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Gastric neuroendocrine tumor with *Helicobacter pylori*-associated chronic gastritis

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ABSTRACT

INTRODUCTION: Development of gastric neuroendocrine neoplasms in subjects infected with *Helicobacter pylori* is rare and it occurs through pathogenetic mechanisms related to gastrin.
PRESENTATION OF CASE: We report a case of gastric neuroendocrine tumor in a patient infected with *Helicobacter pylori* and normal gastrin levels. He was treated by endoscopic mucosal dissection after eradication of *Helicobacter pylori* infection. Histologically the tumor was consistent with a grade 2 well differentiated neuroendocrine tumor. It was characterized by the presence of lymphoid aggregates around and inside the neoplasia.
DISCUSSION: Helicobacter pylori-associated chronic gastritis can rarely cause the development of gastric neuroendocrine tumors through mechanisms unrelated to gastrin.
CONCLUSION: The one related to a chronic *Helicobacter pylori* infection may be considered a distinct type of gastric neuroendocrine tumor.

1. Introduction

This case report has been reported in line with the SCARE criteria [1].

Gastric neuroendocrine tumors (G-NETs) are rare lesions derived from the enterochromaffin-like cells (ECL-cells) of the gastric mucosa. They are neoplasms with a reported incidence of 1-2 cases/1000000 [2]. In 2018, World Health Organization released a new classification of gastrointestinal NETs, dividing them based on the number of mitoses or the expression of Ki67 index into low grade (G1), intermediate grade (G2) and high grade (G3) NETs. Clinically, G-NETs are categorized into types I, II, III and IV. The basis for these subtypes is rooted in gastric pathophysiology [3]. Gastrin is produced by G cells in the stomach after ingestion of food. Gastrin binds to cholecystokinin-2 receptors on ECL cells which subsequently release histamine to activate parietal cells to produce hydrochloric acid. Acid production is regulated by negative feedback so that D cells in the antrum produce somatostatin that inhibits G cell production of gastrin. Therefore, in states of achlorhydria (autoimmune atrophic gastritis) there is a compensatory G cell hyperplasia and an hypergastrinemia that leads to ECL hyperplasia in an effort to boost acid production. Diffuse to micronodular ECL cell hyperplasia develops and is followed by multiple ECL tumors after a latent period of many years. Hypersecretory states with unchecked gastrin production, such as Zollinger- Ellison syndrome (ZES), are also predisposed to ECL cell hyperplasia/dysplasia and NET growth. Type I and II G-NETs are related to high gastrin levels and occur, respectively, in patients with autoimmune chronic atrophic gastritis and in the setting of MEN1, that is associated with a ZES. Type III G-NETs are solitary tumors that develop with no known correlation to gastrin production. Type IV G-NET is a higly aggressive variant occurring in patients with hypergastrinaemia, but without ZES. The development of these NETs is associated with an intrinsic acid secretion abnormality of the parietal cells [4,5].

Helicobacter pylori (*H. pylori*) has been reported to cause chronic atrophic gastritis [6] and an alteration of the gastric secretion [7]. Chronic gastritis caused by *H.pylori* can be a risk factor for gastric cancer, but the occurrence of NET in the stomach of patients infected with *H. pylori* is very uncommon [8].

We herein report on a patient infected with *H. pylori* presenting an unusual solitary gastric body NET. G-NET related to a chronic *H. pylori* infection may be considered as a distinct type of G-NET.

2. Case report

A 68-year-old man was referred to the endoscopy department for an oesophagogastroduodenoscopy (OGD) due to the incidental finding of a small nodule in the gastric fundus. He had a past

