Brain metastasis from KRAS wild-type pancreatic cancer and organoid correlates: a case report

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Background: Although pancreatic cancer is an aggressive malignancy with a propensity for metastatic spread, brain metastases (BrMs) remain exceptionally rare (<1% incidence).

Case Description: We present a case of BrMs in a 69-year-old pancreatic cancer patient. This patient initially presented with a history of chronic pancreatitis, abdominal and back pain, and significant weight loss. After the diagnostic biopsy confirmed pancreatic cancer, the patient was enrolled onto the PASS-01 clinical trial and was treated with standard of care chemotherapy before progressing and developing BrMs 10 months after cancer diagnosis. The BrMs were removed via craniotomy, and the patient also underwent radiation and chemotherapy before enrolling onto the MYTHIC clinical trial for PKMYT1 inhibitor, RP-6306. Successful generation of a BrM-derived organoid line enabled high-throughput drug screening, which recapitulated the patient's clinical resistance to standard therapies [gemcitabine/nab-paclitaxel, 5-fluorouracil (5-FU)], and showed sensitivity to afatinib, everolimus and RMC-6236.

Conclusions: This case report demonstrates the importance of precision medicine to characterize patient tumor and identify actionable targets and potential therapies. Physicians should also be aware that *KRAS* wild-type pancreatic cancer with atypical amplifications is likely to exhibit unique metastatic tropisms. Finally, we suggest that patient-derived organoids pharmacotyping can mirror clinical drug responses and help evaluate therapeutic avenues for patient treatment.

Keywords: Case report; pancreatic cancer; brain metastasis (BrM); organoids; precision medicine

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Introduction

Pancreatic cancer is widely regarded as one of the most aggressive and deadly cancers, currently ranked as the third leading cause of cancer-related deaths in the United States (1). The most prevalent subtype, pancreatic ductal adenocarcinoma (PDAC), accounts for over 85% of pancreatic cancer cases and is still challenging to treat, often showing resistance to conventional therapies (2). Although surgery is considered its only potential cure, PDAC is often inoperable when found in patients due to the lack of symptoms or diagnostic tools to identify early disease, as well as its invasive nature (3,4). PDAC is thus usually diagnosed as advanced or metastatic disease in up to 80% of cases (3). Its most common metastatic sites include the liver (76–80%), peritoneum (48%), and lungs (45%) (5,6). Brain metastases (BrMs) are an exceptionally rare complication, with an estimated incidence of less than 1% (7,8). This is likely due to the rapid progression of pancreatic cancer where patients often die before developing or showing symptoms of brain disease (9). Furthermore, brain imaging is not recommended in the initial diagnosis and follow-up routine assessments of asymptomatic pancreatic cancer as per the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines. As efforts to cure pancreatic cancer progress and survival rates improve, previously rare metastases may become more common, underscoring the importance of studying and understanding whether particular molecular drivers may induce unusual tropism, as such findings could be targets for personalized medicine (10).

Patient-derived organoids (PDOs) are three-dimensional cell culture models highly valued in cancer research because they retain key molecular characteristics and the heterogeneity of the original tumor, providing a valuable framework for testing drug responsiveness and resistance specific to an individual's cancer (11,12). The aims of this case report are to describe a clinically significant case of BrM in a patient with PDAC, highlight the importance of sequencing and precision medicine to characterize rare and aggressive cancers, and demonstrate the potential of PDOs in exploring interesting, targeted therapies. We present this article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-aw-818/rc).

Highlight box

Key findings

- This report details a rare brain metastasis (BrM) from a molecularly distinct, *KRAS/TP53* wild-type pancreatic cancer patient. Genomic analysis revealed amplifications in *CCNE1* and *ERBB3*, alterations linked to brain tropism. A patient-derived organoid (PDO) model from the BrM mirrored clinical drug resistance and identified potential targetable sensitivities.

What is known and what is new?

- Pancreatic ductal adenocarcinoma (PDAC) BrM are rare (<1%) and have poor prognosis. Meanwhile, routine brain screening is not standard.
- We provide deep molecular characterization of a *KRAS/TP53* wild-type BrM, highlighting *CCNE1/ERBB3* amplifications as potential drivers of this tropism. We demonstrate the first successful biobanking and pharmacotyping of a BrM-derived PDO, confirming its clinical predictive value. This case signals that rare metastatic sites may increase as therapies improve survival and would benefit from thorough characterization.

What is the implication, and what should change now?

- Clinical vigilance for BrM in asymptomatic PDAC patients is needed. Comprehensive molecular profiling of metastases enables identification of actionable targets for personalized medicine.
- Investment in faster, clinically integrated PDO platforms is crucial to translate functional drug data into timely treatment decisions for aggressive variants.

Case presentation

Clinical case presentation

A 69-year-old male with a history of smoking (40 pack-years), presented to Memorial Sloan Kettering in May 2022 with complaints of back and abdominal pain, early satiety, and unexplained weight loss (*Figure 1A*,*1B*). He was previously diagnosed with chronic pancreatitis and prescribed pancreatic enzymes and a proton pump inhibitor, both of which had negligible effect on his symptoms. Computed tomography (CT) imaging of the chest, abdomen, and pelvis showed coarse calcifications in the pancreatic head and uncinate process, as well as extensive retroperitoneal adenopathy surrounding the pancreas and major arteries (*Figure 1C*,*1D*). The patient underwent a diagnostic biopsy of the retroperitoneal lymph node in June 2022, part of which was sent for PDO establishment, though this first attempt was unsuccessful (Appendix 1). Pathological assessment and immunohistochemical staining of the biopsy revealed poorly differentiated carcinoma with focal CDX2 expression; CK7, CK20, TTF1, trypsin, chymotrypsin, and NKX3.1 were negative

