

Chronic Autoimmune Gastritis

Subjects: Allergy

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Helicobacter pylori (HP) infection and the autoimmune inflammation of the gastric mucosa are recognized as the leading etiological factors of chronic atrophic gastritis, a disease associated with an increased risk of stomach cancer development. Additionally, in relation to HP-associated gastritis, there is international and national consensus on the diagnosis and treatment of infection; however, with regard to autoimmune inflammation, clinicians have faced diagnostic difficulties. At the same time, autoimmune inflammation of the gastric mucosa, in addition to the formation of atrophy and an increase in the risk of stomach cancer, carries additional risks, both in relation to neoplasms (neuroendocrine tumors) and in relation to the deficiency of a number of micronutrients with the involvement of other organs and systems.

Keywords: chronic autoimmune gastritis ; atrophic gastritis ; nutritional status ; vitamin B12 deficiency ; megaloblastic anemia ; neuroendocrine tumors ; gastric adenocarcinoma ; gastric neuroendocrine hyperplasia

1. Introduction

The role of nutrition in the development of autoimmune inflammation has not been reliably established. It is believed that a widespread Western diet, which is high in calories, simple carbohydrates, refined foods, saturated fats, and red meat, and low in omega-3 and omega-9 polyunsaturated fatty acids and plant fiber, may increase the risk of autoimmune diseases [1] [2]. For the prevention and inhibition of autoimmune inflammation, an autoimmune protocol diet was developed, which is a modification of the Paleolithic diet with the elimination of specific foods, including cereals, beans, solanaceous family, dairy products, eggs, coffee, alcohol, nuts and seeds, refined sugars, oils, and food additives [3].

CAG is characterized by a decrease in the absorption of valuable micronutrients, primarily vitamin B12 and iron, with the development of their deficiency symptoms, which can help in identifying such patients (**Table 1**).

Table 1. Micronutrient deficiency in autoimmune gastritis: prevalence, development mechanisms, clinical manifestations (adapted from Cavalcoti et al., 2017).

Micronutrient	Development Frequency	Development Mechanisms	Manifestations
Vitamin B12	37–69%	Decreased production of intrinsic Castle's factor by parietal cells of the gastric body and decreased absorption of vitamin B12 in the ileum	Hematological, gastroenterological, neuropsychiatric disorders
Iron	52%	The presence of erosive lesions of the mucous membrane and possible latent blood loss, concomitant infection with <i>H. pylori</i> and bacteria competition for dietary iron, hypochlorhydria, and increased hepcidin synthesis against a background of a concomitant inflammatory process	Microcytic anemia
Vitamin C	Unknown	Breakdown of ascorbic acid in the stomach due to increased pH (hypo-, achlorhydria) and concomitant bacterial overgrowth in the small intestine	Decreased antioxidant defense, immunity, and protein synthesis
Calcium	Unknown	Dissolution, ionization, and absorption of calcium salts decrease under conditions of hypo-, achlorhydria	Osteopenia/Osteoporosis
Vitamin D	12.1%	Not determined	Secondary hyperparathyroidism, osteopenia/osteoporosis, decreased immunity, increased risk of autoimmune disease development

According to epidemiological studies, the prevalence of concomitant autoimmune diseases in patients with CAG reaches 40%, and the most common disorders are thyroid diseases, type 1 diabetes mellitus, hemolytic anemia, vitiligo, alopecia, rheumatoid arthritis, psoriasis, autoimmune hepatitis, myasthenia, and Sjogren disease [4]. The spectrum of autoimmune diseases associated with CAG is presented in **Table 2**.

Table 2. Autoimmune diseases associated with autoimmune gastritis (adapted from Massironi et al., 2019).

