Autoimmune Gastritis. A Clinicopathologic Study of 25 Cases

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Summary

The histopathological diagnosis of autoimmune gastritis (AG) in its early stages can be a diagnostic challenge. Even some advanced cases with complete atrophy of the corpus mucosa may be difficult to recognize. To establish the diagnosis of autoimmune gastritis, several histological features should be assessed and combined with immunostains for enterochromaffin cell-like (ECL) cells and G-cells. The main histological criteria include a mononuclear infiltrate within the lamina propria, foci of destruction of oxyntic glands, intestinal metaplasia (IM), pyloric metaplasia, and parietal cell pseudohypertrophy. These criteria were evaluated in our series of 25 patients with achlorhydria and/or megaloblastic anemia. Some of our patients presented with nonspecific gastrointestinal symptoms. The age ranged between 46 and 79 years; one male patient was only 31 years old. Histologically, the corpus mucosa displayed in all cases chronic inflammation with focal complete IM and advanced pyloric metaplasia. In 4 patients, oxyntic glands were destructed in some sites. There was a pancreatic metaplasia of acinar type in 2 patients and a minimal focal pseudohypertrophy of parietal cells in the 31-year-old man. A tubular adenoma with a low-grade dysplasia was found in one female patient. Immunohistochemically, chromogranin-A highlighted linear or nodular hyperplasia of ECL cells in 19 patients, and adenomatoid ECL hyperplasia in one case (80%). In the remaining cases hyperplasia of ECL cells could not be recognized from their normal count. In 13 cases (52%) a few ECL cells were seen also in IM. Regarding associated pathology, in one woman with nodular ECL cell hyperplasia, a gastric carcinoid was removed endoscopically. The reaction with gastrin antibody revealed in 11 cases (44%) a small number of G cells in IM in the corpus mucosa. In 18 patients, antral mucosa was examined as well. In 8 patients, the mucosa was normal; in 10 cases, a mild chronic inactive gastritis was diagnosed, and in 15 patients G-cell hyperplasia was found. In accordance with other studies, we show that the diagnosis of AG may be established microscopically in endoscopic specimens of the gastric body mucosa when histologic features and immunohistochemical detection of ECL and G cell hyperplasia are combined.
Key words: autoimmune gastritis – histology – immunohistochemistry - ECL cell hyperplasia – G cells

Souhrn
Autoimunní gastritis. Klinickopatologická studie 25 případů

Bioptické hodnocení autoimunní gastritidy (AG) je v časné fázi onemocnění a často i u pokročilého zánětu s kompletní atrofií korporální sliznice žaludku obtížné. Ke stanovení diagnózy AG se v posledních letech doporučuje posuzování několika histologických nálezů, doplněné imunohistochemickým průkazem buněk podobných enterochromafinním (ECL) buňkám a G buněk. Histologické nálezy zahrnují mononukleární infiltraci lamina propria, ložiskovou destrukci oxyntických žlazek, intestinální metaplazii (IM), pylorickou metaplazii a pseudohypertrofii parietálních buněk. Tato kritéria autoři použili při bioptickém vyšetřování korporální sliznice žaludku u 25 nemocných s achlorhydrií a/nebo megaloblastickou anémií; u části nemocných byly uvedeny nepříznačné gastrointestinální potíže. U 24 nemocných se věk pohyboval mezi 46–79 lety, jeden muž byl 31letý. Histologický nález v korporální sliznici žaludku odpovídal u všech nemocných chronické gastritidě s ložiskovou kompletní IM a s pokročilou pylorickou metaplazií, u 4 nemocných byla nalezena fokální destrukce oxyntických žlázek, u dalších dvou pankreatická metaplazie acinárního typu a u 31letého muže minimální ložisková pseudohypertrofie parietálních buněk. U jedné ženy byl diagnostikován tubulární adenom s dysplazií nízkého stupně. Imunohistochemické vyšetření s chromograninem-A prokázalo u 20 nemocných (80%) lineární nebo nodulární a jednou adenomatoidní hyperplazii ECL buněk, u ostatních nebylo možno rozlišit prostou hyperplazii od normálního počtu ECL buněk. U jedné ženy s nodulární hyperplazií ECL buněk byl při endoskopickém vyšetření odstraněn karcinoid. V reakci s protilátkou proti gastrinu se v 11 případech (44 %) v IM korporální sliznice vyskytovaly ojedinělé G buňky. U 18 nemocných byla sou-

