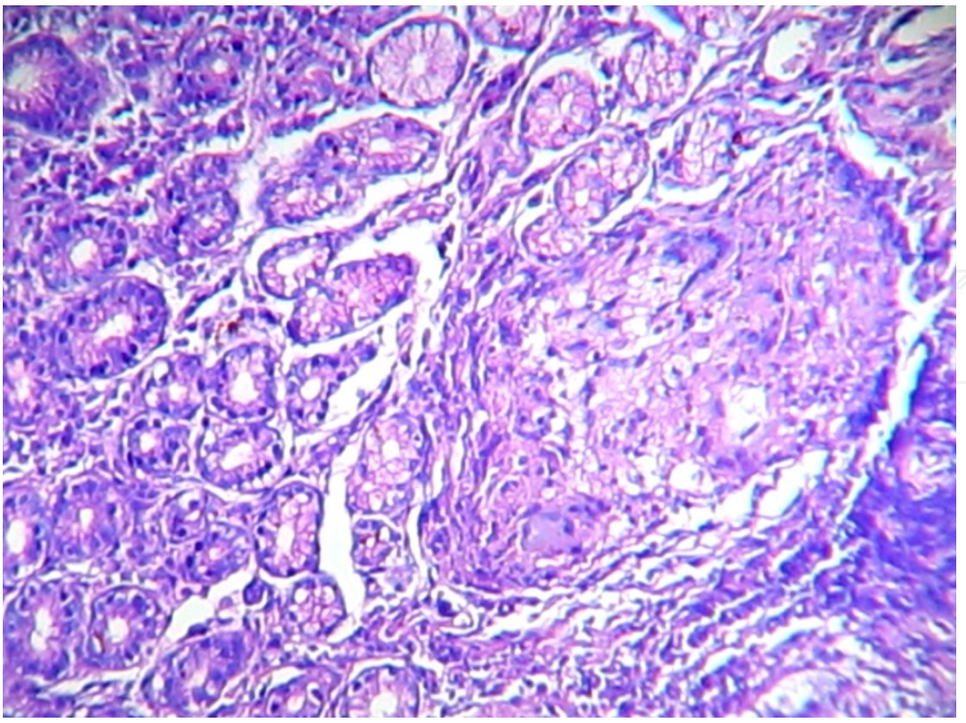


Figure 12. Gastric Crohn's disease. HE x 200.

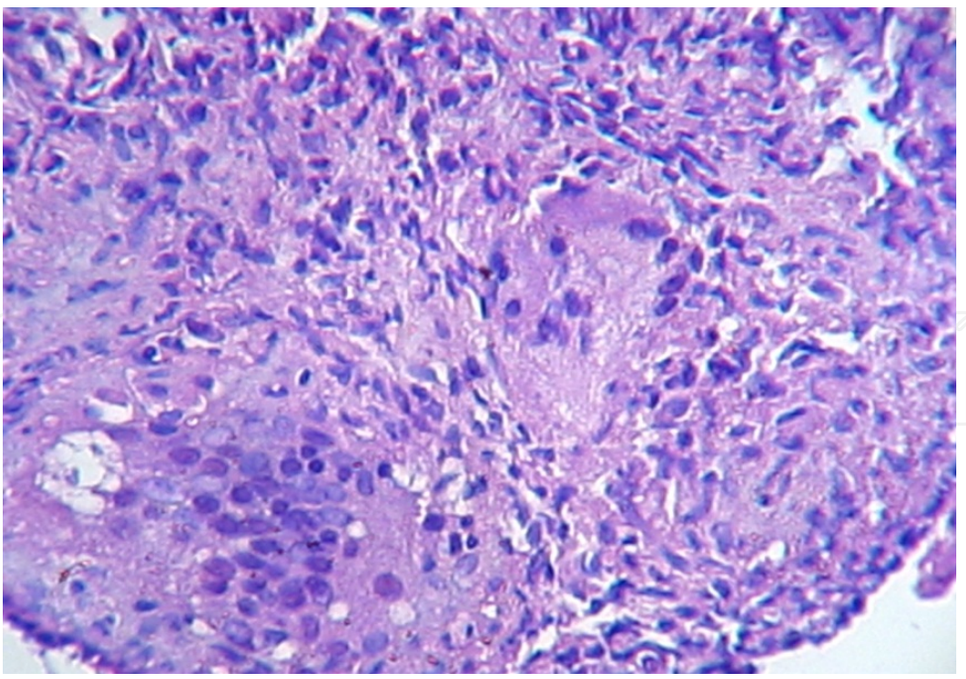


Figure 13. Non-necrotizing granulomas in the deep mucosa. HE x 400.

Another particular case is that of a patient aged 77, with gastroscopic modifications of diffuse erythematous gastritis of the antrum, of mild intensity. Although the gastric body did not appear modified, histopathological exam showed a rich lymphoplasmocytic infiltrate in the lamina propria, very frequent intraepithelial lymphocytes (at the level of the surface epithelium and in superficial glands), vacuolizations of epithelial cells, a slight glandular atrophy, discrete activity and absence of bacterial colonization (Fig. 14 and 15). Histopathological image was characteristic for lymphocytic gastritis, a rarely encountered form.

