Int Surg 2022;**106:**48–52
DOI: 10.9738/INTSURG-D-20-00004.1

Case Report

A Case Report of a Gastric Neuroendocrine Tumor Arising From Gastric Adenoma

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Background: Composite glandular/exocrine-endocrine neoplasms of the gastrointestinal tract are a special tumor type. There are only 3 reports in English on secondary gastric neuroendocrine tumor (G-NET) arising from gastric adenoma. Here, we describe a rare case of a G-NET arising from a gastric adenoma.

Case presentation: A 69-year-old man underwent esophagogastroduodenoscopy as part of a general health check-up. An endoscopic examination revealed a 5-mm elevated tumor on the fornix of the stomach. Further, atrophic changes in the gastric mucosa were not noted. The tumor was diagnosed as a gastric adenoma; thus, endoscopic submucosal dissection (ESD) was performed. Histologically, the tumor was composed of 2 components, an epithelial component, which was diagnosed as an adenoma, and a depth component, which was diagnosed as a neuroendocrine tumor. The neuroendocrine tumor was diagnosed as a Grade 2 G-NET arising from the gastric adenoma. Histologically, the tumor invaded the submucosal layer (>1000 μm), invading the lymph vessels, and additional gastrectomy was performed. The pathologist revealed no remaining tumor or lymph node metastases in the resected specimen.

Conclusions: We report this extremely rare case of a G-NET (Grade 2), initially diagnosed as a gastric adenoma, that is considered to have originated from the gastric adenoma. Pathologists, endoscopists, and surgeons should be aware of the occurrence and association of NETs with adenomas in the stomach because small submucosal NETs of the stomach have relatively high metastatic rates.

Key words: Neuroendocrine tumor – Gastric adenoma – Composite tumor – Laparoscopy

Adenomas are the most common type of gastric neoplasms, whereas gastric neuroendocrine tumors are relatively uncommon. However, composite glandular/exocrine-endocrine neoplasms of the gastrointestinal tract are a special tumor type. A simple nomenclature for these neoplasms has been proposed as follows: (1) mixed or composite tumors with an admixture of glandular and endocrine

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components; (2) collision tumors, where the 2 components are distinct and juxtaposed; and (3) amphicrine cell tumors, composed predominantly of cells that exhibit dual endocrine and nonendocrine differentiation. Collision tumors are believed to result from 2 separate but adjacent neoplasms (biclonal malignant transformation), whereas composite tumors are thought to arise through multidirectional differentiation of a single neoplasm.[1,2]

Regarding the World Health Organization (WHO) classification, mixed adenoendocrine carcinomas (MANECs) have both exocrine and endocrine components. Arbitrarily, at least 30% of either component should be identified to qualify for this definition, Recently, the new term mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) was proposed to replace the old terminology used in the WHO 2010 Classification.[3] To the best of our knowledge, only 3 cases of gastric neuroendocrine tumor (G-NET) arising from gastric adenoma have been reported in the English literature.[4–6]

We present a case of a gastric composite tumor displaying the features of both adenoma and neuroendocrine tumor and discuss the histogenesis of these unusual tumors.

Case Presentation

Although there were no symptoms, a 69-year-old man underwent esophagogastroduodenoscopy as part of a general health check-up. He has undergone this procedure every year, and no other neoplasms, ulcers, or atrophies had been previously noted. The patient had taken medication for diabetes and hypertension for approximately 20 years, and his previous physical examinations and familial history were unremarkable. An endoscopic examination revealed a 5-mm elevated lesion on the anterior wall of the fundus on a background of no atrophic gastritis (Fig. 1). The lesion was diagnosed as a gastric adenoma via endoscopic forceps biopsy, and he underwent endoscopic submucosal dissection (ESD). Histologically, the tumor was composed of 2 components (Fig. 2), and it showed submucosal and lymphatic vessel invasion. One component was an epithelial component, which had a glandular structure and was diagnosed as an adenoma, and the other component was a depth component, which exhibited nesting, trabeculae, proliferation of small uniform cuboidal cells, and no glandular structures, which was diagnosed as a neuroendocrine tumor. Mitotic figures and enterochromaffin-like (ECL) cell hyperplasia around the tumor were not observed.

