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# Four Cases of Large Cell Neuroendocrine Carcinoma of the Stomach: Findings on CT and Barium Studies[1]

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A large cell neuroendocrine carcinoma of the stomach is extremely rare. We have reviewed the medical records and imaging studies of the four patients that presented with a large cell neuroendocrine carcinomas of the stomach. On a barium study and CT imaging, a gastric large cell neuroendocrine carcinoma is depicted as an ulcerofungating tumor with minimal peritumoral infiltration and metastatic lymphadenopathy in the perigastric area. These findings are similar to findings for advanced gastric cancer, especially Borrmann type II. However, a gastric large cell neuroendocrine carcinoma is highly malignant with a significantly worse prognosis than a usual adenocarcinoma.

**Index words :** Stomach
Stomach neoplasms
Tomography, X-Ray Computed
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Carcinoma, neuroendocrine

A large cell neuroendocrine carcinoma of the stomach is extremely rare and represents only a small percentage of all endocrine tumors. According to the WHO classification of gastric tumors, there are two subtypes of gastric endocrine tumors based on the histopathological classification (1). A well-differentiated endocrine tumor and poorly-differentiated endocrine carcinoma are the two major types of lesions; the well-differentiated endocrine tumor is equivalent to a carcinoid and the majority of poorly differentiated endocrine carcinomas is equivalent to a small cell carcinoma. A large cell neuroendocrine carcinoma, which is in the minority of poorly-differentiated neuroendocrine carcinomas, is composed of large cells having organoid, trabecular, and palisading patterns that are suggestive of endocrine differentiation (2). Primary and metastatic large cell neuroendocrine carcinomas have not been well described in the stomach because of their extreme rarity. Although radiological studies such as CT imaging or barium studies can be useful for the determination of tumor staging and the evaluation of the morphological appearances of gastric tumors, to the best of our knowledge, there has been no radiology report describing the imaging features of a gastric large cell neuroendocrine carcinoma. We report here the appearance of primary large cell neuroendocrine carcinomas of the stomach based on barium

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studies and CT imaging findings in four patients. In addition, we review the clinical outcome of the patients with a gastric large cell neuroendocrine carcinoma.

***Case 1***

A 60-year-old male underwent endoscopy due to the presence of epigastric pain and dyspepsia. On en-

