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Pancreatic Mixed Acinar-neuroendocrine Carcinoma in a Patient With a Germline *PTEN* Variant: A Case Report and Genomic Literature Review

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Abstract

Background/Aim: Cowden syndrome (CS)/PTEN hamartoma tumor syndrome (PHTS) is a hereditary disorder caused by germline *PTEN* variants. While patients with CS/PHTS have increased risk of various cancers, pancreatic cancer is not typically associated with this syndrome. We report a rare case of pancreatic mixed acinar-neuroendocrine carcinoma in a patient with a germline *PTEN* variant, aiming to understand its molecular characteristics and clinical implications.
Case Report: A male in his late 40s presented with pancreatic cancer and hepatic metastases. His medical history included thyroid cancer and familial gastrointestinal malignancies. Liver biopsy revealed mixed acinar-endocrine carcinoma. Cancer genome profiling identified pathogenic variants in *GNAS* and *TP53*, along with a germline *PTEN* variant (V201fs*1), leading to a diagnosis of CS. Notably, *KRAS* mutations, commonly found in pancreatic cancer, were absent. The patient showed extreme resistance to multiple chemotherapy regimens, including FOLFIRINOX, gemcitabine plus nab-paclitaxel, and cisplatin plus etoposide, resulting in rapid clinical decline.
Conclusion: This case highlights a rare presentation of pancreatic cancer in CS/PHTS with distinct molecular and histological features. The absence of *KRAS* mutation and presence of germline *PTEN* variant may have contributed to the aggressive clinical course and treatment resistance. These findings underscore the need for further research into the molecular mechanisms of PTEN-associated pancreatic cancers and the development of targeted therapeutic strategies.

Keywords: Cowden syndrome, PTEN, pancreatic cancer, germline variant, genome profiling testing.

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Introduction

Cowden syndrome (CS)/PTEN hamartoma tumor syndrome (PHTS) is a hereditary disorder characterized by autosomal dominant inheritance, caused by germline pathogenic variants in phosphatase and tensin homolog (*PTEN*) gene (1). Many CS/PHTS cases present with macrocephaly, distinctive facial skin lesions, and oral mucosal abnormalities (2), as well as developmental features such as autism spectrum disorders (3). These characteristics often lead to early diagnosis and referral to genetic clinics. However, cases without prominent external features may remain undiagnosed until adulthood. While the detailed mechanisms are not fully elucidated, *PTEN* loss-of-function leads to carcinogenesis. CS/PHTS patients are at increased risk for characteristic tumors such as breast, endometrial, and follicular thyroid cancer, often presenting at a younger age and potentially proving fatal.

We report a case of a patient who remained undiagnosed with CS/PHTS until middle age, developed pancreatic cancer (not typically associated with CS/PHTS), and was diagnosed with CS/PHTS through genomic testing. In 2019, Japan implemented national health insurance coverage for cancer genomic profiling tests, facilitating the widespread adoption of various panel-based assays. Among these, the OncoGuide™ NCC Oncopanel System (Sysmex Corporation, Kobe, Japan) has emerged as a notable platform for comprehensive genomic analysis in oncology. This system is distinguished by its capacity to analyze both tumor specimens and blood samples concurrently, thereby enabling the discrete identification of somatic and germline variants. The tumor exhibited mixed acinar cell and neuroendocrine histology and demonstrated poor treatment response. Given the rarity of this case, we present it along with data from genomic database searches of CS/PTEN cases.

Case Report

A man in his late 40s, 172 cm tall and weighing 92 kg, presented with a one-month history of persistent nausea. He had a history of occasional alcohol consumption and had quit smoking 22 years ago after a 5-year habit of 20 cigarettes per day. His medical history included duodenal and colon polyps (details unknown, age 35), and post-operative follicular thyroid cancer (pT3N0M0, Stage I, age 40), none of which were being followed-up by any medical institution. Family history revealed his father had prostate cancer in his 70s, and multiple paternal relatives had a history of gastrointestinal cancers, but no individuals with episodes suggestive of polyposis or CS/PHTS (Figure 1).

Initial examinations led to a diagnosis of pancreatic cancer with liver metastasis (Figure 2A). Blood test results are shown in Table I. A liver needle biopsy revealed cells with high Nuclear/Cytoplasm ratio and strong atypia forming glandular structures. Immunohistochemistry showed positive staining not only for CAM5.2 but also for Chromogranin A (suggesting neuroendocrine differentiation) and BCL10 (suggesting acinar cell differentiation) in some cells (Figure 3). This led to a diagnosis of the rare histological type, mixed acinar-neuroendocrine carcinoma.