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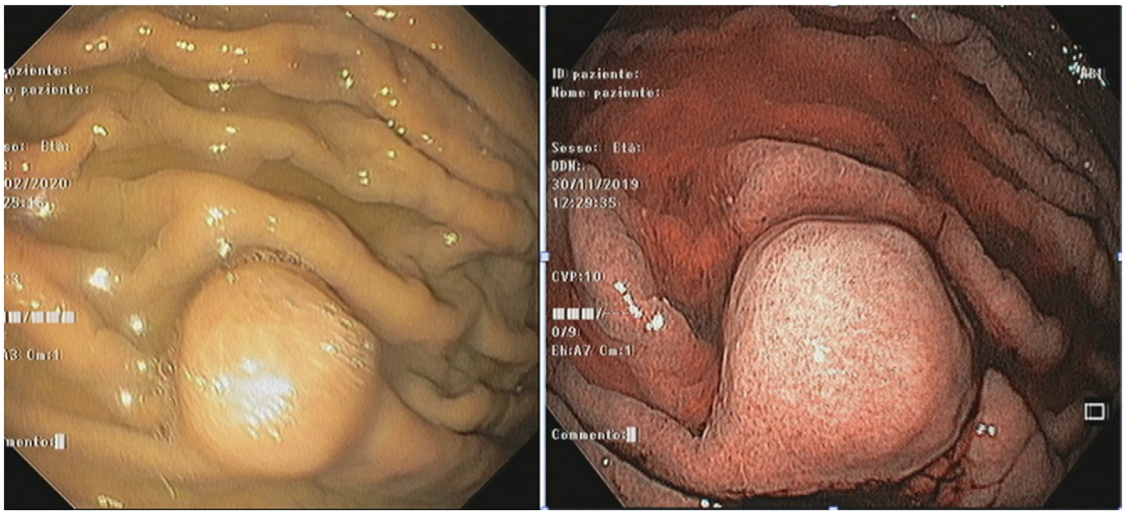

Fig. 1. Endoscopic view of the gastric lesion, showing a round lesion covered with normal appearing mucosa both at high resolution white light (a) and at virtual chromoendoscopy with narrow-band imaging (b), compatible with a sub-epithelial lesion.

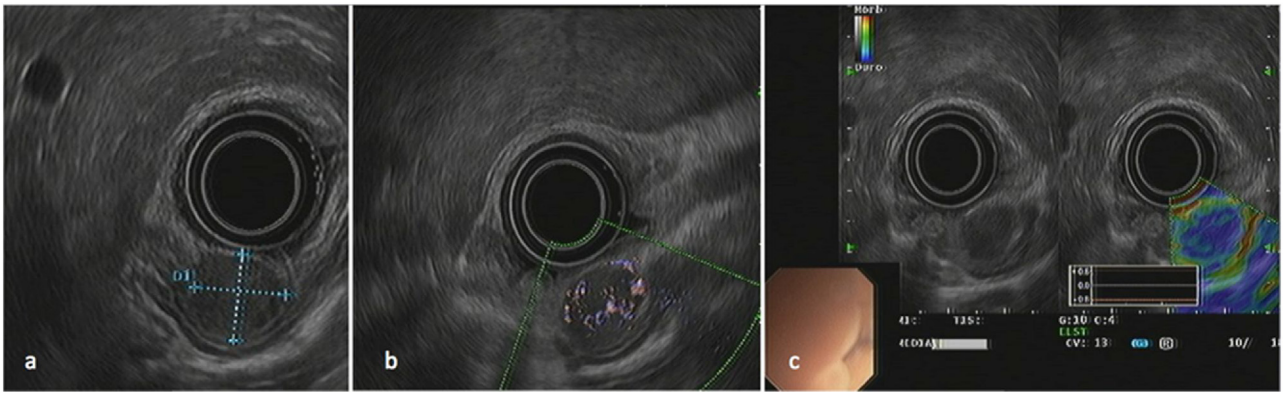

Fig. 2. Endoscopic ultrasonography view of the gastric lesion, showing a round lesion, with definite margins, homogeneously hypoechoic (a) with visible internal vascularization (b), a hard texture at elastography (c), measuring 10 mm × 9 mm. The lesion originated from the submucosal layer (3rd layer) of the stomach with no involvement of the other layers of the gastric wall (a).

