CASE REPORT

Successful Conversion Surgery for Locally Advanced Unresectable Anaplastic Pancreatic Carcinoma after Neoadjuvant S-1-Based Chemoradiotherapy

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ABSTRACT

Anaplastic pancreatic cancer is a very rare type of invasive ductal carcinoma with poor prognosis. This is the first report on a successful curative conversion surgery for anaplastic pancreatic cancer after neoadjuvant chemoradiotherapy. The patient had a locally advanced unresectable pancreatic cancer which involved the celiac axis and the left side of the hepatoduodenal ligament. An endoscopic ultrasonography-guided needle biopsy of the tumor revealed anaplastic carcinoma. He underwent neoadjuvant S-1-based chemoradiotherapy, and subsequently the tumor reduced in size after completion of chemoradiotherapy. Aggressive surgery including total pancreatectomy, left hepatectomy and total gastrectomy was performed. Postoperative pathology revealed no residual tumor in resected specimens. After surgery the patient did not receive chemotherapy or radiotherapy. At 1.5 years after diagnosis and 1 year after surgery, the patient was in good health and free from recurrence. S-1-based chemoradiotherapy followed by aggressive conversion surgery is one of the promising treatment options for locally advanced unresectable anaplastic pancreatic cancer.

INTRODUCTION

The prognosis of pancreatic cancer (PC) remains dismal. Only 10–20% of PC is resectable at diagnosis and the 5-year overall survival rate is <6% [1, 2]. Anaplastic pancreatic carcinoma (APC) is one of the very rare types of invasive ductal carcinoma, which comprises only 2–7% of all PCs with poor prognosis [3-6]. APC is also known as giant cell carcinoma, undifferentiated pancreatic carcinoma, pleomorphic pancreatic carcinoma and sarcomatoid carcinoma. None of the previous studies have reported that chemotherapy and radiotherapy are effective in treating APC. To the best our knowledge, ours is the first report on a successful curative conversion surgery for APC after neoadjuvant chemoradiotherapy (CRT).

CASE REPORT

A sixty-four-year-old male with upper abdominal pain and decreased body weight visited our hospital. Ultrasonography revealed a hypoechoic mass in the pancreatic head. A computed tomography (CT) scan detected a large low-density mass in the pancreatic head (**Figure 1a)**, which involved the root of the celiac axis (CA), the common hepatic artery (CHA) and the splenic artery. Furthermore, the invasion of the tumor was extended along the left side of the hepatoduodenal ligament into the umbilical portion of the liver. When the portal vein (PV) and the superior mesenteric vein (SMV) were also involved, the tumor was judged to be unresectable (**Figure 1b)**. Lymph node metastasis or distant metastasis were not detected by CT scan. Fluorodeoxyglucose positron emission tomography (FDG-PET) showed a hypermetabolic lesion in the margin of the tumor (**Figure 1c).** A laboratory examination was not specific and tumor markers (CA19-9, CEA and IL-2R) were not elevated. An endoscopic ultrasonography-guided needle biopsy of the tumor revealed poorly differentiated carcinoma, and almost all of the tumor cells were spindle-shaped like sarcoma (**Figure 2a).** Immunohistochemically, the tumor cells were reactive for anti-smooth muscle actin, desmin, vimentin and AE1/AE3 (multi cytokeratin antigen) (**Figure 2b and c);** on this basis the tumor was diagnosed as an APC.

After discussion involving the institutional tumor board, neoadjuvant S-1 (Taiho Pharmaceutical, Tokyo, Japan) based CRT was initiated. S-1 was given orally twice daily (120 mg/day) for 4 weeks followed by 2 weeks of drug

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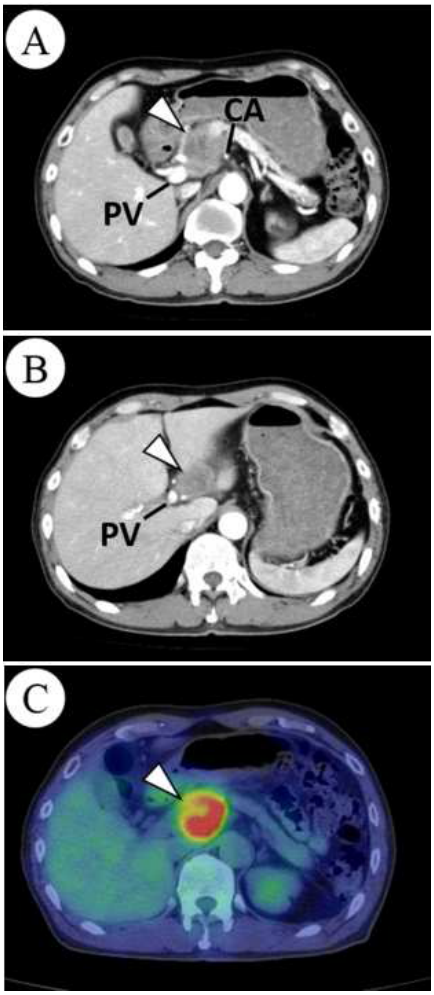

