An Autopsy Case of Anaplastic Carcinoma of the Pancreas in a 39-Year-Old Woman that Developed from Hereditary Pancreatitis

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: **Female, 39-year-old**
Final Diagnosis: **Anaplastic carcinoma of the pancreas • pancreatic cancer**
Symptoms: **Epigastralgia • jaundice**
Medication: **—**
Clinical Procedure: **—**
Specialty: **Gastroenterology and Hepatology • Oncology**

Objective: **Rare disease**
Background: Anaplastic carcinoma of the pancreas (ACP) is a rare type of cancer with an extremely poor prognosis. Hereditary pancreatitis is a rare autosomal-dominant disease. It progresses to chronic pancreatitis at a young age, increasing the risk of pancreatic cancer.

Case Report: A 39-year-old woman was diagnosed with chronic pancreatitis at the age of 18 years. The patient was referred to our hospital for epigastralgia and jaundice. We identified a tumor mass at the head of the pancreas using contrast computed tomography (CT) and endoscopic ultrasound (EUS) of the abdomen. Tissue biopsy revealed ACP of the spindle cell type. We started the patient on combination chemotherapy using gemcitabine and nanoparticle albumin-bound (nab) -paclitaxel, but she died 1 month after her first visit. An autopsy revealed a mixture of tubular adenocarcinoma and anaplastic carcinoma. We performed genetic analysis using DNA samples from the biopsy tissues but did not find mutations in the PRSS1 and SPINK1 genes associated with hereditary pancreatitis.

Conclusions: The risk of pancreatic cancer generally increases in patients with hereditary pancreatitis after 50 years of age. However, in this case, the development of pancreatic cancer occurred at a younger age, suggesting the importance of early detection in such cases. Furthermore, this case suggests that EUS is a useful method for monitoring patients with hereditary pancreatitis and the diagnosis of ACP.

Keywords: **Endoscopic Ultrasound-Guided Fine Needle Aspiration • Genetic Diseases, Inborn • Pancreatic Neoplasms • Pancreatitis, Chronic • Adenocarcinoma • Carcinoma, Pancreatic Ductal**

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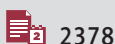
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Background

Anaplastic carcinoma of the pancreas (ACP) is a rare type of cancer known to progress faster than pancreatic ductal adenocarcinoma, causing poor prognosis. According to the World Health Organization guidelines, ACP is defined as a malignant epithelial neoplasm in which the main component of the neoplasm does not differentiate in a directed manner; thus, it is classified as an undifferentiated carcinoma [1]. Depending on the morphology of the cells, ACP can be divided into 3 different types: pleomorphic type, spindle cell type, and ACP with osteoclast-like giant cells.

Furthermore, hereditary pancreatitis is an autosomal-dominant disease that develops acute pancreatitis from early childhood and progresses to chronic pancreatitis at a younger age. Additionally, the risk of pancreatic cancer is high for patients with hereditary pancreatitis. The existing case reports indicate that the cumulative mortality rate of pancreatic cancer at the age of 70 years is in the range of 18.8-40% [2-4]; however, this patient developed cancer at a much younger age than that of past cases. As this is the first known case where ACP developed from hereditary pancreatitis, we report our findings in the context of the existing literature.

Case Report

A 39-year-old woman visited a clinic complaining of pain in the epigastric region and jaundice. She was suspected of having obstructive jaundice due to a tumor in the pancreas and was referred to our hospital. She had a past history of recurrent upper abdominal pain since the age of 6 years. At 18 years of age, she was found to have calcifications in the pancreas and was diagnosed with chronic pancreatitis. The patient also had type 2 diabetes and received medications for the same. She neither consumed alcohol nor smoked. Her family history indicated that her father developed chronic pancreatitis at a young age and died at 56 years of age. Blood tests indicated a decrease in amylase (29 U/L) and lipase (1 U/L) levels, whereas there was an increase in the levels of hepatobiliary enzymes, including total bilirubin (14.3 mg/dL), aspartate aminotransferase (45 U/L), alanine aminotransferase (41 U/L), γ-glutamyl transpeptidase (837 U/L), and alkaline phosphatase (2924 U/L). Furthermore, we observed an increase in tumor markers, including CEA (10.7 ng/mL), CA19-9 (>12000.0 U/mL), and DUPAN-2 (724 U/mL), and HbA1$_c$ was high at 10.2%.

A contrast computed tomography (CT) scan of the abdomen revealed calcification of the pancreas and a poorly marginated mass of approximately 40 mm in diameter at the head of the pancreas (Figure1A-1D). Additionally, we observed a low absorption region during the late arterial phase with a gradual contrast effect (Figure 1A-1D). The intrapancreatic bile duct was displaced due to the tumor mass and the intrahepatic bile duct had enlarged (Figure 1E). We suspected invasion of the tumor, as the region between the stomach and duodenum was poorly marginated (Figure 1F). No findings supported distal metastasis in the liver and lungs, and there was no substantial enlargement of the lymph nodes.

Endoscopic ultrasound (EUS) showed a tumor with unclear boundaries of approximately 55 mm in diameter with parts of a low-absorbance region indicating tumor necrosis. We observed a high-absorbance region near the tumor with an acoustic shadow, which may be the calcified region of the pancreas (Figure 2A). Furthermore, there was an enlargement of the common bile duct and embolism of the portal vein due to the tumor (Figure 2B). Contrast enhancement with perflubutane deeply stained the entire tumor, excluding the areas of tumor necrosis, which indicated a hypervascular tumor (Figure 2C).

