Clinical and Morphological Features of Dysplasia and Early Gastric Cancer in the Patients with Autoimmune Gastritis


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Aim: to analyze a series of cases of dysplasia and early gastric cancer developed in patients with autoimmune gastritis (AIG), and to identify their clinical and morphological features.

Materials and methods. The study included six cases of detection of early gastric cancer on the background of AIG. Four out of six patients underwent endoscopic treatment, and in three out of six cases patients underwent endoscopic mucosectomy with dissection in the submucosal layer. One patient underwent endoscopic surgery in 2017, he continues annual dynamic follow-up without signs of tumour recurrence. A female patient with type 1 neuroendocrine tumour and mild dysplasia is awaiting treatment.

Results. In five out of six patients with AIG, the localization of lesions prevailed in the stomach body, while all detected tumours were early ones, and according to the immunophenotype — of a gastric type. The presented cases of tumours were not accompanied by hyperplasia of neuroendocrine cells directly in the area of the tumour itself, but only in the surrounding gastric mucosa. Additionally, several cases of early gastrointestinal stromal tumours were found, which were characterized by low proliferative activity and had small sizes.

Conclusion. The predominance of pseudopyloric metaplasia in the surrounding mucosa allows us to consider pseudopyloric metaplasia as a potentially significant change in the gastric mucosa of patients with AIG that may precede the development of gastric cancer.

Keywords: autoimmune gastritis, early stomach cancer, dysplasia, gastric adenocarcinoma, pseudopyloric metaplasia

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Клинико-морфологические особенности дисплазии и раннего рака желудка, возникшего на фоне аутоиммунного гастрита

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Цель исследования: проанализировать серию случаев дисплазии и раннего рака желудка, развившихся на фоне аутоиммунного гастрита (АИГ), и выявить их клинико-морфологические особенности.

Материалы и методы. В исследование было включено шесть случаев обнаружения раннего рака желудка на фоне АИГ. Четверо из шести пациентов прошли эндоскопическое лечение в 2022 г., в трех из шести случаев пациентам была выполнена эндоскопическая мукозэктомия с диссекцией в подслизистом слое. Одному пациенту эндоскопическая операция была проведена в 2017 г., он продолжает ежегодное динамическое наблюдение по настоящее время без признаков рецидива опухоли. Пациентка с сочетанием слабой дисплазии и нейроэндокринной опухолью 1-го типа ожидает лечения.

Результаты. У пяти из шести пациентов с АИГ опухоли были локализованы в теле желудка, при этом все выявленные случаи рака были ранними, а по иммунофенотипу — желудочными. Представленные случаи раннего рака не сопровождались гиперплазией нейроэндокринных клеток непосредственно в зоне самой опухоли, а только в окружающей слизистой оболочке желудка. В двух случаях дополнительно были
Introduction

Gastric cancer is one of the most urgent problems of modern medicine. According to statistics, stomach cancer ranks fifth in incidence and fourth in mortality from cancer worldwide [1].

Currently, the development of gastric cancer (primarily of the intestinal type according to the P. Lauren classification [2]) is considered as a multistage process that includes a sequence of changes in the mucous membrane: chronic inflammation, atrophy, intestinal metaplasia, dysplasia, and adenocarcinoma [3]. The tactics of managing patients with precancerous conditions and changes in the stomach is determined by such risk factors for the development of gastric cancer as Helicobacter pylori (H. pylori) infection, aggravated family history, atrophic gastritis, including autoimmune gastritis (AIG) [4, 5].

AIG is the result of an autoimmune attack on T cells; activation of T-dependent B-lymphocytes causes the production of autoantibodies to parietal cells and intrinsic factor of Castle, leading to the destruction of parietal cells with progressive hypochlorhydria and hypergastrinemia. Thus, over the years, AIG, characterized by malabsorption of vitamin B₁₂, can lead to pernicious anemia [6, 7].

