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Rectal cancer with v600e BRAF gene mutation: A two-case report from Hue Central Hospital

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ABSTRACT

BRAF gene mutations are rare in cancer, especially in colorectal cancer. BRAF gene mutations can be found in ovarian tumors, thyroid cancer, colorectal cancer, melanoma, and other cancers. Compared to individuals without mutations, colorectal cancer patients with a BRAF gene mutation at position V600E have a poorer prognosis. As soon as cancer was discovered, Hue Central Hospital used a real-time PCR technology to identify several cases of BRAF gene mutation at V600E with lymph node metastases. The article's goal is to gather information and examine the literature in order to learn more about this particular form of colorectal cancer sickness.

Keywords: rectal cancer, v600e BRAF, gene mutation

INTRODUCTION

Colon cancer is common in both men and women. In 2020, Vietnam had over 16,000 new instances of colon cancer and over 8,200 deaths from the disease, according to GLOBOCAN figures [1]. Recent studies have revealed how gene changes (mutations) lead to progression from normal colon tissues to true carcinoma [2-11].

According to Fernández-Medarde et al., the importance of RAS in regulating cell proliferation is illustrated by the presence of K-RAS-activating mutations in approximately one-third of human cancers., comprising as much as 50% of colorectal malignancies [12].

Additionally, 20% of colorectal cancers with wild-type KRAS genes have BRAF-activating mutations [13]. In the RAS-RAF-MAPK pathway, which is involved in the development of colorectal cancer, mutations in KRAS and BRAF are critical. The RAF family of genes, which encode kinases that modulate cellular reactions to growth signals, is regulated by Ras. Three isoforms of the RAS family—H-RAS, K-RAS, and N-RAS—share a substantial amount of sequence similarity. One important pathway that controls cell division is the RAS signaling cascade. RAS proteins can integrate external signals from many receptor types [14].

About 7-10% of individuals with metastatic CRC have been identified to have BRAF mutations [15]. Many research studies and meta-analyses have consistently connected the BRAF mutant metastatic colorectal cancer (mCRC) to a unique phenotype, which is best described by the BRAF V600E mutation. Over 70-year-olds and females are more likely to get BRAF tumors. BRAF is not linked to a diagnosis before 60 years of age [16].

Nevertheless, in metastatic colorectal cancer (mCRC), BRAF suppression had disappointing outcomes. A large-scale phase II trial examined vemurafenib use in patients with BRAF MT mCRC who had undergone at least one prior treatment. Seven of the twenty-one patients who underwent treatment met the RESIST criteria for stable disease, and one had a partial response [17]. There is a 5% response rate overall, and the median progression-free survival is 2.1 months. Despite

encouraging results, the authors concluded that single-agent vemurafenib did not show any clinically meaningful action in patients with BRAF V600E MT mCRC [17].

The objective of this study is to examine the pathological features of colorectal cancer with BRAF mutations at the V600E and to evaluate the literature to gain further insight into the pathophysiology and prognosis of this illness.

CASE REPORT

From January 1st 2022, to February 10th 2023, we have done the test of NRAS, KRAS, and BRAF genomic mutations in 62 colorectal cancer cases at Hue Central Hospital in which two cases with BRAF gene mutation at V600E point have been detected (accounted for 3.2%). Especially when these two patients were pathology diagnosed with colon cancer, they had metastasized lymph nodes (pT4N2aMx). Some pathologic characteristics in two patients with BRAF mutations are shown in Table 1. Magnetic resonance imaging of case 2 is demonstrated in Figure 1. For these two patients, the new target therapy procedure according to the NCCN guideline version 6.2023, the response to treatment according to the above procedure, is very good. They enjoyed both life activities and spirituality. MRI at 3-month follow-up of case 2 is revealed in Figure 2.

Table 1. Pathologic characteristics in two patients with BRAF mutations

	Case 1	Case 2
Age	35	51
Sex	Female	Male
Histology type	Adenocarcinoma, moderately differentiated, invasive	Adenocarcinoma, moderately differentiated, invasive
Metastasis of lymph node	Yes	Yes
Gene mutation	BRAF V600E	BRAF V600E

Tumor site	Rectum	Rectum
Tumor size	4x4x6cm	3x4x5cm

DISCUSSION

Of the 62 rectal cancer cases examined for BRAF gene mutations, we found 2 cases with BRAF gene mutations at the V600E point. In two rectal cancer patients with mutations in the BRAF gene, the tumors were detected at clinical stage 3 or higher, and nodal metastases were detected simultaneously. The ratio of rectal cancer to BRAF gene mutation is 3.2%.

Ardekani et al. showed that mutations in the BRAF-V600E gene are present in about 9.6% of patients with advanced colorectal cancer. Although survival rates for advanced colorectal cancer have significantly increased, individuals with BRAF mutations often have a dismal prognosis, generally surviving fewer than 12 months on average [18].

Clinicians must be knowledgeable about this subtype due to the varying treatment strategies. Alternative treatment alternatives to traditional chemotherapy are crucial for improving results, and the effectiveness of anti-EGFR therapy by itself is still a topic of debate. Recent studies using combinations of molecularly targeted drugs have displayed some potential [19].

