Original paper

Gastric hyperplastic polyps coexisting with early gastric cancers, adenoma and neuroendocrine cell hyperplasia

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Gastric hyperplastic polyps (GHP) constitute up to 93% of all benign epithelial polyps of the stomach. The average probability of malignant transformation in GHP is 0.6-22% in large series. The aim of the study was to present the coexistence of GHP with early gastric cancer (EGC), gastric adenoma (GA), neuroendocrine cell hyperplasia (NH) and well-differentiated neuroendocrine tumour (NET G1). Three cases were studied to reveal clinical data and morphological changes and to assess the relationship between GHP and accompanying gastric neoplastic lesions.

Key words: early gastric cancer, adenoma, gastric hyperplastic polyp, neuroendocrine cell hyperplasia, neuroendocrine tumour.

Introduction

Gastric hyperplastic polyps (GHP) constitute 30-93% of all benign epithelial gastric polyps [1]. They have a wide distribution but are more common with increasing age (65.5 to 75 years on average) [2]. They can occur as a single lesion usually in the antrum or as multiple lesions throughout the stomach [1]. Polyp formation is strongly associated with chronic gastritis, *Helicobacter pylori*-associated gastritis, pernicious anaemia and reactive or chemical gastritis when it is adjacent to ulcer erosions and around gastroenterostomy sites [1, 3, 4]. Grossly, they are sessile or pedunculated. The size of GHP is usually less than 1 cm. However, 10% of hyperplastic polyps are greater than 2 cm [3]. Gastric hyperplastic polyps histologically are characterised by marked elongation of the pit region. Glands within the polyp are lined with foveolar epithelium with branching, resulting in a corkscrew or cystic dilatation with architectural disarray, often with surface erosions. The stroma in the lamina propria is oedematous and infiltrated by lymphocytes, plasma cells, eosinophils, neutrophils, mast cells and macrophages [5]. The incidence of intestinal metaplastic foci within GHP is 1.6-16% depending on the series [3, 6]. The malignant transformation of GHP significantly correlates with the size > 1 cm, pedunculated shape, post-gastrectomy state and synchronous neoplastic lesions [7]. Therefore, endoscopic polypectomy should be considered in these GHP to avoid the risk of missing neoplastic potential [7].

Gastric adenomas (GA) comprise 0.5-3.75% of all gastric polyps in the Western hemisphere, in contrast to 9-20% in high-risk areas for gastric adenocarcinoma [2]. They are in most cases solitary lesions and can be found anywhere in the stomach, commonly in the antrum [1]. Gastric adenomas frequently arise against a background of atrophic gastritis and intestinal metaplasia [1]. They are histologically classified into tubular, villous and tubulovillous types [1]. Gastric adenomas are lesions that, by definition, exhibit low and high grade dysplasia (HGD) [2]. High grade

dysplasia regresses only in 0-16% of cases and progresses in 10% to 100% of cases to invasive carcinoma [9]. For this reason, lesions diagnosed as HGD at endoscopic forceps biopsy should be removed by an endoscopic submucosal dissection (ESD) [9].

Gastric neuroendocrine tumours (NETs) can be divided into four different types [11]. Endoscopically, the often multifocal type 1 NETs are mostly located in the corpus and fundus of the stomach [10, 11]. They include 70-80% of all gastric NETs [3, 10]. Type II gastric NET is rare gastric neoplasm associated with the Zollinger-Ellison or MEN-I syndromes. Type III is a sporadic NET, accounting for 10-15% of all gastric NETs, and appear to be more related to neuroendocrine carcinomas than types I and II [10]. Type IV is a sporadic neuroendocrine carcinoma with high malignant potential [11].

So far, early gastric cancer (EGC) has been infrequently described in GHP. The biological significance of neuroendocrine cell hyperplasia (NH) for the development of gastric adenoma and adenocarcinoma in the gastric mucosa with GHP or within GHP is still unclear. However, the question remains whether the presence of NH and NET in the gastric mucosa with GHP may constitute an additional risk factor for adenoma and gastric cancer that occur not only within GHP but also as independent tumours.

