

Case Report

An Autopsy Case of Anaplastic Pancreatic Ductal Carcinoma (Spindle Cell Type) Multiple Onset in the Pancreas

Hiroyuki Ito^a Shin-ichiro Hiraiwa^b Tomoko Sugiyama^b Takuma Tajiri^b
Hisamichi Yoshii^c Hideki Izumi^c Yoko Yamaji^a Motoki Kaneko^a
Shingo Tsuda^a Hitoshi Ichikawa^a Junko Nagata^a Seiichiro Kojima^a
Shinji Takashimizu^a Takayuki Shirai^a Norihito Watanabe^a

^aDepartment of Gastroenterology, Tokai University Hachioji Hospital, Tokyo, Japan;

^bDepartment of Pathology, Tokai University Hachioji Hospital, Tokyo, Japan;

^cDepartment of Surgery, Tokai University Hachioji Hospital, Tokyo, Japan

Keywords

Cancer · Pancreatic cancer · Pancreatic carcinoma · Anaplastic pancreatic ductal carcinoma · Multiple pancreatic tumors

Abstract

This is a case of a 75-year-old man who was diagnosed with anaplastic pancreatic ductal carcinoma (spindle cell type). His image findings showed pancreatic head cysts and pancreatic head, body, and tail tumors respectively. EUS-FNA was performed to the pancreatic head and pancreatic body tumors, and the same high atypical type cells suspected of cancer were obtained from either specimen, and finally total pancreatectomy was performed. On the specimen, there were 4 lesions in the pancreas; histology showed that the same anaplastic pancreatic ductal carcinoma (spindle cell type) was obtained from the pancreatic head cyst and the pancreatic tumors.

© 2019 The Author(s)
Published by S. Karger AG, Basel

Introduction

Anaplastic pancreatic ductal carcinoma is a relatively rare cancer that is classified as a type of invasive pancreatic ductal cancer. It is a highly malignant cancer with rapid tumor development and it shows hematogenous/lymphogenous metastasis from early stages, in addition to showing expansive development of hemorrhagic necrosis and tumors accompanied by cystic degeneration. In this case, the same tissues were found in the cystic nodules and tumors of the pancreas, showing an initial form that was different from those previously reported. We reported a suggestive case in considering the features and progressive forms of anaplastic pancreatic ductal carcinoma.

Case Report

A 75-year-old man consulted a primary doctor for the chief complaint of epigastric pain. A pancreatic head cyst was identified during imaging and he was referred to our hospital. Previously, he was treated for myocardial infarction, which developed when he was at the age of 62, and a bypass graft was performed. A physical examination showed that he had no anemia, no jaundice, no visual abdominal swelling, or tenderness, and had no noticeable features except a postoperative scar from the bypass graft. A blood showed no abnormalities in biochemistry (white blood count of 9,200/ μ L, hemoglobin level of 14.4 g/dL, platelet count of Plt 24,200 / μ L, serum glutamic-oxaloacetic transaminase level of 24 IU/L, serum glutamic-pyruvic transaminase level of 19 IU/L, lactate dehydrogenase level of 242 IU/L, total bilirubin level of 0.9 mg/dL, international normalized ratio of 1.05, and c-reactive protein level of 0.09 mg/dL) and tumor markers (carcinoembryonic antigen level of 3.6 ng/mL, CA19–9 level of 9.7 U/mL, SPAN-1 level of 7.3 U/mL, soluble IL-2R level of 325 U/mL, IRI antibody level of 0.4 U/mL, gastrin level of 400 pg/mL, and vasoactive intestinal peptide level of 5 pg/mL).

