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Case report

Unusual survival for more than 2 years with peritoneal metastases of gastric cancer

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Abstract

We report a patient with peritoneal metastases who was successfully treated with a novel oral fluoropyrimidine anticancer drug, TS-1, as first-line chemotherapy. The patient was a 72-year-old man who had undergone curative resection for type 4 gastric cancer with peritoneal dissemination that was located only at the greater omentum. Final findings were P1, T4, N1, and stage IV. Eighteen months after the gastrectomy, his cancer recurred with peritoneal metastases; these were diagnosed by the presence of multiple stenoses of the colon, an abdominal mass, and elevated levels of the serum tumor markers, carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9. He was treated with 100 mg/day of TS-1, given orally, for 28 days, followed by 14 days' rest, as one course. Two courses of the treatment resulted in a marked reduction of the abdominal tumor, without severe toxicity. After 3 courses, barium enema revealed dramatic improvement in the stenoses. Laparoscopy after 11 courses showed neither peritoneal dissemination, nor ascites, and peritoneal lavage cytology was negative. The serum tumor markers were reduced to almost normal levels. Two years after the onset of the peritoneal metastases, the patient is alive without any sign of progressive disease. Our report is the first to demonstrate the advantages of TS-1 as chemotherapy for the treatment of peritoneal metastasis of gastric cancer.

Key words Gastric cancer · Peritoneal metastasis · TS-1 · Survival

Introduction

Peritoneal metastasis is a predominant mode of recurrence in advanced gastric cancer [1–3], and the prognosis for the metastasis remains poor. Among the recurrence patterns of gastric cancer, the prognosis of the peritoneal recurrence is the worst, with a mean survival of 6 months [3]. However, the role of surgery for secondary cure is extremely limited because of the disseminated tumors [3,4], and little is known about the efficacy of chemotherapy. Surgical resection for nonhepatic intraabdominal recurrence of gastric cancer is the choice of treatment for selected patients [5]. Intraperitoneal chemotherapy with various anticancer agents has been tested for the treatment of peritoneal dissemination [6,7], but a survival benefit has not been confirmed.

Since the introduction of the novel oral fluoropyrimidine anticancer drug TS-1, we have evaluated its efficacy as a first-line agent for peritoneal metastasis of gastric cancer, because of its high excellent response rate, acceptable toxicities, and convenience of oral administration [8]. We report a patient with peritoneal metastases of gastric cancer who was treated successfully with TS-1 for more than 2 years, and we discuss the imaging findings of metastatic colon cancer.

Case report

A 72-year-old man underwent total gastrectomy for type 4 gastric cancer containing signet-ring cell carcinoma. Final findings showed that the tumor was H0, P1, T4, N1, CY0, and stage IV according to the Japanese classification of gastric carcinoma [9]. The peritoneal metastases were located in the greater omentum with a few small nodules, which were completely resected. Preoperative levels of the serum tumor markers, carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9, were 2.9 ng/ml and 47.4 U/ml, while postoperative levels of the markers were reduced to 1.5 ng/ml and 17.0 U/ml, respectively (Table 1). Oral administration of UFT (tegafur and uracil) as adjuvant chemotherapy was discontinued after 2 weeks because of nausea.

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Table 1. Levels of serum tumor markers

Tumor marker	Normal range	Pre-gastrectomy	Post-gastrectomy	At peritoneal recurrence	After 11 courses of chemotherapy
CEA	<2.5 ng/ml	2.9 ng/ml	1.5 ng/ml	10.6 ng/ml	3.8 ng/ml
CA19-9	<37 U/ml	47.4 U/ml	17.0 U/ml	53.8 U/ml	24.8 U/ml
CA125	<65 U/ml	14.7 U/ml	28.4 U/ml	24.3 U/ml	7.0 U/ml

Levels of the serum tumor markers, CEA and CA19-9, were elevated above the normal range at recurrence, but were almost normalized after chemotherapy. CA125 levels were normal during the entire course
CEA, Carcinoembryonic antigen; CA, carbohydrate antigen

Eighteen months after the surgery, the patient complained of abdominal discomfort and diarrhea, with a frequency of up to ten times a day. Although the motions were watery, they did not contain blood or mucus. Upon physical examination, a gross tumor, approximately 5 cm in size, was palpable in the right upper quadrant of the abdomen, with a small amount of ascites. The levels of the serum tumor markers, CEA and CA19-9, were elevated above the normal range (10.6 ng/ml and 53.8 U/ml, respectively; Table 1). Barium enema revealed multiple stenoses in the ascending, transverse, and descending colon (Fig. 1); with these lesions being located mainly in the transverse colon. Intermittent narrow segments showed unilateral and marginal serration at the hepatic flexure and concentric narrowing without tapering in the transverse and the descending colon, with the presence of normal segments; neither longitudinal ulcer scar, nor cobblestone appearance, nor polypoid lesion was present. This configuration was highly suggestive of metastases from gastric cancer. The symptoms and physical signs, the imaging, and the elevated serum tumor marker levels were consistent with a diagnosis of metastatic colon cancer originating from gastric cancer, and we initiated treatment for the peritoneal recurrence in the patient.