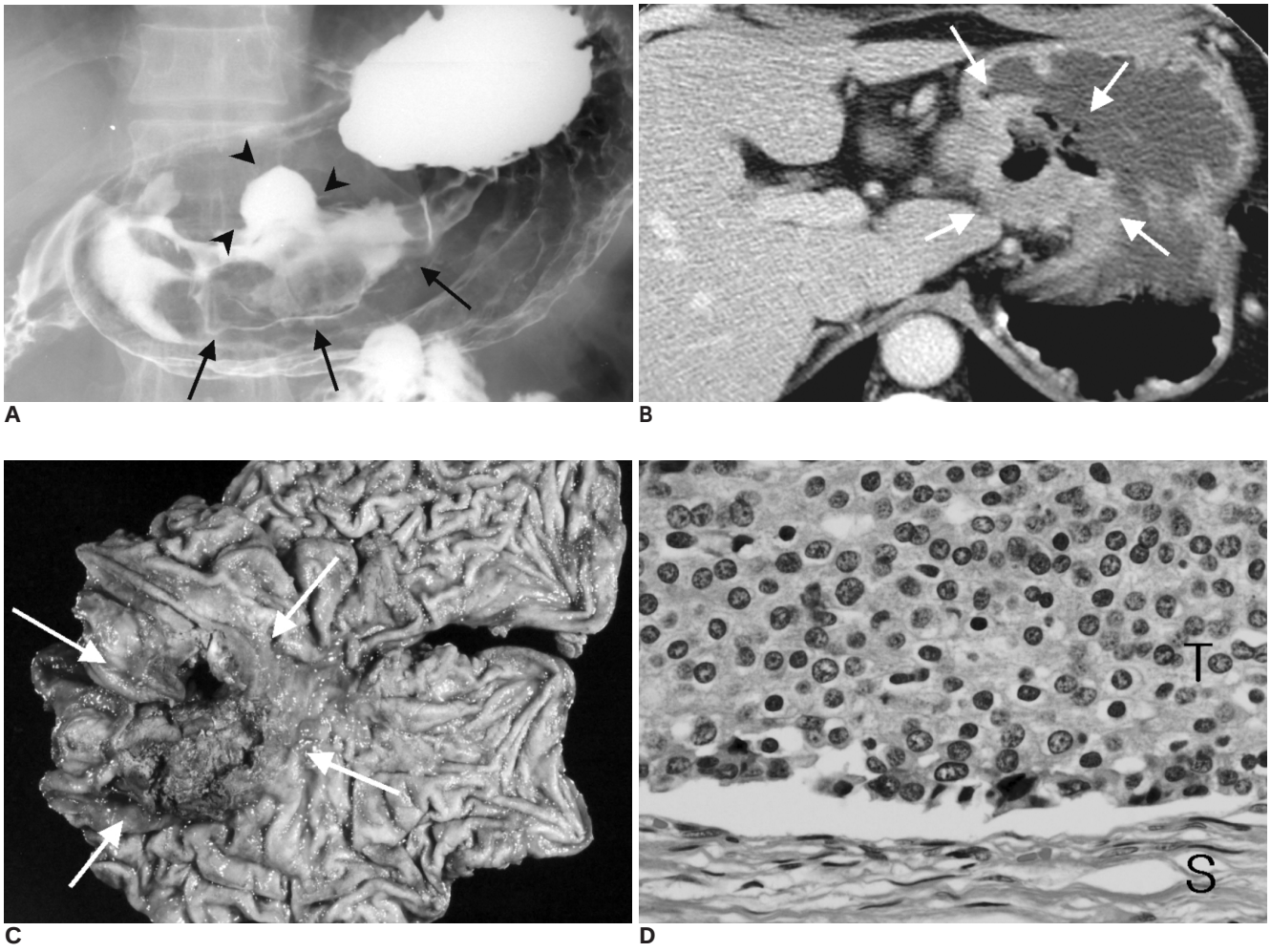



**Fig. 1.** A 60-year-old male with a large cell neuroendocrine carcinoma of the stomach.

**A.** A barium study shows a 7-cm, well-marginated mass (arrows) with a large ulceration (arrowheads) at the lesser curvature of the antrum.

**B.** A contrast-enhanced CT scan with negative contrast media (water) shows a large, poorly enhanced, ulcerated mass (arrows) from the mid-body to the antrum with minimal peritumoral infiltration. A 2-cm enlarged lymph node was observed around the lesser curvature (data not shown).

**C.** A photograph of a resected specimen shows a 7 × 7 cm-ulcerated mass (arrows) from the mid-body to the antrum along the lesser curvature. On the pathology reports, it was reported that this tumor mimicked a Borrmann type II advanced gastric carcinoma Borrmann type II (ulcerofungating lesion).

