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Case Report

Acinar Cell Carcinoma of the Pancreas Successfully Controlled by IRIS: A Case Report and Literature Review

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Acinar cell carcinoma (ACC) of the pancreas is a rare pancreatic tumor with poor prognosis. We present the first case of ACC of the pancreas successfully controlled by S-1 combined with a colorectal regimen. A 49-year-old Japanese female was referred to our clinic for right upper quadrant pain. Imaging studies demonstrated 2 solid tumors under the pancreas, and pancreatoduodenectomy with tumor resection was performed. Based on pathologic examination, the diagnosis of ACC of the pancreas was made according to the World Health Organization criteria. Eleven months after surgery, lymph node recurrence with elevations in serum concentrations of carbohydrate antigens (CA) 19–9 and CA125 were recognized. Treatments with carboplatin combined with paclitaxel, docetaxel, and gemcitabine, respectively, were attempted; however, there were no significant responses to these regimens. After starting S–1/irinotecan combination chemotherapy (IRIS), the concentrations of the tumor markers declined, accompanied by a reduction in tumor size. Because S-1 is an oral anticancer agent used on an outpatient basis with a low incidence of side effects, we believe that S–1-based chemotherapy is a strong candidate for the first-line treatment of recurrent or unresectable ACC.

Key Words: Acinar cell carcinoma – Pancreas – IRIS – S-1 – Irinotecan

Acinar cell carcinoma (ACC) of the pancreas is a rare neoplasm, accounting for only 1 to 2% of all pancreatic tumors.[1] Although the postoperative survival and resection rates are reported to be superior to pancreatic ductal carcinoma, ACC is still considered to be highly malignant and generally has a poor prognosis.[2,3] The median overall survival time is 18 to 34 months for patients with

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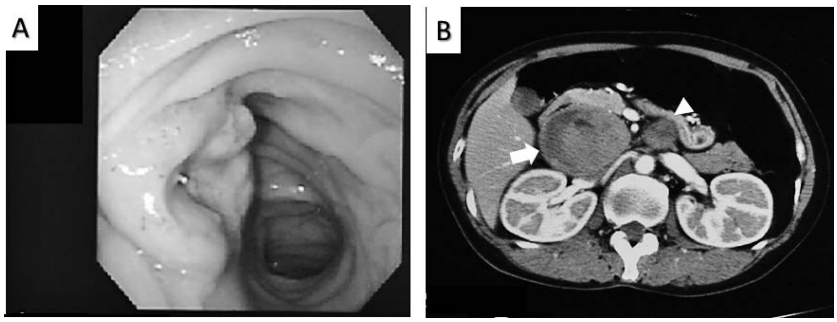

Fig. 1 (A) Ulcerative lesion in the second part of the duodenum. (B) Abdominal CT demonstrated the presence of 2 solid tumors, 4.7 cm (arrow) and 2.2 cm (arrowhead) in diameter, located under, but distinct from, the pancreas.

metastatic or unresectable disease[4,5] and 27 to 123 months for those with resectable tumors.[4–7] Complete resection is the first treatment of choice.[8] However, ACC shows high recurrence rates ranging from 72 to 100% after resection.[7,9] Because of the rarity of this tumor, little has been reported about the effectiveness of chemotherapy, and it is difficult to standardize a strategy for handling recurrent or unresectable cases.

In this case report, we describe a case of ACC of the pancreas that was successfully controlled by S–1/irinotecan combination chemotherapy (IRIS). Because of the recent discovery of genetic identity between ACC and colorectal carcinoma, the chemotherapy regimens used in colorectal carcinoma are currently being highlighted as potentially applicable for the treatment of ACC. To the best of our knowledge, this is the first report of S–1 combined with a colorectal regimen for the treatment of ACC.