Disease	Association Degree
Autoimmune thyroiditis (Hashimoto's thyroiditis) and Graves' disease	++++ (multiple cohort studies, two crossover studies, and two case-control studies)
Type 1 diabetes mellitus	+++ (one case-control study and several cohort studies)
Vitiligo	++ (one cohort study and several clinical observations)
Alopecia	++ (several cohort studies)
Celiac disease	++ (several cohort studies)
Myasthenia gravis	+ (single clinical observations)
Connective tissue disease	++ (one cohort study and several clinical observations)
Primary biliary cholangitis	++ (one cohort study and several clinical observations)
Primary sclerosing cholangitis	+ (single clinical observations)
Autoimmune hepatitis	+ (single clinical observations)
Addison's disease	+ (single clinical observations)
Primary ovarian insufficiency	+ (single clinical observations)
Primary hypoparathyroidism	+ (single clinical observations)
Lambert-Eaton syndrome	+ (single clinical observations)
Oral lichen planus	+ (single clinical observations)

2. Diagnostic Approaches

There is no gold standard for the diagnosis of CAG, so the diagnosis is established on the basis of a set of data from a survey and examination of a patient, as well as the results of laboratory and instrumental research methods.

2.1. Laboratory Methods

Serological research methods are not an independent diagnostic tool, since they do not have absolute specificity and sensitivity in relation to CAG. Thus, antibodies to parietal cells are considered a highly sensitive marker and are found in 80–90% of patients with CAG, but they can also be present in 7.8–19.5% of healthy adults, as well as in persons infected with HP or with other autoimmune diseases such as type 1 diabetes mellitus or Hashimoto's thyroiditis [5][6]. The determination of antibodies to parietal cells using the method of immunofluorescence or ELISA increases the sensitivity of the test by 30%. It should be noted that, in the later stages of the disease, as the atrophy of the gastric mucosa progresses, the loss of the target autoantigen antibodies to parietal cells may not be detected [5]. Antibodies to the intrinsic Castle's factor are more specific for CAG (98.6%), but their sensitivity is not high (30–60%) [7][8]. At the same time, it was found that antibodies to the intrinsic Castle's factor correlated well with atrophy of the gastric mucosa; this was revealed by histological examination of gastrobiopsy specimens [9].

Atrophy and loss of functional activity of parietal cells of the gastric body with the development of hypo- or achlorhydria, on the one hand, leads to hyperplasia of gastrin-producing cells of the antrum and hypergastrinemia, and on the other hand, to a decrease in the production of pepsinogen I. At the same time, if the pathological process does not involve the glands of the antrum, the level of pepsinogen II does not change significantly, but the ratio of pepsinogen I to pepsinogen II decreases, which, together with hypergastrinemia, are characteristic signs of CAG [5]. These indicators are included in the test "GastroPanel" (Biohit, Finland), which received the figurative name "serological biopsy" [10][11]. It has been reported that a decrease in pepsinogen I of less than 30 µg/L and a pepsinogen I/pepsinogen II ratio of less than three, in combination with an increase in gastrin-17 levels of more than 30 pmol/L, reliably helps in the identification of

asymptomatic patients with CAG at the stage of atrophy [12]. In this case, the sensitivity of the method is 74.5% and the specificity reaches 100%.

It is fundamentally important for both diagnosis and prognosis to assess a patient's nutritional status with a mandatory study of cyanocobalamin, iron, ferritin, total iron-binding capacity, calcium, vitamin D, and ascorbic acid levels in the blood serum.

Determination of chromogranin A in blood serum, whose level correlates with the degree of the ECL cells' hyperplasia, can be considered as an auxiliary marker for assessing the risk of NET formation [13][14][15][16]. The sensitivity and specificity of chromogranin A as a possible marker of NET is low; therefore, its determination result should be assessed taking into account the clinical picture and the histological examination data. For example, the concentration of chromogranin A can increase in patients with inflammatory bowel disease, hepatocellular carcinoma, non-alcoholic fatty liver disease, renal failure, and long-term use of proton pump inhibitors [17][18]. The summarized data on laboratory markers of CAG are presented in **Table 3**.

Table 3. Laboratory markers of CAG.

