Good Response Chemotherapy for Late-recurring Gastric Cancer in the Gluteals, with Peritoneal and Retroperitoneal Dissemination

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A 64-year-old woman presented with advanced gastric cancer (signet ring cell carcinoma) and underwent total gastrectomy in 1996. Postoperative recovery was good, and she was monitored regularly on an outpatient basis. Abdominal computed tomography in 1999 revealed a soft tissue shadow ventral to the origin of the celiac artery. Careful monitoring was continued on an outpatient basis. The patient began to experience gluteal swelling and pain in April 2008. Symptoms rapidly exacerbated and the patient was hospitalized for further examination. Gluteal muscle biopsy revealed signet ring cell carcinoma and bilateral hydronephrosis. Gluteal recurrence of the original gastric cancer was suggested, and systemic chemotherapy consisting of S-1 at 100 mg/day (3 weeks on, 1 week off) and CDDP (day 8) was started. Following the 6th cycle of chemotherapy, gluteal symptoms disappeared and the patient was judged to have achieved clinical complete response (CR). No adverse events or image findings suggesting new recurrence have since been identified. The patient received a total CDDP dose of 585 mg and clinical CR has been maintained as of 14 years after total gastrectomy and 18 months after recurrence.

Key words: S-1; CDDP; late recurrence after gastrectomy; retroperitoneal dissemination; intraperitoneal dissemination

INTRODUCTION

Advanced gastric cancer with peritoneal dissemination is one of the most difficult forms of gastric cancer to treat, and prognosis has remained poor despite the application of various interdisciplinary approaches to treatment. We recently encountered a patient who developed recurrent gastric cancer in the gluteal muscles 12 years after total gastrectomy, bilateral hydronephrosis due to retroperitoneal dissemination, and a 15-mm-thick area of soft tissue running along the ascending colon that was suspected to represent recurrence in the intraperitoneal cavity. We report here details of this patient with late-recurring gastric cancer who responded to standard chemotherapy and has maintained clinical complete response (CR) for 18 months.

PATIENTS AND METHODS

Patient: A 64-year-old woman.

Chief complaints: Gluteal swelling and pain.

Past history: Surgery for appendicitis at 14 years old.

Familial history: Nothing of note.

Current disease history: The patient complained of loss of appetite in 1996 and underwent upper gastrointestinal endoscopy, revealing erosion of the posterior wall of the upper gastric body. This lesion bled easily, and contrast imaging using indigo carmine showed faint staining of the erosion with formation of an island in the erosion. The endoscopic diagnosis was IIc (Fig. 1). Biopsy of the same site led to a diagnosis of signet ring cell carcinoma. Partial gastric resection was planned on the basis of endoscopic findings that yielded a diagnosis of IIc disease, but total gastrectomy was performed because intraoperative findings showed that the cancer had invaded as far as the serosa and the initial resected stump was positive for tumor cells. Histopathological studies of the resected specimen obtained at this time led to a diagnosis of $T_3N_0M_0$ Stage II. Postoperative course following discharge was good, and the patient was periodically monitored on an outpatient basis. Upper gastrointestinal endoscopy was performed annually, but no findings indicated recurrence. Abdominal computed tomography (CT) performed in 2002 revealed a soft-tissue shadow ventral to the origin of the celiac artery (Fig. 2). This shadow was thought to represent a swollen lymph node. Thereafter, the course of the patient was followed carefully on an outpatient basis by imaging examinations, including echography and CT. However, no significant changes in shape or size of the lymph nodes were noted. The patient began to experience gluteal swelling and pain in April 2008. Symptoms rapidly worsened and the patient was hospitalized for further examination. Magnetic resonance imaging (MRI) of the gluteal region showed diffuse swelling of the gluteus maximus (Fig. 3), and abdominal CT revealed swelling of the lymph nodes around the celiac artery and bilateral hydronephrosis (Fig. 4a, b). No findings of swelling of other lymph nodes, ascites or gross lesions were identified. With regard to gluteal swelling and pain, muscle

