CASE REPORT

Unusual endoscopic findings of gastric neuroendocrine tumor

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Abstract : Gastric neuroendocrine tumor (NET) is sometimes found as a submucosal tumor on upper gastrointestinal endoscopy. Gastric NET with malignant profile and neuroendocrine carcinoma (NEC) show various forms which are difficult to distinguish from gastric cancer and other disease. We report a case of a cauliflower-shaped NET of the stomach. A 61-year-old man was referred to our hospital with a complaint of abdominal fullness. Upper gastrointestinal endoscopic examination revealed an unusual, whitish cauliflower-shaped tumor that belongs to Borrmann type I on the lesser curvature of the gastric antrum. Histological examination of the biopsy specimen revealed NET G2, because the tumor cells were CD56- and synaptophysin-positive by immunohistochemical analysis. A distal gastrectomy with D2 lymphadenectomy was performed. A recurrence in the liver was revealed by follow up computed tomography after 11 months from operation. Combined chemotherapy with irinotecan (CPT-11) plus cisplatin (CDDP) was treated. The patient achieved a partial response, but he died after 31 months from gastrectomy. There is no independent, large-scaled prospective study and no standard treatment for gastric NETs with distant metastases. Our case is reported with a literature review of the treatment of metastatic gastric NET G2. J. Med. Invest. 62 : 251-257, August, 2015

Keywords **:** *NET, neuroendocrine carcinoma, gastric carcinoma, CD56, synaptophysin*

INTRODUCTION

Neuroendocrine tumors (NET) were previously called carcinoid tumors (1). NET can be divided into five types of tumors according to World Health Organization (WHO) classification of tumors of the digestive system, 2010 : NET G1, NET G2, neuroendocrine carcinoma (NEC) (large cell or small cell type), mixed adenoneuroendocrine carcinoma (MANEC), and hyperplastic and preneoplastic lesions (2). Most cases are classified into former three groups. NET is a rare neoplasm that includes carcinoid, neuroendocrine carcinoma and small cell carcinoma. G stands for grading according to mitotic count and Ki-67 index. NET G1 is usually benign, whereas NET G2 and NEC are malignant. Tumor capacity is measured by Ki-67 staining with Ki-67 index < =2% seen in G1 tumors, 3%-20% in G2 tumors, and > 20% tumor cell involvement in NEC (2). NEC is a relatively rare tumor in the stomach (3, 4). It exhibits aggressive growth which results in vascular invasion and early distant metastasis, and has a poor prognosis (5, 6).

Here we report a case of NET G2 in the stomach that showed an intriguing endoscopic finding.

CASE REPORT

A 61-year-old Japanese male patient presented with a 1-month history of abdominal fullness. Patient interview revealed no particular past history, family history or social history. On physical examination, right upper quadrant or epigastric hard mass was easily palpable. A blood laboratory test showed anemia (hemoglobin 10.5 g/dl), hyperleukocytosis (10,800/mm^3 with 7,660/mm^3 of neutrophils), raised C-reactive protein (3.3 mg/dl) and elevated erythrocyte sedimentation rate (64 mm/hour). Serum CEA and CA19-9 were within normal range. Examination by esophagogastroduodenoscopy revealed a whitish cauliflower-shaped Borrmann type I tumor on the lesser curvature of the gastric antrum (Fig. 1). Histological biopsies of the lesion revealed the diagnosis of NET G2. Computed tomography (CT) showed a gastric tumor with another big mass which seems to be a lymphadenopathy around the posterior of the hepatic left lobe and epigastric lesion (Fig. 2). Whole body positron emission tomography (PET)/CT image demonstrates an intense uptake of 18F-fluoro-2-deoxyglucose (FDG) in the lesser curvature of the stomach (SUVmax 10.4) and in several perigastric lymph nodes (SUVmax 5.3), but did not detect any distant metastasis. Endoscopic and transabdominal ultrasonography (EUS) showed an isoechoic tumor mainly in the mucosal and submucosal layer and the tumor developed into deeper layer (Fig. 3). He underwent a distal gastrectomy with D2 lymphadenectomy. A Billroth type I anastomosis was done. The resected tumor showed Borrmann type I mass 6×7 cm in size. Microscopically, the tumor was composed of malignant large cells with rich cytoplasm, and large, round, clear nuclei. The tumor cells were arranged to form solid nests or sheet-like structures. Immunohistochemical analysis revealed that the tumor cells were positive for CD56 and synaptophysin, but negative for chromogranin A (Fig. 4). The tumor had infiltrated the subserosal layer and lymph node metastasis was found in 6 of 42 lymph nodes. The Ki-67 labeling index was 10%. These findings led to the diagnosis of NET G2 according to the 2010 WHO criteria. His performance status (PS) has been 3 after operation. Therefore, he was not treated by adjuvant chemotherapy. His PS improved into 1 by inpatient and outpatient