Material and methods

The study concerns three patients with multiple lesions in the stomach, diagnosed in the Department of Gastroenterology and the Department of Pathology of the Pomeranian Medical University in Szczecin. The cases were studied to assess the possible association of EGC and GA with GHP and NH. Clinical and morphological characteristics of patients are shown in Table I. Gastric hyperplastic polyps were found in the gastric mucosa in all patients. In two cases (cases 1 and 2) features of NH were present. EGC was found in two cases (cases 1 and 3), and in case 2 GA with HGD was diagnosed additionally with NET G1 as synchronous tumours. All patients had chronic gastritis with foci of intestinal metaplasia in adjacent gastric mucosa.

Gastric biopsies and larger tissue specimens were fixed in 10% neutral buffered formalin and processed routinely. Haematoxylin and eosin (HE)-stained slides as well as immunohistochemical reactions were performed on paraffin-embedded and formalin-fixed tissue using primary antibodies against chromogranin A (Dako IR 502 FLEX), synaptophysin 38 (Dako IR 776 FLEX) and Ki67 (Dako IR 626 FLEX) and visualised by the EnVision System (Dako). The percentage of Ki67 positive cells was counted using the Aperio Scan Scope image analysis system. The HE stained histological slides as well as the immunohistochemical stainings were evaluated in each case and assessed by two pathologists, who arrived at a consensus on the pathological diagnoses and the assessment of immunoreactivity. Dysplasia in GA was classified according to the Vienna classification [12]. The EGC was classified according to macroscopic criteria proposed by the Paris endoscopic classification of superficial neoplastic lesions [13], and microscopic WHO and Lauren classifications respectively [14, 15]. NH was diagnosed based on the presence of three or four cells per gland and more than four neuroendocrine cells with continuous distribution [16]. *H. pylori* organisms were not present in the samples.

Results

Clinical data

Case 1. A 60-year old woman was found to have multiple lesions: the largest, a pedunculated mucosal polypoid lesion 20 mm in diameter with focally rough surface at the apex, located in the lower gastric

Table I. Clinical and morphological characteristics of patients

Case	Number of lesions	Main lesions	Remaining gastric mucosa
1	4	four GHPs Including one EGC bearing-GHP	chronic gastritis, intestinal metaplasia, NH
2	4	GHP/LGD GHP GHP/GA/HGD NET G1	chronic gastritis, intestinal metaplasia, NH
3	2	EGC GHP	chronic gastritis, intestinal metaplasia

EGC – early gastric cancer; GHP – gastric hyperplastic polyp; LGD –- low grade dysplasia; GA – gastric adenoma; HGD – high grade dysplasia; NET G1 – neuroendocrine tumour grade 1; NH – neuroendocrine cell hyperplasia