Indicant	Value	Comments
Antibodies to parietal cells	↑	They are found in 80–90% of patients with CAG, but they can also be present in 7.8–19.5% of healthy adults, as well as in people infected with HP or with other autoimmune diseases. They may not be determined in the later stages of the disease, as atrophy of the gastric mucosa progresses.
Antibodies to the intrinsic Castle's factor	↑	Specificity—98.6%, sensitivity—30–60%. They correlate with atrophy of the gastric mucosa.
Pepsinogen I	↓	It is produced by the main cells of the stomach's body. A decrease in the indicator shows the presence of atrophy in the mucous membrane of the stomach's body. Serum level decreases in proportion to the severity of atrophy.
Pepsinogen II	Not changed	It is produced mainly in the stomach's antrum and duodenum; therefore, it does not change with CAG.
Pepsinogen I/Pepsinogen II	↓	They decrease linearly with increasing severity of atrophy of the stomach's body glands.
Gastrin-17	↑	It is produced by gastrin-producing cells of the stomach's antrum. With a decrease in acid production against the background of the stomach's body glands atrophy, it increases by the mechanism of a negative feedback loop.
Chromogranin A	↑	It correlates with the degree of ECL cell hyperplasia under conditions of hypo- and achlorhydria. Due to the low sensitivity and specificity, its widespread use in routine practice is limited.

2.2. Endoscopic Examination

Endoscopic examination plays an important role in the diagnosis of CAG, since the quality of the morphological assessment of gastric mucosa damage depends on the adequacy of the endoscopist's actions while collecting gastrobiopsy specimens. At the initial stages of CAG, the endoscopic picture may not be changed or correspond to minimal inflammatory changes, which are more pronounced in the body of the stomach. Macroscopically, the gastric mucosa in patients with CAG is usually thinner than normal, with a smoothing of the relief and disappearance of folds, as well as the presence of highly visible vessels of the stomach's submucosa. As the atrophy of the glands progresses, an unevenly expressed flattening of the relief of the mucous membrane occurs in the area of the stomach's body and its fundus. Uneven distribution of the atrophy's foci gives the surface of the gastric mucosa a pseudopolypoid character due to the presence of intact areas [19]. Such a macroscopic picture forces one to take biopsy material from different parts of the gastric mucosa during endoscopic examination, given the flattened and polypoid nature of the surface, which makes it possible to adequately assess the nature of the changes.

The diagnostic value of endoscopic signs of CAG depends on the research method utilized.

According to the Guidelines for the Management of Precancerous Conditions and Lesions in the Stomach (MAPS II), in the diagnosis and staging of precancerous conditions and changes in the gastric mucosa, the capabilities of high-resolution endoscopy in combination with chromoscopy are higher than those of white light endoscopy [20]. Whenever possible, virtual chromoscopy should be used during biopsy for staging the atrophic process, as well as to identify

suspicious areas of neoplasia and conduct targeted biopsy. For an adequate assessment of precancerous diseases of the stomach during endoscopic examination, it is necessary to perform a biopsy from at least four points: from the stomach's antrum and body, along the lesser and greater curvature. If the risk of gastric cancer is assessed using the Operative Link for Gastritis Assessment of Atrophic Gastritis (OLGA) or Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) systems, an additional biopsy sample from gastric incisura angularis is advised. The recommended frequency of endoscopic examination in patients with autoimmune gastritis is once every 3–5 years.

2.3. Morphological Examination

Histological examination of gastric biopsy specimens is the gold standard for diagnosing chronic gastritis as well as for assessing the presence and severity of inflammatory or atrophic changes.

In microscopic examination, the main feature of the uncomplicated course of CAG (that is to say, in the absence of dysplasia, cancer, or neuroendocrine hyperplasia) is a diffuse lesion of the mucous membrane, limited to the area of the stomach body [21]. The state of the mucous membrane of the stomach's antrum may correspond to a normal histological structure or may have a mononuclear inflammatory infiltrate, focal absolute, and/or metaplastic atrophy. Many patients may also show signs of foveolar hyperplasia ("reactive gastropathy"), probably reflecting the effect of hypergastrinemia, with a decrease in mucus-producing activity of the integumentary epithelium. As a rule, hyperplasia of gastrin-producing cells is present. In the case of the addition of HP infection (combined lesion), all the corresponding signs of damage to the mucous membrane of the antrum appear.