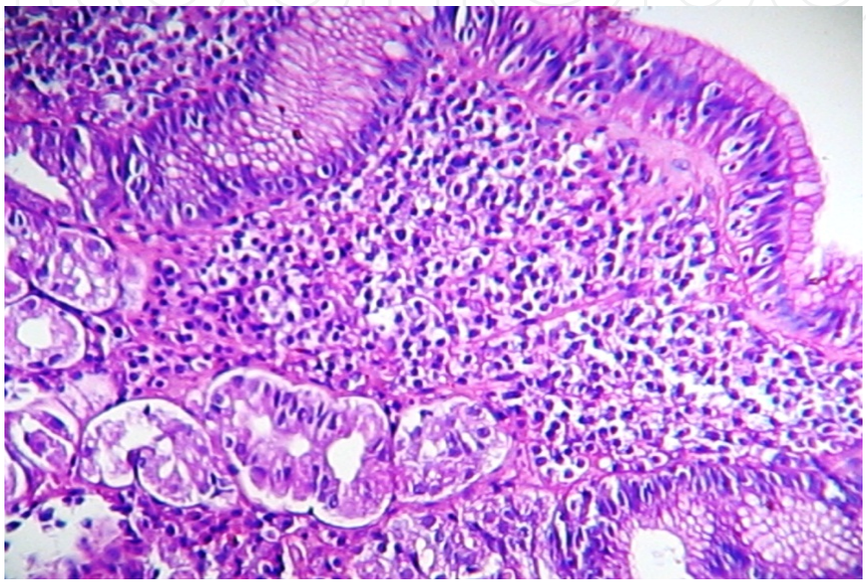


Figure 14. Lymphocytic gastritis. HE x 200.

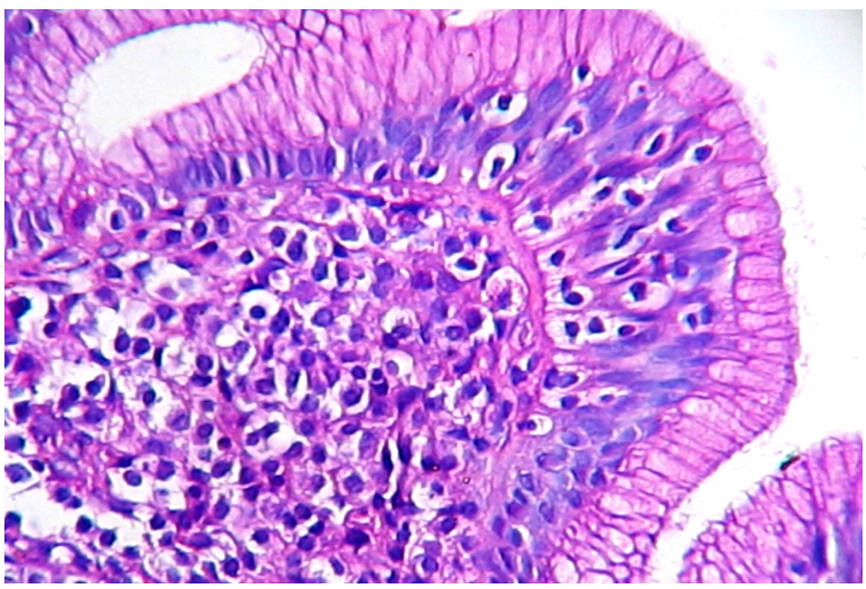


Figure 15. Lymphocytic gastritis. Numerous intraepithelial lymphocytes. HE x 400.

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4. Discussions

For the endoscopists, evaluation the presence or absence of gastritis based on the endoscopic aspect of the gastric mucosa represents a common practice. Throughout the years, the concept of "endoscopic gastritis" has gained credibility, its existence being recognized by the Sydney System of classifying gastritis [8,9,10]. Numerous studies followed the concordance between endoscopy and histopathological exam regarding the diagnosis of gastritis. The results of these works are contradictory, most of them supporting a low degree of concordance. However, the significant correlation between the gastroscopic and histopathological aspects in severe forms of gastritis are mentioned, and exclusion of active gastritis in case of a normal endoscopic aspect [11].

Epidemiological and clinicopathological studies have proved that the extent, the intensity and the distribution of gastric atrophy and inflammation are closely correlated with the incidence of gastric cancer [12,13]. Presently, the idea is accepted that only histopathological examination of gastric mucosa can correctly assess the risk of neoplastic progression of a gastric lesion, through identifying the modifications called preneoplastic: atrophy, intestinal or pyloric metaplasia, epithelial dysplasia [14].

Following the studies performed by Siurala M. in Finland and Estonia [15], Correa P. in Columbia and numerous Japanese authors [4], initially separate entities such as superficial chronic gastritis, atrophy, metaplasia, dysplasia and carcinoma were integrated in a hypothetical sequence, called "the cascade of Correa" [16]. This hypothesis of gastric carcinogenesis, presented in 1984, was lacking the triggering etiologic element. The discovery in the same year of H. pylori [17] placed the infection of gastric mucosa with this bacterium on the first step of the carcinogenesis cascade [18].

Histopathological lesions regarded as preneoplastic are represented by chronic atrophic gastritis, intestinal metaplasia and dysplasia. In their evolution, these entities can be regarded as a pyramid with a very wide base, composed of the population infected with H. pylori. A segment of this population (greater in the developing countries, compared with industrialized countries) will present the evolution of lesions towards atrophic gastritis, with or without intestinal metaplasia. Only a small part of the population will develop lesions of dysplasia and possibly gastric adenocarcinoma. In the cascade of carcinogenesis, the closer a lesion is of neoplasia, the greater is its risk to progress towards gastric carcinoma [14]. Thus, chronic gastritis is a remote and uncertain precursor of gastric cancer, which constitutes rather a predisposing condition. High-grade dysplasia is a true neoplastic lesion [19,20].

