



Complete pathological response to pembrolizumab in pretreated pancreatic acinar cell carcinoma

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Abstract

Background Therapeutic approach used for pancreatic ductal adenocarcinoma is usually translated also for the rarer acinar counterpart, which shows a different mutational landscape nevertheless. While dMMR/MSI-H status is rare in the ductal histotype, it appears to be more prevalent in pancreatic acinar cell carcinoma (PACC).

Case presentation We report the case of a patient with locally advanced MSI-H PACC in whom the treatment with the anti-PD-1 pembrolizumab, administered as third line, made possible surgical resection, achieving even an exceptional pathological complete response.

Conclusions Treatment of PACC should be tailored based on the peculiar molecular features that distinguish PACC from ductal adenocarcinoma. Evaluation of potentially therapeutically targetable alterations should be mandatory in case of PACC diagnosis.

Keywords Pancreatic cancer · Immunotherapy · Acinar cell carcinoma · pCR · Surgical resection · Neoadjuvant therapy

Introduction

Pancreatic acinar cell carcinoma (PACC) constitutes only 1–2% of exocrine pancreatic tumors, despite acinar cells being predominant in pancreatic tissue compared to the ductal counterpart (Klimstra 2007).

The incidence of PACC has a bimodal distribution with peaks at 8–15 and 60 years (Lack et al. 1983). Males are affected three times more often (Schmidt et al. 2008).

Patients diagnosed with PACC typically manifest non-specific symptoms, such as weight loss, pain, nausea, and vomiting, while jaundice is relatively uncommon (Calimano-Ramirez et al. 2022). Lipase hypersecretion can cause the "Schmid's Triad", characterized by subcutaneous fat necrosis, polyarthralgia, and eosinophilia (Schmid 1957).

PACC tumors are solid, well-circumscribed, and often bulky tumors, and are most frequently localized in the pancreatic head (Qu et al. 2022). Larger lesions may present necrosis, cystic changes and intratumoral haemorrhage. Approximately half of tumors show local invasion of the surrounding organs and a similar proportion of patients present with metastatic dissemination, more often to the liver, peritoneum and distant lymph nodes (Rosa et al. 2012; Takahashi et al. 2021). Microscopically, PACC is characterized by minimal stroma and a predominant acinar or solid architecture. Immunohistochemical staining for pancreatic enzymes, including trypsin, chymotrypsin, elastase, or lipase, supports the histological diagnosis (Klimstra et al.

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1992). Bcl-10 can also be used for identifying acinar cell differentiation.

Patients affected by PACC may exhibit elevated levels of carbohydrate antigen 19–9 (CA-19.9), alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA), besides serum lipase increase (Calimano-Ramirez et al. 2022).

Different molecular pathways are involved in PACC tumorigenesis compared to pancreatic ductal adenocarcinoma (PDAC). Key PDAC carcinogenesis genes are less frequently mutated in PACC, such as p53 (13.7%), SMAD4 (15.1%), p16 (11.6%), or rarely altered, such as KRAS (3.8%) (Florou et al. 2023; Moore et al. 2001; Wilde et al. 2011; Jiao et al. 2014). Activation of the Wnt pathway, including APC inactivating mutations and CTNNB1 activating mutations, has been reported in about 20% of cases (Abraham et al. 2002). Chromosomal instability also characterizes PACC, partly explaining reported resistance to therapy (Jiao et al. 2014; Butturini et al. 2011). Notably, more than one-third of PACC exhibit potentially therapeutically targetable alterations, including BRCA1, BRCA2, PALB2, ATM, BAP1, BRAF and ALK (Jiao et al. 2014; Kryklyva et al. 2019). Some series report over half of PACC cases harbouring germline pathogenic variant affecting homologous recombination and DNA damage response genes (Mandelker et al. 2023). BRAF and RAF1 alterations, observed in about 23% of PACC, are mutually exclusive with inactivating mutations in DNA repair genes (Chmielecki et al. 2014). A variable proportion ranging from 2.1% to 14% of PACC exhibits microsatellite instability (MSI)/defective mismatch repair (dMMR) (Ikezawa et al. 2023; Luchini and Scarpa 2023).