Endoscopic retrograde cholangiopancreatography (ERCP) revealed tumor invasion in the minor duodenal papilla. We detected a stenosis of the lower region of the bile duct about 6 cm in length, and endoscopically placed a covered self-expandable metal stent (Figure 3).

We performed tissue biopsy of the exposed tumor region at the minor duodenal papilla. Histopathological analysis revealed the growth of atypical glandular epithelium, and spindle cells in the stroma were observed. Immunohistochemistry showed that the tumor cells were positive for CAM5.2 and AE1/AE3 and negative for vimentin in the epithelial regions. The atypical cells in the stroma were positive for CAM5.2, AE1/AE3, and vimentin, but they were negative for desmin, SMA, and S100. Ki-67 labeling index was high for both epithelial and stromal regions (Figure 4).

The patient was diagnosed with ACP of spindle cell type by pathological examination. Contrast computed tomography showed a tumor 70 mm in size in contact with at least half of the circumference of the vessel walls of the portal vein and the superior mesenteric artery. Tumor invasion to the stomach and the duodenum was observed, but there was no evidence of lymph node metastasis or distal metastasis. Thus, the lesion was diagnosed as locally advanced pancreatic cancer (stage IIIA) according to the National Comprehensive Cancer Network guidelines and the American Joint Committee on Cancer 8th edition [5,6]. We treated the patient with combination