časně vyšetřena sliznice antra žaludku. U 8 z nich měla sliznice normální nález, 10krát byla přítomna mírná chronická neaktivní gastritida a u 15 nemocných hyperplazie G buněk. Naše nálezy, podobně jako výsledky předchozích studií, prokázaly, že histologické vyšetření, doplněné imunohistochemickým průkazem ECL a G buněk umožňuje stanovit diagnózu AG v endoskopických biopsiích korporální sliznice žaludku.

Klíčová slova: autoimunní gastritis – histologie - imunohistochemické vyšetření – hyperplazie ECL buněk – G buňky

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Autoimmune gastritis (AG), or type A atrophic gastritis, is a chronic inflammatory process that typically involves the corpus mucosa in a diffuse manner (4, 8, 18). A high proportion of patients have circulating autoantibodies against the microsomes of parietal cells and intrinsic factor autoantibodies, which are detected in 55–60% cases. Thus a proportion of patients with AG will develop pernicious anemia due to vitamin B 12 deficiency (4). There is also a common association with other organ-specific autoimmune diseases, and patients frequently have shared autoantibodies against the various tissues (14). AG is a dynamic disease in which involvement of the mucosa increases in severity with age. In fully established AG, the body mucosa is inflamed and shows extensive atrophy with replacement of the oxyntic glands by intestinal and pyloric metaplastic epithelium, and enterochromaffin-like (ECL) cell hyperplasia. The antral mucosa tends to be spared, although there may be associated mild chronic gastritis. There is an absolute increase in the number of antral gastrin+ cells (G cells) in response to the hypochlorhydria, and this is accompanied by raised serum levels of gastrin. The hypergastrinemia has a trophic effect on the ECL cells in the glands of the body mucosa, leading to ECL cell hyperplasia (4, 9, 13, 18). Patients with AG may present with achlorhydria, hypergastrinemia, anti-parietal cell and/or anti-intrinsic factor antibodies, and pernicious anemia. In some cases, however, the manifestation of AG is nonspecific with gastrointestinal symptoms such as dyspepsia, nausea, vomiting, gastrointestinal reflux disease (13, 18) or unexplained microcytic anemia (18). A histologic diagnosis under these clinical manifestations of AG is difficult. Therefore, in our study of 25 cases of AG, we employed the recommended histological criteria and immunostains for chromogranin (to evaluate for ECL cells presence and hyperplasia) and gastrin (to exclude antral and antral-oxyntic transitional gastric mucosa) (4, 8, 13, 18), to establish the diagnosis of AG in endoscopic specimens of gastric body mucosa.

Material and Methods

The group of 25 patients included 14 men and 11 women. The age of 24 of them ranged between 46 and 79 years (mean age: men 68, women 65 years). One patient was only 31 years old. In 16 patients achlorhydria and/or megaloblastic anemia and atrophic gastritis were diagnosed clinically. Nine patients suffered merely from nonspecific gastrointestinal symptoms. Anti-parietal cell antibodies, anti-intrinsic factor antibodies, and serum gastrin level were not examined in any patient. The endoscopic examination with a biopsy was repeated once or twice in 4 men and 4 women in an interval of 1 month – 5 years. No patient had any other autoimmune disease. Proton pump inhibitors (PPI) were not applied in any patients. On endoscopy, one or two samples of the gastric body mucosa were obtained from each patient. In 18 patients, 1–2 samples of the antral mucosa were obtained as well (without an information of precise localization).