Gastric atrophy is defined as a numeric reduction of the self glandular structures of the gastric mucosa [21,22]. This definition, purely morphological, implies a disappearance of glands characteristic for an area of the gastric mucosa, for instance specialized glands from the gastric body, and their replacement either with extracellular matrix, fibroblasts or collagen, or by intestinal type or pseudopyloric glands. These modifications imply the alteration of physiological mechanisms, for instance, anomalies of the secretion of mucins and acid.

Atrophic lesion is defined by the presence of atrophy areas in the gastric mucosa. The most frequent causes are the long-term infection with H. pylori and autoimmune gastritis. In the actualized Sydney system, the term of "atrophic gastritis" is used to differentiate this entity by the "non-atrophic gastritis" or simply "gastritis", a lesion with severity expressed in the antrum and identified in most patients infected with H. pylori.

Atrophic gastritis is characterized by the numeric decrease or disappearance of typical gastric glands, the expansion of antral type mucosa in the gastric body (antralization or pseudopyloric metaplasia) and areas of intestinal metaplasia. This entity presents a significant epidemiologic risk for the gastric adenocarcinoma, the prognostic implications being determined by the extent and distribution of atrophic areas [14,16,23,24].

Studies from literature have shown that the presence of atrophic gastritis has an annual incidence of progression to gastric cancer of approximately 0.5-1%, and that the extent of atrophic gastritis within the stomach correlates with the risk of progression to carcinoma [25-28].

The two forms of atrophic gastritis are represented by corporal autoimmune and by multifocal atrophic gastritis, the later being more common, associated with H. pylori infection, and with lesions of metaplasia. The presence of infection has been associated with an approximately 10-fold increased risk of atrophic gastritis development. There has been demonstrated an important regional variation in the prevalence of atrophic gastritis in H. pylori-infected individuals, with an increase of about 3-fold in Asia, in comparison with Western countries [29,30].

The pathophysiology associated with the increased risk of gastric cancer in patients with gastric atrophy may be related to achlorhydria, which predisposes to gastric bacterial overgrowth, accumulation of N-nitroso compounds, and diminished ascorbate secretion into the gastric lumen. Moreover, low acid output determines increased serum gastrin levels that may contribute to abnormal cell growth and increased risk of neoplastic progression [31].

In our study, the endoscopic aspect of atrophic gastritis was rarely encountered. Some authors signal the reduced percentage of atrophic gastritis cases diagnosed endoscopically, the lesions being obvious only for the severe forms as intensity [32]. In the cases studied we did not observe any case of antral atrophic gastritis. In the gastric body, atrophic gastritis, was noted in 6 elderly patients

For this lesion we noted a poor correlation between the conventional endoscopic investigation and histopathological examination. Out of the total number of biopsies included in the study, we observed lesions of atrophic type in 46 antral biopsies (48%) and 52 biopsies of the gastric body (54.2%); location of the atrophy was encountered more frequently at the level of the gastric body, but without statistical significance (p=0.386). Location of the chronic atrophic gastritis predominantly at the level of the gastric body is mentioned in specialty literature. This lesion presents a multifocal disposition with individual foci, initially developed at the level of the gastric angle. The foci extend and merge along the small curvature and on the anterior and posterior walls of the stomach [27]. In a recent study it is shown that most gastric carcinomas of intestinal type develop on the background of a wide terrain of atrophic

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gastritis, with small dispersed areas of intestinal metaplasia, which progresses proximally towards the large gastric curvature [33].

For the antral location we noted 10 cases with mild atrophy (21.7%), 34 cases with moderate atrophy (74%) and 2 cases with severe atrophy (4.3%). The glandular atrophy of the gastric mucosa was encountered much more frequently in patients with older ages (over 61 years old). The biopsies graded with score 3 for atrophy pertain only to patients with ages ≥ 71 year.

Glandular atrophy was encountered more frequently in biopsies of the gastric body, being predominant in patients with average and old ages. Especially moderate and mild forms of atrophy were noted (14 cases with mild atrophy – 27%; 34 cases with moderate atrophy – 65.4%; 4 cases with severe atrophy – 7.6%). All patients with severe glandular atrophy pertain to the age group of ≥ 71 years. In concordance with other studies [27,34] we noted an association between atrophic gastritis, and gastritis in general, predominant in the gastric body and old age of patients.

Intestinal metaplasia represents the replacement of the gastric lining and glandular epithelium by one composed of cells of the intestinal type (small or large intestine). Multiple attempts to classify the various forms of intestinal metaplasia led to a complex terminology, difficult to apply in the medical practice (complete or incomplete, type 1, 2a and 2b, etc.). The most used classification is the one proposed by Jass and Filipe, which includes 3 types of intestinal metaplasias:

- type I intestinal metaplasia (the complete type or of small intestine type) is characterized by relatively normal glandular architecture, with straight crypts and glands lined with absorbent cells non-secreting mucus, with striated plate and goblet cells with flattened nuclei and with widened apical pole, these two cellular types being encountered in approximately equal proportions. Occasionally, at the base of the glands Paneth cells can be observed. Goblet cells secrete AA-positive sialomucins. Reaction with paraphenyldiamine is negative;
- type II intestinal metaplasia (the incomplete type or enterocolic type) presents slight architectural modifications, with prolonged and tortuous crypts, with focal areas of foveolar hyperplasia and columnar cells in variable number, which contain a mixture of neutral mucines and sialomucins, but not sulfated material. The proportion of goblet cells is greater than in type I. PAS-AA positive reaction translates through mixed PAS-positive and alcyanophil areas, representing neutral and acid mucines. The positive material is located in the apical portion of epithelial cells, in the lumen of certain glands and in goblet cells;
- type III of intestinal metaplasia (the incomplete type or colonic type) is characterized morphologically through important glandular distortions, with ramified glands, lined with columnar cells which secrete sulfomucins and goblet cells secreting sialomucins and sulfomucins. PAS reaction is negative, but the HID-AA reaction appears intensely positive, through both coloring solutions. The positive substrate appears in goblet cells (blue), in

the apical portion of columnar cells and in the lumen of some metaplastic glands (dark-brown) [14,27,35].