In the mucous membrane of the stomach's body, a wide range of atrophic changes (from minimal signs of inflammation to severe atrophy of the glands) can be detected, characterized by varying degrees of the acid-producing glands' damage, as well as the development of intestinal, pyloric (pseudopyloric metaplasia), and ECL cell hyperplasia. The process of restructuring the mucous membrane can be divided into three stages or phases. In the first, initial stage, there is a diffuse or multifocal infiltration of the lamina propria of the mucous membrane by lymphocytes and plasma cells up to the formation of pronounced infiltration and involvement of the entire thickness of the mucous membrane, often with an admixture of eosinophils and mast cells (**Figure 1**). Focal destruction of individual glands by components of the inflammatory infiltrate takes place. Hyperplasia of parietal cells is also characteristic, reflecting the state of hypergastrinemia. At this stage of the disease, intestinal metaplasia is rare and focal [22][23].

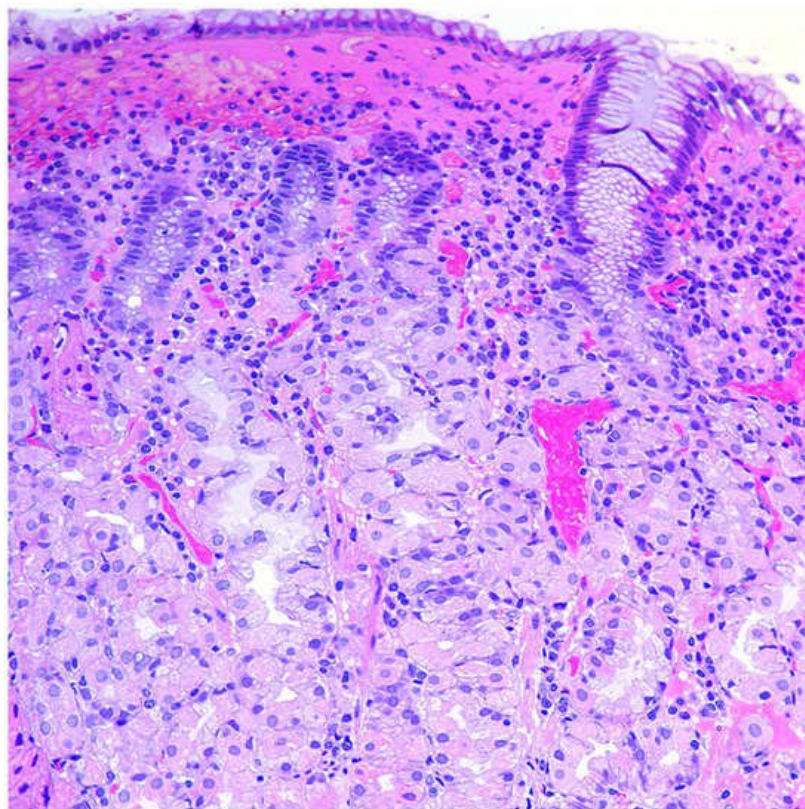


Figure 1. Autoimmune gastritis: initial stage. Biopsy from the gastric body. Lymphoplasmacytic inflammatory infiltration of the lamina propria with damage to the fundic glands. Hematoxylin and eosin stain. ×200 (from the personal archive of Professor S.I. Mozgovoi).

In the second stage, or expanded (florid) stage, pronounced atrophy of acid-producing glands develops; diffuse lymphoplasmacytic infiltration of the lamina propria is characteristic of a decrease in the height of the glands and an increase in the thickness of the foveolar component. The prevalence of intestinal metaplasia is higher than in the previous phase, but pseudopyloric metaplasia plays the main role in the remodeling of gastric mucosa (**Figure 2**). In recent years, this type of metaplasia, with the formation of glands resembling the antral glands, is associated with a separate phenomenon—a cell line with the expression of spasmodic polypeptide (SPEM—spasmodic polypeptide-expressing metaplasia). The appearance of this cellular rearrangement is associated with an increased risk of an intestinal-type gastric cancer developing in patients with CAG [24][25][26]. In this stage, due to the presence of pronounced atrophic changes with selective involvement of the stomach's glands, the morphological picture becomes pathognomonic. However, establishing the presence of antibodies to parietal cells and intrinsic factors also remains necessary to confirm the diagnosis.