Abdominal contrast computed tomography (CT) and magnetic resonance cholangiopancreatography revealed a massive cyst of 55 mm in the pancreatic head, a 20 mm mass with a gradually increasing contrast effect on the caudal side of the cyst, and nodular lesions of 10 mm each with a contrast effect in the pancreatic body and tail (Fig. 1a–c). The pancreatic parenchyma was somewhat thinner overall and there was no extension into the main pancreatic duct. There was no lymph node enlargement around the pancreas, and extrapancreatic mass lesions were not observed. Endoscopic retrograde cholangiopancreatography did not show papilla opening and mucosal irregularities around the duodenal papilla, and in endoscopic retrograde pancreatography (ERP), slight stenosis was found along a 15 mm stretch of the cystic region, but obstruction of the pancreatic duct was not observed. There were no malignant findings in pancreatic juice cytology or pancreatic ductal scratch cytology. In endoscopic ultrasonography (EUS), a 45 × 36 mm cyst at the pancreatic head was recognized with specular formation containing debris and though there was a separate wall, no internal nodule was recognized in the cyst. On the caudal side of the cyst, there was an 18 mm tumor with marginal low echo and internal high echo, and partial calcification was observed. A mass of 18 × 15 mm in the pancreatic body and a mass of 12 mm in the pancreatic tail were observed; each tumor's margin was clear and exhibited a marginal low echo and an internal high echo. Fibrosis was not recognized in the pancreatic parenchyma and no extension into the main pancreatic duct was observed. Endoscopic ultrasonography-fine needle aspiration (EUS-FNA) was performed to the pancreatic head and pancreatic body masses respectively (Fig. 1d); a strong variance of acinar cells and pancreatic ductal epithelium were seen from both specimens, and they both

had the same histology (Fig. 2a). Immunohistochemistry showed that vimentin and desmin were positive, but cytokeratin AE1/AE3, CD56, synaptophysin, chromogranin A, leukocyte common antigen, S-100, and c-kit were negative. These findings suggested a nonepithelial malignant tumor different from normal ductal carcinoma.

Although we could not confirm the diagnosis from the EUS-FNA specimen, we regarded the tumors as being resectable and performed a total pancreatectomy at a later date. Four lesions, including cysts, were found in the resected specimen macroscopically, and the resected specimens were independently presented with normal pancreatic tissue interposed; the resected margin was negative (R0). The pancreatic head cyst was accompanied by multiple small walled nodules, and the same histological findings were obtained from each cystic wall nodule and pancreatic tumor (Fig. 2b). Morphologically, the cells with strong polymorphism such as a spindle shape or polynuclear formation proliferated densely, and osteogenesis was also recognized in the lesion, which is a characteristic of anaplastic pancreatic ductal carcinoma (Fig. 2c). In the lumen of the cysts, the mucinous epithelium was lined and formed low papillary lesions; these findings were suggestive of branch duct type intraductal papillary mucinous neoplasm (IPMN). Immunohistochemistry showed that cytokeratin AE1/AE3, CAM5.2 (a small molecule keratin), S-100, and CD68 were negative, but vimentin and smooth muscle actin were positive (Fig. 2d). The presence of CD56 indicated an osteosarcoma component with adenocarcinoma as CD56 is positive in osteoid forming tumors. We finally diagnosed the patient with spindle cell type of anaplastic pancreatic duct carcinoma.

Though diabetic complications due to insufficient insulin secretion were observed, the patient was discharged 23 days after surgery and adjuvant chemotherapy (Tegafur/Gimeracil/Oteracil) was introduced after discharge. However, a peritoneal recurrence occurred soon after discharge and the patient died 4 months later.

Autopsy under family consent showed multiple metastases in the abdominal cavity and retroperitoneum, and internal necrosis accompanied by bleeding was recognized in the right retroperitoneal metastatic tumor. In addition, metastasis to the left lower lobe of the lung, the hilar bile duct, the right adrenal gland, and the thoracolumbar vertebrae was also observed, indicating a high degree of multiorgan metastasis in a short period of time. Right brain stem infarction and multiple infarctions of both kidney were also recognized, likely from Trousseau syndrome due to disseminated intravascular coagulation caused by cancer.

