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Case Report

From Crisis to Cure: A Case Report of Pathologic Complete Response in a Young Male with BRAF-mutant dMMR Metastatic Colorectal Cancer after Immunotherapy

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Abstract

Metastatic colorectal cancer (mCRC) with a $BRAF^{V600E}$ mutation is an aggressive subtype with poor prognosis and limited response to standard chemotherapy. However, coexisting deficient mismatch repair (dMMR) is associated with improve outcomes with immunotherapy. We present the case of early-onset $BRAF^{V600E}$-mutated dMMR mCRC in a 38-year-old male diagnosed in 2019. After progression on FOLFIRINOX plus bevacizumab and intolerance to second-line targeted therapy with cetuximab/dabrafenib/trametinib, he began third-line treatment with nivolumab and low-dose regorafenib in June 2020. A remarkable clinical and pathological response was achieved, with complete tumor regression and no recurrence for over 4 years. This case highlights the potential for a dramatic response in BRAF-mutated dMMR mCRC through early immunotherapy, and that the combination of low-dose regorafenib and nivolumab may offer a synergistic effect. The early use of immune checkpoint blockade should be considered in this subset of patients, and further studies are needed to optimize treatment sequencing.

Keywords: BRAFV600E mutation, case report, colorectal cancer, deficient mismatch repair (dMMR), immunotherapy

Introduction

Metastatic colorectal cancer (mCRC) harboring the $BRAF^{V600E}$ mutation is a distinct and aggressive molecular subtype with a notably poor prognosis. These tumors are typically characterized by a poorer response to conventional therapies, a high burden of lymphatic and peritoneal dissemination, and direct invasion into adjacent structures in advanced cases.[1] Large-scale studies have shown that the median overall survival (OS) for patients with $BRAF^{V600E}$-mutated mCRC is approximately 14–18 months, nearly half that of BRAF wild-type counterparts.[2,3] However, concurrent deficient mismatch repair (dMMR) can significantly improve outcomes, and patients with both $BRAF^{V600E}$ mutation and dMMR can achieve a median OS of up to 30.5 months.[4]

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Several studies in recent years have explored the distinct subset of mCRC patients with coexisting $BRAF^{V600E}$ mutation and dMMR. Here, we present a rare case of early-onset mCRC diagnosed in 2019, characterized by this molecular profile. The patient showed limited responses to first-line FOLFIRINOX plus bevacizumab and to second-line triplet targeted therapy with cetuximab, dabrafenib, and trametinib. However, a complete pathological remission was achieved after treatment with nivolumab in combination with low-dose regorafenib, and the patient has remained disease free with no evidence of recurrence since December 2020.

Case Report

A 38-year-old male with no significant past medical history presented in April 2019 with more than 2 months of watery diarrhea during which his body weight decreased from 68 to 52 kg. The initial evaluation was performed at a local hospital, where his initial labs revealed anemia (Hb 11.5 g/dL) and markedly elevated carcinoembryonic antigen (CEA) level (727 ng/mL). Flexible sigmoidoscopy confirmed a large sigmoid tumor with nearly complete obstruction. Computed tomography (CT) and positron emission tomography-CT revealed a 6–7 cm hypermetabolic pelvic mass with direct invasion to the urinary bladder and associated right hydronephrosis and hydroureter. A biopsy showed poorly differentiated adenocarcinoma. Molecular analysis revealed a $BRAF^{V600E}$ mutation by polymerase chain reaction and loss of MLH1/PMS2 expression in immunohistochemical staining, confirming dMMR status. He received two cycles of FOLFOX chemotherapy plus cetuximab before seeking further management at our institution.

Due to the aggressive disease pattern in this locally advanced stage of the disease, the case was discussed in a multidisciplinary team meeting. The patient was considered unresectable because of the extent of disease involvement, which would need major surgery and the sacrifice of multiple vital organ structures. Therefore, upfront systemic therapy was recommended as the initial treatment approach. A self-expandable metallic stent was placed for decompression, and a right double-J stent was inserted due to ureteral involvement.