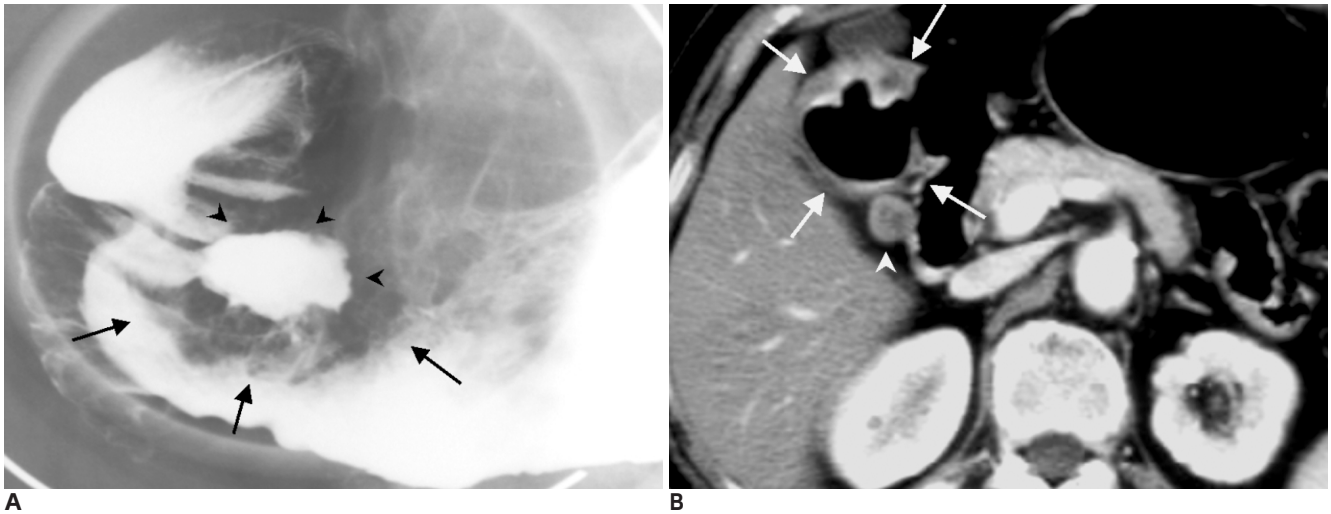
**D.** A photomicrograph (hematoxylin and eosin staining; original magnification, ×400) of the resected specimen shows a nest of tumor (T) cells in the submucosa. Note the large cells with a polygonal shape, abundant cytoplasm and vesicular or coarse nuclear chromatin. Tumor cells were also found in the mucosal layer and serosa (data not shown). S (stroma)

**E.** A photomicrograph with synaptophysin immunochemical staining for synaptophysin (original magnification, ×400) shows positive immunoexpression in the cytoplasm (arrows, dark brown color) of the tumor cells, indicative of a neuroendocrine tumor.

doscopy, a huge ulcerofungating mass was also seen from the mid-body to the antrum. The impression of the endoscopist was advanced gastric cancer, and an endoscopic biopsy identified a neuroendocrine carcinoma. A barium study that was performed in the patient demonstrated the presence of a 7-cm, well-marginated mass with a large ulceration in the lesser curvature of the antrum (Fig. 1). The prospective radiologic report indicated Borrmann type II advanced gastric cancer (an ulcero-fungating lesion) (3). A CT scan depicted a large, poorly-enhanced, ulcerated mass from the mid-body to the antrum with minimal peritumoral infiltration (Fig. 1). A 2-cm enlarged lymph node was also noted around the lesser curvature. There was no distant metastasis detected on the CT image. This patient underwent extended a total gastrectomy followed by adjuvant chemotherapy. At surgery, a metastatic lymph node was found in the perigastric area. On a pathological examination, large mass extension to the perigastric adipose tissue and invasion of perineural tissue were found (stage T3N1). Immunohistochemical staining demonstrated that the samples were positive for expression of synaptophysin, cytokeratin and chromogranin A (Fig. 1). As there was no evidence of a neuroendocrine carcinoma involving the other organs, we diagnosed the lesion as a primary large cell neuroendocrine carcinoma of the stomach. Follow-up CT Imaging obtained from 6 months to 26 months after surgery did not show tumor recurrence. However, CT scans obtained 32 months after surgery showed the presence of massive metastatic lymphadenopathy near the anastomotic site and tumor recurrence at the anastomotic site. The patient died of disseminated metastases 83 months after surgery.

***Case 2***

A 66-year-old female suffered from dyspepsia. A barium study showed the presence of a 6-cm, well-defined mass with central ulceration in the anterior wall and at the lesser curvature side of the antrum (Fig. 2). A prospective radiological report documented Borrmann type II advanced gastric cancer. On endoscopy, a deep excavated lesion with surrounding nodular mucosa and spontaneous bleeding was seen on the anterior wall of the antrum. The pathology of the endoscopic biopsy specimen revealed a poorly differentiated adenocarcinoma. The CT scan showed a large, well-marginated, moderately enhancing, ulcerated mass with no peritumoral infiltration and multiple lymphadenopathy located along the lesser curvature of the antrum (Fig. 2). This patient underwent a partial gastrectomy. At surgery, six metastatic lymph nodes were found in the perigastric area. A pathological examination of the surgical specimen showed that the mass was extended to the proper muscle. Immunohistochemical staining was positive for expression of chromogranin A and synaptophysin, and the presence of a large cell neuroendocrine carcinoma was confirmed (stage T2N2). A follow-up CT scan obtained 16 months after surgery showed the presence of a



A B

**Fig. 2.** A 66-year-old female with a large cell neuroendocrine carcinoma of the stomach.
**A.** Barium study shows a 6-cm, well-defined mass (arrows) with central ulceration (arrowheads) in the anterior wall and the lesser curvature side of the antrum.
**B.** A contrast-enhanced CT scan shows a well defined, large, ulcerated enhancing mass (arrows) in the antrum with no peritumoral infiltration and an enlarged lymph node (arrowhead).