AIG increases the risk of gastric cancer [7]. A meta-analysis showed that in pernicious anemia, the relative risk of gastric cancer is 6.8 (95% confidence interval (95% CI): 2.6–18.1) [8], and in autoimmune gastritis — 11.05 (95% CI: 6.39–19.11) [9]. When followed up for an average of 5 years (1 to 17 years) in patients with atrophy limited only to the body of the stomach, the primary incidence per person-year of follow-up was 0.5% for gastric cancer and 0.6% for high-grade dysplasia. Low-grade dysplasia — 2.8%, type 1 neuroendocrine tumor — 3.9% [10]. However, M. Rugge et al. in a seven-year follow-up of 211 patients with AIH (10,541 person-years), who had carefully excluded H. pylori infection in history and during the study, did not reveal an increased risk of gastric cancer. The increased risk of adenocarcinoma recorded in patients with AIG is considered by the authors to be the result of an undetected (or unaccounted for) previous/current H. pylori infection [11].

The purpose of the case series study was to evaluate early cancer associated with AIG and identify potentially significant changes in the gastric mucosa of patients with AIG that may precede the development of gastric cancer.

Materials and methods

The study included six cases of detection of gastric tumors against the background of AIG, which were diagnosed in the clinics of the I.M. Sechenov First Moscow State Medical University (Sechenov University) in the period from 2017 to 2022. Four out of six patients were operated on in clinics in 2022. In three out of six cases, patients underwent endoscopic mucosectomy with dissection in the submucosal layer. One patient was operated on in 2017 and continues annual follow-up until now with no signs of tumor recurrence. A patient with a neuroendocrine tumor (NET) and mild dysplasia was offered endoscopic tumor removal and is awaiting treatment.

Processing of morphological biopsy and surgical materials was carried out according to the generally accepted method. The obtained histological material was fixed in 10% buffered formalin, processed in a histological wiring apparatus from Leica ASP200 (Germany), and embedded in paraffin. Next, the prepared serial sections were stained with hematoxylin and eosin. Immunohistochemical (IHC) study was performed on an automatic immunohistotainer Leica BOND III (Germany) according to standard protocols recommended by the manufacturer.
<table>
<thead>
<tr>
<th>Case number</th>
<th>Gender</th>
<th>Age, years</th>
<th>Associated autoimmune diseases</th>
<th>H. pylori (morphological diagnostics)</th>
<th>Localization of epithelial tumours</th>
<th>Tumour immunophenotype</th>
<th>Localization of mesenchymal tumours</th>
<th>Characteristics of metaplasia in the body of the stomach</th>
<th>Hypersensitivity cells (NEK)</th>
<th>Type of OESG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F / Ж</td>
<td>63</td>
<td>None / Her</td>
<td>Not detected</td>
<td>Body of the stomach</td>
<td>Diffuse type</td>
<td>Gastric</td>
<td>Disseminated pseudopyloric and focal complete intestinal metaplasia</td>
<td>Linear, nodular</td>
<td>Линейная</td>
</tr>
<tr>
<td>2</td>
<td>F / Ж</td>
<td>68</td>
<td>Autoimmune thyroiditis, lung sarcoidosis</td>
<td>Not detected</td>
<td>Cardiac part of the stomach</td>
<td>Diffuse type</td>
<td>Gastric</td>
<td>Disseminated pseudopyloric metaplasia</td>
<td>Linear</td>
<td>Линейная</td>
</tr>
<tr>
<td>3</td>
<td>М / М</td>
<td>57</td>
<td>Autoimmune thyroiditis</td>
<td>Not detected</td>
<td>Body of the stomach</td>
<td>Mixed type</td>
<td>Mixed (gastrointestinal)</td>
<td>Disseminated pseudopyloric and complete intestinal metaplasia</td>
<td>Linear</td>
<td>Линейная</td>
</tr>
<tr>
<td>4</td>
<td>F / Ж</td>
<td>71</td>
<td>None / Her</td>
<td>Not detected</td>
<td>Body of the stomach</td>
<td>Gastric</td>
<td>–</td>
<td>Disseminated pseudopyloric metaplasia</td>
<td>Linear</td>
<td>Линейная</td>
</tr>
<tr>
<td>5</td>
<td>F / Ж</td>
<td>64</td>
<td>Berger’s disease</td>
<td>Not detected</td>
<td>Body of the stomach</td>
<td>Gastric</td>
<td>–</td>
<td>Disseminated pseudopyloric metaplasia</td>
<td>Linear</td>
<td>Линейная</td>
</tr>
<tr>
<td>6</td>
<td>F / Ж</td>
<td>55</td>
<td>None / Her</td>
<td>Not detected (history of eradication therapy)</td>
<td>Antrum of the stomach</td>
<td>Intestinal</td>
<td>–</td>
<td>Disseminated pseudopyloric metaplasia</td>
<td>Linear</td>
<td>Линейная</td>
</tr>
</tbody>
</table>

