

# Pancreatic-Type Mixed Acinar Neuroendocrine Carcinoma of the Stomach: A Case Report And Review of Literature

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## Case Report

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# Abstract

**Background:** A majority of gastrointestinal tumors are adenocarcinoma. Rarely, there is also a type of tumors such as acinar cell carcinoma, which are often called pancreatic-type acinar cell carcinoma. Among those, some are differentiated into neuroendocrine components. A few of them can be called MiNENs.

**Case presentation:** The patient was an 80-year old male who was referred to our hospital for treatments of a pedunculated gastric tumor. It was 5 cm in diameter and detected in the upper gastric body with upper GI endoscopy conducted for investigation of anemia. In the biopsy, although a kind of hyperplasia of gastric gland cell was pointed out, no tumor cells were found. Retrospectively, the diagnosis was turned out to be a misdiagnosis. An operation was arranged because bleeding from the tumor was suspected as a cause of anemia and because a surgical resection was considered to be desirable for accurate diagnosis. Hence, laparoscopy and endoscopy cooperative surgery was performed. In pathological examination, several types of epithelial cells which proliferated in the area between mucosa and deep inside the submucosa were observed. These consisted of acinar-glandular/trabecular patterns and solid pattern. A diagnosis of pancreatic-type acinar cell carcinoma of the stomach with NET G2 and G3 was made based on characteristic cellular findings and the result of immunostaining tests. Each of them consisted of more than 30% of the lesion; a diagnosis of pancreatic-type mixed acinar neuroendocrine carcinoma (pancreatic-type MiNEN) of the stomach, or a type of gastric MiNEN was obtained. Anemia was resolved after operation, and the patient was discharged from the hospital without perioperative complications.

**Conclusions:** Pancreatic-type ACC of the stomach which is differentiated into neuroendocrine tumor is very rare. Hence, we report this case along with several literature reviews.

## Background

Acinar cell carcinoma (ACC) is a rare type of tumor which consists of 1–2% of pancreatic tumors<sup>1</sup>. In 2002, Fukunaga<sup>2</sup> reported for the first time an ACC case which developed in the stomach. Since then, several cases of pancreatic-type acinar cell carcinoma of the stomach have been reported. The term of “pancreatic-type acinar cell carcinoma”, which Sun et al.<sup>3</sup> firstly used in a case of gastric cancer, has been also used in gastrointestinal and hepatobiliary system except stomach.

In 2019, WHO classification of neuroendocrine neoplasms was modified; Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN) are mixed epithelial neoplasms in which a neuroendocrine component is combined with a non-neuroendocrine component, each of which is morphologically and immunohistochemically recognizable as a discrete component and constitutes > 30% of the neoplasm<sup>4</sup>. ACCs which develop in extra-pancreatic tissues and MiNENs are so rare that the characteristics of them have not yet been well understood. We report here a case of pancreatic-type mixed acinar neuroendocrine carcinoma (pancreatic-type MiNEN) of the stomach (gastric MiNEN) with some reviews.

## Case Presentation

The patient was an 80-year old male who had been followed up for hypertension and dyslipidemia. His height was 167 cm and weight 69.7 kg, and he had a surgical history of appendectomy for appendicitis. Anemia was observed in the conjunctiva. The abdomen was flat and soft without tenderness. There was a surgical scar from appendectomy. No superficial lymph node was palpated.

In the blood test, Hb level was 10.2, suggesting anemia. AMY at 66 IU/L was within a reference range, and no abnormality was observed in other blood biochemistry tests. Tumor markers were CEA 1.9 ng/mL and CA19-9 13.6 U/mL, both were within the reference range. A pedunculated gastric tumor was detected in the upper gastric body with upper gastrointestinal endoscopy (Fig. 1). Reddish change which may indicate epithelial tumor was detected on the apex of the tumor. Ulcer formation was observed, and invasion to the submucosal tissues could not be denied. There was no obvious bleeding detected in this examination. A biopsy was performed, and histopathologically malignancy was not revealed. A kind of gastric gland cell hyperplasia was made, probably because it seems that no clear atypia was found in the specimen.

