

# Metastatic multiple gastric neuroendocrine tumors with a long history of proton pump inhibitor use: A case report

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## Abstract

It is widely accepted that gastric neuroendocrine tumors (NETs) develop due to enterochromaffin-like (ECL) cell proliferation following exposure to hypergastrinemia, which causes hyperplastic-dysplastic-neoplastic changes. Here we describe the case of a 46-year-old female patient diagnosed with metastatic NETs by liver biopsy and evaluated at an external center. At our hospital, nodular structures extending from the cardia to the antrum were observed by gastroscopy, considered the primary tumor focus. Histopathological examination revealed a trabecular-insular pattern, with microNETs consisting of monotone cells with round-oval nuclei and surrounding neuroendocrine cell hyperplasia foci and fundic gland polyps. The patient had a history of regular proton pump inhibitor (PPI) use for 10 years and a serum gastrin of 9240 pg/mL. A 3-cm metastatic lesion in the left lobe of the liver was observed in whole-body imaging with octreotide. By gastrectomy, we observed a large number of nodular lesions in the corpus-antrum and a 3-cm diameter lesion in the hepatectomy material. Histopathological examination revealed NETs in multiple foci with submucosal invasion in the stomach. The Ki-67 proliferative index was 3%. Metastatic tumors of similar morphology were found in the liver and three of the greater curvature lymph nodes. We made a diagnosis of multiple gastric NETs (Grade 2). In Type I gastric NETs, the neuroendocrine cell proliferation spectrum up to NET is observed as a result of hypergastrinemia due to atrophic gastritis. Also, in experimental studies, prolonged hypergastrinemia has been reported to cause ECL cell neoplasms in animals treated with PPIs. Although our case could be accepted as Type 1 NET, the possibility of developing NET secondary to long-term PPI use should also be considered.

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## Informed Consent

The authors stated that the written consent was obtained from the patient presented with images in the study.

## Conflict of Interest

No conflict of interest was declared by the authors.

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## Introduction

Gastric neuroendocrine tumors (NETs) are observed at a rate of 8% among gastrointestinal NETs [1, 2]. Although it is rare, since endoscopic examinations are routinely used as a screening method, and awareness of these lesions has increased, NET diagnosis has been included in pathology reports in recent years [1-3].

The widely accepted opinion in the pathogenesis of gastric NETs that develops as a result of enterochromaffin-like (ECL) cell proliferation is exposure to hypergastrinemia, which causes hyperplastic-dysplastic-neoplastic changes [4, 5].

Gastric NETs are classified into three groups: Type 1 NET due to hypergastrinemia in the background of atrophic gastritis, Type 2 NET due to hypergastrinemia secondary to Zollinger-Ellison Syndrome (ZES)/Multiple Neuroendocrine Neoplasia-1 (MEN), and Type 3 NET with normal serum gastrin level which is sporadic [6]. Recently, ECL cell NET has been associated with an intrinsic defect in parietal cell acid secretion [6]. Proton pump inhibitors (PPI), widely used in the treatment of acid-related diseases, also inhibit gastric acid secretion, causing gastric hypoacidity and secondary hypergastrinemia due to chronic use [7].

In addition, PPI induces ECL cell hyperplasia. A few experimental studies have reported that long-term hypergastrinemia causes ECL cell neoplasms in animals (rats) treated with PPI [8]. However, it is controversial whether PPI affects humans in this direction [9-13].

We present a very rare case of metastatic gastric NET characterized by multiple foci, who had a history of long-term use of PPIs which was successfully treated with total gastrectomy.

## Case presentation

A 46-year-old female patient attended an external center with dyspeptic complaints, such as nausea, burning, and heartburn. The abdominal ultrasonographic examination revealed grade 1 steatohepatitis and a  $23 \times 17$  mm hyperechogenic solid lesion in the second segment of the liver. In the additional magnetic resonance (MR) examination, the lesion found in the lateral segment of the left lobe was  $40 \times 35 \times 30$  mm in size with a smooth contour. Histopathological examination of the needle biopsy performed on the lesion, which was interpreted in favor of adenoma in the imaging, resulted in NET.

Following admission to our hospital with these findings, additional examinations were performed primarily in terms of the possibility of a primary NET originating from the extrahepatic organ due to the rare NETs in the liver.