The specimens for microscopic examination were fixed in 10% neutral formol, embedded in paraffin using standard procedures and stained with hematoxylin-eosin, Periodic acid Schiff/-Alcian blue at pH 2.5, and with silver impregnation technique according to Warthin-Starry.

For immunohistochemistry, the following primary antibodies were employed: chromogranin-A (DAK-A3 pepsin 1:400 DAKO Glostrup), gastrin (Gastrin pepsin polyclonal, 1:500 DAKO Glostrup), MUC2 (Cep58, MW 1:400, Novocastra, Newcastle), MUC5AC (CLH2, MW 1:400, Novocastra, Newcastle), MUC6 (CLH5, MW 1:400, Novocastra, Newcastle). Sections 4 μ thick were cut from the specimen and placed on slide coated with 3-aminopropyltriethoxy-silane (Sigma). The sections were then deparaffinized and predigested by pepsin. The primary antibodies were visualized using the supersensitive streptavidin-biotin peroxidase complex (BioGenex, San Ramon, CA, USA). The color was

developed with diaminobenzidine, supplemented with hydrogen peroxide.

The severity of inflammatory changes was scored according to the Sydney classification (7). Using immunohistochemical reaction with chromogranin -A, the presence of ECL cells was evaluated as normal count – simple hyperplasia – linear and nodular hyperplasia (18). The number of G cells was assessed as normal or hyperplasia (9).

Results

In 25 patients, the corpus mucosa was diagnosed as chronic gastritis with focal complete IM and with pyloric metaplasia of majority of the glands (Fig. 1). Of these, in 24 patients the chronic gastritis was merely mild and inactive, while in the 31-year-old man it was mild active. Scarce residual oxyntic glands were found only in 7 patients. Focal lymphocytic destruction of oxyntic glands was identified in 4 cases (Fig. 2). Pancreatic metaplasia of acinar type was found in 2 specimens and cystic dilatation of one or several foveolas and/or glands was seen in seven patients (28%) (Table 1). The corpus mucosa of the 31-year-old man with juvenile AG showed practically the same features as the adult AG form, and, in addition, it displayed a minimal focal pseudohypertrophy of parietal cells.

Tab. 1. Histological findings in gastric mucosa in 25 patients with AG

Histologic findings in corporal mucosa	**Male**	**Female**	**Total**
Chronic inflammation	14	11	25
Intestinal/pyloric metaplasia	14	11	25
Parietal cell pseudohypertrophy	1	0	1
Pancreatic metaplasia	2	0	2
ECL hyperplasia	11	9	20
Carcinoid	0	1	1
Adenoma	0	1	1
Histologic findings in antral mucosa			
Normal	5	3	8
Chronic inflammation	7	3	10
G cell hyperplasia	11	4	15

A linear, nodular, and exceptionally also adenomatoid hyperplasia of ECL cells was detected using immunohistochemical visualization of chromogranin-A in 20 cases (80%) (Fig. 3). In the remaining cases, it could not be reliably differentiated between simple ECL cells hyperplasia and normal count of ECL cells. ECL cells were found in residual corpus glands and in pyloric metaplasia. In nodular hyperplasia, these elements were scattered in small groups in the deep parts of the lamina propria, sometimes adjacent to the muscularis mucosae. Further, in 13 cases (52%) ECL cells were present in metaplastic intestinal epithelium in small numbers. Rare individual G cells were dispersed in IM of 11 patients (44%) (Fig. 4), but were never seen outside IM.

Goblet cells in the intestinal metaplastic epithelium were visualized using MUC2 immunostain. In all cases, foveolar zone hyperplasia representing at least a half of the corpus mucosa thickness was highlighted using MUC5AC antibody. In some cases, the foveolar epithelium reached as far as to the lowest third of the corporal mucosa. MUC6 decorated not only advanced pyloric metaplasia, but also less differentiated mucous glands.

