Curative Surgical Treatment after Preoperative Chemotherapy for Primarily Inoperable Locally Advanced Pancreatic Carcinoma: Report of a Case

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Pancreatic cancer is considered resectable only when there are no distant metastases or infiltration of surrounding organs or arteries. We describe a patient with primarily inoperable locally advanced pancreatic adenocarcinoma who underwent curative surgical treatment after preoperative chemotherapy. A 61-year-old woman was admitted for further evaluation of a pancreatic head mass discovered fortuitously on a health screening. Examination revealed locally advanced pancreatic cancer with infiltration of the superior mesenteric artery. After a partial response was obtained by chemotherapy with gemcitabine (GEM) and S-1, we performed pancreaticoduodenectomy. Microscopically, the main tumor was replaced with fibrotic tissue, and there were only a few residual adenocarcinoma cells in the pancreatic head. The radicality of the surgery was R0, according to the TNM classification. Our results suggest that neoadjuvant treatment with GEM/S-1 on a sustainable regimen offers the possibility of a multimodal treatment concept for all patients and a higher radical-resection rate in patients with otherwise unresectable pancreatic cancers.

Key words: Neoadjuvant chemotherapy, pancreatic cancer, curative resection

INTRODUCTION

In Japan, pancreatic adenocarcinoma is the fourth most common malignancy of the digestive system and has the fifth highest mortality cancer among cancers [1]. The disease is rarely cured [2], and surgical resection is the only treatment modality that has curative potential, although most patients present with locally advanced pancreatic cancer at primary diagnosis. To reduce the high rate of recurrence and metastasis after potentially curative resection, several neoadjuvant and adjuvant strategies for pancreatic cancer have been developed. Recently, many new preoperative radiochemotherapy regimens have been developed in Europe and the United States, and it is hoped that these will improve long-term survival and resectability rates in patients with locally advanced pancreatic cancer [3–13]. However, the use of neoadjuvant chemotherapy alone rarely permits radical resection of inoperable locally advanced pancreatic cancer. There has been only one case of advanced pancreatic cancer successfully treated by chemotherapy alone followed by curative resection [14]. The purpose of chemotherapy before surgery for pancreatic cancer is to downstage otherwise unresectable tumors, thereby enabling surgical resection.

Our criteria for respectability, using computed tomography (CT) and magnetic resonance imaging (MRI) findings, are the absence of extrapancreatic disease and tumor encasement of the superior mesenteric artery (SMA) or celiac axis. The presence of tumor encasement of the superior mesenteric portal vein (SMPV) confluence is not a contraindication. Here, we describe a patient with primarily inoperable locally advanced pancreatic adenocarcinoma who underwent curative surgical treatment after preoperative chemotherapy.

CASE REPORT

A 61-year-old woman was admitted for further evaluation and surgical treatment of a mass at the head of her pancreas. The lesion was discovered fortuitously on a health screening, before which there had been no signs or symptoms of illness. Upon physical examination at admission blood pressure was 128/64 mm Hg, pulse rate was 72 beats/min, and body temperature was 36.7 °C. There was no sign of cervical lymphadenopathy; however, gallbladder swelling without tenderness was palpable in the right hypochondrium. There were no significant findings on a rectal examination. Her past medical history was unremarkable except for a complete hysterectomy for dysplasia of the uterine cervix. Family history included colon cancer in her father and inoperable pancreatic cancer in her mother. Laboratory findings were as follows: WBC count, 4900/mm^3; hemoglobin (Hb), 13.1 g/dl; platelets (Plt), 20.4 x 10^4/μl; total bilirubin, 0.7 mg/dl; alkaline phosphatase, 370 U/l; aspartate aminotransferase (AST), 24 U/l; alanine aminotransferase (ALT), 25 U/l; and serum amylase 20 U/l. The serum levels of carbohydrate antigen 19–9 and carcinoembryonic antigen were 97.5 U/ml and 4.9 ng/ml, respectively in tumor maker analysis. Ultrasonography

