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Case Report

A Case of Large Cell Neuroendocrine Carcinoma of the Colon Responding to FOLFOX

Seiya SUSUMU,[1] Shigetoshi MATSUO,[1] Ryuji TSUTSUMI,[1] Nozomu SUGIYAMA,[1] Takashi AZUMA,[1] Satoshi YAMAGUCHI,[1] Naoe KINOSHITA,[2] Tomayoshi HAYASHI[2]

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

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

A 48-year-old woman was admitted to our hospital with abdominal fullness and pain. A barium enema and endoscopy revealed a Borrmann type II-like tumor of the sigmoid colon. Biopsy specimens showed poorly differentiated adenocarcinoma. Sigmoidectomy with lymph nodes dissection was performed. The tumor histologically consisted of proliferation of large and polygonal cells showing an organoid, trabecular or rosette-like pattern. Many mitotic figures were also observed. The tumor cells were immunohistochemically positive for chromogranin A. These findings led us to a diagnosis of large cell neuroendocrine carcinoma (LCNEC). Six months after surgery, liver metastases, para-aortic lymph node metastases and local recurrence were identified, and we commenced to administer FOLFOX, a combination of l-leucovorin and 5-fluorouracil with oxaliplatin. After six courses, a partial response was observed. This entity of the colon is not clearly recognized at present. The clinicopathological characteristics of LCNEC of the colon must be defined so that an appropriate treatment can be developed. Since LCNEC of the lung has been reported to be of high-grade malignancy, LCNEC of the colon must be treated as potentially highly malignant. In addition, the present case suggested that FOLFOX is a promising treatment for LCNEC of the colon.

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Introduction

Large cell neuroendocrine carcinoma (LCNEC) has not been described well in the colon or rectum because of their obviously low frequency.[1,2] Recently, the World Health Organization (WHO) classified neuroendocrine tumor (NET) of the colon and rectum into the following three categories because of the difference in epidemiology, clinical behavior and therapeutic strategy: carcinoid tumor, small cell carcinoma (SCC) and LCNEC.[3] It is important to establish the clinicopathological characteristics of LCNEC of the colon and rectum for developing appropriate treatment. We herein present a case of LCNEC of the colon, with liver metastases, para-aortic lymph node metastases and local recurrence, which demonstrated a marked response to systemic chemotherapy by a combination of l-leucovorin (l-LV) and 5-fluorouracil (5-FU) with oxaliplatin (FOLFOX).

Case report

A 48-year-old woman was admitted to Nagasaki Prefectural Shimabara Hospital in January 2006, having experienced abdominal fullness and pain for the last one month. On admission, a palpable mass, which measured about 8 cm × 8 cm and felt slightly soft, was present in the left lower quadrant of the abdomen. Laboratory data were within normal limits except the 23.6 ng/mL of carcinoembryonic antigen (CEA) (normal range: 0-5 ng/mL). Barium enema revealed lumen slightly narrowed by wall thickening in the sigmoid colon (Figure 1). Endoscopy revealed a Borrmann type II-like tumor of the sigmoid colon, and biopsy specimens revealed poorly differentiated adenocarcinoma. Abdominal computed tomography (CT) revealed a bulky and poorly enhanced mass encircling the sigmoid colon (Figure 2).

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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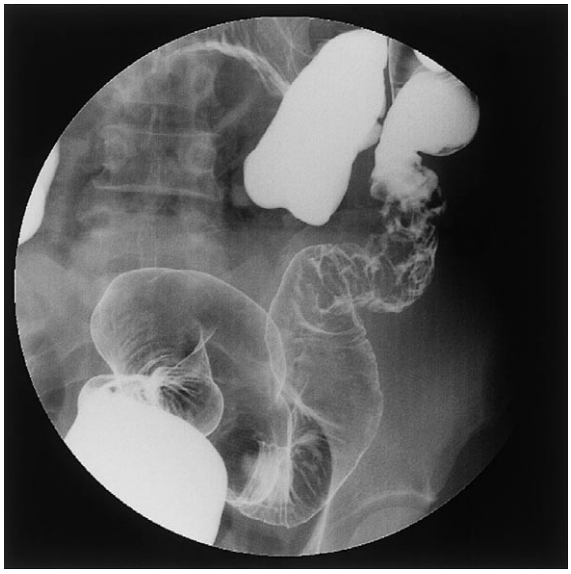

Figure 1. Barium enema revealed lumen slightly narrowed by wall thickening in the sigmoid colon.