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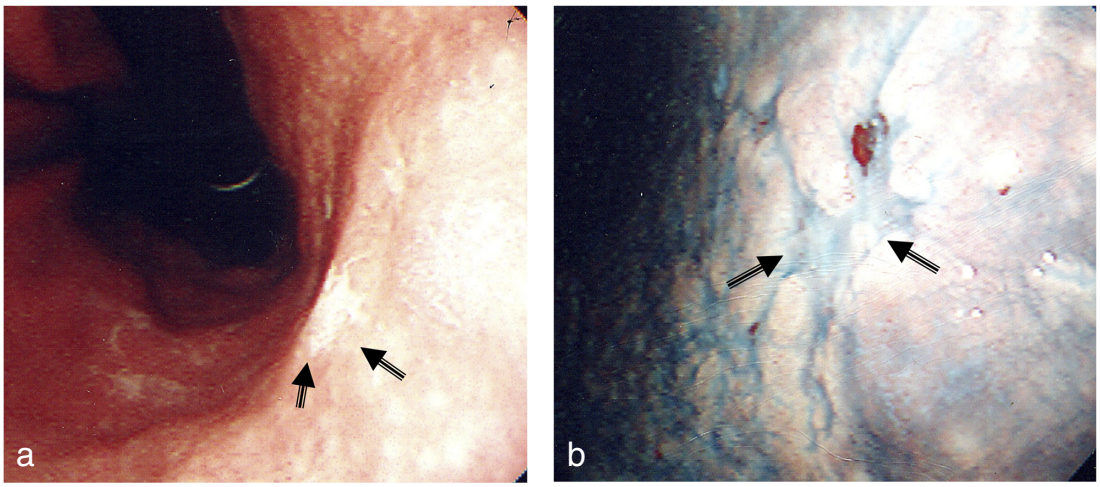

Fig. 1 Images from upper gastrointestinal tract endoscopy performed on November 7, 1996.
a) An easily bleeding erosion is seen on the posterior wall of the upper gastric body (arrows).
b) Contrast imaging of this lesion using indigo carmine shows faint staining of the erosion with formation of an island in the erosion. The endoscopic diagnosis was IIc (arrows).

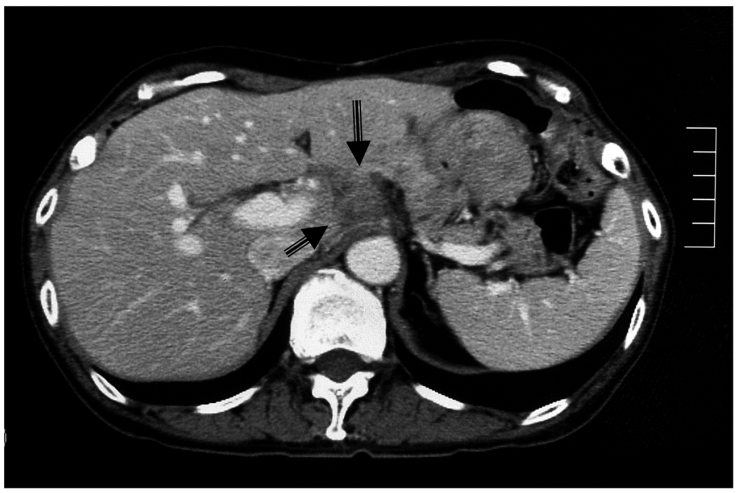

Fig. 2 Abdominal CT performed on May 13, 2003.
Swelling of soft tissue around the celiac artery (arrows) was noted for the first time in October 2002. This was subsequently monitored by regular examinations on an outpatient basis, but no marked changes were noted.

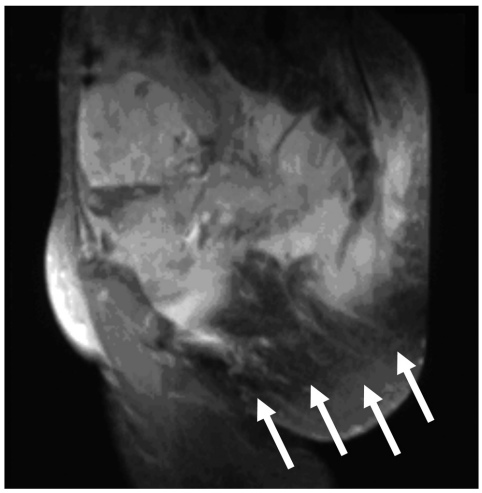

Fig. 3 Sagittal T2-weighted MRI of the gluteal region at the time of admission to the previous hospital (June 31, 2008). The gluteus maximus shows diffuse swelling (arrows).

