CASE REPORT

Favorable response of colonic mixed adenoneuroendocrine carcinoma to streptozocin monotherapy

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Abstract Mixed adenoneuroendocrine carcinoma (MANEC) of the colon is rare and has a poor prognosis. Here, we report a case of MANEC in the ascending colon, in which streptozocin monotherapy achieved a partial response. A 36-year-old woman underwent right hemicolectomy for colonic polyposis, which included ascending colon cancer. Pathological examination revealed that some mucosal polyps were adenocarcinoma while one submucosal polyp was neuroendocrine carcinoma. Adjuvant chemotherapy was not administered, and 5 months after the operation, multiple liver metastases were identified. She was started on modified (5-FU, leucovorin, oxaliplatin) followed by XELOX (capecitabine, oxaliplatin) plus bevacizumab. Although these regimens helped achieve stable disease, computed tomography showed that the hepatic metastatic lesions had enlarged 4 months later. Subsequently, the regimen was changed to streptozocin monotherapy (1000 mg/m², weekly). After 5 cycles, the regimen achieved partial response and was continued for a total of 17 courses without significant adverse events until progressive disease. As

a third-line chemotherapy regimen, cisplatin plus etoposide (EP) was administered. The EP regimen reduced the size of the hepatic and ovarian metastatic lesions but severe neutropenia and anemia was observed. Amrubicin monotherapy was also administered as fourth-line chemotherapy but a good clinical response was not detected, and the patient died 20 months after the operation. Streptozocin monotherapy has the potential to be a therapeutic option for mixed adenoneuroendocrine carcinoma of the colon.

Keywords Mixed adenoneuroendocrine carcinoma · Neuroendocrine carcinoma · Streptozocin

Introduction

Neuroendocrine carcinoma (NEC) of the colon is rare and has an extremely poor prognosis. In 2010, the World Health Organization described the classification of

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neuroendocrine tumor (NET) and NEC. This includes a grading system of neuroendocrine tumors depending on their proliferation potential, Ki-67 index, and mitotic counts [1]. In the classification, mixed adenoneuroendocrine carcinoma (MANEC) is defined as a tumor consisting of at least 30% adenocarcinoma and neuroendocrine carcinoma. Streptozocin-based chemotherapy has proven effective as treatment for neuroendocrine tumors, especially G1 and G2 grades [2, 3]; however, the effectiveness of streptozocin in MANEC of the colon remains unknown. Here we report a case of MANEC of the ascending colon in which streptozocin monotherapy was effective.

Case report

A 36-year-old woman without a family history of colorectal cancer presented with colonic polyposis. Colonoscopy revealed more than 100 polyps in the entire colon and rectum, mainly in the right colon. Some of these were type 0–I sp polyps that measured 3 and 5 cm in diameter in the ascending colon, and 3.5 cm in the transverse colon. Additionally, many other smaller polyps were observed. Three large polyps were observed, which were suspected to be tumors slightly invading the submucosa. Computed tomography (CT) showed neither lymph node metastasis nor distant metastasis. Finally, these examinations have revealed cT1bN0M0 Stage I (UICC-TNM ver.7), and familial adenomatous polyposis (FAP). We recommended proctocolectomy to her but she was afraid of decreasing her quality of life due to increasing frequency of defecation. Thus, she decided to undergo a right hemicolectomy, and after the surgery we planned polypectomy and intensive follow-up by colonoscopy. Pathological findings reported that the three large polyps were composed of tubular adenomas and tubular adenocarcinomas invading the mucosa but not the submucosa (Fig. 1a, b). However, the largest tumor in the ascending colon consisted of mainly tubular adenocarcinoma and small round cells showing rosette formation in the submucosa (Fig. 2a). Both represented more than 30% of the tumor. Immunohistochemistry test revealed that the small round cells were positive for synaptophysin and CD56 (Fig. 2b, c), partially positive for TTF-1, and negative for CD20 and CD3. In addition, the Ki-67 index was above 70% (Fig. 2d). These findings confirmed the diagnosis as mixed adenoneuroendocrine carcinoma. There was no lymph node metastasis. Venous invasion was not identified but lymphatic invasion was Grade 1. Finally, pathological diagnosis was mixed adenoneuroendocrine carcinoma, pT1b N0 M0 pStage I. We proposed genetic test about FAP specific genes, but we could not obtain the agreement of her and her husband. After the operation, she was observed with no adjuvant chemotherapy. Three months after the operation, total

colonoscopy was performed but only two small polyps were identified while CT showed no recurrence. However, she developed multiple liver metastases (Fig. 3a) and impaired liver function 5 months after the operation. For the first-line chemotherapy, modified FOLFOX6 (5-fluorouracil, oxaliplatin, leucovorin) was administered. After three cycles were completed, the regimen was changed to XELOX (capecitabine and oxaliplatin) owing to infection of the central venous catheter and port system. Prior to the second course of XELOX regimen, CT showed some of the multiple liver metastasis had decreased in size (Fig. 3b), but bone metastasis was suspected based on the whole-body bone scintigraphy findings. Subsequently, two further courses of XELOX with bevacizumab were administered. Nevertheless, CT showed that the multiple liver metastasis had worsened (Fig. 3c). Following this, the regimen was changed to streptozocin monotherapy (1000 mg/m², weekly) as the second-line chemotherapy. After 5 courses of the regimen were administered, CT revealed that all the liver metastases had reduced in size (Fig. 3d) and the regimen achieved partial response by the RECIST ver. 1.1 criteria [4]. The regimen was continued for 17 courses without remarkable adverse events, and dose reduction was not necessary. Moreover, the performance status indicated a good condition. After 17 courses of the chemotherapy, CT showed that the multiple liver metastases had become larger (Fig. 4a), and another metastasis was detected in the ovary. Therefore, the regimen was changed to cisplatin plus etoposide (EP) as the third-line chemotherapy. In the first course of the chemotherapy, the patient experienced Grade 4 neutropenia, Grade 4 anemia, Grade 3 thrombocytopenia, and Grade 2 hair loss. Because of these adverse events, a 50% dose reduction was necessary in the subsequent courses of the third-line chemotherapy. After the first course of the third-line chemotherapy, CT showed that metastatic lesions in the liver, ovary, and lymph nodes had become smaller (Fig. 4b) but the bone metastasis had not change. Although the third-line chemotherapy was continued for a further 4 courses, the metastatic lesions developed into progressive disease. Amrubicin monotherapy was administered to the patient as the fourth-line chemotherapy. However, a clinical response was not observed and the patient died 20 months after the operation. Streptozocin monotherapy and EP treatment both achieved a good clinical response for the hepatic metastasis, but not the bone metastasis. A lack of response in the bone metastasis proved critical for the patient.