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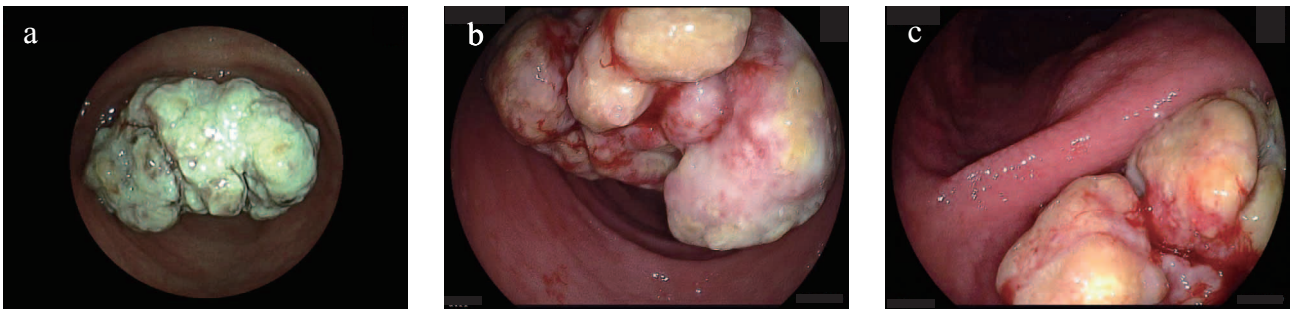

Fig. 1 The esophagogastroduodenoscopy finding revealed a whitish cauliflower-shaped Borrmann type I tumor on the lesser curvature of the gastric antrum.

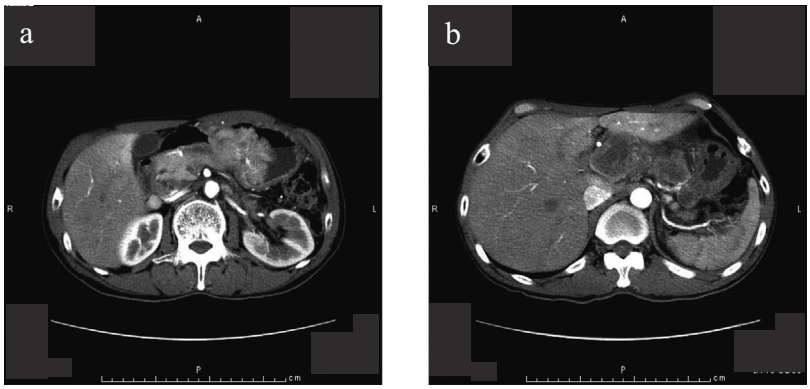

Fig. 2 Abdominal computed tomography (CT) findings of the patient. CT revealed a mass in the lesser curvature of the gastric antrum (a) and enlarged lymph nodes (b).

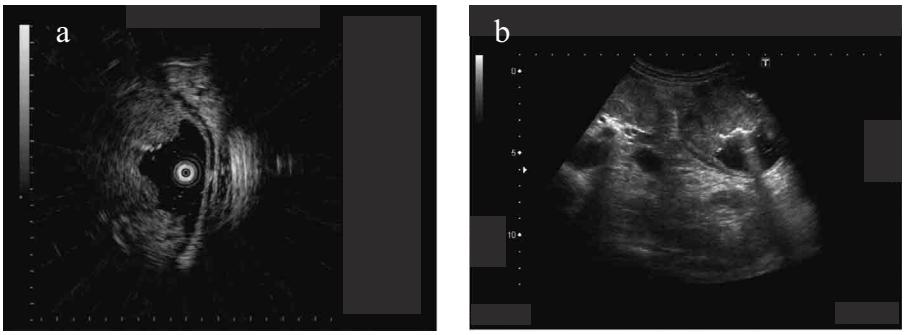

Fig. 3 Endoscopic (a) and transabdominal (b) ultrasonography showed an isoechoic mass located in the mucosal and submucosal layers and invaded partially into deeper layer.