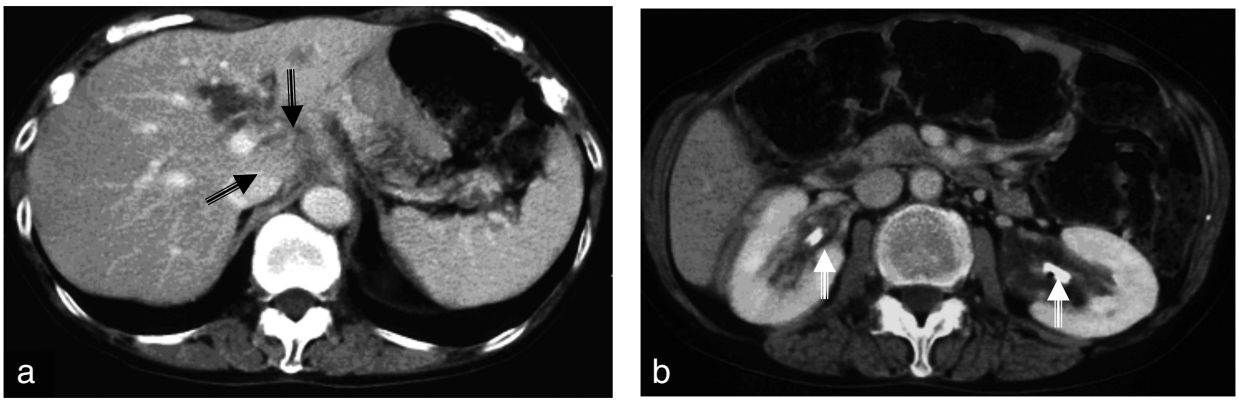

Fig. 4 Abdominal CT during hospitalization in the previous hospital (May 5, 2008).
a) A soft tissue shadow around the origin of the celiac artery, which was thought to represent a lymph node (arrows).
b) Bilateral hydronephrosis was detected, so bilateral ureteral stents were put in place (arrows).

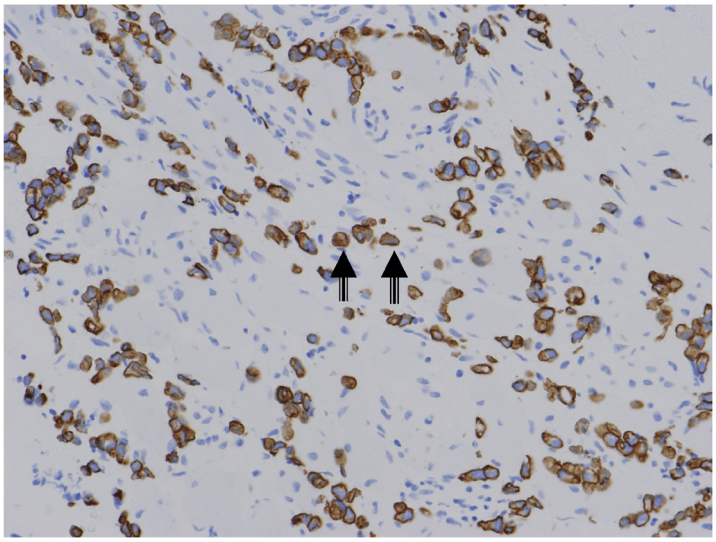

Fig. 5 Immunostaining (CAM5.2) of a biopsy of the gluteus maximus taken during hospitalization in the previous hospital, showing diffusely scattered signet ring cells. This finding led to a diagnosis of recurrent gastric cancer (arrows).

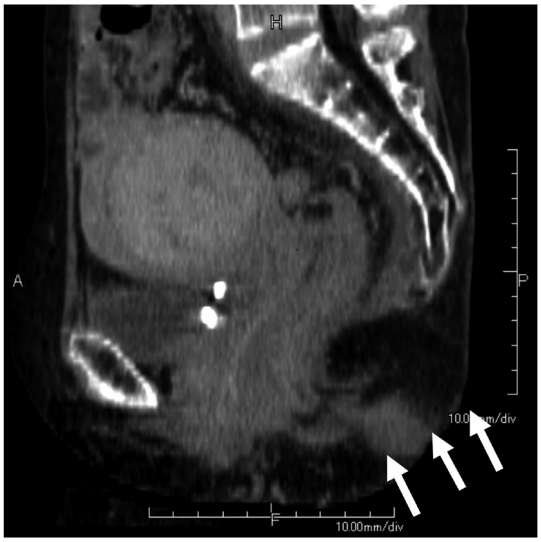

Fig. 6 Abdominal CT taken 18 months after starting chemotherapy (January 7, 2010). The swelling has disappeared from the gluteal region, and clinical remission was diagnosed (arrows).