Currently use classifications take into consideration the presence of Paneth cells (complete metaplasia) or crescent architecture changings, dedifferentiation, and degree of absence of Paneth cells (incomplete metaplasia), and also the pattern and type of mucin expression. Type I metaplasia displays decreased expression of gastric mucins (MUC1, MUC5AC, and MUC6), and expression of the intestinal mucin MUC2. In type II and III metaplasia gastric mucins (MUC1, MUC5AC, and MUC6) are coexpressed with MUC2 [36]. However, the use of immunohistochemistry or other special techniques in order to subtype intestinal metaplasia is not widespread in routine practice.

Another pattern of metaplasia- spasmolytic polypeptide expressing metaplasia (SPEM), has been described in recent years. This type is characterized by the expression of the TFF2 spasmolytic polypeptide that is associated with oxyntic atrophy and usually develops in the gastric body and fundus. SPEM appears to share some characteristics with pseudopyloric metaplasia, and has a strong association with chronic infection with Helicobacter pylori and with gastric cancer. Studies suggests that it may represent another pathway to gastric neoplasia [37].

The presence of type I intestinal metaplasia confers a very low risk of malignant transformation. However, type III is considered a true dysplastic lesion

Type I metaplasia does not seems to raise the risk of gastric carcinoma. Numerous studies have shown that the presence of type II or III intestinal metaplasia is associated with a 20-fold increased risk of gastric cancer [38-40]. Intestinal metaplasia represents a preneoplastic lesion for the intestinal type of gastric cancer, 42% of patients with type III intestinal metaplasia developing early gastric cancer within five years of follow-up [41].

It remains unclear whether gastric carcinoma arises from areas of intestinal metaplasia or whether this lesion represents only a marker for higher cancer risk. The prevalence of intestinal metaplasia (similar to atrophic gastritis) in H. pylori-infected individuals is higher in Asia (about 40%) in comparison with Western countries [29,30].

Atrophic gastritis and intestinal metaplasia are often unevenly distributed throughout the stomach. The updated Sydney System is the most widely accepted for classification of gastritis and recommends five biopsies, two from the antrum (3 cm from the pylorus, greater and lesser curvatures), one from the incisura and two from the corpus (one from the lesser curvature, 4 cm proximal to the incisura, and one from the middle of the greater curvature) [10]. Although this biopsy protocol generally establishes with accuracy H. pylori status and chronic gastritis, the number of biopsies is controversial with regard to staging of precancerous gastric lesions, mainly because of their multifocal disposition [42-44].

For an accurate staging and grading of gastric precancerous conditions, the Guideline of the European Gastrointestinal Endoscopy recommends at least four non-targeted biopsies of two topographic sites (at the lesser and greater curvature, from both the antrum and the corpus) and additional target biopsies of lesions [45].

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Although the updated Sydney system have contributed to a uniform description of preneoplastic lesions, in order to predict gastric cancer risk it has been established OLGA staging system (operative link for gastritis assessment). This system offers a standardized report of histopathological data with information about the topography and the extent of the atrophic changes and subgrouping of patients by gastric cancer risk [46,47]. Gastritis stages (0 to IV) express increasing extents of atrophy, proved on antral and corpus biopsies. Studies have allocated a small minority of gastritis patients to stages III and IV, associating this subgroup of population with a significantly higher cancer risk and thus with endoscopic follow-up programs [48,49]. Because the OLGA system is based on the severity and extent of atrophy, which held a low interobserver agreement, it was introduced a modified system-based on intestinal metaplasia, OLGIM (operative link for gastric intestinal metaplasia), with a high level of interobserver concordance [50]. Implementation of OLGIM system was associated with an easier histological assessment and the advantage of including of fewer patients into the high risk stages, therefore a smaller population for whom endoscopic surveillance would be needed [51].

The surveillance of premalignant gastric lesions may be important for early detection of gastric cancer and improved survival. Globally, gastric cancer risk is too low to justify endoscopic follow-up in all patients with atrophic gastritis and intestinal metaplasia. Studies have shown that cancer risk increases in patients with extensive intragastric lesions [26,28,52]. The two forms of extensive intestinal metaplasia, the so-called "magenstrasse" or "transitional zones" distribution (intestinal metaplasia found over the lesser curvature from cardia to pylorus) and the "diffuse distribution" show an increase risk for cancer (odds ratio [OR] = 5.7 and 12.2, respectively) [53]. In order to establish the extent of atrophy and intestinal metaplasia, it can be used endoscopic assessment, histological assessment of multiple biopsies and serology. Serologic testing for pepsinogens, gastrin and H.pylori antibodies can establish the extent of atrophic gastritis and identifies patients at increased risk of developing gastric cancer [54].

The Guideline of the European Gastrointestinal Endoscopy recommends that endoscopic surveillance should be offered to patients with extensive atrophy and/or intestinal metaplasia every 3 years after diagnosis [45].

Correct classification of intestinal metaplasia requires performing some relatively sophisticate histochemical techniques, whose interpretation was not standardized up to present day. From the histochemical methods recommended by specialty literature, in our study we used coloration methods PAS-AA at a pH of 2.5 and reaction with colloidal iron diamine-AA (HID-AA).