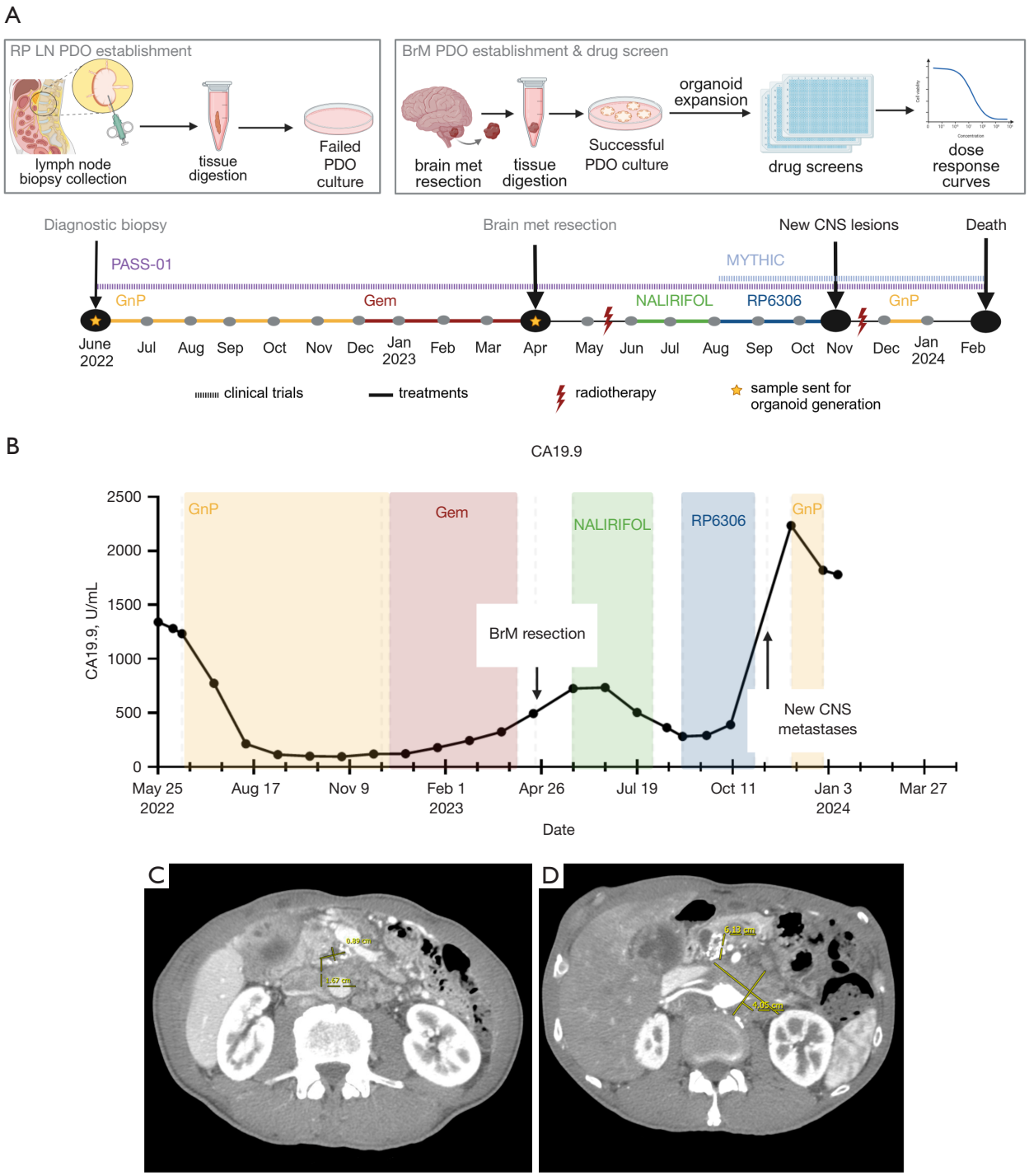

Figure 1 Patient disease timeline and primary tumor imaging. (A) Case report timeline. (B) Patient's CA19.9 levels. (C,D) Baseline CT imaging, cystic lesion in the uncinate process of the pancreas (C) and left para-aortic adenopathy (D). BrM, brain metastasis; CA19.9, carbohydrate antigen 19-9; CNS, central nervous system; CT, computed tomography; Gem, gemcitabine; GnP, gemcitabine nab-paclitaxel; PDO, patient-derived organoid; RP LN, retroperitoneal lymph node.

Table 1 Somatic mutations

Gene	Mutation	Blood VAF	CSF VAF	BrM VAF	PDO VAF
ARID5B	K647N	35.18%	35.18%	–	–
ATRX	R246C	96.26%	96.26%	62.66%	100.00%
MSH3	C252F	49.87%	49.87%	29.70%	49.40%
PDGFRB	R370C	48.77%	48.77%	32.42%	49.80%
TSC2	K1544R	41.65%	71.38%	64.41%	75.30%
WT1	A109V	44.94%	44.94%	38.94%	51.70%
XPO1	Y841C	32.49%	32.49%	22.70%	–

BrM, brain metastasis; CSF, cerebrospinal fluid; PDO, patient-derived organoid; VAF, variant allele frequency.

and expression of SMAD4 was retained. Hematoxylin and eosin (H&E) staining confirmed adenocarcinoma with well-formed glandular structures lined by tumor cells containing intracytoplasmic mucin, which excluded testicular cancer, lymphoma or infection, which can also present with retroperitoneal adenopathy. TTF-1 and NKX3.1 negativity made a lung or prostate primary unlikely. Pancreatobiliary carcinomas lack a definitive site-specific immunohistochemical marker, however, given the characteristic morphology and exclusion of the most common histologic mimickers by immunohistochemistry, we were confident that the findings are most consistent with a pancreatic primary. Next generation sequencing of circulating tumor DNA (ctDNA) showed somatic mutations in *TSC2* and *PDGFR*β, amplifications in *MYC*, *ERBB3*, and *MDM2* as well as rearrangement in *STK11*, among others. No *KRAS* or *TP53* mutations were found (*Tables 1*,*2*). Upon these findings, the patient was diagnosed with metastatic pancreatic ductal adenocarcinoma (PDAC). He was enrolled in the Pancreatic adenocarcinoma signature stratification for treatment-01 (PASS-01) clinical trial (NCT04469556) and randomized to the gemcitabine nab-paclitaxel (GnP) arm of the study. He received six months of treatment, followed by four months of maintenance therapy with monotherapy gemcitabine after developing progressive neuropathy, a common adverse effect of nab-paclitaxel (13) (*Figure 1A*,*1B*).

