Pancreatic Ductal Adenocarcinoma Development in the Remnant Pancreas after Pancreatectoduodenectomy for Acinar Cell Carcinoma: A Case Report

Running title: Recurrence after ACC surgery

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Abstract

We report the case of a pancreatic ductal adenocarcinoma (PDAC) in the remnant pancreas of a 78-year-old man after pancreaticoduodenectomy for acinar cell carcinoma. Acinar cell carcinoma is a relatively rare pancreatic neoplasm. Following the diagnosis of pancreatic carcinoma, subtotal stomach-preserving pancreaticoduodenectomy was performed. The pathological diagnosis was acinar cell carcinoma of the pancreas, disease stage IA, pT1, pN0, M0, without regional lymph node invasion. Twenty-two months after the surgery, cancer antigen 19-9 levels gradually increased, and computed tomography showed 2 solid tumors, approximately 1.1 and 2.1 cm in diameter, respectively, at the site of the remnant pancreas. Endoscopic ultrasound fine-needle aspiration revealed pancreatic ductal adenocarcinoma. The tumor cells were not immunoreactive for trypsin. Both tumors were diagnosed as PDAC of the remnant pancreas. The patient refused treatment with curative resection. Thus, as an alternative treatment, chemoradiotherapy was initiated. However, 28 months after surgery, the patient succumbed to the disease. Because this is an extremely rare case, further cases and studies are needed to understand its pathogenesis.
Key words

Acinar cell carcinoma, Pancreatic ductal adenocarcinoma, Pancreatectomy, Pancreatic cancer
Introduction

Acinar cell carcinoma (ACC) is a relatively rare pancreatic neoplasm. Although the pancreas predominantly consists of acinar cells (82% total pancreatic volume), ACC accounts for approximately 1% of all pancreatic neoplasms. The reason for the low prevalence of ACC remains unclear, although some researchers have speculated that acinar cells may undergo metaplasia into ductal cells when they encounter genetic instability. The prognosis of ACC remains controversial because some patients show poor prognosis, while others show a better prognosis compared with patients with pancreatic ductal adenocarcinoma (PDAC). Patients who present with localized disease show a better prognosis than those with metastases. However, even after curative resection, there is still a high rate of recurrence. Some authors have reported that most patients develop either local or liver recurrence. Currently, there is no report in the literature regarding other types of carcinoma recurring in the remnant pancreas.

Here, we discuss the case of a PDAC in the remnant pancreas of a patient after pancreaticoduodenectomy for ACC.
Case report

A 78-year-old man presented with hematuria at our clinic. He had no risk factors, including a family history of pancreatic cancer, medical history of diabetes, obesity, or alcohol abuse. Enhanced abdominal computed tomography (CT) was performed to examine the cause of hematuria, and it revealed an approximately 2 cm in diameter mass lesion in the head of the pancreas (Fig. 1). Blood test results showed normal values, as well as normal levels of tumor markers carcinoembryonic antigen and cancer antigen 19-9 (CA19-9). Endoscopic ultrasound (EUS) showed a low-echoic mass in the head of the pancreas (Fig. 2). Poorly differentiated carcinoma was suspected based on EUS fine-needle aspiration biopsy. For the diagnosis of pancreatic carcinoma, subtotal stomach-preserving pancreaticoduodenectomy was performed. Macroscopically, the tumor appeared well circumscribed, and the cut surface showed a solid tumor (Fig. 3). Microscopically, the tumor cells were arranged in combination patterns, with solid or trabecular anastomosing structures and glandular cells (Fig. 4a).

Immunohistochemically, the tumor cells were immunoreactive for trypsin and amylase but were negative for chromogranin, synaptophysin, and CD56 staining (Fig. 4b). The non-cancerous region of the pancreas showed chronic pancreatitis, and the dissected peripancreatic tissue margin was negative for carcinoma. The pathological diagnosis
was ACC of the pancreas, stage IA pT1, pN0, M0 (Union for International Cancer Control staging, 8th edition), without regional lymph node invasion.

The postoperative course was uneventful, with the patient being discharged on the 12th postoperative day. After the operation, no adjuvant therapy was administered because the patient refused the treatment. Twenty-two months after surgery, CA19-9 levels gradually increased to 163 U/mL. Therefore, a recurrence of pancreatic cancer was suspected but was not detected on an enhanced abdominal CT scan. Three months later, a CT scan revealed 2 solid tumors of approximately 1.1 and 2.1 cm in diameter at the site of the remnant pancreas with invasion of the descending colon (Fig. 5a). A positron emission tomography scan showed an abnormal accumulation of fluorodeoxyglucose in the remnant pancreas (SUVmax = 5.4), with the absence of any distant metastasis (Fig. 5b). EUS confirmed the presence of two low-echoic masses and EUS fine-needle aspiration revealed ductal adenocarcinoma (Figs. 6a, 6b, 6c). The tumor cells were negative for immunoreactivity for trypsin (Fig. 6d). We diagnosed both tumors as PDAC of the remnant pancreas.

The patient refused treatment with curative resection. Thus, as an alternative treatment, chemoradiotherapy was initiated. Radiation therapy was delivered at 1.8 Gy per day for
a total dose of 50.4 Gy. On days 1 and 7, chemotherapy with gemcitabine (250 mg/m²) was administered concurrently with radiation. Despite chemoradiotherapy treatment, the CA19-9 levels increased to 2000 U/mL. Weight loss and asthenia subsequently developed. Twenty-eight months after surgery, the patient was transferred to the palliative care unit, and he succumbed to the disease.