The prognosis of this rare pancreatic cancer subtype is generally better than that of PDAC, with a 5-year survival rate of about 21–43% (Ikezawa et al. 2023). Surgical resection is recommended for localized disease and is associated with longer survival in various series (Holen et al. 2002; Distler et al. 2009).

Limited data guide optimal PACC treatment. In the absence of randomized trials for this subtype, patients with advanced PACC are typically treated with the same chemotherapeutic regimens as PDAC. Some retrospective evidence suggests higher response rates to fluoropyrimidines, particularly in oxaliplatin-based regimens, compared to gemcitabine-based therapies (Butturini et al. 2011; Lowery et al. 2019; Kruger et al. 2016; Yoo et al. 2017). The role of adjuvant treatment remains controversial, and no guidelines are available. Neoadjuvant strategies also lack prospective studies.

Genomic profiling evidence supports a high fraction of druggable targets in PACC. Tailored approaches, such as BRAF, ALK and NTRK inhibition, have shown generally good results (Florou et al. 2023; Li et al. 2018; Cramer et al. 2020; Gaule et al. 2022; Gupta et al. 2021).

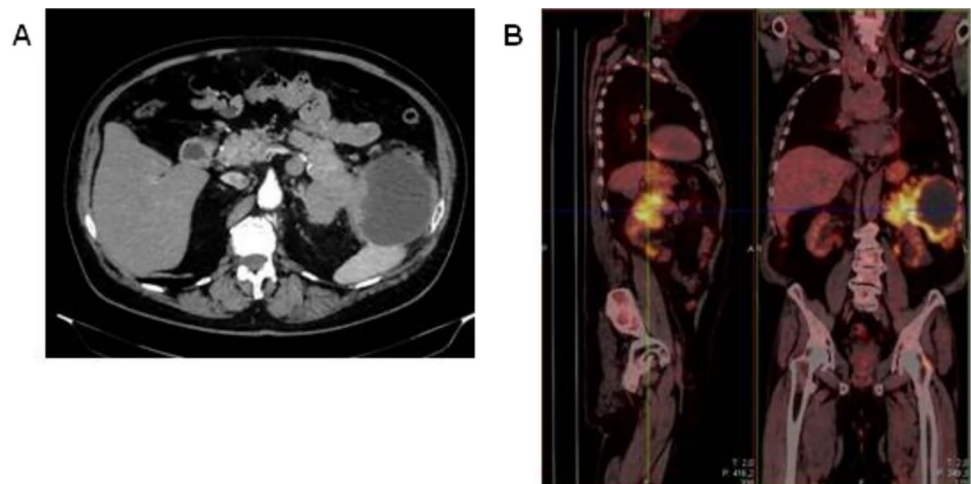
Here, we present the first reported case of a patient with microsatellite instable PACC achieving a pathological complete response to anti-PD1 therapy.

Case Presentation

A 69-year-old man presented with abdominal pain, dyspepsia and hyporexia, leading to diagnosis of PACC. His medical history included hypertension and hypercholesterolemia, and he was an active smoker (50 pack-years). Family history indicated unspecified tumors in his grandmother and uncle.

Computed tomography (CT) revealed confluent masses with a central hypodense component, occupying an area of 15 cm in the pancreatic tail. This lesion appeared not dissociable from the ascending colon, bordered the large gastric curvature, the left adrenal gland, the spleen and the abdominal wall (Fig. 1A). Gross locoregional lymphadenopathies were shown. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) confirmed an extensive hypermetabolic

Fig. 1 CT (A) and PET (B) scans at baseline



infiltrating neoplastic mass, with locoregional lymph nodal metastases (Fig. 1B). The patient underwent endoscopic ultrasonography with fine-needle aspiration (EUS-FNA). The cytological examination revealed the diagnosis of pancreatic acinar adenocarcinoma, supported by immunohistochemical positivity for BCL-10 and negativity for chromogranin A and synaptophysin (Fig. 2A–D). CEA resulted over the upper limit, while CA-19.9 and AFP showed normal levels.