Laboratory findings [Hb: 11.8 g/dL (reference: 13.6–17.2), Hct: 37.6% (reference: 39.5–50.3), MCV: 72.2 fL (reference: 80.7–95.5), MCH: 22.7 pg (reference: 27.2–33.5)] results were evaluated as microcytic anemia. Tumor markers [CEA: 0.82 ng/mL (reference: 0–4.0), CA19-9: 21.35 IU/mL (reference: <27), CA125: 15.59 IU/mL (reference: <35) and AFP: 5.34 ng/mL (reference: <7)] was within normal limits. In the whole abdominal computed tomography (CT) examination, an anteromedial subcapsular lesion, approximately  $28 \times 27$  mm in size, at the liver segment 2 level, with a smooth border, accompanied by millimetric calcification in the central and mild heterogeneity in the upper contour, was observed. No feature was found in thorax CT.

In the patient's medical history, there was a history of operation for urolithiasis and parathyroid adenoma and a history of regular use of proton pump inhibitors at a dose of 30 mg/day for 10 years.

In the gastric endoscopic examination performed during systemic scans, hard, nodular structures raised from the mucosa, starting from the cardia and reaching the antrum, were observed. Biopsies with a diameter of 0.4–0.3 cm were taken with the preliminary diagnosis of gastric carcinoma and neuroendocrine tumor. In one of the samples, we noted tumoral infiltration in the trabecular pattern, which is 0.5 cm in size, and consists of round cells in the lamina propria, containing a nucleus with a uniform, salt-black pepper chromatin structure and small round nests of different sizes, consisting of similar cells in the surrounding mucosa. The immunohistochemical study observed positive staining in these cells with synaptophysin and chromogranin (MRQ-40 and LK2H10 Cell Marque, USA). Also, hyperplasia and cytoplasmic apical budding were observed in the parietal cells. There were fundic gland polyps in a few fragments. With these findings, it was diagnosed as a "microneuroendocrine

tumor and neuroendocrine cell hyperplasia in the surrounding mucosa".

It was interpreted that the present pathological findings might be related to the long-term use of proton pump inhibitors in the clinical history, and it was recommended to evaluate the whole stomach in terms of NET spread. A liver biopsy, which was evaluated in an external center, was also re-examined in our department. The tumor observed in its cross-sections and having a morphology similar to that seen in stomach biopsies was verified as a "metastatic neuroendocrine tumor".

The gastrin level was 9240 pg/mL (reference: 13.0–115.0). In addition, intense In-111 octreotide uptake, representing a solitary metastatic lesion in the left lobe of the liver, was observed on body imaging with octreotide. Radiopharmaceutical uptake in other areas of the body was within physiological limits. As a result of all examinations, the patient underwent total gastrectomy and left liver segmentectomy operation. The entire gastrectomy specimen was sampled. On gross examination, multiple nodular lesions, the largest of which were 0.8 cm in diameter, with a smoothly circumscribed cross-section, were gray-white and firm. Numerous nodular lesions were noted on the entire gastric mucosa (Figure 1). The lesions were more common in the fundus and corpus. Macroscopic examination of the liver revealed two gray-white colored nodular lesions,  $3 \times 3 \times 2.5$  cm in size and 0.1 cm in diameter, adjacent to the capsule.

Figure 1: a-b: Numerous tumor foci in sections of gastric resection material.



Histopathological examination revealed numerous nodular structures in the gastric tissue that invaded the submucosa and showed a trabecular-insular pattern containing a myxoid stroma in the focal areas (Figure 2, 3a). Mitosis was 1–2 at 10 high power fields in tumor foci with a morphological appearance similar to those observed in the endoscopic biopsy (Figure 3b), and the Ki-67 proliferative index (SP6 Cell Marque, USA) was 3% (Figure 4b). Widespread neuroendocrine cell hyperplasia foci of micronodular, adenomatoid, and dysplastic types (Figure 5a) and fundic gland polyps were observed in most areas (Figure 5b). Intestinal metaplasia was observed in focus in mostly atrophic mucosa. Neuroendocrine tumor metastasis was

detected in three large curvature lymph nodes (Figure 6a). Liver sections showed metastatic tumor foci (Figure 6b), anastomosing with each other, forming trabecular structures, and solid islands in a hyalinized stroma with a tumor-like morphology in the stomach. In the immunohistochemical study performed on tumor tissues in the stomach and liver, cells were stained positively with synaptophysin and chromogranin (Figure 4a). With these findings, a "Multifocal Neuroendocrine Tumor Grade II" diagnosis was made for gastric tissue and a "Metastatic Neuroendocrine Tumor" for tumor foci in the liver and three large curvature lymph nodes. During the follow-up of the patient, who had been followed up by the oncology clinic for 6 years and did not receive additional treatment, no pathological finding was detected. The patient has given written consent for this case report.