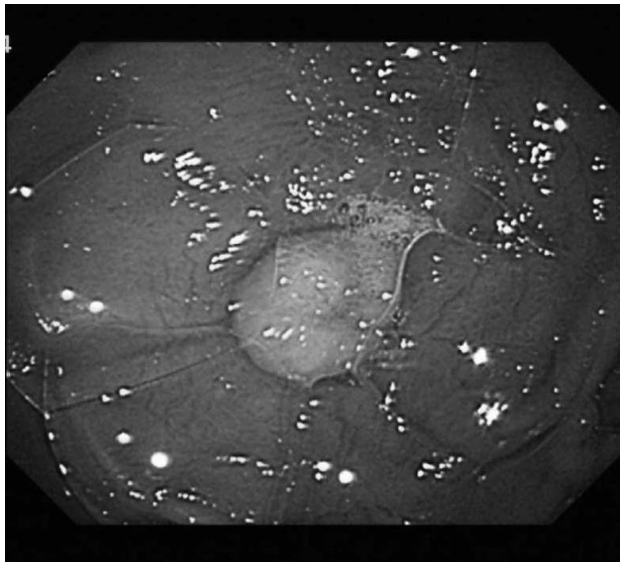

Fig. 1 Endoscopic view. Endoscopic examination revealed a 5-mm elevated lesion on the anterior wall of the fundus without an atrophic gastritis background.

Immunostaining showed that the tumor cells were positive for chromogranin A, synaptophysin, and CD56, and the Ki-67 labeling index was weakly positive (3%∼5%) (Fig. 3). The scattering of neuroendocrine cells within the transitional zone was more frequent than ordinary adenoma, and Ki-67 staining of the glandular structure was relatively strongly positive in the basal part of the adenoma, which is recognized as the proliferative zone (Fig. 4). Therefore, the tumor was pathologically diagnosed as a composite tumor, meaning a G-NET (G2) arising from the gastric adenoma in accordance with the WHO 2010 Classification.[3] But due to lymphatic vessel and submucosal layer invasion, he was diagnosed as non-curative resection of the tumor after ESD. A whole-body contrast-enhanced computed tomography (CT) scan did not reveal any evidence of occupied lesions such as distant metastasis. G-NET(G2) without distant metastasis is ordinally treated as gastric cancer; gastrectomy with lymphadenectomy was recommended. Thus, laparoscopic proximal gastrectomy with D1+ lymphadenectomy according to early gastric carcinoma was performed. Pathologically, in the surgically resected specimen there was no residual tumor in the ulcer scar after ESD and no lymph node metastases. The patient was discharged from our hospital on the 10th postoperative day uneventfully.

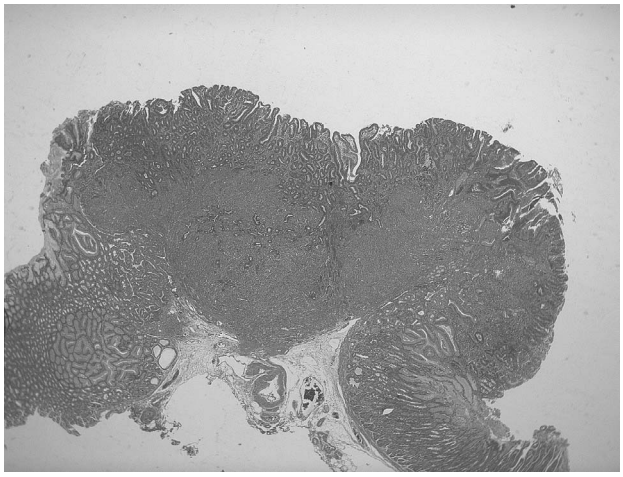

Fig. 2 Neuroendocrine tumor infiltrating the submucosa of an adenoma. Histologically, the tumor was composed of 2 components.