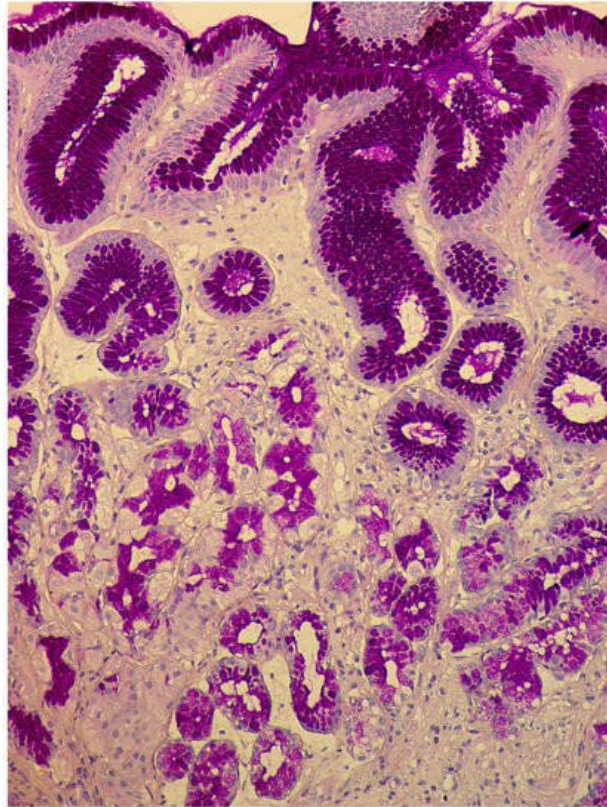


Figure 2. Autoimmune gastritis. Biopsy from the gastric body. Severe pseudopyloric metaplasia with the appearance of mucus-producing cells in place of the fundic glands (cytoplasm magenta staining). Periodic acid-Schiff stain. ×200 (from the personal archive of Professor S.I. Mozgovoi).

In the final stage of the disease, there is a pronounced reduction in acid-producing glands with the development of foveolar hyperplasia, the appearance of hypermucoidized cells, the formation of hyperplastic polyps, and an increase of the areas with pyloric (pseudopyloric), pancreatic, and intestinal metaplasia (**Figure 3**).

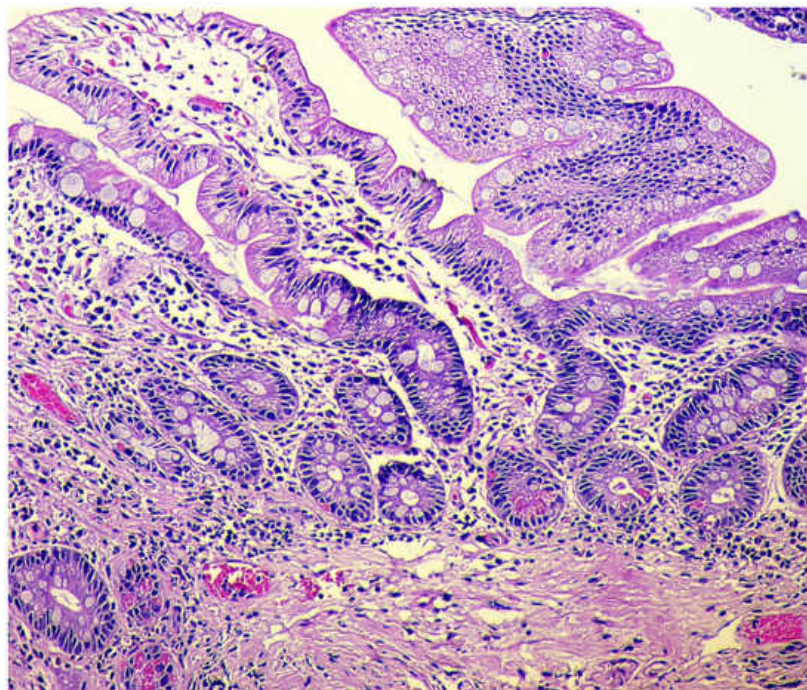


Figure 3. Autoimmune gastritis. Biopsy from the gastric body. Severe intestinal metaplasia (type I, complete), with intestinalization of gastric mucosa and villous transformation with absorptive and goblet cells; Paneth cells with acidophilic granular cytoplasm are presented at the base of the glands. Hematoxylin and eosin stain. $\times 200$ (from the personal archive of Professor S.I. Mozgovoi).