Figure 1. Pretreatment images of the tumor. CT scan showing a low-density large mass in the pancreatic head (white arrowhead) **(a.).** The mass can be seen invading along the left side of hepatoduodenal ligament to the umbilical portion **(b.).** FDG-PET scan showing a hypermetabolic lesion in the surrounding tumor **(c.).** CA, celiac artery; PV, portal vein.

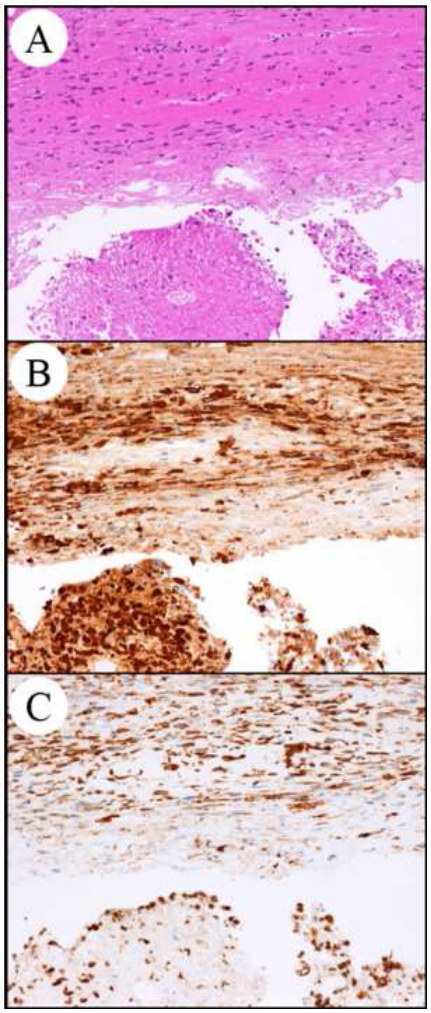

Figure 2. Pathological findings. HE stained tumor composed of spindle-shaped atypical cells **(a.).** (magnification, ×20). Tumor cells showing positive immunohistochemical staining of AE1/AE3 **(b.).** and vimentin **(c.).** (magnification, ×20).

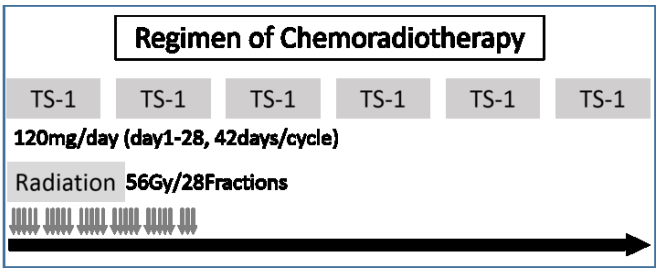

Figure 3. Chemoradiotherapy regimen. S-1 was given orally twice daily (120 mg/day) for 4 weeks followed by 2 weeks of drug holiday in one course. Radiotherapy including a dose of 56 Gy in 28 fractions was given for 6 weeks and chemotherapy was undertaken consecutively for 36 weeks (6 courses).

holiday in one course. Radiotherapy at a total of 56 Gy in 28 fractions was administered for 6 weeks and chemotherapy was undertaken consecutively for 36 weeks (6 courses). **Figure 3** shows the regimen of this S-1-based CRT. A follow-up CT scan after completion of CRT revealed a significant reduction in tumor size. Only a small residual portion of the low density tumor was seen adjacent to the CHA (**Figure 4).** In a FDG-PET scan, the hypermetabolic lesion had disappeared. After an extensive discussion involving a multidisciplinary team, curative resection was intended. Aggressive surgery, including total pancreatectomy and splenectomy and CA resection concomitant with total gastrectomy, was necessary because of the extent of the tumor prior to CRT. Furthermore, left hepatectomy with proper hepatic artery resection were also necessary, because of the invasion of the tumor along the left side of the hepatoduodenal ligament into the umbilical portion of the liver. **Figure 5, 6** depicts the extent of the tumor spread before and after CRT. All of the organs were resected en bloc. The right hepatic artery was reconstructed using a left greater saphenous vein graft anastomosed to the right iliac artery. The PV and SMV were anastomosed end-to-end. The biliary reconstruction was performed using choledochojejunostomy. The operation time was 803 min and the estimated blood loss was 2089 ml, for which six units of red blood cells were transfused.