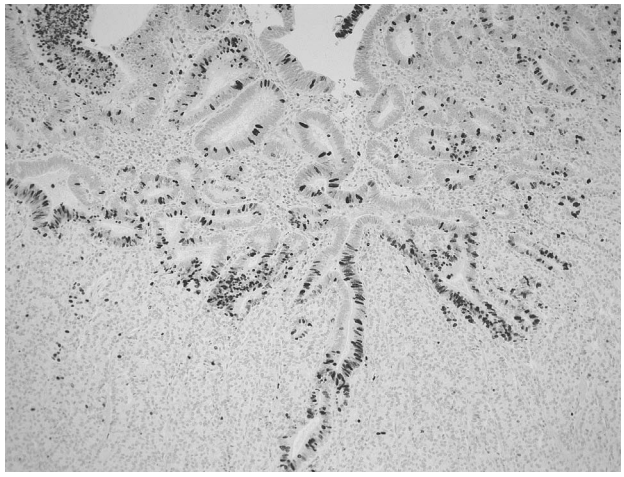

Fig. 4 Immunohistochemistry for Ki-67. Ki-67 staining in the glandular structure was relatively strongly positive in the basal part of the adenoma, which is recognized as the proliferative zone.

Discussion and Conclusions

In this rare case report, we present one important clinical finding: that low-grade NETs can arise from an adenoma. The concept of a mixed adenoma/NET tumor in the gastrointestinal tract was first introduced by Moyana[7] in 1988. Composite glandular/exocrine-endocrine neoplasms of the gastrointestinal tract have been categorized as follows: (1) mixed or composite tumors with an admixture of glandular and endocrine components; (2) collision tumors, where the 2 components are distinct and juxtaposed; and (3) amphicrine cell tumors, composed predominantly of cells that exhibit dual endocrine and nonendocrine differentiation.[8]

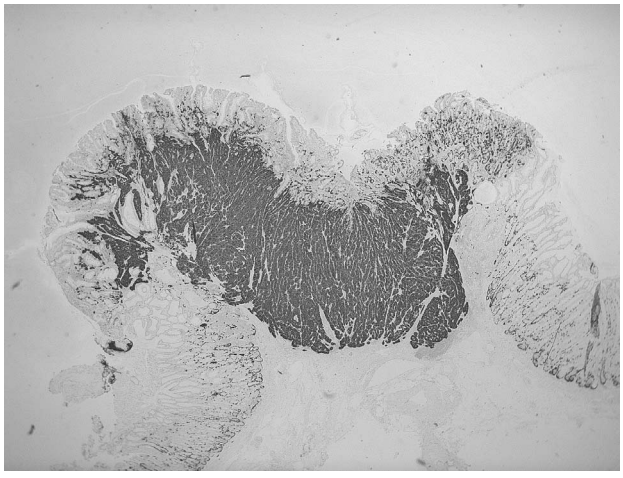

Fig. 3 Immunohistochemistry for chromogranin A. The staining for chromogranin A was positive in lower part of the adenoma and in the neuroendocrine tumor cells.

These 2 components most likely arise from one common precursor cell with divergent differentiation.[9] The neuroendocrine component of composite tumors in the large intestine is always incidentally found during the pathologic examination of adenomatous polyps. The well-established role of adenomatous polyposis coli (APC) gene alterations in the development of colorectal adenomas as well as the occurrence of composite adenomas/NETs in patients with familial adenomatous polyposis (FAP) syndrome suggest involvement of the APC/β-catenin pathway early in the progression in these neoplasms.[9–11] Microcarcinoid, which was first described by Pulitzer in 2006, has been recognized as a rare intestinal tumor consisting of intermingled adenomatous and well-differentiated neuroendocrine components.[12]

Microcarcinoid does not form grossly evident masses and has been described in the setting of chronic inflammatory disorders of the gastrointestinal tract, such as atrophic gastritis and type A gastritis. Most composite tumors of the stomach are malignant tumors arising from atrophic gastritis.[13–17]

We report a rare case of a gastric adenoma containing a low-grade NET. In our case, a NET G2 and adenoma were intermixed without distinct boundaries and showed a histologic transition between them. Accordingly, we concluded that this case was a composite tumor of a NET G2 and adenoma.