Case Report

A 49-year-old woman was referred to our clinic for right upper quadrant pain. She had no previous history of hospitalization. Physical examination revealed slight tenderness in the right upper quadrant of the abdomen. Biochemical examination showed microcytic anemia (hemoglobin 8.7 g/dL) and elevations in the serum concentrations of carbohydrate antigen (CA) 19–9 (207 U/mL) and CA 125 (1200 U/mL). Esophagogastroduodenoscopy revealed an ulcerative lesion in the second portion of the duodenum, near the papilla of Vater (Fig. 1A). A solid pseudopapillary tumor, ACC, or neuroendocrine tumor was first suspected after pathologic analysis of biopsy samples. Abdominal CT demonstrated the presence of 2 solid tumors (4.7 $\times$ 3.6 cm and 2.2 $\times$ 1.9 cm) located in the mesenteric region near the superior mesenteric artery and vein, with distinct separation from the pancreas (Fig. 1B). Abdominal MRI demonstrated well-defined lesions with heterogeneous, low signal intensities on T1 weighted images, and heterogeneous, iso-high signal intensities on T2 weighted images. Pancreatoduodenectomy with tumor resection was planned.

During laparotomy, the tumors were dissected from the pancreatic tissue. The larger tumor showed invasion into the duodenum. The operation was successfully performed, and reconstruction was performed using the modified Child method.

Pathological findings

Macroscopically, the larger tumor was separated from the pancreas by a fibrous capsule, with invasion into the duodenum 4 cm distal to the papilla of Vater (Fig. 2A). On the cut surface, the

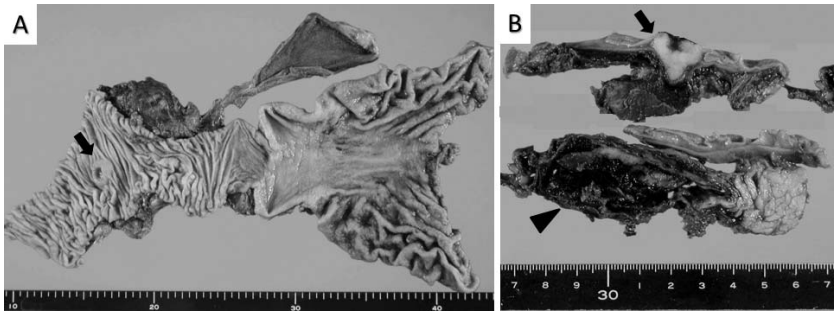

Fig. 2 (A) The larger mass was demarcated from the pancreas by a fibrous capsule. There was invasion into the duodenum, 4 cm from the papilla of Vater (arrow). (B) On the cut surface, the tumor was solid and white to beige in color (arrow). There was a large area of necrosis (arrowhead).

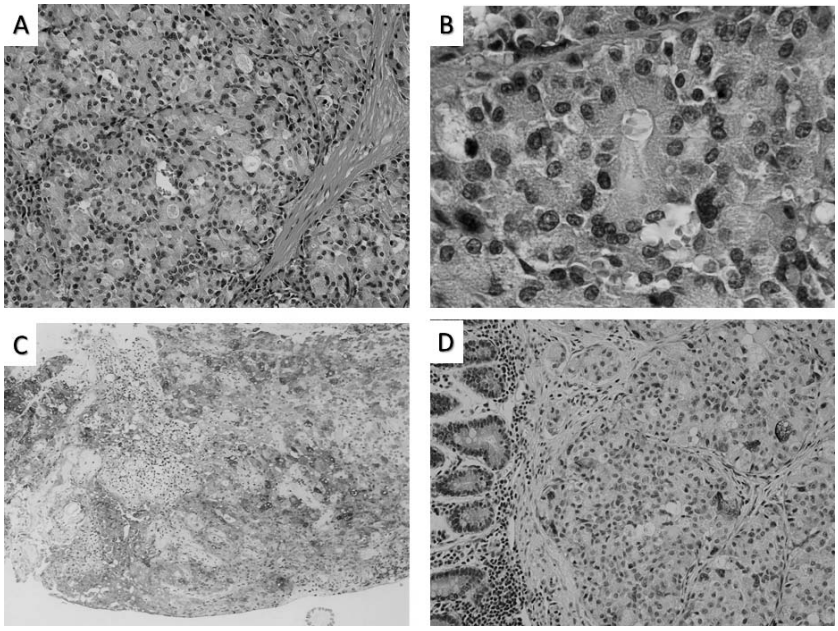

Fig. 3 (A) The tumor showed characteristic formation of an acinar pattern (H&E). (B) The tumor cells were round to oval with prominent nucleoli and a minimal to moderate amount of cytoplasm (H&E). (C) The tumor cells were diffusely positive for α-1-antichymotrypsin. (D) The tumor cells were focally positive for trypsin.

tumor was solid and white to beige in color. There was a large area of necrosis (Fig. 2B).

