Poorly differentiated adenocarcinoma in the ascending colon with peritoneal dissemination : case report of a patient who survived more than eleven years

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Abstract

Poorly differentiated adenocarcinoma of the large bowel is a rare condition known as having a poor prognosis. We report herein a case of a patient with a poorly differentiated adenocarcinoma in the ascending colon with peritoneal dissemination who survived more than eleven years thanks to adjuvant chemotherapy. A 53-year-old woman with continuous diarrhea was referred to our hospital. Physical examination revealed a fist-sized mass in the right lower quadrant. Barium enema study and colonoscopy showed an ascending colon tumor. Abdominal computed tomography showed extensive ascites and masses besides the ascending colon and in the upper abdomen. Laparotomy confirmed dissemination to the peritoneum, the pouch of Douglas and the omentum. Right hemicolectomy was performed and two masses of the omentum were removed in a palliative intent. Twenty mg of mitomicin C were given intraperitoneally. The resected specimen revealed an ulcerated hard mass 5 × 5 cm in size with unclear margin. Histology showed a poorly differentiated adenocarcinoma with dissemination to the omentum. A continuous infusion of 3000 mg of 5-fluorouracil per 48 hours was given weekly for four weeks followed by 450 mg of oral UFT-E (Uracil:Tegafur) per day as post-operative chemotherapy. The postoperative course was uneventful. Although she underwent removal of a breast cancer eight years after the operation for colon cancer, no sign of tumor progression has been observed for 132 months since the initial operation, by taking UFT-E without any adverse events. (Acta gastroenterol. belg., **2008**, 71, **321-324**).

Key words : colon cancer, dissemination to the peritoneum, prognosis, chemotherapy, UFT.

Introduction

Poorly differentiated adenocarcinoma of the large bowel is far less frequent than other histological grading of adenocarcinoma (1). Distant metastases are more frequent and prognosis is poorer in this entity than in well or moderately differentiated adenocarcinomas (1). 5-fluorouracil (5-FU) is now widely favored for the treatment of colorectal carcinoma. Various protocols involving the combination of 5-FU with other drugs, such as leucovorin, CPT-11 and oxaliplatin have been tried to control the tumor (2,3). UFT (uracil; tegafur at 4:1 molar ratio, Taiho Pharmaceutical Co., Ltd., Tokyo, Japan), which is a 5-FU derivatives, has been often used in Japan because it can be used orally with mild toxicity (4). A marked response to 5-FU and 5-FU derivative has been reported in limited patients with stage IV colorectal carcinoma (5,6). However, there are no reports that patients with colorectal carcinoma and extensive dissemination to the peritoneum achieved more than a 10-year survival. We report herein the case of a patient with a poorly differentiated adenocarcinoma in the ascending colon with extensive dissemination to the peritoneum who achieved a more than 11-year survival by taking UFT-E after palliative right hemicolectomy without any adverse events.

Case report

A 53-year-old woman with a 2-month history of continuous diarrhea was referred to our hospital in March, 1996. She had a history of hypertension. As for her family history, her mother died of gastric cancer. She was 156 cm tall and weighed 60 kg. Physical examination revealed a fist-sized mass in the right lower quadrant. Laboratory data were within normal limits except for RBC 415 × 10^4, Hb 10.3 g/dl, Hct 32.4% and high levels of the carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 at 21 ng/ml and 606 U/ml respectively. Barium enema study revealed a defect in the ascending colon approximately 7 cm in length with an irregular surface. Colonoscopy demonstrated the tumor with an ulcer of the ascending colon though a limited view prevented us from taking a biopsy. Abdomonal computed tomography (CT) showed masses with irregular surface besides the ascending colon and in the upper abdomen. Extensive ascites was seen around the liver and in the pelvic cavity. Abdominal ultrasonography (US) and a CT scan did not show any abnormality in the liver. Roentgenographic examination of the intestine revealed no stenosis of the small intestine. There was no abnormality on a plain chest X-ray.

