CASE REPORT

Pancreatic Adenocarcinoma, From Hospice To The Dance Floor—A Case Report

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ABSTRACT

This case report describes a 73-year-old male with pancreatic adenocarcinoma expressing a KRAS G12R mutational variant among KRAS-mutated PDACs. The patient demonstrated a response to treatment with a combination of gemcitabine, nab-paclitaxel, and the MEK inhibitor, Cobimetinib. Imaging revealed resolution of abdominal distention and the CA 19-9 laboratory marker regressed into a normal range. Molecular profiling revealed distinct differences between G12R PDAC tumors, including lower PD-L1 expression, immune infiltration, and metabolic markers in G12R tumors, suggesting reduced immunogenicity. However, the G12R population showed the highest overall survival among codon 12 variants. This case highlights the potential vulnerability of G12R PDAC to targeted MEK inhibition alongside standard chemotherapy, leading to clinical benefits. Further investigation into the unique biology of G12R tumors may uncover novel therapeutic strategies.

INTRODUCTION

Over 64,000 individuals are projected to receive a pancreatic cancer diagnosis in the United States [1]. Estimates suggest that by the year 2030, pancreatic cancer will rank as the second leading cause of cancer-related deaths in the United States [2]. Currently, surgical intervention is the only curative approach; however, only about 20% of patients are eligible for this option [3].

Currently, there exist two standard chemotherapeutic regimens for advanced pancreatic cancer: FOLFIRINOX and the combination of Abraxane/Gemzar. The overall survival rate associated with modern polychemotherapy is approximately one year [4].

Our recent findings have demonstrated that the addition of the MEK inhibitor Cobimetinib to the standard chemotherapeutic regimen significantly increases the survival rate of pancreatic cancer patients expressing the G12R mutation on the KRAS codon 12. In our case study, the patient received a combinatorial treatment comprising the MEK inhibitor Cobimetinib and the chemotherapeutic agents Gemzar/Abraxane [5].

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CASE PRESENTATION

A 73-year-old male presented with a few months of epigastric pain, abdominal distension, and loose stools. The workup revealed a mass at the head of the pancreas with dilatation of the pancreatic duct **(figure 1)**. The pathology report confirmed a well-differentiated pancreatic adenocarcinoma. Subsequently, laboratory studies demonstrated an elevated bilirubin level.

The underwent stent placement and began FOLFIRINOX chemotherapy. After his second cycle of FOLFIRINOX, the CA 19-9 laboratory studies demonstrated improvement. However, he experienced severe diarrhea and weight loss, necessitating the deferral of FOLFIRINOX. The patient received hydration. Due to poor tolerance of chemotherapy, the treatment was switched to Gemzar/Abraxane.

Given toxicity symptoms such as chills and persistent hypotension following his first cycle of Gemzar/Abraxane, the patient was to proceed with chemotherapy at an attenuated dose. The patient received his second cycle of Gemzar/Abraxane with dose attenuation (Gemzar from 1000mg/m2 to 800mg/m2, Abraxane from 125mg/m2 to 100mg/m2). To address his ascites, an interventional radiology paracentesis was performed, and 3 liters of ascitic fluid were drained from the abdomen.

Histology was obtained from the head of the pancreas via fine needle aspirate and submitted to CARIS Life Sciences. As his Next-Generation Sequencing results were obtained, it was found that he carried the G12R KRAS mutation. The progression of the disease with an accumulation of ascites despite the continuation of chemotherapy **(Figure 2)**.

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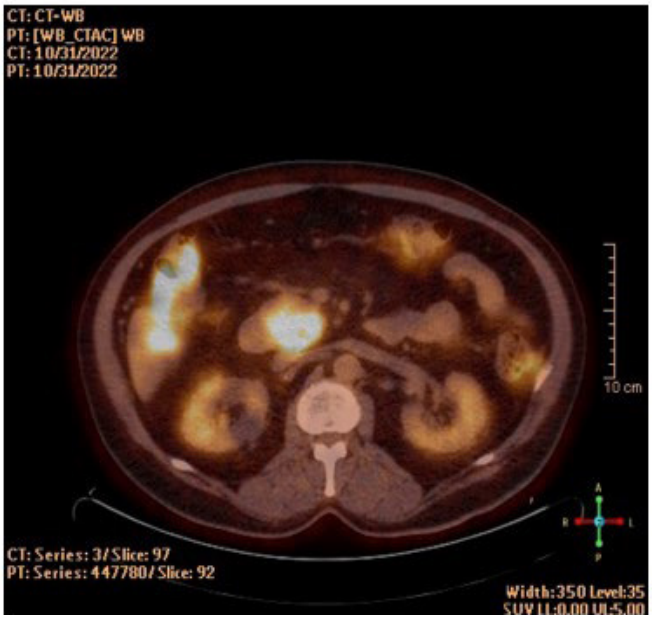

Figure 1: PET/CT scan at baseline (10/2022). Pancreatic head mass visualized with FDG avidity.

