International Journal of Biomedicine 14(3) (2024) 524-528
http://dx.doi.org/10.21103/Article14(3)_CR1

CASE REPORT

INTERNATIONAL JOURNAL OF BIOMEDICINE

Colorectal Cancer with the *BRAF* V600E Mutation: Two Case Reports and Literature Review

Nguyen Cuong Pham[1], Van Linh Ho[2*], Victoria Ton-Nu[3], Minh Tri Ngo[4], Huu Son Nguyen[5]

[1]*Pathology Department, Hue Central Hospital, Hue City, Vietnam*
[2]*Digestive Surgery Department, Hue Central Hospital, Hue City, Vietnam*
[3]*University of California, Irvine, CA, USA*
[4]*Department of Radiology, Hue Central Hospital, Hue City Vietnam*
[5]*Pediatric Center, Hue Central Hospital, Hue City, Vietnam*

Abstract

Colorectal cancer usually develops from stepwise, multiple mutations involving oncogenes and tumor suppressor genes. Mutations in the *BRAF* and *RAS* genes that dysregulate MAPK signaling are strongly associated with human malignancies. Colorectal cancer with the *BRAF* V600E mutation that causes cell proliferation without the need for growth factors has a worse prognosis than those without mutations. A *BRAF* V600E mutation was identified as an adverse prognostic factor for progression-free and overall survival. In this study, we analyze two cases of colorectal cancer with the *BRAF* V600E mutation and the literature data to investigate potential pathophysiologic mechanisms underlying metastatic colorectal cancer.**(International Journal of Biomedicine. 2024;14(3):524-528.)**

Keywords: rectal cancer • *RAS* genes • *BRAF* V600E mutation

For citation: Pham NC, Ho VL, Ton-Nu V, Ngo MT, Nguyen HS. Colorectal Cancer with the *BRAF* V600E Mutation: Two Case Reports and Literature Review. International Journal of Biomedicine. 2024;14(3):524-528. doi:10.21103/Article14(3)_CR1

Abbreviations

CRC, colorectal cancer; **mCRC**, metastatic colorectal cancer; **EGFR**, epidermal growth factor receptor; **MSI**, microsatellite instability; **VEGF**, vascular endothelial growth factor.

Introduction

Colorectal cancer (CRC) is a commonly occurring cancer in both men and women. According to GLOBOCAN statistics for 2020, Vietnam recorded nearly 16,000 new cases of colon cancer and more than 8,200 deaths from this disease.[1]

Colorectal cancer usually develops from stepwise, multiple mutations involving oncogenes and tumor suppressor genes.[2-11] Mutated *RAS* genes were the first cellular oncogenes identified in human tumors more than 40 years ago. RAS interacts with a large number of effector proteins, most notably the RAF kinases (ARAF, BRAF, and CRAF) that coordinate various cellular responses.[12] Mutations in *BRAF* and *RAS* genes that dysregulate MAPK signaling are strongly associated with human malignancies.[13] Mutations in *RAS* genes are estimated to be responsible for approximately 20% of all human cancers.[14] Among the three *RAS* genes, mutations in *KRAS* are responsible for 75% of RAS-driven cancers, followed by mutations in *NRAS* (17%) and *HRAS* (7%).[14] *KRAS* mutations are common events detected in 40-45% of all CRC samples analyzed.[15] The B-Raf proto-oncogene serine/threonine kinase (*BRAF*) gene encodes a cytoplasmic serine-threonine kinase BRAF that acts immediately downstream of KRAS in the MAPK signaling pathway. About 10% of colorectal cancer cases with wild-type

***Corresponding author:** Van Linh Ho, Digestive Surgery Department, Hue Central Hospital. Hue City, Vietnam. E-mail: tslinh2020@gmail.com*

KRAS gene have the mutated *BRAF* gene, which can affect response to anti-epidermal growth factor receptor (EGFR) antibody therapy.[15-18] Mutations in *KRAS* and *BRAF* are crucial in the RAS-RAF-MAPK pathway in the development of CRC. About 7-10% of individuals with metastatic CRC have been identified to have *BRAF* mutations.[19] The *BRAF* mutant metastatic colorectal cancer (mCRC) is consistently linked to a distinct phenotype in many research papers and meta-analyses, particularly characterized by the *BRAF* V600E mutation, a valine-to-glutamate change at the residue 600 (V600E), that causes cell proliferation without the need for growth factors. *BRAF*-mutated tumors are more prevalent in females and in patients of advanced age, typically >70 years.[20]