chemotherapy using gemcitabine (1000 mg/m^2) and nanoparticle albumin-bound (nab)-paclitaxel (125 mg/m^2) on days 1, 8, and 15. However, she rapidly became debilitated and suffered from portal vein embolism due to the tumor, accompanied with worsening of ascites and edema of the legs. The patient died 1 month after the initial visit to our hospital.
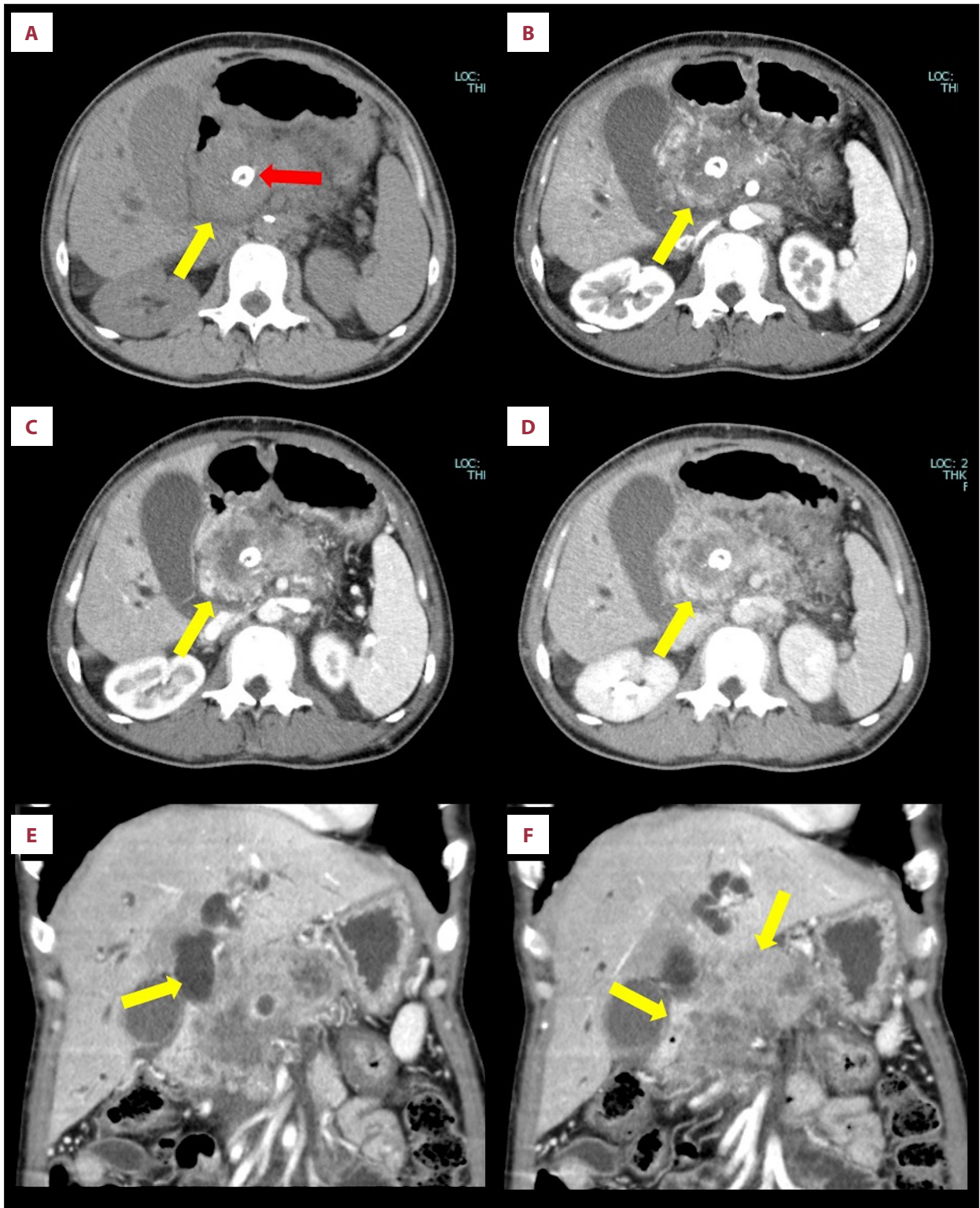
Figure 1. Findings of the contrast computed tomography (CT) scan of the abdomen. (**A**) Un-enhanced, (**B**) arterial, (**C**) portal, and (**D**) delayed CT scans. Gradual contrast effect was observed in areas surrounding the tumor (yellow arrow) with calcification in the inner region (red arrow). (**E**) The intrapancreatic bile duct in the pancreas was displaced by the tumor with dilatation of the intrahepatic bile duct (yellow arrow). (**F**) The boundary between the stomach and duodenum was unclear, and tumor invasion was suspected (yellow arrow).
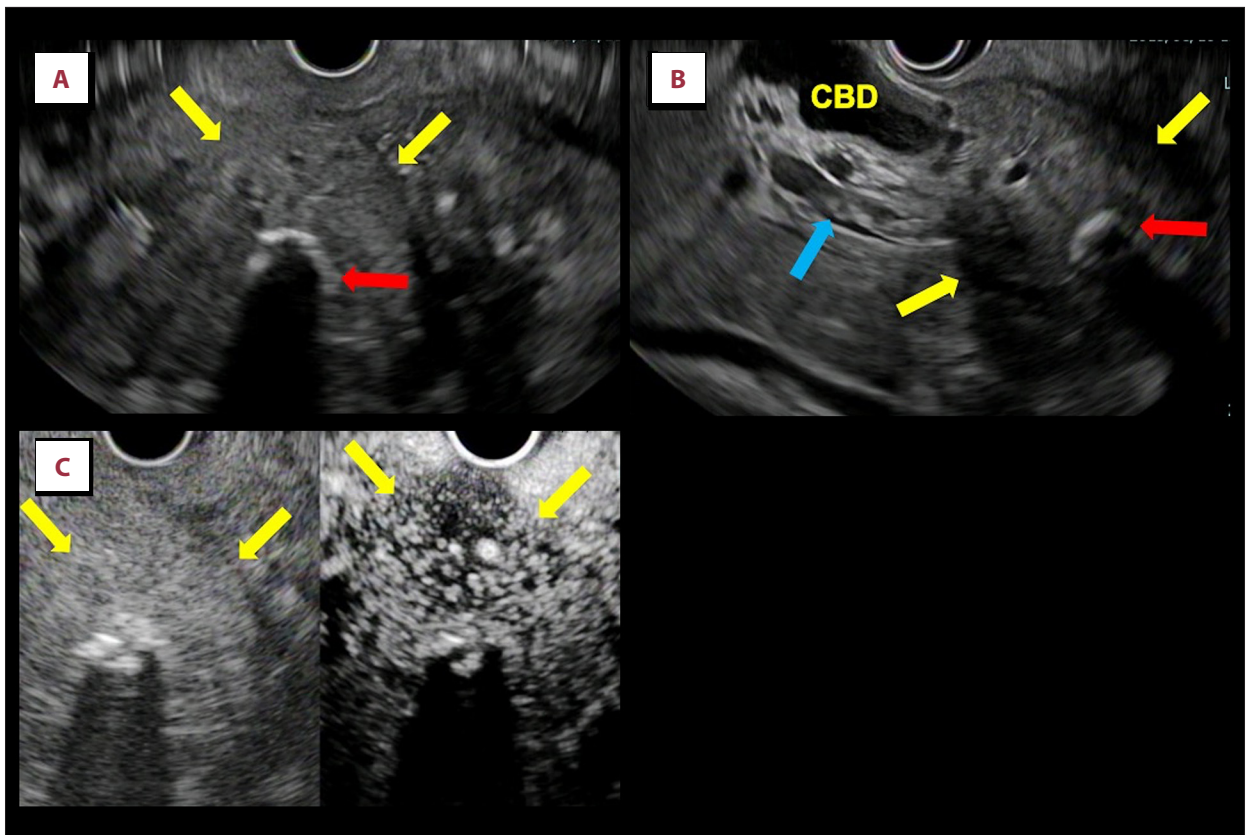
Figure 2. Endoscopic ultrasound images. (**A**) Tumor mass consisted of partial low-absorption regions considered to be the areas of tumor necrosis (yellow arrow) and high-absorption regions with an acoustic shadow considered to be the calcification of the nearby tumor (red arrow). (**B**) The common bile duct had expanded, and the tumor obstructed the portal vein (blue arrow). (**C**) Contrast-enhancement was achieved with perflubutane.
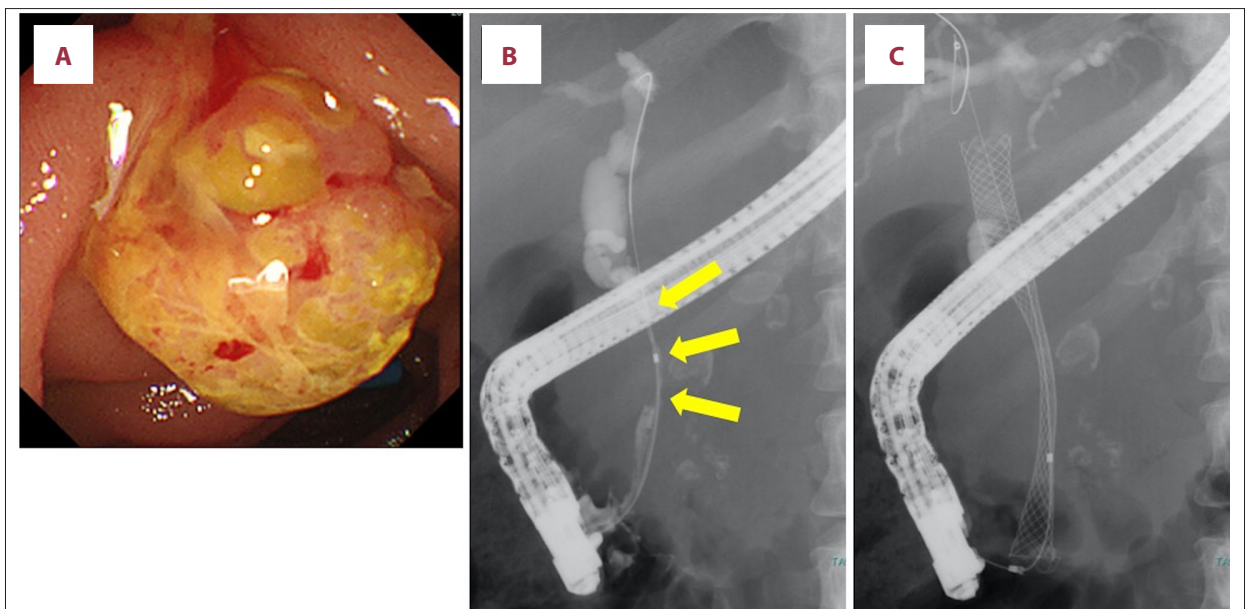