The antral mucosa was obtained in 18 patients (72%). Eight biopsies were normal, and ten biopsies showed a mild chronic inactive inflammation. G cells positive for gastrin were detected in 15 cases on immunohistochemistry. In one case, the G cell count was normal, and in additional 2 cases their presence could not be assessed, as a superficial part of the mucosa was available only.

The results of a repeated examination of the gastric body mucosa conformed to the original diagnosis of AG in eight cases. Additionally, a carcinoid was diagnosed in a woman with chronic atrophic inflammation and nodular ECL cell hyperplasia. Another patient developed a low-grade tubular adenoma of the gastric body mucosa.

Discussion

Autoimmune gastritis typically presents in older persons, usually over the age of sixty. Histologically, in the early stage of the disorder, an increased number of mononuclear inflammatory cells are evident in the foveolar layer of the lamina propria. As the disease advances, typically over many years, the inflammatory reactions extend into the glandular layer of the mucosa with a progressive destruction of the specialized glands. Over time, the mucosa is replaced by a mixture of areas of foveolar hyperplasia, IM, and prominent pyloric gland metaplasia. Cases displaying a complete loss of the specialized glands and a minimal inflammation probably represent the end stage of the disease (4, 13, 14, 18).

Regarding pernicious anemia it may, albeit rarely, occur already in later childhood or adolescence. Three forms of juvenile pernicious

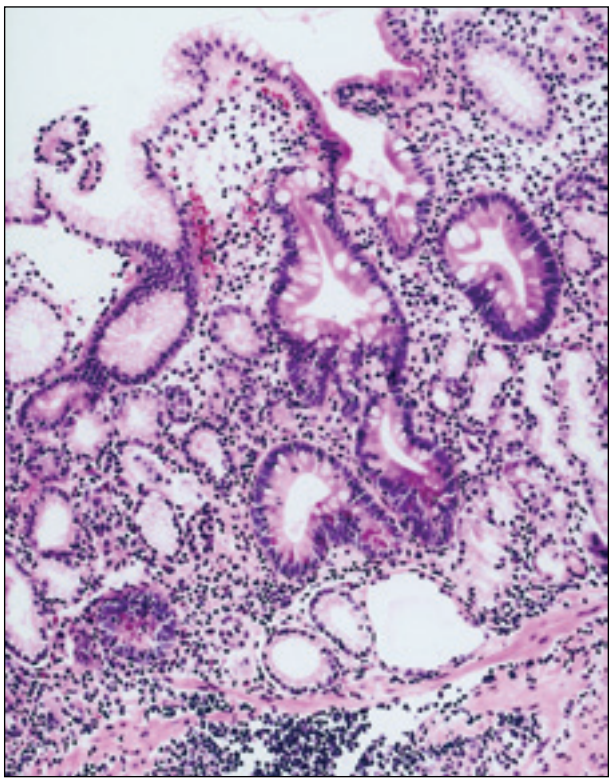

Fig. 1. Autoimmune gastritis. A diffuse mild chronic inactive inflammation with atrophy, focal complete intestinal metaplasia and pyloric metaplasia of the oxyntic glands. HE, x200

