

# Gastric Mixed Adenoneuroendocrine Carcinoma Occurring 50 Years after a Gastroenterostomy with Braun Anastomosis

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## Key Words

Neuroendocrine carcinoma · Gastroenterostomy · Mixed adenoneuroendocrine carcinoma · Braun enteroenterostomy

## Abstract

A 75-year-old man was diagnosed with gastric cancer. Fifty years previously, he had undergone gastroenterostomy with a Braun enteroenterostomy. At present, a distal gastrectomy and small intestinal partial resection were performed. Intraoperatively, the tumor was localized to the previous stomal site. HE staining showed that the tumor comprised two elements: a tubular adenocarcinoma on the gastric side and a neuroendocrine carcinoma (NEC) on the jejunal side. The final pathologic diagnosis was mixed adenoneuroendocrine carcinoma based on an immunohistochemical analysis of endocrine markers and an elevated Ki-67 labeling index. The risk of later cancer development cancer recurrence near the gastrojejunoostomy site is well known. Potentially, chronic enterogastric bile reflux may irritate the gastric mucosa and act as a promoter. Gastric NEC has a strong malignant potential. We suspect that, in the present case, the constant exposure to secondary bile may have induced a gastric mucosal adenocarcinoma, which finally differentiated into a NEC.

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## Introduction

Distal gastrectomy is a well-known risk factor for developing gastric stump cancer later [1]. In particular, cancer frequently occurs near the gastrojejunostomy site in the remnant stomach following a Billroth II reconstruction [2]. Gastroenterostomy (GE) may also result in the later development of gastric cancer [3]. One proposed theory is that the enterogastric reflux of bile and pancreatic secretions chronically irritate the gastric mucosa promoting neoplasia [1]. Gastric neuroendocrine carcinoma (NEC) is an uncommon tumor with a strong malignant potential and an extremely poor prognosis [4]. In the present case report, we describe a patient who had undergone GE with Braun enteroenterostomy (BEE) 50 years prior to presentation and had developed a mixed adenoneuroendocrine carcinoma (MANEC) at the anastomotic site. This is the first known case reported.

## Case Report

A 75-year-old man was diagnosed with gastric cancer in June 2012 at Showa University Fujigaoka Hospital. Fifty years previously, he had undergone a gastric bypass operation with a loop gastrojejunostomy to treat stenosis caused by a duodenal ulcer.

His medical history included chronic renal failure (managed with hemodialysis), right idiopathic pleural effusion, third degree AV block (managed by a pacemaker), and myelodysplastic syndrome. As of 2006, chronic gastric hemorrhage had been observed at the GE anastomotic site, and endoscopy was performed. In June 2012, an upper gastrointestinal endoscopy revealed a slightly irregular mucosa surrounded by a smooth elevated area at the stomal site. The irregular mucosa was biopsied, and a papillary and tubular adenocarcinoma were diagnosed. Endoscopic ultrasonography revealed that the tumor extended to the muscularis propria. CT showed an enlarged lymph node on the lesser curve of the stomach, which is suggestive of metastasis. However, the gastric wall did not appear thickened, which can occur secondary to neoplasia, and there was no indication of distant metastasis. The cancer was diagnosed as T2 N1 M0 stage IIB according to the TNM classification. Since the patient already had poor systemic function, surgery carried a very high risk of morbidity and mortality. Similarly, cancer chemotherapy could not be initiated. The surgeon repeatedly discussed the treatment options with the patient who ultimately elected surgical excision to avoid potential obstruction and hemorrhage at the stomal site. In October 2012, a distal gastrectomy, a small intestinal partial resection (afferent and efferent loops) and a Roux-Y reconstruction were performed.

During the laparotomy, hepatic sclerosis and ascites were observed. The significant collateral vasculature and the strong adhesion between the stomach and the liver and between the jejunum and the transverse colon from the previous GE made surgery difficult. Numerous firm and small lymph nodes were identified in the lesser omentum and suspected to be metastatic. A small intestinal partial resection, including the BEE site, was performed followed by a distal gastrectomy. Metastasis was observed in the common hepatic arterial lymph nodes similar to the metastasis observed in the para-aortic nodes, and a curative resection was deemed impossible. The surgery lasted 6 h, and there was a 1,492-ml intraoperative hemorrhage. Immediately after transferring the patient to the intensive care unit, he suddenly stopped breathing, and resuscitation was initiated. It progressed into multiple organ failure and the patient died in December 2012.