Ten months after the first PDAC diagnosis, in April 2023, the patient presented with dizziness. Magnetic resonance imaging (MRI) of the brain showed lesions consistent with bilateral supra- and infratentorial BrMs, including a 4.6 cm × 2.7 cm mass in the left cerebellum (*Figure 2A*), 0.9 cm foci in the right basal ganglia and 0.5 cm foci in the right anterior frontal lobe. The patient underwent a craniotomy to remove the left cerebellar mass, followed by whole-brain and targeted radiation therapy (RT). A part of the resected BrM was sent for PDO establishment, which was successful. Histologic and genomic assessment of the resected mass and sequencing of the metastasis and cerebrospinal fluid (CSF) ctDNA confirmed that the BrM was a PDAC metastasis, showing phenotypic similarities to the primary lesion and previously sequenced blood ctDNA (*Figure 2B*, *Tables 1*,*2*). In addition, this new round of sequencing revealed many copy number alterations such as a CCNE1 amplification, not previously picked up due to low cellularity. After the craniotomy and radiation, the patient was switched to nano-liposomal irinotecan (SN-38), 5-fluorouracil (5-FU), and leucovorin (NALIRIFOL) for three months due to disease progression before being consented to the MYTHIC clinical trial in August 2023 (NCT04855656), where he received RP-6306, a PKMYT1 inhibitor that has shown efficacy in CCNE1-amplified cancers (14). He remained on this treatment for 2 months.

In November 2023, 6 months after the BrM diagnosis, new brain, and osseous spinal metastases, as well as leptomeningeal disease (cervical, thoracic, and lumbar spine) were detected on MRI (*Figure 2C*). At this time, the patient received 10 fractions of proton RT to the central nervous system (CNS) before being switched to a GnP regimen for one month as GnP had previously seemed to control his non-CNS disease. The patient developed progressive pain and weakness related to progression of his extracranial disease, while his BrM stabilized following RT. The patient then transitioned to hospice care and passed away in February 2024, 9 months after the BrM diagnosis and 21 months after the original diagnosis.

All procedures performed in this study were in accordance with the ethical standards of the institutional

Table 2 Copy number alterations

Gene	Cytoband	Blood	CSF	BrM	PDO
ABL1	9q34.12			DeepLoss	HetLoss
ACVR1	2q24.1			DeepLoss	HetLoss
AKT3	1q44			DeepLoss	HetLoss
ALOX12B	17p13.1			DeepLoss	HetLoss
AR	Xq12			DeepLoss	HetLoss
ARAF	Xp11.23			DeepLoss	HetLoss
ATRX	Xq21.1			DeepLoss	HetLoss
AURKB	17p13.1			DeepLoss	HetLoss
BABAM1	19p13.11			DeepLoss	HetLoss
BCL2	18q21.33			DeepLoss	HetLoss
BCL2L11	2q13			DeepLoss	HetLoss
BCL6	3q27.3			DeepLoss	HetLoss
BCOR	Xp11.4			DeepLoss	HetLoss
BRAF	7q34			DeepLoss	HetLoss
BRCA2	13q13.1			DeepLoss	HetLoss
BRD4	19p13.12			DeepLoss	HetLoss
BTK	Xq22.1			DeepLoss	HetLoss
CARD11	7p22.2			DeepLoss	HetLoss
CARM1	19p13.2			DeepLoss	HetLoss
CBFB	16q22.1			DeepLoss	
CCNE1	19q12		AMP	AMP	AMP
CEBPA	19q13.11		AMP		AMP
CTCF	16q22.1			DeepLoss	
DNAJB1	19p13.12			DeepLoss	HetLoss
EP300	22q13.12		AMP		
ERBB3	12q13.2	AMP	AMP	AMP	AMP
HNF1A	12q24.31			DeepLoss	HetLoss
JAK3	19p13.11		AMP		HetLoss
MALT1	18q21.32		AMP		HetLoss
MDM2	12q15	AMP	AMP	AMP	AMP
MPL	1p34.2		AMP	AMP	
MYC	8q24.21	AMP	AMP	AMP	AMP
NOTCH3	19p13.12		AMP		HetLoss
PIK3R2	19p13.11			DeepLoss	HetLoss
PRKCI	3q26.2		AMP	AMP	AMP

Table 2 (*continued*)

Table 2 (*continued*)

Gene	Cytoband	Blood	CSF	BrM	PDO
SMARCA4	19p13.2		AMP		HetLoss
TRAF2	9q34.3		AMP	AMP	AMP
U2AF1	21q22.3		AMP	AMP	AMP
UPF1	19p13.11		AMP		HetLoss
VEGFA	6p21.1			AMP	AMP
STK11	Rearrangement	✓	✓	✓	

✓, detected. AMP, amplification; BrM, brain metastasis; CSF, cerebrospinal fluid; DeepLoss, deep deletion; HetLoss, heterozygous loss; PDO, patient-derived organoid.

