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Molecular Case Studies

RESEARCH REPORT

Potential benefit of treatment with MEK inhibitors and chemotherapy in BRAF-mutated KRAS wild-type pancreatic ductal adenocarcinoma patients: a case report

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Abstract This is the first case report of a 60-yr-old female who underwent therapy for metastatic pancreatic cancer with fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX). Upon the progression of her disease, she was switched to gemcitabine and nab-paclitaxel. Per genomic sequencing, her tumor was found to be a KRAS wild-type and BRAF V600E mutation, which then warranted treatment with the MEK1 and MEK2 inhibitor, cobimetinib. The patient has achieved a complete response (CR) to a combination of gemcitabine, nab-paclitaxel, and cobimetinib. It has been 16 mo since the start of the treatment, and the patient continues to demonstrate a complete durable response both serologically and radiologically.

INTRODUCTION

Pancreatic cancer is a fatal disease that is currently on the rise, often discovered in its late stages. Despite advancements made in surgical technique, chemotherapy, and neo-adjuvant chemoradiotherapy, the 5-yr survival rate is only 2%–9% (McGuigan et al. 2018). Pancreatic cancer has one of the worst prognoses among cancers and is often viewed by patients as a death sentence. By 2030, it is estimated to become the second most common cause of cancer-related death in the United States—a sharp ascent from its current position as the fourth most common (Siegel et al. 2017; Bray et al. 2018). Only 10%–15% of patients diagnosed at an early stage are able to undergo surgical resection (Lim et al. 2003). For these reasons, it is imperative to learn more about the characteristics of pancreatic ductal adenocarcinoma (PDAC) via baseline genomic testing, and discover significantly effective, tailored treatments (Pishvaian et al. 2020).

Potential treatments may include the targeting of the RAS/MAPK pathway via MEK inhibitors. This promising focus is posited because of the genetic mutations commonly observed in pancreatic cancer. The KRAS is a part of the RAS/MAPK pathway, a signaling pathway involved in cell proliferation and differentiation. The KRAS isoform is mutated in 84% of all RAS-mutant cancers. Specifically, in PDAC, KRAS mutations drive nearly 100% of the cases (Waters and Der 2018). The BRAF oncogene is also a part of the same MAPK/ERK pathway as one of the three RAF serine-threonine kinases (ARAF, CRAF/RAF1, and BRAF) that substantially modify KRAS-driven PDAC (Waters and Der 2018). Only ~3% of patients with PDAC demonstrate a BRAF V600E mutation (Witkiewicz et al. 2015). Non-V600E BRAF in-frame

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mutations have been reported in an additional 1% of PDAC patients (Aguirre et al. 2018). A retrospective study analyzed genomic profiles of 3594 PDAC samples from an international cohort; KRAS wild-type samples were found to have a higher rate of BRAF V600E mutations (11%) in contrast to KRAS-mutant samples (0.4%) (Singhi et al. 2019). In BRAF V600E-mutated patients, selective MEK1/2 inhibitors, such as cobimetinib, have been used to regress tumor growth (Hoeflich et al. 2012). At the present time, the standard of therapy relies heavily on systemic cytotoxic chemotherapy with a lack of targeted treatment. In preclinical studies, pancreatic ductal-derived tumors were transplanted in mice and subsequently treated with MEK inhibitor plus chemotherapy, which demonstrated a greater tumor regression than either agent alone (Kawaguchi et al. 2018). We report a patient with a KRAS wild-type (WT) and BRAF V600E mutation who was ultimately treated with a MEK inhibitor in combination with other chemotherapies.

