CASE REPORT
Journal of Digestive Cancer Reports 3(1):26-29, 2015
ISSN 2288-1581
http://www.gicancer.or.kr

A Case of Gastric Large Cell Neuroendocrine Carcinoma with Multiple Liver Metastasis Treated with Hepatic Artery Infusion Chemotherapy Followed by Surgery

Sung Bum Kim, Kook Hyun Kim, Tae Nyeun Kim

Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea

A 73-year-old male visited our hospital with a complaint of general weakness. He underwent pyloric preserving pancreatoduodenectomy due to ampullary cancer three years ago. Abdominal computed tomography scan at initial visit revealed multiple hepatic masses. A PET-CT scan showed multiple FDG uptakes at whole liver. He underwent hepatic artery infusion chemotherapy (HAIC) for five cycles. During the first cycle of HAIC, he developed gastric ulcer bleeding and endoscopic hemostasis was done successfully. Esophagogastroduodenoscopy after the 5th cycle of HAIC revealed ulcer scar at gastric angle. PET-CT scan at 12 months showed no FDG uptake at liver, but a focal FDG uptakes at stomach and peri-gastric lymph nodes were newly developed. Esophagogastroduodenoscopy revealed about 3 cm sized mass at gastric angle. He underwent surgery and pathologic examination revealed large cell neuroendocrine carcinoma. We report a case of gastric large cell neuroendocrine carcinoma with liver metastasis treated with HAIC followed by surgery.

Key Words: Neuroendocrine carcinoma, Liver metastasis, Intra-arterial chemotherapy

INTRODUCTION

Neuroendocrine neoplasms are defined as epithelial neoplasms with predominant neuroendocrine differentiation showing positive immunohistochemical stains for synaptophysin and chromogranin A.[1] Neuroendocrine neoplasms are classified as neuroendocrine tumor grade 1, 2 and neuroendocrine carcinoma grade 3 according to the level of cellular proliferation by 2010 World Health Organization (WHO) classification.[2] Neuroendocrine carcinoma grade 3 includes small and large cell neuroendocrine carcinoma which shows poorly differentiated morphology, featuring aggressive tumor behavior, and 5-year-survival rate of large cell neuroendocrine carcinoma has been reported to be 31.1% in a previous study.[3] We report a case of gastric large cell neuroendocrine carcinoma with liver metastasis treated with hepatic artery infusion chemotherapy (HAIC) followed by surgery.

Received: May 26, 2015. Accepted: June 24, 2015
Corresponding Author: **Tae Nyeun Kim**, MD, PhD
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Yeungnam University College of Medicine, 170, Hyeonchung-ro, Daemyeong-dong, Nam-gu, Daegu 705-703, Korea
Tel: +82-53-620-3842, Fax: +82-53-654-8386
E-Mail: tnkim@yu.ac.kr

CASE REPORT

A 73-year-old male visited our hospital with a complaint of general weakness for a few months. The patient underwent pyloric preserving pancreatoduodenectomy due to ampulla of Vater cancer three years ago and pathologic examination of surgical specimen showed moderate differentiated adenocarcinoma of ampulla of Vater with focal duodenal invasion. The resection margins were free of tumor and TNM stage of the ampulla of Vater cancer was ll. The patient had medical history of benign prostatic hyperplasia, hypertension, chronic kidney disease and cerebrovascular accident. He had no significant familial history, and was a non-smoker. On the review of system, he complained of general weakness, easy fatigue, poor oral intake and weight loss. Physical examination on the abdomen revealed a palpable mass at the right upper quadrant area without tenderness. He had stable vital signs and the initial laboratory evaluation showed a white blood cell 6,890 cells/μL, hemoglobin 11.7 g/dL, platelet 1.84×10^5 cells/μL, total protein 6.14 g/dL, albumin 3.49 g/dL, total bilirubin 0.56 mg/dL, aspartate aminotransferase 31 IU/L, alanine aminotransferase 23 IU/L, alkaline phosphatase 255 IU/L, γ-glutamyl transpeptidase 116 IU/L, lactate dehydrogenase 492 IU/L, blood urea nitrogen 49.13 mg/dL, and creatinine 3.14