After multidisciplinary evaluation, the patient was offered a neoadjuvant treatment with combined chemotherapy with oxaliplatin, irinotecan, folinic acid and fluorouracil (mFOLFIRINOX). After six chemotherapy courses, an imaging re-evaluation with CT scan and PET

revealed a stable disease. Given the neoadjuvant intent of the treatment and considering the increasing CEA levels, the patient was switched to a combination regimen with gemcitabine plus nab-paclitaxel. Unfortunately, after three months a progression of primary tumor was detected by the imaging. The patient worsened, showing asthenia, dysphagia and hyporexia.

Given the absence of other efficacious therapies and the proportion of targetable alterations in PACC, the patient was candidate to next generation sequencing (NGS) analysis through liquid biopsy. FoundationOne Liquid CDx assay revealed MLH1 mutation and MSI-high status. Thirty-two mutations per Mb was the blood tumor mutational burden. A complete report of the NGS assay is reported in Table 1.

Fig. 2 Pathological features of the tumor. **A–D** cytologic specimen at the time of diagnosis; **A** Hypercellular cytologic smear (Hematoxylin–eosin rapid stain, original magnification 40X). **B, D** Cell block showing numerous neoplastic cell with round nuclei and eosinophilic cytoplasm; on the left normal pancreatic parenchyma (**B** Hematoxylin–eosin, original magnification 10X; **C** Bcl-10, original magnification 10X; **D** Synaptophysin, original magnification 10X). **E–F**: surgical specimen. **E** Tumor bed (Hematoxylin–eosin, original magnification 4X). **F** Lymph node with response to therapy (Hematoxylin–eosin, original magnification 2X). (magnification, ×20)