The patient was referred to our hospital for systemic chemotherapy. PET/CT also identified a tumor lesion in the sigmoid colon (Figure 2B). Endoscopic examination revealed glycogenic acanthosis in the esophagus, multiple polyps in the stomach and duodenum (Figure 2C), and colonoscopy showed multiple polyps throughout the colon and a type 1 tumor suggestive of malignancy in the sigmoid colon (Figure 2D), although pathological examination only reached Group 4. Considering pancreatic cancer as the prognostic determinant and the patient's burden, additional lower endoscopy biopsies were not performed. Chemotherapy was initiated with FOLFIRINOX, following the standard for pancreatic ductal adenocarcinoma, but the first efficacy assessment showed progression. Subsequently, gemcitabine plus nab-paclitaxel was administered, but again, the first efficacy assessment showed progression. Finally, cisplatin plus etoposide was administered, following the regimen for neuroendocrine carcinoma, but this too proved ineffective at the first efficacy assessment. The patient died 7 months after the initial diagnosis.

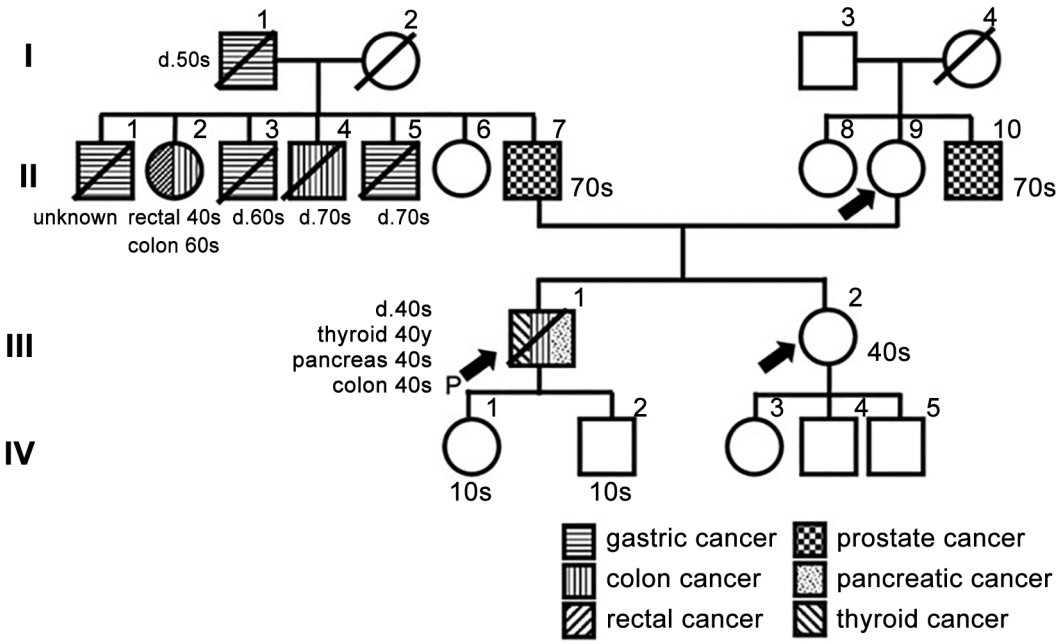

Figure 1. *Pedigree of the patient's family. The arrow indicates the consultant, and 'P' denotes the proband.*