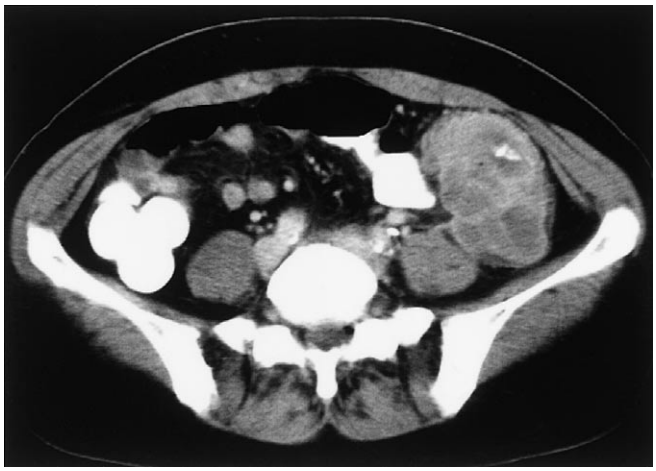

Figure 2. CT at arterial phase revealed a bulky and poorly enhanced mass encircling the sigmoid colon.

Sigmoidectomy with regional lymph node dissection was performed 5 days after admission. The surgical findings were T3, N1, M0, and the stage was classified as IIIA.[4] Resected specimens revealed a Borrmann type II- like tumor measuring 8.0 cm × 7.5 cm. The tumor mainly grew to extralumen (Figure 3). The tumor histologically consisted of proliferation of large and polygonal cells showing an organoid, trabecular or rosette-like pattern. Many mitotic figures were also observed (Figure 4 A, B and C). The tumor cells showed immunohistochemically positive staining for epithelial membrane antigen and chromogranin A (Figure 4 D), while showing slightly positive staining for neuron-specific enolase and negative staining for synaptophysin. Based on these histological and immunohistochemical findings, we diagnosed the case as LCNEC.

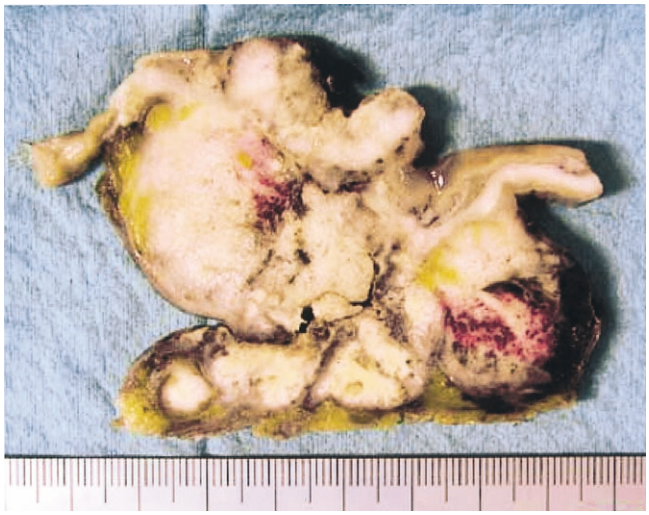

Figure 3. Resected specimens revealed a Borrmann type II-like tumor measuring 8.0 cm × 7.5 cm. The tumor mainly grew to extralumen.

The patient was treated with S-1 (TS-1) as an adjuvant chemotherapy. The schedule was to repeat 80 mg/ body weight of TS-1 (day 1-28, orally) with 2-week drug-free interval. In July 2006, the CEA level was increased to 193.0 ng/mL, and abdominal CT revealed liver metastases, para-aortic lymph node metastases and local recurrence (Figure 5 A and C). Systemic chemotherapy with FOLFOX was started and was scheduled as follows: to administer 85 mg/m^2 of oxaliplatin by 2-hour infusion on day 1; to administer 100 mg/m^2 of l-LV by 2-hour infusion on days 1 and 2; subsequent intrabolus of 400 mg/m^2 of 5-FU, then administration of 600 mg/m^2 of 5-FU with ambulatory pump over 22 hours on days 1 and 2 every 2 weeks (FOLFOX4). After six courses of FOLFOX4, the liver metastases and local recurrence showed a marked reduction in size and were judged to be showing a partial response (Figure 5 B and D). The CEA level was then decreased to 7.0 ng/mL.