Figure 2: Tumor tissue with submucosal invasion (HE,  $\times 40$ ).

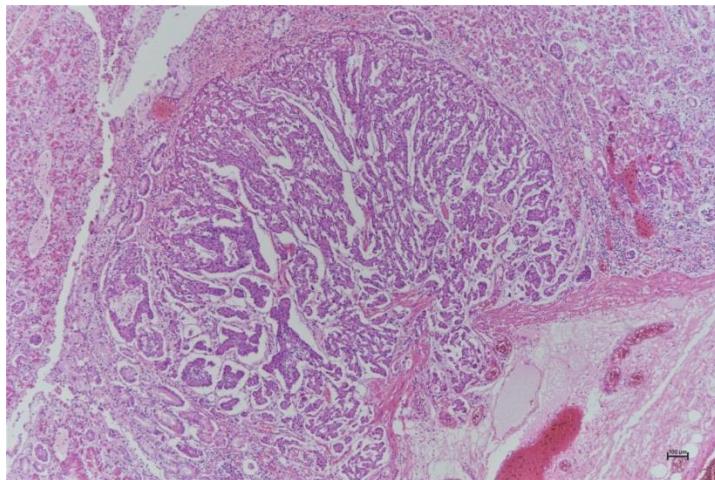


Figure 3: a: Cells with eosinophilic cytoplasm and round nuclei in tumor tissue consisting of solid islands (HE,  $\times 200$ ). b: Mitotic figure (HE,  $\times 400$ ).

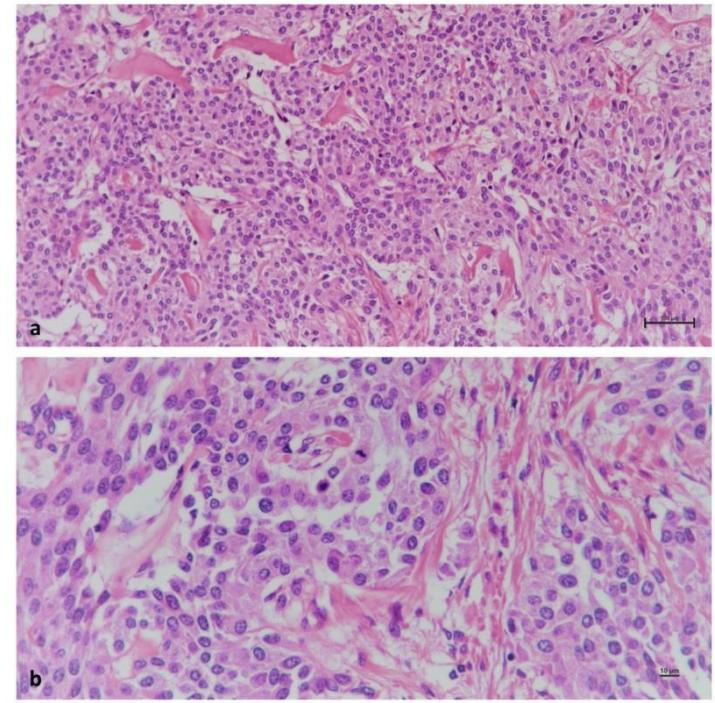


Figure 4: a: Chromogranin expression in tumor cells ( $\times 20$ ). b: Ki-67 expression in tumor cells ( $\times 400$ ).

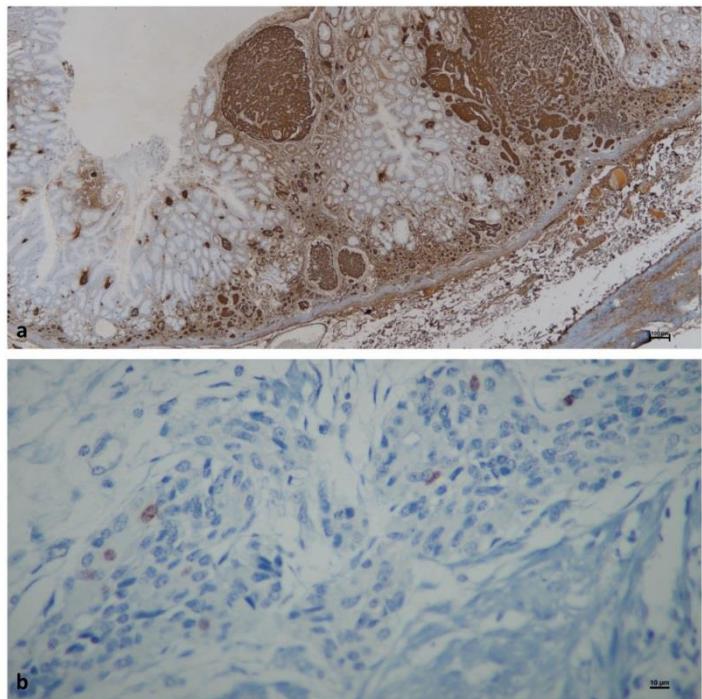


Figure 5: a: Fundic gland polyps in the surrounding stomach tissue (HE,  $\times 40$ ). b: Neuroendocrine cell hyperplasia foci in the surrounding gastric mucosa (HE,  $\times 100$ ).

