

# Composite Neuroendocrine Carcinoma with Adenocarcinoma of the Stomach Misdiagnosed as a Giant Submucosal Tumor

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A composite glandular/exocrine-endocrine carcinoma of the gastrointestinal tract is characterized by the co-existence of two adjacent, but histologically-distinct tumors in an organ. Composite glandular/exocrine-endocrine carcinomas are a special type of tumor comprised of common adenocarcinomas and neuroendocrine components that account for at least one-third of the entire tumor area. Composite tumors have been reported in a range of organs, but are relatively rare in the stomach. We report a case of a composite neuroendocrine carcinoma with an adenocarcinoma of the stomach (mixed exocrine-endocrine carcinoma), which was misdiagnosed as a giant submucosal tumor preoperatively based on esophagogastroduodenoscopy and a contrast-enhanced axial computed tomographic scan.

**Key Words:** Composite tumor, Stomach, Submucosal tumor

## Introduction

Human cancers exhibiting a combination of conventional (glandular, squamous, or urothelial) and neuroendocrine features occur in various organs. Such lesions are classified into two subgroups: composite and collision-type tumors.(1,2) Composite neuroendocrine carcinomas with adenocarcinomas occur throughout the gastrointestinal tract, but rarely occur in the stomach.(3) The histogenesis of composite tumors is unclear, but both types of carcinomas may be derived from the same cell, most likely a pluripotent stem cell. Composite neuroendocrine carcinomas with adenocarcinoma in the stomach can be diagnosed if neuroendocrine marker shows a positive reaction in the immunohistochemical staining of the component of the neuroendocrine carcinoma.(4)

We report a case of a composite neuroendocrine carcinoma with adenocarcinoma of the stomach (mixed exocrine-endocrine

carcinoma), which was misdiagnosed as a giant gastric submucosal tumor preoperatively by esophagogastroduodenoscopy (EGD) and contrast-enhanced axial computed tomographic (CT) scan. By immunohistochemical staining of the neuroendocrine carcinoma component, the tumor was identified as a composite neuroendocrine carcinoma with adenocarcinoma of the stomach. We report this rare case with a review of the literature.

## Case Report

A 62-year-old woman underwent EGD, abdominal CT and abdominal ultrasonography as part of an evaluation for epigastric discomfort. Her past medical and family histories were unremarkable. The physical examination on admission, routine blood tests, and urine analysis were also unremarkable. The levels of tumor markers were within the reference range, as follows: carcinoembryonic antigen (CEA), 5.21 ng/ml (normal,  $\leq 8$  ng/ml); CA 19-9, 10.49 U/ml (normal,  $\leq 37$  U/ml); and CA 72-4, 0.289 ng/ml (normal,  $\leq 6.9$  ng/ml).

The EGD revealed a huge, well-defined, fungating, submucosal mass with eccentric ulceration characterized by an ill-defined margin in lesser curvature of the gastric antrum (Fig. 1). An EGD