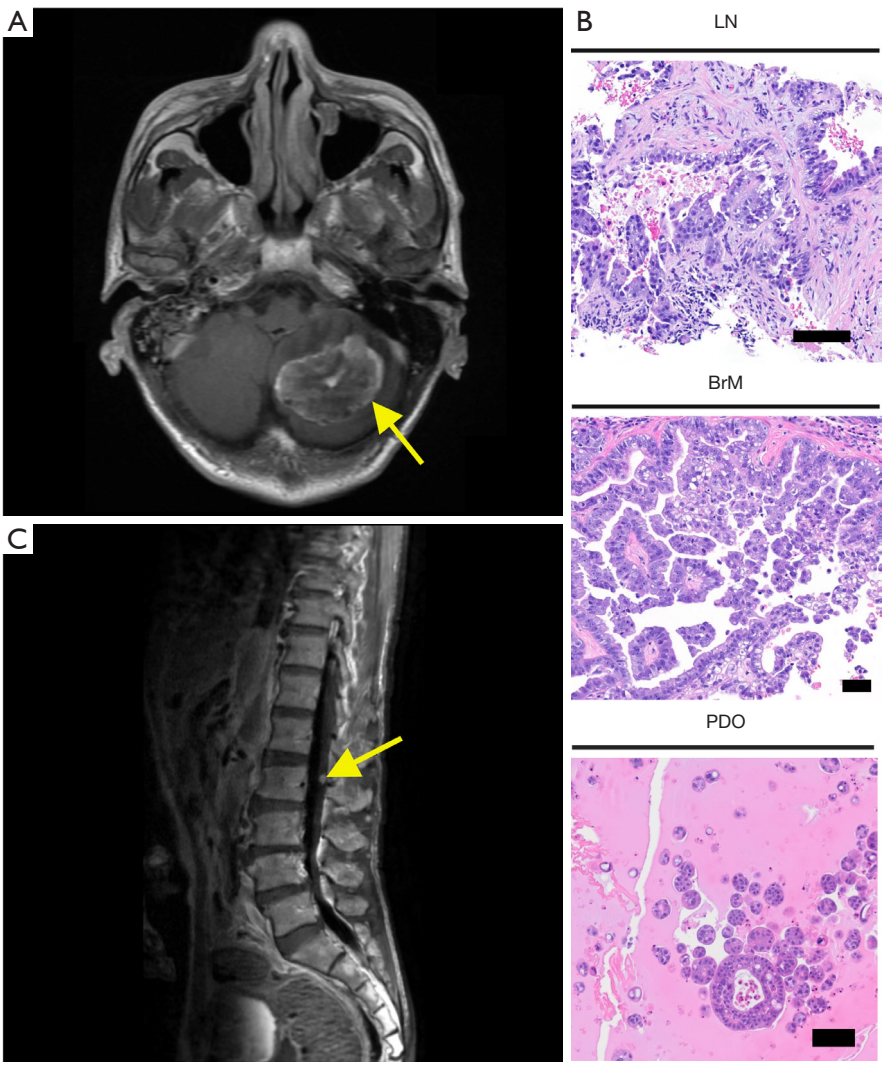

Figure 2 Genomic and histologic overview of patient and CNS lesions imaging. (A) MRI imaging left cerebellum metastasis. (B) H&E staining of patient primary tumor, brain metastasis and PDO. Scale: black, 100 nm. (C) MRI imaging, enhancing nodule along the posterior cauda equina at L1–L2. The yellow arrows show tumor lesions. *Figure 1A,1B* were made using BioRender. BrM, brain metastasis; CNS, central nervous system; H&E, hematoxylin and eosin; LN, lymph node; MRI, magnetic resonance imaging; PDO, patient-derived organoid.

and/or national research committee(s) and with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from the patient for publication of this case report and accompany images. A copy of the written consent is available for review by the editorial office of this journal.

PDO presentation

Upon tissue receipt in April 2023, the BrM-derived PDO was cultured, biobanked, and sequenced (*Figure 3A*). Genomic sequencing results of the PDO aligned with the patient's sequencing data, showing the same KRAS wild-type (WT) and TP53 WT statuses as the BrM (*Tables 1*,*2*). Histologic evaluation by a board-certified pathologist further confirmed the PDO as a high-grade carcinoma, phenotypically similar to the patient's lymph node and BrM lesions (*Figure 2B*). Together, these findings confirmed the PDO as a faithful model of the patient's cancer.

The PDO was screened against over 100 compounds, including standard-of-care (SOC) chemotherapies, targeted drugs, and investigational compounds (*Figure 3B*,*3C)*. Comparison with a previously published organoid biobank (11) revealed that the PDO exhibited resistance to SOC treatments. The patient had received gemcitabine and paclitaxel until the development of the BrM from which the PDO was derived. Following BrM resection, SN-38 and 5-FU were administered but did not improve the patient's condition as he continued to progress. In both cases, the PDO's responses mirrored the patient's clinical outcomes, underscoring its ability not only to replicate but also potentially predict therapeutic responses. Although the patient also received RP-6306, the compound was unavailable for research during the experimental design phase. This highlights a common challenge in research, where drugs in advanced clinical trials are still inaccessible, hindering new discoveries.

However, the PDO showed sensitivity to afatinib and everolimus (*Figure 3B*,*3C*). Afatinib, an ErbB family inhibitor targeting HER2 and EGFR, shows increased efficacy in KRAS WT cancers compared to KRAS-mutant cancers (15). Everolimus, a rapamycin derivative and mTOR inhibitor, is highly effective in TSC2-mutated cancers (16). Despite the patient's TP53 WT status, the PDO exhibited resistance to Nutlin-3, a p53-MDM2 inhibitor, possibly due to MDM2 amplification leading to reduced sensitivity. Although the PDO was KRAS WT, its growth was inhibited by the pan-RAS inhibitor RMC-6236, suggesting that RAS signaling is still a key driver of malignant proliferation (*Figure 3B*). These findings illustrate how PDO-based precision medicine could help find potentially beneficial treatments for patients. In fact, for tumors with atypical profiles (e.g., KRAS WT, targetable amplifications), PDOs could offer a platform to empirically find therapies when clinical trial options are limited.

Unfortunately, by the time drug screening from the BrM PDO was completed, the patient was in hospice care, and the findings could not be incorporated into his treatment plan.

Discussion

BrMs from PDAC are exceptionally rare, with limited documented cases in the literature. While synchronous BrM rates are currently reported at less than 1%, an autopsy study revealed a 10% incidence of post-mortem BrM in pancreatic carcinoma patients (17). This discrepancy may stem from the fact that head imaging is not part of the standard diagnostic and follow-up workup for PDAC, suggesting that BrMs could be underdiagnosed and more prevalent than previously recognized. Notably, the advent of RAS inhibitors for KRAS-mutated cancers and other targeted therapies is expected to prolong PDAC patient survival, potentially increasing the likelihood of symptomatic BrMs and other unique metastatic presentations.

To our knowledge, the first ante-mortem diagnosed PDAC BrM cases were reported in South Korea in 2003. Our literature review found 28 cases from 2003 to 2023, with a median age at PDAC diagnosis of 59 years (range, 34–80 years) and a slight male predominance (64%) (*Tables 3*,*4*). Most patients received chemotherapy (82%), surgery (50%), or radiation (11%) for their primary disease, with a median time to BrM development of 11 months (range, 0–82 months). Common BrM treatments included radiation (68%), surgery (46%), and chemotherapy (25%), with a median overall survival of 6.5 months (range, 0–132 months). Synchronous metastases often involve the liver (32%), lungs (29%), lymph nodes (29%), and bones (2%), with one case presenting concurrent spinal cord metastasis (*Table 4*). In our report, a 69-year-old male developed BrM 10 months after PDAC diagnosis and underwent surgery, radiation, and chemotherapy.