In abdominal/pelvic computed tomography (Fig. 2), a neoplastic lesion of 5 cm in diameter was observed in the upper gastric body. As it located on the pyloric side of the upper gastric body, pyloric obstruction was also suspected. There was no finding which suggested pancreatic tumor, lymphadenopathy, or metastatic lesions. No ascites was observed.

A surgical operation was arranged due to the following reasons: bleeding from the tumor was suspected as a cause of anemia, ball valve syndrome had been induced by the tumor, possibility of malignancy could not be ruled out, and risk of incomplete resection or bleeding was considered high with endoscopic resection.

A tumor incarcerated from the greater curvature of the upper gastric body to the duodenum was guided into the gastric cavity under endoscopic observation, and laparoscopy endoscopy cooperative surgery was performed. The first port was inserted through the umbilicus by minilaparotomy, and the operation was started with a total of 4 ports. No abnormality was detected on the surface of gastric serosa. The omental bursa was released at the greater curvature of the middle gastric body and separated up to near the root of the left gastroepiploic blood vessel in order to mobilize the stomach. Under endoscopic observation, the tumor which had been incarcerated into the duodenum was guided inside the gastric cavity using forceps. The tumor was located at the greater curvature of the upper gastric body. After leaving a mark, the blood vessels around the tumor were processed. A small incision of about 6 cm was made on the left upper abdomen, and the stomach was guided out the body. An incision was made on the caudal side of the tumor, and to flip the tumor. Full thickness resection was performed while maintaining about 10 mm of margin. The resected site was closed with layer-to-layer suture to complete the operation.

Macroscopically, an elastic-hard grayish-white solid neoplastic lesion of 3.5 × 3.3 × 2.5 cm protruded inside the gastric cavity was observed. Some parts were edematous on the sectional surface, and no necrosis or bleeding was observed (Fig. 3, 4).

Whole section slides from the resected tissues were made. Histologically, the lesion was consisted of a remarkable proliferation of several types of epithelial cells in the mucosa and submucosa. The border of the lesion was very irregular in the mucosa or the upper layer of the lesion, however, clear in the submucosa or middle and deep inside layer of the lesion with partial fibrosis and capsule. The propria muscularis was not involved. Proliferating epithelial cells showed basically acinar-glandular, trabecular and solid patterns (Fig. 5). These patterns were seen separately in some parts and intermingled with one another in other parts. Small amounts of stromal mucus deposition were found in some parts of the upper layer of the lesion. As for the general tendency, the solid pattern was mainly found in the mucosa or the upper and superficial layer of the lesion, while the acinar-glandular and the trabecular patterns were observed in the submucosa or middle and deep inside of the lesion. Since the morphological atypia of these proliferative epithelial cells was not outstanding and these cells resembled well pancreatic acinar cells, a possibility of a special type of ectopic pancreas was considered at first. However, normal pancreatic cells (e.g. acinar, ductal, islet cells) which support a diagnosis of heterotopic pancreas were not revealed at all.

The cells which proliferated as acinar-glandular and trabecular patterns (Fig. 5a and 5b) had contained eccentric nuclei, which appeared to be slightly swollen presenting clear nucleoli, as well as eosinophilic granules inside the cells. The cells which proliferated as the solid pattern (Fig. 5c) had oval nuclei, presenting salt and pepper-like chromatin which had distributed heterogeneously, and slightly eosinophilic granules inside the cells. Aggregation/mixture of small cells and large cells were also observed on an image (Fig. 5d). Although clear atypical cells were rare for each type, the characteristics of the nuclei and nucleoli of the cells above mentioned and irregularity of the border of the lesion in the mucosa or the upper layer led us to an idea that the lesion may be acinar cell carcinoma with some neuroendocrine features.