The surgical specimen is illustrated in [figure 1](#). A 5 × 4 cm type-5 lesion was identified in the posterior wall at the stomal site on gross pathologic examination. HE staining ([fig. 2](#))

showed that the tumor histologically comprised two elements: a tubular adenocarcinoma on the gastric side and NEC-like cells in a typical mass lesion comprising infiltrating nests of small uniform tumor cells on the jejunal side, which made up 40% of the tumor. The gastric mucosa adjacent to the tumor did not show evidence of gastritis. Immunohistochemistry (fig. 3) showed that the NEC-like cells were positive for neural cell adhesion molecules and partially positive for synaptophysin and somatostatin receptor type 2, but negative for chromogranin A. The Ki-67 labeling index was >20%. The final pathological diagnosis was MANEC, according to the 2010 WHO classification system for digestive neuroendocrine tumors.

## Discussion

Since the first reports of carcinoma developing at the gastric remnant after gastrectomy appeared in the 1950s, numerous cases have been reported [3]. Notably, patients who underwent a Billroth II gastrectomy developed stump carcinomas most frequently in the anastomotic area, whereas in patients who underwent a Billroth I gastrectomy, neoplasia was more frequently located outside the surgical stump [2]. A late development of stomal gastric cancer has also been reported following GE without concurrent gastric resection [3]. A prior study of anastomotic carcinoma revealed that the tumor rarely invades the jejunum at the stoma [3]. Persistent secondary bile reflux promotes chronic gastritis and eventual metaplasia, which is a likely precursor of neoplasia [1]. Nishidoi et al. [5] hypothesized that duodenogastric reflux causes the development of remnant gastric carcinoma in MNNG-treated rats. In a clinical study by Tanigawa et al. [6], p53-positive cells increased at the anastomosis site of Billroth II procedures, which may reflect increased DNA damage secondary to active gastritis. In 1893, Braun introduced the enteroenterostomy anastomosis between the afferent and efferent limbs immediately distal to a GE. Using radionuclide biliary scanning, Vogel et al. [7] found that BEE adequately diverts a substantial amount of bile from the stomach in patients undergoing GE or Billroth II resection. This would presumably prevent stomal cancer development secondary to bile reflux. However, using a rat model, Wieman et al. [8] found that the diversion of duodenal secretions away from the GE did not alter the carcinoma incidence. Similarly, in a clinical study of 22 Japanese patients who developed stomal cancer after GE, Ichikawa et al. [9] reported that BEE did not prevent cancer development in the 10 patients who underwent the procedure. In our case, stomal cancer could also not be prevented by BEE.

Gastric NEC is an uncommon tumor, which reportedly comprises 0.1–0.6% of gastric cancers [10] and typically possesses adenocarcinoma components [4]. Definitive diagnosis of mixed NEC by endoscopic biopsy is thought to be difficult; in previous reports, the adenocarcinoma portion covered the surface mucosa [11], while the NEC developed in the submucosa and deeper layers [12]. Indeed, although our patient underwent annual endoscopies yearly, his anastomotic NEC was quite advanced at the time of diagnosis.

According to the 2010 WHO classification system, neuroendocrine neoplasms of the digestive system are a diverse group that includes neuroendocrine tumors, which are well differentiated and graded according to their proliferative activity as G1 or G2 as well as NECs, which are poorly differentiated and graded as G3. Adenocarcinoma components constituted >30% of the tumor in our case, fulfilling the criteria for a MANEC as defined by the WHO classification [13]. The prognosis of patients with gastric NEC is extremely poor because the tumor behaves aggressively and frequently metastasizes to the liver and lymph nodes, even during the early stages [10].

This particular case of NEC at a GE anastomotic site is the first known report in the English literature. In Japan, 6 cases with various diagnoses of stomal NECs, including neuroendocrine cell carcinoma, endocrine cell carcinoma, and small cell carcinoma, have been reported so far (table 1) [14–19]. These cases were diagnosed by histochemical neuroendocrine markers but were not evaluated according to their proliferative activity. The Ki-67 labeling index is the most characterized proliferation-associated marker and has been proposed as an important parameter in defining NECs [20]. In 5 of the aforementioned Japanese patients who underwent GE without BEE, the duration between initial surgery and stump carcinoma diagnosis ranged from 20 to 47 years. BEE was performed only in the present case, which had the longest duration between initial surgery and cancer development. Except for case 6, the patients diagnosed with stomal NEC had a short survival time lasting less than 1 year.