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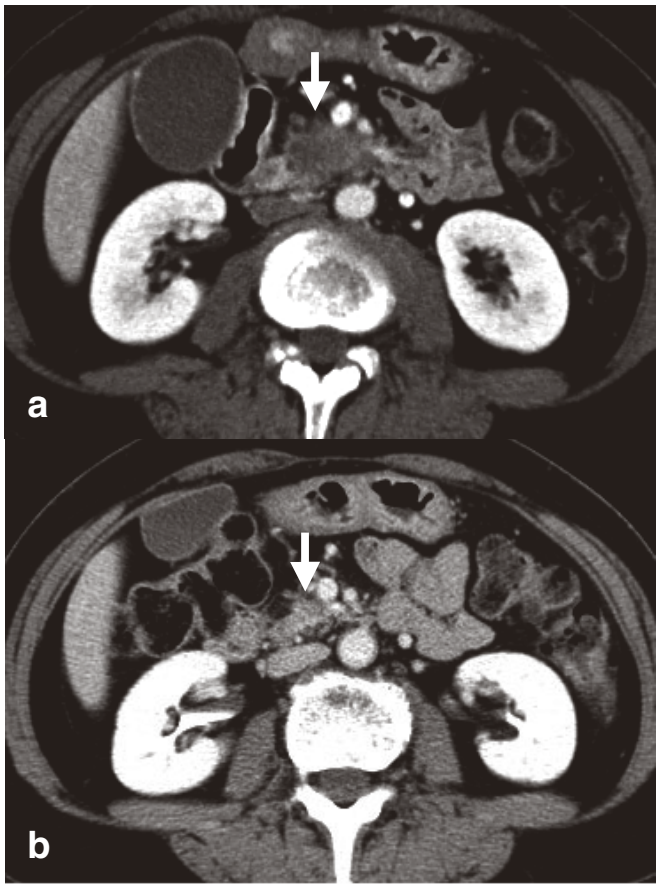

Fig. 1a, b Computed tomography scans show changes in the tumor during chemotherapy. **a** Abdominal computed tomography scan shows a low-density mass measuring 30 x 25 mm at the pancreatic head (*white arrow*), adjacent to the superior mesenteric vein. **b** After 11 cycles of chemotherapy with gemcitabine and S-1, the pancreatic tumor had shrunk to 11 x 13 mm in size (*white arrow*).

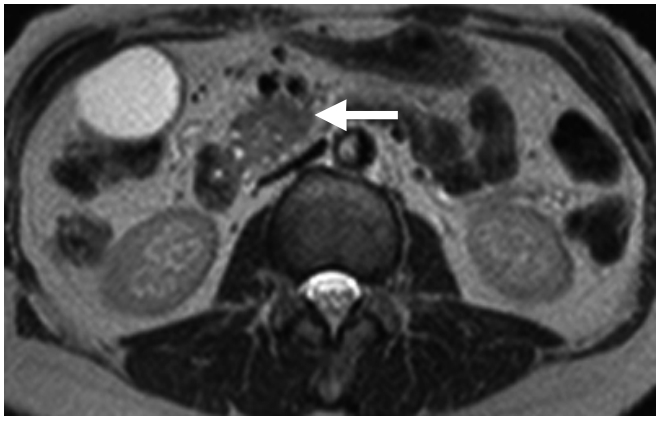

Fig. 2 Magnetic resonance imaging shows the pancreatic mass in the uncinate process infiltrating not only the SMV, but the SMA (*white arrow*).

(US) revealed a hypoechoic, solid mass 30 x 23 x 29 mm in diameter, with an irregularly shaped, unclear border. The mass was adjacent to the superior mesenteric vein (SMV), along which it spanned 11 mm; the distance between the tumor and the superior mesenteric artery (SMA) was only 2 mm. The common bile duct and the main pancreatic duct on the distal side of the mass were dilatated 11 mm and 5 mm, respectively. Additional evaluation revealed a 30 x 25 mm hypovascular mass at the uncinate process of the pancreas on an abdominal computed tomography (CT) scan (Fig. 1a). The fatty tissue around the mass was disordered and the mass was slightly enhanced in late-phase dynamic CT. There was no evidence of lymph node metastasis, peritoneal dissemination, or distant organ metastasis. Magnetic resonance imaging (MRI) also showed dilatation of the bile duct and the main pancreatic duct. In addition, on MRI the mass appeared to infiltrate not only the SMV, but the SMA as well (at least dissected peripancreatic nerve plexus margin around the SMA) (Fig. 2). Our tentative diagnosis was locally advanced pancreatic adenocarcinoma greater than 2.0 cm in size, with infiltration of the common bile duct, SMV, SMA, and retroperitoneal tissue, i.e., T4N0M0 clinical stage III on the TNM classification of the International Union Against Cancer (UICC). Because surgical treatment was not indicated under our criteria for resectability, we recommended systemic, neoadjuvant chemotherapy. She was treated with combined chemotherapy comprising gemcitabine (GEM) and the oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium). The patient was administered biweekly cycles of GEM 800 mg/m^2 intravenously and S-1 orally twice daily after meals, at a dose of 60 mg/m^2/day with a 5-day administration/2-day off cycle, i.e., a weekday-on and