Note: * — patient’s age at diagnosis.
Примечание: * — возраст пациента на момент постановки диагноза; ГИСО — гастроинтестинальная стромальная опухоль; НЭК — нейроэндокринные клетки; НЭО — нейроэндокринная опухоль.
Results

Five of the six patients were female, median age made 64 years (minimum age — 55 years, maximum age — 71 years). Three of the six patients had other autoimmune diseases, which is characteristic of AIG [12]: one patient had autoimmune thyroiditis and pulmonary sarcoidosis, the second had autoimmune thyroiditis, and the third had Berger’s disease.

Clinical and morphological data of patients with AIG included in the study are presented in Table.

Case 1

A 63-year-old female patient was examined due to complaints of dyspepsia. Previously, the patient underwent EGDS three times, the results of which were interpreted as “superficial gastritis”, however, the latest study revealed a flat ulcerative defect in the upper third of the body of the stomach along the lesser curvature of 0.8 × 1.0 cm, histological examination revealed the growth of cricoid-cell cancer. Diagnosis: Cancer of the upper third of the stomach st2N0M0, stage 1. Based on the results of the interdisciplinary oncological consultation, it was decided to conduct surgical treatment in the amount of total gastrectomy with D2 lymph node dissection.

Histological examination of the surgical material confirmed the diagnosis of early ring cell carcinoma of the body of the stomach with focal invasion into the submucosa (pT1b G3) (Fig. 1). No signs of perineural and vascular invasion were found (LV—, Pn—). Lymph nodes had no signs of metastatic disease (N0).

Outside the tumour — a picture of chronic atrophic autoimmune gastritis with widespread pseudopyloric and focal complete intestinal metaplasia, foci of foveolar hyperplasia, severe inflammation with moderate activity. In the muscular membrane, a nodule formed by elongated cells was found, the cells formed chaotically directed bundles, mitoses were not detected, pronounced hypertrophy of the muscular membrane attracted attention. The results of the IHC study in the form of a positive reaction of tumour cells with CD117 and DOG-1 corresponded to the emerging gastrointestinal stromal tumour (GIST) of the stomach, a spindle cell variant of the structure with low proliferative activity (G1). Also, according to the results of IHC reactions with chromogranin A, an increased content of positively stained...
cells along the glands and the formation of multiple small nodules were revealed, which indicated hyperplasia of neuroendocrine cells of the gastric mucosa and testified in favour of AIG (Fig. 2).

Case 2

Three years ago, a highly differentiated NET of the body of the stomach (T1N0M0) was detected in a 71-year-old female patient, and therefore, argon plasma coagulation was performed. She applied to this hospital with complaints of heartburn and dyspepsia.

EGDS was conducted. In the cardial part of the stomach, along the lesser curvature, a polypoid formation was found on a wide base with the convergence of vessels to this formation with hyperemic mucosa and retraction in the centre. Histological examination of the mass revealed a moderately differentiated cT1NxM0 adenocarcinoma. Laparoscopic atypical resection of the stomach, biopsy of paracardial lymph nodes and lymph nodes of the celiac trunk, as well as drainage of the abdominal cavity were performed.