This patient was enrolled in the PASS-01 trial, a phase II randomized study comparing GnP and modified FOLFIRINOX (mFFX) in metastatic PDAC. The trial

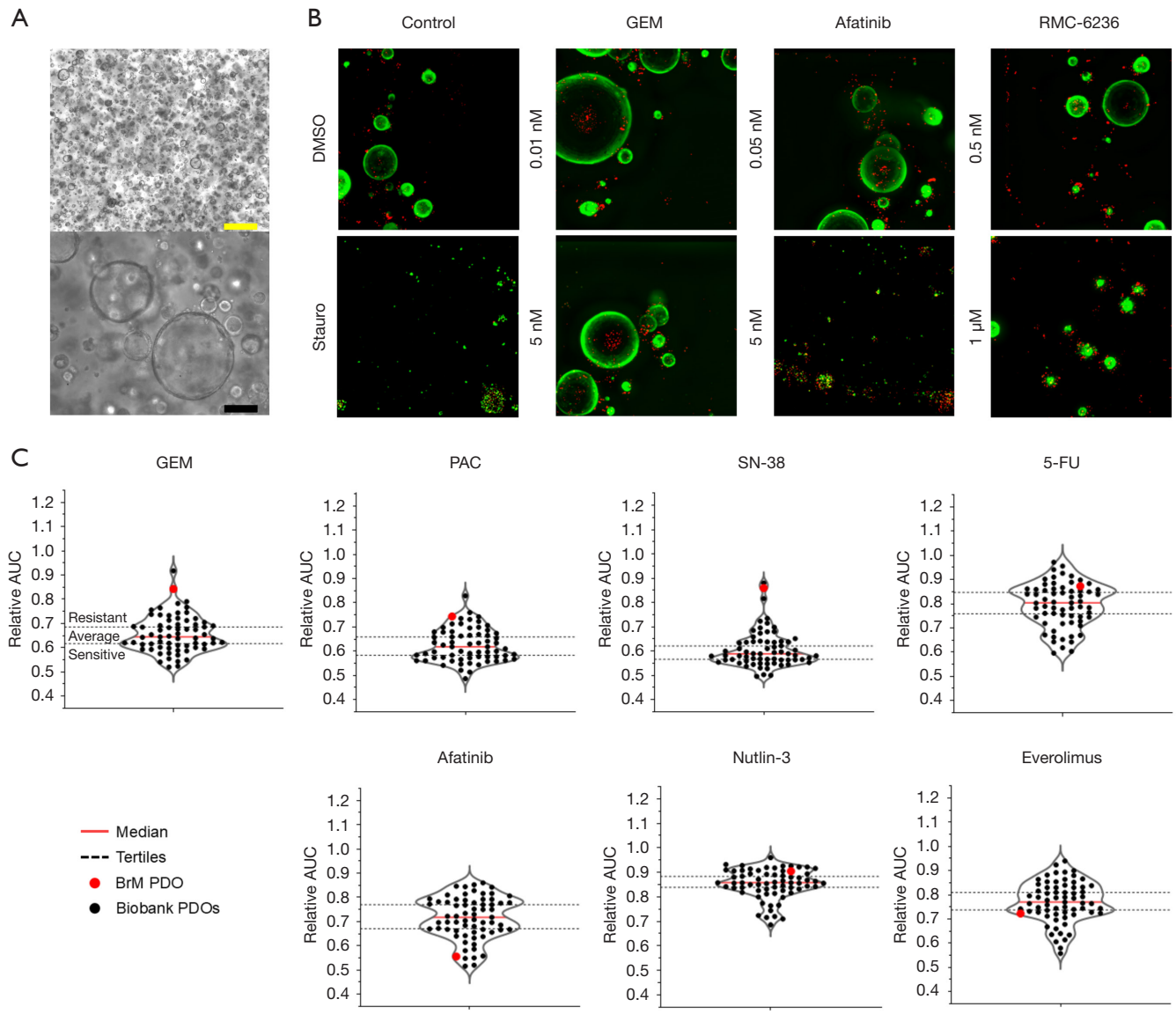

Figure 3 PDO drug screening and response. (A) PDO brightfield images at ×4 and ×20. Scale: black, 100 nm, yellow, 500 nm. (B) High content images of BrM PDO at ×10, stained with AOPI live/dead stain (green = live, red = dead). Staurosporine as positive control (dead), DMSO as negative control (live). (C) Violin plots of BrM PDO drug response, using AUC (red) compared to previously published PDO cohort (11) (black). 5-FU, 5-fluorouracil; AFA, afatinib; AOPI, acridine orange and propidium iodide; AUC, area under curve; BrM, brain metastasis; DMSO, dimethyl sulfoxide; GEM, gemcitabine; PAC, paclitaxel; PDO, patient-derived organoid; SN-38, active form of irinotecan; Stauro, staurosporine.

incorporates multi-pass core biopsies for pathology, whole-genome/RNA sequencing, and PDO generation with pharmacotyping (13). This approach aims to personalize treatment based on genetic, transcriptional, and pharmacological profiles. Despite a median overall survival of 9.7 months for GnP-treated patients in PASS-01 (13), our patient survived 21 months—likely attributable to his unique *KRAS/TP53/CDKN2A* wild-type (WT) tumor, which harbored a *CCNE1* amplification and qualified him for the MYTHIC trial. *KRAS* WT PDACs are associated with better prognoses and higher rates of actionable alterations (37), underscoring the importance of including

Table 3 Literature review demographics

Literature review demographics	Patients' statistics
Age (years)	60 (34–80)
Sex	
Male	18 [64.3]
Female	10 [35.7]
PDAC stage	
I	1 [4]
II	1 [4]
III	3 [11]
IV	6 [21]
NR	17 [61]
PDAC treatment	
Surgery	14 [50]
Chemotherapy	23 [82]
Radiation	3 [11]
Time to BrM (months)	11 (0–72)
BrM treatment	
Surgery	13 [46]
Chemotherapy	7 [25]
Radiation	19 [68]
OS from BrM (months)	6.5 (0–132)

Data are presented as median (range) or n [%]. BrM, brain metastasis; NR, not reported; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma.

genomic profiling in the clinical setting.