15-cm metastatic tumor in the right hepatic lobe. The patient died of progression of metastasis 18 months after surgery.

***Case 3***

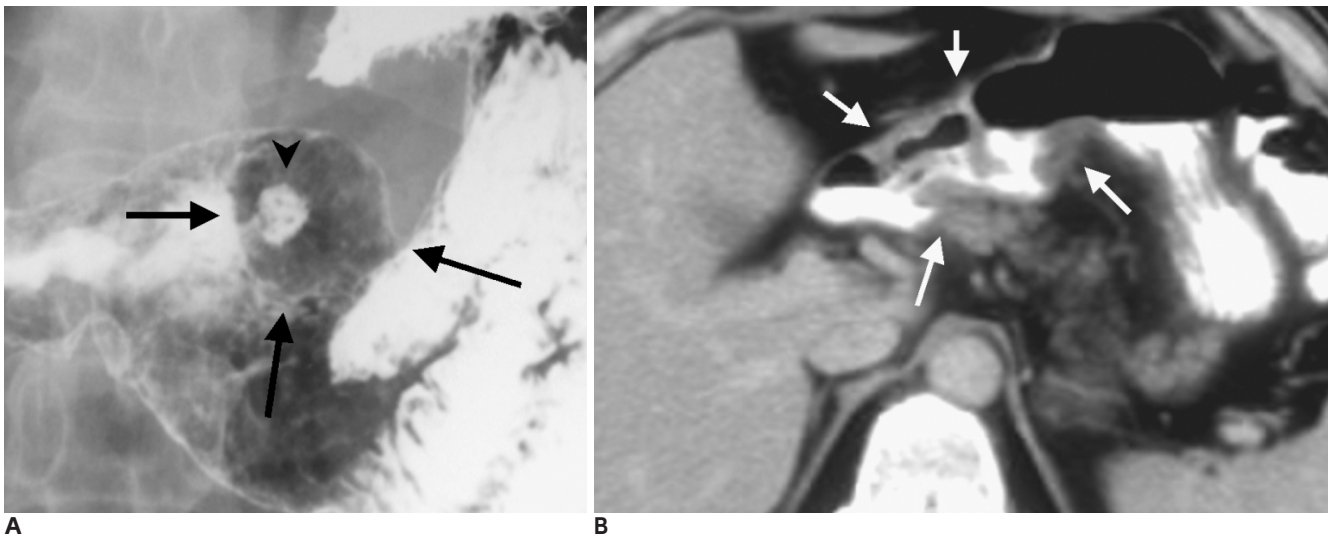
In a 63-year-old male, a barium study showed the presence of a 4-cm, well-circumscribed mass with central ulceration at the lesser curvature side of the antrum (Fig. 3). A prospective radiological report indicated a Borrmann type II advanced gastric cancer. A CT scan showed abnormal wall thickening with moderate enhancement and minimal peritumoral infiltration located in the lesser curvature side of the antrum with several enlarged lymph nodes in the perigastric area (Fig. 3). This patient underwent a total gastrectomy without endoscopy in our hospital; the patient was referred from an outside hospital with a pathological finding of gastric cancer. At surgery, six metastatic lymph nodes were found in the perigastric area. On a pathological examination, the mass was extended to the subserosa, and endolymphatic tumor emboli were found (stage T2N2). A follow-up CT scan obtained 7 months after surgery showed the presence of multiple recurrent tumors around the anastomotic area. The patient died of tumor progression 11 months after surgery.