Histological examination of the surgical material confirmed moderately low-grade adenocarcinoma of the cardia of the stomach with invasion into the submucosal layer (pT1b), dense lymphocytic infiltration of the tumour tissue (TIL+) (Fig. 3). Perineural, lymphovascular invasion was not detected (Pn–, LV–), tumour metastases to the lymph nodes were also not detected (N0). In the outer layers of the muscle wall — nodular growth with a diameter of about 1 cm of tumour tissue formed by spindle-shaped cells, which was an accidental finding at operation. In the gastric mucosa outside the tumour — a picture of chronic gastritis with moderate activity, with areas of atrophy with widespread pseudopyloric metaplasia, foci of foveolar hyperplasia, hyperplastic lymphoid follicles with germinal centres.

An IHC study of adenocarcinoma tissue revealed a loss of expression of microsatellite instability markers MSH2 and MSH6, while maintaining the expression of DNA repair proteins MLH1 and PMS2, and therefore the tumour was classified as microsatellite unstable (dMMR/MSI). The index of proliferative activity according to Ki67 reached 70 % in some fields of vision. Her2-status of the stomach tumour was negative. When reacting with PD-L1, positively stained immune cells accounted for 20 % of the area occupied by tumour cells (CPS = 20), tumour cells had negative staining. In reaction with antibodies to chromogranin A and synaptophysin, positive

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Figure 2. Case 1. Female patient, 63 years old. Hyperplasia of neuroendocrine cells in the mucosa of the body of the stomach: simple, linear and nodular. IHC reaction with antibody to chromogranin A, ×200

Рисунок 2. Случай 1. Пациентка 63 лет. Гиперплазия нейроэндокринных клеток в слизистой оболочке тела желудка: простая, линейная и нодулярная. ИГХ-реакция с антителом к хромогранину A, ×200
staining of individual tumour cells was obtained, as well as simple and linear hyperplasia of neuro-endocrine cells with the presence of five or more consecutive cells in the epithelium of the glands in the surrounding gastric mucosa outside the tumour. Immunophenotyping of gastric GIST nodule showed positive staining of tumour cells in reactions with antibodies to CD117 and DOG-1, Ki67 proliferation index was less than 3 % (G1) (Fig. 4).

Case 3

A 64-year-old male patient has been observed for AIG since 2015. Biopsy from 2015 detected reactive changes in the epithelium and focal hyperplasia of the foveolar layer in the mucous membrane of the antrum of the stomach; in the body of the stomach — chronic atrophic gastritis with extensive areas of pseudopyloric and complete intestinal metaplasia, thickening of the muscularis mucosa and small lymphoid accumulations. The glands of the body of the stomach were not found in the studied biopsies. In 2017, a highly differentiated adenocarcinoma of the lower third of the body of the stomach was diagnosed (Fig. 5), for which the patient underwent endoscopic removal of the tumour. IHC study of tumour tissue with antibodies to MLH1, MSH2, MSH6, and PMS2 revealed positive expression of these markers preserved in the nuclei of tumour cells; therefore, the tumour was classified as microsatellite stable (pMMR/MSS). When carrying out the reaction with antibodies to MUC5AC mucins, diffuse positive staining of the cytoplasm of tumour cells and focal positive staining in the reaction with MUC2 were obtained. The immunophenotype of the tumour was regarded as mixed gastrointestinal with a predominance of gastric (Fig. 6).

During the planned EGDS in 2022, no signs of tumour growth were found, an endoscopic picture of gastritis with atrophy was established, and a biopsy was taken according to OLGA to assess the dynamics of atrophy. Histological examination revealed chronic mild inactive superficial gastritis of the antrum with focal hyperplasia of the foveolar layer (grade 1, stage 0), as well as chronic mild inactive atrophic gastritis of the body of the stomach with widespread complete intestinal metaplasia (80 % of the biopsy area), focal pseudopyloric metaplasia, solitary cysts and hyperplasia of the
Figure 4. Case 2. Female patient, 71 years old. Gastrointestinal stromal tumour nodule. IHC reaction with anti-CD117 antibody (c-KIT), ×200