In our review, we observed only a few PDAC BrM reported cases having genomic data on the patients' tumors. A study from 2018 in showed that mutations in *KRAS*, *TP53* and *MYC* amplification were most common in their PDAC BrM cohort (38). In lung adenocarcinomas, *MYC* is also one of the most altered genes in BrMs, along with *EGFR* alterations (39). The patient in this case report however harbored both *MYC* and *ERBB3* amplifications. ERBB3, or HER3, is a member of the EGFR family which has been identified in the majority of BrMs from breast and non-small cell lung cancers (40). Additionally, HER3 binds to neuregulin-1 (NRG1), a growth factor highly present in the brain as it is secreted by both microglia and neurons. In fact, Momeny *et al.* have shown that NRG1 and HER3 interact, along with HER2, and promote a blood-brain barrier trans-endothelial migration of human breast cancer cell lines (41). *CCNE1* amplification was also enriched in the CSF of patients with gastric cancer and leptomeningeal metastases (42). Additionally, unlike the majority of published case reports, this patient's BrM is poorly differentiated, lacking common epithelial markers like CK7. Together, these may be key factors explaining the brain tropism in this patient.

PDOs, generated through dissociation of tumor tissue into single cells, have demonstrated remarkable fidelity in recapitulating the genetic and transcriptional profiles of patient tumors (11). This makes them powerful models for drug sensitivity testing and precision medicine applications (12). While the PDO data in this particular case could not guide clinical decisions due to the extended establishment timeline, this technology holds significant promise for real-time therapeutic guidance in other patients and for expanding our understanding of individual tumor biology. Within the PASS-01 trial, successful PDO generation was achieved for 50% of patients, with an average turnaround time of approximately two months from tissue acquisition to drug screening results (43). Notably, a subset of cases yielded pharmacotyping data within just one month—a timeline that could meaningfully inform second-line therapy selection for many patients. In this report, the PDO identified patient sensitivity to therapies that may not have been routinely considered and demonstrated resistance to standard of care regimen, which the patient received and progressed on. This case exemplifies how integrating PDO-based pharmacotyping with comprehensive molecular profiling can identify novel treatment strategies for rare PDAC variants. The combined analysis of clinical, genomic, and functional model data thus establishes a valuable framework for investigating atypical cancer presentations and optimizing personalized therapeutic approaches.

Conclusions

This report presents a rare case of PDAC BrM alongside the successful generation and pharmacotyping of a PDO. Our findings emphasize the transformative potential of precision medicine in characterizing and treating rare PDAC manifestations through multidisciplinary approaches. Additionally, we propose that *KRAS* WT and *ERBB3*-amplified PDAC patients might be candidates for closer follow up, including routine brain imaging, and that PDO protocols be improved to be useful in rapidly progressing

Table 4 Literature review

First author	Publication year	Age (years) (sex)	PDAC location	Stage at PDAC dx	PDAC surgery	PDAC chemotherapy	PDAC radiation	Time to BrM dx (months)	BrM location	BrM surgery	BrM chemotherapy	BrM radiation	OS from BrM (months)	Genomics	Pathology	Synchronous metastases
Park (10)	2003	51 (M); 62 (M); 48 (M); 52 (M)	NR; NR; NR; NR	NR; NR; NR; NR	N; N; N; Y	N; N; Y; Y	N; N; N; N	0; 0; 4; 5	Left frontal; left frontal, left basal ganglia; cerebrum; left parietal	N; N; N; N	N; N; N; N	N; N; Y; Y	NR*; NR*; NR*; NR*	NR; NR; NR; NR	NR; NR; NR; NR	Lung, liver and bone; lung; lung; liver
El Kamar (18)	2004	56 (M)	Tail	IV	N	Y	N	6	Cerebrum, pons	N	N	N	0*	NR	CK7, CA19-9 positive; CK20, TTF-1 negative	NR
Caricato (19)	2006	65 (M)	Head	NR	Y	Y	Y	24	Cerebellum	Y	Y	N	16	NR	NR	Lymph node
Marepally (20)	2008	36 (F)	Tail	NR	Y	Y	N	11	Cerebellum	Y	N	N	NR*	NR	Adnab-9 monoclonal antibody positive	NR
Matsumura (21)	2009	64 (M)	Tail	IV (T4N2M0)	Y	Y	N	11	NR	Y	N	Y	22	NR	NR	Lymph node
Lemke (22)	2011	66 (M); 48 (F)	Tail; tail	II; I	Y; Y	Y; Y	Y; N	11; 64	Cerebrum; cerebellum	Y; Y	N; N	Y; Y	132; 132	NR; NR	NR; NR	Lymph nodes; liver
Rajappa (23)	2013	67 (M)	NR	NR	N	Y	N	48	Right occipital lobe, parieto-occipital lobe, right scapula, cerebellum, thalamus	Y	Y	Y	36*	NR	CK7, CK19, CA19-9, CDX2 positive; TTF-1, PSA negative	Liver, lung
Matsumoto (24)	2015	68 (M)	Head	IV (T3N1M1)	N	N	N	0	Temporoparietal	Y	N	N	3*	NR	CK7 positive; CK20, TTF-1 negative	NR
Yoo (25)	2015	80 (M)	Body	IV	N	N	N	0	Cerebellum, tempoparietal lobes, pineal gland	N	N	Y	NR*	NR	NR	Lymph nodes, liver
Johnson (26)	2018	53 (M)	Head	NR	N	Y	N	29	Cerebrum	N	Y	Y	9*	NR	CK7 positive; CK20, CEA, TTF-1 negative	Liver, spinal cord
Matsuo (27)	2019	60 (F)	Tail	NR	N	Y	N	16	Cerebellum	Y	N	N	0.75*	NR	NR	Lung
Sasaki (28)	2019	72 (F); 78 (M)	NR; NR	NR; NR	N; Y	Y; Y	N; N	19; 33	Frontal lobe; cerebrum	N; N	N; N	Y; N	13*; 1*	NR; NR	NR; NR	Liver; NR
Luu (29)	2020	51 (F); 46 (M)	NR; head	III (T3N1M1); III (T2N1M0)	Y; Y	N; Y	N; N	1; 20	Right frontal lobe; right occipital lobe	N; N	N; N	Y; Y	3*; 5*	NR; NR	NR; NR	NR; liver
Oka (30)	2021	68 (M)	Tail	IIA (T3N0M0)	Y	Y	N	8	Parietal lobe	Y	N	Y	NR*	NR	CAIX, MUC1, MUC5AC positive; CDX2, MUC2 negative	Lungs
Ou (31)	2021	34 (M)	Body and tail	NR	N	Y	N	12	NR	N	Y	N	12	Reciprocal *ALK* fusion, *ARID1B* del, *KEAP1* del, *AMER1* mut, *ATR* mut, *CCND2* mut, *CHEK1* mut, *CREBBP* mut, *ERCC4* mut, *IL7R* mut, *MRE11A* mut, *SETD2* mut	CK7, CK18, CK19, CA19-9, AE1/AE3, MUC5AC positive; CDX2, CK20, MUC6 negative	Lymph node
DeVito (32)	2021	43 (F)	Body and tail	IV	N	Y	N	12	Cerebellum	N	Y	Y	NR*	*KRAS* G12D, *TP53* mut, *ERBB2* amp	HER2 positive; MLH1, PMS2 negative	Lymph node, liver, lungs
Yim (33)	2022	Late 50s (F)	Head and body	NR	N	Y	N	10	Right occipital lobe	N	N	Y	0.75*	*BRIP1* germline mut	CK7, CK20, CDX2 positive; TTF negative	Liver and lymph nodes
Utsunomiya (34)	2022	64 (M)	Tail	III (T3N2M0)	Y	Y	N	29	Left frontal lobe, left cerebellum	Y	N	Y	6	*KRAS* G12C, *BRCA2* mut, *CDKN2A/B* loss, *MTAP* loss, *TP53* mut	CK7, CK19, CDX2 positive; S100 negative	Lymph nodes