TS-1, at a dose of 100 mg daily, was administered orally for 28 days, followed by 14 days' rest, as one course. Two courses of treatment resulted in a marked reduction of the abdominal tumor, with no diarrhea, and no severe toxicities. After 3 courses, a barium enema revealed an improvement in the stenoses (Fig. 2). Grade 1 stomatitis (according to the WHO toxicity criteria) occurred after 7 courses, and, therefore, subsequent courses were resumed after 4 weeks, rest, with a reduced dose of 80 mg daily. Laparoscopy after 11 courses showed neither peritoneal dissemination nor ascites, nor positive peritoneal lavage cytology. The levels of the serum tumor markers, CEA and CA19-9, were almost normalized, to 3.8 ng/ml and 24.8 U/ml, respectively (Table 1). He was treated at an outpatient clinic entirely after the recurrence. Two years after the onset of the peritoneal metastases, the patient is alive without showing disease progression or side effects of the treatment.

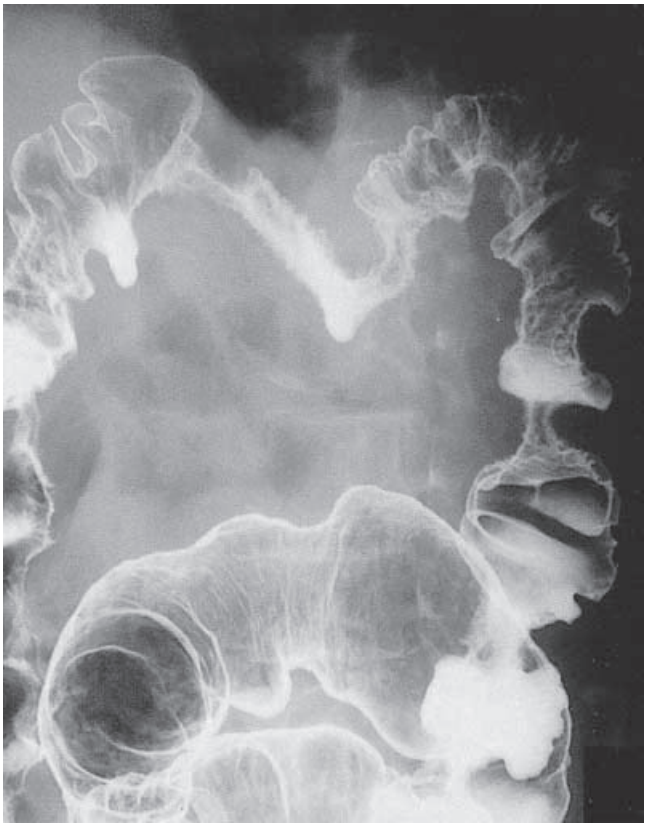

Fig. 1. Before chemotherapy, barium enema demonstrated multiple stenoses, with normal segments, in the ascending, transverse, and descending colon, without longitudinal ulcer scar, cobblestone appearance, or polypoid lesion. This configuration was highly suggestive of metastases from gastric cancer

Discussion

In the patient described here, barium enema demonstrated intermittent multiple stenoses in the transverse as well as the ascending and descending colon. The ascending and descending colon were located outside the range of surgery. We perform laparoscopy for patients in whom we suspect peritoneal metastases, in order to detect peritoneal metastases at an early stage with histological confirmation [10]. The present patient, however, was diagnosed as having peritoneal

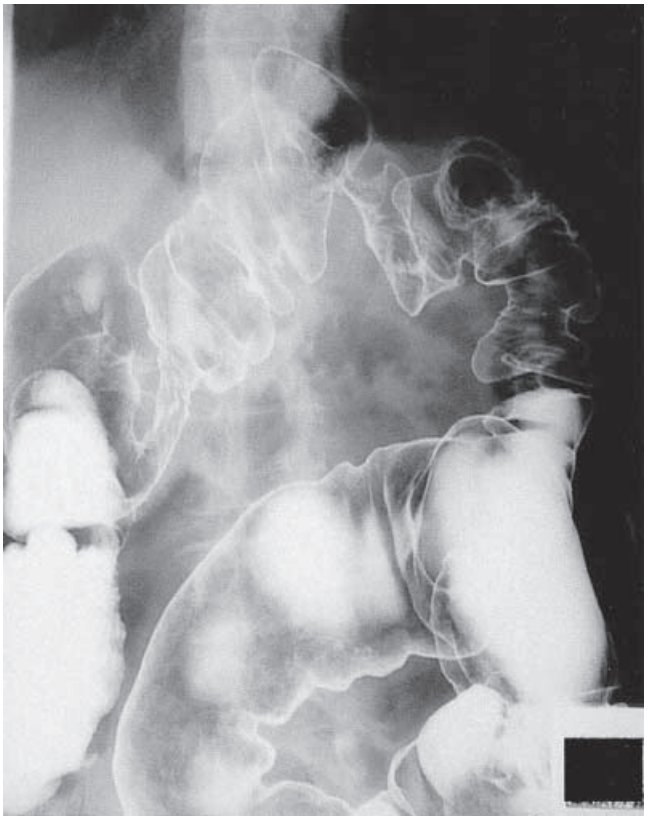

Fig. 2. Barium enema revealed improvement of stenoses after three courses of TS-1 (see text for constituents)