***Case 4***

A 70-year male underwent barium study because of epigastric discomfort. The barium study identified a 5-cm, well-defined mass at the lesser curvature side from the lower body to the antrum (Fig. 4). A prospective radiological report documented Borrmann type II advanced gastric cancer. CT scans showed diffuse wall thickening from the lower body to the antrum with minimal peritumoral infiltration and multiple enlarged lymph nodes in the perigastric area (Fig. 4). On endoscopy, a gastric tumor with uneven based, round ulceration was seen, and spontaneous bleeding was observed. A pathological examination confirmed a neuroendocrine carcinoma following an endoscopic biopsy. This patient underwent a partial gastrectomy followed by adjuvant chemotherapy. At surgery, nine metastatic lymph nodes were found in the perigastric area. On a pathological examination of the resected stomach, the tumor had extended to the subserosa, and endolymphatic tumor emboli were found (stage T2N1) (Fig. 4). The last follow-up CT obtained 22 months after surgery did not show tumor recurrence.

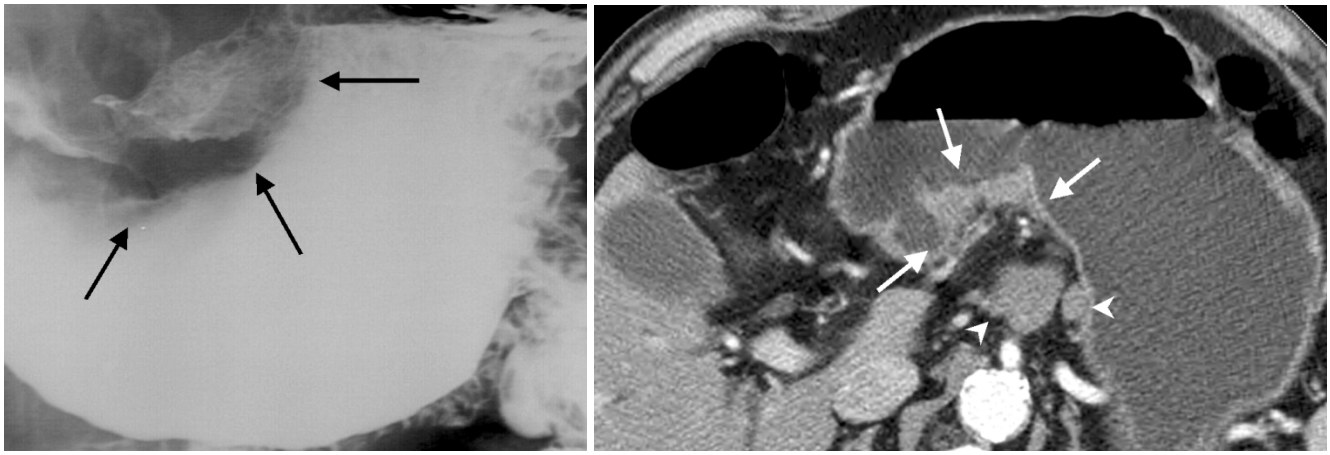
## Discussion

Large cell neuroendocrine carcinoma in the stomach is an extremely rare disease, and there have been no reports on the radiological findings of this disease. Neuroendocrine tumors arise from embryonal neural crest cells, which are abundant in the epithelia of the gas-



A B

**Fig. 3.** A 63-year-old male with a large cell neuroendocrine carcinoma of the stomach.
**A.** A barium study shows a 4-cm, well-circumscribed mass (arrows) with central ulceration (arrowhead) at the lesser curvature side of the antrum.
**B.** A contrast-enhanced CT scan with the use of positive contrast media shows abnormal wall thickening with moderate enhancement (arrows) and minimal peritumoral infiltration located at the lesser curvature side of the antrum. Several enlarged lymph nodes were found in the perigastric area (data not shown).