Discussion

Anaplastic pancreatic ductal carcinoma is a rare cancer first reported by Sommers et al in 1954 [1]. In the 2010 WHO classification, it was classified as an invasive pancreatic duct carcinoma [2]. Depending on the morphology of the cells, it can be classified as giant cell type, pleomorphic type, or spindle cell type, and a carcinoma with osteoclast-like giant cells is classified as a giant cell carcinoma of the osteoclastoid type. Higuchi et al reported in 2004 that among 85 patients with anaplastic pancreatic ductal cancer, 30 cases (35.3%) were of the giant cell type, 18 cases (21.2%) were of the osteoclastoid type, 25 cases (29.4%) were of the polymorphic cell type, and 12 cases (14.1%) were of the spindle cell type [3]. According to the summary from the National Cancer Database reported in 2016, of 247,493 total pancreatic cancers registered from 1998 to 2011, 192 patients (0.08%) had anaplastic pancreatic ductal carcinoma, with an average patient age of 67; the number of males was 103 and females was 89, and 97 had tumors in the pancreatic head and 95 in the pancreatic body and tail [4]. These data were not different from normal invasive pancreatic ductal cancer cases. The reported

tumor diameter was 15–180 mm (average of 45 mm), and this case had the smallest reported diameter of 10 mm. Detection from multiple small tumors and from cystic wall nodules showed characteristics which were significantly different from those of previously reported anaplastic pancreatic ductal carcinoma cases [5]. Anaplastic pancreatic ductal carcinoma is rapidly progressing and has a poorer prognosis as compared with other types of invasive pancreatic ductal carcinoma, developing hematogenously in the lymph nodes, liver/peritoneum, lungs, and adrenal gland. According to Higuchi et al, direct invasion into the stomach, duodenum, mesenterium, and peritoneum were observed in 8 of 11 patients with anaplastic pancreatic ductal carcinoma (73%), and distant metastasis were observed in 10 cases (83%) in which progression was identified. The mean survival time was the shortest (4.9 months) in the spindle cell type, followed by 7.3 months in the polymorphic cell type and 19.6 months in the osteoclast type [6].

As a characteristic feature of image findings, the tumor is characterized by large hemorrhagic necrosis and cystic degeneration, unlike other types of invasive pancreatic ductal carcinoma, and in abdominal enhanced CT, it is depicted as a low absorption tumor with a cystic component and tumor margins with contrast [7]. This indicates that the center of the tumor is necrosed due to the rapid growth while the periphery of the tumor is able to maintain the blood flow even in the advanced stage of tumor development. In ERP, reports of discontinuation, stenosis, and retraction of the pancreatic duct with anaplastic pancreatic ductal carcinoma have no obvious difference from that of normal invasive pancreatic ductal carcinoma, but in angiography, anaplastic pancreatic ductal carcinoma is often expressed as a hypervascular tumor; an angiography is therefore useful for distinguishing anaplastic pancreatic ductal carcinoma from normal invasive pancreatic ductal carcinoma [8].

Initial symptoms include back pain, abdominal distension, and weight loss. In the early stage of tumor development, blood data reflect the invasion of inflammatory cells into the tumor from the early stage, but tumor marker levels are normal or are only mildly increased, and these are not specific [9, 10].

In histopathological findings, various forms of tumor cells with strong heterogenous nuclei are observed and cell binding is often coarse [11]. It is hypothesized that these characteristics cause cell adhesiveness to decrease, tumor development to expand, and early vascular metastasis to occurs. It is believed that the spindle cell type is due to mutation from differentiated adenocarcinoma to sarcoma, and epithelial markers such as keratin are positive in sarcoma because spindle cells originated from epithelial cells. In immunohistochemical staining, mesenchymal markers such as vimentin, and epithelial markers such as keratin and epithelial membrane antigen are positive at a high rate, while c-kit, which is positive in 77% of normal invasive pancreatic ductal carcinoma is negative [12]. In this case, although vimentin and desmin were positive, both cytokeratin AE1/AE3 and c-kit were negative. It was a different finding from previous reports on spindle cell type anaplastic pancreatic ductal carcinoma because keratin, which is an epithelial marker, was negative.