In conventional endoscopy, modifications of the type of intestinal metaplasia of gastric mucosa were evident in 7 patients (4 males and 3 females) with ages between 54 and 76 years, with location at the level of the gastric body.

The incidence of intestinal metaplasia identified histopathologically at the level of the antrum was of 20.8% (20 cases), and at the level of the gastric body of 25% (24 cases), without any significant differences between the antral location and the location at the level of the

gastric body, respectively, of the metaplasia (p=0.492). At the antral level we noted 18 cases with focal disposition (score given 1 and 2) and only 2 cases with diffuse disposition (score 3), interesting almost entirely the gastric glandular epithelium. Following the extension of the intestinal metaplasia in relation with patients` age, we observed the great frequency of types II and III in patients over 61 years old. For the biopsies of the gastric body we did not note intestinal metaplasias with score 3, but we identified 18 cases of metaplasias with score 1 and 6 cases with score 2. These metaplastic transformations appear more frequently in elderly patients, but also in patients from the age groups 31-40 years and 41-50 years.

For both locations we remarked the predominance of type I intestinal metaplasia (11.4% for antral biopsies and15.6% for biopsies of the gastric body, without statistically significant differences between the two locations, p=0.398). Type III was a lesion rarely encountered in our study, being slightly more frequent in the gastric body (5.2%), in comparison with the antrum (3.1%) and noted especially in patients over the age of 50. Type II intestinal metaplasia presented a relatively uniform distribution in all age groups. In the large study of Suriani R. and collaborators [55], which included 1750 patients, type III intestinal metaplasia was noted in 6.7% of cases, from which 5.7% identified only in the antral mucosa.

Neoplasia constitutes the final stage of phenotypic and genetic progressive changings which affect the normal cellular morphology, resulting in a new cell characterized through uncontrolled proliferation and potential of migrating and implanting. In epithelial tissues, the first noticeable modification in optical microscopy is the alteration of cell morphology. Tumoral cells present large nuclei, with prominent nucleoli and granular chromatin or in rough blocks. In comparison with the nucleus, the cytoplasm is poorly represented, the nucleus-cytoplasm ratio being much increased. Cytological alterations are associated with various degrees of architectural anomalies. Such epithelial changings can appear in two situations: in epithelial injuries, followed by processes of reparation and in neoplastic alterations. For the first situation the term of reactive atypia is used, and for the second the term of dysplasia.

Throughout several decades, the pathologists have tried to standardize the criteria of diagnosis and grading for epithelial dysplasia. Pathologists from around the world united their efforts, but their opinions have coincided only in regard to the epithelial dysplasia of the mucosa of large intestine and the dysplasia in the Barrett epithelium. The discovery of the H. pylori bacterium and its relationship with gastric cancer focused the attention of researchers upon the gastric preneoplastic lesions. It was suggested that the eradication of this infection can prevent or even reduce the regression of these lesions. Unlike metaplasia or atrophy, whose types and classifications were established without major disputes, specifying the definition and diagnosis criteria for dysplasia created significant controversies among the Western and the Japanese pathologists. Japan represents one of the countries with the greatest incidences for gastric adenocarcinoma and at the same time, with the best survival rates in gastric cancer. The reasons invoked for exceptional results are: implementing the early diagnosis programs, introducing innovating endoscopic techniques and especially including some borderline lesions in the group of carcinomas, while other pathologists include them in the category of dysplasia [14].

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There were differences between Japanese and European/North American pathologists in categorizing intraepithelial neoplasia; for instance, lesions interpreted by the latter as high-grade intraepithelial neoplasia (dysplasia) have been frequently classified by Japanese pathologists as "noninvasive intramucosal carcinoma". In an attempt to resolve this issue, several proposals have been made regarding terminology of the morphological spectrum of lesions ranging from non-neoplastic changes to early invasive cancer.

Thus, in order to eliminate the existent dissensions, an international forum was formed, and in 1996, Schlemper RJ organized a seminar with this topic, the results being published in the Lancet magazine in 1997 [56]. Subsequently, several study groups were constituted formed by Japanese pathologists and Western pathologists who made their goal to establish a consensus on the classification of preneoplastic lesions. One of these classifications, accepted by the World Health Organization, was presented at the seminar from Padua, Italy in 1998, and represents a model of histopathological interpretation and of choosing the therapeutic conduit [57,58].

The Padua Model includes the definition of dysplasia as pre-invasive neoplasia and the classification of gastric neoplasia in 5 categories:

1. negative for dysplasia;

2. non-defined for dysplasia;

3. non-invasive neoplasia;

4. suspicion of invasive cancer;

5. gastric cancer.

These lesional categories are similar with the lesions included in the Japanese Classification of the Gastric Cancer. Each category corresponds to one or several sub-categories, in order to cover the entire spectrum of epithelial alterations [14].

In 1998, on occasion of the World Congress of Gastroenterology in Vienna, a consensus was reached in regard to the terminology for the gastrointestinal epithelial dysplasia, named **"The VIENNA Classification"** [19]. In this classification, the diagnosis of "high-grade dysplasia/adenoma", "carcinoma *in situ* (CIS)", and "suspicion of invasive carcinoma" were grouped in a single category (category 4), called "high-grade non-invasive neoplasm", due to the therapeutic recommendation which was similar for all these sub-groups.