mg/dL. Of tumor marker, carbohydrate antigen 19-9 level was 12.42 U/mL (reference range: 0-37 U/mL). Abdominal computed tomography (CT) scan at admission revealed multiple low density lesions at whole liver, suggesting metastasis (Fig. 1). A positron emission tomography-computed tomography (PET-CT) scan revealed multiple ^{18}F-fluorodeoxyglucose (FDG) uptakes at both lobes of liver (Fig. 2A). HAIC was planned for the treatment of metastatic liver masses. The patient underwent hepatic arteriography to place indwelling catheter for HAIC and after placing coils at A6-7 branches of hepatic artery, a tip of 5.8-F indwelling intra-arterial catheter was successfully placed at the proper hepatic artery under fluoroscopic guidance. The regimen of HAIC consisted of 5-FU (750 mg/m^2) and cisplatin (25 mg/m^2) on days 1-4 every four weeks. On the 2nd day of first cycle of HAIC, the patient developed hematochezia and esophagogastroduodenoscopy (EGD) demonstrated about 3 cm sized ulcer with oozing at anterior wall of gastric angle (Fig. 3A) and endoscopic hemostasis was done successfully using injection of 30 cc of diluted epinephrine and cauterization with mono-polar probe. Due to acute kidney injury caused by gastric ulcer bleeding, he underwent hemodialysis for 10 days. After recovering from acute kidney injury, the patient underwent rest cycle of the HAIC. After the 3rd cycle of HAIC, a PET-CT scan showed decrease in FDG uptake and the number of hepatic masses, suggesting partial response (Fig. 2B). After the 5th cycle of HAIC, the patient developed grade 4 neutropenia and thrombocytopenia according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) scale.[4] Follow-up EGD after the 5th cycle of chemotherapy revealed ulcer scar at gastric angle (Fig. 3B), however, biopsy was not performed due to severe thrombocytopenia caused by chemotherapy. Further chemotherapy could not be performed due to risk of side effects. Follow-up PET-CT scan at 12 months illustrated the contracted hepatic masses without FDG uptake in liver, but with a newly developed focal FDG uptake at stomach and lymph node around left gastric artery (Fig. 2C). An EGD demonstrated about 3cm sized fungating mass at gastric angle (Fig. 3C) and biopsy specimen was histologically confirmed as neuroendocrine carcinoma. The patient underwent wedge resection of the gastric lesion combined with lymph node dissection and the resected specimen was pathologically confirmed as large cell neuroendocrine carcinoma with poor differentiation and lymph node metastasis (1/3) in which medium-sized tumor cells were arranged in sheets or trabecular patterns with fine fibrous connective tissue, showing positive immunohistochemical staining for chromogranin A, synaptophysin and CD56 (Fig. 4 A and B). The level of cellular proliferation showed 65 mitoses per 10 high-power fields

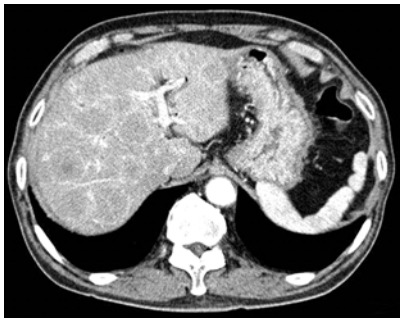

Fig. 1. Abdominal computed tomography scan at initial visit demonstrated multiple low density lesions at whole liver, suggesting metastasis.

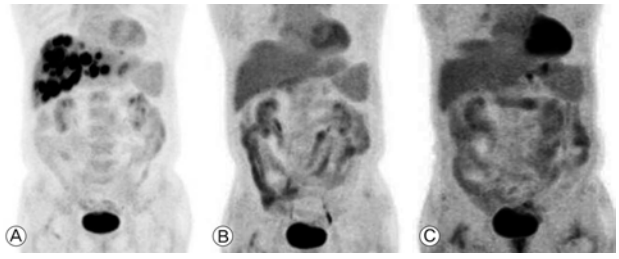

Fig. 2. PET-CT scan (**A**) at initial visit showed multiple hypermetabolic spots at liver, (**B**) after the 3rd cycle of HAIC demonstrated decrease in FDG uptake and number of hepatic masses, suggesting partial response and (**C**) at 12 months showed no demonstrable FDG uptake at liver, however, showed the newly developed FDG uptake at stomach and lymph node around left gastric artery.