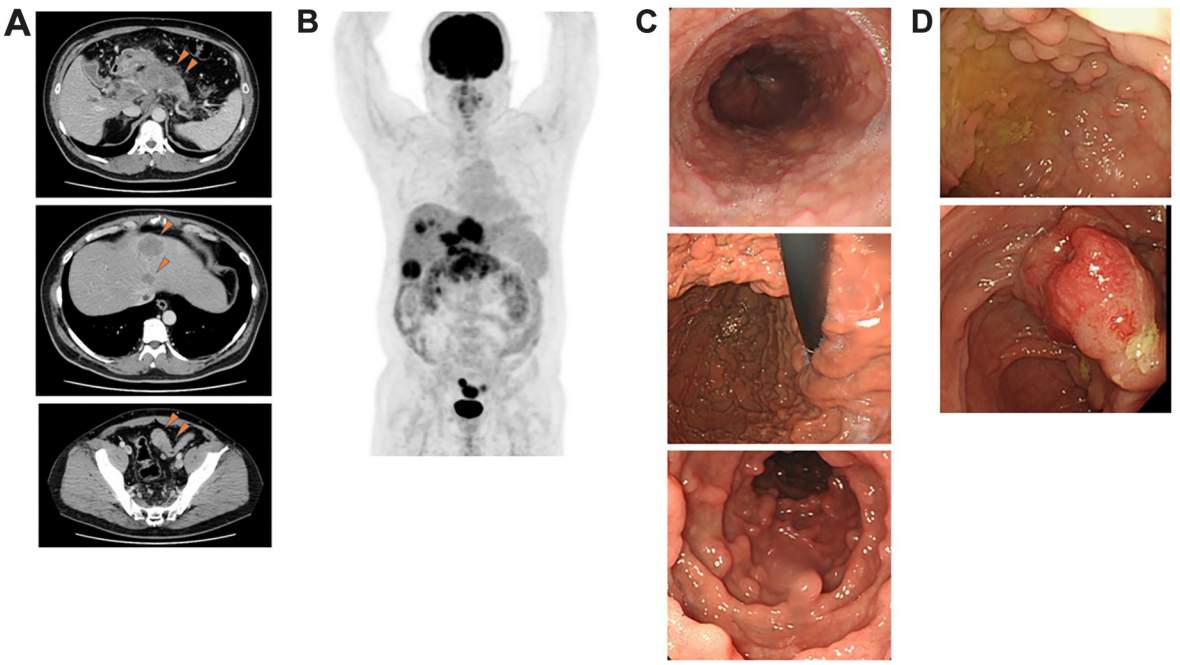

Figure 2. *Key images. (A) Contrast-enhanced computed tomography (CT) scans: (top) A hypodense mass in the pancreatic head to body; (middle) Multiple liver masses; (bottom) Wall thickening with contrast enhancement in the sigmoid colon. (B) Positron emission tomography (PET)/CT: Fluorodeoxyglucose (FDG) uptake in the pancreas, liver, and sigmoid colon. (C) Upper gastrointestinal endoscopy: (top) Esophageal glycogenic acanthosis; (middle) Multiple gastric polyps; (bottom) Multiple duodenal polyps. (D) Lower gastrointestinal endoscopy: (top) Multiple polyps throughout the colon; (bottom) Type 1 tumor in the sigmoid colon.*

Table I. *Initial blood test results.*

Biochemistry			Immunology			Tumor markers		
TP	7.5	g/dl	CRP	0.81	mg/dl	CEA	6.04	ng/ml
Alb	3.9	g/dl	KL-6	250	U/ml	AFP	43.1	ng/ml
AST	31	U/l				CA19-9	10.4	U/ml
ALT	26	U/l	Hematology			DUPAN2	31	U/ml
ALP	415	U/l	WBC	6,160	/μl	ProGRP	40.2	pg/ml
γ-GT	293	U/l	Hb	13.3	g/dl	Span-1	13.4	U/ml
Cre	0.7	mg/dl	Plt	10	10^4/μl	NSE	74.6	ng/ml
UN	11	mg/dl						
Na	138	mmol/l	Coagulation					
K	4.2	mmol/l	APTT	96.4	s			
Cl	101	mmol/l	PT%	92	%			
IP	6.4	g/ml	D-dimer	6.35	μg/ml			
LDH	927	U/l						
Total-Bil	1.6	mg/dl						
d-Bil	0.8	mg/dl						
i-Bil	0.8	mg/dl						

CRP: C-reactive protein; KL-6: Krebs von den Lungen-6; CEA: carcinoembryonic antigen; AFP: alpha-fetoprotein; CA19-9: cancer antigen 19-9; NSE: neuron-specific enolase.

During the course of treatment, with the consent of the patient and family, cancer genome profiling (OncoGuide™ NCC Oncopanel System) was performed, which detected a germline variant of V201fs*1 in *PTEN* (Table II). This frameshift variant resulting in a truncated protein was judged pathogenic by hereditary tumor specialists, clinical geneticists, and certified genetic counselors at an expert panel in a designated cancer genome hospital.

Based on the diagnostic criteria (Table III), a re-examination revealed macrocephaly (head circumference 61 cm, positive at 97th percentile above 60 cm), penile glans pigmented macules, and mucocutaneous lesions (limited to areas covered by clothing, except for the gums). Tumor cell analysis did not detect the *KRAS* pathogenic variant commonly seen in pancreatic cancers, but did detect pathogenic variants in *GNAS* (with potential pathogenic implications, often seen in acinar cell carcinoma) and *TP53* (seen in many tumors) (Table II).