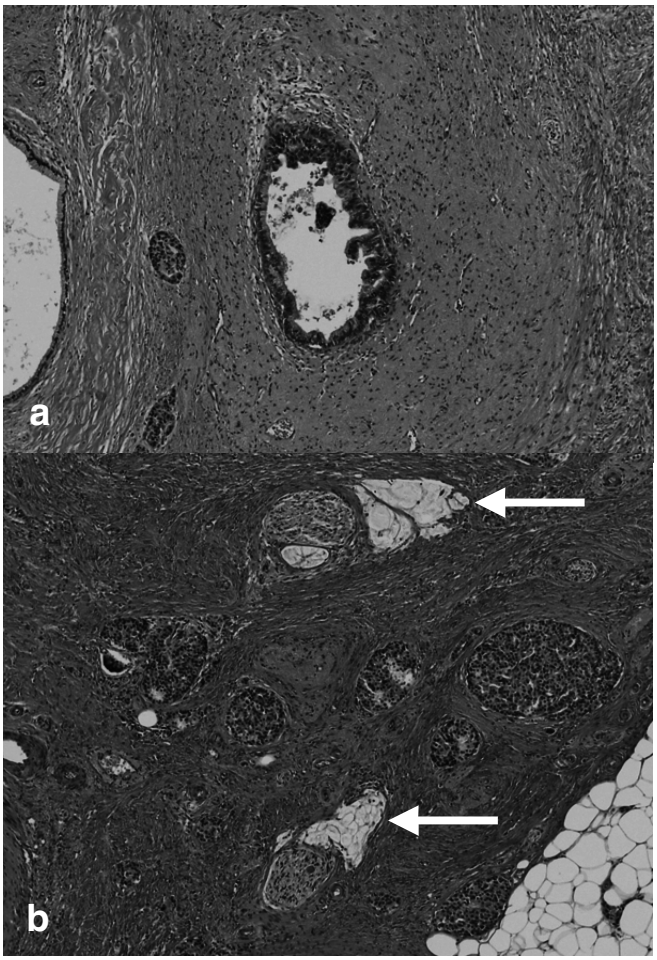

Fig. 3a, b Microscopic findings of the specimen. **a** There are a few residual adenocarcinoma cells in the branched pancreatic duct. **b** The perineural area is free of tumor cells, but mucous retention suggests that they had been present (*white arrows*); fibrotic change in the stroma is also evident.

weekend-off schedule [15]. One course consisted of one administration of GEM, with S-1 administration for 10 days and 4 days' rest. No toxic events due to therapy were observed. Tumor maker CA19-9 -201.0 U/ml at the first chemotherapy- normalized, and the size of the pancreatic head tumor decreased to 16 x 14 x 15 mm on follow-up US and CT after 4 courses. Chemotherapy was given on an outpatient basis, and the patient maintained good quality of life. She underwent 11 courses and the total dose of administered GEM was 1.1 grams. Finally, tumor size decreased to 13 x 11 x 13 mm on US. CT and MRI revealed no tumor encasement of the SMA and no extrapancreatic disease (Fig. 1b). Our evaluation indicated that a partial response had been obtained. After a downstaging to T1N0M0 clinical stage IA that resulted from preoperative chemotherapy, we performed pancreaticoduodenectomy with wedge resection of the SMV, which was suspected had been invaded by the tumor. Histological examination of the excised specimen confirmed a few residual adenocarcinoma cells in the branched pancreatic duct (Fig. 3a). The specimen also showed fibrotic change and fat replacement of the main tumor, with moderate atrophy of the pancreas. The perineural area contained no tumor cells, but mucous retention indicated that they had been present (Fig. 3b). No invasion of the common hepatic duct, duodenal wall, or other organs was evident histopathologically. No lymph node metastases were detected in the resected specimen or intraoperatively, and there was no vessel or neural invasion. Therefore, the tumor was classified as TisN0M0 pathological stage 0 which was usually expected almost 100% in five-years survival rates in pancreatic cancer. The patient had an uneventful recovery and was discharged on postoperative day 18. The patient was not given adjuvant chemotherapy because of the satisfactory pathological findings. During the 12 months of follow-up since then, there has been no evidence of local recurrence, or distant metastasis or peritoneal dissemination.