Suppressing BRAF in metastatic colorectal cancer (mCRC) yielded unsatisfactory results. An expansion phase II study examined vemurafenib in mCRC patients with *BRAF* V600E mutation who have had at least one line of prior therapy.[21] Of the 21 patients treated, 1 had a partial response, and 7 other patients had stable disease by RESIST criteria. The median progression-free survival was only 2.1 months, and the objective response rate was 5%. The authors concluded that single-agent vemurafenib did not show meaningful clinical activity in patients with *BRAF* V600E-mutated mCRC.

In this study, we analyze two cases of colorectal cancer with the *BRAF* V600E mutation and the literature data to investigate potential pathophysiologic mechanisms underlying colon cancer.

Case Reports

From January 1st, 2022, to February 10th, 2023, 62 colorectal cancer cases at Hue Central Hospital were tested for *NRAS*, *KRAS*, and *BRAF* genomic mutations. In two cases (3.2%), the *BRAF* V600E mutation was detected using a real-time PCR technique. These two patients had colon cancer with lymph node metastases (pT4N2aMx). Some pathologic characteristics of two mCRC patients with the *BRAF* V600E mutation are shown in Table 1.

Table 1.

Characteristics in mCRC patients with BRAF mutations.

	Case 1	Case 2
Age, years	35	51
Sex	Female	Male
Histology type	Adenocarcinoma, moderately differentiated, invasive	Adenocarcinoma, moderately differentiated, invasive
Lymph node metastases	Yes	Yes
Gene mutation	BRAF V600E	BRAF V600E
Tumor site	Rectum	Rectum
Tumor size	4×4×6 cm	3×4×5 cm

MRI of Case 2 is demonstrated in Figure 1. Currently, these two cases are being actively treated with the NCCN Guidelines for rectal cancer (version 6. 2020). Figure 2 presents an MRI at a 3-month follow-up of Case 2. Until now, patients still have a good quality of life, and the disease is under control.

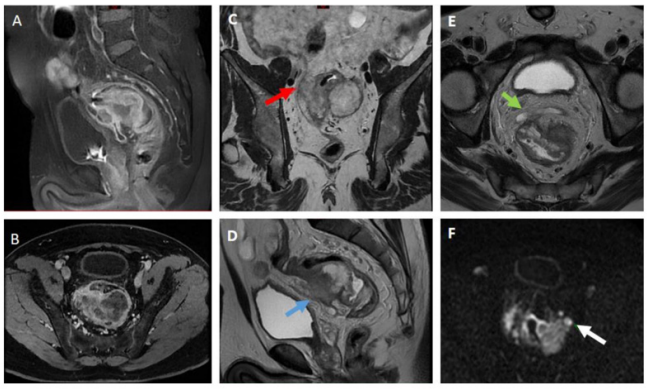

Fig. 1. *MRI of patient DO VAN M. (Case 2) with high rectal cancer cT4aN2aMx.*

A and B: High rectum mass demonstrates heterogeneous enhancement; C: There is the involvement of the mesorectum (red arrow) [MRF (+)]; D: Tumor invasion of the peritoneum (blue arrow) [T4a tumor]; E: Perirectal abscesses associated with fistula development (green arrow); F: Lymph node metastasis (white arrow).

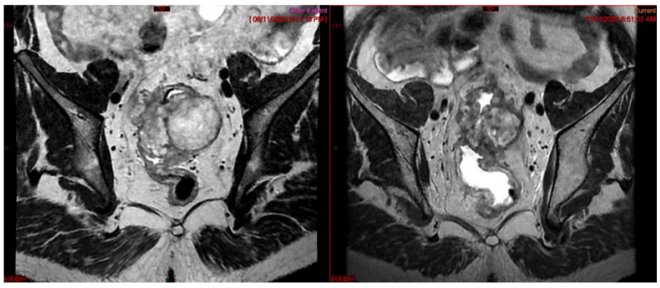

Fig. 2. *MRI at 3-month follow-up of patient Do Van M. (Case 2). Tumor size reduction after the first chemotherapy course. MRI: tumor regression grade 3 (moderate).*

Discussion

Of the 62 rectal cancer cases examined for gene mutations, we found 2 cases (3.2%) with the *BRAF* V600E mutation. In these cases, tumors were detected at clinical stage 3 or higher, and nodal metastases were detected simultaneously. Safaee Ardekani et al.[22] showed that the average prevalence of the *BRAF* V600E mutation was 9.6% in colorectal cancer, and the *BRAF* V600E increases the risk of mortality in colorectal cancer patients more than two times; HR = 2.25 (95% CI: 1.82-2.83).

