

Adenocarcinoma and Neuroendocrine Collision Tumor in a Giant Gastric Hyperplastic Polyp

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Screening esophagogastroduodenoscopy of a 65-year-old man revealed a 4.7-cm polypoid in the gastric high body. Clinical and laboratory findings, including serum gastrin level (460 pg/mL) and biopsy findings, were consistent with a diagnosis of type I neuroendocrine tumor (NET). Histologically, the mass consisted of dilated tortuous glands at the surface and grade 1 NET in deeper tissue. Some hyperplastic glands exhibited a transition to adenocarcinoma, which invaded the NET, simulating a “tumor in tumor” appearance. Next-generation sequencing revealed that the adenocarcinoma component harbored a *TP53* mutation, whereas the NET component showed no pathogenic mutation. To our knowledge, this unusual collision of adenocarcinoma and NET within a single gastric hyperplastic polyp has not been previously described. This case suggests that large gastric hyperplastic polyps should be carefully examined because of the possibility of underlying NET and malignant transformation of surface epithelium. (J Nippon Med Sch 2020; 87: 157–161)

Key words: hyperplastic polyp, neuroendocrine tumor, adenocarcinoma, stomach

Introduction

Hyperplastic polyp (HP) is the second most common type of gastric epithelial polyp. Gastric HP is a hyper-regenerative process triggered by longstanding mucosal injury or inflammation, which is mainly caused by *Helicobacter pylori* infection and autoimmune gastritis¹. In addition to HP, tissue response to chronic gastritis produces various stomach lesions. Neuroendocrine hyperplasia and neuroendocrine tumor (NET) are frequently detected in persons with chronic atrophic gastritis². Because of their overlapping histogenetic origins, HP and NET can coexist.

Most gastric HPs do not harbor oncogenic genetic mutations, and intraepithelial neoplasia in HP is exceptional. Only 2% to 3% of gastric HP—usually larger polyps (>1-2 cm)—exhibit epithelial dysplasia or adenocarcinoma³. Herein, we describe a large gastric HP, in a patient with

H. pylori-associated chronic gastritis, that exhibited collision of adenocarcinoma and NET.

Case Presentation

A healthy 65-year-old man was referred to our tertiary hospital for evaluation of a subepithelial tumor-like lesion discovered on a screening upper gastrointestinal series. At initial presentation, he had no abnormal gastrointestinal symptoms or systemic symptoms such as fever or weight loss. Esophagogastroduodenoscopy was performed to evaluate the mass.

In the upper one-third of the stomach corpus, an approximately 5-cm polypoid mass with an ulcerative surface was observed (**Fig. 1A**). The background gastric mucosa was moderately atrophic and nodular, which suggested intestinal metaplasia. Endoscopic ultrasonography was performed by using a high-frequency catheter probe

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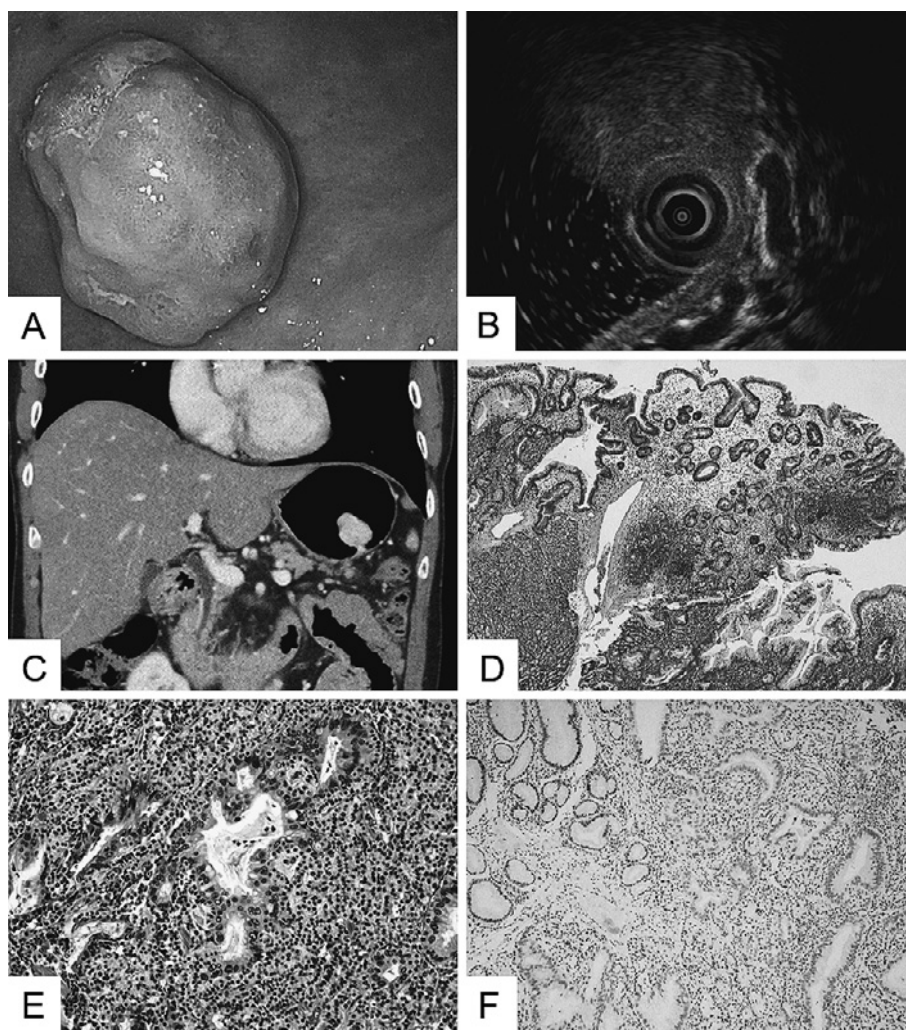


