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Case Report

Large Cell Neuroendocrine Carcinoma of the Stomach

Seiya SUSUMU,[1] Shigetoshi MATSUO,[1] Takashi AZUMA,[1] Nozomu SUGIYAMA,[1] Satoshi YAMAGUCHI,[1] Tomayoshi HAYASHI,[2] Takashi KANEMATSU[3]

[1] Departments of Surgery, Nagasaki Prefectural Shimabara Hospital, Nagasaki, Japan

[2] Department of Pathology, Nagasaki Prefectural Shimabara Hospital, Nagasaki, Japan

[3] Division of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

A 69-year-old man was admitted to our hospital with loss of appetite, constipation and diarrhea. Upper gastrointestinal barium study and endoscopy revealed a Borrmann type III-like gastric cancer. Biopsy specimens showed poorly differentiated adenocarcinoma. Total gastrectomy with lymph nodes dissection was performed. The tumor histologically consisted of diffuse proliferation of large and round cells presenting as an organoid, trabecular or sheet-like structure accompanied by a small amount of multinuclear giant cells. The tumor cells were histochemically positive for Grimelius stain and were immunohistochemically, extensively and diffusely positive for chromogranin A. These findings led us to a diagnosis of large cell neuroendocrine carcinoma (LCNEC). This entity of the stomach is not clearly recognized at present. Clinicopathological characteristics of LCNEC of the stomach must be defined so that an appropriate treatment can be developed.

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Introduction

Large cell neuroendocrine carcinoma (LCNEC) has not been well described in the alimentary tract because of their apparently low frequency.[1] In contrast, neuroendocrine tumor (NET) of the lung was clearly classified into three categories in the new WHO classification as low-grade typical carcinoid (TC), intermediate-grade atypical carcinoid (AC), and high-grade neuroendocrine carcinoma (NEC) including small cell neuroendocrine carcinoma (SCNEC) and LCNEC because of the difference in their epidemiology, clinical behavior, and therapeutic strategy.[2] It is important to establish the clinicopathological characteristics of LCNEC of the stomach for developing appropriate treatment. We herein present a case of LCNEC of the stomach and discuss this rare entity.

Case report

A 69-year-old man was admitted to Nagasaki Prefectural Shimabara Hospital in August 2005, with loss of appetite, constipation and diarrhea since one month before admission. On admission, a palpable mass, which was 8 cm × 8 cm and slightly tender to touch, was present in the upper abdominal region. The results of complete blood counts and blood chemistry were within normal limits. Tumor markers such as carcinoembryonic antigen and cancer antigen 19-9 were within normal limits. An upper gastrointestinal series showed a large ulcerative tumor on the anterior to posterior wall of the middle body to the antral lesser curvature of the stomach (Figure 1 A). Endoscopy showed a narrowing of the gastric lumen caused by the tumor. Biopsy specimens revealed poorly differentiated adenocarcinoma. Abdominal computed tomography showed a thickening of the gastric wall.

A total gastrectomy with regional lymph nodes dissection was performed in August 2005. The surgical findings were T3N2M0, which is classified as Stage IIIb.[3] Resected specimens revealed a Borrmann type III tumor measured 11.5 cm × 10.5 cm (Figure 1 B). Histologically, the tumor consisted of diffuse proliferations of large and round cells with a small amount of multinuclear giant cells presenting an organoid, trabecular or sheet-like structure (Figure 2 A, B and C). The tumor cells were histochemically positive for

Address correspondence: Seiya Susumu, M.D., Department of Surgery, Nagasaki Prefectural Shimabara Hospital, 7895 Shimokawajiri, Shimabara, Nagasaki 855-0861 JAPAN