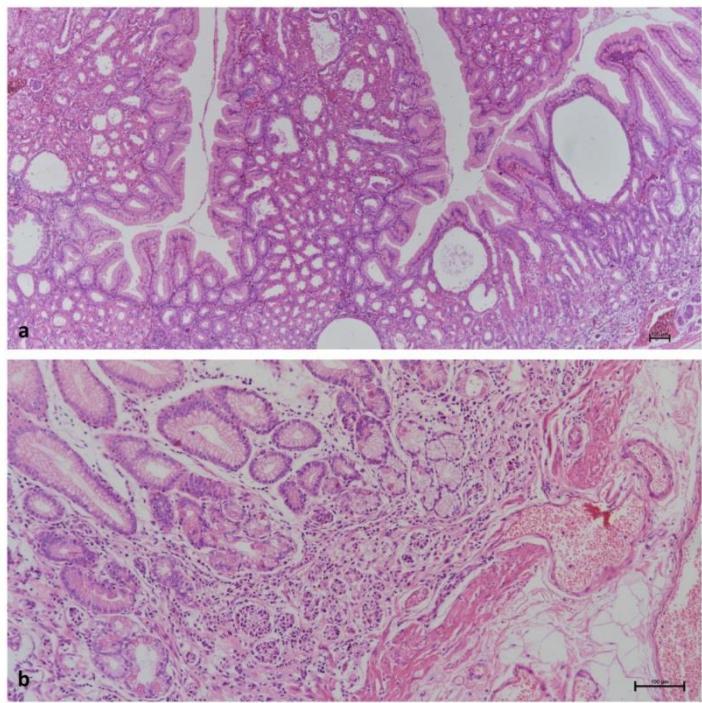
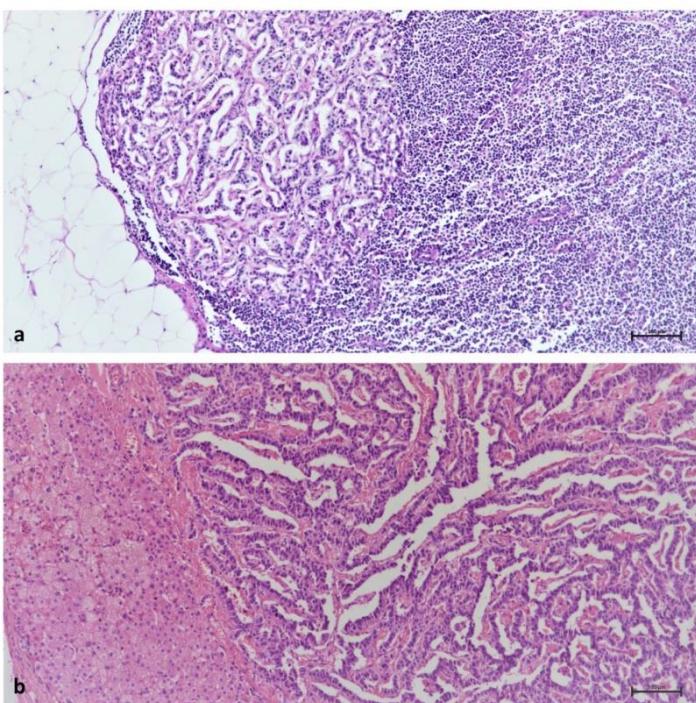


Figure 6: a: Metastasis focus in the lymph node in the greater curvature region (HE,  $\times 100$ ). b: Metastatic focus in liver (HE,  $\times 100$ ).



## Discussion

In the stomach, the neuroendocrine cell component is scattered throughout the gastric epithelium. This component, mostly composed of ECL cells (15–30%), also includes G cells, D cells, A cells, enterochromaffin cells, and X cells. ECL cells and G cells are prominent in gastric NET pathology. ECL cells are mostly localized in the fundus. G cells are located in the neck region of the mucous glands in the antrum and pylorus [5].

