Concomitant multifocal gastrinomas and adenocarcinoma in the stomach: A case report and literature review

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A B S T R A C T

The stomach is an uncommon location for gastrinomas. Here we report a rare case of multifocal gastrinomas in the antrum with concomitant gastric adenocarcinoma and neuroendocrine cell hyperplasia. The patient was a 35-year-old man who presented with mild upper abdominal discomfort for 3 months. Serum gastrin level was elevated to 542 pg/mL (normal: <100 pg/mL). Endoscopic examination revealed multiple polyps in the antrum, which proved to be carcinoid tumors on biopsy. Partial gastrectomy was performed. The surgical specimen contained multiple pedunculated polyps measuring up to 2 cm in greatest dimension. Additionally, many small, sessile polyps with central umbilication were identified in the antrum and the pylorus. Histological and immunohistochemical studies of the polyps showed nests of low-grade tumor cells that were positive for gastrin, confirming a diagnosis of multifocal gastrinoma. Incidentally, one large polyp was found to harbor a focus of poorly-differentiated adenocarcinoma with signet ring cell features. Diffuse enterochromaffin-like cell hyperplasia and small carcinoid tumors were identified in the body of the stomach. Regional lymph nodes were positive for both adenocarcinoma and gastrinoma. In addition, Helicobacter pylori-like organisms were detected in the antral mucosa. The post-operative course was uneventful, and the patient’s serum gastrin level dropped to 100 pg/mL. He is currently receiving chemotherapy for the adenocarcinoma. This is a rare case of multifocal gastrinoma in an unusual location. It has already been established that hypergastrinemia plays a role in the pathogenesis of gastric adenocarcinoma and neuroendocrine neoplasms. Therefore, it is important to rule out these concomitant lesions, both clinically and pathologically, when dealing with a proven gastrinoma.

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1. Introduction

Gastrinomas are gastrin-producing neuroendocrine tumors that lead to elevated serum gastrin levels, excessive gastric acid production, development of peptic ulcers, and diarrhea—the constellation of signs seen in Zollinger-Ellison syndrome. Gastrinomas can be sporadic or associated with genetic changes such as those present in multiple endocrine neoplasia type 1 (MEN1) syndrome. In MEN1 syndrome, gastrinomas are usually multifocal and arise in the duodenum. Less frequently, MEN1 patients may have a single gastrinoma in the pancreas. Most gastrinomas are found in the so-called “gastrinoma triangle,” which is defined by the junction of the neck and body of the pancreas, the point of transition of the second part of the duodenum into the third, and, finally, the confluence of the cystic and common bile ducts [1]. Gastrinomas outside of the triangle are rare and only a few cases have been reported in the liver, omentum, or gastric antrum [2]. Here we report a case of multifocal gastrinomas present in the antrum of the stomach. More interestingly, the patient was simultaneously found to have adenocarcinoma in the antrum, along with neuroendocrine cell hyperplasia and carcinoid formation in the body of stomach. These findings highlight the importance of a thorough work-up and extensive tissue sampling in gastrinoma patients.

2. Case summary

A 35-year-old man presented with mild upper abdominal pain for 3 months. Endoscopic examination revealed multiple antral polyps in the stomach. Serum gastrin level was elevated to 542 pg/mL (normal: <100 pg/mL). Microscopic analysis of the gastric biopsies showed that the polyps were carcinoid tumors. Since no other lesions were found in the duodenum or pancreas, partial gastrectomy and hepatic artery lymph node dissection were performed.

The surgical specimen included part of the corpus of the stomach as well as the antrum, proximal duodenum, and several lymph nodes. Six large, pedunculated polyps, measuring 1–2cm in diameter, and multiple (>20) small sessile polyps with central umbilication were grossly identified in the antrum and pylorus (Fig. 1). Pathological examination demonstrated that five out of the six large polyps and all of the small sessile polyps were composed of nests and trabeculae of tumor cells.
The tumor cells were monotonous with round nuclei, fine chromatin, conspicuous nucleoli, and rare mitotic figures. Immunohistochemistry on representative sections showed that the tumor cells were positive for gastrin, synaptophysin, and chromogranin A (Fig. 2C), confirming the diagnosis of multifocal well-differentiated gastrinomas.

One large polyp showed histology that was distinct from the other polyps of the gastrinomas (Fig. 3). It had irregular glands with prominent nuclear atypia and single cells with signet ring cell features. The tumor invaded into the submucosal tissue. The morphology was consistent with a poorly differentiated adenocarcinoma.

Two lymph nodes taken from the area around the hepatic artery were involved by metastatic gastrinoma (Fig. 2D), while a third lymph node near the duodenum was positive for metastatic adenocarcinoma.

Prominent neuroendocrine cell hyperplasia was present in the mucosa of the body of stomach (Fig. 4). These cells formed small clusters in the lamina propria and also showed a linear pattern at the base of the pits. A few foci of neuroendocrine cell hyperplasia were N0.5 mm in diameter and showed rare mitotic figures, fulfilling the diagnostic criteria of well-differentiated carcinoid tumor [3]. These hyperplastic foci and carcinoid tumors were positive for synaptophysin, yet negative

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for gastrin, suggesting they might be of enterochromaffin-like cell origin with the hyperplasia representing a response to the hypergastrinemia.

The antral mucosa showed moderate active chronic gastritis with numerous *Helicobacter pylori* organisms. No intestinal metaplasia or features of atrophic gastritis were identified. Immunostaining for gastrin demonstrated linear hyperplasia of gastrin-producing cells in the glands of antrum.