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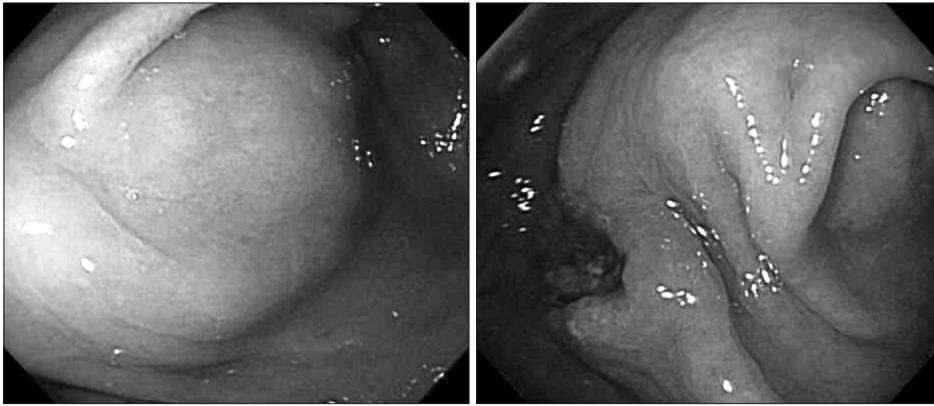
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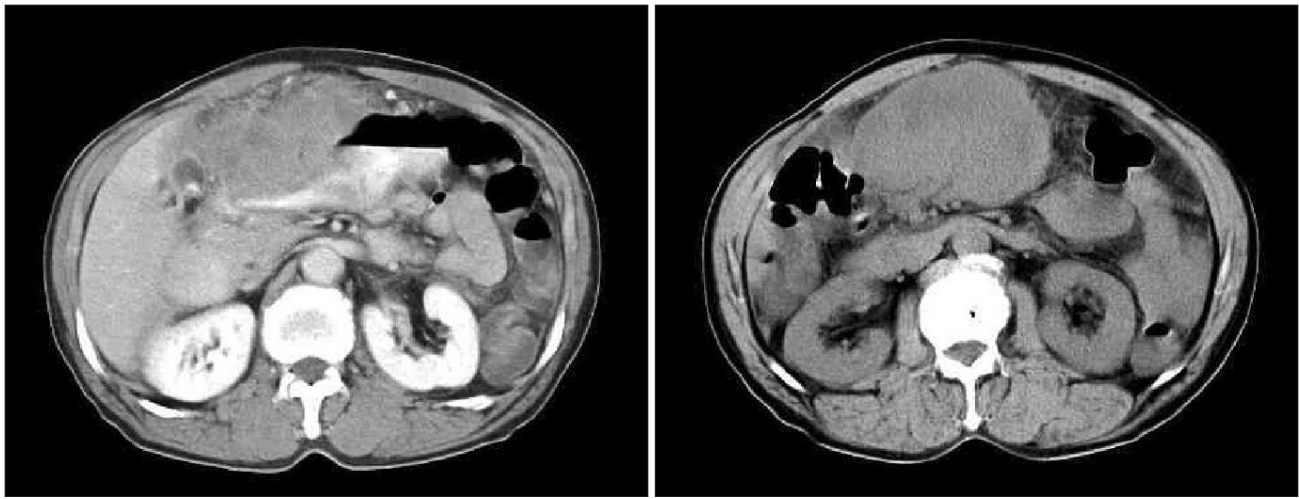
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**Fig. 1.** Gastroduodenoscopy shows a huge, well-defined fungating submucosal mass, measuring 10 cm in its largest dimension with eccentric ulceration and an ill-defined margin in the gastric antrum, lesser curvature.



**Fig. 2.** Preoperative contrast-enhanced axial CT scan shows a huge, solid, ovoid, heterogeneous and exophytic mass measuring approximately 15×10 cm in the prepyloric antrum of the stomach.

biopsy was not performed because a biopsy is not generally recommended for the diagnosis of gastric submucosal tumors. A contrast-enhanced axial CT scan demonstrated a huge, solid, ovoid, heterogeneous, exophytic mass measuring approximately 15×10 cm in the pre-pyloric antrum of the stomach with several metastasis into the lymphatic glands around the stomach was observed (Fig. 2). A diagnosis of a giant submucosal tumor of the stomach with lymph node metastasis was made, and a radical subtotal gastrectomy with D2 lymph node dissection was subsequently performed.

Grossly, a diffuse submucosal bulging mass was noted in the surgically-resected stomach. The mass-measure 17×15×6.5 cm, and had an intact mucosa, with the exception of a small polypoid nodule with a central ulcerated umbilication measuring 1.5×1 cm. On sectioning, the cut surface of the mass showed a diffuse, geographic, hemorrhagic, necrotic area with a cleft-like cystic change and grayish-brown solid area which infiltrated to the surrounding omental fat tissue.