At the beginning of the year 2000, the Vienna classification was reviewed, in category 4 including a new subcategory, namely, the intramucous carcinoma [59]. The terminology of this consensus makes a distinction between high-grade intraepithelial neoplasia, without the actual invasion of the lamina propria, and respectively with the invasion of the lamina propria, the last term being named intramucous carcinoma at the level of the esophagus and of the stomach. At the level of the colon, the risk of nodal invasion is null in this situation, for which reason in the West there is the tendency to avoid the term "carcinoma" for the lesions without invasion of the submucosa, since they are treated completely only through local ex-

cision. Beyond this stage, all neoplastic lesions with invasion of the submucosa are termed invasive carcinomas.

The Vienna Classification reviewed of gastrointestinal epithelial neoplasia:

Category 1: Negative for dysplasia/neoplasia

Category 2: Non-defined for dysplasia/neoplasia

Category 3: Low-grade epithelial neoplasia:

- low-grade adenoma/dysplasia

Category 4: High-grade epithelial neoplasia:

4.1. High-grade adenoma/dysplasia

4.2. Non-invasive carcinoma (carcinoma „in situ")

4.3. Suspect of invasive carcinoma

4.4. Intramucous carcinoma

Category 5: Carcinoma with invasion of the submucosa.

At the end of the year 2000 the work Classification of the WHO revised was published, in which category 4 in the Vienna classification was adopted under the name of "high-grade intraepithelial neoplasia" and is defined as "modification of the mucosa with cytological and architectural aspects of malignity without the invasion of the stroma; it includes the lesions of severe dysplasia and carcinoma in situ" [60].

In our study we evaluated the incidence and forms of epithelial dysplasia encountered in patients with dyspeptic symptoms. In accordance with the Vienna classification, the dysplastic modifications were classified in low-grade dysplasia and high-grade dysplasia.

Current **WHO classification** [61] considers the following conditions as precursor lesions of invasive neoplasia (intraepithelial neoplasia) of the stomach:

- gastritis-associated dysplasia:

– adenomatous (type 1)

– foveolar (type 2)

- adenoma:

– intestinal type

– pyloric-gland type

– foveolar type

- fundic gland polyp-associated dysplasia.

According to the **WHO classification of tumors of the stomach 2010**, the following categories of gastric intraepithelial neoplasia (dysplasia) should be considered:

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1. *Negative for intraepithelial neoplasia (dysplasia).* This subgroup includes benign mucosal processes that are inflammatory, metaplastic, or reactive in nature.
2. *Indefinite for intraepithelial neoplasia (dysplasia).* This term is usually used when an ambiguous morphological pattern is encountered, but is not a final diagnosis. This category is usually used were there is doubt as to whether a lesion is neoplastic or non-neoplastic (i.e. reactive or regenerative), particularly in small biopsies exhibiting inflammation. The dilemma is usually solved by cutting deeper levels, by obtaining additional biopsies, or after treating for possible etiologies.
3. *Intraepithelial neoplasia (dysplasia).* This category includes epithelial neoplastic proliferation characterized by variable cellular and architectural atypia, but without convincing evidence of invasive growth. Intraepithelial neoplasia (gastric epithelial dysplasia) can have polypoid, flat or slightly depressed growth patterns. The flat or slightly depressed patterns may show an irregular appearance on chromoendoscopy or microvasculature anomalies on narrow-band imaging, aspects that are not apparent with conventional white-light endoscopy. In the western countries, the term "adenoma" has been applied when the neoplastic proliferation produces a protruding lesion. By contrast, in Japan, "adenomas" include all gross types (flat, elevated and depressed).

In the stomach, most cases of dysplasia have an intestinal phenotype (adenomatous; type I) resembling colonic adenomas with crowded, tubular glands lined by atypical columnar cells; the cells present overlapping, hyperchromatic and/or pleomorphic nuclei, with pseudostratification and inconspicuous nucleoli, mucin depletion, and lack of surface maturation [62].

The other variant is represented by the gastric phenotype (foveolar or pyloric phenotype; type II) in which the cells are cuboidal or low-columnar, with clear or eosinophilic cytoplasm, and round to oval nuclei [62].

These two variants may be differentiated by expression of mucin, CD10, and CDX2, as well as by background changes in the gastric mucosa. The intestinal/adenomatous type expresses MUC2, CD10, and CDX2, and the gastric/foveolar type expresses MUC5AC, the absence of CD10 and low positivity of CDX2 [63,64]. Intraepithelial neoplasia (dysplasia) is stratified into two grades, low or high.

5. Intramucosal invasive neoplasia/intramucosal carcinoma

This category defines carcinomas invading lamina propria and that are distinguished from intraepithelial neoplasia by desmoplastic changes that can be minimal or absent, and also by marked glandular crowding, excessive branching, and budding.

The diagnosis of intramucosal carcinoma indicates that there is an increased risk of lymphatic invasion and lymph-node metastasis. Novel endoscopic techniques can allow treatment of some of these patients without open surgery, particularly for lesions of < 2 cm in size and for those that are well-differentiated [65].

6. Invasive neoplasia

This category defines carcinomas that show invasion beyond lamina propria. In the stomach, this diagnosis is associated with a varying risk of nodal and distant metastasis and overall prognosis. The recommended treatment consists in surgical resection, sometimes with neoadjuvant therapy.

Histopathological examination of the 96 cases showed dysplastic lesions in 10 patients, the incidence being of only 10.4%. According to the data in the literature, the prevalence of dysplasia varies between 0.5 - 4% in Western countries and between 9-20% in areas with high risk for gastric cancer [66]. The high frequency of epithelial dysplasia, observed in our study, can also be explained through the modality of taking the biopsies for each case (the large number of biopsies/case, the different location of taking the sample), method of work that eliminates somehow the errors connected with the focal, dispersed characteristic of dysplastic lesions.