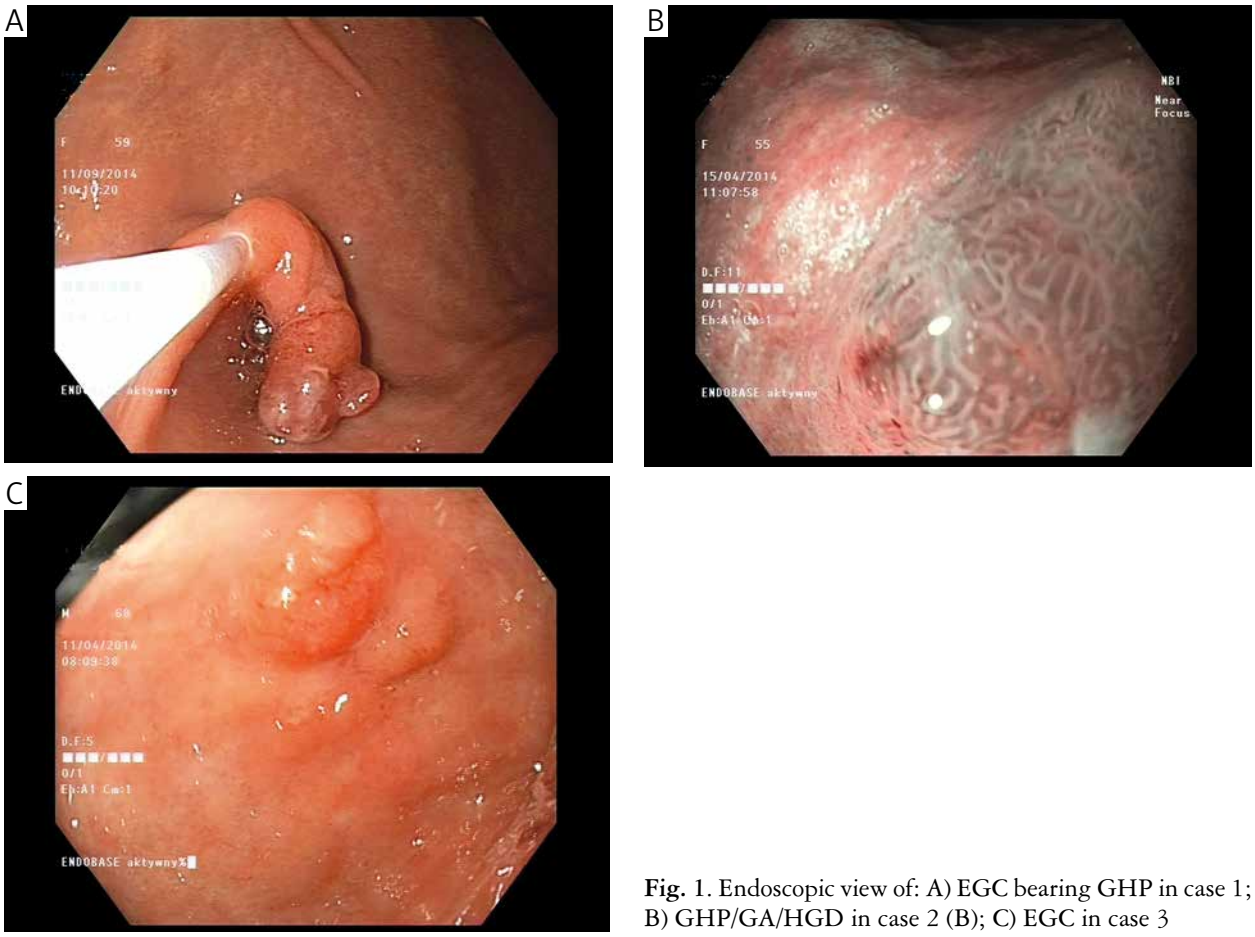

Fig. 1. Endoscopic view of: A) EGC bearing GHP in case 1; B) GHP/GA/HGD in case 2 (B); C) EGC in case 3

corpus, and three smaller polyps, 5 mm in longitudinal diameter each. Two of them were located in the corpus and one in the antrum (Fig. 1A).

Case 2. A 55-year-old woman was diagnosed with four gastric lesions removed from the stomach using an endoscopic submucosal dissection (ESD). The first three lesions were located in the antrum: 1) a translucent polyp with a smooth surface that measured 8 mm, removed with a fragment of tissue of size 16 × 10 mm, 2) a tan-coloured polyp 4 mm in diameter, 3) a superficial, elevated lesion, 10 mm in longitudinal diameter, which was located in the ESD specimen which measured 25 × 15 mm (0-IIa in the Paris endoscopic classification) (Fig. 1B). The fourth specimen was removed from the corpus of the stomach. It was a fragment of tissue measuring 20 × 18 mm and had a rather smooth surface with a delicate elevation in an area 10 mm in diameter.

Case 3. An endoscopic examination of the upper digestive tract in a 69-year-old man revealed two gastric lesions: the first lesion, measuring 11 mm in longitudinal diameter, was slightly elevated and partially superficial shallow, classified as 0-IIa and 0-IIc in the Paris endoscopic classification [13], located in the ESD specimen measuring 30 × 26 mm and removed from the gastric antrum (Fig. 1C). The second lesion was a small, translucent polyp removed from the body of the stomach.

Microscopy

Case 1. All four polyps in case 1 had features of hyperplastic polyps. The lesions were basically composed of dilated glands lined with foveolar epithelium with irregular branching and cystic dilatation in the oedematous lamina propria, inflamed by plasma cells, scant neutrophils, eosinophils and macrophages. In the largest polyp, scant, prominent and ectatic, thin-walled blood vessels were also present in the lamina propria and the submucosa. A part of the polyp surface at the apex was replaced with moderately differentiated tubular, intestinal-type adenocarcinoma in the WHO and Lauren classification respectively. The malignancy was limited to the mucosal layer. The muscularis mucosae was not infiltrated by cancer cells. The lesion was completely resected with clear laterals and deep margins. Immunohistochemically, the EGC focus showed positive Ki67 labelling in 78% of cells. The adjacent, non-polypoid hyperplastic mucosa in all lesions showed evidence of mild