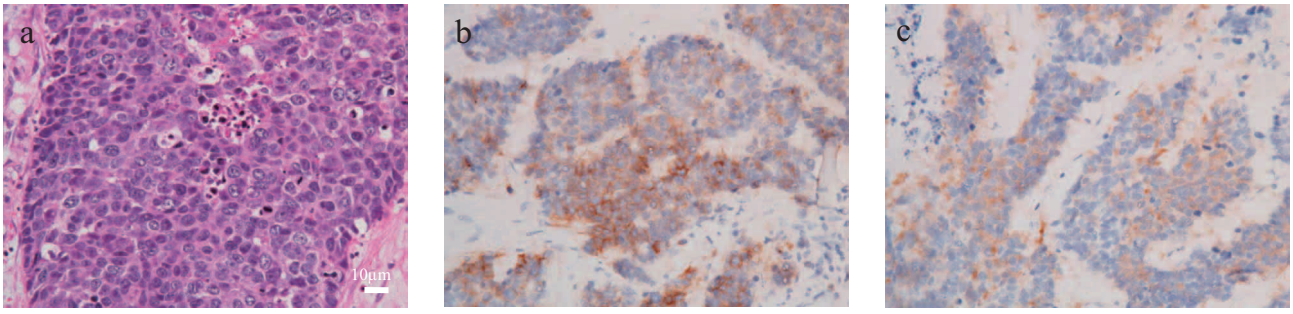

Fig. 4 Hematoxylin and eosin (H&E) staining and immunohistochemical stainings of the tumor cells. Large cells with high nuclear to cytoplasm ratio (a). The cells were positive for CD56 (b) and synaptophysin (c). (a×400, b, c×200)

hospital treatment, but liver and lymph node metastases were revealed by follow up computed tomography 11 months later. Biweekly irinotecan (CPT-11) plus cisplatin (CDDP) chemotherapy (CPT-11 60 mg/m^2 and CDDP 30 mg/m^2 on day 1) was treated since then. The patient had a partial response at first and received them for 9 months. His anorexia and liver injury got worse into grade 3 and the chemotherapy was impossible to be continued. The tumor was regrown and he died of multiple hepatic metastases after 31 months from operation.

DISCUSSION

Gastric NEC is a rare tumor, which reportedly comprises 0.1-0.6% of gastric cancers (3, 7, 8). NEC is deeply invasive and metastatic. The diagnostic rate by biopsies under esophagogastroduodenoscopy is very low (11-27%) (9, 10), because the tumors of most cases contain adenocarcinoma components. The biopsied specimen of our case was immune-stained positively with synaptophysin and CD56. It comprises NET G2 and seems to be classified as a pure type according to the pathological examination of the resected tumor (5). The Ki-67 labeling index of this tumor was 10% in the component and the diagnosis was NET G2 according to the 2010 WHO classification. But the growth was very progressive and invasive. The clinical course of our case seems to be defined as carcinoma. Spampatti *et al.* (11) reported the case of gastric NET G1 with 6 mm in size and a Ki-67 of less than 2% which proceeded into 7 cm of NEC with both hepatic and massive peritoneal metastases (Ki-67 40%) after 8 years. Gastric NET G1 or G2 may have a malignant potential and should be followed up carefully. Large cell neuroendocrine carcinoma of the stomach is rare and also a small percentage of all gastric endocrine tumors (12). It is significantly more aggressive than that of gastric adenocarcinoma (12). Pathological examination of this component in our case is large cell type. The clinical course of large cell type NET G1 or G2 may be similar with gastric NEC.

Rindi *et al.* (13) classified gastric NETs into three types based on the clinical characteristics. Type 1 NETs are the most frequent (70-80% of all cases) and associated with type-A chronic atrophic gastritis. Type II NETs are rare and occur in association with Zollinger-Ellison syndrome in multiple endocrine neoplasia type I (MEN-1). Type III NETs are the second most common and occur in a sporadic and solitary large form. Our case had *Helicobacter pylori* positive gastritis, and his tumor is classified into type III NET.

Apart from the regional lymph nodes, the liver is the most frequent site of NET and liver metastases are major prognostic factor of NET (14). Our patient with gastric NET G2 developed liver metastasis 11 months after gastrectomy. Shin *et al.* reported that one of eight patients who have gastric NET with liver metastases was G2 and others were NEC (15). Another factor, like unknown primary tumor as reported (15), other than histological grade may affect the prognosis.