Low-grade dysplasia, encountered in 8 patients, is characterized by glandular architecture mostly preserved, sometimes with the presence of pseudovilli, cystically dilated glands or slightly irregular glands, with discrete intraluminal papillary projections or serrated aspect. Glandular structures are lined with high, crowded cells, with or without mucous vacuoles. The nuclei, discretely pleomorphic, appear elongated and pseudostratified, situated in the inferior half of the cytoplasm. The mitotic activity is discrete.

In all cases, dysplastic lesions were diagnosed histopathologically at the level of the biopsies taken from the antrum. In literature the predominantly antral location of premalignant gastric lesions is mentioned, except for the atrophic gastritis associated with pernicious anemia, which is identified especially at the level of the gastric body [27].

Epithelial dysplasia is encountered especially in patients over 51 years old. In the cases studied we encountered dysplastic lesions of low grade in a young 36-year-old patient.

Data reveal that low-grade dysplasia may regress in up to 60% of cases, and progress to high-grade dysplasia in 10-20% of cases [67,68]. High-grade dysplasia rarely regresses, being associated with an annual incidence of progression to carcinoma of 2-6%; it can be uni- or multifocal, and it is often associated with synchronous cancer. A prospective study from the Netherlands has shown that high-grade dysplasia was associated with a markedly increased risk of progression to carcinoma (adjusted hazard ratio, 40.1) [5,69].

While routine surveillance for Barrett's esophagus is recommended and guidelines for the surveillance for other gastrointestinal premalignant conditions are available [70,71], in the last years the management for gastric premalignant conditions varied from surgery to annual surveillance for dysplasia and from no treatment to surveillance every 3 to 5 years for less advanced lesions [72-75]. Data showed that endoscopic mucosal resection and routine surveillance of advanced premalignant gastric lesions may significantly decrease the mortality and morbidity associated with gastric cancer. Yeh and collaborators [76] have elaborated a simulation model of gastric cancer natural history for a cohort of U.S. men with a recent inci-

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dental diagnosis of gastric precancerous lesions, and they estimated that among 50-year old men with dysplasia, approximately one in every twenty will develop gastric cancer in their lifetime, which is similar to the risk of colorectal cancer in the like-aged general U.S population or persons with Barrett's esophagus. This study highlighted that EMR with surveillance every 1 to 5 years for dysplasia is promising for secondary cancer prevention because it can reduce gastric cancer risk by 90%, and it is considered cost-effective in the U.S. Endoscopic surveillance of less advanced lesions does not appear to be cost-effective, except possibly immigrants from high-risk countries.

The Guideline of the European Gastrointestinal Endoscopy [45] recommends that patients with low grade dysplasia, in the absence of an endoscopically defined lesion, should receive follow-up within 1 year after diagnosis. If there is an endoscopically visible lesion, endoscopic resection should be considered in order to obtain a more accurate diagnosis. For patients with high grade dysplasia, if there are no endoscopically defined lesions, endoscopic reassessment with extensive biopsy sampling and surveillance at 6-month to 1-year intervals is recommended. In the case of endoscopically defined lesions, resection needs to be considered, either through endoscopy (endoscopic mucosal resection) or surgery.

From an endoscopic point of view, the patients presented more frequently aspects of antral diffuse erythematous gastritis (in 7 cases). In the case of a 66-year old patient, the antral mucosa did not show visible macroscopic modifications on conventional endoscopy. Though the quality of the images obtained through standard endoscopy was improved substantially in the past few decades, the modifications observed during conventional endoscopy are correlated in a smaller measure with the histopathologicaldiagnosis of atrophic gastritis, intestinal metaplasia and dysplasia. These results are due to the unsatisfactory viewing of the structure of the mucosa, its color and vascularization, important elements in the differential diagnosis between premalignant lesions and incipient gastric cancer [27]. So, data show that conventional white light endoscopy cannot accurately diagnose premalignant gastric lesions. Magnification endoscopy and narrow band imaging (NBI), with or without magnification, improve the diagnosis of these conditions [45]. Some studies concluded that correlation between white light endoscopy and histology was poor [77]. Absence of rugae and presence of visible vessels in the gastric mucosa can predict severe atrophy but with a low sensitivity [78]. Intestinal metaplasia may appear endoscopically as thin, white mucosal deposits, but the value of some endoscopic signs for its diagnosis it is still unclear [79]. In addition to low accuracy, the lesions detected on conventional endoscopy were associated also with low reproducibility [80,81]. Therefore current data show that white light endoscopy cannot be relied upon to accurately diagnose patients with atrophy and intestinal metaplasia.

Recent studies have followed the performances of endoscopy by magnification in the detection of premalignant gastric lesions. The correlation between the endoscopic aspects and histopathological diagnosis proved to be exceptional [82-84]. Detailed visualization of the superficial gastric mucosa allows classifying the patterns that the gastric folds and foveoles can take in different pathological conditions. The model of superficial micro-vascularization identifies the chronic gastritis induced by H. pylori and other entities classified as preneo-

plastic. In H. pylori positive gastritis, collector venules lose their regular aspect, "sea star"-like, in some cases being invisible. In atrophic gastritis, the alterations in the subepithelial capillary network and of the collector venules are correlated with the degree of atrophy. The areas of intestinal metaplasia are suspected in the presence of depressions with wide and elongated epithelial rigs, separated by deep grooves [83]. Data show that high resolution magnifying endoscopy appears superior to standard endoscopy, allowing accuracy for the diagnosis of H. pylori gastritis, intestinal metaplasia and dysplasia [85,86].