He began FOLFIRINOX (irinotecan 125 mg/m^2; oxaliplatin 85 mg/m^2; fluorouracil 2600 mg/m^2; and calcium folinate 150 mg) plus bevacizumab 5 mg/kg in June 2019. However, after only two cycles, he developed hyperammonemic encephalopathy and grade 4 neutropenia. The dose of chemotherapy was reduced and eventually discontinued after 6 months after a total of 10 cycles due to disease progression. Repeat imaging showed an enlarging pelvic mass (~9 cm) with bladder and possibly prostatic invasion [Figure 1], and the CEA level had elevated to 2332 ng/mL.

Given the BRAF-mutant dMMR phenotype, he was transitioned to a triplet targeted regimen in February 2020: cetuximab 400 mg/m^2 every 2 weeks (EGFR inhibitor), dabrafenib 150 mg/BID (BRAF inhibitor), and trametinib 2 mg/QD (MEK inhibitor). Unfortunately, treatment was complicated by a severe acneiform rash, and disease progression with rectovesical fistula also developed after 3 months.

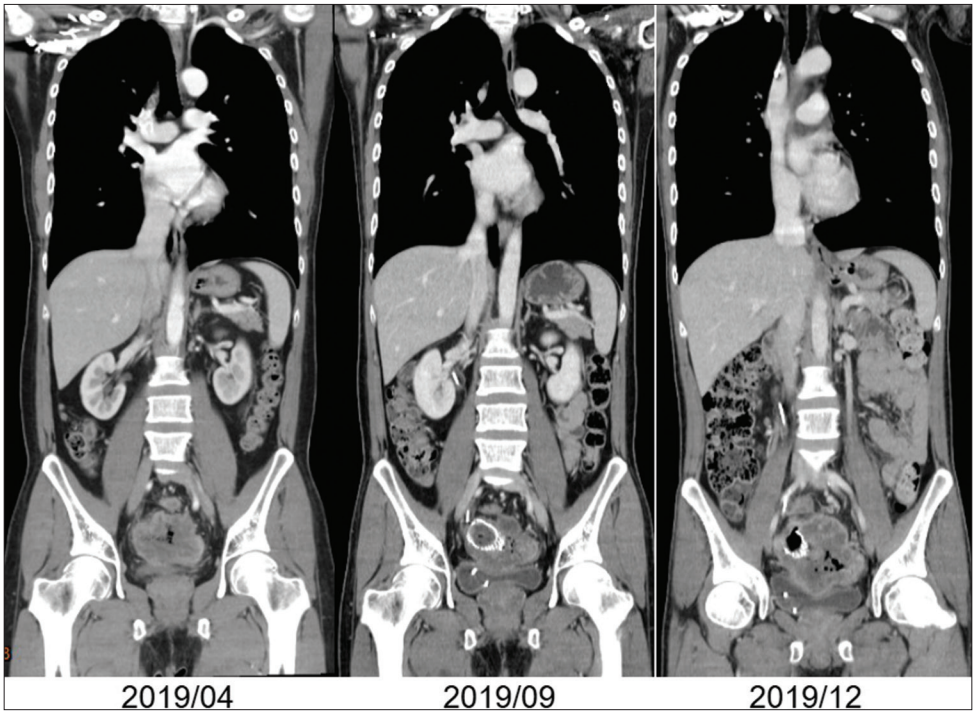

Figure 1: The tumor progressively enlarged from June 2019 (6 cm) to December 2019 (9 cm) after 10 cycles of first-line treatment with FOLFIRINOX plus bevacizumabplus bevacizumab

In June 2020, he began treatment with nivolumab (anti-PD-1 immune checkpoint inhibitor) 3 mg/kg every 2 weeks. Regorafenib at a low dose of 80 mg/day orally for 3 weeks on/1 week off was added as a synergistic partner in July 2020. In September, CT imaging demonstrated marked tumor regression from 9.0 cm to 5.5 cm, and it had almost disappeared in November 2020 [Figure 2]. The CEA level also dramatically declined from 2332 ng/mL to 12.5 ng/mL.

Given the impressive response, a multidisciplinary team meeting recommended curative resection. On December 10, 2020, he underwent sigmoid colectomy with partial cystectomy and resection of surrounding tissues [Figure 3]. Surgical pathology revealed no residual viable tumor, indicating a complete pathological response (ypT0N0M0). Immunotherapy was resumed postoperatively but only continued for three cycles due to price concerns.

The patient has remained recurrence-free for over 4 years. Serial imaging (CT and colonoscopy) from 2021 to 2024 confirmed no evidence of disease, and the CEA level has stabilized to under 2 ng/mL. He underwent colostomy closure in September 2022 and remains in a good condition with preserved renal function and quality of life.

