**Case History**

A 77-year-old man taking the proton pump inhibitor (PPI) pantoprazole for several years to treat gastroesophageal reflux underwent an upper endoscopy during which a polyp in the gastric body was identified. A repeat endoscopy several months later found three additional polyps at the same location. Figure 1 shows a representative section of the polypectomy specimen and a section of the polypectomy specimen found at a repeat endoscopy is shown in Figure 2.

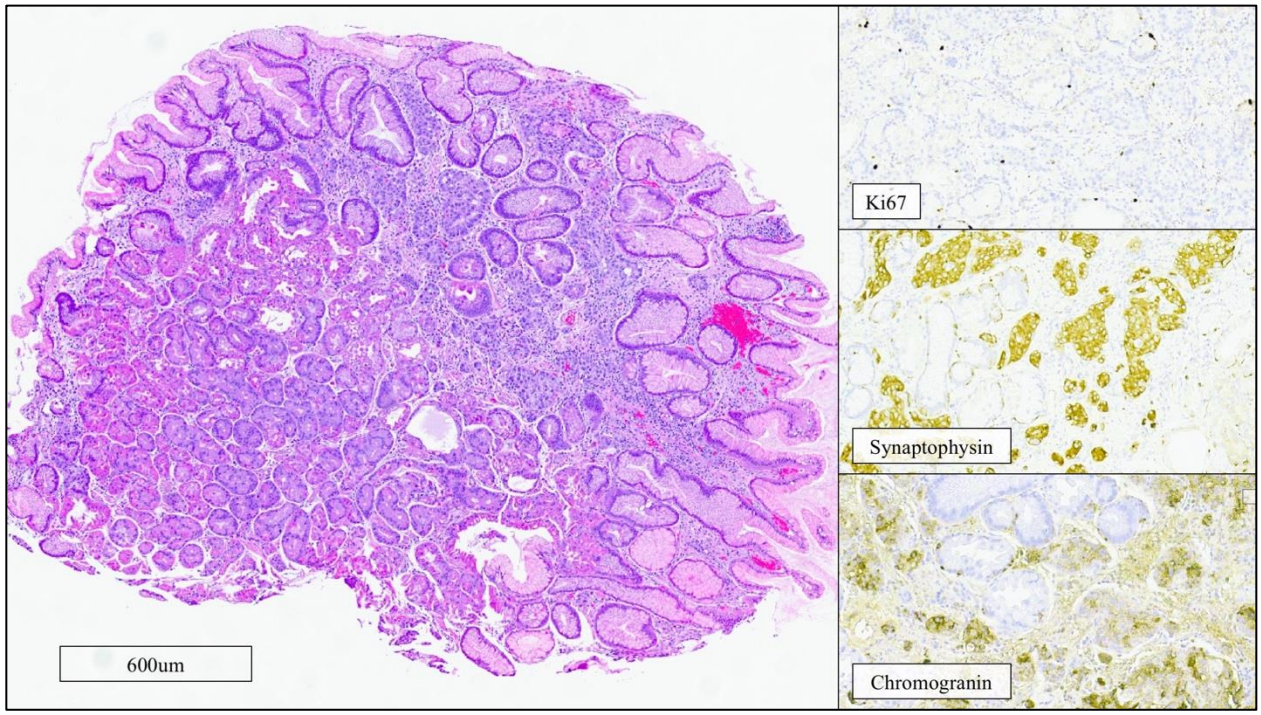


**Figure 1.** Representative section of the polypectomy specimen from the initial endoscopy.

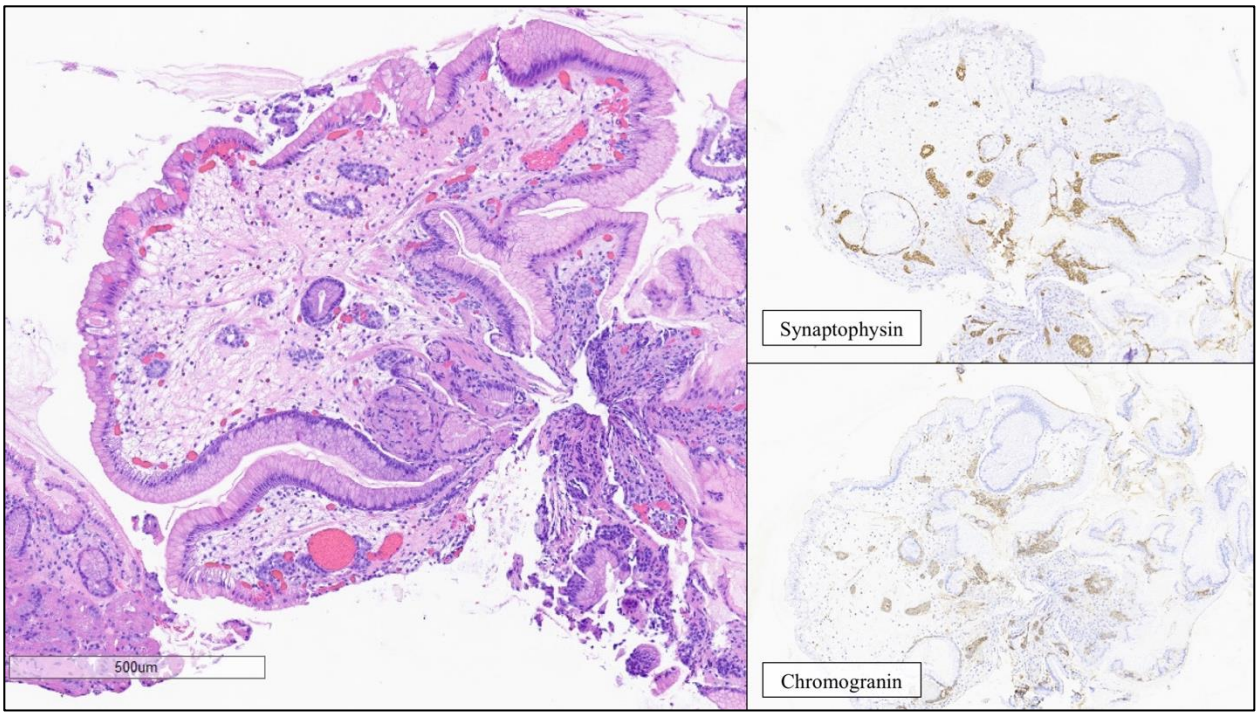


**Figure 2:** Representative section of the polypectomy from the follow-up endoscopy.

What is the most likely diagnosis for the lesion illustrated on Figure 1?

A. Fundic gland polyp and a well-differentiated neuroendocrine tumor, type 1

B. Fundic gland polyp and a well-differentiated neuroendocrine tumor, type 2

C. Fundic gland polyp and a well-differentiated neuroendocrine tumor, type 3

D. Fundic gland polyp and a well-differentiated neuroendocrine tumor, type 4

E. Fundic gland polyp and a well-differentiated neuroendocrine tumor, type 5 (PPI-related).

**Correct diagnosis: (E).** Fundic gland polyp and a well-differentiated neuroendocrine tumor, PPI-related
The polyp found on the gastric body during the initial endoscopy is composed of dilated gastric fundic glands which are intimately associated with a proliferation of bland chromogranin and synaptophysin positive endocrine cells (Figure 1). The endocrine cell population represents a well-differentiated neuroendocrine tumor (NET), grade 1 (Ki67 index is <2% and absent mitotic figures) arising in a non-dysplastic fundic gland polyp[1]. The follow-up endoscopy several months later showed a fundic gland polyp (FGP) with micronodular endocrine cell hyperplasia (Figure 3).