RESULTS

A 60-yr-old female diagnosed with metastatic pancreatic adenocarcinoma presented to our clinic. Initially, the patient was seen by her primary care physician with symptoms of abdominal pain, which was attributed to a history of gallstones. She was referred to a gastroenterologist. An esophagogastroduodenoscopy and colonoscopy were performed by the gastroenterologist, both were found to be normal. Subsequent, the patient underwent a computed tomography (CT) scan of the abdomen and pelvis, which indicated a mass on the head of the pancreas with extensive metastatic lesions to the liver. A CT-guided biopsy of her liver lesions revealed metastatic adenocarcinoma of pancreaticobiliary origin (Fig. 1). Immunohistochemistry was performed on the patient's tumor sample: positive for CK6 and CDX2 with negative staining for CK20, SATB2, TTF-1, GATA3, and PAX8. She was then started on a regimen of fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX)X in October 2019, CA19-9, levels initially responded. Pretreatment CT scan and positron-emission tomography (PET) demonstrating extensive metastatic lesions on the left lobe of the liver (Fig. 2).

The patient then began to complain of back pain, which prompted requesting a magnetic resonance image (MRI) of her thoracic spine. This MRI indicated a metastatic T10 lesion (Fig. 3). She received targeted radiation to the spinal lesion. Because of progressing disease, the patient's drug regimen was switched to gemcitabine and nab-paclitaxel every 15 d. Her tumor sample was sent out for next-generation sequencing (NGS), which revealed microsatellite stability, KRAS wild-type (WT), and a BRAF V600E mutation (Table 1; Shen et al. 2019). Therefore, the patient was placed on cobimetinib, a known MEK inhibitor that does not directly mediate a BRAF inhibition, but via mediated signal through MEK inhibition. Over

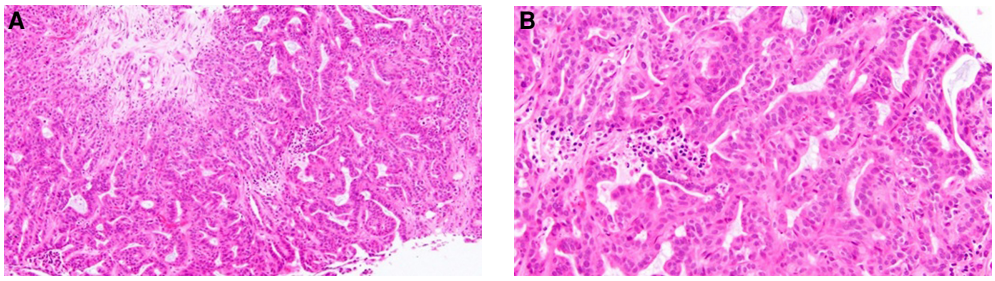

Figure 1. Metastatic pancreatic adenocarcinoma. (*A*) 10× and (*B*) 20×. Biopsy of a liver lesion demonstrated a moderately differentiated adenocarcinoma immunomorphologically compatible with metastasis from the patient's pancreatic primary.

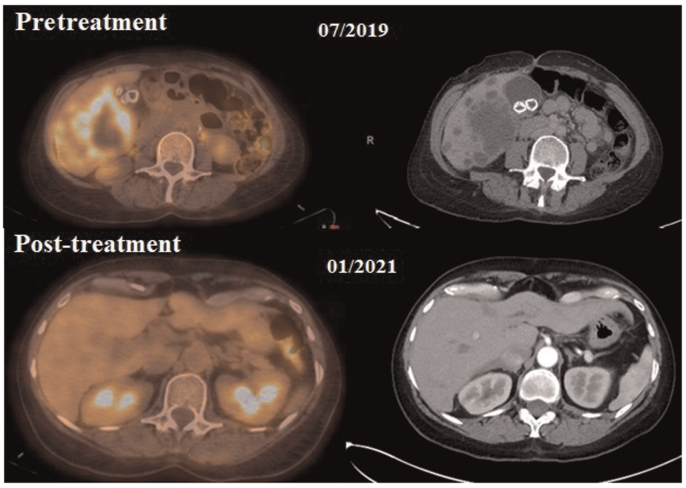

Figure 2. Pretreatment positron-emission tomography (PET) scan and computed tomography (CT) scan with contrast versus post-treatment PET scan and CT scan. Pretreatment scans (*top*) indicate extensive metastatic lesions to the right lobe of the liver. This is also demonstrated on the PET scan. After treatment (*bottom*) 15 mo after switch, patient's scan demonstrates no evidence of disease.

the past 16 mo she has received the full dose of chemotherapy and the full dose of the target therapy. She has not experienced any significant side effects—namely, no skin rashes or cardiovascular toxicities. She has maintained full daily functioning and has not been admitted to a hospital for any medical emergencies. She obtained a complete radiological response within 6 mo from the initiation of the therapy. We have followed the patient with weekly laboratory testing including complete blood count (CBC), complete metabolic panel (CMP), and carbohydrate antigen 19-9 (CA19-9) along with CT and PET scans every 3 mo (Fig. 4).