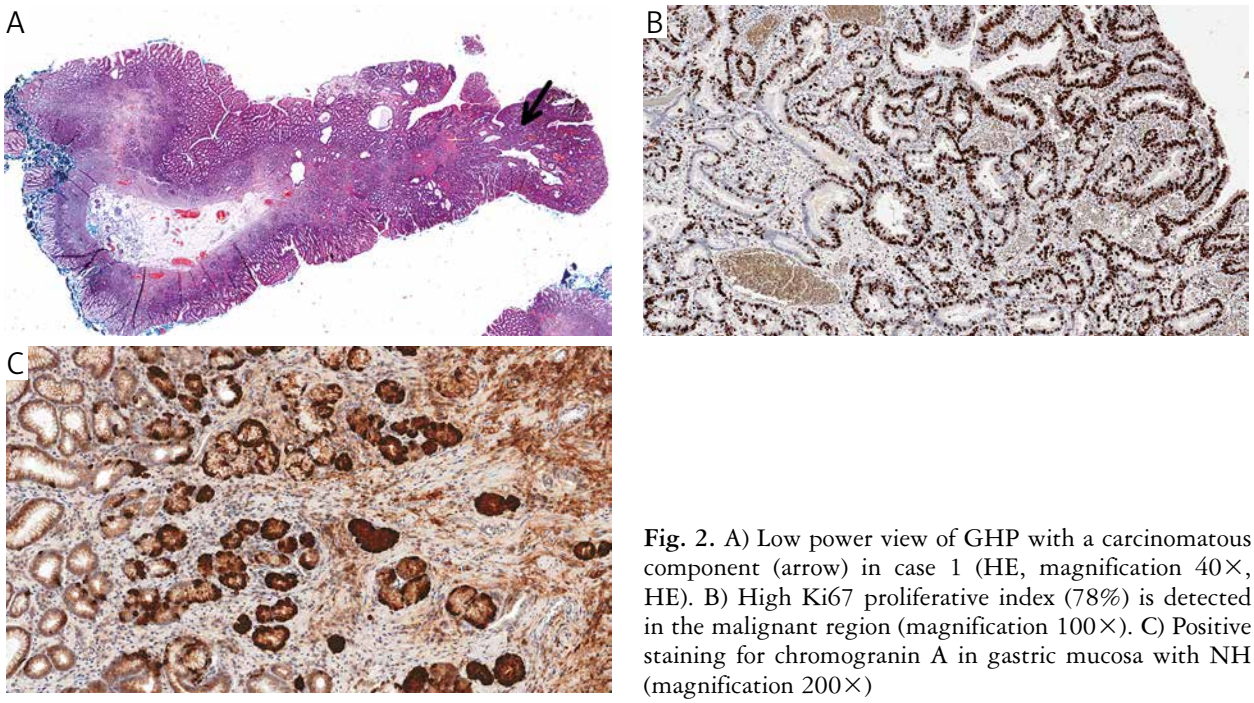

Fig. 2. A) Low power view of GHP with a carcinomatous component (arrow) in case 1 (HE, magnification 40×, HE). B) High Ki67 proliferative index (78%) is detected in the malignant region (magnification 100×). C) Positive staining for chromogranin A in gastric mucosa with NH (magnification 200×)

chronic atrophic gastritis and foci of intestinal metaplasia. The neuroendocrine cells were clearly seen in immunohistochemically stained slides of all polyps. There were more than four cells per gland with regular, linear proliferation at the abluminal aspects and the gastric glands in some of them or around them in the gastric mucosa with chronic inflammation at the base of all polypoid lesions. NH was not found in hyperplastic tubules or EGC in the largest polyp (Table I, Fig. 2A-C).

Case 2. Histopathological examination revealed the coexistence of four mucosal lesions in the stomach: two antral hyperplastic polyps. The larger polyp, 8 mm in diameter, had some glands with low grade dysplasia (LGD) and linear and nodular NH (Fig. 3A). LGD was present not only within the gastric mucosa in the base of the polyp but also in hyperplastic glands. The third lesion, 10 mm in diameter, had a complex histological architecture. It was a tubulovillous adenoma (TVA) with HGD located at the top and laterally surrounded by GHP (GHP/GA/HGD) (Fig. 3B, C). Immunohistochemical staining for the presence of chromogranin and synaptophysin revealed a complex pattern of NH: a linear and nodular pattern of NH within mucosal glands adjacent to the adenoma and also focal neuroendocrine differentiation in groups of dysplastic tubules within the GA (Fig. 3D). The fourth lesion, located in the gastric corpus, was classified as NET G1. Histologically, this tumour was composed of uniform cells with a low (< 2%) Ki67 proliferative index and no mitotic figures. Groups and solid nests of neuroendocrine cells infiltrated the mucosa and muscularis mucosae and spread deeper into the submucosa. The tumour was removed with clear surgical margins (Table I).