Genetic counseling was provided to the patient and family based on these results. At present, there appear to be no findings suggestive of CS/PHTS in blood relatives, and a plan for continued discussions was established.

Table II. *Next-generation sequencing results.*

Tumor nuclei percentage	20
Mean depth (tumor)	1,329
ΔΔCq	0.06
Tumor mutational burden (/Mbp)	3.1
Microsatellite instability score	0.4

Origin	Gene	Variant	Allele frequency
Somatic	*TP53*	C135G	0.252
Somatic	*GNAS*	R201P	0.166
Germline	*PTEN*	V201fs*1	0.53

The allele frequency of *PTEN* indicates the germline frequency. The OncoGuide™ NCC Oncopanel System was used, which compares normal and tumor tissue samples.

Discussion

PTEN (4), located on the long arm of chromosome 10 at 10q23.31, is a representative tumor suppressor gene. It is believed to suppress carcinogenesis by inhibiting the PI3K/Akt/mTOR pathway (5). CS/PHTS, a condition characterized by pathogenic germline variants in *PTEN* gene, follows an autosomal dominant inheritance pattern and is one of the most crucial syndromes associated with

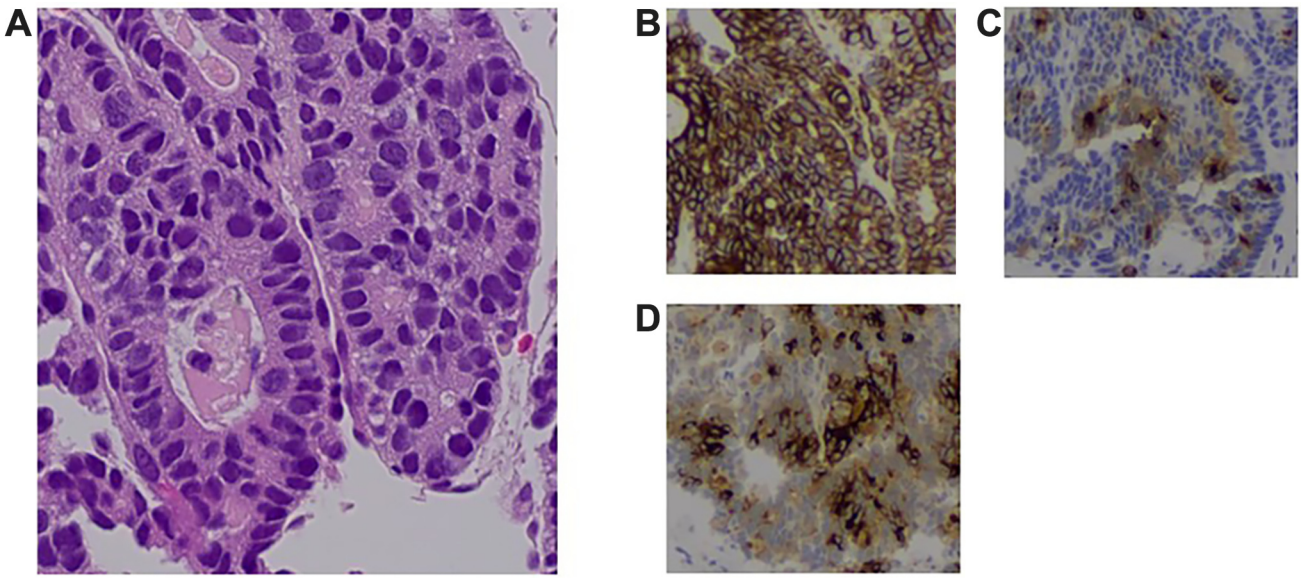

Figure 3. *Liver biopsy pathology: (A) Hematoxylin and Eosin staining, (B) CAM5.2 immunostaining, (C) Chromogranin A immunostaining, (D) BCL10 immunostaining.*

increased risk of many malignancies, including breast and thyroid cancer (6). The impact on asymptomatic carriers is significant, including the need for lifelong surveillance (7). The penetrance is reported to be very high at approximately 80% (8).