Figure 3. Endoscopic retrograde cholangiopancreatography images. (**A**) The tumor invaded the minor duodenal papilla. (**B**) Stenosis of the bile duct was visible by contrast-enhancement of the biliary tract (yellow arrow). (**C**) For the regions of stenosis, a covered self-expandable metallic stent was placed endoscopically.
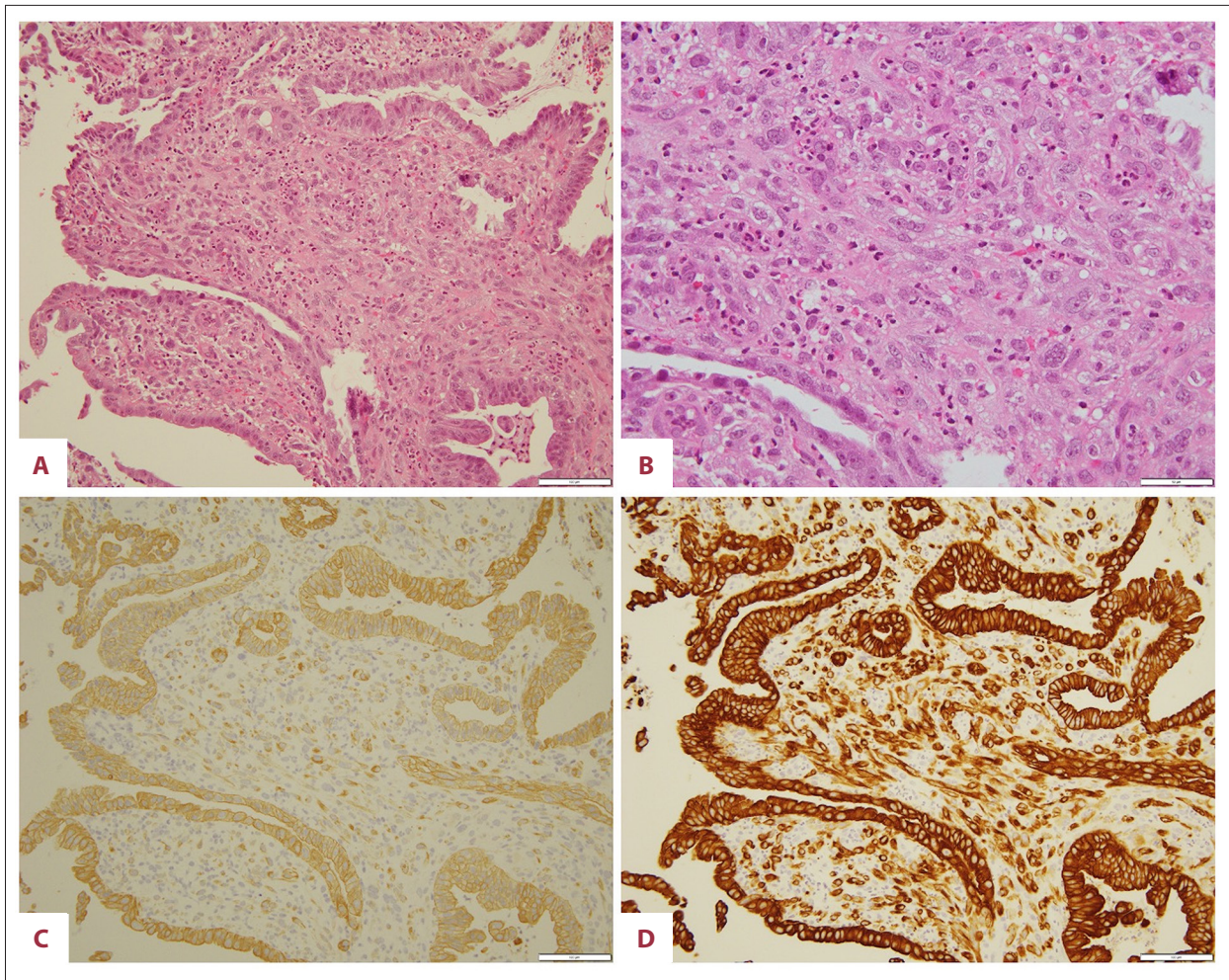
Figure 4. Tissue biopsy of the minor duodenal papilla. Hematoxylin and eosin staining of the tumor under (**A**) 20× and (**B**) 40× magnification. Immunohistochemistry images of (**C**) AE1/AE3 and (**D**) CAM5.2 under 20× magnification.