Рисунок 4. Случай 2. Пациентка 71 года. Узелок гастроинтестинальной стромальной опухоли. ИГХ-реакция с антителом к CD117 (c-КИТ), ×200

Figure 5. Case 3. Male patient, 64 years old. Highly differentiated intramucosal adenocarcinoma of the body of the stomach. Staining with hematoxylin and eosin, ×280

Рисунок 5. Случай 3. Пациент 64 лет. Внутрислизистая высокодифференцированная аденокарцинома тела желудка. Окраска гематоксилином и эозином, ×280
foveolar layer (grade 2, stage 3). The integral indicator of gastritis according to the OLGA system was grade 2, stage 3.

**Case 4**

In April 2021, female patient C., aged 71, was diagnosed with erosive gastritis not associated with *H. pylori*.

Routine endoscopy in 2022 showed the gastric mucosa with minimal edema and hyperemia, without erosion. Attention was drawn to the reduction of gastric folds of greater curvature due to the thinning of the mucous membrane in the body of the stomach. In the middle third of the body of the stomach, closer to the posterior wall, an area with a depression (0–IIc) up to 3 mm in size was visualized (Fig. 7), when viewed in a narrow spectrum with an irregular tortuous pit and capillary pattern. In the antrum, the epithelium of the mucous membrane is also somewhat thinned. Endoscopic picture of diffuse atrophic gastritis, probably of an autoimmune nature.

Morphological study of the lesion in the body of the stomach showed that the biopsy contained foci of well-formed glands of a convoluted shape, branched in places and closely located with signs of weak dysplasia (low grade dysplasia) of the gastric epithelium (category 3 according to the Vienna classification) (Fig. 8). In the deep sections, mucous glands with an enlarged lumen were found. In the superficial sections, areas with an eroded surface were determined. Chronic mild inactive superficial gastritis of the antrum with focal hyperplasia of the foveolar layer (grade 1, stage 0) was revealed, as well as chronic mild inactive atrophic gastritis of the body of the stomach with widespread pseudopyloric metaplasia and hyperplasia of the foveolar layer (grade 1, stage 2). The integral indicator of gastritis according to the OLGA system was grade 1, stage 2.

Endoscopic mucosectomy with submucosal dissection was performed. The tumour was removed within the unaffected tissues (Fig. 9). Immunophenotyping yielded a gastric phenotype of tumour cells with diffuse expression of mucin MUC5AC (Fig. 10).

**Case 5**

A 64-year-old female patient was hospitalized with complaints of dyspepsia. According to EGDS data, in the arch, upper, middle, lower thirds of the body of the stomach and along the greater curvature, the mucous membrane was diffusely significantly thinned, atrophic, without extensive foci of intestinal metaplasia of the epithelium. In the middle third of the body of the stomach along
Figure 7. Case 4. Female patient, 71 years old. Endoscopic picture of the lesion with depression (0–IIc) in the middle third of the body of the stomach closer to the posterior wall, up to 3 mm in size (endophoto)

Рисунок 7. Случай 4. Пациентка 71 года. Эндоскопическая картина очага поражения с депрессией (0–IIc) в средней трети тела желудка ближе к задней стенке размером до 3 мм (эндофото)

Figure 8. Case 4. Female patient, 71 years old. A focus of weak epithelial dysplasia. Staining with hematoxylin and eosin, ×200

Рисунок 8. Случай 4. Пациентка 71 года. Очаг слабой дисплазии эпителия. Окраска гематоксилином и эозином, ×200
Figure 9. Case 4. Female patient, 71 years old. A focus of weak epithelial dysplasia. Endoscopic resection material. Staining with hematoxylin and eosin, ×100

Рисунок 9. Случай 4. Пациентка 71 года. Очаг слабой дисплазии эпителия. Материал эндоскопической резекции. Окраска гематоксилином и эозином, ×100

Figure 10. Case 4. Female patient, 71 years old. Gastric immunophenotype of weak dysplasia focus cells. IHC reaction with an antibody to MUC5AC, ×120

Рисунок 10. Случай 4. Пациентка 71 года. Желудочный иммунофенотип клеток очага слабой дисплазии. ИГХ-реакция с антителом к MUC5AC, ×120
Figure 11. Case 5. Female patient, 64 years old. Endoscopic picture of an elevated epithelial neoplasm up to 8 mm in diameter, with characteristic branched vessels on the surface in the middle third of the body of the stomach along the lower wall (endophoto).