DISCUSSION

Pancreatic cancer remains a major unsolved health problem, because conventional cancer treatments having little impact on disease course. Nearly all patients with pancreatic cancer develop metastases and die [2]. This disease is considered resectable when there are no distant metastases or infiltration of surrounding organs or arteries. Adjuvant chemotherapy improves survival, but not all patients can receive this treatment because of complications related to surgery. Preoperative (neoadjuvant) treatment offers several theoretical advantages over adjuvant treatment; it is a multimodal treatment concept for all patients, it has a potentially higher R0 resection rate, and it can be used to treat micrometastases before surgery [2, 11, 16, 17].

Before GEM was used clinically, pancreatic adenocarcinoma was notoriously resistant to chemotherapy. The best available strategy for unresectable disease includes combination therapy with chemotherapy and

radiotherapy. In an attempt to improve patient outcome after chemoradiotherapy, various clinical trials of treatments for pancreatic cancer have been conducted in Japan. These trials were designed to evaluate novel chemotherapy regimens combined with conventional radiotherapy, or intensive radiotherapy in combination with chemotherapy.

GEM is a nucleoside analog with structural similarities to cytarabine. Its cytotoxic effect results from the incorporation of its triphosphate metabolite into growing strands of DNA, which leads to inhibition of DNA synthesis [18]. Two initial phase II studies found that GEM induced modest activity in pancreatic cancer [19, 20]. In a randomized trial in which 126 patients with metastatic pancreatic cancer were randomized to receive either GEM or 5-fluorouracil (5-FU) [21] treatment with GEM resulted in better survival outcome than 5-FU in patients with advanced disease. Based on the results of this trial, the current standard chemotherapy for patients with pancreatic cancer is a regimen containing GEM [22, 23], which has been investigated as a chemotherapeutic agent and/or radiosensitizer for the treatment of locally advanced pancreatic cancer in a number of trials.

S-1 is a novel oral anticancer drug that is also being intensively evaluated in Japan for the treatment of locally advanced pancreatic cancer. It is composed of tegafur (FT), gimestat (CDHP), and otastat potassium (Oxo) at a molar ratio of 1: 0.4: 1, which is based on the biochemical modulation of 5-FU. CDHP inhibits dihydropyrimidine dehydrogenase (DPD), an enzyme that degrades 5-FU, thereby maintaining prolonged 5-FU concentrations in blood and tumors. Oxo is distributed throughout the gastrointestinal tract at a high concentration after oral administration and alleviates gastrointestinal toxicity due to 5-FU. S-1 improves the tumor-selective toxicity of 5-FU by the actions of two modulators, CDHP and Oxo [24]. S-1 can be added to GEM to increase the efficacy of chemotherapy and to improve convenience for patients [25–30]. Combination chemotherapy with S-1 plus GEM appears to be effective and well tolerated as a first-line treatment in patients with advanced/metastatic pancreatic cancer [25]. Furthermore, it improves quality of life and the nutritional status of affected patients, and result in favorable overall and disease-free survival. Our chemotherapy regimen for patients with primarily inoperable pancreatic cancer is combination chemotherapy with GEM and repeated oral administration of S-1 on a sustainable schedule, as described above.

Recent reports indicated that neoadjuvant chemoradiotherapy in patients with potentially resectable pancreatic cancer enabled surgical treatment in patients who were previously ineligible for such treatment and resulted in longer survival with acceptable treatment toxicity [31–35]. However, there are few reports of preoperative chemotherapy without radiotherapy for potentially unresectable locally advanced pancreatic cancer [14, 36, 37]. To our knowledge, this is the second English-language report of curative surgical treatment of inoperable pancreatic cancer after neoadjuvant chemotherapy alone. The number of cases responding successfully to neoadjuvant chemotherapy has increased recently, giving new hope for patients [14, 36, 38–40]. In the present case, histopathological examination reliably confirmed the effects of chemotherapy. Additional data collection and clinicopathological analysis of patients with pancreatic cancer who respond favorably to chemotherapy would provide invaluable information and increase hope for a curative treatment [13, 41, 42]. Pancreatic cancer remains a challenging problem. However, improvements in chemotherapy can be expected to result in greater benefits for patients with this disease who undergo surgical treatment.

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