Fukui et al. [21] previously reported on concurrent gastric adenocarcinoma and duodenal neuroendocrine cell carcinoma. They described a pyloric tumor extending to the duodenum beyond the pyloric ring. Histopathological examination revealed that the gastric portion was an adenocarcinoma, while the duodenal portion was a NEC. The NEC component was clearly distinguishable from the pyloric ring adenocarcinoma, not only at the anatomic junction, but also at the environmental border between these two organs. Similarly, in our case we observed an NEC on the jejunal side of the tumor and an adenocarcinoma inside the tumor. Previous studies have reported on neuroendocrine differentiation in the gastric adenocarcinoma [20]. In a genome-wide LOH study, Kim et al. [22] concluded that most mixed glandular gastric NECs evolved from a glandular precursor prior to neuroendocrine differentiation, and occasionally, dual differentiation concurrently arose from a single precursor. We surmise that in our case, the constant exposure to secondary bile may have induced a gastric mucosal adenocarcinoma, which finally differentiated into a NEC. The aforementioned Japanese cases were mostly pure NEC, and the mixed type was only observed in one case. Eventually, the remaining adenocarcinoma portion in our case might have been replaced by the NEC.

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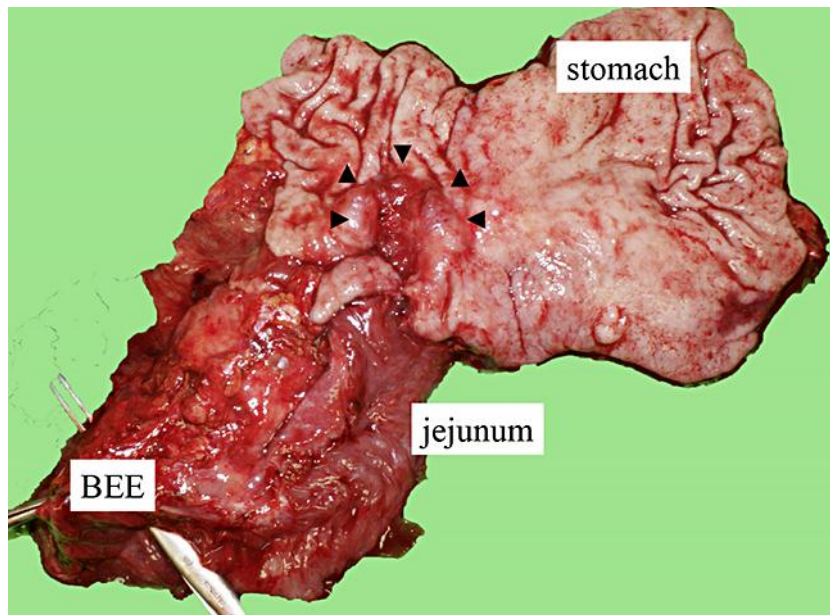
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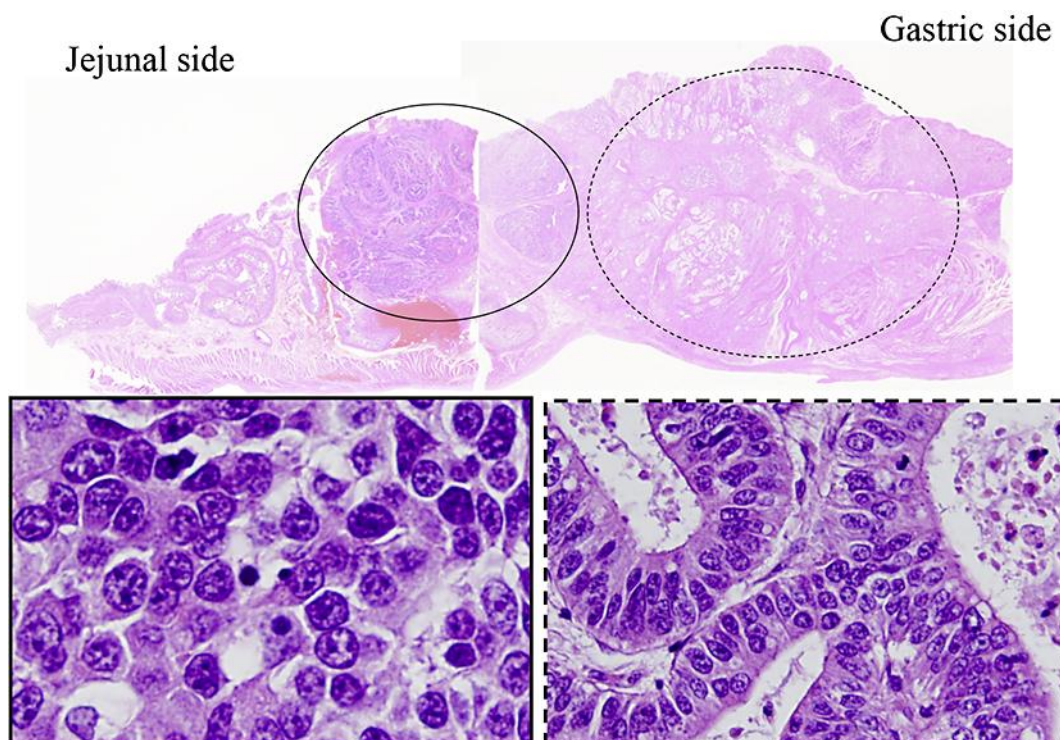
**Table 1.** Diagnosed stomal NECs following gastroenterostomy in Japanese patients