Fundic gland polyps are a common finding during endoscopy[2]. A recent study on 3400 people by Notsu et al found a FGP prevalence of 30.3%[3]. Most FGPs are not syndromic, but a subset is associated with polyposis and gastric cancer syndromes (i.e. familial adenomatous polyposis and gastric adenocarcinoma and proximal polyposis syndrome)[4]. The increased incidence of FGPs during the last few decades has been attributed to the use of proton pump inhibitors (PPI) first introduced in 1989[5,6]. These drugs are the most potent inhibitors of acid secretion currently available which result in a feedback mechanism that causes an increase in gastrin production by antral G-cells and G-cell hyperplasia[7]. Gastrin stimulation causes parietal cell hyperplasia with the resulting hypereosinophilic appearance of fundic glands. Apocrine-like changes (hobnailing) with bulging of the apical membrane of oxyntic cells and formation of microcysts are other common features. Microcyts are almost invariably present in FGPs. In addition to parietal cells, the cysts may contain chief and mucinous foveolar cells. The surface foveolar epithelium has either a normal or flattened appearance. Dysplastic changes occur almost exclusively in syndromic cases and, even in this scenario, the development of invasive carcinoma is extraordinarily rare except in patients with gastric adenocarcinoma and proximal polyposis syndrome[8,9].