DISCUSSION

The described patient has undergone a combination of systemic chemotherapy with a MEK1 and MEK2 inhibitor (cobimetinib) for >16 mo and continues to be well. Initially she was given first-line FOLFIRINOX, but because of disease progression, her regimen was switched to second-line gemcitabine-paclitaxel. In pancreatic cancer, ~95% of patients are KRAS mutated. However, our patient is a KRAS wild-type and BRAF V600E mutated, and thus she was offered a combination of chemo and a MEK1 and MEK2 inhibitor (Zeitouni et al. 2016). This is the first report of a patient with metastatic pancreatic cancer with the above-described molecular changes to be treated with the combination of chemotherapy plus a targeted agent who has achieved a durable complete response with no concurrent toxicities. In the literature we found five other case reports with a similar molecular profile.

In the first reported case found in the literature, Sasankan et al. reported a 49-yr-old female pancreatic KRAS wild-type and BRAF V600E mutated patient who was treated with a combination of MEK1/2 and BRAF inhibitors after progressing on standard-of-care chemotherapy. The patient was begun on second-line dabrafenib and trametinib. It is reported that shortly after beginning the targeted agents, the patient was admitted for septic shock and neutropenic fever. Because of toxicity, the dosage of both agents were reduced by half, to which the patient responded well for ~8 mo. After that time, however, the patient developed a new singleton lesion that was treated with radiotherapy. No appropriate follow-up has been documented by the investigators (Sasankan et al. 2020).

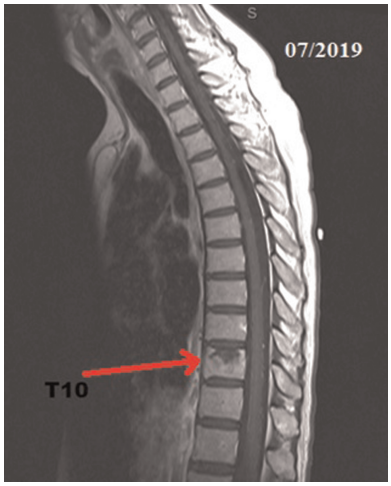

Figure 3. Pretreatment magnetic resonance imaging (MRI) thoracic spine with contrast (07/2019). MRI of the thoracic spine indicating a metastatic lesion in the T10 vertebral body.

The second reported case in the literature was a 65-yr-old male with metastatic pancreatic cancer who progressed after standard-of-care therapies. NGS was performed indicating a KRAS wild-type and BRAF N486-P490 variant. The patient received fourth-line dabrafenib and trametinib from a pharmaceutical company for off-label use. As the patient was unwell at the beginning of therapy, he was begun on dabrafenib alone, at a reduced dose (Wrzeszczynski et al. 2019). The patient initially responded with a decrease in CA19-9 on the monotherapy; however, the response was transient, and progressed after 4– 6 mo on monotherapy treatment.

Two other cases in the literature reported by Grinshpun et al. had similar genomic profiles. Both reported cases were metastatic pancreatic cancer patients who presented with KRAS wild-type and BRAF mutations who were previously treated and failed first-line therapy. Because of a BRAF mutation, they both were started on dabrafenib and trametinib. Both patients were on the treatment regimen briefly before passing away (Grinshpun et al. 2019).