Autopsy revealed an 80×50×40 mm yellowish-white, elastic hard tumor at the head of the pancreas. A pancreatic stone of about 10 mm was observed in a cavity continuous with the pancreatic duct. The tail of the pancreas was almost necrotic, but there was no obvious tumor infiltration in the periphery of the necrotic area, which excluded the possibility of degeneration due to tumor necrosis. Acinar cells had disappeared from any region of the remaining pancreatic tissues, in which fibrosis and aggregation of the islets of Langerhans alone in the adipose tissue were observed. The tumor had invaded the portal vein, which expanded upstream from the site of invasion. Histological analysis exhibited the proliferation of the atypical cells, mainly in the white-colored areas, and invasion of the tumor mass into the surrounding fat tissue and lymph nodes. The tumor had 2 main portions: an area of tubular adenocarcinoma and an area of anaplastic carcinoma. In the tubular adenocarcinoma section, there were irregular tubular structures with varying size and flat or cubic cells. The anaplastic carcinoma section had sporadic cellular infiltration with marked polymorphism without any binding activity. The cells were not morphologically uniform. There were mixed spindle-shaped and polygonal cells. Although the boundaries of the areas were not clearly defined, anaplastic carcinoma cells were mainly observed in the duodenum, bile duct, and Vater papilla, while tubular adenocarcinoma cells were mainly identified in the pancreatic body and sites distant from the duodenum.