biopsy performed in July 2008 led to a final diagnosis of signet ring cell carcinoma (Fig. 5). Upper gastrointestinal endoscopy was also performed, but no findings of recurrence at the anastomotic site were evident. Lower gastrointestinal endoscopy and gynecological echography showed uterine myoma, but no primary lesions that would have caused metastasis to the gluteal muscle. Gluteal swelling and pain were therefore attributed to postoperative recurrence of the initial gastric cancer, while the bilateral hydronephrosis was considered due to dissemination from the retroperitoneum. Ureteral stents were inserted to relieve bilateral hydronephrosis.

Physical findings on admission to the previous hospital (August 2008): height, 158 cm; weight, 46 kg; hip girth, 104 cm; no anemia or jaundice; and no abdominal swelling or palpable body surface lymph nodes.

Test findings on admission to the previous hospital (August 2008): no abnormalities in blood, biochemical or tumor marker (carcinoembryonic antigen, carbohydrate antigen 19−9) examinations.

Course of treatment: Late recurrence of gastric cancer was diagnosed, so systemic chemotherapy comprising S-1 at 100 mg/day (3 weeks on, 1 week off) and CDDP at 80 mg/day (day 8) was started in August 2008. Mild myelosuppression (cause unknown) occurred during the 1st cycle, so the CDDP dosage was reduced to 65 mg/day (day 8) from the 2nd cycle onward. A total of 6 cycles were administered. By completion of the 6th cycle, gluteal swelling and pain had disappeared, and hip girth had deceased markedly from 104 cm to 90 cm. Almost no adverse events due to chemotherapy were encountered, and all symptoms resolved. For that reason, the patient and her family requested that S-1+CDDP chemotherapy be continued, but this request was declined as the hospital has found no evidence supporting administration of CDDP for ≥ 7 cycles. On that basis, the patient was referred to our hospital in March 2009. Abdominal ultrasonography was performed and revealed a 15-mm-thick area of soft tissue running directly below the right lower abdominal wall, lateral to the ascending colon. This soft tissue was initially thought to present this configuration either because it was a desmoid tumor or because of adhesion to the intestinal tract following appendectomy. The previous hospital had performed colonoscopy, but had not performed biopsy because the mucosa of the colon was intact. Accordingly, this swelling was not thought to represent colon cancer. This led to a strong suspicion of peritoneal dissemination. We took into account the cumulative toxicity of CDDP and began treating the patient with systemic chemotherapy consisting of S-1 at 100 mg/day (3 weeks on, 1 week off) supplemented with CDDP at 50 mg in cycles 7, 10 and 13, and 30 mg in cycle 18. CDDP was not administered in cycles 8−9, 11−12, 14−17 or 19, which comprised S-1 alone. As of the time of writing, 18 months after the start of chemotherapy, no adverse reactions have been encountered and no elevations of tumor markers (CEA, CA19−9), recurrence of gluteal symptoms or changes in image findings have been seen (Fig. 6).

DISCUSSION

Although no clear definition has been given for late recurrence of gastric carcinoma, most reports have described cases recurring > 5 years after surgery. Ito *et al.* [1] reported that late recurrence was comparatively rare, with only 10 cases in 311 patients (3.2%) following curative resection. With regard to the mode of recurrence, Nishi *et al.* [2] reported the most common mode as peritoneal recurrence, followed by hematogenous, local and gastric remnant recurrences. In the present case, a soft tissue shadow was noted postoperatively in 2002 and was thought to represent a lymph node at the celiac artery bifurcation. The patient was subsequently carefully followed up by annual abdominal CT on an outpatient basis for approximately 10