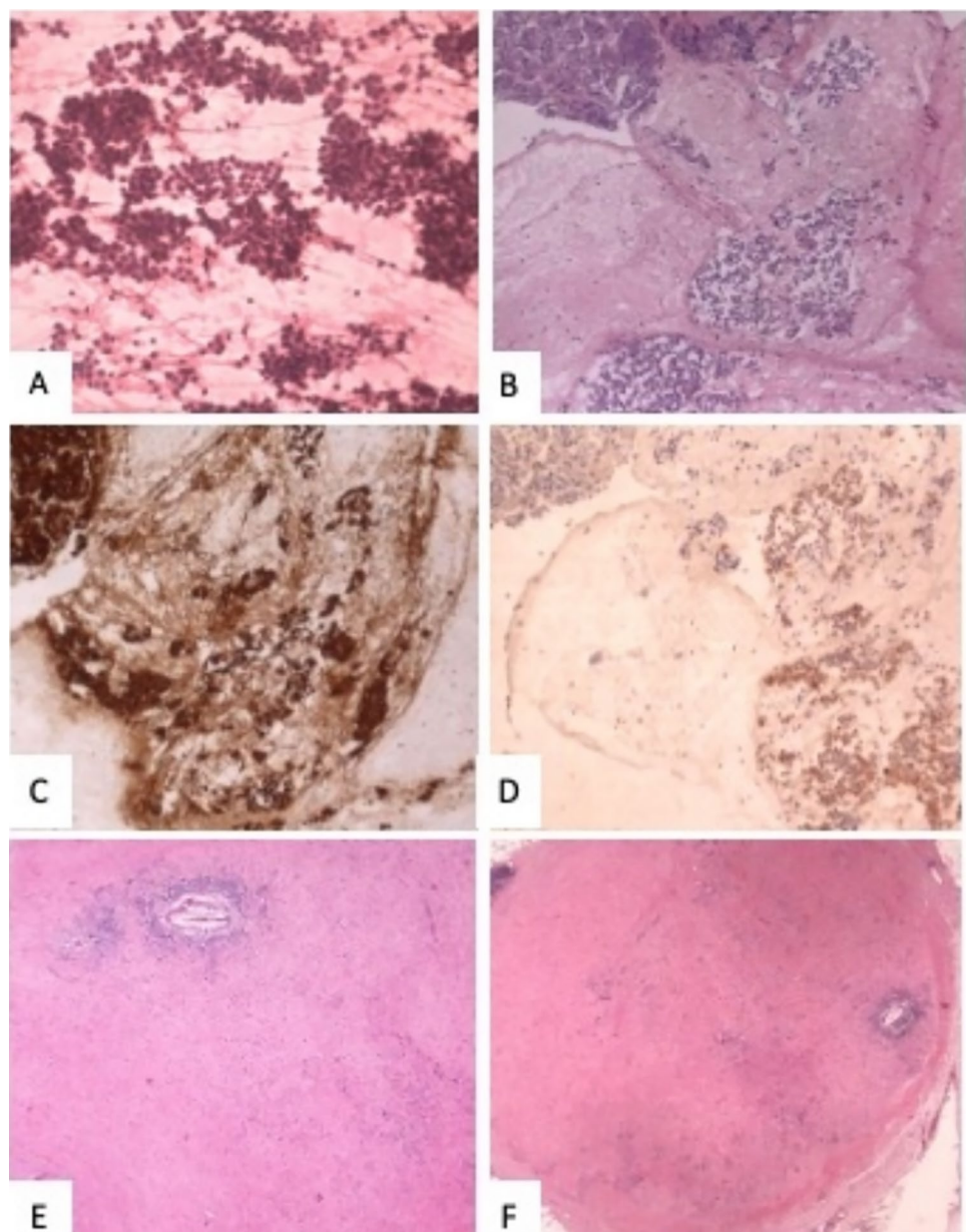


Table 1 Gene alterations identified with NGS assay

Altered gene	Gene alteration	VAF%
PI3KCA	E545D	4.2
ARID1A	Q1519fs*8	0.88
CTNNB1	D32Y	8.5
PTCH1	R1308fs*64	13.0
RAF1	rearrangement intron 7	4.0
ASXL1	G645fs*58	14.2
BCORL1	P1681fs*20	1.1
BRD4	Q256fs*27	8.9
CDH1	splice site 163 + 1G > A	0.61
CREBBP	splice site 3836 + 1G > A	7.5
JAK1	K860fs*16	0.46
MLH1	E178fs*24	8.8
RB1	R73fs*36	10.1
TP53	R181H	11.3
	A138V	7.6
	E294fs*51	0.85

VAF% variant allele frequency percentage

Given its activity in patients with MSI, pembrolizumab can be considered in these cases. The agnostic use of this immune checkpoint inhibitor is recognized by FDA, but not by EMA. Although in Italy pembrolizumab use in MSI patients with pancreatic cancer is possible only in off-label

indication, it was proposed to this patient. After the first administration symptoms reported by the patient improved already and CEA levels rapidly dropped. The CT scan after 4 administrations of pembrolizumab demonstrated size reduction of the polylobate mass and of the solid-cystic component (Fig. 3). The subsequent CT scans after 10 and 15 cycles revealed further response (Fig. 3). Given the clinical improvement and both radiological and biochemical response, after multidisciplinary evaluation, the patient was proposed for surgery after 17 cycles of pembrolizumab. He underwent left subtotal splenopancreatectomy with extended resection of the retroperitoneum and of the left adrenal gland (radical antegrade modular pancreateosplenectomy, RAMPS). The histological examination of the surgical specimen demonstrated a pathological complete response (pCR), with 0 tumor regression grade according to modified Ryan score (Fig. 2E). Twenty lymph nodes were removed and six of them showed response to therapy (Fig. 2F). A large area of dense and loose fibrosis was found up to the capsule of the pseudocyst.

At the time of the present report, six months after surgery, the patient is alive and disease-free, undergoing periodic imaging evaluations.

The patient performed a genetic testing because of the somatic MLH1 mutation observed. However, Lynch syndrome was not detected, and no germinal alterations have been identified in a panel of 25 genes.