TEL: +81-(0)957-63-1145, FAX: +81-(0)957-63-4864, E-mail: susumu_gi@mac.com

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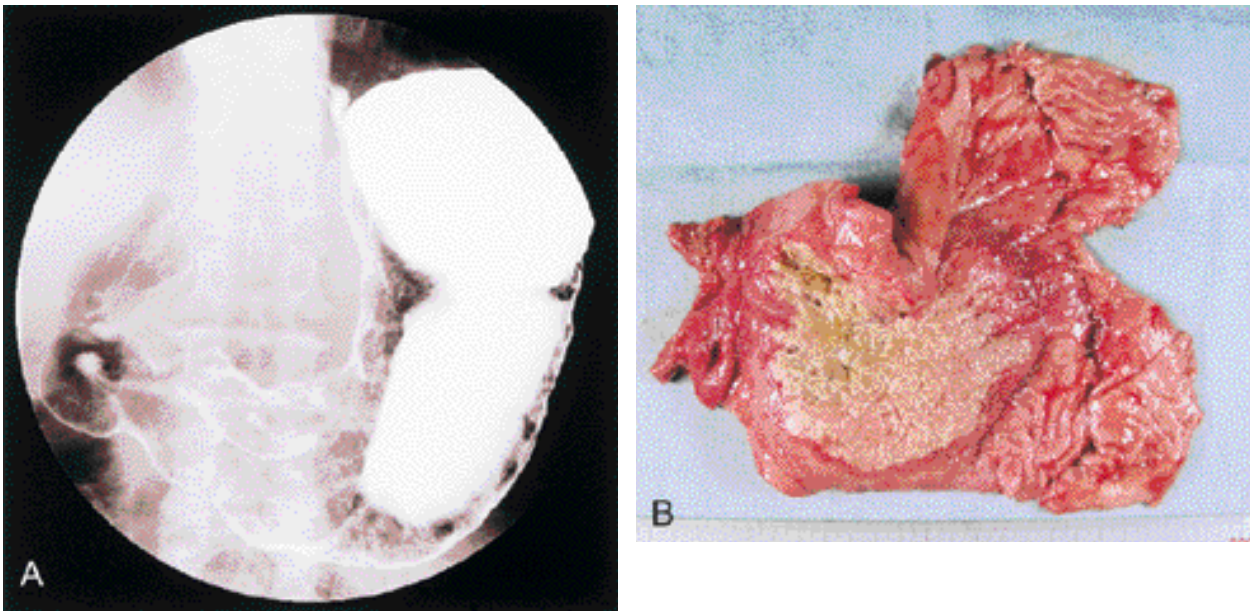

Figure 1. A. Upper GI series showing a large ulcerated tumor located in the lesser curvature of the stomach. **B.** Resected specimen showing a Borrmann type III-like tumor.

