A Case of Pancreatic Acinar Cell Carcinoma with Invasion of the Main Pancreatic Duct Treated by Total Pancreatectomy

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Abstract
We encountered a case of pancreatic acinar cell carcinoma (ACC), which is a somewhat rare clinical entity. The patient was a 78-year-old woman who had been examined elsewhere for persistent upper abdominal pain that had begun a few months earlier. The examination revealed a neoplastic lesion in the head and tail of the pancreas. Contrast-enhanced abdominal computed tomography revealed a tumor measuring 42 x 59 mm in the tail of the pancreas with distinct margins and internal heterogeneity. Furthermore, solid portions suggestive of invasion of the main pancreatic duct were seen. Endoscopic retrograde pancreatography was performed, and cytologic examination of the pancreatic fluid led to a diagnosis of class V carcinoma. The tumor was located mainly in the pancreatic tail, but the ductal invasion extended into the pancreatic head. Thus, we performed radical total pancreatectomy. Histopathologic examination revealed proliferation of tumor cells with eosinophilic cell bodies as the main intraductal component, whereas the primary tumor comprised adenoid, cribriform, and solid structures. Upon immunohistochemical staining, the cells tested positive for Bcl-1 and negative for synaptophysin and chromogranin A, so pancreatic ACC was diagnosed (pT2N0M0-fStageIB). Pancreatic acinar cell carcinoma accounts for 0.4% of all pancreatic cancers in Japan, and invasion of the main pancreatic duct is rare.

Key words
Pancreas, ACC, invasion, main pancreatic duct

Introduction
Acinar cell carcinoma (ACC) of the pancreas is relatively rare, accounting for approximately 0.4% of all pancreatic cancers in Japan.¹ Fabre et al.² were the first to report purely intraductal ACC, and a number of similar reports have been published since theirs. Pancreatic ACC usually arises from acinar cells at the margin of the pancreatic parenchyma, and whereas the growth pattern of such ACC is usually expansive and tumor capsule formation commonly occurs, invasion of the main pancreatic duct and subsequent deformation of the duct occurs, but only rarely.² We report a case of pancreatic ACC that had invaded the main pancreatic duct, the surgical and adjuvant chemotherapy we provided, and the patient’s current status.

Case report
A 78-year-old woman was admitted to our hospital with complaints of epigastric pain that had persisted for a few months. She had undergone mitral valvuloplasty at age 63 years, and she had no allergies.

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History of presenting illness: The patient had consulted a physician because of persistent epigastric pain that had begun a few months earlier. Detailed examination had revealed a neoplastic lesion in the head and tail of the pancreas, so she was referred to St. Marianna Medical University Hospital for surgical treatment.

Blood chemistry and tumor marker tests (Table 1): Blood chemistry and tumor marker tests performed, preoperatively, showed the patient to be anemic, with a hemoglobin concentration of 8.9 mg/dL. CRP was elevated to 11.63 mg/dL. Of the tumor markers tested, only elastase-1 (4292 mg/dL) was elevated.

Contrast-enhanced abdominal computed tomography (CT): CT, performed preoperatively, revealed an oval 42 x 59-mm tumor with distinct margins in the tail of the pancreas. The interior of the tumor was of heterogeneous soft-tissue density, and some parts exhibited weak contrast enhancement (Fig. 1a). Furthermore, the tumor appeared to be continuous with solid components in the main pancreatic duct that were enhanced (Fig. 1b), and tumor that was consistent with contrast enhancement in the main pancreatic duct was seen in the head of the pancreas (Fig. 1b).

Endoscopic retrograde pancreatography (ERP): ERP was also performed preoperatively, and communication between the necrotic cavity of the tumor and the main pancreatica was seen (Fig. 2). We sampled

Table 1. Results of Blood Chemistry and Tumor Marker Tests.

| Test                    | Value           |
|-------------------------|-----------------|
| WBC count               | 6300/μL         |
| Blood urea nitrogen     | 13.2 mg/dL      |
| Hemoglobin              | 8.9 mg/dL       |
| Amylase                 | 74 U/L          |
| MCV                     | 89.2 fL         |
| CRP                     | 11.63 mg/dL     |
| MCH                     | 29.7 pg         |
| Na                      | 140 mEq/L       |
| MCHC                    | 33.20%          |
| K                       | 3.6 mEq/L       |
| Platelet                | 216000/μL       |
| Cl                      | 104 mEq/L       |
| Total protein           | 6.2 g/dL        |
| PT                      | 57%             |
| Albumin                 | 3.4 g/dL        |
| APTT                    | 37.7 sec        |
| Total bilirubin         | 0.4 mg/dL       |
| Blood glucose           | 125 mg/dL       |
| Direct bilirubin        | 0.0 mg/dL       |
| HbA1c                   | 7.40%           |
| AST                     | 34 U/L          |
| CA 19-9                 | 17.0 U/mL       |
| ALT                     | 31 U/L          |
| CEA                     | 2.8 mg/dL       |
| LDH                     | 253 U/L         |
| Elastase 1              | 4292 ng/dL      |
| Creatinine              | 0.52 mg/dL      |
| DUPAN-2                 | <25 U/mL        |