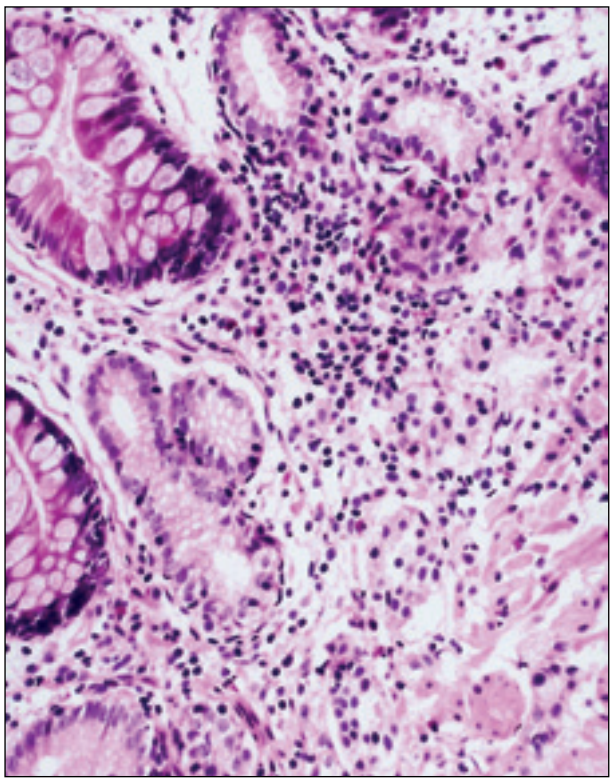

Fig. 2. Focal destructive inflammation of the residual oxyntic glands. Complete intestinal metaplasia and pyloric metaplasia in the surrounding mucosa. HE, x300

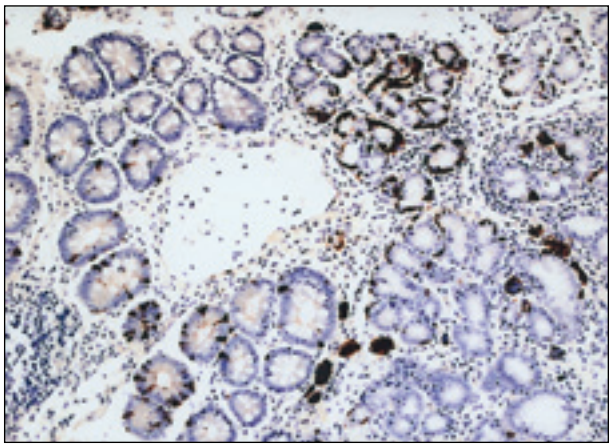

Fig. 3. Linear and nodular ECL cell hyperplasia of the oxyntic mucosa in autoimmune gastritis. Numerous ECL cells are also present in the intestinal metaplasia. Chromogranin A reaction, SABPC technique, x200

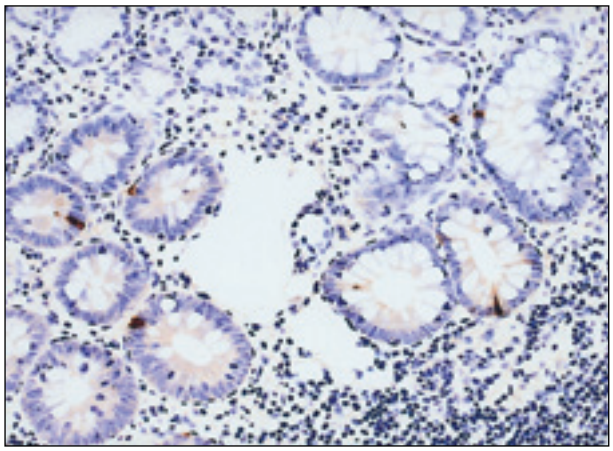

Fig. 4. Scattered G cells immunoreactive in the intestinal metaplastic epithelium in the oxyntic mucosa. Gastrin reaction, SABPC technique, x300

anemia exist, and only one of them is associated with gastric atrophy and probably just representing the adult type in an unusually early age of onset (4). On agreement with this, we diagnosed this type of AG in a 31-year-old man with almost complete atrophy of the corpus mucosa, not differing histologically from the adult form of AG. In the second form of juvenile pernicious anemia the intrinsic factor is not secreted by parietal cells and the mucosa is histologically normal. The third type results from the failure to absorb vitamin B 12 – intrinsic factor complex.