To confirm the idea, immunostaining was performed using various pancreas-related markers or neuroendocrine markers. Immunostaining tests revealed that most of the lesion was strongly positive for BCL-10 antibody (Fig. 6a) and Trypsin, but negative or weak in some small parts of the upper layer of the lesion. In addition, strongly positive results were obtained for Chromogranin A, Synaptophysin, CD56 neuroendocrine markers especially in the upper layer of the lesion, in which the negative or weak parts for BCL-10 and Trypsin were almost positive. As to neuroendocrine reactivity on this case, Chromogranin A was most remarkable among three neuroendocrine markers, suggesting that it accounted for 40% of the lesion (Fig. 6b). Concerning on mitotic rate and Ki-67 index of the lesion, acinar-glandular and trabecular cells proliferated mainly in the submucosa or middle and inside of the lesion were < 2 and < 3% respectively, while solid cells proliferated mostly in the mucosa or upper layer of the lesion were mainly 2–5 and 3–20%. Moreover, in some small parts of the layer, those of them indicated > 20 and 20–40%. Epithelial markers such as CK7, CK20, CAM5.2 and AE1/AE3 were positive in the entire lesion as well as

in the existing gastric mucosal epithelium. CK19 which was known as one of the pancreatic ductal markers showed positive findings in some parts of the upper layer of the lesion and the existing gastric mucosa, but negative in the middle or deep inside of the lesion.

Meanwhile, the tests for pancreatic and digestive tract-related hormones (e.g. insulin, gastrin and so on) were negative. No intranuclear positive finding was observed with beta-catenin either. The immunostaining tests are presented in Table 1.

The nearest resected margin from the lesion was 0.5 cm. and free from the tumor. No fundic gland was observed in the existing gastric mucosa. The mucosa consisted of crypt epithelium with intestinal metaplasia and hyperplasia, and no obvious malignancy was detected.

For the tumor tissues presenting the acinar-glandular and trabecular patterns, a diagnosis of pancreatic-type acinar cell carcinoma of the stomach was made according to the characteristic findings such as clear and swollen nucleoli and the results of immunostaining tests. Most of the tumor tissue which presented a solid pattern showed neuroendocrine tumor (NET) G2 characteristics as well as those of acinar cell carcinoma. However, some parts of that area showed the characteristics of NETG3 without those of ACC.

Considering that each component accounted for more than 30% and that both of them had been mixed and shifted with each other, a diagnosis of pancreatic-type mixed acinar neuroendocrine carcinoma (pancreatic-type MiNEN) of the stomach (gastric MiNEN) was made.

Post-operative course: No perioperative complications were observed; the patient started taking meals on Day 3 after the operation, and on Day 13, he was discharged from the hospital. In the blood test, the Hb level had increased to 14.1, suggesting that his anemia had been resolved. Unfortunately, the patient died of brainstem hemorrhage 4 months after the operation. No autopsy was performed.

## Discussion

In 2002, Fukunaga<sup>2</sup> reported for the first time, a case of acinar cell carcinoma which developed in the stomach. Since then, a total 13 cases have been reported on gastric ACCs (including ACCs which also contained neuroendocrine tumor cells)<sup>3, 5-12</sup>. In addition, there are also other reports of ACC in the duodenum, papilla, small intestine and liver; such ACCs which developed outside the pancreas are often called as pancreatic-type ACCs<sup>13-17</sup>.

Rarely, some gastrointestinal tumors demonstrate both exocrine and neuroendocrine differentiation. In the World Health Organization (WHO) 2010 classification<sup>18</sup>, this group of tumors was named mixed adenoneuroendocrine carcinomas (MANECs), and in the 2017–2019 WHO classification<sup>4, 19</sup>, it has been renamed as mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs). Recently, La Rosa et al.<sup>20, 21</sup> has advocated a detailed classification (Table 2).

It is difficult to obtain a diagnosis of pancreatic-type ACCs of the stomach with endoscopic biopsy<sup>11</sup>, and it also seems even more difficult to diagnose MiNENs, because it seems that the terms and concepts of “pancreatic-type ACC”, “pancreatic-type MiNENs” and “gastric MiNEN” were not widely understood and accepted. Chymotrypsin, and Amylase markers can be useful in these diagnoses<sup>11</sup>. It has been reported recently that immunostaining with anti BCL-10 antibody can be a marker which is high in both sensitivity and specificity for pancreatic acinar cells as well as for cells which present acinar cell differentiation<sup>22</sup>. For this patient, who had been diagnosed as a gastric gland cell hyperplasia before the operation with endoscopic biopsy, the result of an immunostaining test conducted after the operation was strongly positive for anti BCL-10 and Chromogranin A antibody. Hence, immunostaining tests using anti-BCL-10 antibody, etc. can be useful and should be considered for pre-operative diagnosis.