Discussion

The clinical course of this patient provides two important clinical suggestions. First, streptozocin monotherapy may be effective against MANEC of the colon. Second,

Fig. 1 Macroscopic findings showed a lot of polyps mainly in cecum and ascending colon (a). The largest tumor in the ascending colon consisted of mainly tubular adenocarcinoma in mucosa and small round cells showing cord-like structure in the submucosa (b)

Fig. 2 Small round cells in the submucosa showed rosette-like structure (a). Immunohistochemistry showed that small round cells were positive for synaptophysin (b), CD56 (c). Ki-67 index was above 70% (d)

streptozocin monotherapy has few remarkable adverse events, which makes it possible to administer subsequent systemic chemotherapy.

Streptozocin monotherapy was effective against MANEC of the colon. Streptozocin-based chemotherapy has been recommended for the treatment of G1 and G2

neuroendocrine tumors by guidelines worldwide [5–8]. These guidelines recommend streptozocin plus 5-FU or doxorubicin for patients with G1 or G2 pancreatic and enteroneuroendocrine tumors. However, the effectiveness of streptozocin against MANEC has yet to be proved. There are some reports such as one describing the case of a

Fig. 3 CT images showed multiple liver metastases before chemotherapy (a) and after three cycles of mFOLFOX6 and one cycle of XELOX plus bevacizumab (b). CT images before the first

course of streptozocin monotherapy (c) and after five course of streptozocin monotherapy (d). Streptozocin monotherapy achieved partial response

Fig. 4 CT images showed multiple liver metastases before cisplatin plus etoposide (a) and after the first course of the regimen (b). The tumor at lateral lobe especially reduced in size

patient with poorly differentiated endocrine carcinoma who was administered streptozocin-based regimen [8], but the efficacy of the regimen had not been described precisely. In the case of MANEC specifically, we could not find any report in which streptozocin was administered to the patient. This is the first case in which streptozocin

monotherapy induced a partial response for MANEC of the colon.

Streptozocin monotherapy has very few remarkable adverse events, and this makes it possible to administer subsequent third-line chemotherapy, in terms of maintain the patient's quality of life. Presently, the guidelines in

some countries recommend EP regimen for the treatment of pancreatic and enteroneuroendocrine carcinoma [5, 7, 8]. This recommendation is based on the clinicopathological similarity between small cell lung cancer and pancreatic or enteroneuroendocrine carcinoma. Although these regimens have a good response rate, many serious adverse events, particularly hematological toxicity, have been reported [10]. On the other hand, it has been reported that streptozocin-based chemotherapy results in fewer adverse events than cisplatin-based regimens [9, 11]. Streptozocin-based chemotherapy is a useful therapeutic option as it has fewer adverse events and demonstrates good tolerability.

In the case presented here, modified FOLFOX6 plus bevacizumab was chosen as the first-line chemotherapy. EP regimen may have been considered as one of the best choice for NEC so far, but unfortunately, the insurance system in Japan did not cover the regimen for NEC. Although modified FOLFOX6 plus bevacizumab was not commonly used for MANEC, some studies have reported administration of FOLFOX regimen to patients with MANEC and its effectiveness [12, 13]. Additionally, at least 30% of the MANEC tumor comprises adenocarcinoma. Considering this, we chose the regimen as the first-line chemotherapy.

Although it was very important for subsequent treatment to identify histological type of liver metastases, unfortunately, liver biopsy was not performed due to bad condition of the patient when the multiple liver metastases were identified. The patient also did not hope additional invasive examination. However, we finally considered multiple metastases as neuroendocrine carcinoma by the fact that only neuroendocrine carcinoma component was detected in the submucosa and adenocarcinoma component was confined to mucosal layer.

After the streptozocin monotherapy resulted in progressive disease, EP was administered. When the first-line chemotherapy resulted in progressive disease, we proposed EP regimen and streptozocin monotherapy to the patient. Considering predicted effect and adverse event of both regimens, the patient chose streptozocin monotherapy as second-line chemotherapy because of strong adverse events of EP regimen. Despite being the third-line chemotherapy, EP regimen showed efficacy against most of the metastatic lesions. The different mechanisms of these agents may have contributed to these good results.

In conclusion, streptozocin monotherapy was effective against MANEC of the colon and resulted in few remarkable adverse events. Few regimens have proved effective against NEC and MANEC. Therefore, further evaluation of the effectiveness of streptozocin against these diseases is recommended.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval For this type of study formal consent is not required.

Informed consent Written informed consent was obtained from the patient for publication of this case report.

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