Case 3: The antral lesion was diagnosed as intramucosal EGC. Histologically EGC was classified as a moderately differentiated tubular adenocarcinoma in 70% of the tumour area and poorly differentiated, diffuse-type adenocarcinoma in the remaining 30% of the tumour area according to the WHO classification, and the intestinal type of cancer in the Lauren classification. The lesion was removed with a very narrow deep surgical margin and wide lateral margins. A high proliferative index was present in malignant tubules in a well-differentiated component as well as in the nests of cells in a poorly differentiated component. The second smaller lesion was GHP. Foci of intestinal metaplasia were found in the gastric mucosa in the vicinity of the adenocarcinoma and near the GHP. NH was not found in this case (Table I).

Discussion

Gastric cancer is one of the most frequently occurring cancers in the world and the second most common cause of cancer-related death [9]. It is well known that gastric cancer is more likely to develop in a stomach containing hyperplastic polyps [7, 17, 18, 19, 20, 21]. Most GHP were found in the gastric mucosa with a precancerous condition: chronic gastritis – mainly *H. pylori* chronic gastritis [22]. With the recent prevalence of endoscopic treatment of gastric polyps, including ESD, an increased number of cases of dysplasia and carcinoma has been reported in GHP [1, 6]. The average probability of a malignant change in GHP is 0.6-2.2% in large series