The final case reported in the literature by Seghers et al. detailed a 66-yr-old male with metastatic pancreatic cancer with NGS-confirmed BRAF v600E mutation and KRAS wild-type. The patient did not tolerate first-line combination of gemcitabine and nab-paclitaxel well, and thus was switched to second-line vemurafenib and cobimetinib because of the presence of BRAF V600E mutation. His dosage schedule was cobimetinib 60 mg once daily for 3 wk, followed by 1 wk of no medication, followed by vemurafenib 960 mg twice daily. The patient did not tolerate the cobimetinib dosing, and it was therefore discontinued. The patient had a partial response as per response evaluation criteria in solid tumors (RECIST), which was maintained for 6 mo. At 9 mo, however, the patient progressed, and treatment was discontinued (Seghers et al. 2020).

Table 1. Variant table

Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Variant type	Predicted effect	dbSNP/dbVar ID	Genotype
BRAF	Chromosome 7 (7q34)	NM_001374258.1: c.1919T>A	(p.Val600Glu)	SNV	Missense	rs113488022	Heterozygous

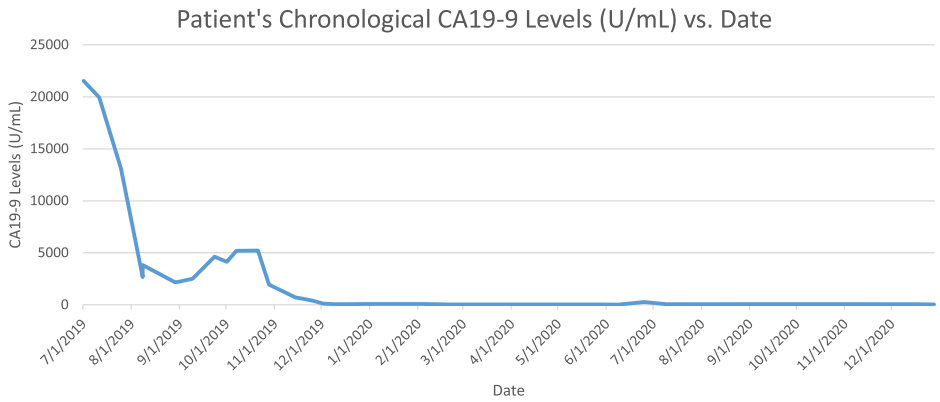

Figure 4. Patient's chronological carbohydrate antigen 19-9 (CA19-9) levels (U/mL) versus date.

Our patient was treated differently from the previously reported cases. During the course of treatment, our patient received full-dose gemcitabine/mab-paclitaxel in a timely manner every 15 d alongside continuous cobimetinib 20 mg twice daily. We particularly looked for dermatological and cardiac toxicities, caused by cobimetinib; however, the patient did not experience this while on therapy. There were no dose reductions of any of the agents throughout the span of her therapy, and the patient has maintained her quality of life (QoL) to 90%. The patient has not been admitted to the hospital since beginning the therapy. Radiological assessments of the patient via CT and PET scans were performed in 3-mo intervals and serologic assessments were performed weekly. After 16 mo, we are continuing the combination of chemotherapy and cobimetinib with no further alterations to the patient's current therapy plan. A comparison of the aforementioned patients is described in Table 2.

In a phase I/II clinical study, PDAC patients were given gemcitabine concurrently with pimasertib, a MEK inhibitor. The combination of gemcitabine and pimasertib did not offer any clinical benefits or progression-free survival when compared to gemcitabine plus placebo. It can be noted that there were no BRAF-mutated patients reported in the study (Van Cutsem et al. 2018).

We present this case report detailing a KRAS wild-type BRAF v600E-mutated pancreatic cancer in a patient presently undergoing a combination of gemcitabine and nab-paclitaxel alongside MEK1/2 inhibitor. To our knowledge, this is the first reported case in the available literature describing a BRAF v600E KRAS wild-type pancreatic cancer patient who has received a combination of chemotherapy and a MEK1/2 inhibitor with associated clinical and radiological responses.