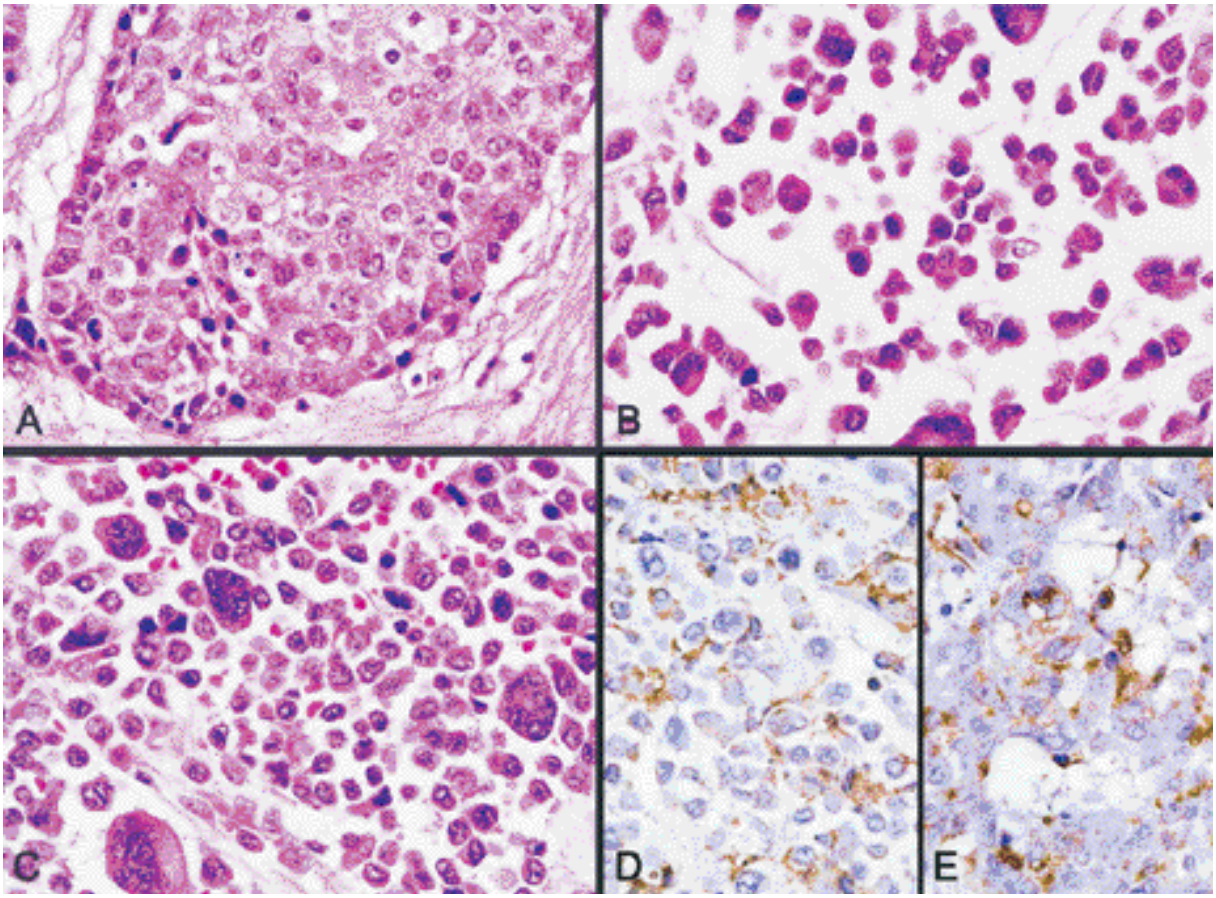

Figure 2. Histologically, the tumor consisted of diffuse proliferation of large and round cells with a small amount of multinuclear giant cells presenting organoid (A), trabecular (B) or sheet-like structure (C). The tumor cells immunohistochemically showed positive staining for epithelial membrane antigen (D) and chromogranin A (E).

Grimelius stain, and immunohistochemically showed positive staining for epithelial membrane antigen and chromogranin A (Figure 2 D and E). The tumor cells showed negative staining for synaptophysin, neuron-specific enolase, and leucocyte common antigen. Based on these histological, histochemical and immunohistochemical findings, we diagnosed this case as LCNEC. Multiple liver metastases occurred two months after operation. Though we suggested chemotherapy, the patient refused any further therapies. He died in July 2006.

Discussion

Pulmonary LCNEC is a newly defined high-grade tumor entity of non-small cell type, which was introduced in the new WHO classification[2] published in 1999 because the previous simple classification into TC, AC, and small cell lung carcinoma was not precise enough.[4,5] In the WHO classification of gastric tumors published in 1990,[6] only carcinoids and small cell carcinomas are included in the NET category. Matsui et al.[1] subdivided NECs of the stomach into two variants, i.e. SCNEC and LCNEC.

Pulmonary LCNEC is uncommon with the prevalence of 3% in surgically resected lung cancers.[7] LCNEC of the stomach is more uncommon with the prevalence of 0.7-1.0% in surgically resected gastric cancers.[1,8]

The most difficult issue in diagnosing LCNEC of the stomach is how to recognize its neuroendocrine morphology. Most LCNECs of the stomach showed solid growth, and the most important issue is to distinguish them from poorly differentiated solid adenocarcinoma.[8,9] In the present patient, the diagnosis of LCNEC was based on both large cell size and morphologic features such as organiod, trabecular and sheet-like structure. Furthermore, there were no adnocarcinoma components. Generally, organoid, trabecular, and pseudoglandular patterns are more frequently observed in LCNEC than in SCNEC. Of these findings, the pseudoglandular pattern is characteristic in LCNEC.[1] However, the pseudoglandular pattern was not seen in our patient. On the other hand, there was no report about the presence of multinuclear giant cells which were observed in our patient. Furthermore, a high mitotic count, large polygonal cells, a low nuclear-cytoplasmic ratio, coarse nuclear chromatin, and conspicuous nucleoli are more frequently observed in LCNEC than in SCNEC by high-power view.[1]

Immunohistochemically, chromogranin A, synaptophysin, and neural cell adhesion molecules were reported to be specific to various neuroendocrine markers.[1,8,10] The aim to subclassify LCNEC of the stomach is to elucidate its prognostic implication. Jiang et al.[8] subdivided histologically suspicious LCNEC into narrowly defined LCNEC and adenocarcinoma with neuroendocrine differentiation (ACNED) according to expressing neuroendocrine markers. Specifically, when neuroendocrine phenotype in tumor cells assessed by immunohistochemistry for chromogranin A and/or synaptophysin exceeded 20%, LCNEC was defined, while ACNED was defined when it was in the range from 1% to approximately 20%. In the present patient, the specimen showed extensively and diffusely positive staining for chromogranin A (approximately 80% of tumor cells) but negative staining for synaptophysin and neuron-specific enolase. These findings led us to the correct diagnosis of LCNEC. The 5-year survival rates for LCNEC (n=65), ACNED (n=20) and conventional adenocarcinoma (n=307) were approximately 30%, 50% and 70% respectively; the difference was significant between LCNEC and conventional adenocarcinoma (p= 0.00469), while it was slightly not significant between ACNED and conventional adenocarcinoma (p=0.0568).[8] There was also no significant difference in survival time between SCNEC and LCNEC of the stomach; the mean survival time was 14.2 months and 15.2 months, respectively.[1]

