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Case Report

Metastatic Pancreatic Adenocarcinoma Downstaged to T0N0 with Chemotherapy and Targeted Therapy, Confirmed by Surgical Pathology: A Case Report

Bach Ardalan[a] Alan Livingstone[b] Dido Franceschi[b] Danny Sleeman[b]
Jose Azqueta[a] Rosali Gonzalez[a] Jonathan England[c]

[a]Department of Medical Oncology, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [b]Department of Surgical Oncology, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [c]Department of Pathology, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA

Keywords
Solitary metastasis · Pancreatic adenocarcinoma · Complete response

Abstract
Introduction: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive human tumor that is typically diagnosed at a later stage when surgery is not possible. ***Case Presentation:*** We report the case of a 62-year-old woman who presented to the emergency department with abdominal pain. Computed tomography (CT) revealed a solitary hepatic lesion and a pancreatic body lesion. The pancreatic body lesion was biopsied endoscopically, and a tissue diagnosis was obtained to confirm the diagnosis of PDAC. She was then treated with 12 cycles of FOLFIRINOX with stable disease on CT. Due to the history of a hepatic lesion, she received 11 cycles of gemcitabine/Abraxane and a combination of a MEK inhibitor, Mekinist, and a BRAF inhibitor, BRAFTOVI. Subsequently, the patient underwent a liver biopsy. The biopsy result was negative, and the tumor was deemed resectable. The patient underwent a distal pancreatectomy. Surgical pathology demonstrated a 1.1-cm low-grade papillary mucinous neoplasm with negative margins and lymph nodes, staged T0N0. Adjuvant chemotherapy was not administered. ***Conclusion:*** To our knowledge, this is the first report of a patient with metastatic pancreatic adenocarcinoma who received prolonged IV and oral chemotherapy. At the time of the operation, the pathological stage was T0N0. The patient has recently been seen 9 months after surgery with no evidence cancer recurrence. Additionally, ctDNA remains negative.

Correspondence to:
Bach Ardalan, bardalan@med.miami.edu

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Background

In 2023, pancreatic cancer was the third leading cause of death in both sexes. In 2015, over 66,440 people were diagnosed with this malignancy, with an annual incidence increase of 1% [1]. It is estimated that by 2030, pancreatic cancer will be the second leading cause of death in the USA [2]. Currently, surgery is the only curative method, with 5-year survival rate of no more than 20% in patients with negative resection margins [3].

Currently, there are two standard lines of chemotherapy for advanced pancreatic cancer: FOLFIRINOX and Gemzar and Abraxane. The overall survival benefit is approximately 1 year [4]. Oncogenic mutations in the KRAS gene are present in over 90% of pancreatic tumors. Mutations most commonly occur on codon 12, and the three most common mutations are KRAS G12D (c.35G>A), KRAS G12V (c.35G>T), and KRAS G12R (c.34G>C) [5].

It has recently been reported that the addition of an MEK inhibitor to the standard chemotherapy regimen significantly increases the survival of pancreatic cancer patients expressing KRAS G12R mutation on codon 12 [6]. Our recent study has further supported the survival benefit of pancreatic patients who have expressed KRAS G12R mutation and were treated with chemotherapy and a MEK inhibitor [7]. Our patient had a KRAS G12R-mutated tumor, and she was treated with a combination of a MEK inhibitor, Mekinist, and a BRAF inhibitor, BRAFTOVI, with concurrent IV chemotherapy. The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539776).

Case Presentation

A 62-year-old woman with a medical history of hypertension, mitral valve prolapse, postoperative hysterectomy, and tubal ligation developed severe abdominal pain. No emesis reported. She presented to her local emergency room where her lipase levels were elevated to 2,914 units/L. The patient underwent an upper endoscopy, which yielded negative results. At that time, she noted a 10-lb unexpected weight loss in the past 2 months. She had a family history of pancreatic cancer on the paternal side and BRCA-negative breast cancer on the maternal side. She denies any history of acute pancreatitis.

A workup was performed, and magnetic resonance cholangiopancreatography revealed dilatation of the pancreatic duct in the body and tail of the pancreas. Focal lesions were not observed. Endoscopic ultrasound revealed a pancreatic tumor, which was positive for pancreatic ductal adenocarcinoma (PDAC) (Fig. 1a).