years. Further testing was performed in July 2008 after observation of gluteal swelling and pain, and gluteal muscle biopsy led to a diagnosis of signet ring cell carcinoma. This patient showed recurrence in the gluteal muscle area, with hydronephrosis due to dissemination from the retroperitoneum. Peritoneal dissemination also appeared to be present. At that time, chemotherapy was considered the best treatment approach, and even after the patient was referred to our hospital, our goal was to maintain good quality of life (QOL) and prolong the lifespan of the patient as much as possible while coexisting with the cancer. Ohtsu *et al*. [3] reported treatment results with S-1+CDDP chemotherapy for advanced gastric carcinoma, showing a high efficacy rate of 76.0% for overall efficacy and 72.2% even for patients with abdominal lymph node metastasis. They reported that the incidence of grade 3 or worse adverse events was low, at 26.6%, suggesting that safety was good. In general, S-I is said to show even better efficacy against undifferentiated gastric carcinoma [4] and high antitumor efficacy even for metastatic lymph nodes [5, 6]. The present patient was able to take medication orally, so consideration was given to administration of S-1 from the outset. However, as gluteal swelling manifested within a very short period of time, this pathology was judged as severe, and in consideration of the therapeutic results reported by Ohtsu *et al*. [3], the decision was made to coadminister CDDP to increase the antitumor effects of therapy. However, following referral of the patient to our hospital after 7 cycles of chemotherapy, the disease showed improvement, subjective symptoms completely disappeared, and we judged that the patient had achieved clinical CR.

In general, no clear consensus has been reached regarding the duration of continuation for chemotherapy after CR has been achieved. However, Sasaki *et al*. [7] maintained that there is no reason to discontinue chemotherapy while the tumor shows no tendency to progress. We share this view, and thus, although no established regimens are available, once a patient attains clinical CR, S-1 should comprise the main treatment with add-on treatment of CDDP at an appropriate dose, while closely monitoring physical findings, hematological data and image findings. As of the time of writing, the present patient has received a total of 18 cycles of S-1+CDDP chemotherapy, with a cumulative CDDP dose of 585 mg. Despite this, the course of the patient has been good, with no adverse reactions to therapy and no deterioration of QOL. A small number of reports have described excellent response to chemotherapy in patients with metastasis to the para-aortic lymph nodes following surgery for gastric cancer [8, 9]. However, to date, no reports have described cases similar to the present, with very late recurrence of gastric cancer and metastasis to the gluteal muscle area 12 years after surgery, bilateral hydronephrosis due to dissemination from the retroperitoneum and simultaneous development of a soft tissue lesion suspected to represent recurrent disease in the peritoneal cavity. In our patient with this unusual course of progression following total gastrectomy, we were able to demonstrate the efficacy of standard chemotherapy consisting of S-1+CDDP in achieving clinical CR for late gastric carcinoma recurrence. No clear consensus has been reached regarding the mechanisms underlying such late recurrence. However, Iwanaga *et al*. [10] discussed several possible contributing factors, including: 1) a very minute amount of residual cancer tissue; 2) a site of residual cancer that is not conducive to progression; 3) slow growth of the cancer; and 4) high level of host resistance. The malignancy in our patient was signet ring cell carcinoma, a very poorly differentiated gastric cancer. However, because a very minute amount of cancer tissue seems likely to have remained in the lymph nodes, which play a key role in immunity, outgrowth of that cancer tissue can be presumed to have been suppressed for 12 years following gastrectomy. The actual time of recurrence might thus have been in 2002, when swelling of the lymph nodes around the celiac artery was first noted. However, since a minute number of cancer cells had by chance remained in the lymph nodes, which are involved in immunity, many years can be presumed to have passed without any change until 2008. Accordingly, the time of recurrence can be validly considered as 2008, when sudden swelling in the gluteal region became clinically apparent. In addition, the rationale for thinking that the gluteal muscle swelling represented recurrence of the gastric cancer is as follows: 1) signet ring cells do not develop in non-epithelial tissues such as the gluteal region; and 2) staining was positive for CAM5.2, a marker expressed in epithelial tumors and for which keratin is stained. According to Ajiki *et al*. [11], 90% of signet ring cell carcinomas occur in the stomach, remaining rare in other organs. They reported one case in the gallbladder (0.52%) from among 191 patients. Moreover, regarding the colon, Goto *et al*. [12] reported 7 cases (0.64%) in 1,091 patients. The incidence of signet ring cell carcinoma in organs other than the stomach, including the gluteal muscle, is thus extremely low.

No elevation of tumor markers or changes in physical or image findings were observed during the long follow-up of this patient, and an issue for the future will be the fact that no clear indicators appear available to help decide the therapeutic strategy. However, close monitoring of the patient for adverse reactions and adjusting the CDDP dose accordingly appear to have contributed greatly to the successful suppression of adverse reactions and new recurrence while maintaining QOL even up to the time of this writing.

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