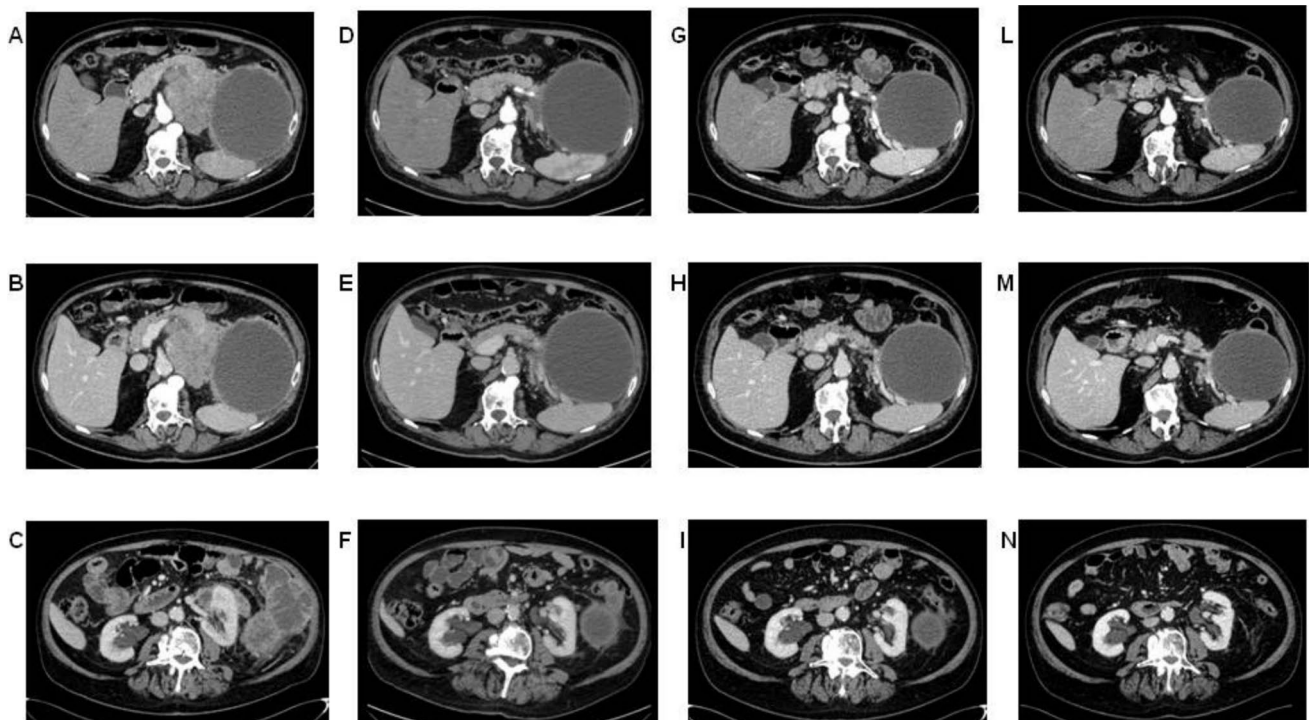


Fig. 3 CT scans after two lines of chemotherapy, before the start of pembrolizumab (A, B, C). CT scans after 3 months (D, E, F), after 6 months (G, H, I) and after 10 months (L, M, N) of pembrolizumab

Discussion

Currently, main international guidelines do not recommend performing NGS in pancreatic cancer, including in subtypes such as PACC (Mosele et al. 2020). However, PACC differs from the more common PDAC in its genomic profile, with a significant proportion of PACC exhibiting potentially targetable genetic alterations or MMR alterations (Florou et al. 2023; Chmielecki et al. 2014).

Based on this evidence, we performed NGS in our patient with advanced pre-treated PACC. Despite the failure of two chemotherapeutic regimens, the disease remained localized, prompting the search for an active therapy able to cytorreduces the mass. The liquid biopsy detected an MSI status determined by MLH1 mutation. Consequently, we opted for pembrolizumab, resulting in a rapid radiological response with improvement in clinical conditions. The most compelling result was the absence of tumor cells in the histologic examination of the surgical specimen.