Discussion

The entity of LCNEC of the colon and rectum showing a large cell proliferation but definite neuroendocrine morphology was introduced in the new WHO classification[3] in 2000. Reports on LCNEC of the colon and rectum are few, totaling approximately 25 patients to date.[1,2,5,6]

Diagnosing as LCNEC seems to be extremely difficult because this is a rare and newly defined entity. Travis et al.[7] proposed a category of LCNEC of the lung, which is characterized by: (i) light microscopic neuroendocrine appearance; (ii) cells of large size (threefold larger than lymphocytes), polygonal shape, low nuclear-cytoplasmic ratio, coarse nuclear chromatin and frequent nucleoli; (iii) a high mitotic rate (>10/10 high-power fields (HPF)); and (iv) neuroendocrine features by immunohistochemistry or electron microscopy.

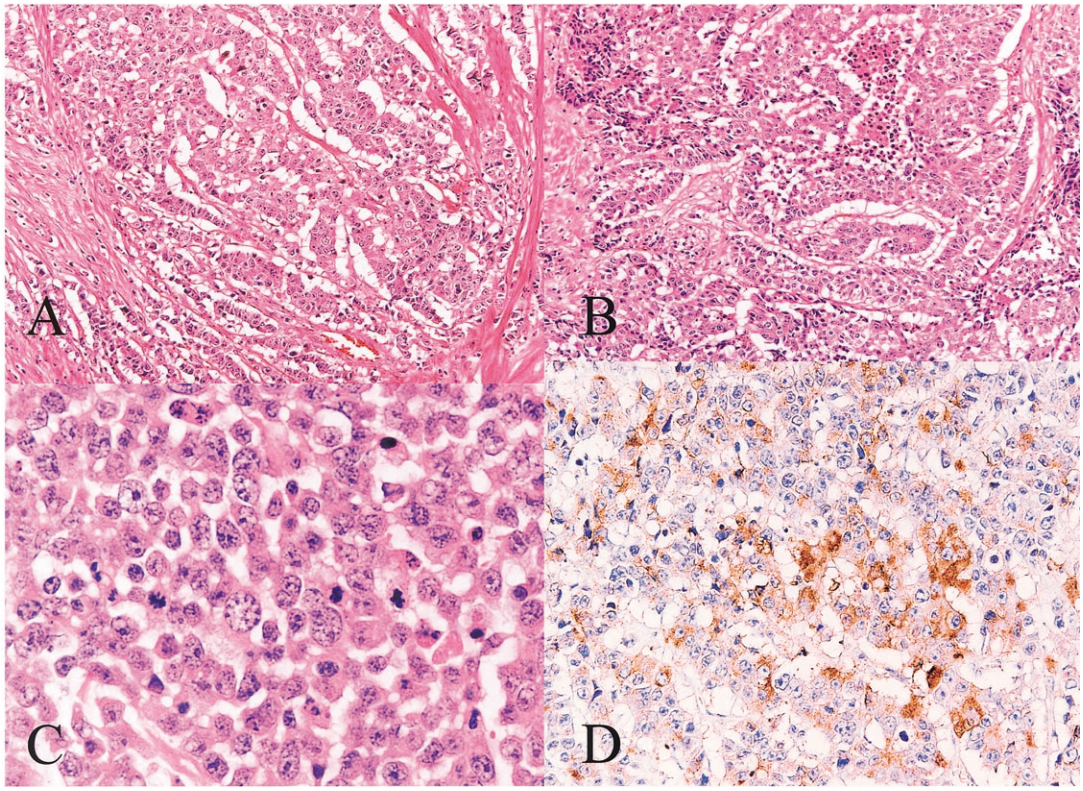

Figure 4. The tumor histologically consisted of proliferation of large and polygonal cells showing an organoid, trabecular or rosette-like pattern. Many mitotic figures were also seen (**A**, **B** and **C**). The tumor cells were immunohistochemically positive for chromogranin A (**D**).