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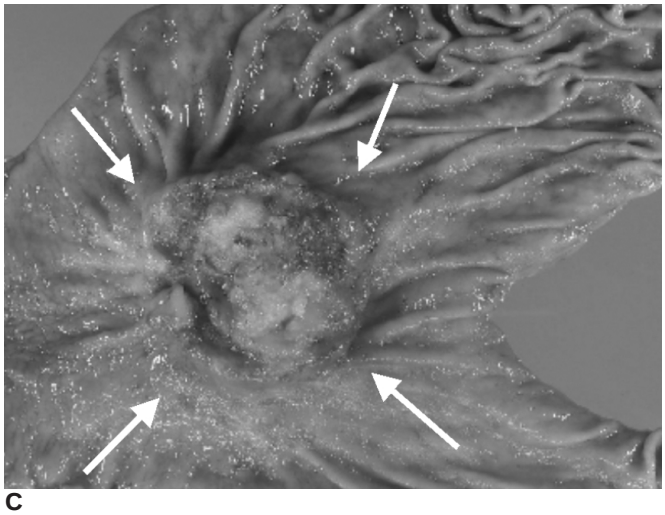

C

**Fig. 4.** A 70-year-old male with a large cell neuroendocrine carcinoma of the stomach.
**A.** A barium study shows a 5-cm, well-defined mass (arrows) in the lesser curvature side of the lower body to the antrum.
**B.** A contrast-enhanced CT scan with negative contrast media (water) shows diffuse wall thickening from the lower body to the antrum (arrows) with minimal peritumoral infiltration and metastatic lymph nodes (arrowheads) in the perigastric area.
**C.** A photograph of the resected specimen shows a 5 × 4 cm ulcerofungating mass (arrows) at the lesser curvature side from the lower body to the antrum. This tumor mimics Borrmann type II advanced gastric carcinoma.
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trointestinal tract and bronchopulmonary system. High-grade neuroendocrine carcinomas, which include small cell carcinomas and large cell neuroendocrine carcinomas, are poorly differentiated tumors that resemble their counterparts arising in the bronchopulmonary system in having an aggressive behavior, a high propensity for lymph node metastases and distant metastases (4 - 7).

A large cell neuroendocrine carcinoma is different from a small cell carcinoma as based on cytological findings, and is characterized by the presence of large cells with a polygonal shape, low nuclear-cytoplasm ratio, coarse nuclear chromatin, high mitotic rate and frequent necrosis (2, 5, 8). Either positive immunohistochemical staining for expression of neuroendocrine markers such as neuron-specific enolase, chromogranin A and synaptophysin, or an electron microscopic depiction of neurosecretory granules is indicative of a diagnosis of a neuroendocrine tumor (8). A recent radiological report of two patients with gastric small cell carcinoma described that CT imaging identified poorly or moderately enhanced ulcerated masses, and barium studies showed the presence of ulcerofungating tumors (9). Another radiological study presented an ulcerofungating mass with moderate enhancement on CT in a patient with a gastric small cell carcinoma (10). These findings are similar to findings for a large cell neuroendocrine carcinoma as well as advanced gastric cancer.

While a carcinoid tumor generally has a benign course, a large cell neuroendocrine carcinoma follows an aggressive course. In our series, local tumor recurrences, metastatic lymphadenopathy, or distant metastases were observed in three of four patients. These patients showed rapid disease progression and poor response to systemic chemotherapy and later died of disseminated metastases.

Based on this report, with the use of a barium study and CT imaging, a gastric large cell neuroendocrine carcinoma was depicted as an ulcerofungating tumor with minimal peritumoral infiltration and metastatic lymphadenopathy in the perigastric area. These features are

similar in appearance to advanced gastric cancer, especially Borrmann type II. It is difficult to make a differential diagnosis of the two-disease entities by the use of imaging findings. However, a gastric large cell neuroendocrine carcinoma is highly malignant with a significantly worse prognosis than a usual adenocarcinoma.

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# 위장에 생긴 대세포 신경내분비암 4예 보고: CT와 바륨검사 영상소견[1]


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위장에서 발생하는 대세포 신경내분비암은 극히 드물다. 저자들은 이 질환을 가진 네 명의 환자들의 의무 기록과 영상소견을 고찰하였다. 바륨검사와 CT에서 위장 대세포 신경내분비암은 궤양융기성 종양으로 보였고, 종양 주변부 침윤과 전이성 림프절들이 위장 주위에서 관찰되었다. 이들 영상소견은 Borrmann 2형 진행성 위암과 비슷하였다. 그러나 위장 대세포 신경내분비암은 보통 위암보다 매우 나쁜 예후를 보이는 악성도가 높은 종양이다.