Subsequently, baseline imaging was performed to determine the extent of disease. Her initial computed tomography (CT) scan in July 2022 showed a lesion in the hepatic dome, measuring 1.9 cm, most likely metastatic disease (Fig. 2a). An initial PET scan performed in October 2022 demonstrated intense FDG activity in the distal body of the pancreas (Fig. 3a).

After 12 treatments with FOLFIRINOX, follow-up CT and PET scans were performed. CT revealed an unchanged pancreatic lesion with stable disease. There was no evidence of any new metastatic disease in the chest, abdomen, or pelvis. In addition, the previously observed liver lesion was no longer visible on the scan.

The patient was then presented to a multidisciplinary tumor board for further recommendations. Due to a suspicious hepatic lesion that was initially observed and subsequently disappeared on therapy, she was deemed unresectable. The patient was recommended to continue further chemotherapy.

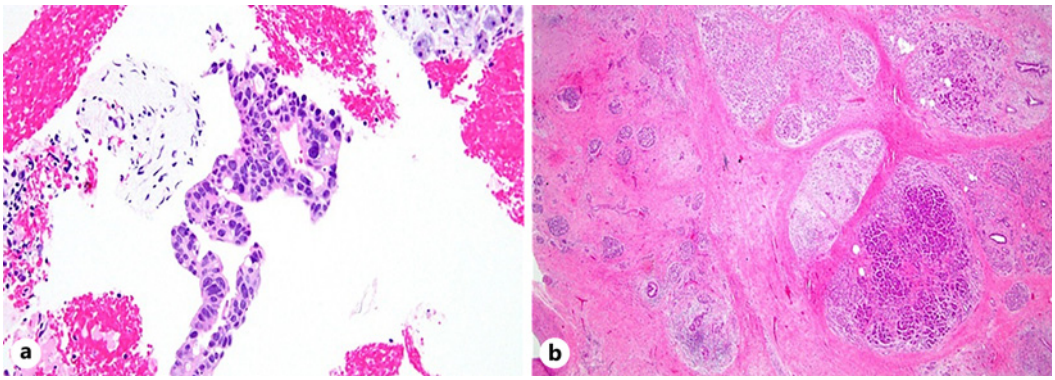

Fig. 1. a Endoscopic biopsies of the pancreatic mass showed infiltrating neoplastic glands within hyalinized stroma as well as clusters of irregular duct-like structures with marked nuclear pleomorphism, diagnostic of moderately differentiated PDAC. **b** Extensive sampling of the pancreaticoduodenectomy (Whipple) specimen showed no evidence of residual PDAC but instead broad areas of fibrosis with scattered inflammatory cells and atrophic acinar lobules with islet cell hyperplasia, compatible with treatment effect.

She received Gemzar and Abraxane therapy with oral chemotherapy, Mekinist 2 mg QD, and BRAFTOVI 75 mg twice daily. The addition of oral medication resulted in grade II hypertension and a macular papillary rash on her face, and grade III lethargy was observed. The oral chemotherapy regimen was modified as follows: oral chemotherapy was administered on weekdays only, with weekends off. Upon completion of 11 treatments with Gemzar and Abraxane chemotherapy, CT scan and PET were performed. CT did not show any evidence of metastatic disease in the liver (Fig. 2b). The pancreatic body lesion was largely stable. PET showed normal uptake throughout the pancreas without evidence of metastatic disease in the chest, abdomen, or pelvis (Fig. 3b). Surgery was recommended to the patient.

The patient underwent a distal pancreatectomy. Surgical pathology revealed a low-grade papillary mucinous neoplasm showing no residual/persistent adenocarcinoma, 1.1 cm in the greatest dimension, twenty-three lymph nodes, negative for carcinoma (0/23), and negative surgical margins. The patient was staged as T0N0 (Fig. 1b). The initial CA19-9 level was greater than 125 U/mL and was subsequently reduced to near normal levels on FOLFIRINOX after 6 months of therapy. Thereafter, on Gemzar, Abraxane, and oral chemotherapy, it was maintained at near normal levels. At the time of surgery and the subsequent 9 months, it has remained at a normal level consistent in keeping with no evidence of recurrent disease.