NETs arising within the stomach traditionally fall into three categories: types 1 and 2 are associated with hypergastrinemia related to atrophic gastritis and a gastrin secreting G-cell tumor respectively, and the sporadic type 3 tumor which is not associated with hypergastrinemia and has a propensity to behave aggressively[1,10-12]. A recent study by Trinh et al investigated the nature of NETs that developed in patients with >1 year of PPI use and compared these tumors with those that arose in patients without predisposing disorders and who did not use PPIs (type 3 NET). The study found that NETs arising in patients with chronic PPI use have a significantly longer overall survival, tend to present at a lower stage and less often show lymphovascular invasion. The authors proposed that gastric NETs arising in association with PPI use could be classified as "Type 5" (the other types are discussed in the answers to questions A to D in the subsequent paragraphs)[13]. An editorial on the subject by Stefano La Rosa and Enrico Solcia proposed to classify gastric NETs into those with normal gastrin levels (Type 3) and those associated with hypergastrinemia (Types 1, 2, 4, and 5)[14]. It should be noted that this classification has not been endorsed by WHO Digestive System Tumors, 5 edition, or AJCC, 8th edition.

**Answer A.** Type 1 gastric NETs arise in an atrophic fundic mucosa that shows an inflammatory pattern characteristic of autoimmune gastritis (AIG)[1]. At variance with *Helicobacter pylori* associated gastritis, the inflammatory process is confined to the corporal / fundic mucosa and targets specialized glands. The injured oxyntic glands are replaced by intestinal or pyloric metaplastic glands. Loss of parietal cells causes hypochlorhydria and, due to the ensuing compensatory hypergastrinemia, ECL-cell hyperplasia develops which manifests initially as intraglandular linear arrays of endocrine cells and, as the disease progresses, endocrine cell clusters referred to as micronodular hyperplasia[15]. When the diameter of these clusters exceeds 0.5 mm they are categorized as well-differentiated neuroendocrine tumors, which may appear endoscopically as small sessile polyps. Biopsies of these lesions reveal endocrine cells intermixed with a fundic mucosa showing inflammation, atrophy and metaplastic changes. Other

endoscopically detected polypoid lesions include oxyntic pseudopolyps (remnants of unaffected oxyntic mucosa), hyperplastic polyps and pyloric gland adenomas[16]. Clinically, type 1 gastric NETs are common (70-80% of gastric NETs) and have an excellent prognosis[12]. Fundic gland polyps, like the one present in our patient, are not increased in frequency in autoimmune gastritis.

**Answer B.** Type 2 gastric NETs develop in the gastric body of patients with G-cell tumors (gastrinomas) resulting in Zollinger-Ellison syndrome (ZES) which consists of hyperacidity and refractory peptic ulcer disease in addition to hypergastrinemia[1]. Gastrinomas arise in the duodenum or pancreas and may be associated with MEN1 syndrome. Type 2 gastric NETs are rare, frequently multifocal and often indolent but have a greater propensity to metastasize than type 1 gastric NETs[12]. Hypergastrinemia induces oxyntic gland and ECL-cell hyperplasia which may appear endoscopically as prominent gastric folds rather than polypoid lesions.

**Answer C.** Type 3 gastric NETs are sporadic, frequently solitary, and behave more aggressively than the previous types with metastases in >50% of patients[1,12]. These tumors arise *de novo* in an otherwise normal appearing mucosa. There is no hypergastrinemia and, thus, no oxyntic or precursor ECL-hyperplasia. Morphologically these neoplasms have typical features of a well-differentiated neuroendocrine tumor and are graded accordingly. High-grade neuroendocrine carcinomas should not be included in this category. They have small cell or large cell morphology similar to high grade neuroendocrine carcinomas that develop in other organs and appear to arise either *de novo* or in association with adenocarcinomas[17].

**Answer D.** The category of type 4 gastric NETs has been proposed for a subtype of tumor that arises in patients who have an inactivating mutation of the *ATP4A* gene which encodes for the alpha-subunit of the gastric proton pump[20]. These patients develop achlorhydria and, consequently, compensatory hypergastrinemia and parietal cell hyperplasia. The background oxyntic mucosal changes are like those

observed in patients with Zollinger-Ellison syndrome and MEN 1[18]. Unfortunately, classifying NETs as type 4 may be of concern since this denomination has previously been used for high-grade neuroendocrine carcinomas[19].

## References

[1]La Rosa S, Rindi G, Solcia E, Tang LH. Gastric neuroendocrine neoplasms. WHO classification of tumors digestive system tumors. 5th ed. Lyon, France: International Agency for Research on Cancer (IARC), 2019;104–109.

[2]Carmack SW, Genta RM, Schuler CM, Saboorian MH. The current spectrum of gastric polyps: a 1-year national study of over 120,000 patients. Am J Gastroenterol. 2009;104(6):1524–1532.