Immunohistochemistry revealed that cells in the tubular adenocarcinoma area were positive for AE1/AE3 and CAM5.2, and negative for vimentin (**Figure 5A-5D**). In contrast, the cells in the anaplastic carcinoma area were positive for epithelial markers, such as AE1/AE3 and CAM5.2, and vimentin (**Figure 5E-5H**). Furthermore, both types of cells were negative for CD34, desmin, SMA, myogenin, and S-100. In addition, p53 was highly expressed. A node of about 6×3 mm in size was found in the upper region of the right lobe of the liver, where liver metastasis was diagnosed. The liver metastasis showed components of anaplastic carcinoma. In contrast,
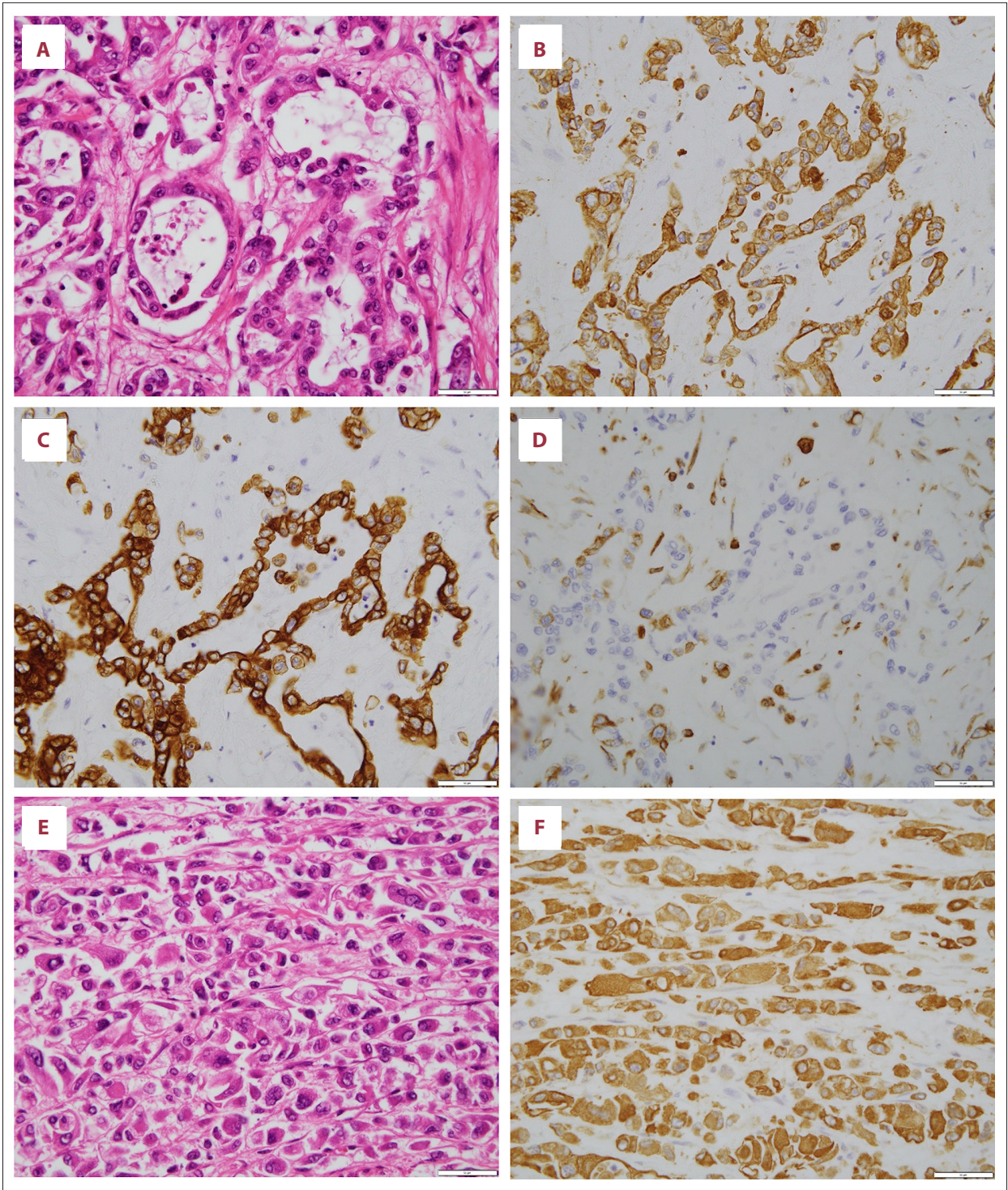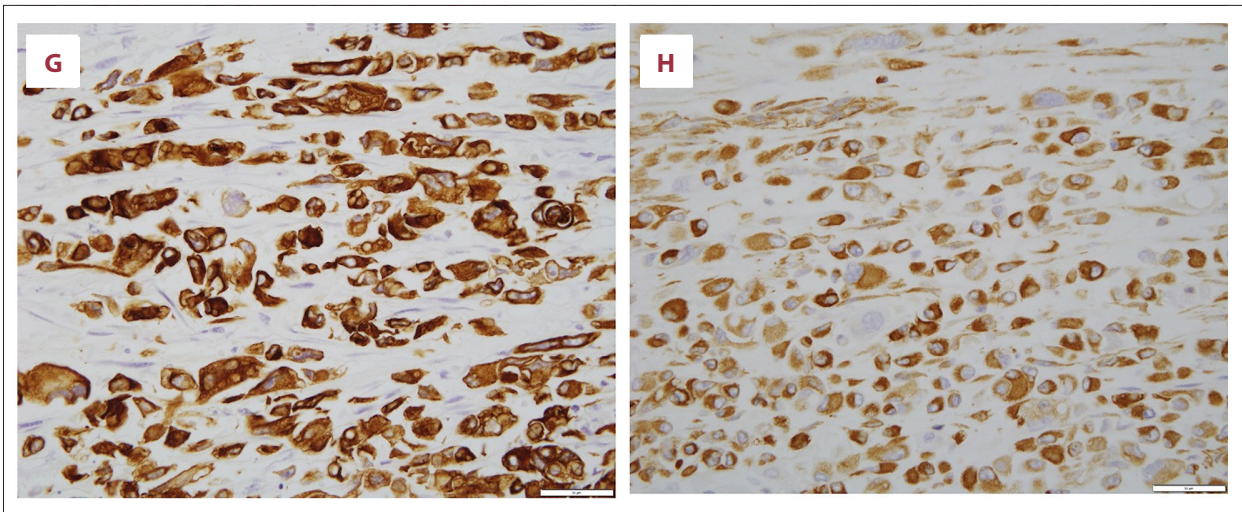
Figure 5. Pathological images of the pancreatic tumor during autopsy. (**A–D**) The area of tubular adenocarcinoma. (**A**) Hematoxylin and eosin staining (×40), (**B**) AE1/AE3, (**C**) CAM5.2, and (**D**) vimentin. (**E–H**) The area of anaplastic carcinoma. (**E**) Hematoxylin and eosin staining (×40), (**F**) AE1/3, (**G**) CAM5.2, and (**H**) vimentin.
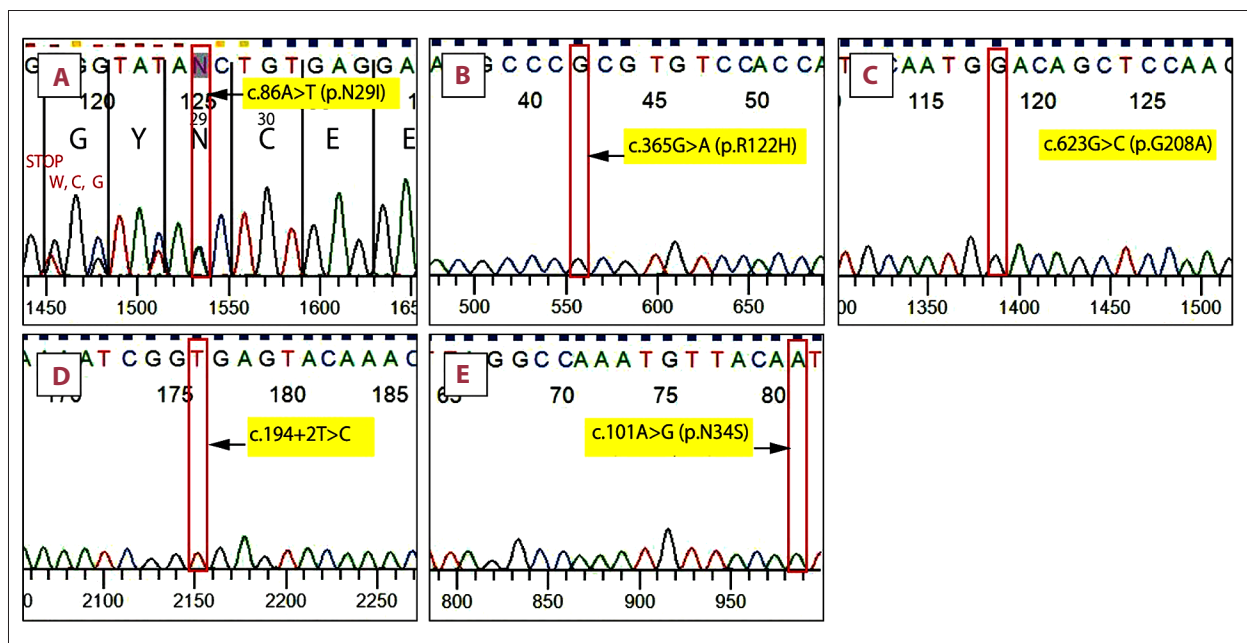

Figure 6. Gene analysis. (**A–C**) PRSS1 gene, (**D, E**) SPINK1 gene. The PRSS1 gene was negative for all p.N29I, p.R122H, and p.G208A mutations. The SPINK1 gene was negative for both c.194+2T>C and p.N34S mutations.

the greater omentum, lungs, and abdominal lymph nodes did not exhibit metastasis.

