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Five Cases of Esophageal and Gastric Neuroendocrine Carcinoma

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Abstract

Gastric or esophageal neuroendocrine carcinoma is very rare disease. Both biological and therapeutic features are different from the common type including pathological findings either squamous cell carcinoma or adenocarcinoma. We have experienced five cases of gastric and esophageal neuroendocrine carcinoma.

A 55-year-old woman visited our hospital complaining of upper abdominal pain. A type 2 tumor in the middle of the esophagus was detected by upper endoscopy, and multiple liver metastases were detected by Computed Tomography (CT). She underwent chemotherapy but she died within 15 months of being diagnosed with her disease.

A 73-year-old man visited our hospital complaining of light inguinal pain. A type 2 tumor in the lower of the esophagus was detected by upper-endoscopy and bone metastatic findings were seen in the left ilium. He underwent chemotherapy but he then developed progressive disease with increasing tumor markers.

A 56-year-old man visited our hospital complaining of digestive obstruction. A type 2 tumor in the lower-esophagus was detected by upper-endoscopy. He received chemotherapy after CT revealed an unrespectable state due to para-aortic lymph node metastasis. He was noted to have progressive disease based on CT. He is being maintained on chemotherapy.

A 74-year-old man visited our hospital complaining of reflux esophagitis. A type 2 tumor in body of his stomach was detected by upper-endoscopy and liver metastatic findings were detected on PET-CT, so we diagnosed neuroendocrine gastric carcinoma. He underwent chemotherapy. He died within 12 months of being diagnosed with his disease.

A 73-year-old man visited a different hospital with complaints of abdominal pain. A type 2 tumor in the antrum of the stomach was detected by upper endoscopy. He underwent surgery but he had a diagnosis of a recurrence in the pancreas.e.

Keywords: Small cell carcinoma • Neuroendocrine carcinoma • Gastric cancer • Oesophageal cancer • Cancer

Introduction

Gastric and esophageal neuroendocrine carcinoma is very rare tumors. Their biological and therapeutic features are different from the common types of tumors, including pathological findings for either squamous cell carcinoma or adenocarcinoma. The therapeutic regimen for neuroendocrine carcinoma is conducted based upon systemic chemotherapy for Small-Cell Lung Cancer (SCLC). Its malignant potential is higher than other pathological types and it has a poor prognosis because it resists anticancer treatment [1].

Literature Review

A 55-year-old woman visited our hospital complaining of upper abdominal pain in August 2012. A type 2 tumor in the middle of the esophagus was detected by upper endoscopy, and multiple liver metastases were detected by Computed Tomography (CT). Pathological findings were poorly differentiated squamous cell carcinoma at the initial diagnosis, but the final diagnosis was neuroendocrine carcinoma based on immunostaining for Neural Cell Adhesion Molecule (N-CAM). She underwent 6 cycles of chemotherapy (cisplatin plus etoposide). She had a partial response on her first follow-up CT. However, we changed her therapy to amrubicine therapy after adrenal metastasis was observed, and then we changed it to irinotecan therapy after brain metastasis occurred. She died within 15 months of being diagnosed with her disease [2].

A 73-year-old man visited our hospital complaining of light inguinal pain in August 2016. A type 2 tumor in the lower of the esophagus was detected by upper-endoscopy and bone metastatic findings were seen in the left ilium on Positron Emission Tomography (PET)-CT. An esophageal biopsy revealed small-sized tumor cells with minimal cytoplasm and hyperchromatic indistinct nucleoli by Hematoxylin Eosin (HE) staining. Because the immune pathological findings were positive for synaptophysin and the Ki67 index was 70%, we made a diagnosis of neuroendocrine esophageal carcinoma. He underwent 4 cycles of chemotherapy (cisplatin plus etoposide). We first decided that he had stable disease because his tumor markers decreased and there were no changes in his local and metastatic lesions. However, he then developed progressive disease with increasing tumor markers. He received amrubicin therapy but died within 10 months after being diagnosed with his disease [3].

A 56-year-old man visited our hospital complaining of digestive obstruction in September 2016. A type 2 tumor in the lower-esophagus was detected by upper-endoscopy. Pathological findings indicated poorly differentiated

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squamous cell carcinoma at the initial diagnosis, but we made a final diagnosis as neuroendocrine carcinoma based on immunostaining for synaptophysin and 26 mitoses per 10 High Power Field (HPF). He received 2 cycles of chemotherapy (cisplatin plus irinotecan) after CT revealed an unrespectable state due to para-aortic lymph node metastasis. He was noted to have progressive disease based on CT. He is being maintained on amrubicin therapy [4].

A 74-year-old man visited our hospital complaining of reflux esophagitis. A type 2 tumor in body of his stomach was detected by upper-endoscopy and liver metastatic findings were detected on PET-CT. Immune-pathological findings were positive for chromogranin, synaptophysin, and N-CAM (Ki67 index 100%), so we diagnosed neuroendocrine gastric carcinoma. He underwent 6 cycles of chemotherapy (cisplatin plus etoposide). He had a partial response on his first follow-up CT. However, we changed his treatment to irinotecan therapy after detecting progressive liver metastasis. He died within 12 months of being diagnosed with his disease [5,6].