The classification of intestinal metaplasia is based on histochemical evaluation of mucins, as follows [27][28]: Complete intestinal metaplasia (type I): non-secretory absorptive cells with brush border and sialomucin-secreting goblet cells. Incomplete intestinal metaplasia type II with columnar cells secreting neutral and acid sialomucin, and goblet cells secreting mainly sialomucin but occasionally sulphomucin. Incomplete intestinal metaplasia type III with columnar cells secreting predominantly sulphomucin and goblet cells secreting sialomucin or sulphomucin.

The thickness of the muscle plate of the mucous membrane can be increased by three to four times. At this stage, parietal cells are difficult to detect, inflammatory infiltration is minimal or absent, and individual clusters of lymphoid cells may remain [23].

To stratify the risk of stomach cancer development in a patient with chronic gastritis, a system of morphological assessment to detect changes in the gastric mucosa was proposed—the Operative Link for Gastritis Assessment of Atrophic Gastritis (OLGA). Integral indicators of the degree and stage of chronic gastritis are determined according to this system, where the degree is understood as the infiltration severity of the lamina propria of the gastric mucosa by inflammatory cells (lymphocytes, plasma cells, and neutrophilic leukocytes). The stage is understood as the presence of atrophic changes, including intestinal metaplasia [29]. It should be emphasized that, with the increase in the stage of chronic gastritis, the likelihood of developing adenocarcinoma of the stomach increases. For example, in patients with stage III–IV, the risk increases by five to six times. In addition, an increased risk of gastric cancer is noted among individuals with incomplete (colonic, type III) and/or widespread intestinal metaplasia of the gastric mucosa [30][31]. The modified OLGIM system (Operative Link on Gastric Intestinal Metaplasia Assessment), being more reproducible, offers only an assessment of the intestinal metaplasia presence as the main indicator of chronic gastritis stage [32][33]. Although the question of comparing these classifications from the sensitivity point remains controversial, since the use of OLGIM, which is more reproducible in practical application, may underestimate the true severity of absolute (non-metaplastic) atrophy [34][35][36].

During the extended and final stage of the disease, due to hypergastrinemia, the proliferation of neuroendocrine ECL cells of the gastric body is stimulated. A similar process also occurs in Zollinger–Ellison syndrome, multiple endocrine neoplasia syndromes, and HP-associated multifocal atrophic gastritis.

The following forms of hyperplasia of neuroendocrine cells in the gastric mucosa are distinguished [37][38]:

- Simple diffuse hyperplasia. This is characterized by a more than two-fold increase in the population of ECL cells. Diagnosis is difficult due to the lack of clear quantitative criteria. The diagnosis is poorly reproduced on biopsy material.

- Linear hyperplasia. The presence in one visual field of at least two groups of linearly located neuroendocrine cells, consisting of five or more cells. Usually, changes are diagnosed in the area of the neck glands (**Figure 4**).
- Micronodular hyperplasia. The presence of the cells' cluster in contact with the basement membrane, but not exceeding the diameter of the gland, up to 150 μm in diameter, or a similar cluster located freely in the lamina propria of gastric mucosa.
- Adenomatous (adenomatoid) hyperplasia. The presence of an aggregate of five or more clusters (**Figure 5**).
- Neuroendocrine cells dysplasia. Merging clusters with diameters of more than 150 μm but less than 500 μm .