Another differential diagnosis that needs to be considered is the glandular differentiation of NETs. NETs are known to show glandular differentiation or mucin production.[18] Certainly a mutation analysis is necessary to confirm that different components within the same tumor have the same origin or not. An allelic imbalance analysis may be helpful for clarifying the origin of the components.[19] But in our case, the transection zone of the glandular component showed no "salt-and-pepper" chromatin pattern, and the Ki-67 labeling index was apparently higher than that of a NET and the surface layer of an adenoma. There was a gradual transitional zone between the NET and adenoma components. Adenoma cells immunohistochemically stained for chromogranin A and synaptophysin were also found in the adenoma area, and the neuroendocrine component showed positive chromogranin A and synaptophysin staining. Thus, our case could be diagnosed as a composite tumor.

Regarding the WHO classification, MANECs have both exocrine and endocrine components. Arbitrarily, at least 30% of either component should be identified to qualify for this definition. The new term MiNEN has being proposed to replace the old terminology used in the WHO 2010 Classification, and ordinarily, gastric neuroendocrine neoplasms are malignant. Our case is a G-NET (G2) arising from an adenoma, which is a benign tumor. Through a sequence of hyperplasia-dysplasia-neoplasia, it is recognized that adenomas transform into malignant tumors. However, in our case, the G-NET(G2) component arose from the adenoma. The growth form of this composite tumor was not MiNEN.

According *to* Rhindi *et al*, G-NETs can be classified into 3 distinct subtypes: type I G-NETs include carcinoids that develop on a foundation of atrophic corporal gastritis, type II G-NETs include carcinoids associated with MEN type I syndrome or Zollinger-Ellison syndrome, and type III G-NETs include carcinoids with malignant features in the absence of hypergastrinemia.[20] In our case, the patient falls into type III, as evidenced by the lack of atrophic gastritis on the endoscopic and blood exams, and the absence of evidence of MEN type I syndrome or Zollinger-Ellison syndrome. In Japan, type III NETs are treated the same as gastric cancer. Thus, gastrectomy with systematic lymphadenectomy is recommended for the treatment of G-NETs without distant metastasis. Therefore, endoscopic resection or local resection is permitted for G-NETs that are smaller than 2 cm according to the National Comprehensive Cancer Network guidelines.[21]

However, in our case, the G-NET was very small in size, and it was positive for lymphatic vessel invasion. Thus, we performed a laparoscopic proximal gastrectomy with D1+ lymphadenectomy.

The prognosis of benign composite neoplasm, adenoma-NET of the stomach cannot be completely determined due to the rarity of the cases. Complete removal of the adenoma is considered curative whereas the combined NET component is the main predictive factor for determining the patient's prognosis. In our case, the NET invaded the submucosal layer and lymphatic vessels; therefore, gastrectomy with lymphadenectomy was performed. However, the pathologic examination showed no residual tumor and no lymph node metastases. But a large study demonstrated that small submucosal NETs of the stomach have relatively high metastatic rates.[22] Therefore, close follow-up is recommended due to the relatively higher metastatic rate.

The most important reason to recognize NET in adenoma is to avoid misdiagnosing these rare lesions as malignant lesions arising from adenomas and collision tumors, and as microcarcinoids, MANECs, and MiNENs. In practice, pathologists, endoscopists, and surgeons should be aware of the occurrence and association of NETs with adenomas in the stomach because small submucosal NETs of the stomach have relatively high metastatic rates.

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