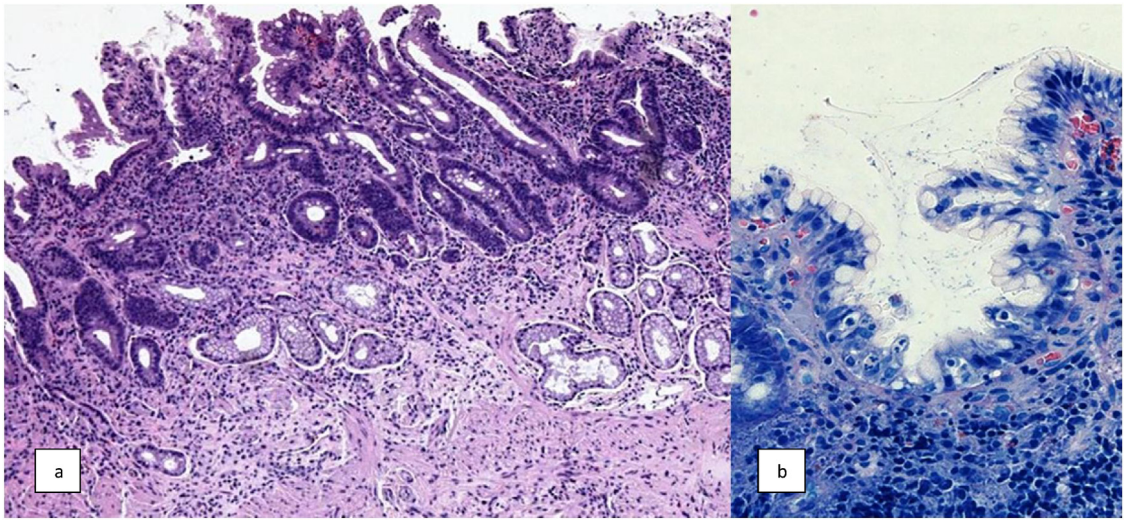

Fig. 3. Chronic active gastritis involving the antral mucosa with glandular atrophy and intestinal metaplasia (a) (hematoxylin-eosin, original magnification ×20). Giemsa stain shows *Helicobacter bacteria* closely aderent to the surface of epithelial cells (b) (original magnification ×40).

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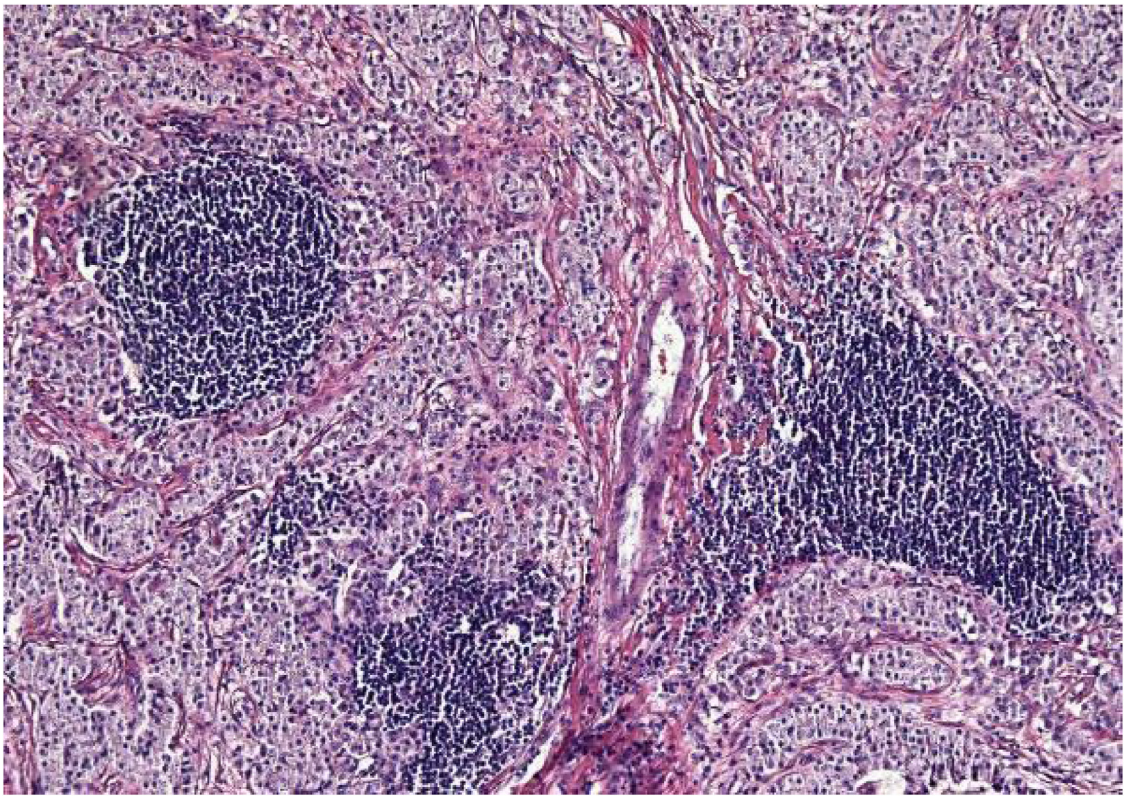