AG can be easily recognized in most patients when the histological features are fully developed, but earlier manifestations of AG before the complete loss of the oxyntic mucosa are more challenging to recognize. Even clinical

findings, including serum level of anti-parietal cell antibody, may not be helpful in such cases (18). Because of these reasons, definitive diagnosis of AG on purely histological grounds was not warranted in the past (6). However, some recent studies indicate that early AG can be diagnosed or at least strongly suggested on base of histologic and immunohistochemical examination (8, 18).

Recently, the following histological features of AG have been described in cases without total loss of the oxyntic mucosa (8, 18): (1) a mononuclear infiltrate within the lamina propria that is often heavier in the glandular portion, (2) foci of lymphocytic infiltration and destruction of oxyntic glands, (3) IM and/or pyloric gland metaplasia, and (4) pseudohypertrophy of the remaining parietal cells. None of these features alone are diagnostic in isolation. It is the pattern of findings that suggests AG.

The immunohistochemical reaction for ECL and G cells has proved to be an important diagnostic tool. The presence of ECL cells and a negative gastrin stain are helpful in insuring that the biopsy specimens are not from the antral-oxyntic transitional mucosa (18). Also in fully developed disease when gastric body specimens show a complete loss of oxyntic glands, the detection of ECL cells helps to distinguish the corpus from antral mucosa.

Immunohistochemistry for chromogranin enables to evaluate not only the presence, but also the number of ECL cells.

ECL cell hyperplasia occurs already in early stages of AG in about one third of patients (13, 18). In our series of 25 AG patients, hyperplasia of linear, nodular, and, in one case, of adenomatoid type (2, 5) was detected in 20 cases (80%). In 5 patients, we could not reliably distinguish between a simple hyperplasia and a normal number of ECL cells. In one female patient with nodular ECL cell hyperplasia, a carcinoid was removed on endoscopy. This tumor arose in consequence of neoplastic transformation of ECL cell hyperplasia (1, 4, 5). ECL cells were found in oxyntic mucosa and in the glands of pyloric metaplasia in all cases and in IM in 13 patients (52%). In nodular hyperplasia, they were rarely found also in the deep parts of lamina propria. Some of these nodules may bud off from adjacent glands, whereas others show more neural characteristics suggesting an origin from the progenitor cells of neural complex of the lamina propria (4). In addition to histamine, the latter may occasionally contain other peptides (1) including gastrin (4). G cells were not present in hyperplastic endocrine cell nodules in our cases. In contrast, scarce G cells were identified in metaplastic intestinal epithelium in 11 of our patients (44%). The finding of G cells in IM in the body mucosa has been reported by Deveci and Deveci (5). Also Bordi et al. (2) mentioned scarce chromogranin B positive cells in IM.

Pancreatic acinar cell metaplasia of „acinar“ type (15) was found in oxyntic mucosa in two of our patients (8%), in addition to constantly present metaplasias of pyloric and intestinal type. Frequency of metaplastic pancreatic acinar cells in oxyntic mucosa has been investigated in the study of Doglioni et al. (7) and Jhala et al. (11). They demonstrated pancreatic metaplasia in 50% of cases of AG. Thus, detection of pancreatic acinar cells in the oxyntic mucosa of patients with gastritis particularly in the combination with IM and pyloric metaplasia strongly suggests an autoimmune pathogenesis (10, 11). A low incidence of pancreatic metaplasia in our series approaches the results of Deveci and Deveci (5), and it may be partly caused by low number of endoscopic specimens per patient.

