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Brief Report

BRIEF REPORT

Remarkable response of *BRAF*^{V600E}-mutated metastatic pancreatic cancer to BRAF/MEK inhibition: a case report

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Introduction

Advanced pancreatic ductal adenocarcinoma (PDAC) has very limited treatment options due to few targetable mutations, and chemotherapeutic treatment is currently the mainstay of palliative therapy for PDAC patients.

Somatic point mutations in the *BRAF* gene (mostly V600E) are present in many tumors, especially in malignant melanomas, with a mutation rate of ~66% [1]. On the other hand, the *BRAF* mutation has rarely been reported to be present in PDAC, with a mutation rate of a mere 2%–3% [2].

Rare as it is, *in vitro* and *in vivo* experiments revealed that *BRAF*^{V600E} induced initiation of pancreatic tumorigenesis and tumor formation [3], indicating the potential application of BRAF inhibition. Furthermore, several case reports have shown promising therapeutic effects in *BRAF*-mutated pancreatic cancer patients [4–6] (Supplementary Table 1). Hyman *et al.* [7] demonstrated that one patient with PDAC responded to vemurafenib; Guan *et al.* [6] reported that another PDAC patient showed prolonged survival with dabrafenib/trametinib combination treatment. However, the same dilemma of subsequent resistance as melanoma is unavoidable. Currently, the mechanism of drug resistance of BRAF/MEK inhibition in PDAC is still unknown and follow-up treatment beyond drug resistance has not been elucidated.

Herein, we present a PDAC patient with extensive tumor metastases who achieved almost complete remission upon targeted therapy with BRAF inhibition based on a *BRAF*^{V600E} driver mutation.

Case presentation

A 34-year-old male with a history of heavy smoking presented to our hospital with cough and fever. Physical examination revealed a painless mass of ~3 × 4 cm in size on the left side of the neck. Initial chest computed tomography (CT) showed massive lung lesions and mediastinal lymphadenopathy. Furthermore, fluorine-18 fluorodeoxyglucose whole-body positron emission tomography revealed multiple lymph-node metastases throughout the neck, chest, and abdomen, multiple nodular masses in both the lungs and the liver (max, 15.2 × 10.9 cm), and a slightly low-density mass (3.5 × 3.4 cm) at the bottom of the pancreas (Figure 1A). Tumor-marker analysis revealed elevated CA19–9 (3,421.0 IU/mL) (Figure 1B). The patient's family history revealed a case of lung cancer in a second-degree relative. Based on these findings, lung cancer was initially highly suspected. However, fiberoptic bronchoscopy did not reveal a positive finding. Later, morphology of fine-needle aspiration biopsy of the neck lymph nodes first suggested a gastrointestinal origin, of which cholangiocarcinoma and PDAC cannot be excluded and need to be confirmed by immunohistochemistry (IHC).

Concerning the high tumor burden, chemotherapy with albumin-bound paclitaxel and oxaliplatin under the assumption of a metastatic digestive system tumor was initiated. Later confirmative IHC findings (AE1/AE3 [3+], CK [3+], CK18 [2+], CK19 [3+], CK7 [1+], CK20 [−], CDX-2 [1+], CEA [1+], CA19-9 [2+], TTF-1 [−], NapsinA [−], Ki-67 [+30%]) were consistent with PDAC and treatment was then immediately changed to