It has also been reported that 42% of ACC of the pancreas would be positive for a neuroendocrine marker<sup>8</sup>. So, it has been said that there are some confusions between diagnoses of acinar cell carcinoma and neuroendocrine carcinoma of the pancreas. In general, a solid pattern is morphologically admitted as one of acinar cell carcinoma patterns of the pancreas<sup>4</sup>. However, it seems valid that the solid pattern in our case can be regarded as a morphologically recognizable discrete component, which applies to the definition of MiNEN.

The case we had was very rare in the way that it was a type of gastric MiNEN which consisted of pancreatic-type ACC and neuroendocrine tumor, that was mixed acinar neuroendocrine carcinoma or pancreatic-type MiNEN of the stomach. In addition, small amount of stromal mucus deposition and some CK19 positive cells were detected in the upper layer of the lesion of our case. These findings slightly suggested that our case might be related to mixed acinar neuroendocrine ductal carcinoma.

There have been 13 cases reported as far as we know on gastric ACCs and gastric MiNENs accompanied by pancreatic acinar cell differentiation<sup>2,3,5-12</sup> (Table 3). As for the onset mechanism, it was considered that they developed from the ectopic pancreas and had been called as “pancreatic-type ACC of the stomach” in some reports. Of these, the ectopic pancreas was detected histologically only in one case<sup>7</sup>. In other cases, it was considered that the ectopic pancreas might have been destroyed and vanished due to tumor proliferation. Gastric MiNENs usually consist of well-differentiated adenocarcinoma and neuroendocrine carcinoma (NEC) component<sup>23</sup>, and there is a tendency in the conditions of their distributions; namely, the latter component often exists deep inside the lesion and the former in the surface of the lesion<sup>24</sup>. For the onset mechanism of MiNENs (MANECs), Makuuchi et al.<sup>24</sup> proposed that during the process in which adenocarcinoma, which originally developed within the mucosa, invades deep inside the lesion, neoplastic endocrine cells which have higher proliferation potency would grow; hence, NEC is observed following MANEC. However, an opposite tendency was observed in the present case. In other words, neuroendocrine tumors existed in the surface of the lesion, and ACC deep inside the lesion. As the ectopic pancreas is commonly detected in the submucosa<sup>25</sup>, it can be considered that these distributions may support the idea that they develop from an ectopic pancreas. As for the site of the onset, the ectopic pancreas in general is likely to develop in the pyloric side<sup>26</sup>. However, in previous

reports, it developed in various sites other than the pyloric side, such as near the cardiac orifice or in the upper gastric body. In the present case, it also developed in the upper gastric body. Metastasis from other organ tumors such as pancreatic tumor could be denied for this patient as there was no clear finding which indicated a primary lesion in imaging studies conducted in this case. Hence, we consider the following 3 conditions, other than development from the ectopic pancreas, as the onset mechanism of this tumor: 1. A tumor which simultaneously contains two distinctive cellular components develops, 2. A tumor which contains two components originated from a pluripotent stem cell with the potential for divergent differentiation, and 3. Some of the non-neuroendocrine tumor are turned into neuroendocrine tumor, or some of the neuroendocrine tumor are turned into non-neuroendocrine tumor. The immunostaining study with the most surface layer of the lesion indicating neuroendocrine neoplasm, revealed partial positive staining on BCL-10. That may suggest the third condition.

Gastric MiNENs usually consist of adenocarcinoma and NEC components. In such a case, it is assumed that the latter component would determine the prognosis of MiNENs <sup>27</sup>.

According to a report on pancreatic tumors, the prognosis of ACCs is better than that of ductal adenocarcinomas, which account for most of the pancreatic tumors. However, it is still challenging as the median survival time is about 19 months and the 5-year survival rate is about 25%. Malignant findings such as clear atypical cells or frequent mitotic cells were rare in this present case. Effects of such morphological characteristics, results of immunostaining tests, and molecular abnormality on disease prognosis have been investigated in recent studies. However, only tumor staging has ever been verified as a factor associated with prognosis <sup>28</sup>.