Gastrin, normally secreted by G cells, is regulated by the luminal hydrogen concentration secreted from parietal cells. Histamine secreted by ECL cells in response to gastrin stimulation stimulates the parietal cells. Endogenous parietal cell destruction due to autoimmune disease or with low acidity hypergastrinemia caused by exogenous drugs such as PPI, hypergastrinemia may also result in ECL cell hyperplasia [5, 8]. Linear, micronodular, and adenomatoid type ECL cell hyperplasia and dysplasia characterized by enlarged or fused micronodules consisting of atypical cells, microinvasion, or newly formed stroma are precursor lesions of NET and are precursor lesions that develop from ECL cells detected histopathologically [5]. In our case, there were precursor lesions consisting of diffuse ECL cells around microNET foci.

ECL cell hyperplasia in the surrounding mucosa is commonly observed in Type 1 and Type 2 gastric NETs. In addition, intestinal and pseudopiloric metaplasia is observed in the atrophic mucosa in Type 1 NET, while the mucosa is hyperplastic in Type 2 NETs. In type 3 NET, the surrounding gastric mucosa is normal. Recently defined ECL cell NET is associated with hypergastrinemia, and multiple lesions similar to Type 1 and Type 2 NETs are observed. In the surrounding mucosa, unlike other types, diffuse dilated oxytic glands containing inspissated material in their lumen are observed [6]. In our case, hypergastrinemia and our morphological findings are more consistent with Type 1 gastric NET with the presence of atrophic mucosa, although intestinal metaplasia is not common.

PPI inhibits acid secretion by blocking the parietal cell's H<sub>+</sub>/K<sub>+</sub> ATPase enzyme system. With this effect, it is a preferred and widely used drug in treating acid-related diseases, such as gastroesophageal reflux and preventing aspirin/nonsteroidal anti-inflammatory drug-related ulcers and recurrences. Hypoacidity caused by PPI may cause an increase in plasma gastrin levels more than three times the normal (<100 ng/mL). Hypergastrinemia can also stimulate the proliferation of ECL cells, which is common in the fundic mucosa [14]. It has been reported that there may be undesirable consequences such as gastrointestinal infection, VitB 12 and iron deficiency, gastric fundic gland polyps, NET, and gastric and colon cancer associated with acid inhibition due to long-term use of the drug [8, 14]. In addition, studies show that it increases the frequency and severity of atrophic gastritis in patients with helicobacter pylorus [15, 16].

In experimental studies, it has been reported that long-term hypergastrinemia in animals (rats) treated with PPI leads to ECL cell proliferation and NET development by neoplastic transformation [8]. Although it causes ECL cell hyperplasia in humans, it is controversial whether it affects tumor development [8, 17]. While there are more case reports in the literature, there are very few studies on this subject [2, 9-13, 18]. While no relationship was found between NET and PPI use in one of the existing studies, it was reported in another study that it was related and that NETs with less aggressive behavior emerged [13, 18].

In our case, many millimeter-sized tumor foci accompanying widespread ECL cell hyperplasia-dysplasia in the surrounding mucosa and the absence of a clinical picture associated with ZES/MEN-1 were absent more compatible with Type I NET among gastric NET types. However, in the case where we did not have information about serum antiintrinsic factor and antiparietal cell antibody levels, the presence of intestinal metaplasia in focus in the mucosa, which is generally atrophic, the presence of diffuse fundic gland polyps and high gastrin level, 10 years of PPI use in the history may be a possible factor in the development of gastric NETs.

In clinics, NETs diagnosed incidentally during routine endoscopic examination mostly progress with nonspecific findings [19, 20]. Therefore, they are typically diagnosed late, as in our case. Therefore, some cases have metastasis at diagnosis [20]. Our case was diagnosed with the detection of a metastatic tumor focused on the liver tissue.

High rates of local recurrences are defined in Type I NETs with low mortality risk. Therefore, surgical treatment may vary with tumor size and spread and approach differences [1, 21, 22]. Our patient, who was found to have liver metastasis, underwent total gastrectomy with lymph nodes due to his clinical condition. No pathology was found during the 6-year follow-up period.

## Conclusion

Although our patient's diagnosis is accepted as Type I NET based on current findings, because of the patient's history, the possibility of developing NETs secondary to long-term PPI use should also be considered. The recent increase in gastric NETs suggests a need for more frequent endoscopic controls, especially in cases with long-term PPI use and high serum

gastrin levels. Large-scale studies involving such cases can also contribute to understanding the pathogenesis of gastric NETs.

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