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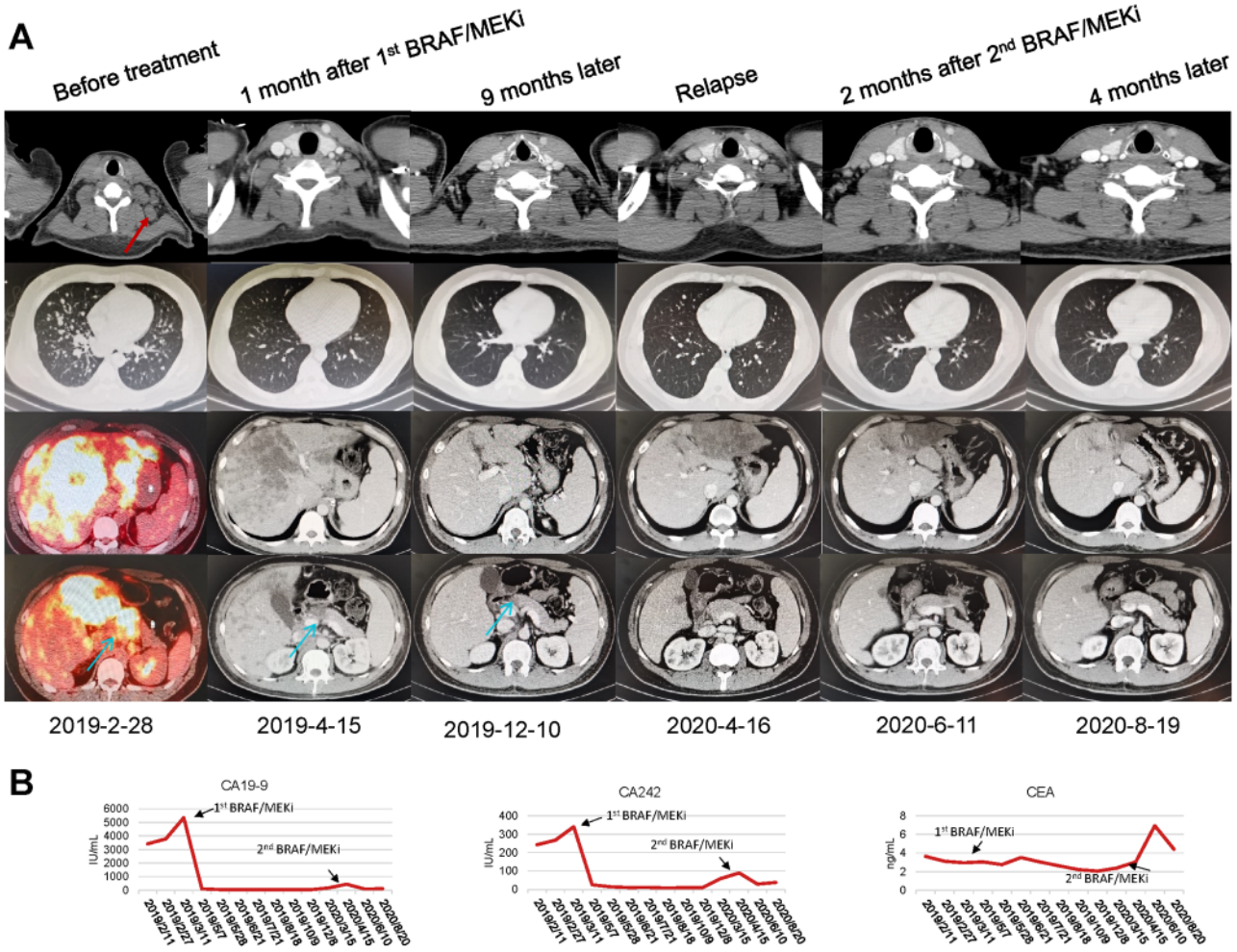

Figure 1. Plots of changes in lesions (A) and tumor markers (B) over time and type of treatment. (A) The first row of images shows left neck lymph-node lesions, the second row of images shows lung lesions, the third row shows liver lesions, and the fourth row shows pancreatic lesions and metastatic lymph nodes. The red arrow represents lymph-node lesions and blue arrows represent pancreatic hypodense lesions. (B) As the disease progressed, CA199 and CA242 levels were significantly elevated and, with the use of BRAF/MEK inhibitors, tumor-marker levels were subsequently reduced and the disease went into remission. BRAF/MEKi, BRAF/MEK inhibition; 1st, first; 2nd, second; CA19-9, carbohydrate antigen 19-9; CA242, carbohydrate antigen 242; CEA, carcinoembryonic antigen; BRAF, v-raf murine sarcoma viral oncogene homolog B1; MEK, mitogen-activated protein kinase; BRAF/MEKi, BRAF/MEK inhibition.