As there is no standard opinion for the treatment of gastric MiNENs, it is considered important to determine a treatment approach for each case according to the tumor components. A management approach for gastric ACCs has not yet been determined as the number of cases are limited. However, a surgical treatment should be the first option for localized pancreatic ACCs <sup>29</sup>. According to a report on 865 cases studied based on National clinical database, satisfactory outcomes were achieved in the surgically treated group compared to the non-surgical treated group; the five-year survival rate was 36.4% (median, 27 months) vs 10.4% (median, 7.1 months). For unresectable or distant metastasis cases, chemotherapy or radiotherapy for a downstaging purpose could be an option to downstage disease to afford surgical resection<sup>30</sup>. In this present case, the outcome was death due to brainstem hemorrhage. However, it was considered to be an accident as the relationships between MiNEN, ACC, NET/NEC and cerebrovascular diseases are currently unknown.

## Conclusion

We experienced a case of pancreatic-type ACC of the stomach. A diagnosis of MiNEN was also made as nearly 40% of the tumor cells had been differentiated into neuroendocrine tumor cells (pancreatic-type mixed acinar neuroendocrine carcinoma or pancreatic-type MiNEN). The number of reports on pancreatic-type ACCs or MiNENs has been increasing due to advanced immunological technologies. However, these

are not yet well-understood as the number of cases is still very small. Further studies are required in order to clarify the characteristics of the tumor, to determine the treatment approach, and to improve the patients' prognoses.

## **Abbreviations**

ACC

acinar cell carcinoma

MINEN

mixed neuroendocrine-non-neuroendocrine neoplasms

NET

neuroendocrine tumor

WHO

World Health Organization

MANEC

mixed adenoneuroendocrine carcinoma

NEC

neuroendocrine carcinoma

## **Declarations**

### **Ethics approval and consent to participate**

Not applicable.

### **Consent for publication**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

### **Availability of data and materials**

The dataset supporting the findings and conclusions of this case report is included within this article.

### **Competing interests**

The authors declare that they have no competing interests.

### **Funding**

Not applicable.

### **Author's contributions**

Y.O. is the first author and prepared the manuscript under the supervision of K.W., I.H., S.T., T.O., S.Y. and H.F. All authors approved the final version of the manuscript.

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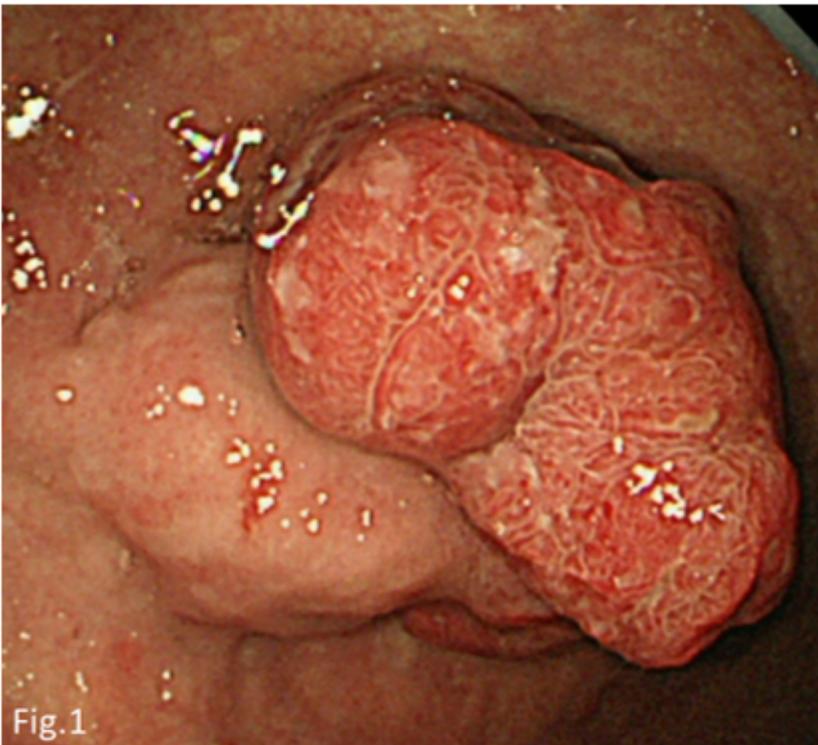
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## Tables

Due to technical limitations, table 1 to 3 is only available as a download in the Supplemental Files section.