Pseudohypertrophy of the residual parietal cells was found in our series only in one case. In the setting of AG it is likely to result from increased gastrin levels that continuously stimulate the parietal cells to produce acid, along with the effect of anti-parietal cell antibodies that block parietal cell acid secretion by binding to the proton pump (13, 16). Parietal cell pseudohypertrophy (so-called parietal cell protrusion) has also been observed in the oxyntic mucosa of patients receiving proton pump inhibitors (PPI) (3, 16, 17, 19) and in several other conditions associated with hypergastrinemia (3). In our 31-year-old man with juvenile AG, without any PPI treatment, parietal cell pseudohypertrophy occurred in a minimal extent only. In the study of Torbenson et al. parietal cell pseudohypertrophy was seen in 85% of the cases (18). However, in a part of their patients, the PPI therapy also very probably contributed to some of this parietal cell protrusion. Parietal cell pseudohypertrophy occurs in preserved islands of relatively normal oxyntic mucosa, appearing as polypoid or nodular lesions on endoscopy (13). The absence of parietal cell pseudohypertrophy in almost all our patients can be explained by a complete atrophy of the corpus mucosa with only exceptionally few oxyntic glands left in 7 patients only.

Retention type cysts lined by mucus cells are a common finding in AG (4). Our findings confirm it. A small number of cysts were present in 2 of our patients, and in 5 others a cystic dilatation of one or several foveolas was seen (28%). One of these changes was identified as a polypoid deformity of the corpus mucosa on endoscopy.

Using the immunohistochemical mucus detection, the precise extent of foveolar hyperplasia (MUC5AC) and less differentiated

metaplastic pyloric glands were visualized (MUC6).

The mild chronic inactive gastritis in the antral mucosa in 10 of our patients is in accordance with other literary data (4, 13, 14, 18). However, the cause of inflammatory changes in the antral mucosa has not been elucidated. It might be a mere extension of the fundic disease into the antrum or coexistence of the two forms of chronic fundic and of chronic antral gastritis in the same patient (14).

A mild G cell hyperplasia was detected in the antral mucosa in 15 patients (60%). Physiological variations of G cell numbers and distribution must be taken into account when evaluating their hyperplasia. They tend to be more numerous in the major than in the lesser curvature. Their number is also influenced by pathological changes, namely by chronic gastritis (9). H. pylori was not identified in corpus and antral mucosa in any of our patients.

The differential diagnosis of AG includes chronic H. pylori gastritis with IM and atrophy of gastric corpus mucosa, multifocal atrophic gastritis and changes induced by PPI treatment. The diagnosis of chronic H. pylori gastritis is excluded by the absence of H. pylori and especially by ECL cell hyperplasia. Difficulties arise often when differential diagnosis is between AG and multifocal atrophic gastritis with localization of inflammation mainly at the antro-corporal junction. The latter lacks ECL cell hyperplasia. Further problems may be posed in cases of parietal cell pseudohypertrophy induced by PPI as parietal cell pseudohypertrophy is seen also in AG in islands of preserved oxyntic mucosa without atrophic inflammation (4, 13). In such cases the differential diagnosis is based on examination of additional specimens from corporal mucosa where more typical atrophic gastritis is present as well as on clinical information (therapy with PPI, achlorhydria).

In summary, our findings corroborate the results of previous studies: AG can be recognized in endoscopic biopsies of gastric corpus mucosa microscopically. The diagnosis of AG, especially in patients with incomplete corpus mucosa atrophy, may be rendered when the following constellation of features is present: chronic inflammation, focal destruction of oxyntic glands, IM, pyloric metaplasia, pseudohypertrophy of parietal cells, and immunohistochemical detection of ECL cells and G cells. The diagnosis of AG is further supported by the presence of pancreatic metaplasia.