albumin-bound paclitaxel and gemcitabine. However, short-term imaging follow-up and elevated CA19-9 levels (Figure 1B) showed progressive disease. Subsequent genetic testing suggested a $BRAF^{V600E}$ mutation (543 genes; Genecast Co. Ltd, Jiangsu, China) (Supplementary Table 2). Treatment with dabrafenib (150 mg orally twice a day) and trametinib (2 mg orally once daily) was initiated, leading to a dramatic decline in the CA19-9 levels (102.1 IU/mL) and partial response (PR) on CT scans after 1 month (Figure 1A). No signs of progression were detected until, 12 months later, increased lung and liver metastases were revealed by a follow-up CT, with an elevated CA19-9 level (442.1 IU/mL) (Figure 1B). A blood next-generation sequencing (NGS) (414 genes) yielded the following mutation profile: $BRAF^{V600E}$, $FGFR^{amp}$, $NOTCH2^{amp}$, and MSS (Supplementary Table 2). The second-line BRAF/MEK inhibition regimen with vemurafenib (960 mg orally twice a day) and cobimetinib (60 mg orally once daily) was then initiated, leading to a rapid decline in the CA19-9 levels again (89.55 IU/mL) (Figure 1B) and a considerable decrease in the size of both lung and hepatic metastatic lesions (PR) on CT scans only 1 month later (Figure 1A). At the 6-month follow-up, the remaining hepatic metastatic lesions and lymph nodes further decreased in size and the initial lung lesions were no longer detectable (Figure 1A). By the submission of the case draft, the patient has survived for >20 months since diagnosis and the progression-free survival was >6 months.

Discussion

In this case, we demonstrated a patient with *BRAF*-mutated pancreatic cancer who had clearly benefited from BRAF/MEK inhibitors twice, thereby indicating the potential of BRAF/MEK inhibitors in *BRAF*-mutated pancreatic cancer and the feasibility of rechallenge treatment after previous drug resistance.

The transient response to BRAF/MEK inhibitors remains a significant therapeutic challenge, similar to the demonstration of our case. Previous studies have indicated that Notch signaling increases tumor-cell proliferation and promotes tumor survival, leading to drug resistance and poor patient outcomes in solid tumors, while maintaining the cancer stem-cell pool and inducing epithelial–mesenchymal transition. In melanoma,

Krepler *et al.* [8] disclosed that co-inhibition of Notch and ERK decreased viability in $BRAF^{V600E}$ melanomas. These results indicate a potential role for Notch in inducing BRAF/MEK inhibition resistance. In this context, interestingly, the success of the BRAF/MEK rechallenge in our case is elusive.

Recently, acquired epigenetic mechanisms have been suggested as important mechanisms of resistance to BRAFi [9]. There is evidence that BRAFi may induce cancer-cell matrix remodeling and secretome adaptation, resulting in temporary resistance to BRAFi. In circumstances where this plastic phenotype may be reversed after the withdrawal of the driving stimulus, retreatment with BRAFi after a therapeutic break would be reasonable. A prospective study enrolling 25 melanoma patients demonstrated that rechallenge with dabrafenib plus trametinib showed favorable efficacy in patients who had previously progressed on BRAFi, indicating rechallenge as a potential new treatment option [10]. Thus, it is reasonable to assume that our case benefited from the rechallenge treatment.

In our study, this *BRAF*-mutated cancer has a high malignancy tendency and appears to be primarily resistant to the standard chemotherapy regimen, indicating that *BRAF* may be a potential negative predictor of response to chemotherapy, which deserves broader evaluation. Clinically, the possibility of *BRAF* mutations should be considered in pancreatic cancer patients who are unresponsive to initial chemotherapy and genetic testing is recommended to provide effective treatment early, especially for wild-type *KRAS* cases because of the mutually exclusive nature of *KRAS*/*BRAF* mutations. If possible, first-line BRAFi therapy may be considered in order to provide early benefits to this subset of patients.

Supplementary Data

Supplementary data is available at *Gastroenterology Report* online.

Authors' Contributions

H.S.L. drafted the manuscript. K.Y. collected the patient's clinical records and relatives' information. Y.W. designed the research and provided careful guidance on the revision of the draft. All authors approved the final version of the manuscript.

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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 were appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient and the patient agreed to publish this article.

Conflict of Interest

None declared.

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