Fig. 1 Clinical and histopathological images.

A: An endoscopic image shows a single, approximately 5-cm mass with surface ulceration at the greater curvature side of the high body of the stomach; the background mucosa was atrophic. B: Endoscopic ultrasound findings show a mass with heterogeneous echogenicity confined to the mucosa, without definite submucosal involvement. C: An abdominal computed tomography scan shows a mass with a short peduncle. Regional lymph node enlargement and distant metastasis were not observed. D: At low magnification ($\times 40$), the polyp shows dilated, tortuous glands on the surface and neuroendocrine tumor in the deeper portion (lower left). Some hyperplastic glands exhibit transition to adenocarcinoma (upper right). E: At high magnification ($\times 400$), the lesion shows adenocarcinoma surrounded by neuroendocrine tumor. F: p53 immunostaining of the adenocarcinoma component shows a null expression pattern, whereas staining of the hyperplastic glands and neuroendocrine tumor component shows patchy nuclear expression.

(20 MHz miniprobe; Olympus, Tokyo, Japan). The mass had a heterogeneous, hypoechoic texture and appeared to be confined to the mucosa because the submucosal layer was intact and there was no evidence of tumor invasion (**Fig. 1B**).

Forceps biopsy was performed in a bite-on-bite manner, to reach as deeply as possible. *H. pylori* infection was confirmed by rapid urease test. Histopathological examination of the biopsy specimen revealed lobular prolifera-

tion of neuroendocrine cells. Laboratory examination showed elevated serum gastrin (460 pg/mL), which suggested Rindi type I gastric NET. Abdominal CT scans revealed a highly attenuated mass, without abnormal thickening of the gastric wall, and no perigastric lymph node enlargement (**Fig. 1C**).

The patient underwent endoscopic mucosal resection for diagnostic and therapeutic purposes. Histological examination showed many dilated tortuous glands at the

Table 1 Summary of cases of epithelial neoplasia/neuroendocrine tumor in a gastric hyperplastic polyp

Case (Ref.)	Sex/ Age	<i>H. pylori</i>	Serum Gastrin	Auto-Ab	Endoscopic findings	Histopathology
1 (5)	F/55	Negative	NA	NA	4 polyps in patient with chronic atrophic gastritis	
					1) 0.8 cm polyp	HP/LGD/Linear and nodular NH
					2) 1.0 cm superficial elevated lesion	HP/HGD/Linear and nodular NH
					3) 0.4 cm polyp	HP
4) 1.0 cm elevated lesion	NET G1					
2 (6)	M/72	Negative	NA	NA	3 polyps in patient with chronic atrophic gastritis	
					1) 2.5 cm polyp with hemorrhage	HP/LGD/HGD/NET G1
					2) 1.3 cm polyp	HP
3) 1.2 cm polyp	HP					
Present case	M/65	Positive	460 pg/mL	NA	Single 4.7 cm polyp with ulceration in patient with chronic atrophic gastritis	HP/EGC/NET G1

Abbreviations: HP, hyperplastic polyp; LGD, low-grade dysplasia; NH, neuroendocrine hyperplasia; HGD, high-grade dysplasia; NET G1, neuroendocrine tumor grade I; EGC, early gastric carcinoma; NA, not available.

surface and NET at the deeper portion invading the submucosa, which occupied 80% of the entire polyp. The NET portion had an organized pseudoacinar or trabecular growth pattern, a low nuclear/cytoplasmic ratio, minimal nuclear atypia, and no mitotic figures. Some hyperplastic glands exhibited transition to well differentiated adenocarcinoma, which invaded the lamina propria and occupied 5% of the polyp (Fig. 1D). The adenocarcinoma partly collided with and invaded the NET, resulting in a tumor-in-tumor appearance (Fig. 1E).