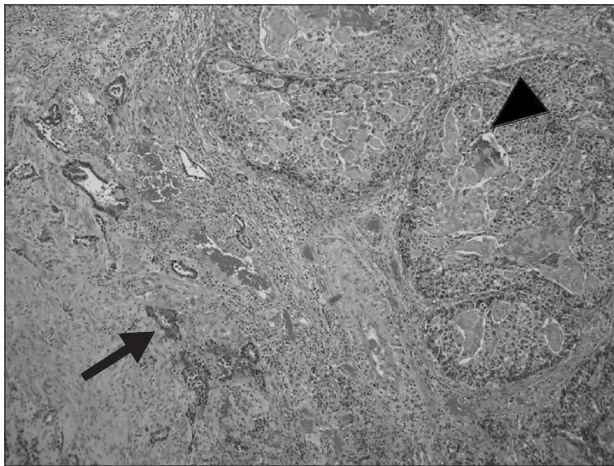
Microscopically, the tumor was comprised of a conventional

adenocarcinoma with anaplastic glandular nests and a neuroendocrine carcinoma with central necrosis (Fig. 3). The glandular carcinoma was confined to the mucosa and submucosa, the neuroendocrine carcinoma had invaded into the serosa and the lymphatic glands. Two of 39 lymph nodes had metastases, and lymphatic and perineural invasion were observed. Immunohistochemically, the tumor cells exhibited immunopositivity for chromogranin A and synaptophysin, but negativity for CD56, CD117, CD34, and SMA. The neuroendocrine carcinoma components showed strong immunopositivity for chromogranin A, but were negative for the adenocarcinoma component (Fig. 4).

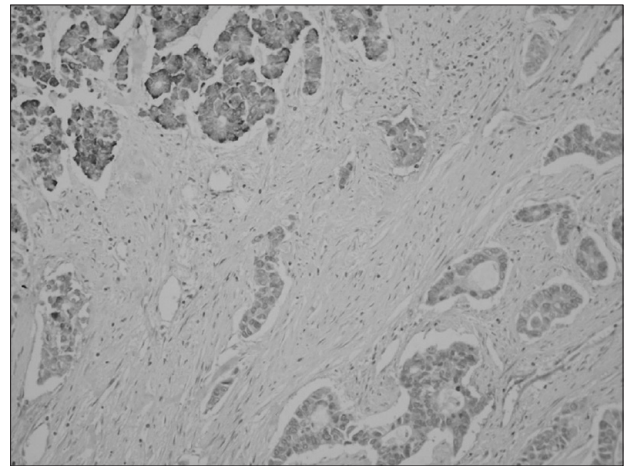
The post-operative course was uneventful and the patient was discharged on the 9th postoperative day.

## Discussion

Submucosal tumors refer to tumors that exist below the mucosal layer and protrude into the lumen in a hemispherical or spherical



**Fig. 3.** The tumor is composed of conventional adenocarcinoma with anaplastic glandular nests (arrow) and neuroendocrine carcinoma with central necrosis (arrow head) (H&E,  $\times 100$ ).



**Fig. 4.** Neuroendocrine carcinoma components show strong immunopositivity for chromogranin A (left upper), but negative immunostaining of adenocarcinoma component (right lower) (Immunohistochemical stain,  $\times 200$ ).

shape because of the surrounding mucosa on the surface.

Submucosal tumors can cause symptoms, such as bleeding, but in most cases, submucosal tumors are detected incidentally during gastroduodenoscopy or an upper GI series. On routine EGD, the rate of diagnosing submucosal tumors is approximately 0.36%. (5) Submucosal tumors that usually occur in the stomach include gastrointestinal stromal tumors (GISTs), leiomyomas, leiomyosarcomas, lipomas, and carcinoids. However, the gastric cancers with a pattern of submucosal tumors are very rare, accounting for 0.1~0.62% of resected gastric cancers.(5,6) The pathologic diagnosis of most gastric cancers is an adenocarcinoma. In our case, a giant protruding lesion covered with gastric mucosa was noted during the pre-operative EGD, and the origin of the tumor was located in the submucosal muscularis propria layer, as demonstrated by a contrast-enhanced axial CT scan. Therefore, we diagnosed the tumor clinically as a malignant gastric GIST and performed a radical subtotal gastrectomy.

Composite glandular/exocrine-endocrine carcinomas of the gastrointestinal tract are special tumors comprised of common adenocarcinomas with neuroendocrine components, and accounts for at least one-third of the entire tumor area. Glandular-endocrine tumors of the digestive tract have rarely been described in the medical literature because the classification, which restricts the term “mixed” to lesions in which the endocrine cells account for between about one-third and one-half of all cells, and proposed a classification for such neoplasms distinguishing (a) composite (or mixed) glandular-endocrine tumors with both elements in more or less equal proportions, (b) amphicrine tumors with dual differentia-

tion within the same cell, and (c) collision tumors in which the two components are juxtaposed, but not admixed.(6) According to this classification, the case herein was a composite glandular-endocrine carcinoma.