61 cases of gastric endocrine carcinoma were reported with description or in the photo of the upper gastrointestinal endoscope. 13 cases (21%) were Borrmann type I, 25 cases (40%) were type II, 15 cases (24%) were type III, 1 case was type IV, 1 case was type V, and 5 cases were type 0 (IIa 1 case ; IIc 3 cases ; IIa+IIc 1 case). One case showed the morphology of submucosal tumor. A rare polypoid type early NEC in the stomach was reported (16). Endoscopic findings of the tumor also demonstrated a polypoid lesion with a broad stalk. The surface showed a white coat, erosion and lobulation and the macroscopic finding was unique and similar with the one of our case. The mass of our case is whitish Borrmann I and looks like cauliflower. The tumor infiltrated into the subserosa in association with lymphangioinvasion. Gastric NEC arises predominantly from endocrine precursor cell clones that develop in the preceding adenocarcinoma component. These clones transform into NEC and the NEC develops rapidly in the submucosal and deeper layer (17). According to the histological examination, a wide range of necrosis by the metastatic cancer was observed in the lymphatic ducts of the tumor. Probably those things contribute to the color and the shape of the tumor.

Treatment of localized gastric NETs usually involves surgical resection, and surgery is the only curative treatment for NETs. Chemotherapy has recently been recommended to be administered to NEC patients following gastrectomy. There is no standardized chemotherapy for gastric NET. Chemotherapeutic regimens including cisplatin, irinotecan, etoposide, doxorubicin, and vincristine are reported. Kulke *et al.* (18) reported a very low response rate to cisplatin plus irinotecan for extra-pulmonary NETs, however, Okita *et al.* (10) reported the response rate to cisplatin plus irinotecan for gastric poorly differentiated NEC was 75%. Large-scale retrospective analyses for advanced neuroendocrine carcinoma of the digestive system by Japanese group demonstrate that irinotecan plus cisplatin (IP) and etoposide plus cisplatin (EP) are the most commonly used regimens (19). IP was the most commonly selected regimen, especially for the gastrointestinal tract in the Japanese study (19), while EP was the most commonly selected regimen in the Nordic study (20). The response rate of IP was slightly better than that of EP for the treatment of NEC, even after adjusting patient background by multivariate analysis. The median overall survival of gastric NEC patients is 13.3 months. We chose IP chemotherapy and the overall survival of our case was much longer, although the tumor is classified into NET G2 and our case is hard to compare with the cases of NEC simply. Because a part of NET G2 actually embraces a very aggressive profile and has rather a G3-NET-like behavior, chemotherapy might become the first option therapy (21). However, gastric NETs are not discussed in independent, large-scaled prospective studies and tend to be excluded from clinical trials, because the cases are few (22). Systematic study of the treatment for NET G2 of digestive system should be considered in the future.

Somatostatin analogues (SSAs) have shown to be effective in the treatment of midgut NETs (23). Type I and II gastric NETs are gastrin-dependent and associated with conditions inducing hypergastrinemia. SSAs have been increasingly used in the treatment of patients with type I and II gastric NETs (24), based on their capability to lower the elevated gastrin levels and suppress enterochromaffin like cell hyperplasia. As stated above, our case seemed to belong to type III gastric NET and serum gastrin level in our case was within normal range (our case 184 pg/ml ; normal values 42-200 pg/ml) (11, 25). Management of type III gastric NET is comparable to that used for gastric adenocarcinomas. SSAs are considered to be a beneficial treatment in well-differentiated NET G1 and might also be applied to control clinical symptoms in NET G2 with higher proliferation like our case (26).

Interferon alpha along with SSAs has been used as a treatment of midgut NETs, although often with potentially high toxicity (27). Everolimus, an inhibitor of mammalian target of rapamycin (mTOR), and sunitinib, an inhibitor of multi-targeted tyrosine kinase, are reported to give a statistically significant survival benefit in enteropancreatic NET (28, 29).

Recently, bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), has shown promising results in gastroenteropancreatic NETs, because gastroenteropancreatic neuroendocrine tumors are known as hypervascular tumors with increased expressions of VEGF and VEGF receptors (30, 31). Table 1 summarizes clinical trials for gastroenteropancreatic NET G1/G2. The combination with bevacizumab, SSAs, cytotoxic chemotherapy or mTOR inhibitors may be a promising strategy in the patients with gastric NET G1/G2.