Beyond cancer incidence and prevention, CS/PHTS is considered an extremely important hereditary syndrome due to its wide range of phenotypes, including neurodevelopmental disorders such as autism spectrum disorder (9). While reports of malignant tumor development are diverse, the major criteria for diagnosis include breast, follicular thyroid, and endometrial cancer. The minor criteria include colorectal cancer, renal cell carcinoma, and thyroid cancer (papillary or follicular variant of papillary) (6, 10, 11) (Table III).

In our case, the patient had a history of follicular thyroid cancer, meeting one of the major criteria. Although the biopsy only reached a pathological diagnosis of Group 4, colorectal cancer was strongly suspected clinically, potentially meeting one of the minor criteria. However, pancreatic cancer is not common in CS/PHTS, with only sporadic case reports (12) and a xenograft model (13).

In routine pancreatic cancer care and genomic profiling analysis, *PTEN* detection is extremely rare at less than 1% (14). Characteristic mutations typically detected include *KRAS* (observed in about 90% of cases), as well as *TP53*, *SMAD4*, and *CDKN2A* (15, 16). Since ductal adenocarcinoma accounts for the vast majority of pancreatic cancers, acinar cell carcinoma and its mixed type (mixed acinar-endocrine carcinoma) (17) are extremely rare, and their relationship with *PTEN* is currently unclear. While *GNAS* is observed in about 10% of acinar cell carcinomas in pancreatic cancer, it is more prominently observed in approximately half of intraductal papillary mucinous neoplasms (IPMN) (18). The GNAS variant detected in this case is not registered in major variant databases including the National Institutes of Health ClinVar, Catalogue of Somatic Mutations in Cancer, and OncoKB. However, variants at the same codon, such as R201C are known to be pathogenic, suggesting that this variant may have potential implications for tumor development, though its precise significance remains to be determined.

There are reports from Japan of cases with concurrent acinar cell carcinoma and IPMN (19). While we cannot rule

Table III. *Diagnostic criteria for Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS).*

Major criteria
1 Breast cancer
2 Endometrial cancer
3 Follicular carcinoma of the thyroid gland
4 Gastrointestinal hamartomas
5 Adult-onset Lhermitte-Duclos disease
6 Macrocephaly
7 Macular pigmentation of the glans penis
8 Multiple mucocutaneous lesions
Minor criteria
1 Autism spectrum disorder
2 Colorectal cancer
3 Esophageal glycogenic acanthosis
4 Lipoma
5 Intellectual disability
6 Renal cell carcinoma
7 Testicular lipomatosis
8 Thyroid papillary carcinoma or follicular variant of papillary
9 Thyroid structural lesions
10 Vascular anomalies

A diagnosis of CS/PHTS is established if the patient fulfills one of the following criteria:
1) Three or more major criteria, one of which is macrocephaly, adult-onset Lhermitte-Duclos disease, or gastrointestinal hamartomas
2) Two or more major criteria and three or more minor criteria
The patient's family members will be diagnosed with CS/PHTS if they meet one of the following criteria:
1) Two or more major criteria
2) One major criterion and at least two minor criteria
3) At least three sub-criteria

out the possibility of other tissue types apart of the pancreas in our case, based on disease frequency and the extremely poor course, we determined that the pancreatic tumor was likely the same Mixed acinar-endocrine carcinoma that was confirmed by biopsy in the liver lesion. Referring to reports from other organs, the prognosis for similar histological types is poor (20, 21). Our case was also unresponsive to both standard pancreatic cancer chemotherapy (22, 23) and chemotherapy used for neuroendocrine carcinoma (24), resulting in an extremely poor outcome.