Given that the patient had multiple cycles of therapy (23 total, 12 treatments of FOLFIRINOX and 11 treatments of Gemzar and Abraxane), no adjuvant chemotherapy was recommended. The patient has subsequently been seen every 3 months with no recurrence of cancer on CT and a negative ctDNA laboratory result. The plan is to keep the patient on a surveillance protocol. At the time of submission of this manuscript, the patient is nine from the time of surgery.

Discussion

Pancreatic cancer is known to have a high mortality rate and poor prognosis. Commonly presented as PDAC, it has only a 5-year survival rate of approximately 20% [3]. It is an incurable cancer, with a survivorship of approximately 6–12 months following diagnosis [3]. Multiagent chemotherapy remains the backbone of treatment for patients with PDAC. FOLFIRINOX that consists of 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan (Campostar) as well as gemcitabine

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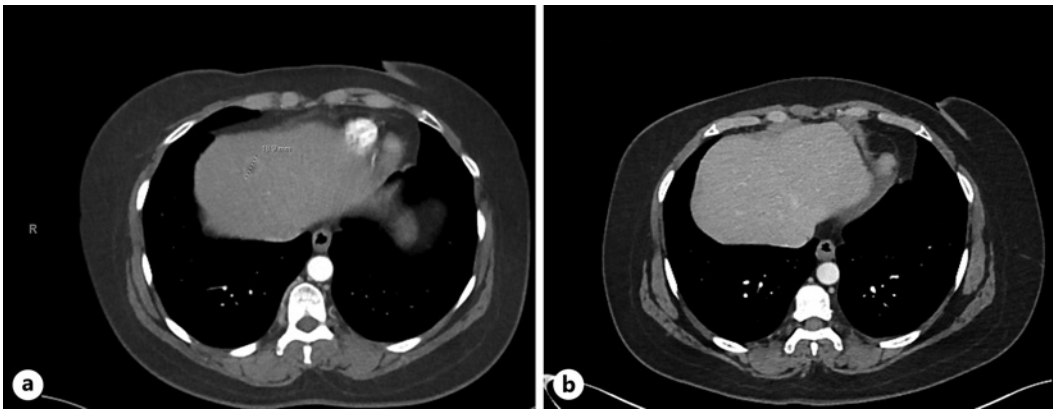

Fig. 2. a Baseline CT scan performed on July 2022 showing a hepatic lesion with rim enhancement measuring 1.9 cm. **b** CT scan performed a year later on August 2023 showing lesion no longer present.

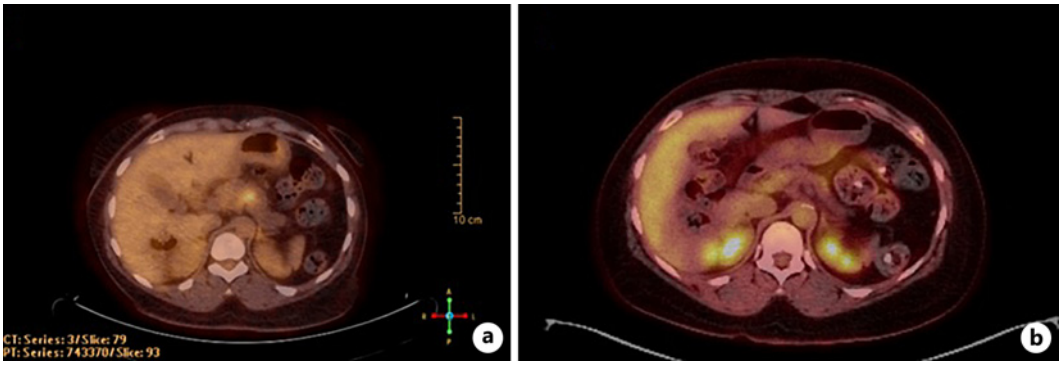

Fig. 3. a October 2022 PET/CT scan showing FDG activity of the distal body lesion. **b** Repeat PET/CT June 2023 PET/CT scan showing activity of the pancreatic body lesion. The interim PET/CT scan showed no change.