Genetic mutation is associated with the etiology of anaplastic pancreatic ductal carcinoma and in 2013, Krasinskas et al. reported that mutant allele-specific imbalance, which refers to the specific amplification of mutant alleles, occurs during the progression from normal invasive pancreatic ductal carcinoma to anaplastic carcinoma [13]. In this case, we hypothesized that the following tumor progressive process occurred. At first, branch duct type IPMN occurred in the head of the pancreas, followed by the occurrence of IPMN-derived cysts with inner wall nodules and multiple pancreatic ductal carcinoma concomitant with IPMN. Finally, the cancer cells underwent a morphological change to anaplastic pancreatic ductal carcinoma instead of normal invasive pancreatic ductal carcinoma via genetic mutations.

Despite R0 surgery and the early administration of adjuvant chemotherapy, recurrence occurred in a short period. In this case, initial image findings characteristic of anaplastic pancreatic duct carcinoma such as size of tumor, cystic degeneration, and contrast effect of tumor margin were not detected. Before surgery, multiple small tumors with contrast and a giant cystic lesion did not strongly suggest malignancy. As a learning point from this case, even in cases of atypical image findings, the possibility of a tumor with high malignancy should be considered. We suggest that appropriate EUS-FNA diagnosis and medical examination considering the possibility of early recurrence after surgery are needed.

Statement of Ethics

This article does not contain any studies with human participants performed by any of the authors. Written informed consent was obtained from the patient using the hospital default informed consent form.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no financial support for the research, authorship, and/or publication of this article.

References

- 1 Sommers SC, Meissner WA. Unusual carcinomas of the pancreas. *AMA Arch Pathol*. 1954 Aug;58(2):101–11.
- 2 Bosman FT, Carneiro F, Hruban RH. WHO classification of tumours of the digestive system. World Health Organization. Lyon: IARG Press; 2010.
- 3 Highuchi R, Hatori T, Fukuda A, et al. A spindle cell type of carcinoma of the pancreas. *Suizou*. 2004;19:516–21.
- 4 Panizza A, Hosokawa PW, Schulick RD, Henderson W, Kaplan J, Gajdos C. A matched-cohort analysis of 192 pancreatic anaplastic carcinomas and 960 pancreatic adenocarcinomas: A 13-year North American experience using the National Cancer Data Base (NCDB). *Surgery*. 2016 Aug;160(2):281–92.
- 5 Clark CJ, Graham RP, Arun JS, Harmsen WS, Reid-Lombardo KM. Clinical outcomes for anaplastic pancreatic cancer: a population-based study. *J Am Coll Surg*. 2012 Nov;215(5):627–34.
- 6 Hoshimoto S, Matsui J, Miyata R, Takigawa Y, Miyauchi J. Anaplastic carcinoma of the pancreas: case report and literature review of reported cases in Japan. *World J Gastroenterol*. 2016 Oct;22(38):8631–7.
- 7 Tschang TP, Garza-Garza R, Kissane JM. Pleomorphic carcinoma of the pancreas: an analysis of 15 cases. *Cancer*. 1977 May;39(5):2114–26.
- 8 Nakanishi Y, Sato M, Kawada M, Gyoubu H, Hisai H, Tateno K, et al. A Case of Anaplastic Carcinoma of the Pancreas (Spindle cell type). *Jpn J Gastroenterol Surg*. 2006;39(6):689–95.
- 9 Strobel O, Hartwig W, Bergmann F, Hinz U, Hackert T, Grenacher L, et al. Anaplastic pancreatic cancer: Presentation, surgical management, and outcome. *Surgery*. 2011 Feb;149(2):200–8.
- 10 Okazaki M, Makino I, Kitagawa H, Nakanuma S, Hayashi H, Nakagawara H, et al. A case report of anaplastic carcinoma of the pancreas with remarkable intraductal tumor growth into the main pancreatic duct. *World J Gastroenterol*. 2014 Jan;20(3):852–6.
- 11 Vilmann P, Jacobsen GK, Henriksen FW, Hancke S. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. *Gastrointest Endosc*. 1992 Mar-Apr;38(2):172–3.