For reference, we searched the Center for Cancer Genomics and Advanced Therapeutics utilization database, a representative genomic profiling database in Japan. We found 160 registered cases of pancreatic cancer with *PTEN* pathogenic variants (not limited to germline) from June 2019, for FoundationOne® CDx and OncoGuide™NCC oncopanel, from July 2023, for Guardant360 CDx, and from August 2023 to April 2024, for GenMineTOP cancer genomic profiling system. The proportion of cases that showed disease control was 62% for gemcitabine-based regimens and 68% for fluoropyrimidine-based regimens. From the perspective of cases without *KRAS* pathogenic variants, similar analysis showed 50% for gemcitabine-based regimens and 83% for regimens containing fluoropyrimidine. While these remain exploratory reference findings, the relationship between the poor treatment response in our case and the presence of *PTEN* or the absence of *KRAS* detection is not clear. However, although the number of cases is extremely limited, there are three cases of pancreatic cancer with germline *PTEN* pathogenic variants registered, including our case, and all three cases suggested a trend of poor response to chemotherapy (Table IV). While the cause is not clear from our search, many factors favorable for tumor growth have been reported, including the importance of *PTEN* in tumor immunity (25) and its role as a crucial molecule in tumor progression such as migration (26). Further research is needed on the current status and factors of treatment resistance in cases with germline *PTEN* pathogenic variants. While capivasertib is used for breast cancers with *PTEN* loss-of-function variants (27), no findings on its use for germline variants were found in our search range. Treatment targeting *PTEN* loss-of-function is also considered a future research topic. Additionally, in this case, partly due to the patient's explanation that only one colon polyp had been completely removed, the outpatient doctor could not reach a diagnosis of CS/PHTS, and hereditary tumor findings were incidentally discovered by genomic testing. As the possibility of germline findings increases with the spread of genomic testing (28) in daily clinical settings, it becomes increasingly important to obtain informed consent regarding the possibility of germline findings and disclosure preferences in advance, and to provide genetic counseling according to the wishes

Table IV. *Clinical characteristics of three pancreatic cancer cases with germline PTEN mutations identified from a cohort of 20 PTEN mutation carriers in the Center for Cancer Genomics and Advanced Therapeutics database.*

Case	Sex	Age	*PTEN*	Panel	Histology	Family history	Metastatic site	Germ-based therapy	5-FU-based therapy	TMB	Somatic gene alterations
1	Male	69	c.-156C>G	NOP	Adeno	None	Peritoneal	NE	PD	86	*CDKN2A* loss, *BRCA2* F625fs*19, *KRAS* G12V, *MLH1* F80fs*12, *MAP3K4* N160fs*8, *NTRK1* V321M, *POLE* N1978fs*21, *TP53* A278V, *TP53* K382fs*40
2	Male	46	L247fs*6	NOP	Adeno	Unspecified	Liver	PD	SD	2.3	*KRAS* G12D, *TP53* E271
Our	Male	40s	V290fs*1	NOP	Acinar +NEC	Reference figure 1	Liver	PD	PD	3.1	*GNAS* R201P, *TP53* C135

NOP: OncoGuide™NCC oncopanel; Adeno: adenocarcinoma; NEC: neuroendcrine carcinoma; NE: not evaluated; PD: progressive disease; SD: stable disease; TMB: tumor mutational burden.

of patients and their families when such findings are confirmed (29). For this case as well, we have conducted repeated interviews at the request of the family, and a certain follow-up system including physical examination was established.

While CS/PHTS often has characteristic medical history and external features, making it relatively obvious at the initial visit, in cases like ours where skin lesions are limited to areas covered by clothing or when the patient incorrectly remembers polyp information, we reaffirmed the importance of taking a thorough medical history, family history, and physical examination in tumor care settings.

In conclusion, we experienced a case of pancreatic cancer, not considered a CS/PHTS-related tumor, with distinctive molecular and histological features, high treatment resistance, and a germline *PTEN* variant.

Conclusion

We encountered a case of pancreatic cancer that was not considered to be a CS/PHTS-related tumor with distinctive molecular and histological features, high treatment resistance, and a germline PTEN variant. The molecular profile of this mixed acinar-neuroendocrine carcinoma was atypical for pancreatic cancer, lacking *KRAS* mutations while harboring pathogenic variants in *GNAS* and *TP53*. The case demonstrated extreme resistance to multiple standard chemotherapy regimens, resulting in a particularly aggressive clinical course. These findings emphasize the importance of comprehensive genomic profiling in clinical oncology, not only for identifying potential therapeutic targets but also for uncovering underlying hereditary cancer syndromes. Our observations suggest the need for further research into molecular mechanisms, including PTEN, and improvements in treatment strategies for these challenging cases.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization: Y.S. and S.S., Data Curation; Y.S. and S.S., Formal Analysis: Y.S. and S.S. Funding Acquisition: S.S. and T.Y., Investigation: Y.S. and S.S., Methodology: Y.S. and S.S., Resources: Y.S., S.S., T.S., and K.K., Software: Y.S. and S.S., Supervision: S.S., T.S. and K.K., Validation: S.S., Visualization: Y.S., Original Draft, Writing: Y.S. and S.S., Review & Editing: Y.S., S.S., T.S., K.K., H.O., Y.N., Y.Y., K.S, K.T., R.K., T.F., and T.Y.

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