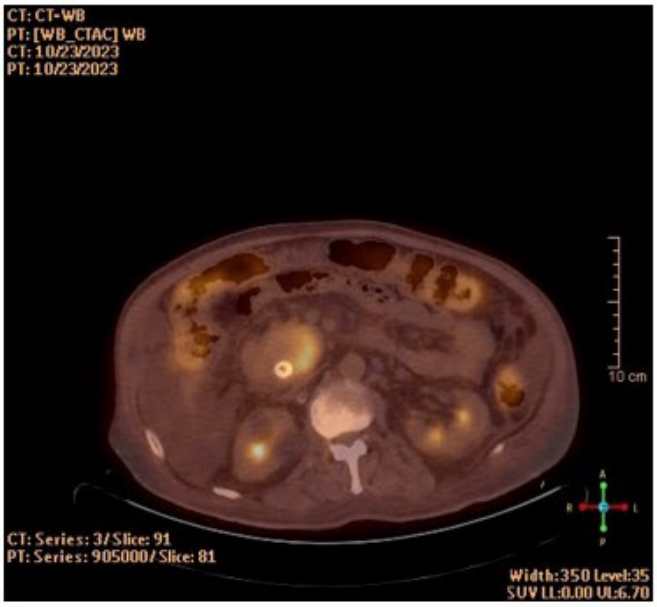

Figure 2: PET/CT dated 10/2023, a year after initial PET/CT and diagnosis. Between scans there was a decrease in metabolic activity of the FDG avid pancreatic lesion.

Given this finding, the patient commenced treatment with Cobimetinib at a dose of 20mg twice daily. At this stage of treatment, the patient underwent regularly scheduled interventional radiology paracentesis procedures every two weeks.

A follow-up PET/CT scan was performed to assess the interim treatment response. It revealed the following findings: Decreased metabolic activity of the FDG-avid pancreatic lesions, resolved metabolic activity of the mesenteric lymph nodes, a small new left-sided pleural effusion, and moderate volume abdominopelvic ascites **(Figure 3)**. The CA 19-9 laboratory studies continued to demonstrate improvement **(Figure 4)**.

The patient continued to receive prolonged chemotherapy with Gemzar/Abraxane in combination with the MEK inhibitor Cobimetinib at a dose of 20mg twice daily. Subsequently, the patient's symptomatology exhibited improvement, with resolution of abdominal distension, and the CA 19-9 laboratory marker regressed into the normal range.

A PET/CT scan performed externally showed near-background levels, corroborating the resolution of abdominal distension. The patient continues to receive ongoing treatment. At the time of writing this manuscript, the patient has a good quality of life, and has danced with his granddaughter at her graduation.

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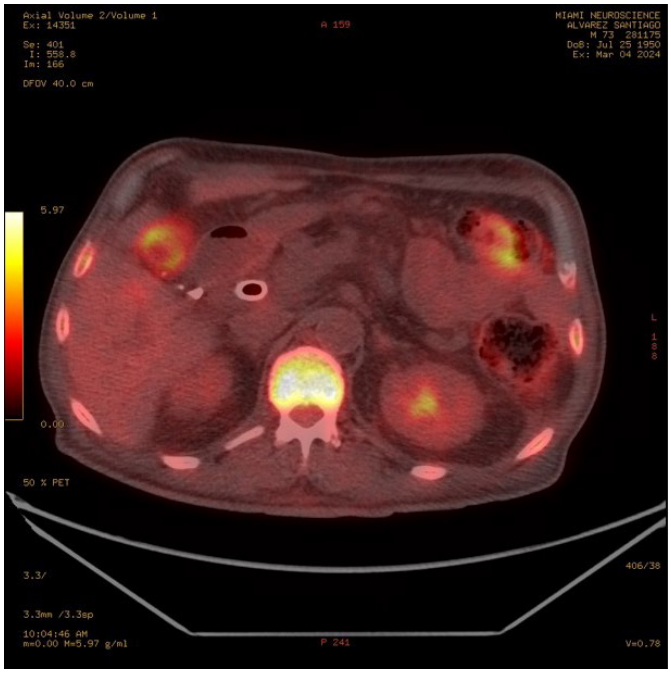

Figure 3: Most recent PET/CT 03/2024 showing little FDG activity at the pancreatic head and resolution of ascites.