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References

1. **Bordi, C., Ferrari, C., D Adda, et al.:** Ultrastructural characterisation of fundic endocrine cell hyperplasia associated with atrophic gastritis and hypergastrinaemia. Virchows Arch. A Pathol. Anat. Histopathol., 409, 1986, s. 335–347. – 2**. Bordi, C., Yu, J-Y., Baggi, M.T., et al.:** Gastric carcinoids and their precursor lesions. A histologic and immunohistochemical study of 23 cases. Cancer, 67, 1991, s. 663–672. – 3. **Cats, A., Schenk. B.E., Bloemena, E., et al.:** Parietal cell protrusions and fundic gland cysts during Omeprazole maintenance treatment. Hum. Pathol., 31, 2000, s. 684–690. – 4. **Day, D.W., Jass, J.R., Price, A.B., et al.:** Morson and Dawson@s gastrointestinal pathology, 4th edition. Blackwell Publishing Company, 2003. Massachusetts – Oxford – Carlton – Berlin. – 5. **Deveci, M.S., Deveci, G.:** Altered distribution of metaplastic Paneth, gastrin and pancreatic acinar cells in atrophic gastritic mucosa with endocrine cell lesions. Tohoku J. Exp. Med., 202, 2004, s. 13–22. – 6. **Dixon, M.F., Genta, R.M., Yardley, J.H.** and the participants in the International Workshop on the Histopathology of Gastritis, Houston 1994: Classification and grading of gastritis. Am. J. Surg. Pathol., 20, 1996, s. 1161–1181. – 7. **Doglioni, C.,Laurino, I., Dei Tos, A.P., et al.:** Pancreatic (acinar) metaplasia of the gastric mucosa: histology, ultrastructure, immunocytochemistry and clinico-pathologic correlation of 101 cases. Am. J. Surg. Pathol., 17, 1993, s. 1134–1143. – 8. **Eidt, S., Oberhuber, G., Schneider, A., et al.:** The histopathological spectrum of type A gastritis. Path. Res. Pract. 192, 1996, s. 101–106. – 9. **Fenoglio-Preiser, C.M., Noffsinger, A.E., Stemmermann, G.N., et al.:** Gastrointestinal Pathology Lippincott-Raven Publishers 1999. – 10. **Haber, M.M., Lu, L., Jhala, N., Lechago, J.:** Histology of autoimmune gastritis (AG) in gastric mucosal biopsies. Mod. Pathol., 13, 2000, s. 81A. – 11. **Jhala, N.C., Montemor, M., Jhala, D., et al.:** Pancreatic acinar cell metaplasia in autoimmune gastritis. Arch. Pathol. Lab. Med., 127, 2003, s. 854–857. – 12. **Koppert, L.B., Wijnhoven, B.P.L., Tilanus, H.W., et al.:** Neuroendocrine cells in Barrett@s mucosa and adenocarcinomas of the gastroesophageal junction. Int. J. Surg. Pathol., 12, 2004, s. 117–125. – 13. **Krasinskas, A.M., Abraham, S.C., Metz, D.C., et al.:** Oxyntic mucosa pseudopolyps. Am. J. Surg. Pathol., 27, 2003, s. 236–241. – 14. **Ming, S-C., Goldman, H.:** Pathology of the gastrointestinal tract. Second edition. Williams and Wilkins 1998. Baltimore-Philadelphia-London-Paris-Bangkok-Hong Kong-Munich-Sydney-Tokyo-Wroclaw. – 15. **Stachura, J., Konturek, J., Urbanczyk, K., et al.:** Pancreatic metaplasia of the human gastric mucosa is associated with high expression of transforming growth factor alpha but not of epidermal growth factor. Histopathology, 27, 1995, s. 509–515. – 16. **Stolte, M., Baumann, K., Bethke, B., et al.:** Active autoimmune gastritis without total atrophy of the glands. Z. Gastroenterol., 30, 1992, s. 729–735. – 17. **Stolte, M., Bethke, B., Seifert, E., et al.:** Observation of gastric glandular cysts in the corpus mucosa of the stomach under omeprazole treatment. Z. Gastroenterol., 33, 1995, s. 146–149. – 18. **Torbenson, M., Abraham, S.C., Boitnott, J., et al.:** Autoimmune gastritis: distinct histological and immunohistochemical findings before complete loss of oxyntic glands. Mod. Pathol., 15, 2002, s. 102–109. – 19. **Vieth, M., Stolte, M.:** Fundic gland polyps are not induced by proton pump inhibitor therapy. Am. J. Clin. Pathol., 116, 2001, s. 716–720.

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