Table 4 (*continued*)

Table 4 (*continued*)

First author	Publication year	Age (years) (sex)	PDAC location	Stage at PDAC dx	PDAC surgery	PDAC chemotherapy	PDAC radiation	Time to BrM dx (months)	BrM location	BrM surgery	BrM chemotherapy	BrM radiation	OS from BrM (months)	Genomics	Pathology	Synchronous metastases
Rajpal (35)	2022	73 (F)	NR	IV (T3N1M1)	Y	Y	Y	51	Frontal lobe	Y	N	Y	7*	NR	CK7, MUC1, CDX2, CK20 positive; TTF-1 negative	NR
Law (36)	2023	60s (F); 70s (M); 50s (F)	Head; neck; head	IB (ypT2N0); NR; IIB (ypT3N1)	Y; N; Y	Y; Y; Y	N; N; Y	9; 12; 72	Right frontal lobe; left parietal lobe; left parietal lobe, bilateral temporal lobes, vertebrae	Y; N; Y	N; Y; Y	Y; Y; Y	9; 24; 4*	NR; NR; NR	NR; NR; NR	NR; kidney; lung and bone
This publication	2026	69 (M)	Head	IV (TxNxM1)	N	Y	N	10	Cerebellum, frontal lobe, basal ganglia	Y	Y	Y	9	View *Table 1*	CDX2 positive (focal); CK7, CDK20, TTF1, Trypsin, Chymotrypsin, NKX3.1 negative	Lymph nodes, spine

*, death. BrM, brain metastasis; dx, diagnosis; F, female; M, male; N, no; NR, not reported; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; Y, yes.

diseases.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from the patient for publication of this case report and accompany images. A copy of the written consent is available for review by the editorial office.