Immunohistochemistry revealed that the NET portion was strongly stained with chromogranin A and synaptophysin and negatively stained with CD56. The Ki-67 labeling index was 1%, suggesting grade 1 NET. Immunostaining with chromogranin A and synaptophysin indicated linear neuroendocrine hyperplasia, which occupied 20% to 40% of the lining cells in several overlying hyperplastic glands. In contrast to the NET portion of the biopsy, staining intensity in the neuroendocrine hyperplasia portion was weak and patchy. P53 immunostaining revealed null expression (a truncating mutation pattern) in the adenocarcinoma component and patchy expression (wild-type pattern) in the hyperplastic glands and neuroendocrine tumor (Fig. 1F).

After tissue microdissection, OncoPrint Comprehensive Assay V3 (Thermo Fisher Scientific, MA, US)-based targeted next-generation sequencing was used to analyze all

tissue samples of adenocarcinoma and NET components. Genetic analysis of the adenocarcinoma component showed 1 pathogenic frameshift mutation in *TP53* (9.9%) and 1 missense mutation of unknown biological significance, *NF1* L1085R (11.3%). The NET component had 3 mutations of unknown biological significance: an *ATM* splice site mutation (4.2%), *NOTCH1* A2356 G (4.1%), and *SLX4* P1030 L (7.3%).

Discussion

Chronic gastritis can cause HP and NET. Park et al. reported that the 2 most common types of gastric lesion arising in autoimmune atrophic gastritis were HP and NET, which occurred synchronously or metachronously⁴. Synchronous HP and NET may appear separately in multiple masses or, rarely, together in a single mass⁴⁻⁶. Development of intraepithelial neoplasia consisting of HP and NET in a single mass was previously described in only 2 patients^{5,6}.

The characteristics of HP accompanied by intralesional NET and epithelial neoplasia are briefly summarized in Table 1. Previously reported cases had multiple gastric polyps arising in chronic atrophic gastritis but no evidence of *H. pylori* infection, and none of the polyps showed overt malignant transformation of the epithelium^{5,6}. The present patient had a single HP with adenocarcinoma and NET, which arose in a patient with

H. pylori-associated chronic atrophic gastritis.

H. pylori infection and autoimmune gastritis are risk factors for chronic atrophic gastritis. Autoimmune gastritis is best diagnosed by confirmation of serological autoantibodies to parietal cells or intrinsic factor. However, when analyzing the differential diagnosis for atrophic gastritis in South Korea, these autoantibodies are not usually assessed, since the prevalence rate of *H. pylori* infection is as high as 51%, whereas the incidence of autoimmune gastritis is very low⁷. Because of the low prevalence rate of autoimmune gastritis in Korea and the positive result of the rapid urease test in the present case, the initial cause of the present gastric lesions was much more likely to be *H. pylori* infection than autoimmune gastritis.

Gastric NETs can be classified by pathogenesis as type I gastrin-dependent, type II Zollinger-Ellison syndrome-related, and type III gastrin-independent NETs⁸. Although not specific, characteristic endoscopic findings of gastric NETs are relevant to subtype. Type I NETs usually present as multiple diminutive polyps in the stomach body or fundus. Type III NETs usually appear as a solitary nodule larger than 1 cm, and their biological behavior is the most aggressive of the 3 types⁹. In light of the biopsy diagnosis of NET and elevated serum gastrin level in the present case, we performed active tumor resection for diagnostic and therapeutic purposes, as the lesion was atypical because of the presence of mixed type I/III gastric NET features. The endoscopic appearance of the lesion was more concordant with type 3 NET, whereas the elevated serum gastrin level favored type 1 NET. The mixed histological features of this lesion may explain its atypical clinical presentation. In retrospect, the mixture of large HP and type I NET resembled the endoscopic appearance of type III NET.

Physicians can distinguish tumors with dual differentiation from simple collision of two tumor types by the presence of adenocarcinoma entrapped by NET. In fact, mixed adenoneuroendocrine carcinoma (MANEC) is a well-known disease entity in gastric neoplasia. The pathogenesis of MANEC is regarded as dual differentiation from a single multipotent stem cell¹⁰. Histologically, the present case is distinguishable from MANEC by the absence of high-grade cytological features and the presence of organized architectures in the neuroendocrine component. Using P53 immunostaining and genetic analysis, we proved that adenocarcinoma and NET components were clonally different, which supports tumor collision rather than dual differentiation.

To our knowledge, mixture of pathological entities within a single gastric HP has not been previously reported. This case suggests that large gastric HP should be carefully examined because of the possibility of underlying NET and malignant transformation of surface epithelium.

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Conflict of Interest: The authors declare no conflicts of interest regarding this study.

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