Pathological findings revealed no residual tumor cells in the specimen and only a small amount of fibrous tissue was observed (pathological complete response). The postoperative course was complicated by two episodes of small-intestinal perforation at 1 and 3 weeks after the first surgery. The patient was discharged from the hospital at 3 months after surgery. No adjuvant chemotherapy was

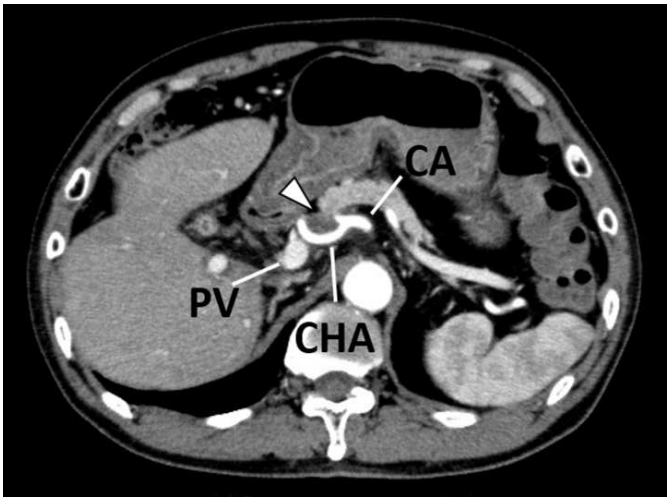

Figure 4. Follow-up CT showing the decreased low density area (white arrowhead) and the small residual lesion located in the pancreas head in contact with common hepatic artery (CHA). CA, celiac artery; PV, portal vein.

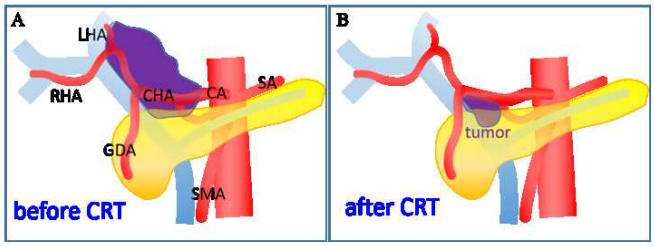

Figure 5. Diagrams showing the extent of the tumor before **(a.).** and after **(b.).** CRT.

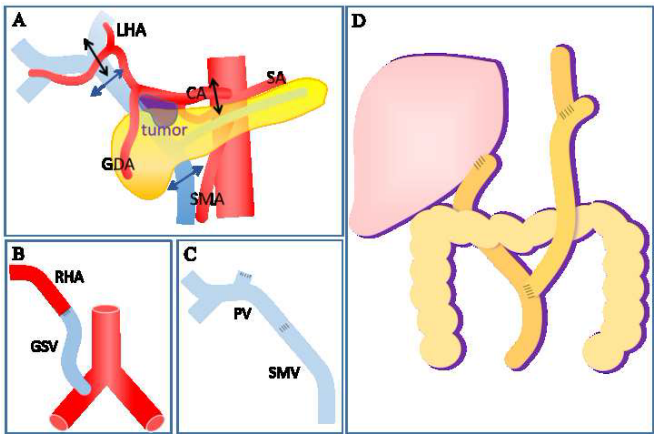

Figure 6. Diagrams showing resection and reconstruction. **(a.).** Resection of the celiac artery (CA), right hepatic artery (RHA), portal vein (PV) and superior mesenteric vein (SMV). **(b.).** Reconstruction of the RHA with a left greater saphenous vein graft anastomosed to the right iliac artery **(c.).** The PV and SMV are anastomosed end-to-end. **(d.).** Digestive and biliary reconstruction performed using esophagojejunostomy and choledochojejunostomy.

given. At 1.5 years after diagnosis and 1 year after surgery, the patient was in good health and free from recurrence.