Fig. 4. G-NET with solid-trabecular pattern containing follicular lymphoid aggregates (hematoxylin-eosin, original magnification ×20).

medical history of lung adenocarcinoma for which he underwent a lobectomy in 2016. A follow-up computed tomography (CT) scan revealed a 12 mm enhancing nodule in the gastric fundus. The patient was asymptomatic and, on direct questioning, reported no upper gastrointestinal symptoms such as dyspepsia, heartburn, pain, nausea or vomit. The OGD revealed a centimetric round lesion located at the transition between the gastric fundus and the body, covered with normal appearing mucosa, compatible with a sub-epithelial lesion (Fig. 1). The remaining gastric mucosa of the fundus and the body was normal, while the antral mucosa was erythematous with small erosions. Biopsies for histology and H. pylori were taken according to the Sydney protocol (2 in the antrum, 1 at the angular incisura and 2 in the body at lesser and greater curves). Microscopic examination showed *H. pylori*-associated chronic gastritis in the antrum and corpus, active, with moderate glandular atrophy and multifocal intestinal metaplasia in the antrum (Fig. 2). A sequential eradication regimen was prescribed with amoxicillin followed by metronidazole and clarithromycin. *H. pylori* eradication was confirmed through a fecal test 2 months after the completion of the eradication regimen. To further characterize the sub-epithelial lesion, a diagnostic endoscopic ultrasonography (EUS) was scheduled. This was performed using a radial echoendoscope (GF UE160-AL5; Olympus, Tokyo, Japan) which showed a round lesion, with definite margins, homogeneously hypoechoic with visible internal vascularization, a hard texture at elastography, measuring 11 mm × 9 mm. The lesion originated from the submucosal layer (3rd layer) of the stomach with no involvement of the other layers of the gastric wall (Fig. 3). No lymph nodes were observed in abdominal and mediastinal stations. Following multidisciplinary discussion, considering the size of the lesion, its characteristics and the absence of signs of extraluminal involvement, the patient was referred for endoscopic resection. The lesion was removed using a 27 mm hot snare (Sensation; Boston Scientific, Natick, Massachusetts, USA) after submucosal injection of saline solution and methylen blue. Two metal hemostatic clips were positioned on the resection base to close the mucosal defect. The procedure was uneventful and the patient was discharged home 1 h afterwards. The specimen was sent for pathology examination. Serum gastrin and Chromogranin A levels were within normal range.

3. Pathology

Histologic examination of the specimen revealed a 1 cm well circumscribed tumor located mainly within the submucosa layer closer to the muscularis propria. Neoplastic cells showed a predominantly trabecular to solid architecture with both nested and gyriform patterns seen focally. These cells were large with clear and granular cytoplasm and round or oval nuclei with clumped or finely granular ("salt and pepper") chromatin and small nucleoli. Numerous nodular lymphoid aggregates, some of which with germinal centers, were also seen within the tumor (Fig. 4). Mitotic activity was inconspicuous with a mitotic count of 1 mitosis in 10 high power fields (2 mm^2). There was no evidence of vascular or perineural invasion. The fundic mucosa above the tumor was flattened and contained some lymphoid aggregates with germinal centers located in close proximity to the muscularis mucosae at the base of the lamina propria (Fig. 5). They were consistent with acquired mucosa-associated lymphoid tissue (MALT). There was no active inflammation with polymorph in the lamina propria or inside the glandular lumina, nor evidence of *H. pylori* infection. Horizontal and vertical margins were free of tumor cells.

Immunohistochemical staining showed tumor cell positivity for cytokeratin and neuroendocrine markers including Chromogranin A and Synaptophysin. Tumor cells were negative for CDX2, glucagon, insulin, gastrin, somatostatin and serotonin. Ki67 staining showed a proliferative index of 5% (Fig. 6). Lymphoid aggregates consisted of a central part of mature CD20 positive B cells sur-