Discussion

In Taiwan, $BRAF^{V600E}$ mutations are detected in 8%–10% of mCRC cases, while dMMR or microsatellite instability-high (MSI-H) phenotypes occur in approximately 5%–7% of cases.[5,6] Interestingly, $BRAF^{V600E}$ mutations are frequently associated with dMMR/MSI-H status, particularly in sporadic dMMR tumors. We previously reported that $BRAF^{V600E}$ mutations were present in nearly 40% of dMMR/MSI-H tumors, with MLH1/PMS2 loss (dMMR type 1) being the most prevalent pattern.[6]

For fit patients with $BRAF^{V600E}$-mutated mCRC, current first-line recommendations favor FOLFOXIRI or FOLFIRINOX plus bevacizumab, as supported by the TRIBE trial. On the other hand, for patients with dMMR/MSI-H mCRC, current first-line recommended treatments are immune checkpoint inhibitors based on the CheckMate-142 trial, KEYNOTE-177 trial and other related studies.[7,8] However, our patient was diagnosed in 2019 when these clinical trials were still ongoing, so we chose FOLFIRINOX plus bevacizumab as our initial treatment strategy. 5-fluorouracil–based chemotherapy regimens offer limited efficacy in this population, with median progression-free survival (PFS) ranging from 4 to 7 months and median OS of 17 months.[4,9] Targeted therapies involving dual BRAF and MEK inhibition (dabrafenib and trametinib) have shown some benefit in previously treated $BRAF^{V600E}$-mutated mCRC,[10] and further benefits have been shown in trials using triple inhibition of EGFR, BRAF, and MEK, including an open-label study of dabrafenib, trametinib, and panitumumab which reported superior outcomes.[11] Accordingly, our patient received cetuximab, dabrafenib, and trametinib as second-line treatment starting from February 2020. At the same time, the landmark phase III BEACON trial demonstrated that this kind of triplet regimen yielded a median OS of 9.3 months, median PFS of 4.3 months, and an overall response rate (ORR) of 20%, which were significantly better than the standard second-line options (OS 5.4 months, PFS 1.5 months, ORR <5%).[12]

Despite these advances, our patient had a limited treatment response and developed disease progression after 4 months of triplet EGFR/BRAF/MEK inhibition therapy. This may be explained by emerging evidence indicating that $BRAF^{V600E}$-mutated CRC can be classified into two transcriptomic subtypes – BM1 and BM2. The BM1 subtype is characterized by epithelial–mesenchymal transition and activation of the AKT/mTOR pathway, and it tends to have a more aggressive behavior. In contrast, BM2 tumors display dysregulated cell-cycle checkpoints and tend to have better overall outcomes. However, BM1 patients may have higher response rates and longer survival (PFS 7.4 months; OS 19.8 months) on triplet EGFR/BRAF/MEK inhibition therapy than BM2 patients (PFS 3 months; OS 6.3 months). Notably, dMMR/MSI-H status is more prevalent in BM2 tumors (65%) than in BM1 tumors (43%).[13,14] It is possible that our patient had the BM2 subtype that failed to respond well to triplet targeted therapy, however additional molecular profiling would be needed to confirm this hypothesis.

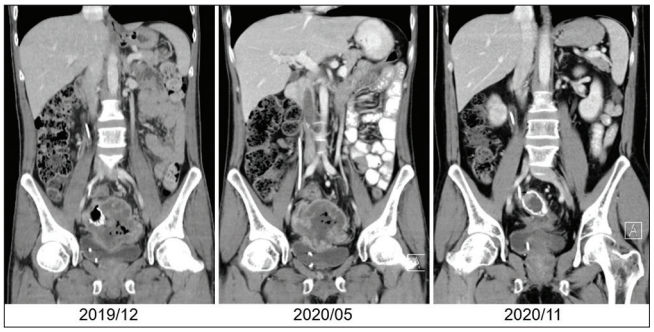

Figure 2: Disease progressed after triplet therapy with cetuximab/dabrafenib/trametinib from February 2020 to May 2020. However, the tumor shrunk and almost disappeared after using nivolumab plus regorafenib from June 2020 to July 2020