A laparotomy was performed to resolve the possible obstruction under the diagnosis of carcinoma of the ascending colon with dissemination to the peritoneum. Thirty-five hundred ml of a yellowish fluid was seen in the abdominal cavity at surgery. The tumor had invaded the abdominal wall. The lymph nodes along the superior mesenteric artery were swollen. The tumor was markedly disseminated into distant peritoneum, the pouch of

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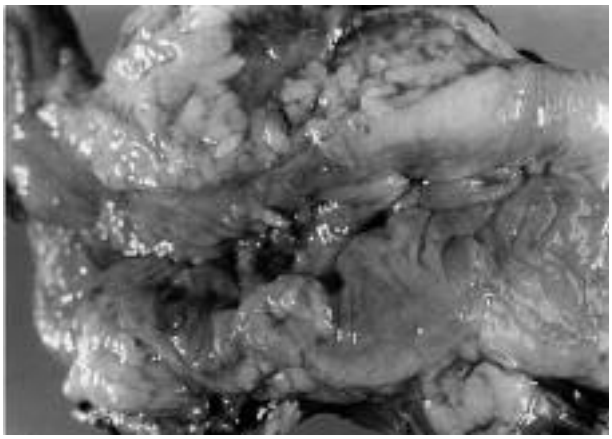

Fig. 1. — The resected specimen revealed an ulcerated hard mass of the ascending colon 5 × 5 cm in size with unclear margin.

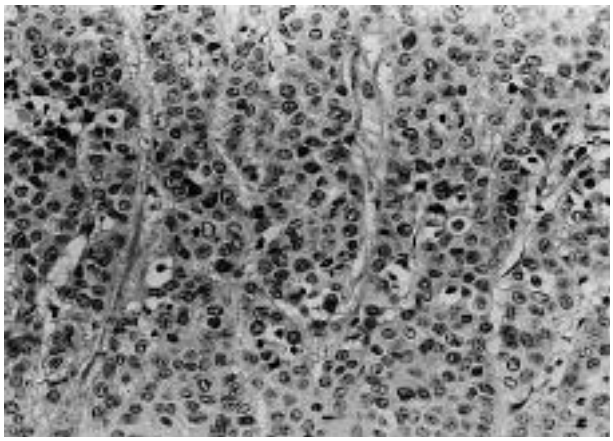

Fig. 2. — Histopathological finding showed the tumor consisted of round to polygonal cells with a high N/C ratio, and cells were arranged in a sheet-like pattern. Rosette –like pattern was also found occasionally.

Douglas and the omentum forming a hardened and thickened mass 4 cm in size. The grade of disseminated diseases was diagnosed as P3 according to the Japanese classification of colorectal carcinoma (7). Right hemicolectomy was performed and two masses of the omentum were removed as palliative intent, however, small-disseminated diseases were left. Ascites was not taken for cytology. A solution of 20 mg of mitomicin C (MMC) in saline was spread intraperitoneally before closure of the abdomen, however, continuous hyperthermic peritoneal perfusion (CHPP) was not performed because of unavailable for CHPP in our hospital.

The resected specimen revealed an ulcerated hard mass 5 × 5 cm in size with unclear margin in the ascending colon (Fig. 1). Microscopically, the tumor consisted of round to polygonal cells with a high N/C ratio, and was arranged in a sheet-like pattern. Rosette–like pattern was also found occasionally. In addition, cellular atypia, irregularity in arrangement, and high mitotic ratio were recognized (Fig. 2). The carcinoma cells invaded into the serosa with regional lymph node metastases (pT3, pN2). Moderate venous and severe lymphagetic invasions were observed according to the Japanese classification of colorectal carcinoma (7). Carcinoma cells were diffusely positive to immunostainigs for CEA and p53, but negative to chromogranine A, neuron specific enolase (NSE) and synaptophysine. Carcinoma cells showed low level of expression (less than 30%) of thymidylate synthase (TS), and carcinoma cells were negative to dihydropyrimidine dehydrogenase (DPD) and thymidine phosphorylase (TP). The histopathological findings of the resected tumor of the omentum were similar to the findings of the tumor of the colon. It was diagnosed as a poorly differentiated adenocarcinoma of the ascending colon with extensive dissemination to the peritoneum.

A continuous infusion of 3000 mg of 5-fluorouracil per 48 hours was given weekly for four weeks followed by a 450 mg of UFT-E (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) per day from day 28 after the operation as post-operative chemotherapy. She was discharged 30 days after the operation without any complications. She was given UFT-E for 105 months after the operation. She did not suffer from any adverse effect from taking UFT-E. We discussed with the patient and her family about the cessation of the chemotherapy several times over the five years since the operation was performed. However, the patient insisted to continue taking UFT-E due to no adverse effects and allowable medical expense under the Japanese insurance system. She entered our hospital again due to the left breast tumor in December, 2004 and underwent the partial resection of the left breast with the dissection of axillary lymph nodes. Pathological findings showed scirrhous carcinoma 2 × 2 cm in size without any lymph node metastases (T1, N0, M0). She was given 50 mg of cyclophosphamide and 800 mg of doxifluridine (5'DFUR) from day 21 after the operation for the breast cancer for two years. No sign of tumor regression has been observed for 132 months since the initial operation.