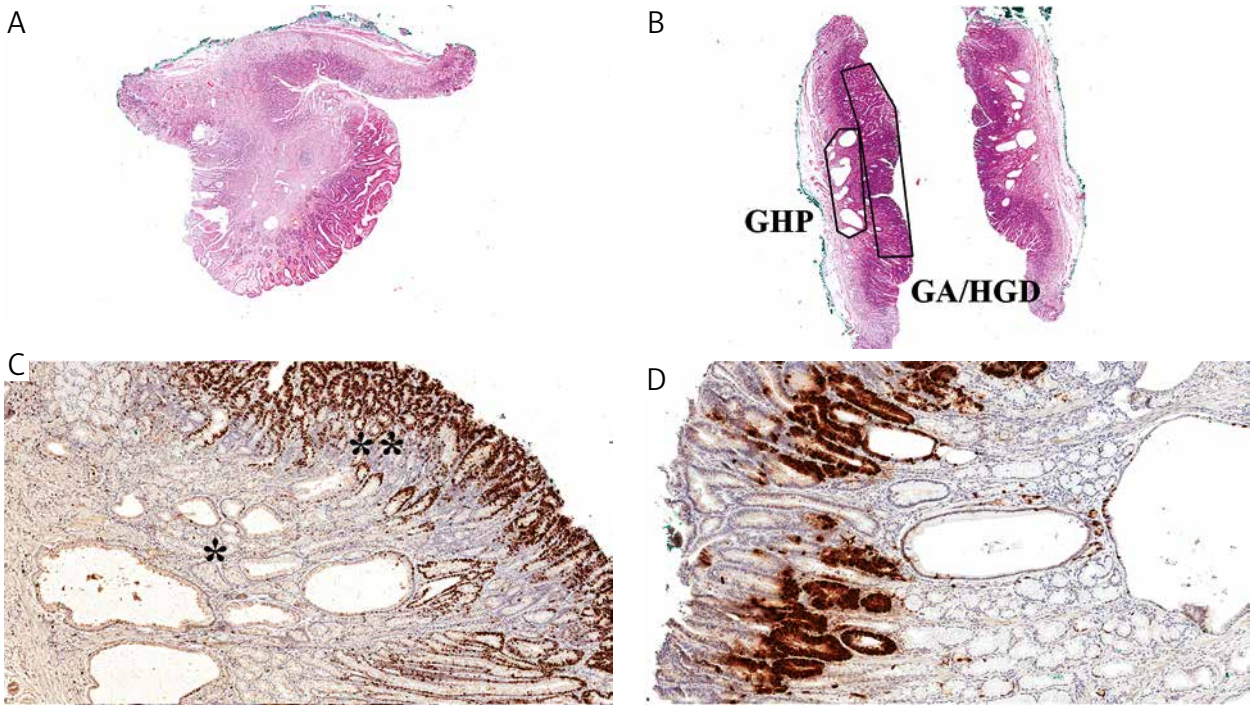

Fig. 3. Case 2. A) GHP with LGD (HE, magnification 40×). B) GHP/GA/HGD (HE, magnification 40×). C) GHP/GA/HGD – high Ki67 proliferative index (84%) in GA/HGD area** compared with low Ki67 proliferative index (1.2%) in GHP area* (magnification 100×). D) Foci of neuroendocrine differentiation, positive immunohistochemical expression for chromogranin A in tubules in GA/HGD area (magnification 200×)

[6, 8, 21]. The histological criteria of Nakamura for the malignant transformation of GHP are as follows: 1) the coexistence of benign and malignant lesions in the same polyp; 2) sufficient evidence that the malignant lesion was previously a benign polyp; and 3) sufficient cellular and structural atypia in the malignant lesion. Polyps found to be positive for these criteria are to be diagnosed as cancerous [23]. The cases of GHP with malignant transformation discussed in the present paper also fulfilled these criteria. In case 2, the architecture of the polyp with HGD, which covered the histological structures belonging to GHP, was particularly unusual.

Cases 1 and 2 show the presence of LGD and HGD and a focus of well-differentiated adenocarcinoma in GHP. They provide strong evidence to support the theory of carcinogenesis as a multistep and progressive process, which begins with hyperplasia and progresses through LGD and HGD to carcinoma. GHP with a small EGC, which occupies only a small part of the polyp and is not a dominant process, will be the subject of future observation concerning additional abnormalities in the gastric mucosa, which may play a role in the malignant transformation.

Our paper highlights the unusual environment in which EGC may occur: the association of GHP and NH in the gastric mucosa. Silvermann *et al*. reported the association of GHP with multifocal carcinoid of the stomach in two patients [24]. Chetty *et al*. described three cases of hyperplastic polyps with NH and neuroendocrine tumours within hyperplastic glands with foci of LGD and HGD in one of the lesions [25]. The above authors focused mainly on the unusual coexistence of GHP and neuroendocrine neoplastic proliferation and did not discuss the presence of dysplasia in one of the lesions.

A limited body of literature reports the coexistence of gastric cancer with NH or NET G1 [26, 27]. In 2004, Lahner *et al*. published the first study regarding the occurrence of gastric cancer and type 1 carcinoid in patients with atrophic body gastritis [28]. In case 2 of our study, the presence of adenoma/HGD and NET G1 in the stomach was found. Wang *et al*. studied the clonality of neuroendocrine cells in gastric adenocarcinoma [29]. They developed two hypotheses that need further investigation: 1) neuroendocrine and gastric carcinoma cells may derive from the same stem cells; 2) neuroendocrine cells can act as parenchyma of carcinoma and can secrete hormones to promote carcinoma. We found that adenoma with HGD in case 2 presented focal neuroendocrine differentiation and NH was also seen in the gastric mucosa that surrounded the tumour. The presence of neuroendocrine cells in gastric cancer has long been established [30]. Neuroendocrine differentiation occurs in 39.6% of gastric cancer cases and more frequently in poorly differentiated cancers than in well-differentiated tumours [29]. Adenocarcinomas containing

endocrine cells appear to be as biologically aggressive as the usual adenocarcinomas of the stomach [30]. In this study, we take a close look at the risk of developing either EGC or adenoma in the gastric mucosa, both with neuroendocrine cell proliferation (NH, NET G1) and with hyperplastic polyps. Waldum *et al*. found that NH in the gastric mucosa is an additional factor promoting carcinogenesis [31].

Taking into account all the cases presented in the study, similarly as Silverman [24], it can be stated that the presence of GHP in the gastric mucosa is an indication for a close patient follow-up to observe the development of both endocrine and non-endocrine gastric neoplasms. Studies with larger sample sizes are required to better understand the etiology of this unusual occurrence. A statistically significant number of cases needs to be analysed to find out whether or not the coexistence of GHP and NH in the gastric mucosa may be actually regarded as a marker for dysplasia and EGC as well as to specify the exact mechanism that may play a role in the malignant transformation of GHP.

The authors declare no conflict of interest.

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