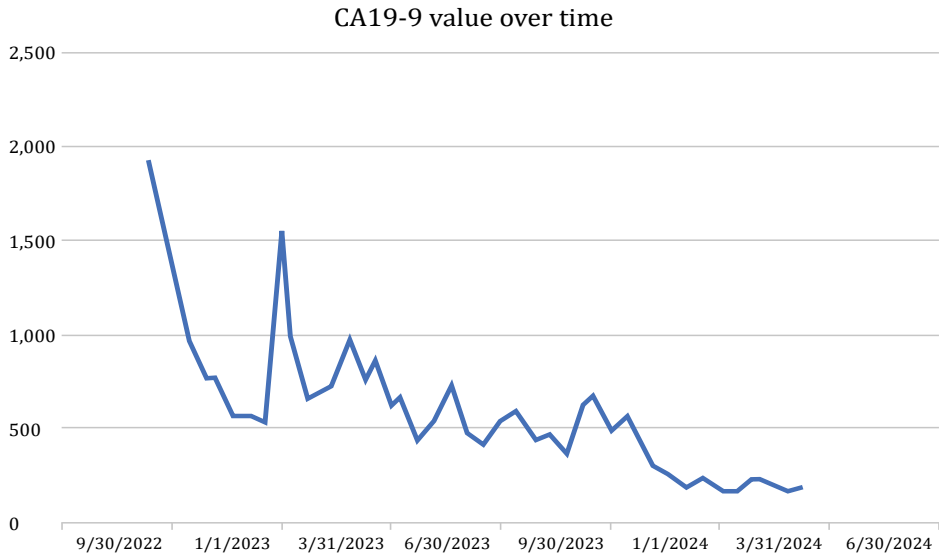

Figure 4: CA19-9 over the course of the patient's treatment.

DISCUSSION

Pancreatic cancer is known for its high mortality rate and poor prognosis. Commonly presented as pancreatic ductal adenocarcinoma (PDAC), it has a dismal five-year survival rate of about 10% in individuals. It is an incurable cancer, with an average Stage IV prognosis of approximately 12 months after diagnosis. Multiagent chemotherapies remain the backbone of treatment for patients with pancreatic ductal adenocarcinoma. FOLFIRINOX, consisting of 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and irinotecan (campostar), as well as gemcitabine (gemzar) and protein-bound paclitaxel (abraxane), are the chemotherapy drugs being used for treatment [6]. However, multiagent chemotherapy agents are associated with high toxicity; therefore, new strategies are necessary to improve survival in diagnosed patients. Targeted therapeutic agents can be added to treatment in oral form. These regimens include inhibitors for BRAF inhibition with encorafenib (BRAFTOVI) and MEK inhibition with trametinib (MEKINIST) and cobimetinib [7]. The common tumor suppressor and oncogene mutations involved in PDAC include KRAS, TP53, CDKN2A, and SMAD4. The mutational frequency of these genes ranges from 50 to 98% in PDAC [8]. KRAS is mutated 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. KRAS G12D and G12V mutants are the most common amino acid substitutions [9].

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Additionally, G12R mutants are associated with the best overall prognosis. In this case report, our patient was genetically characterized to express the G12R mutation through Next-Generation Sequencing techniques provided by CARIS Life Sciences. This mutational profile demonstrates a unique pathway for the mechanism of action. The KRASG12R mutation fails to bind the PI3K catalytic subunit p110α, an essential effector for KRAS-driven cancer initiation and maintenance, resulting in KRAS-independent micropinocytosis. This nutrient uptake process is necessary for PDAC tumor growth [10]. Our research revealed that the G12R population exhibited the highest overall survival rate among the codon 12 variants, despite displaying the least immunogenic markers [11, 12]. From PDACs that underwent comprehensive molecular profiling, the immune contexture in G12R-driven tumors is distinct from G12D, as reflected by reduced PD-L1 staining and decreased levels of multiple checkpoint receptors [12]. Significant molecular differences were observed between KRAS G12R and KRAS G12D tumors, including PD-L1 expression, immune cell infiltration, MAPK pathway gene expression, markers of immune activation, and genes involved in glucose and glutamine metabolism [13]. Most of these markers were lower in the G12R group compared to G12D, indicating that overall G12R PDAC tumors may be less immunogenic [14, 15, 16, 17, 18].

The case report demonstrates the successful use of a targeted therapy approach by incorporating a MEK inhibitor (Cobimetinib) in combination with chemotherapy for treating metastatic pancreatic adenocarcinoma harboring the G12R KRAS mutation. This personalized treatment strategy led to a favorable response and progression-free survival for the patient. The favorable response and progression-free survival observed in this case report can be attributed to the targeted inhibition of the MEK pathway, which is dysregulated in pancreatic cancer cells expressing the G12R KRAS mutation. By combining the MEK inhibitor Cobimetinib with chemotherapy, the treatment regimen effectively targeted the patient's tumor. This case report also underscores the importance of exploring and understanding the unique molecular characteristics associated with specific KRAS mutations, as they may have implications for targeted therapy selection and treatment response prediction. Further large-scale studies are required to validate the efficacy of this treatment approach in patients with the G12R KRAS mutation.

CONCLUSION

In managing pancreatic ductal adenocarcinoma (PDAC), performing genomic sequencing to detect the specific KRAS mutation variant is imperative. Most mutations occur at codon 12, with our patient categorizing as a G12R variant. In this manuscript, we are describing a case report of advanced metastatic pancreatic adenocarcinoma, which has been treated with a combination of chemotherapy and the MEK inhibitor Cobimetinib, leading to progression-free results for the past five months. This phenomenon has not been observed extensively and warrants further discussion within oncological societies. This case report is a good example of in-vitro and in-vivo model successes transcending to clinical benefits.

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