Based on these findings, we determined that the patient had developed pancreatic head cancer accompanied with anaplastic carcinoma and a moderately differentiated tubular adenocarcinoma. We concluded that the cause of death was circulatory failure from the obstruction of the portal vein and debilitation of the body due to tumor proliferation.

Additionally, we performed genetic analysis using the DNA samples from the tissues extracted during biopsy. The PRSS1 gene was negative for all p.N29I, p.R122H, and p.G208A mutations (**Figure 6A-6C**). There was a mutation in the codon corresponding to p.N29I; however, this was likely an artifact of tissue fixation and not a true p.N29I mutation. Similarly, the SPINK1 gene was negative for both c.194+2T>C and p.N34S mutations (**Figure 6D, 6E**).

Discussion

ACP is a type of carcinoma in which the mechanism of cell differentiation is unknown. However, as it frequently displays the components of pancreatic duct cancer, this carcinoma could be a type of pancreatic duct cancer. The mechanism for the development of ACP is predicted to be the de-differentiation of pancreatic duct cancer. The following are the proposed characteristics of ACP [7,8]: 1) mutation that leads to a change from tubular adenocarcinoma to having a sarcomatoid component; 2) characteristics of epithelial cells in spindle cells; and 3) tumor cells positive for epithelial cell markers, such as cytokeratins and the epithelial membrane antigen.

In the present case, immunohistochemistry showed that both epithelial markers (AE1/AE3 and CAM 5.2) and a mesenchymal marker (vimentin) were positive. This suggests a mechanism by which epithelial-derived pancreatic ductal carcinoma develops into anaplastic carcinoma through differentiation and de-differentiation. In addition, p53 gene mutations are reportedly associated with a poor prognosis [8], and, in the present case, p53 was highly expressed.

Furthermore, Krasinskas et al reported that normal invasive pancreatic duct cancer progresses into ACP due to a phenomenon called mutant allele-specific imbalance, in which the mutated allele of KRAS is specifically amplified [9]. The accumulation of genetic mutation is necessary for the progression of normal invasive pancreatic duct cancer to ACP, suggesting that ACP would be more commonly seen in the elderly. A population-based study done in the United States found that the average age at diagnosis of ACP was 68 years, whereas that in Japan was 61.5 years [10,11].

However, hereditary pancreatitis is a rare genetic disease that causes chronic pancreatitis. Gross et al proposed the following as defining characteristics of hereditary pancreatitis: 1) more than 3 blood relatives with pancreatitis; 2) development of the disease at a young age; 3) no other causes of developing chronic pancreatitis (eg, heavy drinking of alcohol); and 4) development of pancreatitis in more than 2 generations in the family [12]. The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer also defines hereditary pancreatitis as chronic or recurrent pancreatitis with no known causes for the development of the disease and with more than 2 first-degree relatives or more than 3 second-degree relatives in 2 or more generations who also developed it [2]. The patient in this report developed chronic pancreatitis at a young age without any risk factors for developing the disease, such drinking alcohol; however, her father also developed chronic pancreatitis at a young age. Thus, the patient was diagnosed as having hereditary pancreatitis.

Furthermore, in 1996, the p.R122H mutation of the PRSS1 gene was reported in a family that developed hereditary pancreatitis [13]. The PRSS1 and SPINK1 genes were identified as the causal genes of hereditary pancreatitis [14]. A nation-wide study in Japan between 2005 and 2014 showed that within the families that underwent genetic testing, 41% (p.R122H 33% and p.N291 8%) were positive for the PRSS1 gene mutation, whereas 36% (p.N34S 22%, c.194+2T>C 14%, and p.P45S 1%) were positive for the SPINK1 gene mutation [15]. The causal gene was unknown for the remaining families who received the genetic testing; similarly, we were unable to identify the causal gene in our patient.

Hereditary pancreatitis is caused by a mutation in the gene coding for trypsin, leading to unregulated trypsin activity [13]. Most of these patients develop acute pancreatitis before 10 years of age and chronic pancreatitis before 20 years of age. In addition, the risk of developing pancreatic cancer is higher after 50 years of age [16]. The patient in the present study developed the disease at a much younger age. Histological examination of the autopsy specimen revealed approximately equal areas of anaplastic carcinoma and differentiated tubular adenocarcinoma. It is likely that the differentiated tubular adenocarcinoma developed given the background of chronic pancreatitis resulting from hereditary pancreatitis at a young age before tumor differentiation resulted in anaplastic carcinoma of the pancreatic duct. This suggests that patients with hereditary pancreatitis have an increased risk of developing pancreatic cancer, even at a young age. This case illustrates the importance of surveillance from young adulthood in patients with hereditary pancreatitis who developed chronic pancreatitis at a younger age. Further accumulation of cases is needed to determine when to start surveillance and at what frequency it should be performed. As many patients with hereditary pancreatitis develop chronic pancreatitis before 20 years of age, annual screening with imaging modalities may be preferable for patients older than 20 years.