## Figures



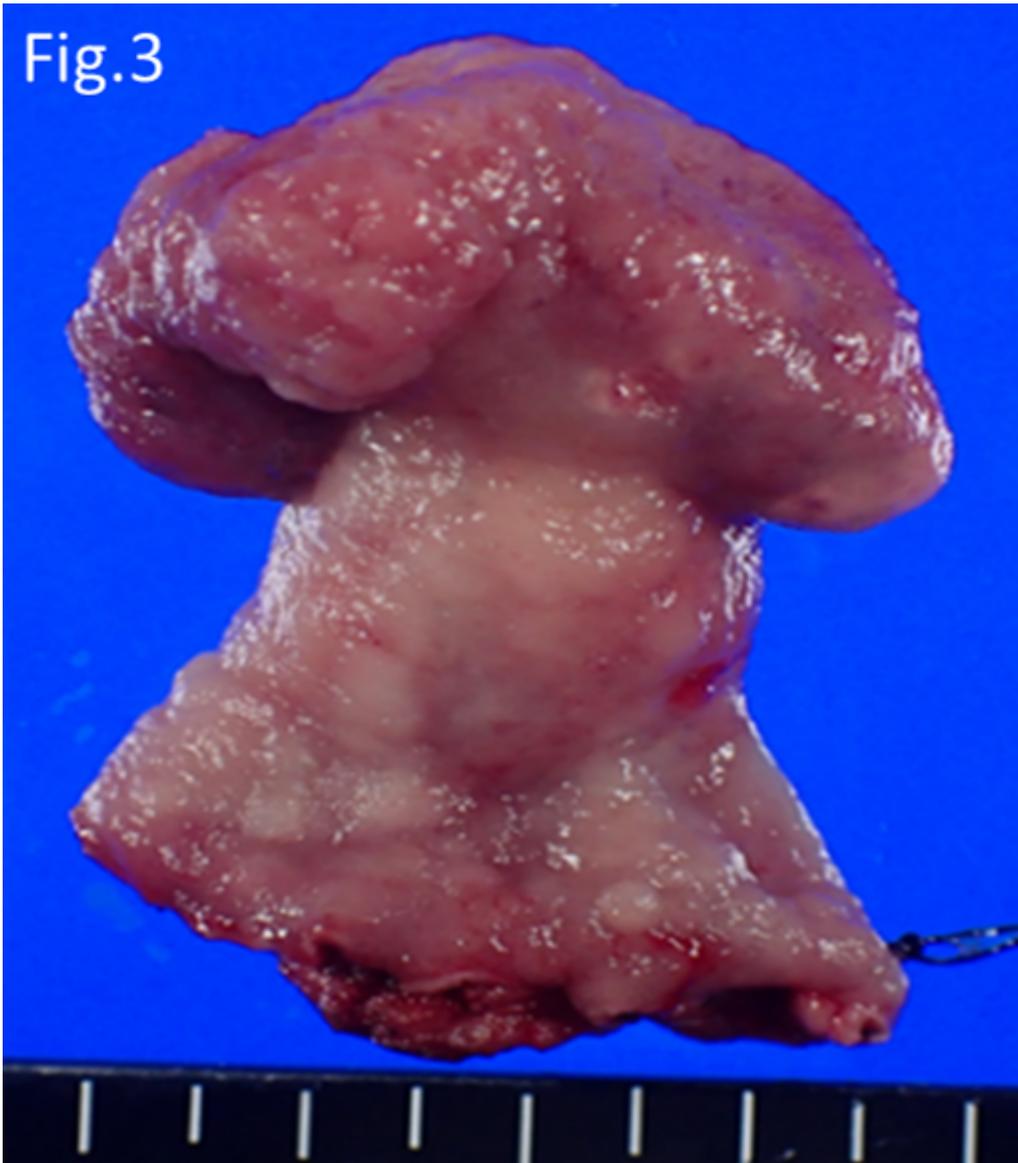
**Figure 1**

Esophogogastroduodenoscopy findings. A large ulcerated fungated mass in the gastric upper body.