Case number	Age, years	Metastasis	WHO classification	Immunohistochemical staining	Original surgery	BEE	Time between original surgery and NEC diagnosis (years)	Survival time, months
1 [14]	75	L	SCC	NSE (+)	B-II	(-)	44	2
2 [15]	73	L, Ad, N	ECC	Serotonin (+)	B-II	unknown	22	3
3 [16]	69	N	NEC	CA (+), Sy (+)	B-II	(-)	20	7
4 [17]	83	N	ECC Adenocarcinoma	Sy (+)	B-II	(-)	46	8
5 [18]	82	N	ECC	Sy (+), NCAM (+), NSE (+), CA (-)	B-II	(-)	45	6
6 [19]	57	N	SCC	Sy (+), NSE (+), CA (+)	GE	(-)	47	21
Our case	75	N	MANEC	Sy (+), NCAM (+), SSTR2 (+), CA (-)	GE	(+)	50	1.5

All patients were male. L = Liver; Ad = adrenal gland; N = lymph node; SCC = small cell carcinoma; ECC = endocrine cell carcinoma; CA = chromogranin A; Sy = synaptophysin; NCAM = neural cell adhesion molecule; SSTR2 = somatostatin receptor 2; B-II = Billroth II gastrectomy.

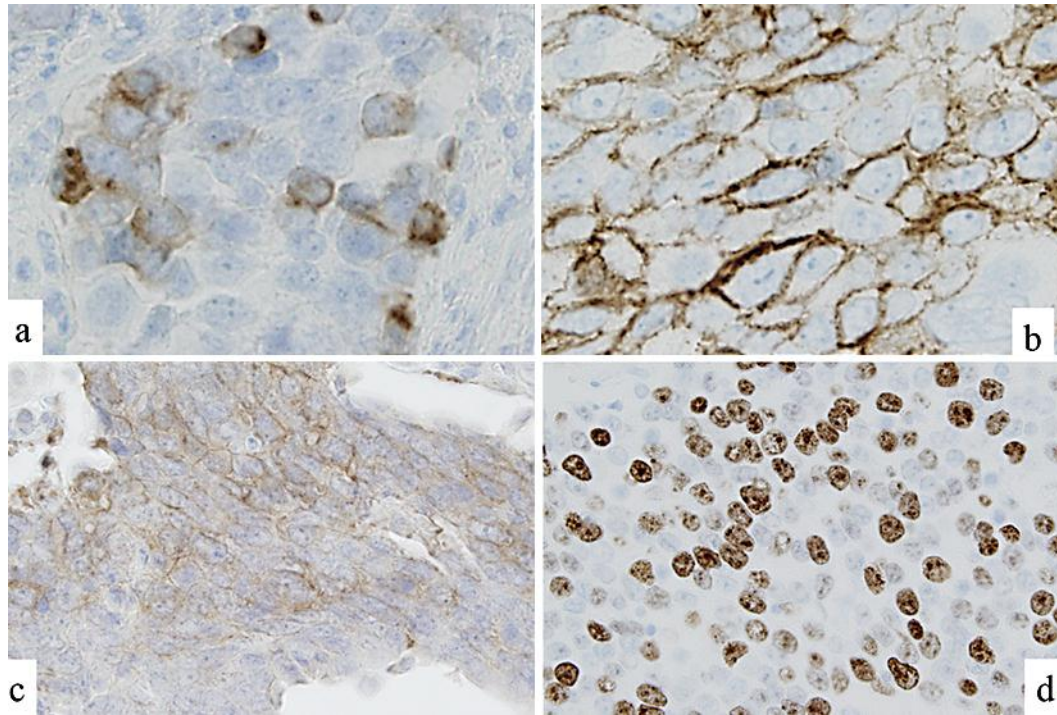


**Fig. 1.** Macroscopic appearance of the resected surgical specimen. Arrowheads: anastomotic cancer at the GE stomal site.



**Fig. 2.** Histological findings of the stomal cancer by HE staining. The tumor histologically comprised two elements: a tubular adenocarcinoma on the gastric side (dashed line), and NEC-like cells in a typical mass comprising infiltrative nests of small uniform tumor cells on the jejunal side (solid line).

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**Fig. 3.** Immunohistochemical staining of the NEC-like jejunal cells. **a** Partially positive staining for synaptophysin. **b** Positive staining for neural cell adhesion molecules. **c** Partially positive staining for synaptophysin and somatostatin receptor type 2. **d** The Ki-67 labeling index was >20%.