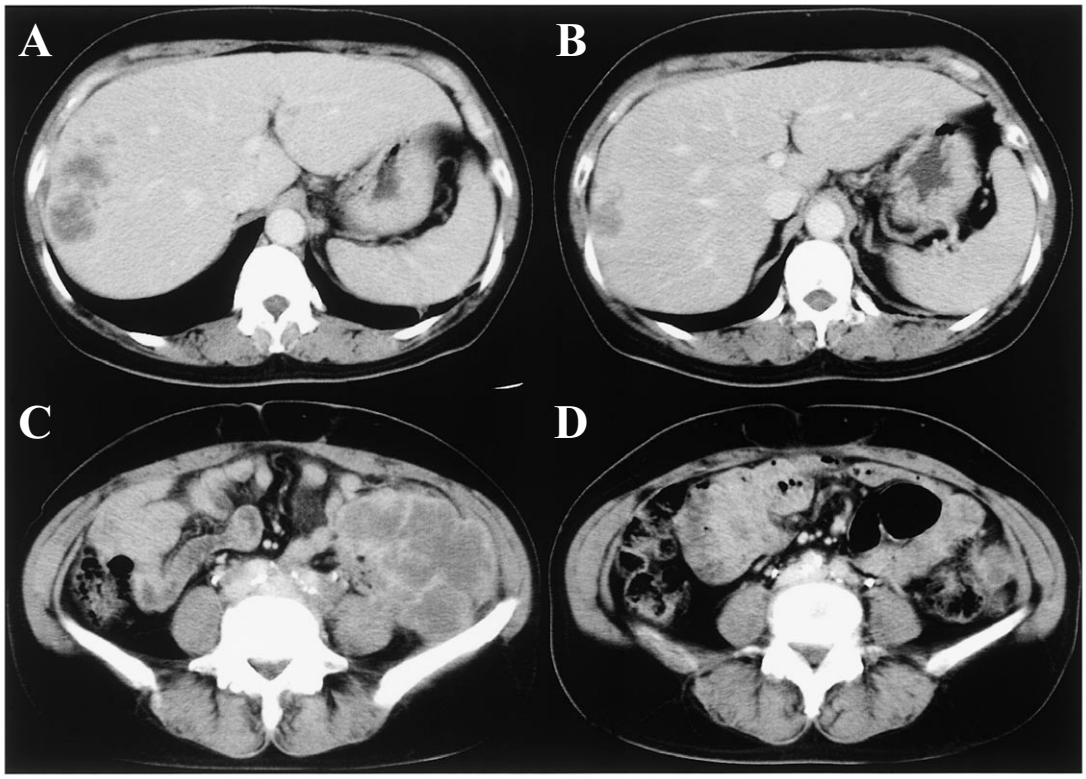

Figure 5. CT at venous phase revealed liver metastases and local recurrence (**A** and **C**). After 6 courses of FOLFOX4, the liver metastases and local recurrence showed a marked reduction in size and were judged to be exhibiting a partial response (**B** and **D**).

The present case fulfilled most of these criteria of LCNEC already described herein. We therefore diagnosed the present case as LCNEC of the sigmoid colon. LCNEC of the colon and rectum may be diagnosed as poorly differentiated adenocarcinoma or other adenocarcinoma because immunohistochemical studies by using various neuroendocrine markers are essential for the definitive diagnosis of LCNEC. If cancer of the colon and rectum show morphologically any neuroendocrine appearances such as organoid, trabecular or rosette-like pattern, immunohistochemical study should be recommended.

The aim to subclassify NET of the lung was to elucidate its prognostic implication. There is a highly significant difference in survival between patients with typical carcinoid (TC) and atypical carcinoid (AC), and between patients with AC and LCNEC.[8] The 5-year survival rate was reported to be 94% in TC, 55% in AC, 9% in SCC, and 27% in LCNEC.[9,10] In a comparison between SCC and LCNEC of the colon and rectum, the mean survival time has been reported to be 10.4 months and 10.7 months, respectively. In addition, there was no significant difference in the overall survival curve between SCC and LCNEC.[1] These statistics suggest that LCNEC of the colon and rectum has a poor prognosis similar to that of LCNEC of the lung.

Patients with LCNEC of the lung have a very poor prognosis, but the benefits of chemotherapy for these patients have not been established,[11] and the benefits are even less clear in LCNEC of the colon and rectum.

In conventional carcinoma of the colon and rectum, FOLFIRI and FOLFOX are standard first-line regimens[12-14]; FOLFIRI is a combination of l-leucovorin and 5-fluorouracil with irinotecan. According to one report,[2] FOLFIRI administered to a patient with LCNEC of the colon could not reduce the tumor size, and the tumor was judged as no response. On the other hand, the use of FOLFOX for LCNEC of the colon and rectum has not been reported till now. The present study is the first case report on the use of FOLFOX for LCNEC colon and rectum. We observed a marked response suggesting that FOLFOX would be a promising candidate for chemotherapy of LCNEC of the colon and rectum.

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