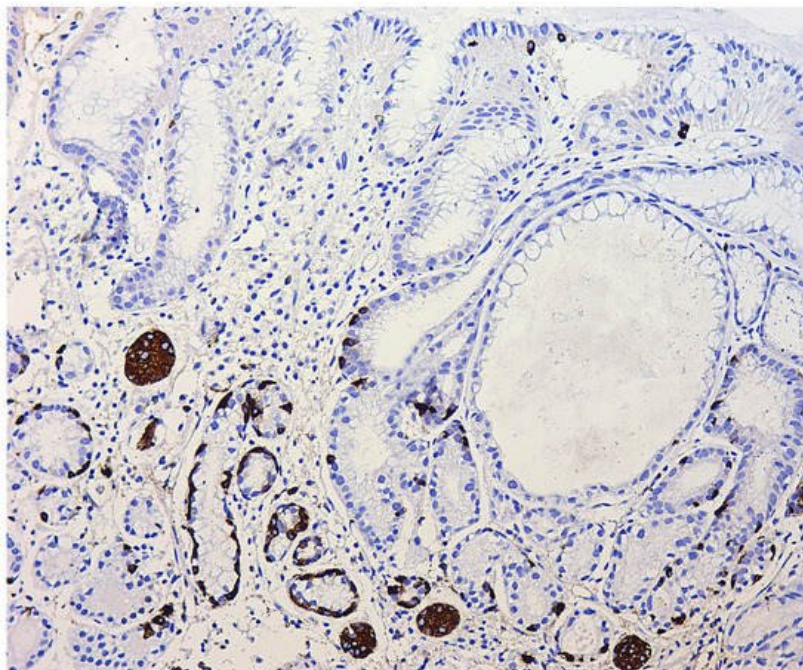


Figure 4. Autoimmune gastritis. Biopsy from the gastric body. Marked pseudopyloric metaplasia. Signs of linear and micronodular hyperplasia of neuroendocrine cells. Immunohistochemical reaction with antibodies to chromogranin A. $\times 200$ (from the personal archive of Professor S.I. Mozgovoi).

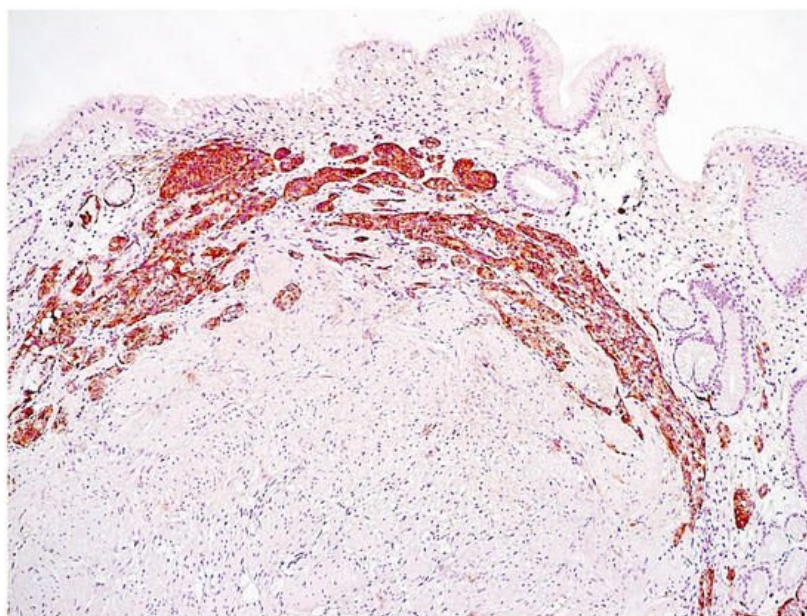


Figure 5. Autoimmune gastritis. Biopsy from the gastric body. Severe atrophy of the glands with pseudopyloric metaplasia. Adenomatous hyperplasia of neuroendocrine cells with the presence of cluster aggregates. Immunohistochemical reaction with antibodies to chromogranin A. $\times 100$ (from the personal archive of Professor S.I. Mozgovoi).

NETs associated with ECL cell hyperplasia occur in 5–8% of patients with autoimmune gastritis and comprise 70 to 80% of all gastric NETs [39]. Typically, these tumors have a good prognosis, with a five-year survival in more than 95% of

patients. This is significantly different from the prognosis of sporadic tumors, which are more aggressive, with a five-year survival rate of less than 35% of patients [40]. This circumstance pushes doctors to carefully observe the protocols for the study of biopsy material in pathological practice; in particular, it is imperative to reflect the state of the gastric mucosa, which is the background for the development of a tumor.

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