Рисунок 11. Случай 5. Пациентка 64 лет. Эндоскопическая картина приподнятого эпителиального новообразования диаметром до 8 мм, с характерными ветвистыми сосудами на поверхности в средней трети тела желудка по нижней стенке (эндофото).

the lower wall, an elevated epithelial neoplasm with a diameter of up to 8 mm was visualized, with characteristic branching vessels on the surface (Fig. 11). In the area of the cardia, an additional polypoid formation was suspicious of hyperplasia. According to the conclusion of endoscopy, the endoscopic picture of gastritis with atrophy was suspicious of autoimmune gastritis.

Histological examination of biopsy specimens of the body of the stomach revealed foci of irregularly shaped glands, in some places merging and closely located with signs of epithelial dysplasia, as well as mucous glands with an enlarged lumen and inflammatory infiltration with a significant admixture of leukocytes, which were found in the lumen of dysplastic glands. This picture corresponded to severe dysplasia (high grade dysplasia) of the gastric epithelium (category 4 according to the Vienna classification) (Fig. 12). Additionally, chronic mild inactive superficial gastritis of the antrum with focal hyperplasia of the foveolar layer (grade 1, stage 0), chronic mild inactive atrophic gastritis of the body of the stomach with focal complete intestinal metaplasia (20 and 10 % of the area of biopsy samples), widespread pseudopyloric metaplasia and hyperplasia of the foveolar layer (grade 1, stage 2) were revealed. The integral indicator of gastritis according to the OLGA system was grade 1, stage 2. A biopsy specimen from a polyp of the cardia of the stomach contained hyperplastic ridges with tortuous pits, without signs of epithelial dysplasia — a morphological picture of a hyperplastic polyp of the cardia of the stomach. When conducting an IHC study with an antibody to chromogranin A, areas of dysplasia were surrounded by glands with linear and nodular hyperplasia of neuroendocrine cells. Hyperplasia of neuroendocrine cells was not found in the tumour itself (Fig. 13).

Case 6

A 55-year-old female patient underwent endoscopy due to complaints of dyspepsia, heartburn, bitterness in the mouth and nausea. The mucous membrane of the stomach in the area of the antrum was focally hyperemic, also in the antrum there was an ulcer defect 0.8 × 0.7 cm in size, covered with fibrin without marginal epithelization. In the region of the middle third of the body of the stomach along the greater curvature, a single erosion of up to 6 mm was detected with retraction in the centre, dilated vessels when viewed in the NBI mode.
**Figure 12.** Case 5. Female patient, 64 years old. The focus of severe dysplasia of the epithelium. Staining with hematoxylin and eosin, ×200

**Рисунок 12.** Случай 5. Пациентка 64 лет. Очаг тяжелой дисплазии эпителия. Окраска гематоксилином и эозином, ×200

**Figure 13.** Case 5. Female patient, 64 years old. Hyperplasia of neuroendocrine cells in the mucous membrane of the body of the stomach along the periphery of the focus of severe epithelial dysplasia. IHC reaction with an antibody to chromogranin A, ×200

**Рисунок 13.** Случай 5. Пациентка 64 лет. Гиперплазия нейроэндокринных клеток в слизистой оболочке тела желудка по периферии очага тяжелой дисплазии эпителия. ИГХ-реакция с антителом к хромогранину А, ×200
**Figure 14.** Case 6. Female patient, 55 years old. The focus of low grade dysplasia in the antrum of the stomach. Staining with hematoxylin and eosin, ×200

**Рисунок 14.** Случай 6. Пациентка 55 лет. Очаг слабой дисплазии эпителия в антральном отделе желудка. Окраска гематоксилином и эозином, ×200.