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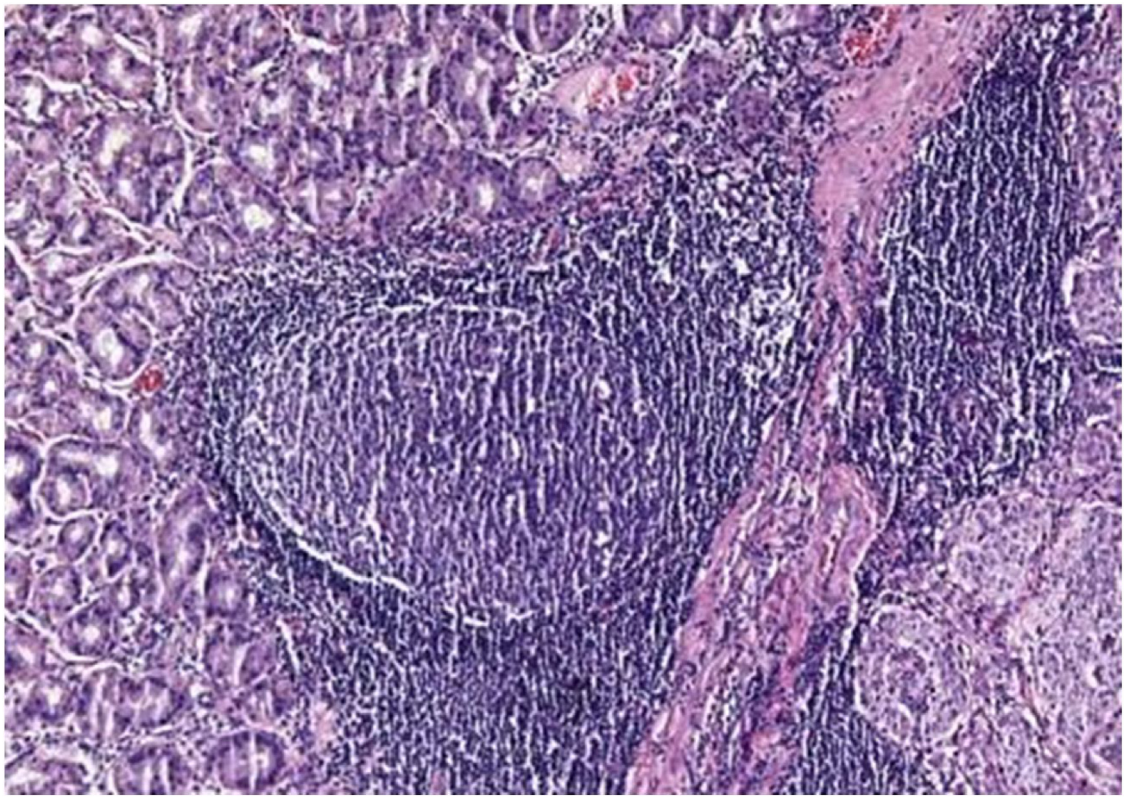

Fig. 5. Lymphoid follicular hyperplasia in the mucosa above the tumor (hematoxylin-eosin, original magnification ×20).

rounded by CD3and CD2 positive T cells. On the periphery of the aggregates, a fair number of plasma cells were highlighted by anti-CD138 staining.

All these findings led to the final diagnosis of a G-NET G2 pT1.

4. Discussion

Most G-NETs derive from ECL-cells in the stomach mucosa. They are rare non-functioning lesions with indolent behaviour and neuroendocrine differentiation. Histologically, all G-NETs appear similar, and biopsies of the non-neoplastic mucosa are critical in distinguishing tumor type, prognosis, and treatment. Based on histologic, serologic and endoscopic findings, they may be further differentiated into types I, II, III and IV, with varying degrees of aggressiveness. The type I comprises 70–80% of all cases and occurs mainly in women at the age of 50–60 [3]. Usually, it is related to chronic atrophic gastritis with or without pernicious anemia, Helicobacter p. infection and it is associated with ECL-cells hyperplasia and hypergastrinemia. Type I G-NETs tend to be multiple, smaller than 1 cm in size, and are often discovered incidentally. Type II G-NETs are very similar to type I but occur in the setting of MEN1, that is associated with ZES. Type II G-NETs account for about 5–7% of gastric NETs and like type I tumors, they are multiple, small and asymptomatic. Type II G-NETs are often more advanced in terms of size, muscular wall infiltration and angioinvasion than type I. Therefore, lymph node metastases are found more often that in type I. Type III G-NETs are sporadic tumors that develop unrelated to chronic atrophic gastritis or MEN1. They represent 10–15% of all gastric NETs and they are typically solitary large tumors, often >2 cm in size. They have the greatest potential to generate metastases. Most cases of type I and II G- NETs are G1 or G2 while type III G-NETs range from G1 to G3.