References

1. Siegel RL, Kratzer TB, Giaquinto AN, et al. Cancer

statistics, 2025. CA Cancer J Clin 2025;75:10-45.
2. Quiñonero F, Mesas C, Doello K, et al. The challenge of drug resistance in pancreatic ductal adenocarcinoma: a current overview. Cancer Biol Med 2019;16:688-99.
3. Jiang Y, Sohal DPS. Pancreatic Adenocarcinoma Management. JCO Oncol Pract 2023;19:19-32.
4. Bazeed AY, Day CM, Garg S. Pancreatic Cancer: Challenges and Opportunities in Locoregional Therapies. Cancers (Basel) 2022;14:4257.
5. Schawkat K, Manning MA, Glickman JN, et al. Pancreatic Ductal Adenocarcinoma and Its Variants: Pearls and Perils. Radiographics 2020;40:1219-39.
6. Miquel M, Zhang S, Pilarsky C. Pre-clinical Models of Metastasis in Pancreatic Cancer. Front Cell Dev Biol 2021;9:748631.
7. Jiang K, Parker M, Materi J, et al. Epidemiology and survival outcomes of synchronous and metachronous brain metastases: a retrospective population-based study. Neurosurg Focus 2023;55:E3.
8. Lemke J, Scheele J, Kapapa T, et al. Brain metastases in gastrointestinal cancers: is there a role for surgery?. Int J Mol Sci 2014;15:16816-30.
9. Zaanan A, Lequoy M, Landi B, et al. Brain metastases from pancreatic adenocarcinoma. BMJ Case Rep 2009;2009:bcr08.
10. Park KS, Kim M, Park SH, et al. Nervous system involvement by pancreatic cancer. J Neurooncol 2003;63:313-6.
11. Tiriac H, Belleau P, Engle DD, et al. Organoid Profiling Identifies Common Responders to Chemotherapy in Pancreatic Cancer. Cancer Discov 2018;8:1112-29.
12. Demyan L, Habowski AN, Plenker D, et al. Pancreatic Cancer Patient-derived Organoids Can Predict Response to Neoadjuvant Chemotherapy. Ann Surg 2022;276:450-62.
13. Knox JJ, Jaffee EM, O'Kane GM, et al. PASS-01: Pancreatic adenocarcinoma signature stratification for treatment–01. J Clin Oncol 2022;40:TPS635.
14. Gallo D, Young JTF, Fourtounis J, et al. CCNE1 amplification is synthetic lethal with PKMYT1 kinase inhibition. Nature 2022;604:749-56.
15. Tougeron D, Lecomte T, Pagès JC, et al. Effect of low-frequency KRAS mutations on the response to anti-EGFR therapy in metastatic colorectal cancer. Ann Oncol 2013;24:1267-73.
16. Kwiatkowski DJ, Choueiri TK, Fay AP, et al. Mutations in TSC1, TSC2, and MTOR Are Associated with Response to Rapalogs in Patients with Metastatic Renal Cell Carcinoma. Clin Cancer Res 2016;22:2445-52.
17. Lee YT, Tatter D. Carcinoma of the pancreas and periampullary structures. Pattern of metastasis at autopsy. Arch Pathol Lab Med 1984;108:584-7.
18. El Kamar FG, Jindal K, Grossbard ML, et al. Pancreatic carcinoma with brain metastases: case report and literature review. Dig Liver Dis 2004;36:355-60.
19. Caricato M, Borzomati D, Ausania F, et al. Cerebellar metastasis from pancreatic adenocarcinoma. A case report. Pancreatology 2006;6:306-8.
20. Marepaily R, Micheals D, Sloan A, et al. Octreotide uptake in intracranial metastasis of pancreatic ductal adenocarcinoma origin in a patient with a prolonged clinical course. Dig Dis Sci 2009;54:188-90.
21. Matsumura T, Ohzato H, Yamamoto T, et al. A case of postoperative brain metastasis originated from pancreatic cancer which was successfully treated by resection and postoperative irradiation. Gan To Kagaku Ryoho 2009;36:2433-5.
22. Lemke J, Barth TF, Juchems M, et al. Long-term survival following resection of brain metastases from pancreatic cancer. Anticancer Res 2011;31:4599-603.
23. Rajappa P, Margetis K, Wernicke G, et al. Stereotactic radiosurgery plays a critical role in enhancing long-term survival in a patient with pancreatic cancer metastatic to the brain. Anticancer Res 2013;33:3899-903.
24. Matsumoto H, Yoshida Y. Brain metastasis from pancreatic cancer: A case report and literature review. Asian J Neurosurg 2015;10:35-9.
25. Yoo IK, Lee HS, Kim CD, et al. Rare case of pancreatic cancer with leptomeningeal carcinomatosis. World J Gastroenterol 2015;21:1020-3.
26. Johnson WR, Theeler BJ, Van Echo D, et al. Treatment of Leptomeningeal Carcinomatosis in a Patient with Metastatic Pancreatic Cancer: A Case Report and Review of the Literature. Case Rep Oncol 2018;11:281-8.
27. Matsuo S, Amano T, Kawauchi S, et al. Multiple Brain Metastases from Pancreatic Adenocarcinoma Manifesting with Simultaneous Intratumoral Hemorrhages. World Neurosurg 2019;123:221-5.
28. Sasaki T, Sato T, Nakai Y, et al. Brain metastasis in pancreatic cancer: Two case reports. Medicine (Baltimore) 2019;98:e14227.
29. Luu AM, Künzli B, Hoehn P, et al. Prognostic value and impact of cerebral metastases in pancreatic cancer. Acta Chir Belg 2020;120:30-4.
30. Oka Y, Takano S, Kouchi Y, et al. Simultaneous brain and lung metastases of pancreatic ductal adenocarcinoma after curative pancreatectomy: a case report and literature

review. BMC Gastroenterol 2021;21:9.
31. Ou K, Liu X, Li W, et al. ALK Rearrangement-Positive Pancreatic Cancer with Brain Metastasis Has Remarkable Response to ALK Inhibitors: A Case Report. Front Oncol 2021;11:724815.
32. DeVito NC, Kelleher C, Strickland KC, et al. A case report of microsatellite instability (MSI)-high, HER2 amplified pancreatic adenocarcinoma with central nervous system metastasis. AME Case Rep 2021;5:14.
33. Yim E, Leung D. Leptomeningeal disease in BRIP1-mutated pancreatic adenocarcinoma. BMJ Case Rep 2022;15:e249837.
34. Utsunomiya T, Funamizu N, Ozaki E, et al. A case of radical resection for brain metastases of pancreatic cancer after curative chemotherapy for para-aortic lymph node metastases. Surg Case Rep 2022;8:108.
35. Rajpal S, Taha HB, Kvascevicius L, et al. A Rare Case of Brain Metastases in an Elderly Patient With Primary Pancreatic Cancer. Cureus 2022;14:e27578.
36. Law NC, Lomma C. Pancreatic adenocarcinoma with brain metastases. BMJ Case Rep 2023;16:e253557.
37. Singh H, Keller RB, Kapner KS, et al. Oncogenic Drivers and Therapeutic Vulnerabilities in KRAS Wild-Type Pancreatic Cancer. Clin Cancer Res 2023;29:4627-43.
38. Jordan EJ, Lowery MA, Basturk O, et al. Brain Metastases in Pancreatic Ductal Adenocarcinoma: Assessment of Molecular Genotype-Phenotype Features-An Entity With an Increasing Incidence?. Clin Colorectal Cancer 2018;17:e315-21.
39. Skakodub A, Walch H, Tringale KR, et al. Genomic analysis and clinical correlations of non-small cell lung cancer brain metastasis. Nat Commun 2023;14:4980.
40. Tomasich E, Steindl A, Paiato C, et al. Frequent Overexpression of HER3 in Brain Metastases from Breast and Lung Cancer. Clin Cancer Res 2023;29:3225-36.
41. Momeny M, Saunus JM, Marturana F, et al. Heregulin-HER3-HER2 signaling promotes matrix metalloproteinase-dependent blood-brain-barrier transendothelial migration of human breast cancer cell lines. Oncotarget 2015;6:3932-46.
42. Chen X, Bai K, Zhang Y, et al. Genomic alterations of cerebrospinal fluid cell-free DNA in leptomeningeal metastases of gastric cancer. J Transl Med 2023;21:296.
43. Habowski AN, Patel H, Tsang C, et al. Abstract 5998: Patient-derived organoids and precision medicine: Insights from the PASS-01 clinical trial in PDAC. Cancer Res 2025;85:5998.

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