(Gemzar) and protein-bound paclitaxel (Abraxane) are the chemotherapy drugs being used for treatment [8]. Therefore, new strategies are needed to improve patient survival. Common tumor suppressor and oncogene mutations involved in PDAC include K-RAS, TP53, CDKN2A, and SMAD4. The mutational frequency of these genes ranges from 50 to 98% in PDAC [9]. KRAS is the dominant mutation present in 84% of all RAS-mutant cancers, with a near 100% KRAS mutation frequency in PDAC. Typically mutated at codon glycine-12 (G12X), KRAS mutants have X isoforms ranging from D, V, R, C, and S. G12D, and G12V mutants are the most common amino acid substitutions. Targeted therapy agents can be added to treatment [10]. These regimens include BRAF inhibition with encorafenib (BRAFTOVI) and MEK inhibition with trametinib (Mekinist) or cobimetinib [9]. These two oral agents are commonly used in the treatment of melanoma [11].

In this case report, our patient was genetically characterized as KRAS G12R-mutated and BRCA2-negative by liquid biopsy. We attempted to send the tumor sample for next-generation sequencing; however, there was an insufficient amount of sample available for a comprehensive genetic report. Upon presentation, our patient was categorized as having stage 4 disease, with a metastatic site in the liver. The patient received 12 cycles of FOLFIRINOX which led to stabilization of the primary pancreatic mass and the radiological disappearance of the liver metastasis. At that time, the tumor was deemed unresectable. Additionally, she received

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11 treatments of Gemzar and Abraxane, with oral chemotherapy of Mekinist 2 mg QD and BRAFTOVI 75 mg twice daily. The patient was then restaged.

The liver metastasis had disappeared, and the pancreatic lesion was deemed resectable. A biopsy of the presumed liver involvement was normal, and the patient was deemed resectable. Pathology of the distal pancreatectomy showed no evidence of carcinoma. She was staged T0N0. Following surgery, ctDNA examination was ordered at the 3-month mark and was negative.

In our previous investigations, we categorically defined the different subsets of the KRAS oncogene on codon 12. We recently published a large retrospective study of over 5,000 patients with pancreatic cancer whose KRAS mutations were determined by genetic sequencing of available tumors samples. Patients with G12D mutations had significantly lower overall survival rates as compared to the G12R-mutated patient cohort [12].

Several factors likely played a role in our patient achieving a full pathological response. First, she presented with a minimal disease burden, both in her primary tumor and metastatic site. Second, she underwent both standard-of-care treatments over an extended 1-year period. Additionally, her KRAS G12R mutation is associated with a potentially enhanced overall survival compared to other KRAS G12 mutations. Lastly, she received concurrent IV chemotherapy along with BRAF and MEK inhibitors to effectively target the MAPK pathway.

Besides the standard of care, multiple other therapies have been attempted but have not been found to be successful in the treatment of pancreatic adenocarcinoma [13, 14]. Identifying further biomarkers that predict the clinical outcome of patients is imperative and may lead to improved treatment with novel investigational agents.

Conclusion

To our knowledge, this is the first report of a patient with metastatic pancreatic adenocarcinoma who received prolonged IV and oral chemotherapy. At the time of the operation, the pathological stage was T0N0. The patient has recently been seen nine months after surgery with no evidence of cancer recurrence. Additionally, ctDNA remains negative.

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We would like to thank our patient for their cooperation and consent in writing this paper. We would also like to dedicate this paper in memory of Andrew Conrad Ackemann, who died of pancreatic cancer.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and accompanying images. The completed consent report is available from the editor of the journal upon request.

Conflict of Interest Statement

The authors of this manuscript have no conflicts of interest to declare.

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Author Contributions

Bach Ardalan and Danny Sleeman were directly involved in patient care. Jonathan England reviewed the pathology and took photographs for this publication. Bach Ardalan, Jose Azqueta, and Rosali Gonzalez were responsible for writing the manuscript and daily management of data collection. Bach Ardalan, Danny Sleeman, Dido Franceschi, and Alan Livingstone reviewed and edited the final draft for submission.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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