- 12 Dworák O, Kessler H, Riedel C. [Spindle cell carcinoma of the pancreas: a case report with immunohistologic study]. *Pathologe*. 1992 Jul;13(4):221–3.
- 13 Krasinskas AM, Moser AJ, Saka B, Adsay NV, Chiosea SI. KRAS mutant allele-specific imbalance is associated with worse prognosis in pancreatic cancer and progression to undifferentiated carcinoma of the pancreas. *Mod Pathol*. 2013 Oct;26(10):1346–54.

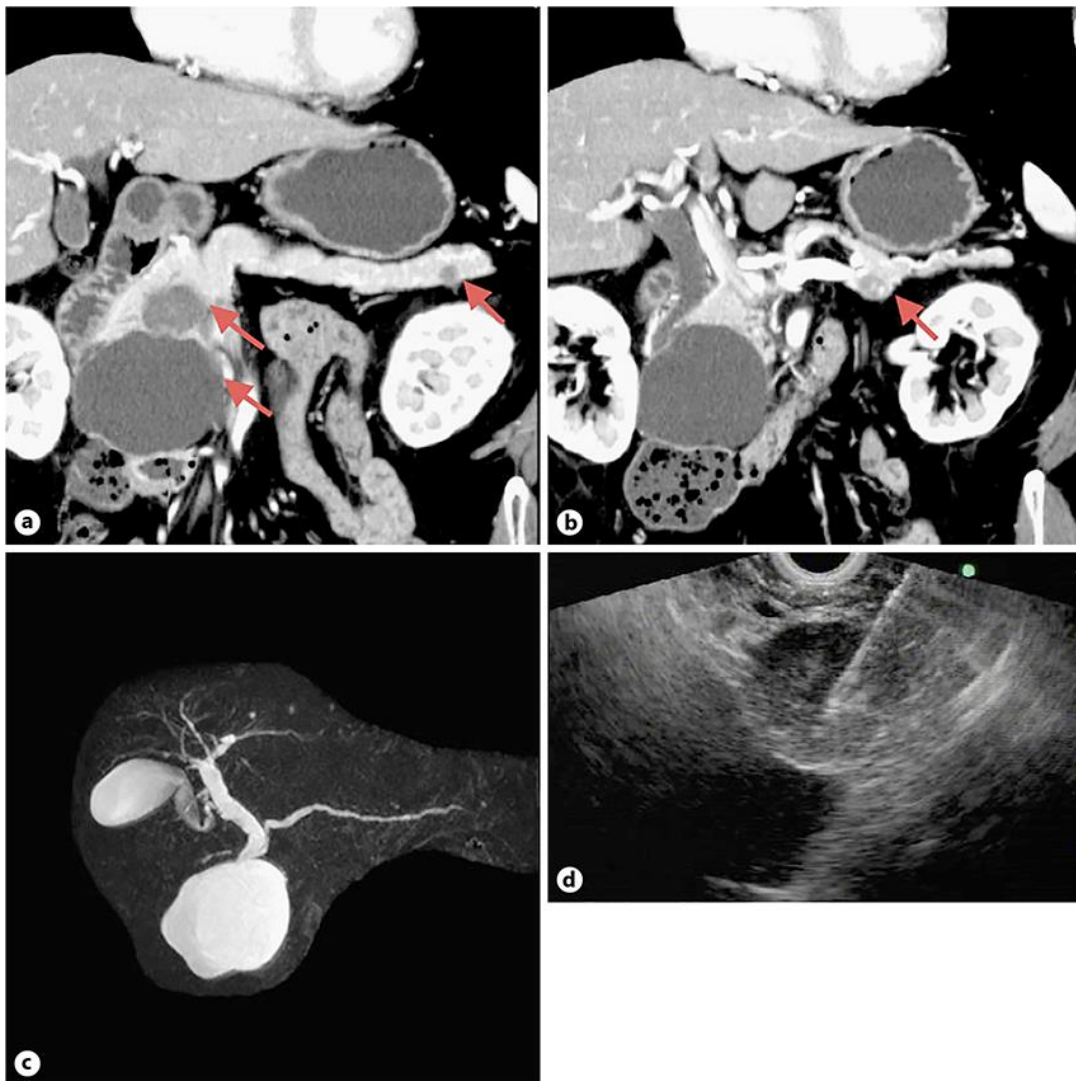


Fig. 1. **a** Abdominal contrast computed tomography showed pancreatic head cysts and pancreatic head and tail tumors (arrows). **b** In another slice from the abdominal contrast computed tomography, a tumor was found in the pancreatic body (arrow). **c** Magnetic resonance cholangiopancreatography showed