Biopsy specimens from the antrum of the stomach contained foci of well-formed glands of the intestinal type, somewhat tortuous, in places branched and closely spaced with the presence of Paneth cells and signs of mild dysplasia (low grade dysplasia) of the gastric epithelium (category 3 according to the Vienna classification) (Fig. 14). In the deep sections, areas of hyperplastic muscular plate of the mucous membrane, mucous glands with an enlarged lumen were found. In the superficial sections, areas with an eroded surface were determined. In biopsy specimens of the body of the stomach in the mucosal lamina propria, nodular tumour foci of a solid structure were found, represented by clusters of cells with rounded nuclei and well-defined cytoplasm, moderate polymorphism was noted, mitoses were not detected. Areas surrounded by a thin fibrous capsule were found.

An IHC study was performed for differential diagnosis. Diffuse intensely positive staining of the cytoplasm of tumour cells was revealed in reactions with antibodies to chromogranin A and synaptophysin. Additionally, there was an increased content of positively stained cells in the surrounding mucosa along the glands (Fig. 15). Ki67 proliferative activity index — positive staining of single tumour cells (< 3 %).

IHC results were consistent with well-differentiated gastric NET, G1. The size of the tumour was less than 0.2 cm, which corresponds to a microcarcinoid (“tumourlet”).

The patient was recommended to perform endoscopic resection of the tumour of the antrum of the stomach, she is currently awaiting treatment.

**Discussion**

Chronic gastritis is a risk factor for developing stomach cancer. The most common cause of chronic inflammation of the gastric mucosa is *H. pylori* infection, but it is equally important to recognize other causes, in particular autoimmune damage, which in some cases can be combined with *H. pylori*.

The direct mechanisms underlying the development of gastric cancer in AIG patients are still the subject of discussion. In 1975, Pelayo Correa first proposed a stepwise model of gastric carcinogenesis, which revolutionized the understanding of the pathogenesis of this disease. It is generally accepted that the development of intestinal-type gastric cancer is preceded by a sequence of mucosal changes: superficial gastritis (non-atrophic gastritis) → multifocal atrophic gastritis without intestinal metaplasia → complete intestinal metaplasia (small intestinal) → incomplete...
intestinal metaplasia (colonic) → low-grade dysplasia (non-invasive low-grade dysplasia) → high-grade dysplasia (non-invasive high-grade dysplasia) → invasive adenocarcinoma [3]. Thus, atrophic gastritis and intestinal metaplasia are considered as precancerous changes in the stomach. However, recently the significance of intestinal metaplasia in the pathogenesis of gastric cancer in the absence of *H. pylori* has been questioned [13, 14].

In AIG, gastric atrophy is more pronounced in the proximal section, while the mucosa in the distal section usually remains intact [10, 11], which was also shown in a Russian study [15]. In contrast, atrophy and metaplasia in *H. pylori*-associated gastritis initially occurs in the distal stomach and gradually spreads towards the proximal stomach [11]. In all presented cases, morphological changes, taking into account the predominant lesion of the body of the stomach, are characteristic of the autoimmune nature of gastritis. At the same time, the lesion of the antrum was characterized by reactive and hyperplastic processes, which is not typical for lesions with *H. pylori* infection, while at least one of the patients had anamnestic data on successful eradication of *H. pylori*.

Against the background of inflammation and atrophy in the stomach, two types of metaplasia can occur: intestinal metaplasia and metaplasia expressing spasmolytic polypeptides (spasmolytic polypeptide-expressing metaplasia — SPEM). Intestinal metaplasia is represented by two main types: complete intestinal metaplasia (small intestinal type) and incomplete intestinal metaplasia (small and large intestinal type). Complete intestinal metaplasia is characterized by the presence of goblet and prismatic absorptive cells, as well as decreased expression of gastric mucin (MUC1, MUC5AC and MUC6) and expression of intestinal mucin MUC2 [16].