metastases from gastric cancer by the physical findings, barium enema imaging, and high levels of serum tumor markers, without the performance of laparoscopy and histology.

Findings of barium enema in metastatic colon cancer were reported to be intermittent multiple narrowed segments, marginal serration in unilateral defects, and concentric narrowing without a tapering margin [11]. In addition, characteristic findings of barium enema from gastric cancer were multiple areas of tethered-fold-type stenoses, with normal segments, and frequent localization in the transverse colon [12]. These findings may occur with primary linitis plastica carcinoma or with inflammatory disease of the colon; however, the incidence of the former is low [13,14], with most of the lesions being located in the sigmoid colon or rectum [15] with a tapering margin [16,17]. Some authors have emphasized that the diagnosis of primary linitis plastica of the colon has to be made only after primary gastric cancer has been excluded [14–18]. The lesions of inflammatory disease of the colon are characterized by longitudinal ulcer scar, cobblestone appearance, and a polypoid shape. Thus, the imagings in the present patient were highly suggestive of metastatic colon cancer. Papp et al. [19] reported that CEA lacked diagnostic utility in primary linitis plastica of the colon; in the present patient, the elevated levels of CEA and the imaging findings coincided with secondary carcinoma originating from the type 4 gastric cancer.

TS-1, a novel oral 5-fluorouracil formula, consists of 1 M tegafur (5-FU), 0.4 M gimestat [20], and 1 M ostat potassium [21]. The response rate to TS-1 in a late phase II study was reported to be 49% in patients with advanced gastric cancer [8]. This response rate was higher than that for UFT (27.7%) and 5′-deoxy-5-fluorouridine (5′-DFUR; 14.3%) [22,23]. Major adverse reactions to TS-1 were reported to be gastrointestinal symptoms and myelosuppression, with little severe toxicity. These data suggested that TS-1 was suitable as first-line chemotherapy for peritoneal metastases of gastric cancer.

The patient has survived for more than 2 years without symptoms after the initiation of treatment with TS-1. Why has he survived for such a long time after the recurrence? We propose the following possible reasons: (1) the effects of TS-1, (2) long-term compliance, and (3) the presence of regional peritoneal metastases with negative lavage cytology. The most important factors may be the absence of peritoneal disseminated nodules and the negative cytology. Arai et al. [24] demonstrated the survival impact of a change to negative washing cytology findings after intraperitoneal chemotherapy. Tamiya et al. [25] reported a long-term survivor who received 5′-DFUR orally and had long-term compliance. Fujimura et al. [26] documented the effectiveness of subtotal peritonectomy with chemohyperthermic peritoneal perfusion for peritonitis carcinomatosa. However, among their ten patients, seven died within 1 year and only one survived for longer than 2 years. We have reported that none of three patients survived for more than 2 years even after curative resection for peritoneal metastases of recurrent colorectal tumor from gastric cancer [4]. Intensive chemotherapy usually requires hospital care, because of its serious side effects, which impair the quality of life.

Tumor response to chemotherapy is used as a surrogate endpoint for survival, and is evaluated mostly by conventional imaging methods, such as endoscopy, computed tomography (CT), ultrasound (US), and X-ray findings. The pitfall of these conventional imaging methods is their low sensitivity for peritoneal metastasis. Because the prognosis of patients with gastric cancer is often dominated by the progression of peritoneal metastasis, there could be a discrepancy between the response rate and survival in some patients. In the present study, laparoscopy was performed to justify the tumor response of peritoneal metastases after chemotherapy. The laparoscopy revealed no peritoneal dissemination and no positive lavage cytology, which are the key prognosticators. We have experienced two

patients in whom tumor response to chemotherapy was altered by adding the laparoscopy [27]. Intraperitoneal examination by laparoscopy provides information on tumor response to chemotherapy in addition to accurate information for survival.

The patient in this report was treated with TS-1, as an outpatient. TS-1 induced a dramatic reduction of the tumors, without serious toxicity. Moreover, our report indicates that laparoscopy is important to evaluate the response of peritoneal metastases to the chemotherapy. This is the first report to demonstrate the advantages of TS-1 as chemotherapy for the treatment of peritoneal metastasis associated with gastric cancer.

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