The techniques of in vivo coloration represent adjuvant methods for the optimal viewing of the lesions during the conventional endoscopy, or with magnification. Methylene blue visualizes the areas of intestinal metaplasia. Architectural modifications from the neoplastic areas are emphasized by using the indigo carmine solution. Unlike conventional endoscopy, chromoendoscopy can identify limited foci of incipient gastric carcinoma [32,87]. Studies suggest that chromoendoscopy, particularly with magnification, helps to identify lesions of intestinal metaplasia and dysplasia. Dinis-Ribeiro et al. proposed a chromoendoscopy classification with methylene blue for these lesions that proved to be reproducible and highly accurate [87]. The use of other solutions, such as indigo carmine, acetic acid, or hematoxylin, has shown a high diagnostic accuracy, especially for dysplasia [88,89].

No comparative study of magnification with or without chromoendoscopy has been made, despite the fact that Tanaka et al [89] have suggested that magnification chromoendoscopy with acetic acid is superior to conventional magnification endoscopy and indigo carmine chromoendoscopy.

However, magnification chromoendoscopy lengthens the time of the endoscopic procedure and may compromise patient tolerance. For these reasons, performance of this technique should be restricted to experienced centers [45].

In the last years new endoscopic techniques were introduced, which utilize certain spectral features of the light, for instance image obtained through narrow band, autofluorescence or fluorescence capturing. The results of implementing this new methods of investigation are only preliminary and in some studies even conflicting, thus their follow-up on long periods of time is necessary [27].

The technique of narrow band imaging (NBI) has been found to have good sensitivity and specificity for the diagnosis of gastric lesions [90-95]. The principle of this new method is based on modification of the spectral characteristics of the optical filter in the light source, leading to improved visibility of mucosal components. With the use of NBI in combination with image magnification, mucosal structures are highlighted with accuracy, because of the increased contrast between surface and vascular pattern [96]. The study of Capelle et al [97] provides evidence that NBI yields more accurate results in the surveillance of patients with intestinal metaplasia and dysplasia than conventional endoscopy. They have shown that considerably more lesions of intestinal metaplasia were detected by NBI compared to white light endoscopy and that the sensitivity for the detection of advanced premalignant gastric lesions increased by 20-71% for NBI.

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Both NBI and chromoendoscopy can reveal the mucosal pattern and microvascular structure of the mucosa that have been considered as distinctive characteristics of early gastric cancer and premalignant gastric lesions. The study of Zhang et al [98] showed that the image quality of magnifying NBI is superior to magnifying conventional endoscopy in respect of morphology, pit pattern and blood capillary form of abnormal gastric zones, but also to magnifying chromoendoscopy concerning blood capillary form.

Angiogenesis represents an important element in gastric carcinogenesis [99], the vascular pattern of gastric cancer and precancerous lesions being differ from that of normal mucosa [100]. Nakayoshi et al [101] studied 165 patients with early gastric cancer with magnifying NBI, showing that 66.1% of differentiated adenocarcinoma had fine microvascular networks, and 85.7% of undifferentiated carcinoma had corkscrew microvascular networks.

The use of auto-fluorescence endoscopy demonstrated a high correlation between Barrett's esophagus and histological diagnosis, but the correlation between gastric cancer and this method is still controversial [102,103].

Confocal endomicroscopy is an endoscopic technique that produces 1000-fold magnification cross-sectional images and can accurately diagnose the presence of early cancer in targeted areas. A recent gastric pit-pattern classification for assessment of gastritis and atrophy showed a high correlation with histological changing and needs further evaluation [104,105]. This technique is too elaborate to be used for assessment of the entire gastric mucosa.

Liu et al [106] studied the microvascular architecture of early gastric cancer with confocal microscopy, and revealed that differentiated gastric cancerous mucosa presented hypervascularity and microvessels of different caliber and shapes, and undifferentiated gastric cancer showed hypovascularity and irregular short branched vessels.

Only in 2 patients we observed high-grade dysplastic modifications. High-grade epithelial dysplasia is characterized histopathologically through intensely distorted glandular architecture, with crowded glands, irregular and ramified, with frequent intraluminal papillary projections, lined with stratified epithelium, with crowded and overlapping nuclei, pleiomorphic, with intense mitotic activity, loss of normal polarity, nuclei that touch the apical pole of the cell. In the neoplastic epithelium, goblet cells and Paneth cells are absent.

The patients diagnosed histopathologically with high-grade epithelial dysplasia were both males, with ages of 64 and 75 years, respectively. In the case of the 75-year old patient, the pangastritis evident endoscopically was characterized by aspects of focal erythematous gastritis of the antrum with mild intensity and petechial gastritis of the gastric body, of severe intensity. For the second patient, gastroscopy showed only aspects of antral diffuse erythematous gastritis with moderate intensity. In both patients, the infection with H. pylori proved negative histopathologically.

7. Conclusions

For the diagnoses of atrophy we noted a poor correlation between the conventional endoscopic investigation and histopathological examination. Type I intestinal metaplasia predominated both for antrum and gastric body. Type III intestinal metaplasia was encountered slightly more frequent at the level of gastric body, especially in patients over 50 years old. About 2% of patients presented high-grade dysplasia needing resection treatment. The use of modern endoscopic techniques may help identifying gastric precancerous lesions. Among our study group, we found some rare types of gastritis, such as gastric Crohn's disease and lymphocytic gastritis, emphasizing the importance of performing multiple biopsies for an accurate histopathological diagnosis of gastritis.

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