Pancreatic-type Mixed Acinar-neuroendocrine Carcinoma of the Stomach: A Case Report and Literature Review

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Abstract. Background: Pancreatic-type mixed acinar-neuroendocrine carcinoma (PMANEC) in the stomach is very rare. We report a case of PMANEC that was initially misdiagnosed as a gastric neuroendocrine tumor. Case Report: A 63-year-old female was found to have a gastric mass by histology and immunohistochemistry. The tumor had a heterogenous histology, with areas resembling pancreatic acinar cell carcinoma and other areas exhibiting neuroendocrine features. Only the neuroendocrine component was present in the initial biopsy, resulting in the erroneous diagnosis of gastric neuroendocrine tumor. Evaluation of the final resected tumor revealed cells expressing pancreatic exocrine markers, including trypsin and chymotrypsin and BCL10 immune signaling adaptor. Large areas of the tumor (>30%) were also positive for chromogranin A and synaptophysin. The final diagnosis was PMANEC. Conclusion: This type of gastric cancer is rare and may cause diagnostic difficulty, especially if only the neuroendocrine component of the tumor is sampled in a biopsy.

Pancreatic mixed acinar-neuroendocrine carcinomas (PMANECs) are rare tumors of the pancreas which were first described in the early 1990s by Klimstra et al. (1, 2). The classification of this tumor type, as described in the 2017 WHO Classification of Tumors of Endocrine Organs (3), requires each of the tumor components to constitute at least 30% of the total tumor. Gastric carcinomas resembling PMANECs are extremely rare, and only a few cases have been reported (4-9). These tumors are usually >10 cm in size and typically present in men over 60 years of age. Patients with these tumors may present with nausea, headaches, vomiting, and weight loss. The pathogenesis of gastric PMANEC is unknown but it may arise from foci of pancreatic heterotopia, which can occasionally be present in the stomach. Pancreatic heterotopia can be observed at multiple sites, including the duodenum, colon, and stomach (usually in the pyloric and antral regions) (10, 11). Here, we report a case of gastric PMANEC that was initially misdiagnosed as a gastric carcinoid tumor and present a review of the English literature on PMANEC.

Case Report

A 63-year-old woman presented with belching and heartburn. An esophago-gastroendoscopic examination identified a stricture in the distal esophagus. An ulcerated area along the stomach’s greater curvature was also identified, and an adjacent small nodule, 7 mm in size, was biopsied. A low-grade neuroendocrine tumor was diagnosed. A computerized tomographic scan of the abdomen showed hepatic hemangiomas, and a follow-up endoscopic ultrasound revealed a 10 mm submucosal nodule on the anterior wall of the stomach and diffuse nodular mucosa of the gastric cardia. A hypoechic round mass involving the submucosa was also identified on the greater curvature of the stomach. The patient underwent a gastric wedge resection. The gross examination identified a 1.2×0.6×0.5 cm mass, which was diagnosed as a PMANEC. The Ki67 proliferation index was 15% in the solid component and 2% in the neuroendocrine component. The carcinoma was staged as T1NxMx according to the American Joint Committee on Cancer classification. Ectopic pancreatic tissue was not histologically identified. Magnetic resonance imaging was performed and showed no evidence of metastatic disease and a normal-appearing pancreas. The
neuroendocrine cells that constitutes at least 30% of the total synaptophysin (Figure 2). Based on these findings, the tumor was diagnosed as a MANEC of the stomach. The areas with trabecular morphology, representing >30% from 52 to 86 years. Most PMANECS, including our case, exhibited a heterogeneous pathology, with distinct acinar and neuroendocrine regions identifiable by light microscopy and immunohistochemistry. However, some PMANECS show a uniform cell population with two lines of differentiation when tested by immunohistochemistry (7, 12). Our case is similar to that reported by Fukunaga et al., who described a tumor with morphologically distinct acinar and neuroendocrine components (9). Of the cases previously reported, three were pure forms of pancreatic-type acinar cell carcinomas, two were PMANECS, and one was not subclassified.