**Discussion**

ACC is a rare type of malignant tumor. During preoperative evaluation, typical features of CT imaging include a large, exophytic, well-circumscribed, and hypovascular tumor. Lipase hypersecretion syndrome is recognized to be secondary to lipase hypersecretion by ACC. ACC may have different histological features, ranging from acinar structures similar to normal pancreatic acini to solid growths composed of large sheets of poorly differentiated neoplastic cells. A pathological diagnosis of ACC is rarely achieved preoperatively, and surgeons should thus be cognizant of ACC when dealing with pancreatic cases. In this report, the patient had no specific features. We could not preoperatively diagnose the tumor as ACC, though EUS-guided fine-needle biopsy and immunohistochemistry are typically utilized when ACC is diagnosed preoperatively.
Although the prognosis of ACC might be better than that of PDAC, it remains poor due to metastatic disease and a high rate of recurrence, as described above. The median survival for ACC ranges from 18 to 33 months\textsuperscript{3,6,11}. Wang et al.\textsuperscript{7} reported a high recurrence rate of 56.3% in resected patients, with recurrence sites including both local disease and liver metastasis. ACC remains aggressive in nature, similar to invasive pancreatic carcinoma, and is often a systemic disease with high recurrence rates\textsuperscript{3}.

Surgical resection with negative margins remains the best first approach for ACC when possible. Both Holen et al. and Wang et al. reported that resected patients had significantly better survival than those not undergoing resection\textsuperscript{3,7}. Aggressive surgical resection, with the goal of achieving R0 margins of resection, is associated with long-term survival\textsuperscript{12}. If ACC is unresectable or recurrent, chemotherapy may prove useful; however, few reports have comprehensively examined the effectiveness of chemotherapy for ACC treatment.

In this case, surgical resection with negative margins was performed for ACC in the head of the pancreas. Twenty-five months after surgery, PDAC developed in the remnant pancreas of our patient. There were different histopathological findings
between the first tumor and two recurrent masses. Though the tumor was resectable, chemoradiotherapy was performed due to the patient’s refusal to undergo surgery.

There are few reports in the literature on pancreatic carcinoma recurrence in the remnant pancreas after pancreaticoduodenectomy. Ishida reported that the incidence rate of secondary PDAC in the remnant pancreas after pancreatectomy for PDAC is markedly high. The cumulative 3- and 5-year incidence rates were 3.1% and 17.7%, respectively. With respect to ACC, there was no report about PDAC development in the remnant pancreas after a pancreaticoduodenectomy.

ACC has histological variants such as mixed acinar-neuroendocrine carcinoma and mixed acinar-ductal adenocarcinoma. In this case, the first ACC tumor did not contain ductal differentiation or a significant neuroendocrine component. However, biopsy of the second tumor in the remnant pancreas showed adenocarcinoma.

Diagnosis based on pathology is limited. We could not accurately diagnose the tumor in the remnant pancreas because the specimens were partially obtained by fine-needle biopsy and not surgery or autopsy. Mixed pathological-type tumor exists in the case of pancreatic cancer and even in secondary tumors. In spite of pathological diagnosis, there
still remains possibility that the remnant pancreatic cancer is a development of mixed-type ACC.

The molecular mechanisms involved in ACC are not completely understood. In general, the typical abnormalities of PDAC, including mutations in KRAS, DPC4, p16, and TP53, are absent or very rare in ACC. ACC has different gene alterations from those of PDAC. In our case, PDAC developed in the remnant pancreas after surgery for ACC. Therefore, there might be some relation of genetic alterations between ACC and PDAC, though genetic profiling was not performed for the tumors in our case.

We reported the first case of PDAC in the remnant pancreas after pancreaticoduodenectomy for ACC. Because this is an extremely rare case, further cases and studies are needed to understand its pathogenesis.
References


Figure Legends

Figure 1. Dynamic contrast-enhanced CT showing a 20-mm-sized heterogeneous tumor in the head of the pancreas (arrow in the arterial phase image).

Figure 2. Endoscopic ultrasound showing a 11×17 mm low-echoic mass in the head of the pancreas (arrows).

Figure 3. Cut surface of the resected specimen showing a solid tumor (arrows).

Figure 4. (a) Hematoxylin and eosin stain showing that atypical cells grew in a solid manner, with structured acinar formations. (b) Immunohistochemically stained tumor cells with trypsin.

Figure 5. (a) Enhanced CT showing two hypovascular tumors in the remnant pancreas (arrows).
(b) Positron emission tomography showing an abnormal accumulation of 18F-fluorodeoxyglucose in the remnant pancreas (SUV max = 5.4).

Figure 6. (a) Endoscopic ultrasound (EUS) showing a low-echoic mass in the remnant pancreas (arrows). (b) Contrast-enhanced EUS using sonazoid showing a slightly enhanced tumor. (c) Hematoxylin and eosin staining showing a tubular adenocarcinoma, which is composed of irregular glands with marked fibrosis. (d) Immunohistochemical labeling for trypsin shows stained tumor cells.
Figure 1.
Figure 2.
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Figure 4.
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