A 73-year-old man visited a different hospital with complaints of abdominal pain in December 2014. A type 2 tumor in the antrum of the stomach was detected by upper endoscopy. He underwent surgery and was given a diagnosis of neuroendocrine gastric carcinoma, pathological stage IIIA (UICC-7). However, he had a diagnosis of a recurrence in the pancreas September 2015. He visited our hospital and received 4 cycles of chemotherapy (carboplatin plus etoposide). He had a partial response on the first follow-up CT. He was diagnosed with progression in the pancreas and died within 12 months after his recurrence [7].

Discussion

Gastric and oesophageal neuroendocrine carcinomas are not common tumours. They occur most commonly in men in their 50s1). Risk factors of their occurrence are unknown. The site of occurrence is most common in the middle oesophagus or body of the stomach and their localization is diagnosed by endoscopy, but their gross morphology is like more common types of cancer [8].

It is important in differential diagnosis to depend on pathological findings. Developmental forms of neuroendocrine carcinoma are like normal types of cancer. Lymph node metastasis is common at the time of diagnosis. Metastasis can occur in various sites and is common in the liver. Classification of clinical stage is based upon guidelines. The local symptoms are like more common types of cancer. We could not make a differential diagnosis for the type 2 tumours in all five cases by endoscopic findings at the initial examination. We could not undertake surgical resection owing to their metastatic state, with two in liver, one in bone, and one in the distal lymph nodes at the time of diagnosis [9,10].

Extra-pulmonary neuroendocrine carcinomas can arise from many different sites, such as:

- Oesophagus
- Stomach
- Colorectal
- Liver
- Biliary-Pancreas
- Genital Organs
- Head and Neck

The mechanism of development of neuroendocrine carcinoma from normal cancer cells is assumed to originate from previous cancer cells, previous carcinoid cells, non-neoplastic multiline age potential cells, or non-neoplastic immature neuroendocrine cells. We assumed that in our cases, occurrence developed from other cancer cells because our five cases had type 2 tumours that partially included other types of cancer.

Pathological findings were a sheet state composed of cells with a size no larger than the size of three resting lymphocyte nuclei. These were round, oval, or angulated, and usually had small amounts of cytoplasm. The nuclei were typically by per chromatic and either had a dispersed "salt and pepper" chromatin or a homogeneous dispersed chromatin. The cells were fragile and the tumors were generally extensively necrotic, both of which may contribute to the difficulty in establishing a histologic diagnosis. A mixture of tumors formed with normal tumor cells such as adenocarcinoma, adenoma, and squamous cell carcinoma were common in pathological findings. Mixed findings were detected with typical squamous cell carcinoma in case and with adenocarcinoma in case [11].

The WHO classifications based on mitosis and neuroendocrine features revised in 2010 (4th edition) were correlated strongly with patients' prognosis. Classifications were as follows: I) Neuroendocrine tumor (NET) Grade 1<2 mitoses/10 HPF and 3%>Ki-67 index), II) NET Grade 2 (2-20 mitoses/10 HPF and 3%-20% Ki-67 index), III) Neuroendocrine Carcinoma (NEC) Grade 3 (>20 mitoses/10 HPF or 20%<Ki-67 index, IV) Mixed Adeno Endocrine Carcinoma (MANEC), V) Hyperplastic and paraneoplastic lesion (a region in an organ or tissue which has suffered damage through injury or disease, such as a wound, ulcer, abscess, or tumour) [12].

Our five cases were diagnosed as NEC or MANEC owing to detection of neuroendocrine features and a high mitotic rate. However, it is difficult to make a differential diagnosis between NEC and MANEC because we have no surgical specimen in a non-operable case. Expression of chromogranin, synaptophysin, and N-CAM are known neuroendocrine features. If one of these markers is positive, the tumour has characteristics of neuro endocrinological features. Moreover, NEC or MANEC can be differentiated if the tumour has pathological findings of high mitoses. Chromogranin A is also known as a highly specific marker. We confirmed the diagnosis in four cases as neuroendocrine carcinoma after checking for neuroendocrine markers and high mitosis.

Neuroendocrine carcinoma has highly malignant potential, and an advanced stage at diagnosis is common. If a metastatic lesion is not detected, these cases should receive surgery based upon standard esophageal guidelines in each country. We tended to apply palliative chemotherapy based upon SCLC's treatment in a metastatic state. Cisplatin plus irinotecan or cisplatin plus etoposide is standard chemotherapy for extending disease of SCLC. However, these are off-label uses for gastric-esophageal neuroendocrine carcinoma in Japan [13].

The regimen based on SCLC's was recommended by the National Comprehensive Cancer Network guideline. Cisplatin plus etoposide therapy was recommended by the European Neuroendocrine Tumour Society guideline. Amrubicin is effective for patients with digestive neuroendocrine carcinoma who are platinum refractory. Response rates of first line therapy including platinum were 37.5% for digestive neuroendocrine carcinoma including oesophageal cancer, 77.8% for SCLC. Three of five cases had a response to platinum regimens in our cases.

Conclusion

In conclusion, we have experienced five cases of gastric and oesophageal neuroendocrine carcinoma. We reported details about these cases to promote discussion about therapy and diagnosis. The prognosis for oesophageal or gastric neuroendocrine carcinoma is very poor and median overall survival has been reported as 14.9 months when it occurs in the esophagus. Four of our cases have already died and their survival time was only 10 to 15 months after diagnosis due to prior metastases or recurrence.

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