Discussion

Carcinoma of the large bowel is histopathologicaly classified as well, moderately, poorly differentiated adenocarcinoma and undifferentiated carcinoma (8-9). Most carcinomas of the large bowel are well or moderately differentiated adenocarcinoma (1). Poorly differentiated adenocarcinoma of the large bowel is an infrequent disease. It often shows the common characteristics of a more advanced stage at diagnosis, aggressive behavior and a high incidence of nodal and distant metastases (1). The prognosis of patients with poorly differentiated adenocarcinoma of the large bowel is obviously worse than that of those with other grades of adenocarcinomas at a

comparable stage (1). The prognosis of the present case was also supposed to be very poor due to disseminated disease, however, a more than 11-year survival has been achieved by post-operative chemotherapy.

5-FU has been used as the most effective chemotherapeutic agent against carcinoma of the large bowel. 5-FU inhibits both DNA and RNA syntheses (10). In terms of its inhibitory effect on DNA synthesis, greater anticancer activity might be obtained by continuous low-dose and long-term administration than by intensive high-dose and short-term administration because 5-FU shows time-dependent activity (11). Continuous infusion of 5-FU was given for four weeks followed by oral UFT-E in the present case. One of the reasons why carcinoma relapse had been suppressed for such a long time in the present case might be the use of UFT-E. UFT-E is a 5-FU derivative, which is a combination of tegafur and uracil. The uracil blocks the degradation of 5-FU, which is derived from tegafur, by dihydropyrimidine dehydrogenase (DPD) (4). TS catalyzes the methylation of deoxyuridine (dUMP) to deoxythymidine monophoaphate (dTMP), an essential step for DNA synthesis (10). The anti-cancer effects of 5FU are biochemically mediated though its metabolic conversion by two additional enzyme (TP and thymidine kinase) into fluorodeoxyuridine monophosphate (FdUMP), which eventually forms a ternary covalent complex with TS and reduced folic acid, resulting in the inhibition of TS activity (10). The expression of TP, which is also identified as an angiogenic factor and identical to platelet-derived endothelial cell growth factor, was associated with poor clinical outcome (12). Recently it has been reported that low expression of TP predicts good responder to 5FU treatment (13,14). As a result, patients with a low expression of DPD, TS and TP, such as our patient, are thought to be the best responders to 5FU therapy (13-17). The concentration of 5-FU in the blood and the tumor tissue would be continuously maintained constant by taking oral UFT-E. UFT has been usually used as adjuvant chemotherapy (18). There are some reports that UFT is effective to improve prognosis for advanced colorectal cancer as an adjuvant consecutive administration after curative surgery without any Grade 3 or grater toxicity (18-20).

In the present days, various protocols involving the combination of 5-FU with other drugs, such as leucovorin, CPT-11 and oxaliplatin have been tried to control the tumor (2,3). More than 20 months of median survival was achieved in patients with unresectable metastases by 5FU with leucovorin in combination with CPT-11 (FOLFIRI) or oxaliplatin (FOLFOX) (21). And further improvement of survival is reported by combining bevacizumab or cetuximab with FOLFOX or FOLFIRI (22,23). However, at the time of her operation, such medicines were not available.

On the other hand, there are some reports to show the efficacy of CHPP for peritoneal dissemination of colon cancer (24,25). Furthermore, the effectiveness of mitomycin-C in intraperitoneal chemotherapy had been also reported by some authors (26,27). However, some equipment to maintain water temperature within 42C to 43C (thermostatic water bath, multichannel electric thermometer and peritoneal cavity expander) is needed to avoid the side-effects of CHPP, including anastomotic leakage, intestinal perforation and adhesion ileus (24,28). We actually did intraperitoneal chemotherapy using mitomycin-C without hyperthermia due to unavailable CHPP in our hospital.

In the present case, cessation of UFT-E has repeatedly been discussed with the patient and her family for more than five years after the operation. UFT-E might have been stopped 5 years after surgery though we allowed continuing medication due to patient's wishes. Our experience suggests that oral 5-FU derivative might be useful for the treatment of stage IV colorectal carcinoma and improvement of quality of life and prognosis. It is important to select good responders to 5-FU for the development of the optimal schedule. It has recently been reported that the intratumor concentration of drug-metabolizing enzymes, such as TS, DPD, PT and PyNPase, is related to the anticancer effect of 5-FU (13-17). Further studies to 5-FU will be required to select good responders.

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