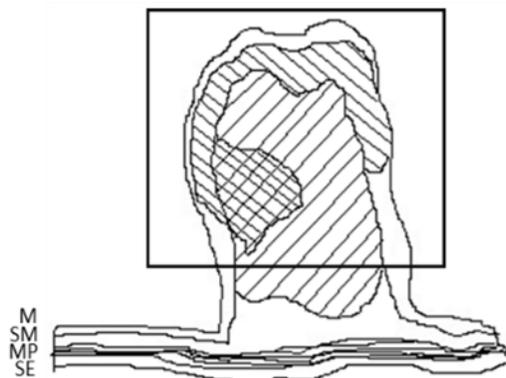
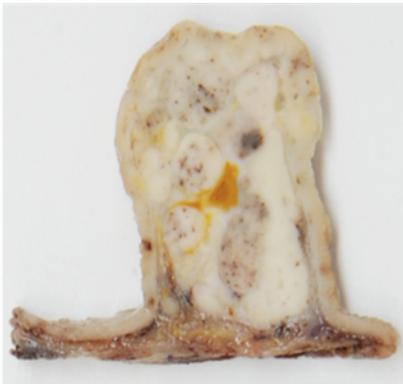
Figure 2

Abdominal computed tomography. Enhanced gastric tumor incarcerated to antrum.



**Figure 3**

Macroscopic findings.