Microscopically, the larger tumor showed acinar structures characterized by either peripherally placed nuclei and small apical lumina or diffuse sheets separated by fibrovascular stroma (Fig. 3A and 3B). There was no microscopic invasion of the pancreas and no definite structures suggesting an ectopic pancreas. The tumor cells were round to oval, with prominent nucleoli and a minimal to moderate amount of cytoplasm (Fig. 3B). Mitotic figures were observed in approximately 7 to 8 cells per 20 high-power fields (HPF). The Ki-67 labeling index was 18%. Adjunctive lymph node metastasis was detected, and vascular invasion was observed near the papilla of Vater. Immunohistochemically, tumor cells were positive for alpha-1-antichymotrypsin (Fig. 3C), trypsin (Fig. 3D), CA 19–9, CEA, neuron-specific enolase, and cytokeratin. Conversely, tumor cells were negative for E-cadherin, glucagon, insulin-like growth factor, estrogen and progesterone receptors, S-100, synaptophysin, CD56, and chromogranin A. β-catenin showed a membranous pattern. These findings match the World Health Organization (WHO) clinicopathologic classification criteria for ACC of the pancreas.[10] The resected margins were free of tumor. The smaller mass was a metastatic lymph node. According to the Union for International Cancer Control guidelines, the final classification was pT3 N1 M0 Stage IIB.

Postoperative course and follow-up

The postoperative course was uneventful. Tumor markers declined to within the normal range. After 11 months, the serum levels of CA 19–9 and CA 125 suddenly increased. Abdominal CT showed 2 enlarged lymph nodes, 0.5 cm and 1 cm in diameter, respectively (Fig. 4A and 4B). Lymph node recurrence was suspected. Her performance status was good, which scored 0 according to Eastern Cooperative Oncology Group Performance Status. Systemic chemotherapy was planned. Paclitaxel (70 mg/m^2) combined with carboplatin (200 mg/m^2) was first administered weekly for 6 months, resulting in a reduction in the levels of CA 125. However, the levels of CA 19–9 continued to increase with enlargement of the nodes. Docetaxel (70 mg/m^2) combined with carboplatin (AUC = 5600 mg/body) was performed triweekly for 5 cycles, and subsequently gemcitabine (1000 mg/m^2) combined with carboplatin (AUC = 5600 mg/body) was attempted triweekly for 2 cycles, but still CA 19–9 increased. After switching to the IRIS regimen, that is, TS-1 (Taiho, Tokyo, Japan) 80 mg/m^2, 2 weeks on/2 weeks off and Topotesin (Daiichi Sankyo Company, Ltd, Tokyo, Japan) 80 mg/m^2, biweekly, CA 19–9 levels started to decline. The tumors decreased in size by 35% on CT 6 months after the start of therapy (Fig. 4B and 4C; Fig. 5). According to the Response Evaluation Criteria in Solid Tumors guideline, partial response was attained. Although the patient experienced grade 2 malaise and nausea,