The origin of gastric PMANECS has been debated, and two hypotheses have been proposed: The first is that gastric PMANECS arise from foci of pancreatic heterotopia or pancreatic acinar metaplasia of the gastric mucosa (10, 11); in the second, gastric PMANECS represent the bidirectional differentiation of pluripotential stem cells undergoing tumorigenesis (6, 7, 14). A heterotopic pancreas is uncommon, is usually found in the duodenum or in the gastric pyloro-antral region and is typically submucosal. Although the arising of ductal adenocarcinomas from ectopic pancreas is well documented (13, 14), heterotopic pancreas was not observed in any of the gastric PMANECS reported to date, including our case. However, in one of the reported cases, pancreatic acinar metaplasia of the gastric mucosa was described near the gastric PMANECS. In addition, it is possible that gastric MANEC derives from mucosal pluripotential stem cells (15), which, once transformed, are capable of giving origin to tumors with acinar and neuroendocrine differentiation.

The molecular characterization of the gastric MANECs reported by Fujita et al. (4) showed that these tumors did not harbor mutations of tumor protein 53 (TP53), Kirsten ras oncogene (KRAS), B-Raf protooncogene (BRAF), guanine nucleotide-binding alpha subunit (GNAS) genes. Instead, the authors reported allelic imbalances in 5q, 8p, 11q, and 22q in the solid component of the tumor and of only 11q in the glandular component. DNA methylation analyses showed a low methylation epigenotype for the tumor.

No molecular analysis was performed on our case. The precise prognosis and sensitivity to chemotherapy of this type of gastric tumor is unknown because of the small number of cases reported to date. Importantly, the original biopsy of our tumor only contained the neuroendocrine component, which was misdiagnosed as a low-grade gastric neuroendocrine tumor. Therefore, it is important to consider this diagnosis when performing a biopsy of a gastric mass showing neuroendocrine differentiation.

In conclusion, we reported a case of gastric MANEC which was misdiagnosed as a gastric neuroendocrine tumor on the initial biopsy containing only the neuroendocrine component. We reviewed the cases of this entity that have been reported to date. Additional studies are needed to clarify the pathogenesis, prognosis, and treatment options for this rare cancer.

Discussion

We present a case of PMANECS of the stomach, which was initially misdiagnosed as a gastric low-grade neuroendocrine tumor. Gastric PMANECS is extremely rare. A review of the English literature on this entity revealed only 13 published cases (6-9, 12, 13). MANEC is a variant of pancreatic acinar cell carcinoma, which was included in the 2017 WHO Classification of Tumors of Endocrine Organs (3). By definition, a PMANECS must contain a component of neuroendocrine cells that constitutes at least 30% of the total tumor (3). Adherence to this criterion is important because approximately 42% of acinar cell carcinomas may contain scattered endocrine cells (1, 2).

Our examination of the PMANECS cases hitherto reported in the English literature showed these tumors to be more common in men, with the average age of diagnosis ranging from 52 to 86 years. Most PMANECS, including our case, exhibit a heterogeneous pathology, with distinct acinar and neuroendocrine regions identifiable by light microscopy and immunohistochemistry. However, some PMANECS show a uniform cell population with two lines of differentiation when tested by immunohistochemistry (7, 12). Our case is similar to that reported by Fukunaga et al., who described a tumor with morphologically distinct acinar and neuroendocrine components (9). Of the cases previously reported, three were pure forms of pancreatic-type acinar cell carcinomas, two were PMANECS, and one was not subclassified.

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Conflicts of Interest

The Authors have no conflicts of interest to report.
Figure 1. The features of gastric pancreatic-type mixed acinar-neuroendocrine carcinoma (hematoxylin and eosin). A: Low-power view showing the tumor’s overall high cellularity, with minimal stroma and no evidence of desmoplastic reaction (bar=200 μm). B: Intermediate-power view showing tumor areas exhibiting a trabecular pattern and acinar structures with small lumina and basally located nuclei (bar=50 μm). C: High-power view showing one of the solid tumor areas characterized by monotonous cells with amphophilic cytoplasm and round nuclei exhibiting prominent nucleoli (bar=20 μm). Several mitoses are present.

Figure 2. Immunohistochemical features of the gastric pancreatic-type mixed acinar-neuroendocrine carcinoma. The tumor stained strongly for chymotrypsin (A; bar=100 μm) and BCL10 immune signaling adaptor (B; bar=100 μm). The neuroendocrine component was strongly and diffusely positive for synaptophysin (C; bar=50 μm). The adjacent area of acinar cell carcinoma component showed focal and weak synaptophysin positivity (C).
Authors’ Contributions

James Saller participated in staining interpretation and formulation of the diagnosis and drafted the article; Brooke Hough collected and tabulated the clinical pathological data and contributed to retrieving and cataloguing the references; Domenico Coppola designed the study, finalized the diagnosis, supervised the study and finalized the article.

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