Clinicians must be knowledgeable about this subtype due to the varying treatment strategies. The clinical benefit in responders treated with anti-EGFR mAbs has been shown to only last 8–10 months.[23,24] As treatment progresses, approximately 80% of responders develop drug resistance.[25] Despite the confusing results of the vemurafenib studies, another BRAF inhibitor, encorafenib, has confirmed the feasibility of dual-targeted EGFR and BRAF treatment to increase the efficiency of anti-EGFR mAbs.[26]

In terms of *BRAF* gene characterization, the serine/threonine BRAF protein kinase is an important player in the mitogen-activated protein kinase (MAPK) - epidermal growth

factor receptor (EGFR) signaling pathway, where it is stimulated and activated by RAS small GTPase. BRAF's influence extends to other RAF isoforms (ARAF and CRAF), significantly impacting the MAPK pathway and various cellular processes like cell growth, proliferation, differentiation, migration (through RHO small GTPases), apoptosis (via BCL-2 regulation), and survival (via the HIPPO pathway). Therefore, it is not unexpected that BRAF was shown to be continuously active due to mutation in 15% of all identified human malignancies.[27]

The bulk of *BRAF* mutations are V600E (a point mutation that involves nucleotide 1799 [thymine to adenine trans-version, c.1799T>A]), which accounts for up to 80% of all *BRAF* mutations; however, mutations can occur at other places.[28] This mutation leads to alterations in amino acids that trigger structural kinase activity. Most *BRAF* mutations result either in acquiring novel phosphomimetic residues or in releasing an autoinhibitory construct imposed by the N-terminus, which enhances kinase domain dimerization, a crucial mechanism for activating kinases. Various firms have produced BRAF inhibitors, with the most often used ones being vemurafenib (sold as Zelboraf by Roche) and dabrafenib (sold as Tafinlar by GSK). Other examples include encorafenib (LGX818; Novartis), XL281 (Exelixis), and CEP-32496 (Ambit Biosciences Corporation).

Regarding the mechanism of colorectal cancer transformation, according to David Barras, adenomatous polyps (~10%) and hyperplastic polyps (~90%) are the two types of colon polyps.[28] On the other hand, hyperplastic polyps do not develop into colorectal cancer. Following the WHO classification, serrated polyps are named for their serrated shape (ICD-O 8213/0). These polyps were formerly believed to be not cancerous; however, several studies have been questioned. Serrated polyps are categorized as conventional serrated adenomas (TSA), serrated hyperplasia, or sessile serrated adenomas (SSAs). SSA and TSA are regarded as premalignant. *BRAF* mutations are thought to cause epithelial changes in TSA and SSA polyps. This means that this mutation is an early event in the development of CRC. Activation of the Wnt signaling pathway in tandem with inactivation of p53 and p16 is present only in the late stages of CRC. BRAF mutant tumors are often right-sided, relapsing more frequently in women, at a higher degree, and are associated with microsatellite instability (MSI) and senescence. MSI is a genetic disorder caused by the absence of a mismatch repair system, leading to increased variability. MSI is considered the most reliable prognostic indicator in colorectal cancer, as instability is associated with a more favorable outcome. Interestingly, the deleterious effects caused by *BRAF* mutations were more pronounced in microscopically stable patients than in unstable (MSI) patients, although not different in statistics. The interaction between the *BRAF* and MSI states is a hotly debated topic. Proximal right CRC is associated with a worse prognosis.[28] *BRAF* mutations have a high frequency in proximal right tumors. The reason for this association is not fully understood. A systematic review and meta-analysis by Petrelli et al.[29] showed that colon cancer side should be acknowledged as a criterion for establishing prognosis in all stages of the disease.