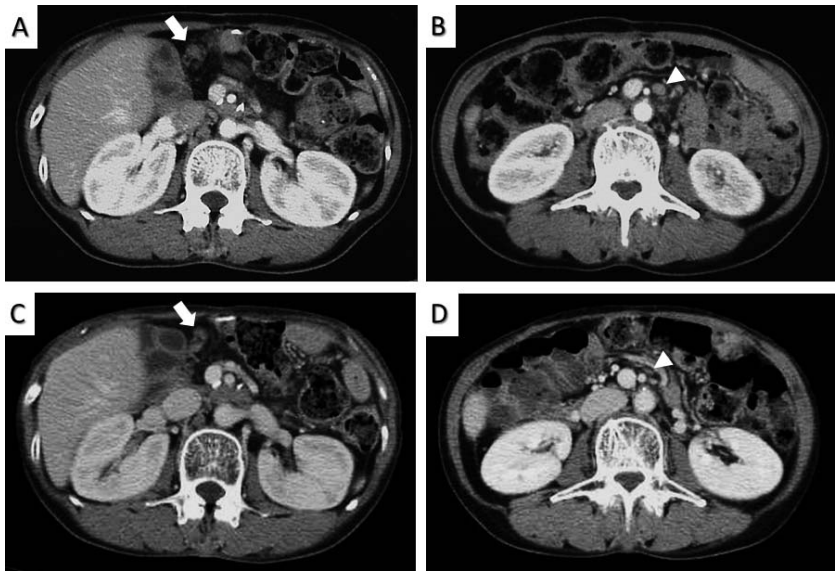

Fig. 4 (A, B) Abdominal CT showed 2 enlarged lymph nodes (arrow and arrowhead). (C, D) After 6 months of IRIS, the lymph nodes decreased in size (arrow and arrowhead).

the therapy was generally satisfactorily tolerated without major side effects.

Discussion

We report a case of ACC of the pancreas that was successfully controlled by IRIS. This case report is significant because reports of chemotherapy for ACC are limited. We believe that S–1-based chemotherapy is a strong candidate for first-line chemotherapy for recurrent and unresectable ACC.

The role of chemotherapy for the treatment of ACC is unclear. According to a recently published study based on the National Cancer database, it was concluded that aggressive surgical resection with negative margins is associated with long-term survival, but adjuvant chemoradiotherapy failed to demonstrate a survival benefit.[5] Conversely, some small series and case reports have documented various successful chemotherapy regimens for locally advanced or recurrent cases. A MEDLINE search of English and Japanese literature revealed 33 previous reports of unresectable or recurrent ACC treated with chemotherapy (Table 1).[4,7–9,11–40] Multiple chemotherapy regimens are reported, with 5-fluorouracil (5FU) and gemcitabine (GEM) based treatments being the most commonly used chemotherapeutic agents in previous reports. GEM has been steadily used since 2000, and in recent years, 5FU has been used as part of combination therapies such as FOLFIRI, FOLFOX, and FOLFIRINOX. It is obvious that the use of radiation therapy has decreased since the late 2000s. Further, several articles report the usefulness of arterial infusion for liver metastasis.[9,12,13,19,23,28,38] Kobayashi *et al*[15] reported the intraperitoneal use of cisplatin (CDDP) associated with a 15-year survival rate. Morales *et al*[37] showed the advantage of using panitumumab as a third-line chemotherapy. Furthermore, it is notable that there are 9 cases in which chemotherapy was used as a first-line treatment for unresectable tumors, but after several cycles of chemotherapy and the recognition of tumor shrinkage, curative surgery was accomplished; this has recently been named "adjuvant surgery."[13,19,24,26,27,32,34–36,41] In most cases, liver resection was performed after gaining control of

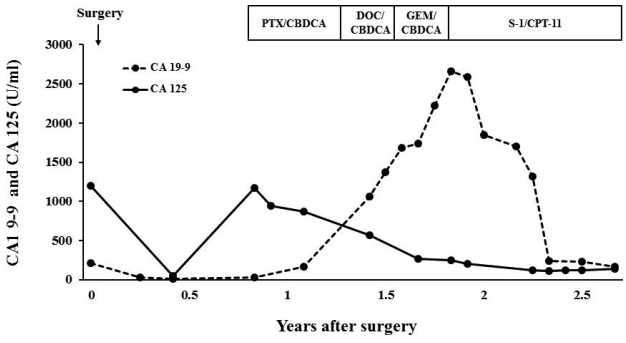

Fig. 5 Tumor markers and chemotherapy regimen. Weekly treatments of carboplatin (CBACA) combined with paclitaxel (PTX), docetaxel (DOC), and gemcitabine (GEM), respectively, were attempted; the CA 125 levels decreased, but the CA 19–9 levels continued to increase. After switching to IRIS, the CA 19–9 levels began to decline.