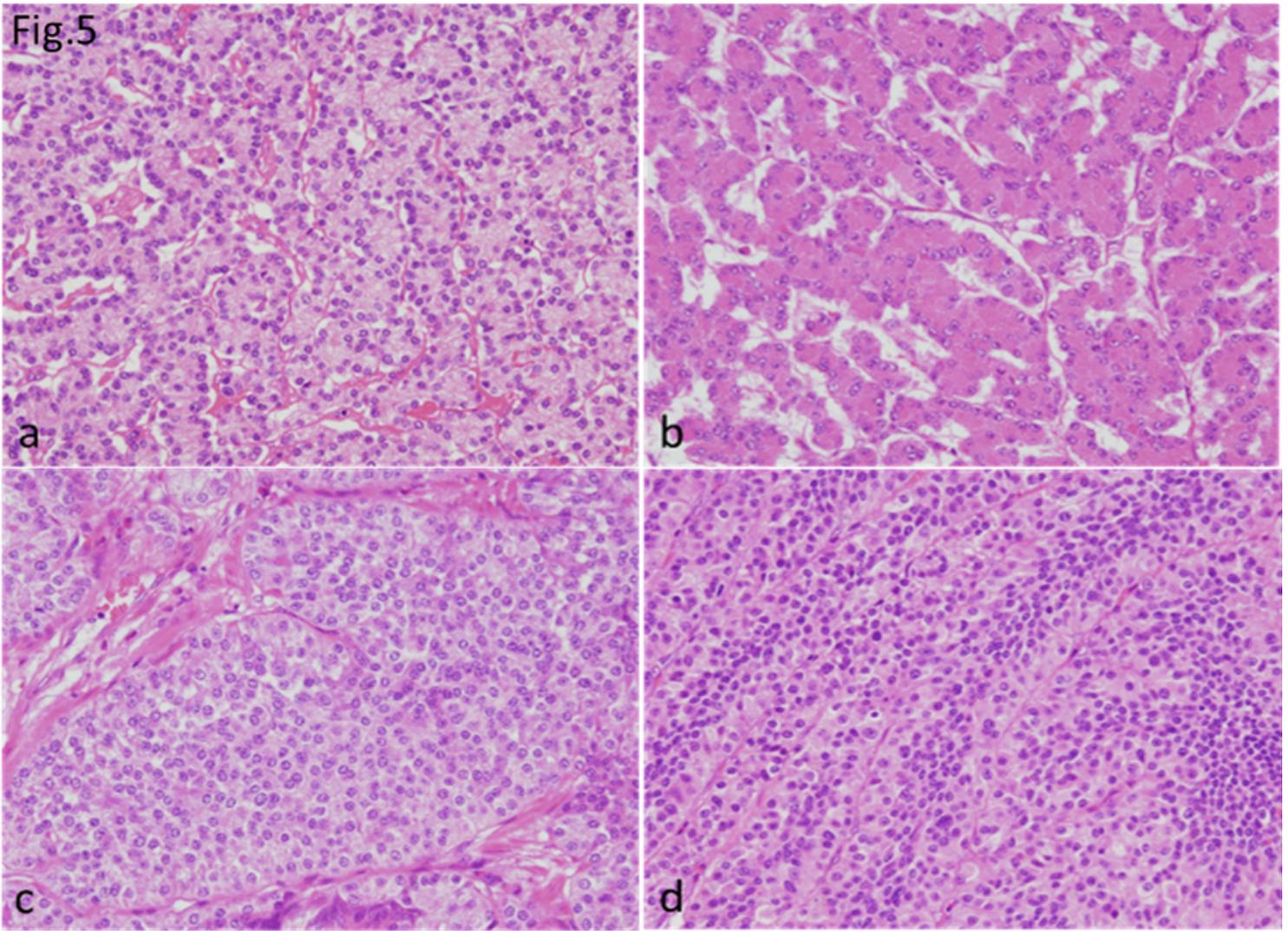


-  Solid pattern
-  Acinar-glandular and trabecular pattern
-  Amphicrine area

**Fig.4**

**Figure 4**

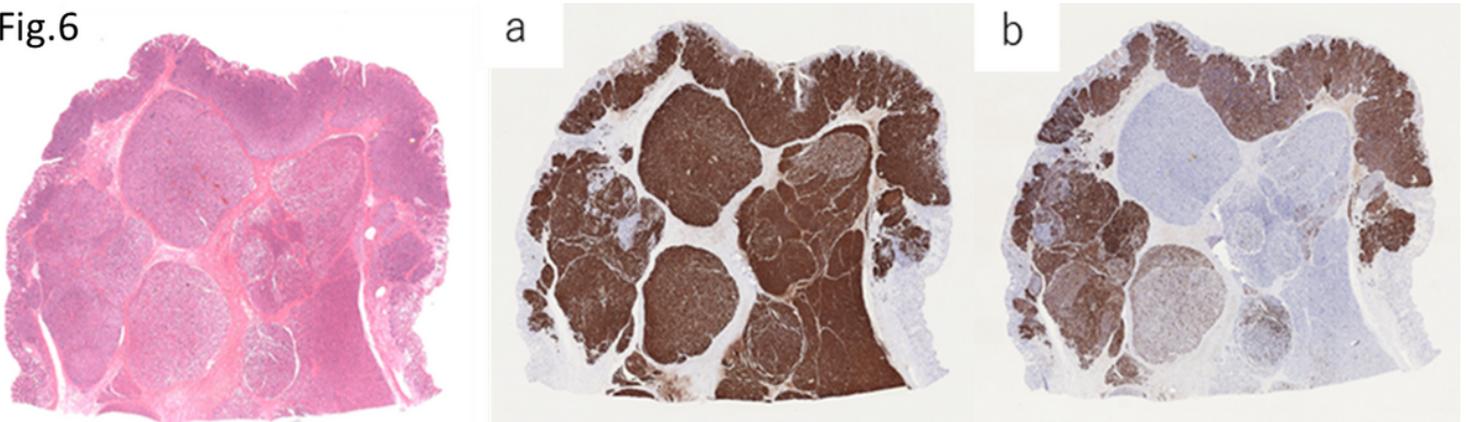
Schematic diagram of each component. The square indicates the area shown in Fig 6.



**Figure 5**

a, b, c, d) a: acinar-glandular pattern  $\times 200$  b: trabecular pattern  $\times 200$  c: solid pattern  $\times 200$  d: solid pattern (large and small cells)  $\times 200$

**Fig.6**



**Figure 6**

(a, b) a: anti BCL-10 antibody staining b: chromogranin A staining

## Supplementary Files

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