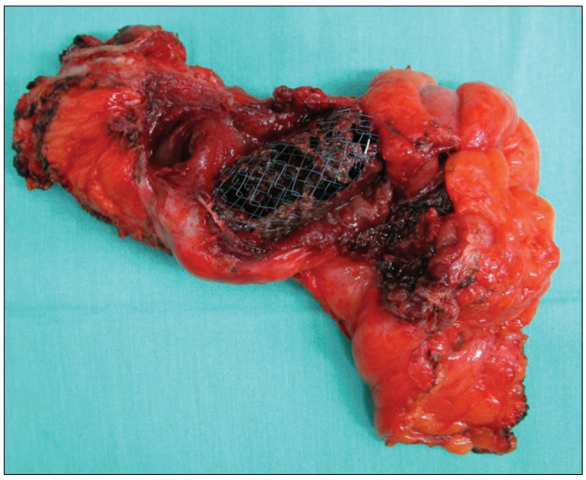

Figure 3: The specimen showed only stent without visible tumor

Given the patient's dMMR status, we transitioned to third-line immunotherapy with nivolumab in June 2020, guided by the results from the CheckMate-142 trial, which demonstrated substantial benefits with immune checkpoint inhibition in heavily pretreated MSI-H/dMMR mCRC, with a PFS of 50.4% and OS of 73.4% after 1 year follow-up.[15] We also considered regorafenib, an oral multikinase inhibitor targeting Vascular Endothelial Growth Factor Receptor (VEGFR), Fibroblast Growth Factor Receptor (FGFR), and other signaling pathways. Although it is a standard third-line agent in Taiwan, its benefit is limited, with median PFS and OS of 3.8 and 10 months, respectively.[16]

Preclinical studies have suggested that regorafenib may modulate the tumor microenvironment by suppressing immunosuppressive macrophages and enhancing cytotoxic T-cell infiltration, thereby synergizing with immunotherapy.[17] Clinical trials such as REGONIVO have reported some efficacy in microsatellite stable (MSS) mCRC, with an ORR of 40% and PFS of 6.3 months at a reduced regorafenib dose of 80 mg/day for 3 weeks on/1 week off.[18] Furthermore, a real-world retrospective cohort in China demonstrated that combination therapy with regorafenib and PD-1 inhibitors significantly extended OS compared to regorafenib monotherapy (13.5 vs. 10.0 months, $P = 0.001$).[19] Therefore, we administered 80 mg daily of regorafenib in combination with nivolumab. The patient demonstrated an exceptional response, achieving pathological complete remission after 6 months.

Most existing literature has focused on the use of regorafenib plus immune checkpoint inhibitors in refractory MSS mCRC. However, in dMMR/MSI-H tumors – where immunotherapy alone yields high response rates (30%–60%) and durable PFS – combination approaches have less often been explored, potentially due to sufficient efficacy with immunotherapy alone, as shown in CheckMate-142 and KEYNOTE-177.[7,8]

In cases of $BRAF^{V600E}$-mutated mCRC with coexisting dMMR, MMR status serves as the primary prognostic and predictive biomarker. While $BRAF^{V600E}$ mutations do not appear to negatively impact immunotherapy outcomes across all lines in dMMR/MSI-H cases, emerging evidence suggests that they may contribute to secondary resistance when immunotherapy is initiated in the first-line setting.[4,20] These findings emphasize the critical importance of integrating immune checkpoint inhibitors early in this subset of patients. Previous studies have also suggested that immunotherapy should be considered as the first-line treatment for these patients before targeted therapy and chemotherapy.[21]

When patients are diagnosed with MSI-H/$BRAF^{V600E}$-mutated mCRC, MMR status should be a key determinant in the treatment plan, as these patients can benefit significantly from immunotherapy. Immunotherapy remains the standard of care for this unique subset of patients, whereas MSS/$BRAF^{V600E}$-mutated tumors may require optimized chemotherapeutic and targeted strategies. Future molecular subclassification such as BM1/BM2 may further refine personalized therapeutic approaches in BRAF-mutant CRC.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Author contributions

Jen-Yu Chuang conceived and designed the study, collected clinical data, and prepared the initial manuscript draft. Johnson Lin contributed to data acquisition, literature review, and manuscript editing. Nai-Wen Su supervised the project, provided intellectual input, and critically reviewed the final manuscript. All authors have read and approved the final version of the manuscript.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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