Postoperatively, the patient's serum gastrin levels dropped to 30 pg/mL. Due to the positive surgical margin for neuroendocrine cell hyperplasia and carcinoid tumor, a completion total gastrectomy was performed, which again showed neuroendocrine cell hyperplasia and small carcinoid tumors in the body and fundus of stomach. The patient uneventfully recovered from the surgeries. He is now receiving chemotherapy and has shown no evidence of recurrence or metastatic disease after more than one year's follow-up.

Work-up for MEN1 syndrome was done and the patient was found to have an elevated PTH level in his blood, as well as enlarged parathyroid glands. However, no tumors were detected in the pituitary gland, pancreas, or duodenum. The patient is currently under close follow up. The patient did not give consent for genetic testing.

### 3. Discussion

Gastrinomas are tumors of gastrin-producing G cells. The majority of gastrinomas are found in the "gastrinoma triangle" including the duodenum and the head of pancreas. Only a few case reports of a gastrinoma arising in the gastric antrum have been published [4,5]. The current case, to our best knowledge, is the first report of multifocal gastrinomas in the antrum. It is interesting to note that the incidence of gastrinomas in different locations does not go along with the number or
concentration of G cells normally present in the tissue at these locations. While G cells are normally abundant in the antral mucosa of stomach, they are present to a much lesser degree, in normal duodenal mucosa [6,7]. In the pancreas, G cells are transiently present in neonates but absent in adults [8]. It remains unclear why most gastrinomas are found in locations such as the duodenum and pancreas, but rarely in the antrum. One hypothesis could be that gastrinomas may derive from some precursors/stem cells instead of differentiated G cells. Experimental studies are warranted to further explore the underlying mechanisms.

In our case, the additional finding of adenocarcinoma was unexpected. Rare cases of co-existing gastric adenocarcinomas and gastrinomas have been reported in the literature, either as a collision tumor [9] or as separate lesions [10]. These clinical observations suggest that gastrinomas may derive from some precursor/stem cells rather than differentiated G cells. Experimental studies are warranted to further explore the underlying mechanisms.

In addition to its role in carcinogenesis, gastrin has trophic effects on the enterochromaffin-like cells in the body and fundus of stomach, leading to neuroendocrine cell hyperplasia and neoplasia. According to the WHO 2010 classification, neuroendocrine cell hyperplasia of the stomach arises in three settings: type A, associated with secondary hypergastrinemia due to autoimmune gastritis; type B, associated with primary hypergastrinemia due to gastrinomas in Zollinger-Ellison or MEN1 syndrome; type C, sporadic tumors. In type B tumors, there is data showing the incidence of neuroendocrine cell tumors is much higher in MEN1 associated gastrinomas than in sporadic gastrinomas, suggesting that genetic factors, such as the MEN1 gene mutation, may sensitize the enterochromaffin-like cells to the trophic effects of gastrin [13]. Neuroendocrine cell hyperplasia and neoplasia arising in type A and B settings are classified predominantly by the size of the lesions: the term hyperplasia is used for lesions no > 150 μm in diameter; dysplasia for nodules 150–500 μm in diameter; micro-neuroendocrine tumor (micro-carcinoid) for nodules 500 μm to 5 mm; carcinoid tumor for nodules larger than 5 mm [3]. In our current patient, his young age, multifocal gastrinomas, and the presence of hyperparathyroidism strongly suggest the possibility of MEN1 syndrome. Based on the aforementioned criteria, this case was classified as type B neuroendocrine cell hyperplasia and carcinoid formation. Neuroendocrine cell tumors of types A and B are usually associated with a good prognosis, but type B tumors may behave more aggressively [14].

Neuroendocrine cell hyperplasia and neoplasia share the similar histological morphology and neuroendocrine marker expression profiles with gastrinomas, therefore, it is important to perform immunostaining for gastrin to differentiate the two entities. In our case, regional lymph nodes were positive for metastases with a neuroendocrine tumor that stained positive with the gastrin immunostain, making the multifocal gastrinomas in the antrum—not the enterochromaffin-like cell hyperplasia/carcinoids in the gastric corpus—the likely source of metastatic disease.

The patient had H. pylori organisms and associated gastritis in the antral mucosa. It is well established that H. pylori infection can cause a cascade of changes in the stomach, including gastritis, mucosal atrophy, decreased acid production, antral G cell hyperplasia, and hypergastrinemia [14]. This hypergastrinemia may contribute to the pathogenesis of adenocarcinoma and neuroendocrine cell hyperplasia and neoplasia. In addition, H. pylori infection by itself, independent of hypergastrinemia, can increase the incidence of gastric adenocarcinoma [11,12]. In our case, gastritis and gastrin-producing cell hyperplasia were seen in the antrum, which suggests that H. pylori infection may have contributed to the development of gastric adenocarcinoma and neuroendocrine cell hyperplasia. However, the gastritis was moderate and severe mucosal atrophy was not present. Therefore, the contribution of H. pylori infection to tumorigenesis in this case may have only been a minor one. Whether H. pylori infection is more carcinogenic in a setting of MEN1 associated gastrinoma remains undetermined.

In summary, this case of concomitant, multifocal gastrinomas, adenocarcinoma, and neuroendocrine cell hyperplasia and neoplasia in the stomach is a unique one. It inspired us to explore the complex roles of gastrin and H. pylori infection in tumorigenesis within the stomach. As for the implications for clinical practice, this case suggests that a thorough work-up should be performed in patients with gastrinoma to rule out any concomitant tumors, especially carcinomas.

References