WBC, white blood cell; MCV, mean corpuscular volume; MCH, average hemoglobin level per red blood cell; MCHC, mean corpuscular hemoglobin concentration; AST, aspartate aminotransferase; ALT, alanine transaminase; LDH, lactate dehydrogenase; CRP, C-reactive protein; Na, sodium; K, potassium; Cl, chloride; PT, prothrombin time; APTT, activated partial thromboplastin time; HbA1c, glycated hemoglobin; CEA, carcinoembryonic antigen
Figure 2. Preoperative endoscopic retrograde pancreatography confirmed communication between the necrotic cavity of the tumor and the main pancreatica.

and submitted pancreatic juice to cytology, which led to a diagnosis of class V carcinoma.

Preoperative diagnosis: The imaging findings suggested that the mass was not a classic invasive pancreatic ductal carcinoma, so our differential diagnosis included intraductal papillary mucinous neoplasm (IPMN) and intraductal tubulopapillary neoplasm (ITPN). There appeared to be no distant metastases. With the patient judged to be suitable for surgery, open total pancreatectomy, as radical treatment, was deemed appropriate.

Surgical procedure and findings: Bilateral subcostal crescentic laparotomy incisions were placed. No ascites, distant organ metastasis, or distant lymph node metastasis was observed. The primary tumor exhibited expansive growth, primarily in the pancreatic tail, and no adhesion to or invasion of surrounding organs was seen. Because the preoperative imaging studies had indicated invasion of the main pancreatic duct in the pancreatic head, total pancreatectomy was performed as planned.

Gross findings: Upon gross examination of the surgical specimen, the primary tumor appeared solid. Invasive growth was seen, primarily in the pancreatic tail. The main pancreatic duct was filled with tumor emboli (Fig. 3a-c).

Postoperative histopathologic findings: Upon histopathologic examination of the surgical specimen the following were noted: Phbt, TS4 (100 mm), ductal type, med, INFa, Ly0, v0, ne0, mpd(+), pT2, pCH0, pDU0, pS0, pRP0, pPV0, pA0, pPL0, pOO0, pBCM0, pPDM(X), pN0, pT2N0M0-fStageIB. Proliferation of tumor cells with eosinophilic cell bodies were seen as the main intraductal component, whereas the primary tumor comprised adenoid, cribriform, and solid structures (Fig. 4a, b). Upon immunohistochemical staining, the cells were positive for Bcl-1 and negative for synaptophysin and chromogranin A. The MIB-1 index was approximately 30% (Fig. 4c). The histopathologic findings led to a final diagnosis of pancreatic ACC. Although tumor cells were found in the pancreatic tail, the tumor was made up mainly of inflamed scar tissue. Tumor cells were seen along the full length of the main pancreatic duct, and mild inflammatory changes were observed in the pancreatic head.

Postoperative clinical course: Immediately following the surgery, continuous intravenous insulin infusion was initiated to control the patient’s blood glucose level. Starting on postoperative day (POD) 5, the patient was given 8 units of long-acting insulin at night and 3 units of short-acting insulin in the morning, at noon, and at night. On POD 3, a left iliacus muscle hematoma was discovered, but this resolved with conservative treatment. Some time passed before the patient’s nutritional intake was satisfactory, precluding early establishment of a regular insulin regimen. In addition, the expected diarrhea was difficult to control. Ultimately, the patient was prescribed 2 units of long-acting insulin to be taken at night, and 5 units, 4 units, and 4 units of short-acting insulin to be taken in the morning, at noon, and at night. On POD 28, she was prescribed oral TS-1 as postoperative adjuvant chemotherapy, administered at 80 mg/day for 4 weeks in 6-week cycles. However, grade 2 general malaise developed as an adverse drug reaction, so the chemotherapy regimen was adjusted to 80 mg/day for 2 weeks in 3-week cycles and continued for 6 months. Eighteen months have passed since the surgery, and the patient remains recurrence free.