Table 1 Review of chemotherapy for unresectable or recurrent acinar cell carcinoma of the pancreas

Year	Author	Age/Sex	Regimen	Adj Surg	Res	Prognosis*
1984	Ono[11]	69/M	5FU/MMC/AraC	-	PD	4M DOD
1996	Sakon[12]	56/M	5FU/CDDP/MMC (IA)	-	PR	6M AWD
1999	Ukei[13]	41/M	5FU/CDDP/MMC (IA)	+	PR	18M DOD
2001	Chen[14]	78/F	GEM + RT	-	PR	13W AWD
2001	Kobayashi[15]	34/F	CDDP (IP)	-	CR	15Y NED
2002	Holen[7]	Unknown	CPT/5FU/LV	-	PR	7M**
		Unknown	AraC/CDDP/caffeine		PR	3M AWD
2003	Lee[16]	43/F	CAP + RT	-	PR	21M AWD
		61/F	CAP + RT	-	PR	15M AWD
2003	Riechelmann[17]	43/F	PXL	-	PR	48M DOD
2005	Mueller[18]	19/M	5FU/LV + RT	-	PR	19M DOD
2006	Kataoka[19]	49/M	S-1/CDDP (IA)	+	PR	48M DOD
2007	Kolb-van Harte[20]	77/M	GEM/MMC	-	PR	7M DOD
2007	Illyes[21]	10/M	IFM/VCR/ADR/CDDP/ETP	-	PR	2Y DOD
2007	Antoine[22]	44/F	GEM/CPT	-	SD	37M DOD
2008	Nishii[23]	60/F	5FU/CDDP (IA)	-	SD	11M AWD
2009	Distler[24]	65/M	5FU	+	PR	18M NED
2009	Sorscher[25]	48/M	GEM/5FU/LV	-	PR	18 AWD
2009	Seki[26]	48/M	GEM	+	SD	17M AWD
		67/M	GEM	-	PD	3M AWD
		67/M	S-1	-	PR	14M AWD
		61/M	GEM	-	SD	7M AWD
2010	Butturini[9]	Unknown	GEM/OHT/CAP	-	-	45M DOD
		Unknown	GEM/CDDP	-	-	52M AWD
2010	Lowery[4]	80/M	GEM/OHT	-	PR	33M AWD
		41/M	5FU + RT	-	SD	57M DOD
		46/M	GEM/CPT	-	SD	30M DOD
		44/M	GEM/CPT	-	SD	35M DOD
		50/M	CDDP/CPT	-	PR	34M DOD
		65/F	CAP/GEM	-	SD	21M DOD
		77/M	GEM/CAP/DOC	-	SD	44M DOD
		82/M	GEM/CAP/DOC	-	SD	11M DOD
		65/M	FOLFORI	-	PR	68M AWD
2010	Morishima[27]	65/M	S-1	+	PR	58M AWD
2010	Fujii[28]	59/M	S-1/CDDP (IA)	-	PR	36M DOD
2011	Moro[29]	79/F	GEM	-	SD	18M AWD
2011	Simon[30]	79/M	FOLFOX	-	PR	23M AWD
2011	Nishimizu[31]	64/M	S-1/GEM	-	PR	18M AWD
2012	Kittaka[32]	66/F	GEM + RT	+	SD	13M NED
2012	Iwatate[33]	79/M	GEM	-	PD	2M DOD
2012	Yamamoto[34]	71/M	S-1	+	PR	32 NED
2013	Cananzi[35]	49/M	DOC/CPT/Cetuximab	+	PR	11Y AWD
2013	Pfrommer[36]	15/M	CDDP/ADR	+	PR	-
			FOLFIRINOX	-	PR	40 NED
2013	Morales[37]	42/M	CAP/OHT	-	PR	12M DOD
		64/M	CAP/OHT	-	PD	13M DOD
2013	Ang[38]	71/M	FORFIRI	-	SD	79M AWD
2014	Asayama[39]	60/M	S-1/GEM	-	PD	14W DOD
2014	Schempf[40]	63/M	FOLFIRINOX	-	PR	30M AWD
2014	Present case	46/F	IRIS (S-1/CPT)	-	PR	30M AWD