Type IV G-NETs consist of multiple large lesions related to an intrinsic defect in acid secretion from parietal cells and they are associated histologically with hypertrophy and hyperplasia of parietal cells with vacuolated cytoplasm. Consequently, achlorhydria, hypergastrinemia and hyperplasia of neuroendocrine cells occur.

Immunohistochemical analysis is essential in NETs. It allows diagnostic confirmation and permits classifying the lesion according to the histologic grades defined by the WHO 2018. For diagnostic confirmation Chromogranin A and Synaptophysin are necessary, while for prognostic definition the proliferative Ki-67 index or the number of mitoses per 2 mm^2 are required. Somatostatin, serotonin and gastrin immunostainings are critical for the diagnosis of rare G-NETs as respectively Somatostatin-producing D-cell NET, EC-cell NET and Gastrin-producing G-cell NET and gastrinoma.

H. pylori is a spiral-shaped, gram-negative organism that has adapted to thrive in acid and grows in close association with the lining of the stomach. Gastric colonization with H. p induces diverse human pathological conditions, including superficial and atrophic active gastritis, peptic ulcer disease, MALT-lymphoma, gastric adenocarcinoma and its precursors. Many models *in vivo* and *ex vivo* have been proposed to explain the mechanisms underlying Hp-associated gastric pathology [9]. The connection between *H. pylori* and gastric MALT-lymphoma is well established. H. pylori infection causes an immunological response, leading to chronic gastritis with formation of lymphoid follicles within the stomach. These lymphoid follicles resemble nodal tissues found throughout the body and they are composed of reactive T cells and activated plasmal cells and B cells. A clonal expansion of these B-cells represents the basis of MALT B-cell lymphoma [10].

The development of gastric neuroendocrine neoplasms in subjects infected with *H. pylori* is believed rare [8], but has been described in animals [11] and, more rarely, in humans [12–14].

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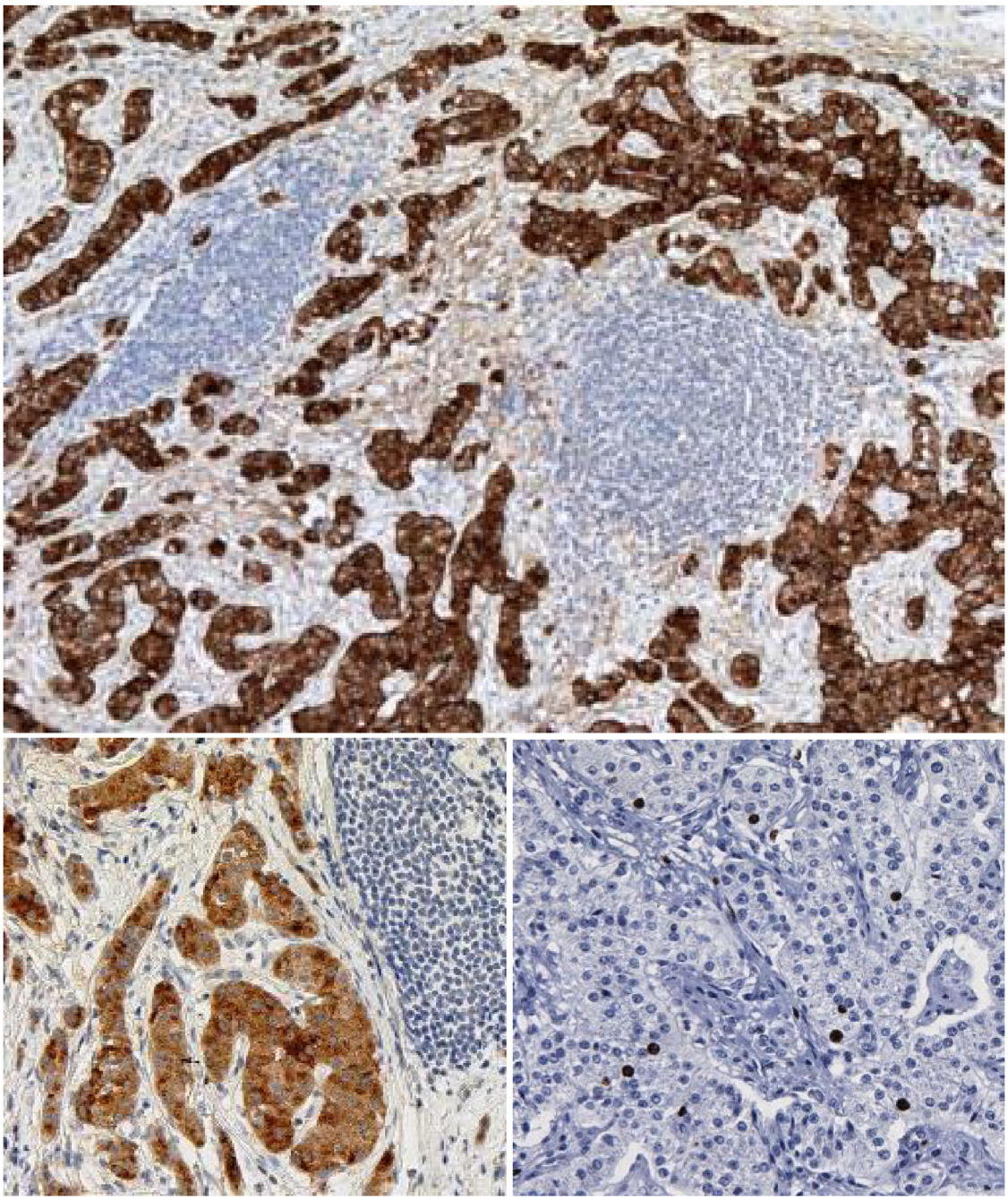