MSI status can be tested by immunohistochemistry for mismatch repair proteins MLH1, PMS2, MSH2, and MSH6, PCR-based micro-satellite testing or NGS-based approaches (Luchini and Scarpa 2023). While dMMR/MSI-H status is rare in PDAC (1–2%), it appears more prevalent in PACC, ranging from 2.1 to 14% (Luchini and Scarpa 2023; Rosa et al. 2015). Available data are resumed in Table 2.

Tumors with MSI/dMMR tumors are known to be sensitive to immunotherapeutic agents. In the 2023 U.S. Food and Drug Administration (FDA) granted full approval of pembrolizumab for the treatment of unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment (FDA 2023). Although the European Medicines Agency (EMA) did not provide a similar agnostic indication, this immune checkpoint inhibitor is approved for some subgroups of MSI or dMMR tumors ([https://www.ema.europa.eu, en, documents, product-information, keytruda-epar-product-information_en.pdf](https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf). xxxx).

The FDA's approval of pembrolizumab was based on data from patients with MSI-H or dMMR cancer enrolled

in five multicenter, single-group clinical trials (Lemery et al. 2017). Among 59 patients with a cancer different than colorectal cancer, six had a pancreatic cancer with a response rate 83%.

Despite the low mutational load and the immune milieu limiting the activity of immunotherapy in pancreatic cancer, MSI pancreatic tumors exhibit a higher infiltration of CD8+ T cells and higher PD-1 and PD-L1 expression compared to the microsatellite stable ones (Ghidini et al. 2021). The majority of MSI/dMMR PDAC also show high TMB (Hu et al. 2018). Nevertheless, high TMB has also been suggested as a predictive marker of response to immunotherapy in PDAC (Lawlor et al. 2021).

Conflicting results have been observed regarding the activity of checkpoint inhibitors in MSI-H PDAC. In the phase II KEYNOTE-158 trial, the objective response rate with pembrolizumab in the subgroup of 22 PDAC patients was only 18.2%, although the duration of response was not reached at last follow up (Maio et al. 2022). However, various other case reports and series have described impressive and durable responses to immunotherapy in MSI-H PDAC patients (Lemery et al. 2017; Hu et al. 2018; Pothuri et al. 2021; Coston et al. 2023).

To our knowledge, this is the first reported case in literature of a patient with PACC in whom the treatment with pembrolizumab, administered in a later therapy (after almost two years from the treatment start), made possible a surgery approach in an upfront unresectable disease, achieving even a pathological complete response. The pathological complete response rate usually occurs infrequently in pancreatic cancer patients: in a recent real-world report on 274 PDAC patients treated with mFOLFIRINOX or with gemcitabine/nab-paclitaxel combination only 13 (6%) patients achieved a pathological complete response (Macedo et al. 2019). In our PACC patient, these chemotherapeutic regimens failed to control the locally advanced disease, while third-line immunotherapy was able to produce a pathological complete response. Patients with MSI tumors within Lynch syndrome are usually more likely to respond to immune checkpoint inhibitors. The exceptional response in the present case is not explained by a germline mutation in MMR genes instead. Furthermore, our case report suggests that immune checkpoint inhibitor could be more active in dMMR/MSI-H PACC than in dMMR/MSI-H PDAC.

The mutational landscape of PACC is significantly different from PDAC, with a higher proportion of MMR pathway alterations. In the presence of a diagnosis of PACC, it could be advisable to test MSI status and other targetable alterations to orient the therapeutic choice. The activity of immunotherapeutic agents in this setting is suggested to be remarkable.

Table 2 Studies reporting dMMR/MSI prevalence in PACC

Ref	Number of patients analyzed for MSI	Proportion of MSI-H
Abraham et al. (2002)	13	7%
Liu et al. (2014)	36	14%
Bergmann et al. (2014)	42	4.8
Florou et al. (2023)	51	2.1
Sakakida et al. (2023)	44	2.6

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Data availability Data used during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Informed consent Informed consent was obtained from the patient before the proceedings of the report.

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