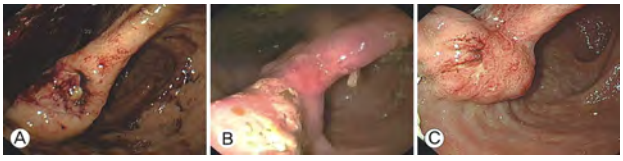

Fig. 3. Esophagogastroduodenoscopy (**A**) at the 2nd day of the first cycle of chemotherapy revealed about 3 cm sized ulcer with oozing at anterior wall of gastric angle, (**B**) after the 5th cycle of chemotherapy revealed ulcer scar at gastric angle and (**C**) at 12 months demonstrated about 3 cm sized fungating mass at gastric angle.

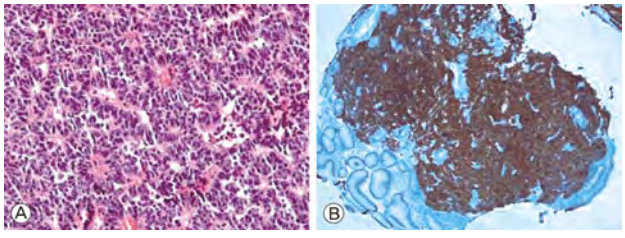

Fig. 4. Microscopic examination of resected specimen revealed (**A**) diffuse proliferation of poorly differentiated, medium-sized tumor cells arranged in sheets or trabecular patterns with fine fibrous connective tissue and (**B**) positive immunostaining for chromogranin A.

and the positivity for 90% of Ki-79 proliferation on immunohistochemical staining. The patient died after 17 months from initial diagnosis.

DISCUSSION

Neuroendocrine neoplasms of stomach are uncommon, comprising 2-6% of all gastrointestinal neuroendocrine neoplasms[5] and gastric large cell neuroendocrine carcinoma which has been designated as neuroendocrine carcinoma grade 3 by 2010 WHO classification are rarely reported, comprising 1.5% of all gastric cancers. Our case showed positive immunohistochemical staining for both synaptophysin and chromogranin A with Ki-79 proliferation of 90% and 65 mitoses per 10 high-power fields, compatible with neuroendocrine carcinoma grade 3 according to 2010 WHO classification. Gastric large cell neuroendocrine carcinoma features aggressive disease behavior with extensive metastasis and showed poor overall survival of 6.6 months and even worse prognosis than gastric adenocarcinoma.[3,6] Our case showed no symptoms of carcinoid syndrome, consistent with previous reports.[7] Gastric neuroendocrine carcinoma can arise in any part of the stomach and in our case, gastric neuroendocrine carcinoma was found at the angle of the stomach. The previous study reported that gastric large cell neuroendocrine carcinoma is known to make metastasis preferentially to lymph node, liver and peritoneum[8] and in this case, metastasis of gastric neuroendocrine carcinoma was found in peri-gastric lymph nodes and liver. Treatment options for hepatic metastasis from neuroendocrine neoplasms include surgery, local ablative therapies, angiography-guided chemoembolization of hepatic artery, and systemic chemotherapy.[9] In our case, HAIC was performed after performing coil embolization of collateral vessels of hepatic artery for treatment of hepatic metastasis from neuroendocrine carcinoma. Complete metabolic remission of hepatic metastasis from gastric large cell neuroendocrine carcinoma was achieved in PET-CT scan at 12 months from initial HAIC. As hepatic artery is the major blood supplier for hepatic metastasis and FDG positivity of PET-CT scan correlates with Ki-67 index and prognosis,[10] HAIC seems to be an effective method for controlling metastasis confined to liver from gastric large cell neuroendocrine carcinoma. Most frequently used systemic chemotherapy regimens for neuroendocrine carcinoma is cisplatin-based regimens, including cisplatin with irinotecan or etoposide, with response rate ranging from 25 to 40%.[11,12] In our case, due to the limitation of medical insurance coverage in Korea, cisplatin and 5-FU was used for HAIC. However, further studies to identify optimal regimen and efficacy of HAIC in patients with hepatic metastasis from neuroendocrine carcinoma are needed. We report a case of gastric large cell neuroendocrine carcinoma with liver metastasis treated with HAIC followed by surgery.