While it is well known that *KRAS* mutations are predictive for cetuximab, there is much disagreement on the predictive importance of mutant *BRAF*. Anti-EGFR has been demonstrated in numerous studies to provide advantages to those with *BRAF* mutations. Rowland et al.[30] conducted a meta-analysis that grouped eight groups, including 351 *BRAF*-mutant patients, including *BRAF* wild-type patients. This analysis revealed that the hazard ratios of patients treated with EGFR-blocking antibodies (cetuximab or panitumumab) were not dependent on the *BRAF* mutation status for overall survival (P=0.43) but were close to significance for progression-free survival (P=0.07). The authors concluded that the *BRAF* mutation was not predictive of benefits provided by anti-EGFR therapies.[30]

Another meta-analysis by Pietrantonio et al.[31] revealed that EGFR-blocking antibodies did not increase the efficacy of standard chemotherapy in *BRAF*-mutant patients. However, this study did not assess the survival differences between *BRAF* wild-type and *BRAF*-mutant patients.

On the other hand, *BRAF* mutations have a well-established prognostic significance in CRC and are typically linked to a much worse prognosis. In a study involving more than 1200 stage II and III patients, a multivariate Cox proportional hazard regression indicated that the BRAF mutation significantly affects the overall survival (hazard ratio: 1.78 [1.15–2.76]; P=0.01), while relapse-free survival was not found to be altered (hazard ratio: 1.30 [0.87–1.95]; P=0.21).[32] *BRAF*-mutated patients had significantly shorter progression-free survival and overall survival than wild-type patients. *BRAF*-mutated CRCs are characterized by a dismal prognosis and resistance to standard therapies, with a median OS (mOS) of approximately 12 months.[33] Innocenti et al.[34] reported the aggressive behavior of *BRAF* V600E-mutated tumors with a mOS of 13.5 months compared to 30.6 months for patients with *BRAF* wild-type tumors.

Previous studies with chemotherapy-based regimens have shown poor outcomes in patients with the *BRAF* V600E mutation.[34-40] International guidelines recommend doublet or triplet chemotherapy with or without vascular endothelial growth factor (VEGF) inhibitors for patients with *RAS* wild-type/*BRAF*-mutated mCRC.[41,42]

The ANCHOR CRC study[43] showed that the scientifically driven combination of encorafenib + binimetinib + cetuximab was active in the first-line setting of *BRAF* V600E-mutated mCRC with a manageable safety profile.

The Triplet plus Bevacizumab (TRIBE) study,[44] a phase 3, randomized, open-label, multicenter trial conducted in 34 Italian centers and involving patients with unresectable metastatic colorectal cancer who had not received chemotherapy or biologic therapy for their metastatic disease but may have received adjuvant chemotherapy earlier in the disease course, showed that combination of fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab (a monoclonal antibody against VEGF), as compared with FOLFIRI (fluorouracil, leucovorin, and irinotecan) plus bevacizumab, improved the outcome in patients with metastatic colorectal cancer and increased the incidence of some adverse events. A *BRAF* mutation was identified as an adverse prognostic factor for progression-free and overall survival in the univariate model. A study by Cremolini et al.[45] showed that FOLFOXIRI + bevacizumab significantly and meaningfully improved the survival of patients with metastatic colorectal

cancer compared with doublets + bevacizumab and provided an advantage in progression-free survival, objective response rate, and R0 resection rate at the price of a moderate increase in toxicity. No increased benefit was observed among patients with *BRAF*-mutant tumors.

Conclusion

Colorectal cancer usually develops from stepwise, multiple mutations involving oncogenes and tumor suppressor genes. Mutations in the *BRAF* and *RAS* genes that dysregulate MAPK signaling are strongly associated with human malignancies. Colorectal cancer with the *BRAF* V600E mutation that causes cell proliferation without the need for growth factors has a worse prognosis than those without mutations. International guidelines recommend doublet or triplet chemotherapy with or without VEGF inhibitors for patients with *RAS* wild-type/*BRAF*-mutated mCRC. Of the 62 rectal cancer cases examined for *BRAF* gene mutations in Hue Central Hospital, 2 cases (3.2%) had the *BRAF* V600E mutation. In these BRAF V600E-mutated cases, tumors were detected at clinical stage 3 or higher, and nodal metastases were detected simultaneously. Currently, these two cases are being actively treated with the NCCN Guidelines for rectal cancer (version 6. 2020). Until now, patients still have a good quality of life, and the disease is under control.

Competing Interests

The author declares that there is no conflict of interest.

Acknowledgments

We want to thank everyone at Hue Central Hospital who supported and helped us to complete this study.

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