Fig. 6. Immunohistochemical stains for Chromogranin A (a), Synaptophysin (b) and Ki-67 (c).

In *H. pylori* associated gastritis, *H. pylor* induces hypergastrinemia [15], the onset of which has been explained in multiple ways. *H. pylori* infection is a risk factor for the development of gastric mucosa atrophy, resulting in low acid output [16]. In addition, antibodies against *H. pylori* may act as autoantibodies to parietal cells [17]. Hypergastrinemia related to *H. pylori* infection would be due to up-regulation of tumor necrosis factor-α and interleukin-β and down regulation of somatostatin [18]. Therefore, *H. pylori* infection is a risk factor for G-NET by inducing hypergastrinemia [13].

Our patient had no hypergastrinemia and this aspect creates difficulties in classifiyng the tumor (type I *vs* type3). Of the few cases of G-NETs associated with *H. pylori* infection reported in the literature, only Antonodimitrakis et al. described a case of G-NET in a patient with normal gastrin levels despite *H. Pylori* infection, similarly to ours. Therefore other onset mechanisms independent of gastrin hypersecretion occur. Cytokines and inflammatory mediators released during chronic inflammation induced by Helicobacter p. infection can promote ECL proliferation and survival. Polymorphism in genes coding for inflammation mediators are associated with an increased risk of gastrointestinal cancer. Striking examples of this link have been seen in inflammatory bowel disease patients developing neuroendocrine tumors [19–21]. Furthermore, *H. pylori* lipopolysaccharide stimulates DNA synthesis in ECL cells, suggesting that it may act on ECL hyperplasia [22].

What makes the present case unique is the close association of G-NET with MALT induced by *H. pylori* infection and disposed around and inside the neoplasia. Lymphoid follicles are in fact absent in the normal stomach and their presence is strongly associated with *H. pylori* infection.

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5. Conclusions

Although H. pylori infection is more likely to cause neoplasms with higher malignant potential than G-NETs, it certainly also plays an important role in developing NETs through different pathogenetic mechanisms. The one related to a chronic *H. pylori* infection represents a distinct type of G-NET, with different histologic, pathogenetic and clinical characteristics compared to the other types of G-NETs. Further studies are necessary to elucidate how H. pylori is implicated in pathogenesis of G-NET.

Declaration of Competing Interest

The authors report no declarations of interest.

Funding

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Ethical approval

The present study is exempt from ethical approval in our institution.

Consent

Written consent was obtained from the patient for the publication of the report.

Author's contribution

GS and ES wrote the manuscript. AD and MAC diagnosed the specimens and collected data. ES and AD performed the operation, pre- and post-operative patient management. All authors read and approved the final manuscript.

Registration of research studies

N/A.

Guarantor

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Provenance and peer review

Not commissioned, externally peer-reviewed.

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