SUMMARY

Large cell neuroendocrine carcinoma of stomach which has been designated as neuroendocrine carcinoma grade 3 by 2010 WHO classification are rarely reported, comprising 1.5% of all gastric cancers. Gastric large cell neuroendocrine carcinoma shows aggressive disease behavior with extensive metastasis and poor overall survival of 6.6 months. Gastric large cell neuroendocrine carcinoma is known to make metastasis preferentially to lymph node, liver and peritoneum in previous reports. Treatment options for patients with hepatic metastasis from neuroendocrine neoplasms includes surgery, local ablative therapies, angiography-guided chemoembolization of hepatic artery, and systemic chemotherapy. In our case, HAIC was performed after coil embolization of collateral vessels of hepatic artery for the treatment of hepatic metastasis from neuroendocrine carcinoma. A PET-CT scan demonstrated complete metabolic remission of hepatic metastasis from gastric large cell neuroendocrine carcinoma. HAIC seems to be an effective method for controlling metastasis confined to the liver originating from gastric large cell neuroendocrine carcinoma. Further studies to identify efficacy and optimal regimen of HAIC in patients with hepatic metastasis from neuroendocrine neoplasms are needed. We report a case of gastric large cell neuroendocrine carcinoma with liver metastasis treated with hepatic artery infusion chemotherapy followed by surgery.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008;9:61-72.
2. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system, World Health Organization, 2010.
3. 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 2006;30:945-953.
4. National Cancer Institute (U.S.). Common terminology crite-

ria for adverse events (CTCAE). Rev. ed. p194 p., Bethesda, Md., U.S. Dept. of Health and Human Services, National Institutes of Health, National Cancer Institute, 2009.
5. Yildiz O, Ozguroglu M, Yanmaz T, Turna H, Serdengecti S, Dogusoy G. Gastroenteropancreatic neuroendocrine tumors: 10-year experience in a single center. Med Oncol 2010;27: 1050-1056.
6. Rindi G, Bordi C, Rappel S, La Rosa S, Stolte M, Solcia E. Gastric carcinoids and neuroendocrine carcinomas: pathogenesis, pathology, and behavior. World J Surg 1996;20:168-172.
7. Boo YJ, Park SS, Kim JH, Mok YJ, Kim SJ, Kim CS. Gastric neuroendocrine carcinoma: clinicopathologic review and immunohistochemical study of E-cadherin and Ki-67 as prognostic markers. J Surg Oncol 2007;95:110-117.
8. Namikawa T, Oki T, Kitagawa H, Okabayashi T, Kobayashi M, Hanazaki K. Neuroendocrine carcinoma of the stomach: clinicopathological and immunohistochemical evaluation. Med Mol Morphol 2013;46:34-40.
9. QModlin IM, Latich I, Kidd M, Zikusoka M, Eick G. Therapeutic options for gastrointestinal carcinoids. Clin Gastroenterol Hepatol 2006;4:526-547.
10. Belhocine T, Foidart J, Rigo P, et al. Fluorodeoxyglucose positron emission tomography and somatostatin receptor scintigraphy for diagnosing and staging carcinoid tumours: correlations with the pathological indexes p53 and Ki-67. Nucl Med Commun 2002;23:727-734.
11. Kulke MH, Wu B, Ryan DP, et al. A phase II trial of irinotecan and cisplatin in patients with metastatic neuroendocrine tumors. Dig Dis Sci 2006;51:1033-1038.
12. Fjallskog ML, Granberg DP, Welin SL, et al. Treatment with cisplatin and etoposide in patients with neuroendocrine tumors. Cancer 2001;92:1101-1107.