Discussion

Pancreatic ACC is generally characterized by expansive, non-invasive growth, and because such tumors are frequently encapsulated, they are unlikely to spread to surrounding organs. For this reason, any changes that occur in the main pancreatic duct and common bile duct tend to be mild, and the disease is frequently detected as a result of abdominal pain or
weight loss\textsuperscript{12}. Mean age of patients in whom ACC of the pancreas is detected is 62 years, and mean tumor diameter at the time of detection is 10.8 cm\textsuperscript{2}. Reported survival rates, per degree of disease progression, are as follows: Stage II: 76.9\%; Stage III: 30.9\%; Stage IVa: 43.9\%; and Stage IVb: 25.1\%, and mean survival time (MST) for patients who undergo resection is 41 months\textsuperscript{3}. In contrast to pancreatic ACCs, which comprise 0.4\% of all pancreatic cancers, invasive intraductal cancers of the pancreas, which are considered typical pancreatic cancers, comprise $\geq70\%$ of all pancreatic tumors. Median age of patients in whom these cancers are detected is 64 years. Reported 5-year survival rates for patients with pancreatic ACC, per disease progression according to the Union for International Cancer Control classification system, are as follows: Stage 0: 85.8\%; Stage Ia: 68.7\%; Stage Ib: 59.7\%; Stage IIa: 30.2\%; Stage IIb: 13.3\%; Stage III: 4.7\%; and Stage IV: 2.7\%\textsuperscript{5,6}. Thus, it is clear that the general prognosis for patients with pancreatic ACC is better than that for patients with a typical pancreatic cancer.

We searched the Igaku Chuo Zasshi database for pertinent reports from Japan published between 2001 and 2017. Using the keywords "acinar cell carcinoma, pancreatic duct invasion" and "acinar cell carcinoma, tumor emboli," we found reports of 19 cases\textsuperscript{8–24}, which, along with our case, are shown on Table 2. Median age, tumor diameter, and survival time in the 19 cases were 66 years, 5.5 cm, and 28
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months, respectively. We noticed that the diameters of ACC tumors that had invaded the pancreatic ducts tended to be smaller than those of typical ACC tumors\(^2\). We believe that the tumor diameter is smaller at the time of detection in cases with pancreatic duct invasion because ACC tends to arise in the pancreatic head, where tumor emboli form, leading readily in turn to obstructive pancreatitis or pancreatic dysfunction. The reported survival times of patients with ACC invading one or more pancreatic ducts were determined at the time the reports were written, so strict comparison is not possible. However, the MST in these cases was longer than the 10.2-month MST reported for typical pancreatic cancers\(^1\). The smaller tumor diameter at the time of resection in these reported cases of ACC, for which the prognosis is already relatively favorable, further increases the chances of a positive patient outcome.

Our patient’s tumor was located primarily in the pancreatic tail, so her chief complaint was that of epigastric pain, and the tumor diameter at the time of detection was 10 cm, which is consistent with the mean tumor diameter of typical ACC. CT findings included an area of low absorption in the main pancreatic duct within the pancreatic body, and the tumor plug in the main pancreatic duct within the pancreatic head appeared as skip lesions. Macroscopic examination of the cut-out specimen revealed tumor in the main pancreatic duct, pathological proof that the tumor had spread throughout the main pancreatic duct. Therefore, even when CT depicts what appear to be skip lesions, rapid intraoperative pathological diagnosis is needed to determine whether radical resection may be necessary.

We treated our patient with S-1, an oral fluoropyrimidine, as adjuvant chemotherapy, based on the regimens used for typical pancreatic cancer, and, as noted above she remains recurrence free. Only two of the reports noted above mention adjuvant chemotherapy: chemoradiotherapy, i.e., S-1 plus radiotherapy, in one case\(^2\)\(^2\) and S-1 in combination with gemcitabine in the other\(^2\)\(^3\). Survival time for the two patients was 2 years 7 months and 3 years 3 months, respectively. Currently, there is no consensus regarding the optimal postoperative chemotherapy regimen for ACC, but we believe that adjuvant chemotherapy improves the prognosis.

The literature teaches us that prognosis of pancreatic ACC is generally more favorable than that of typical pancreatic cancer, and when complete tumor resection can be performed, a good long-term out-

Figure 4. Pathologically examined sections of the surgical specimen. (a) H&E staining revealed invasion of tumor cells in the main pancreatic duct and (b) adenoid, cribriform, and solid structures in the main tumor. (c) Immunohistochemical staining of tumor cells for Bcl-10 was positive.
Table 2. Clinical Details of the 19 Cases of Pancreatic Acinar Cell Carcinoma with Intraductal Growth Reported in Japan.

| Age of patients (years) | 66 (37-78) |
|-------------------------|------------|
| Sex ratio (male:female) | 11:7       |
| Size of tumor (cm)      | 5.5 (2-14.5) |
| Tumor location (H: H-B: H-T: B: B-T: T) | 7: 2: 5: 1: 1: 2 |
| Lymph node metastasis (present:not present) | 3:9 |
| Distant metastasis (present:not present) | 1:14 |
| Recurrence (yes:no)    | 3:8        |
| Survival time (months)  | 28 (8-56)  |
| Surgical method (DP:PD:TP)** | 5:8:5 |

Median (range) values or number of patients are shown.

*H, head; B, body; T, tail

**PD, pancreatoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy

come can be expected, even for patients with pancreatic duct invasion. We therefore believe that surgical treatment should be performed proactively if there is potential for radical resection.

Conflicts of Interest

The authors have nothing to disclose.

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