DISCUSSION

APC is a very rare type of PC with a universally dismal prognosis. Consequently, there have been few reports involving cases with long survival times [7]. Wakatsuki *et al*. reported a case of advanced APC with a complete response to paclitaxel [8]. The patient has been progressing well with no recurrence for 1 year and 11 months since the initial chemotherapy. However, there has been no evidence regarding the effectiveness of surgery for this type of PC, and no standard chemotherapy protocol has been established so far. Nonetheless, National Comprehensive Cancer Network (NCCN) guidelines for this type of PC have not yet been established.

Takahashi *et al* [9]. reported on the effectiveness of gemcitabine (GEM)-based neoadjuvant CRT followed by surgery for resectable as well as borderline resectable PCs. However, there has been little evidence supporting the effectiveness of preoperative CRT even for pancreatic ductal adenocarcinoma [10, 11].Patel *et al*. reported that 11 patients (64.7%) out of 17 patients with borderline resectable pancreatic cancer (BRPC) underwent resection after preoperative CRT and overall survival (OS) was 15.64% [12]. Stokes *et al*. also reported that 11 patients (46%) out of 34 patients with BRPC treated using preoperative CRT underwent resection and the OS time was 23 months [13]. Conversely, regarding unresectable PC, in a previous study only 13 patients (14%) out of 91 patients were reported as being able to undergo resection [14]. A systematic review evaluated the efficiency of neoadjuvant therapy for locally advanced, initially unresectable tumors in 4394 PC patients [15]. The overall resectability rate after neoadjuvant therapy was 33% with a R0 rate of 79.2%. The median OS time for the resected group was 20.5 months, which was significantly higher than that for the non-resected group. This analysis suggests that neoadjuvant therapy could convert one-third of unresectable PCs into BRPCs and may prolong OS.

Recently, monotherapy with S-1 has demonstrated noninferiority to GEM regarding OS for locally advanced and metastatic PC [16]. Furthermore, a Japanese randomized controlled trail reported that patients treated with 6-month adjuvant chemotherapy with S-1 had significantly better 2-year OS than those treated with GEM [17]. Bickenbach *et al*. [18] and Satoi *et al*. [18, 19] reported the results of adjuvant surgery for patients with initially unresectable PCs, but who had responded to anti-cancer treatments. The OS of the adjuvant surgery group was surprisingly high, especially in patients who received anti-cancer treatment for >240 days before surgery [19].

Taking these previous results together, we selected S-1-based CRT as a neoadjuvant therapy. In fact, at 8 months after CRT the size and extent of the tumor had been significantly reduced within a resectable range; subsequently, a curative resection was intended and performed. In this case, the tumor showed negative PET-CT after neoadjuvant therapy. But, it is controversial about the treatment approach and follow-up period because PET-CT cannot detect small tumors. In pancreatic cancer, pathological complete response after neoadjuvant therapy is not very often. We think that conversion surgery is necessary for complete exclusion of cancer tissue. If conversion surgery is not performed, a follow-up CT scan is necessary once every two month. We explained the patient

the risk of this surgery and possibility of re-exacerbation without any treatment, and we decide aggressive surgery. Histologically, no residual tumor cells were detected in the resected specimen (Evans' histological grade, IV) [20]. Although there has been no conclusive evidence concerning S-1-based CRT, we considered that it could be an effective treatment option for APC.

It is a controversial issue as to the size of the tumor margin that should be maintained during conversion surgery after neoadjuvant CRT, considering the fact that only a few patients (<5%) have a complete response. Some reports have indicated that a margin clearance of >1.5 mm is important for long-term survival in PC patients [21, 22]. Nonetheless, the tumor margin should be free from cancer cells and R0 resection should be aimed at curative intent. In our opinion, aggressive and extended surgery is necessary for R0 resection, and this strategy is still acceptable today. Additionally, local fibrosis and adhesion are highly anticipated after a neoadjuvant CRT; therefore, dissection and-complete separation of vessels from tumors could be very difficult. Consequently, if the tumor mass is in contact with blood vessels in preoperative imaging studies, we currently consider that the tumor should be resected with the adjacent vessels. In our case, pathological complete response after preoperative CRT could not be confirmed in preoperative imaging studies. Therefore, all of the area where the tumor mass had existed before CRT had to be resected, which resulted in a complex postoperative course. Although a high possibility of postoperative complications is expected, the indication of conversion surgery should always be considered based on sufficient informed consent and the technical ability of the surgeons.

In conclusion, S-1-based CRT followed by aggressive conversion surgery is one of the promising treatment options for locally advanced unresectable APC. Further accumulation of cases is warranted for this rare type of tumor.

Conflict of interest

Authors have no conflicts of interest.

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