EUS is considered useful for the surveillance of patients with hereditary pancreatitis who are prone to developing chronic pancreatitis at a young age. EUS is useful in evaluating chronic pancreatitis because it is suitable for imaging of the main pancreatic duct and stones. Studies have recently reported the usefulness of EUS based on the Rosemont classification for the diagnosis of early chronic pancreatitis [17] and EUS-elastography [18-20]. EUS has attracted the attention of clinicians owing to its excellent spatial resolution and highly detailed examination of the pancreatic parenchyma.

EUS is also useful for the diagnosis of anaplastic carcinoma of the pancreatic duct. ACP is known to rapidly expand, causing necrosis and hemorrhage in the inner regions of the lesion [21]. Important imaging characteristics include cysts and

low-absorption regions, indicating hemorrhage and necrosis of the central region of the tumor. Images of the surrounding areas of the tumor display a hypervascular region, a characteristic different from the usual hypovascular region visible in the images of a normal pancreatic cancer [22]. EUS easily captures such imaging characteristics, and contrast-enhancement using Sonazoid could enable their clearer identification. Furthermore, as cases with ACP, such as the one studied here, often include regions with differentiated tubular adenocarcinoma, we recommend biopsy from multiple locations to consider the possibility of differing tissue types depending on the region. Thus, EUS-guided fine-needle aspiration is considered to be useful for tissue diagnostics.

Conclusions

We reported a case of ACP that developed from hereditary pancreatitis. In this case, the progression of pancreatic cancer that developed at a young age was rapid. Therefore, it is the important from an early stage to monitor patients with hereditary pancreatitis who develop chronic pancreatitis at a young age. Furthermore, we propose EUS as a useful method for monitoring hereditary pancreatitis and the diagnosis of ACP.

Conflict of Interest

None.

References:

1. Bosman FT, Garneiro F, Hruban RH. WHO classification of tumours of the digestive system. World Health Organization. Lyon: IARG Press, 2010

2. Howes N, Lerch MM, Greenhalf W, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol, 2004;2:252-61

3. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst, 1997;89:442-46

4. Rebours V, Boutron-Ruault MC, Schnee M, et al. Risk of pancreatic adenocarcinoma in patients with hereditary pancreatitis: A national exhaustive series. Am J Gastroenterol, 2008;103:111-19

5. NCCN Clinical Practice Guidelines for Pancreatic Adenocarcinoma from Version 1.2020, 2019

6. The Eighth Edition of the AJCC Staging System for Pancreatic Ductal Adenocarcinoma, 2017

7. Bergmann F, Esposito I, Michalski CW, et al. Early undifferentiated pancreatic carcinoma with osteoclastlike giant cells: Direct evidence for ductal evolution. Am J Surg Pathol, 2007;31:1919-25

8. Paal E, Thompson LD, Frommelt RA, et al. A clinicopathologic and immunohistochemical study of 35 anaplastic carcinomas of the pancreas with a review of the literature. Ann Diagn Pathol, 2001;5:129-40

9. Krasinskas AM, Moser AJ, Saka B, et al. KRAS mutant allele-specific imbalance is associated with worse prognosis in pancreatic cancer and progression to undifferentiated carcinoma of the pancreas. Mod Pathol, 2013;26:1346-54

10. Clark CJ, Graham RP, Arun JS, et al. Clinical outcomes for anaplastic pancreatic cancer: A population-base study. J Am Coll Surg, 2012;215:627-34

11. Hashimoto S, Matsui J, Miyata R, et al. Anaplastic carcinoma of the pancreas: Case report and literature review of reported cases in Japan. World J Gastroenterol, 2016;22:8631-37

12. Gross JB. Hereditary pancreatitis. The exocrine pancreas: Biology, pathology and disease. Raven press, New York, 1986;829-39

13. Whitcomb DC, Gorry MC, Preston RA, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet, 1996;14:141-45

14. Witt H, Luck W, Hennies HC, et al. Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. Nat Genet, 2000;5:213-16

15. Masamune A, Kazuhiro K, Shin H, et al. Nationwide survey of hereditary pancreatitis in Japan. J Gastroenterol, 2018;53:152-60

16. Shelton C, LaRusch J, Whitcomb DC. Pancreatitis Overview. 2014 Mar 13. In: Adam MP, Ardinger HH, Pagon RA et al (eds.), GeneReviews®. Seattle (WA): University of Washington, Seattle, 1993-2020

17. Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: The Rosemont classification. Gastrointest Endosc, 2009;69:1251-61

18. Dominguez-Munoz JE, Iglesias-Garcia J, Gastineira Alvarino M, et al. EUS elastography to predict pancreatic exocrine insufficiency in patients with chronic pancreatitis. Gastrointestinal Endoscopy, 2015;81:136-42

19. Itoh Y, Itoh A, Kawashima H, et al. Quantitative analysis of diagnosing pancreatic fibrosis using EUS-elastography (comparison with surgical specimens). J Gastroenterol, 2014;49:1183-92

20. Kuwahara T, Hiroka Y, Kawashima H, et al. Quantitative diagnosis of chronic pancreatitis using EUS elastography. J Gastroenterol, 2017;52:868-74

21. Yamaguchi K, Nakamura K, Shimizu S, et al. Pleomorphic carcinoma of the pancreas: Reappraisal of surgical resection. Am J Gastroenterol, 1998;93:1151-55

22. Okazaki M, Makino I, Kitagawa 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;20:852-56