Adj Surg, adjuvant surgery; Res, response; M, male; F, female; IA, intra-arterial; IP, intraperitoneal; MMC, mitomycin C; 5FU, 5-fluorouracil; AraC, Cytarabine; CDDP, cisplatin; GEM, gemcitabine; LV, leucovorin; CAP, capecitabine; PTX, paclitaxel; IFM, ifosfamide; VCR, vincristine; ADR, adriamycin; ETP, etoposide; CPT, irinotecan; OHP, oxaliplatin; CBDCA, carboplatin; DOC, docetaxel; Y, year; M, month; PD, progressive disease; SD, stable disease; PR, partial response; DOD, died of disease; AWD, alive with disease; NED, no evidence of disease; RT, radiotherapy.

*After diagnosis.

**Died due to traffic accident.

liver metastasis; however, liver transplantation was performed in one case.[36] These cases enabled longer survival than observed in previous reports, which highlights the importance of selecting the appropriate chemotherapeutic regimens for the first-line treatment. We noticed that oral fluoropyrimidines, capecitabine and S–1, as well as these treatments in combination, are equally used. The present case is the eighth report of S–1 based chemotherapy for ACC in either the English or Japanese literature.

The mechanism of action of 5-FU is associated with the inhibition of thymidylate synthase (TS) and the incorporation of 5-FU into RNA and DNA. The combination of 5-FU with other chemotherapeutic agents has been shown to have a marked synergetic cytotoxic effect on tumors. 5-FU results in the up-regulation of a major mediator of cellular uptake of GEM, thereby increasing tumoral GEM uptake.[42] CDDP increases intracellular pools of hydrofolates, thereby enhancing the formation of 5-fluorodeoxyuridylate-TS complexes, and strongly inhibits TS.[43] CPT reduces the expression of TS in tumors resistant to 5-FU due to the high expression of TS. Recently, combination regimens of infusional 5-FU, CPT, and oxaliplatin (OHP) have been demonstrated to produce high response rates and long survival rates in patients with colorectal carcinoma, and they have shown a survival advantage for patients with metastatic pancreatic ductal carcinoma over GEM.[44] Moreover, the molecular indicators of ACC were identified as distinct from pancreatic ductal carcinoma, and similar to those found in colorectal carcinoma.[45] The shared genetic alternations between ACC and colorectal carcinoma offers a biologic rational for using agents that are active in colorectal carcinoma to manage ACC[4]; and the combination of 5-FU, CPT, and OHP may offer a significant advantage in ACC. In fact, there are 4 successful cases of the use of these combination regimens.[30,36,38,40] However, in these treatments, infusional 5-FU administration was still associated with more complications, discomfort, and inconvenience due to the need for central venous access and portable infusion pumps. Therefore, oral xuoropyrimidine agents are strongly expected to avoid these complications.

S–1 is an oral dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine that was developed by potentiating the antitumor activity and reducing the gastrointestinal toxicity of 5-FU. S–1 shows the highest response rate with advanced gastroenterologic cancers, hepatobiliary and pancreatic cancers, and lung cancers.[46] A randomized phase III study demonstrated that S–1 monotherapy showed noninferiority to GEM with good tolerability regarding overall survival in patients with locally advanced or metastatic pancreatic adenocarcinoma.[47] Our MEDLINE search revealed 7 previous reports of ACC treated with S–1-based chemotherapy. It is obvious that the usage of S–1 has been increasing since the late 2000s. A variety of combinations are reported, mostly with GEM or CDDP, and the majority of cases responded well to the regimen. There were 2 cases in which the dose was decreased due to the emergence of renal dysfunction and platelet decreases, but skipping administration was not necessary.[31,34] Clearly, S–1 is safe and compliant and has promising effects on ACC. Our report is notable in that the combination regimen of S–1 used in colorectal cancer was the applied to a patient with ACC for the first time, and the response was positive. Because S–1 is an oral anticancer agent that is used on an outpatient basis and results in a low incidence of side effects, we believe that S–1-based chemotherapy could be a strong candidate for the first-line treatment for unresectable or recurrent ACC.

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