huge cysts in the pancreatic head, but there was no irregularity or deviation of the pancreatic duct. **d** In endoscopic ultrasonography, the tumor showed clear margins, had low marginal echo, and internal high echo.

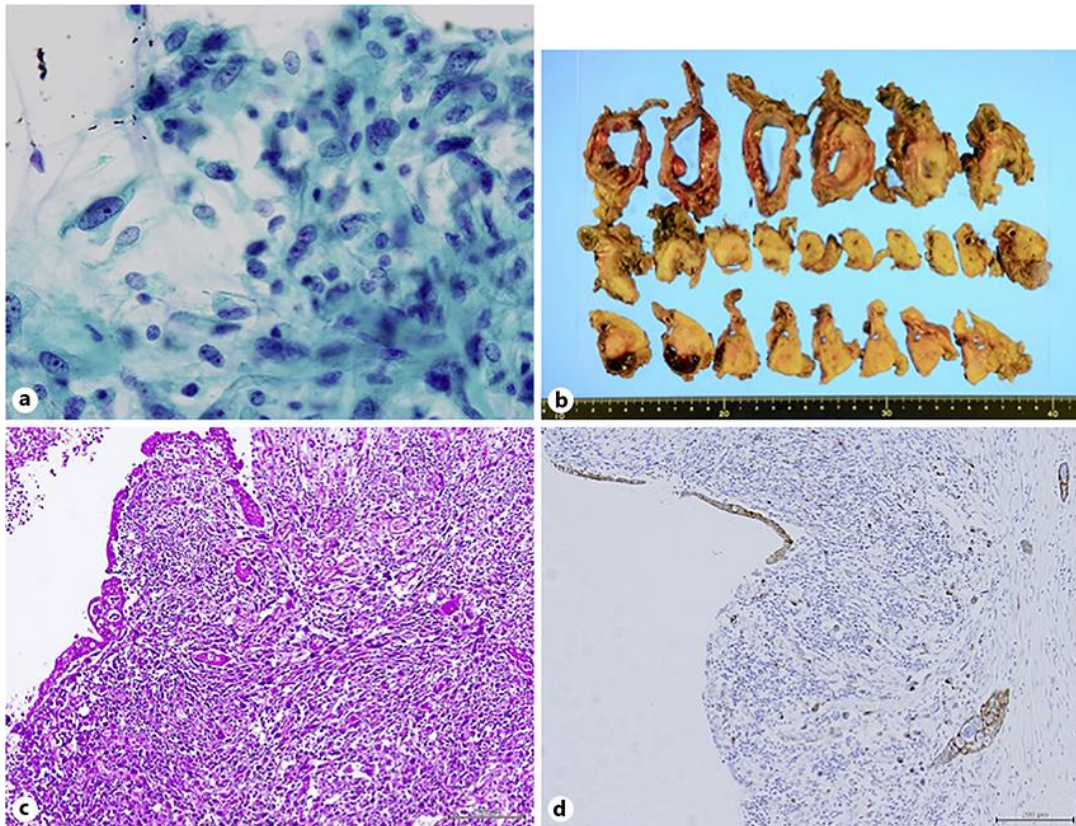


Fig. 2. **a** Cytology showed a strong variance of acinar cells and pancreatic ductal epithelium. **b** The resected specimen showed three tumorous lesions in addition to the huge cyst, and each lesion was independently present with pancreatic tissue interposed. **c** Morphologically, the cells showed strong polymorphism, such as having a spindle shape or polynuclear formation, and proliferated densely; cancer and sarcoma components were mixed. **d** Immunostaining for keratin CAM5.2 was negative.