[3]Notsu T, Adachi K, Mishiro T, Ishimura N, Ishihara S. Fundic gland polyp prevalence according to Helicobacter pylori infection status. J Gastroenterol Hepatol. 2020;35(7):1158-1162.

[4]Jasperson KW, Patel SG, Ahnen DJ. APC-Associated Polyposis Conditions. 1998 Dec 18 [Updated 2017 Feb 2]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1345/

[5]Tran-Duy A, Spaetgens B, Hoes AW, de Wit NJ, Stehouwer CD. Use of Proton Pump Inhibitors and Risks of Fundic Gland Polyps and Gastric Cancer: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2016;14(12):1706-1719.

[6]Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. J Neurogastroenterol Motil. 2013;19(1):25-35.

[7]Helgadottir H, Bjornsson ES. Problems Associated with Deprescribing of Proton Pump Inhibitors. Int J Mol Sci. 2019;20(21):5469.

[8]Straub SF, Drage MG, Gonzalez RS. Comparison of dysplastic fundic gland polyps in patients with and without familial adenomatous polyposis. Histopathology. 2018;72(7):1172-1179.

[9]Worthley DL, Phillips KD, Wayte N, Schrader KA, Healey S, Kaurah P, Shulkes A, Grimpen F, Clouston A, Moore D, Cullen D, Ormonde D, Mounkley D, Wen X, Lindor N, Carneiro F, Huntsman DG, Chenevix-Trench G, Suthers GK. Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): a new autosomal dominant syndrome. Gut. 2012;61(5):774-9.

[10]Rindi G, Luinetti O, Cornaggia M, Capella C, Solcia E. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. Gastroenterology. 1993;104(4):994-1006.

[11]Vanoli A, La Rosa S, Miceli E, Klersy C, Maragliano R, Capuano F, Persichella A, Martino M, Inzani F, Luinetti O, Di Sabatino A, Sessa F, Paulli M, Corazza GR, Rindi G, Bordi C, Capella C, Solcia E. Prognostic Evaluations Tailored to Specific Gastric Neuroendocrine Neoplasms: Analysis Of 200 Cases with Extended Follow-Up. Neuroendocrinology. 2018;107(2):114-126.

[12]Sato Y, Hashimoto S, Mizuno K, Takeuchi M, Terai S. Management of gastric and duodenal neuroendocrine tumors. World J Gastroenterol. 2016;22(30):6817-28.

[13]Trinh VQ, Shi C, Ma C. Gastric neuroendocrine tumours from long-term proton pump inhibitor users are indolent tumours with good prognosis. Histopathology. 2020;77(6):865-876.

[14]La Rosa S, Solcia E. New insights into the classification of gastric neuroendocrine tumours, expanding the spectrum of ECL-cell tumours related to hypergastrinaemia. Histopathology. 2020;77(6):862-864.

[15]Hall SN, Appelman HD. Autoimmune Gastritis. Arch Pathol Lab Med. 2019;143(11):1327-1331.

[16]Coati I, Fassan M, Farinati F, Graham DY, Genta RM, Rugge M. Autoimmune gastritis: Pathologist's viewpoint. World J Gastroenterol. 2015;21(42):12179-89.

[17]Klöppel G. Neuroendocrine Neoplasms: Dichotomy, Origin and Classifications. Visc Med. 2017;33(5):324-330.

[18]Abraham SC, Carney JA, Ooi A, Choti MA, Argani P. Achlorhydria, parietal cell hyperplasia, and multiple gastric carcinoids: a new disorder. Am J Surg Pathol. 2005;29(7):969-75.

[19]Klöppel G, Clemens A. The biological relevance of gastric neuroendocrine tumors. Yale J Biol Med. 1996;69(1):69-74.

[20]Calvete O, Reyes J, Zuñiga S, Paumard-Hernández B, Fernández V, Bujanda L, Rodriguez-Pinilla MS, Palacios J, Heine-Suñer D, Banka S, Newman WG, Cañamero M, Pritchard DM, Benítez J. Exome sequencing identifies ATP4A gene as responsible of an atypical familial type I gastric neuroendocrine tumour. Hum Mol Genet. 2015 May 15;24(10):2914-22.

**Case contributed by**

Christine Orr, MD, Gastrointestinal Pathology Fellow

Jose Jessurun, MD, Professor of Pathology and Laboratory Medicine

Department of Pathology and Laboratory Medicine

NewYork-Presbyterian Hospital / Weill Cornell Medical College

1414 York Ave, New York, NY 10021