More recently, Fujiyoshi et al.(7) reclassified mixed endocrine and non-endocrine epithelial tumors by dividing the tumors into six categories: 1) neuroendocrine cells interspersed within carcinomas; 2) carcinoids (neuroendocrine tumors [NETs]) with interspersed non-endocrine cells; 3) composite glandular-neuroendocrine cell carcinomas containing areas of carcinoid and conventional carcinomas; 4) collision tumors in which NETs and conventional carcinomas are closely juxtaposed, but not admixed; 5) amphicrine tumors predominantly composed of cells exhibiting concurrent neuroendocrine and non-endocrine differentiation; and 6) combinations of the previous types. According to this classification, our case could be classified as a composite glandular-endocrine carcinoma containing mainly a NET with small areas of a conventional carcinoma.

Composite neuroendocrine carcinomas with adenocarcinomas in the stomach can be diagnosed if at least one of the neuroendocrine markers, such as chromogranin A, synaptophysin, and NSE has a positive reaction in the immunohistochemical staining of the neuroendocrine carcinoma component.(4) In the case herein, the component of the neuroendocrine carcinoma had a strong positive response to chromogranin A, which is a neuroendocrine marker, but the adenocarcinoma component was negative (Fig. 4).

With the exception of the appendix, only rare instances of composite tumors have been detected in the esophagus, stomach,

gallbladder, and the small and large bowel. However, it is possible that before the advent of immunohistochemistry, the true incidence of composite tumors was underestimated.

The histologic origin of composite tumors is unclear. In rats with hypergastrinemia, enterochromaffin-like cells have the capacity to dedifferentiate and become potential precursors of gastric adenocarcinomas.(8,9) Some authors have postulated proliferation of a pluripotential precursor cell,(10–12) and studies describing common genetic alterations in the glandular and neuroendocrine component of mixed tumors support the latter hypothesis.(12)

Because of their rarity and uncertain pathologic criteria, the clinical behavior and histogenesis of composite tumors is still unclear, but Volante et al.(13) reported that the clinical behavior of composite carcinomas depends on the adenocarcinomatous component if the associated endocrine component is well-differentiated, and upon the neuroendocrine component if it is poorly-differentiated. In this case, although the glandular carcinoma was confined to the mucosa and submucosa, the neuroendocrine carcinoma had invaded into the serosa and the lymphatic glands. Therefore, the neuroendocrine component of this case was believed to impact heavily on the prognosis and we performed chemotherapy based on the neuroendocrine carcinoma.

Treatment of neuroendocrine cancers that occur in the stomach is based on radical surgical resection. In cases of distant metastasis, such as liver metastasis, a gastrectomy with hepatectomy is effective treatment.(14) Chemotherapeutic regimens, including cisplatin, doxorubicin, and vincristine can be administered to neuroendocrine carcinoma patients. Because combination treatment of cisplatin and etoposide after gastrectomy has been reported to result in reduction of liver metastasis by 96% and lung metastasis by 81%, chemotherapy has recently been recommended to be administered following gastrectomy; however, the efficacy has not been fully verified due to the low incidence.(15)

In summary, we initially misdiagnosed the tumor as a giant gastric submucosal tumor by EGD and contrast-enhanced axial CT scan, and subsequently performed surgical resection. However, in retrospect, metastasis into the lymphatic glands around the stomach was observed in the pre-operative contrast-enhanced axial CT scan, and eccentric ulceration with an ill-defined margin was noted on EGD, which could have been diagnosed as metastasis into the lymphatic glands around the stomach secondary to gastric cancer. Therefore, if a submucosal tumor is large and eccentric ulceration with ill-defined margins is observed with lymphatic gland metastasis around the stomach, an adenocarcinoma, and although ex-

tremely rare, a composite glandular–endocrine carcinoma containing a conventional carcinoma should be taken into consideration in the differential diagnosis.

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