SPEM, also known as pseudopyloric metaplasia, is characterized by the expression of the protein TFF2 and MUC6 and is associated with the development of atrophy of the acid-producing zone, which develops in the corpus and fundus of the stomach. SPEM is not a defined “stage” in the P. Correa cascade, and there is currently no consensus to consider SPEM as a definite precursor to gastric cancer rather than simply as an associated event [17–19].

The morphological data presented in our study can be interpreted as an alternative sequence of changes in gastric cancer in patients with AIG. We
suggest that the sequence of morphological changes “chronic autoimmune gastritis → pseudopyloric metaplasia → low-grade dysplasia → high-grade dysplasia → adenocarcinoma” may be responsible for carcinogenesis in a small percentage of patients with AIG. At the same time, this mechanism is realized without the previous development of intestinal metaplasia, and probably pseudopyloric metaplasia does not transform into intestinal.

According to histological features and immunophenotyping, two main subtypes of gastric dysplasia have been described: intestinal and gastric type. The gastric type can be divided into foveolar and pyloric [20]. These lesions may arise de novo from native gastric mucosa, outside of the multi-stage model of gastric carcinogenesis, and show signs of biological aggressiveness. Mixed phenotypes (intestinal and gastric) are often observed in clinical practice, so most published molecular studies do not distinguish between the two main forms. In addition, most of the available data relate to intestinal-type dysplastic lesions of the stomach with an intestinal phenotype.

Hypergastrinemia, which occurs as a response to a decrease in gastric secretion in autoimmune gastritis, leads to hyperplasia of enterochromaffin cells and the possible development of type 1 NET [7, 21]. In the study of M. Rugge et al. at the beginning of follow-up of patients with AIG, linear/micronodular hyperplasia of ECL cells was detected in 79.1 % of cases, adenomatoid hyperplasia/dysplasia — in 6.6 % of cases, and type 1 NET — in 4.7 % of cases [6]. In the clinical cases presented by us, hyperplasia of neuroendocrine cells was found in all patients, while in two patients it was transformed into NET.

A case of gastric cancer with microsatellite instability (dMMR/MSI) was also identified in our patient cohort. According to available studies, tumours with the MSI subtype are characterized by a high frequency of mutations in the genes responsible for oncogenesis (HER-2, ERBB3) and genes that control the cell cycle. The development of gastric cancer with microsatellite instability is observed in a small percentage of cases, which, according to the literature, is no more than 10–15%. A meta-analysis of four randomized trials of perioperative or adjuvant chemotherapy demonstrated better overall survival in patients with MSI as compared with the MSS phenotype [22].

**Conclusion**

AIG is one of the risk factors for the development of gastric cancer, a molecularly and phenotypically heterogeneous disease, however, the direct mechanisms underlying its development in AIG patients currently cause a lot of discussion. Given the increase in cases of detection of AIG, the problem of the development of tumours against the background of this disease is becoming increasingly relevant.

In our study, we found that in all patients with AIG included in the study, the localization of lesions predominated in the body of the stomach, with the exception of one case, while all detected cancers were early and, according to the immunophenotype, gastric. Interestingly, the presented cases of tumours were not accompanied by NEC hyperplasia directly in the tumour itself, but only in the surrounding gastric mucosa. Additionally, two cases of early GIST were found, which were characterized by low proliferative activity and were small in size.

The P. Correa’s cascade implies a linear progression from chronic gastritis to gastric adenocarcinoma through atrophy of the gastric mucosa. However, taking into account the gastric phenotype of the tumours presented in the series, as well as the absence of severe intestinal metaplasia, it can be assumed that there is an alternative pathway of carcinogenesis in AIG, in which, in our opinion, pseudopyloric metaplasia (SPEM) precedes gastric adenocarcinoma with the following sequence of morphological changes “chronic gastritis → pseudopyloric metaplasia → dysplasia → adenocarcinoma”, bypassing the stage of intestinal metaplasia. In the literature, the significance of SPEM in gastritis is not clearly defined, therefore, for a deeper analysis, further studies are needed in patients with precancerous conditions and changes in the gastric mucosa in AIG.
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