Conclusion

Pancreatic ductal adenocarcinoma remains one of the deadliest cancers, and the prevalence is unfortunately increasing. To the best of our knowledge, this is the first reported case detailing a KRAS wild-type BRAF-mutated pancreatic cancer patient treated with cobimetinib (a MEK1 and MEK2 inhibitor) in conjunction with chemotherapy, which has led to a tolerable and prolonged remission. Patients with BRAF-mutated KRAS wild-type mutations may benefit from treatment with cobimetinib in combination with cytotoxic chemotherapy. CA19-9 levels were found to consistently decrease on treatment with a combination of chemotherapy and cobimetinib (Fig. 4). This case report warrants further investigation regarding the benefits of the combined treatment of chemotherapy and an individualized, tailored therapy, such as a MEK inhibitor, in PDAC BRAF mutated KRAS wild-type patients.

Table 2. Different cases of treated KRAS wild-type (WT) and BRAF-mutant pancreatic ductal adenocarcinoma (PDAC) in the literature

	Case I: 49-yr-old female	Case II: 65-yr-old male	Case III: 56-yr-old male	Case IV: 75-yr-old female	Case V: 60-yr-old male	Case VI: 60-yr-old female
Genomic profile	KRAS wild-type, BRAF V600E, TP53 C176R	KRAS wild-type, BRAF ΔN486_P490	KRAS wild-type, BRAF c1799_1801delTGA mutation	KRAS wild-type, BRAF V600E	KRAS wild-type, V600E	KRAS wild-type, BRAF V600E
Therapy	Dabrafenib + trametinib	Dabrafenib + trametinib	Dabrafenib + trametinib	Dabrafenib + trametinib	Vemurafenib and cobimetinib	Cobimetinib, gemzar, nab-paclitaxel
Duration of response	8 mo	4–6 mo	3 mo	19 d	6 mo	16 mo and ongoing
Dosages	Dabrafenib 300 mg twice a day with trametinib 2 mg once a day, which was later reduced by 50%; dosage of dabrafenib was later increased to 300 mg in the morning, 150 mg at night; trametinib rebegun at 2 mg two days on, one off	Dabrafenib was started at 75 mg po b.i.d. and gradually increased to full dose; trametinib was begun toward the end of treatment.	Dabrafenib 300 mg twice a day, trametinib 2 mg daily	Dabrafenib 150 mg twice daily and 2 mg trametinib once a day	Vemurafenib (960 mg twice daily) and cobimetinib (60 mg once daily, 3 wk on, 1 wk off); cobimetinib discontinued because of toxicity after 1 wk	Standard dosages of gemzar and cobimetinib 20 mg b.i.d. continuously
Side effects	Neutropenic fever and septic shock on starting dosages; tolerated reduced dose with minimal side effects	No significant side effects	Interstitial lung disease	No apparent side effects	Diffuse exanthematous rash	No apparent side effects, quality of life maintained
Line of therapy	Second-line	Fourth-line	Second-line	Second-line	Second-line	Second-line

METHODS

The patient's liver was biopsied and was reviewed by the pathology department at the University of Miami. Pathology was read as moderately differentiated adenocarcinoma of pancreatobiliary origin. Immunohistochemistry was performed indicating the following profile in the tumor cells: positive for CK7, CDX2 (weak); negative for CK20, SATB2, TTF-1, GATA3, and PAX 8. NGS was sent out, and patient was found to be BRAF p.V600E-mutated and KRAS wild type. The patient's tumor is microsatellite-stable (MSS). *BRCA1* and *BRCA2* genes were not mutated.

ADDITIONAL INFORMATION

Data Deposition and Access

Raw sequencing data is not available for deposition. The variant has been submitted to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and can be found under accession number SCV001962698.

Ethics Statement

All procedures performed in this study involving a human participant adhered to the 1964 Declaration of Helsinki and its later amendments. Collection of information in this report complied with the Health Insurance Portability and Accountability Act of 1996. Written consent to publish this case report was obtained from the patient. IRB approval was not needed for a single case report.

Competing Interest Statement

The authors have declared no competing interest.

Referees

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Author Contributions

All the authors equally contributed to the preparation of this manuscript. All authors attest that they meet the current ICMJE criteria for Authorship.

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