Table 1. Summary of the clinical trials for gastroenteropancreatic NET

Regimen	Sites of NETs	No. of cases	Response rate (%)	median OS (months)	median PFS (months)	Author	year	Design
streptozocin + doxorubicin	pancreas	38	69	26.4	18	Moertel *et al.* (32)	1992	Phase III
streptozocin + fluorouracil	pancreas	34	45	16.8	14	Moertel *et al.* (32)	1992	Phase III
chlorozotocin	pancreas	33	30	18	17	Moertel *et al.* (32)	1992	Phase III
dacarbazine	pancreas	50	34	19.3	N/R	Ramanathan *et al.* (33)	2001	Phase II
	intestine	56	16	20	N/R	Bukowski *et al.* (34)	1994	Phase II
temozolomide + thalidomide	pancreas	11	25	Not reached	Not reached	Kulke *et al.* (35)	2006	Phase II
	gastrointestine	15	7	N/R	N/R	Kulke *et al.* (35)	2006	Phase II
temozolomide	pancreas, gastrointestine, bronchus, thymus	36	14	16	7	Ekeblad *et al.* (36)	2007	
bevacizumab + temozolomide	pancreas, midgut, bronchus, unknown	34	15	33.3	11	Chan *et al.* (37)	2012	Phase II
temozolomide + capecitabine	pancreas	30	70	Not reached	18	Strosberg *et al.* (38)	2011	
streptozocin + doxorubicin + fluorouracil	pancreas	84	39	27	18	Kouvaraki *et al.* (39)	2004	
streptozocin + cyclophosphamide	gastrointestine	47	26	12.5	N/R	Moertel *et al.* (40)	1979	
streptozocin + fluorouracil		42	33	11.2	N/R			
dorubicin	gastrointestine	81	21	11.1	N/R	Engstrom *et al.* (41)	1984	
streptozocin + fluorouracil		80	22	14.9	N/R			
dorubicin + fluorouracil	gastrointestine	85	16	15.7	4.5	Sun *et al.* (42)	2005	Phase II/III
streptozocin + fluorouracil		78	16	24.3	5.3			
cisplatin + etoposide	pancreas, gastrointestine (NET G1/G2, NEC)	36	55	19	N/R	Fjallskog *et al.* (43)	2001	
cisplatin + irinotecan	pancreas, gastrointestine (NET G1/G2, NEC)	15	7	11.4	N/R	Kulke *et al.* (44)	2006	Phase II
sunitinib	pancreas	86	9.3	Not reached	11.4	Raymond *et al.* (29)	2011	Phase III
everolimus	pancreas	207	5	Not reached	11	Yao *et al.* (28)	2011	Phase III
everolimus + octretide LAR (RADIANT-2)	pancreas, gastrointestine	173	N/R	N/R	14.3	Pavel *et al.* (45), Anthony *et al.* (46)	2011, 2015	Phase III
everolimus + octretide LAR (ITMO group study)	pancreas, gastrointestine, lung	50	18	Not reached	Not reached	Bajetta *et al.* (47)	2014	Phase II
temsirolimus + bevacizumab	pancreas	56	41	34	13.2	Hobday *et al.* (48)	2014	Phase II
bevacizumab + depot octreotide + PEG-IFN alpha-2b	pancreas	44	18	N/R	16.5	Yao *et al.* (49)	2008	Phase II
bevacizumab + capecitabine (BETTER trial)	gastrointestine	49	18	Not reached	23.4	Mitry *et al.* (50)	2014	Phase II
bevacizumab + 5-FU/ streptozocin (BETTER trial)	pancreas	34	44	Not reached	23.7	Ducreux *et al.* (51)	2014	Phase II
bevacizumab + everolimus	pancreas, gastrointestine	39	26	N/R	14.6	Yao *et al.* (52)	2015	Phase II
bevacizumab + octreotide + metronomic capecitabine	pancreas, gastrointestine	45	17.8	N/R	14.9	Berruti *et al.* (53)	2014	Phase II
Methoxyestradiol + bevacizumab	pancreas, gastrointestine	31	0	N/R	11.3	Kulke *et al.* (54)	2011	Phase II
sorafenib + bevacizumab	pancreas, gastrointestine	44	9.4	Not reached	12.4	Castellano *et al.* (55)	2013	Phase II
bevacizumab + pertuzumab + sandostatin	pancreas, gastrointestine	43	16	Not reached	8.2	Firdaus *et al.* (56)	2012	Phase II
bevacizumab + octreotide + metronomic temozolomide	pancreas, gastrointestine G2	15	64	N/R	9	Koumarianou *et al.* (57)	2012	Phase II
octretide LAR (PROMID trial)	small intestine (midgut)	42	2.3	N/R	14.3	Rinke *et al.* (23)	2009	Phase III
5-fluorouracil + octretide LAR	pancreas, colon, small intestine, unknown	29	24	Not reached	22.6	Brizzi *et al.* (58)	2009	Phase II
pazopanib	pancreas, gastrointestine	37	18.9	Not reached	9.1	Ahn *et al.* (59)	2013	Phase II
thalidomide	pancreas, gastrointestine	18	0	N/R	N/R	Varker *et al.* (60)	2008	Phase II

CONFLICT OF INTEREST

None of the authors have any conflict of interest to declare.

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