These findings suggest that LCNEC of the stomach has poor prognosis as have general NECs of the alimentary tract including the stomach.[9-15]

Patients with LCNEC of the lung have very poor prognosis, and the benefits of surgical treatment or chemotherapy for these patients have not yet been established;[16] benefits are even less clear in LCNEC of the stomach. Clinicopathological characteristics of LCNEC of the stomach must be defined to develop an appropriate treatment.

If gastric carcinomas show morphologically any neuroendocrine appearances such as organoid, trabecular, rosette or pseudoglandular patterns, immunohistochemical study should be recommended.

References

1. Matsui K, Jin XM, Kitagawa M, Miwa A. Clinicopathologic features of neuroendocrine carcinomas of the stomach: appraisal of small cell and large cell variants. *Arch Pathol Lab Med* 122: 1010-1017, 1998
2. Travis WD, Colby TV, Corrin B, Shimosato Y, Brambilla E. In Collaboration with Sobin LH and Pathologists from 14 Countries. *World Health Organization International Histological Classification of Tumours, Histological Typing of Lung and Pleural Tumours, 3rd edition*. Springer-Verlag, Tokyo, 1999
3. Sobin LH, Fleming ID. TNM Classification of Malignant tumors, fifth edition (1997). Union Internationale Contre le Cancer and the American Joint Committee on Cancer. *Cancer* 80: 1803-1804, 1997
4. Hammond ME, Sause WT. Large cell neuroendocrine tumors of the lung. Clinical significance and histopathologic definition. *Cancer* 56: 1624-1629, 1985
5. Travis WD, Linnoila RI, Tsokos MG et al. Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. *Am J Surg Pathol* 15: 529-553, 1991
6. Jass JR, Sobin LH, Watanabe H. The World Health Organization's histologic classification of gastrointestinal tumors. A commentary on the second edition. *Cancer* 66: 2162-2167, 1990
7. Jiang SX, Kameya T, Shoji M, Dobashi Y, Shinada J, Yoshimura H. Large cell neuroendocrine carcinoma of the lung: a histologic and immunohistochemical study of 22 cases. *Am J Surg Pathol* 22: 526-537, 1998
8. Jiang SX, Mikami T, Umezawa A, Saegusa M, Kameya T, Okayasu I. Gastric large cell neuroendocrine carcinomas: a distinct clinicopathologic entity. *Am J Surg Pathol* 30: 945-953, 2006
9. Staren ED, Lott S, Saavedra VM et al. Neuroendocrine carcinomas of the stomach: a clinicopathologic evaluation. *Surgery* 112: 1039-1046; discussion 1046-1037, 1992
10. Brambilla E, Travis WD, Colby TV, Corrin B, Shimosato Y. The new World Health Organization classification of lung tumours. *Eur Respir J* 18: 1059-1068, 2001
11. Mazieres J, Daste G, Molinier L et al. Large cell neuroendocrine carcinoma of the lung: pathological study and clinical outcome of 18 resected cases. *Lung Cancer*

37: 287-292, 2002
12. Rindi G, Luinetti O, Cornaggia M, Capella C, Solcia E. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. *Gastroenterology* 104: 994-1006, 1993
13. Hsu W, Deziel DJ, Gould VE, Warren WH, Gooch GT, Staren ED. Neuroendocrine differentiation and prognosis of extrahepatic biliary tract carcinomas. *Surgery* 110: 604-610; discussion 610-601, 1991
14. Warren WH, Faber LP, Gould VE. Neuroendocrine neoplasms of the lung. A clinicopathologic update. *J Thorac Cardiovasc Surg* 98: 321-332, 1989
15. Staren ED, Gould VE, Warren WH et al. Neuroendocrine carcinomas of the colon and rectum: a clinicopathologic evaluation. *Surgery* 104: 1080-1089, 1988
16. Iyoda A, Hiroshima K, Moriya Y et al. Prospective study of adjuvant chemotherapy for pulmonary large cell neuroendocrine carcinoma. *Ann Thorac Surg* 82: 1802-1807, 2006