In terms of the characterization of the BRAF gene, RAS small GTPase stimulates and activates the serine/threonine BRAF protein kinase, which is a major participant in the mitogen-activated protein kinase (MAPK)-mediated epidermal growth factor receptor (EGFR) pathway. Beyond its effects on ARAF and CRAF, BRAF also affects the MAPK pathway and several other cellular processes, including cell growth, proliferation, differentiation, migration (mediated by RHO small GTPases), apoptosis (regulated by BCL-2), and survival (mediated by the HIPPO system). It follows that the finding that BRAF is permanently active due to mutation in 15% of all human cancers detected is not shocking [20].

Up to 80% of all BRAF mutations are caused by the V600E (1799T>One nucleotide substitution) mutation; however, mutations can also occur at other locations [21]. Amino acid changes brought on by this mutation activate structure kinase. The majority of BRAF mutations either include new phosphomimetic residues or cause the N-terminus to produce an autoinhibitory construct that improves kinase domain dimerization, an essential mechanism for kinase activation. BRAF inhibitors are manufactured by several companies; the two most commonly utilized ones are dabrafenib (marketed as Tafinlar by GSK) and vemurafenib (marketed as Zelboraf by Roche). Additional instances are CEP-32496 (Ambit Biosciences Corporation), XL281 (Exelixis), and LGX818 (encorafenib; Novartis).

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 [21]. 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. It is thought that BRAF mutations cause epithelial changes in TSA and SSA polyps.

This indicates that the genesis of CRC began with this mutation. WNT pathway activation and p53 and p16 inactivation are only seen in advanced stages of colorectal cancer. BRAF mutant tumors are typically right-sided, relapse more frequently and to a greater extent in women, and are linked to senescence and microsatellite instability (MSI). The lack of a mismatch repair system results in greater variability and MSI, a genetic disease. Since instability is linked to a better prognosis, MSI is thought to be the most accurate prognostic biomarker for colorectal cancer. Remarkably, although not statistically different, the harmful effects of BRAF mutations were more prominent in patients who were microscopically stable than in those who were unstable (MSI). There is a lot of discussion

on how the BRAF state and the MSI state interact. A worse prognosis is linked to proximal right colorectal cancer [21].

Proximal right cancers frequently contain BRAF mutations. This association's cause is not entirely clear. The reader will be taken to a recent comprehensive review of tissue analysis, along with a more thorough explanation of the molecular mechanism and early findings about BRAF.

There is considerable debate on the predictive significance of mutant BRAF, even though KRAS mutations are proven to be predictive of cetuximab. Numerous studies have shown that individuals with BRAF mutations can benefit from anti-EGFR. It was not until recently that a formal study was conducted on the effect of acquiring BRAF mutations on the response to anti-EGFR treatment (in contrast to individuals with wild-type BRAF). A meta-analysis that pooled eight groups, involving 351 BRAF mutant patients—including those with rabies BRAF—was used to accomplish a similar work recently. A prevalence of 351 patients with BRAF mutations was revealed by this investigation. For overall survival (interaction trial P-value: 0.43), the risk of patients treated with EGFR-blocking antibodies (cetuximab or panitumumab) was unaffected by the presence of a BRAF mutation, but it was nearly significant for progression-free survival (interaction trial P-value: 0.07) [22].

The scientists concluded that advantages resulting from medicines targeting EGFR were not predicted by mutant BRAF. In BRAF-mutant patients, EGFR-blocking antibodies did not increase the efficacy of conventional chemotherapy, according to a meta-analysis by Pietrantonio et al. The current study did not investigate the variation in survival rates between patients with wild-type BRAF and those with BRAF mutations [23].

However, in colorectal cancer (CRC), BRAF mutations have a well-established prognostic importance and are generally associated with a much worse prognosis. More than 1200 individuals with stage II and III colorectal cancer who had BRAF mutations participated in a study done by Barras. Hazard ratio: 1.78 [1.15-2.76]; p = 0.01) showed that BRAF mutations significantly affect

overall survival, but did not alter recurrence-free survival (hazard ratio: 1.30 [0.87–1.95]; p = 0.21) [21].

Barras claims that most metastatic colorectal cancer patients have the BRAF-V600E mutation, which results in a shorter overall survival (OS) and progression-free survival (PFS) than in individuals with wild-type BRAFs. With the BRAF V600E mutation, researchers have been able to detect early OS shortening in stage II-IV colorectal cancer since 2005. For stage IV colorectal cancer (mOS), the predicted median OS is typically between 29 and 30 months. For the individuals with the BRAF-V600E mutation, however, the usual multi-chemotherapy regimen produced only a small mOS of 12–14 months [21].

What is the best course of treatment for patients with recently diagnosed metastatic colorectal cancer who have a BRAF-V600E mutation? We still don't have a definitive response at this time. CEB was examined in patients with metastatic colorectal cancer who had the BRAFV600E mutation and had not received prior treatment in a phase II trial named ANCHOR CRC [24]. The results of the 4.9-month PFS early report (95% CI 4.4-8.1 months) disappointed the authors, who suggested that CEB alone is insufficient. The combination of 5FU, leucovorin, oxaliplatin, and irinotecan + bevacizumab improved mOS by 19.0 months in the BRAF-V600E mutant group compared with chemotherapy, according to a subgroup analysis (n = 16) in the phase III trial TRIBE. typical value [25]. However, this finding from TRIBE was not confirmed in a recent meta-analysis [26].

CONCLUSION

Less than 10% of rectal cancer cases have BRAF mutations, which are extremely uncommon but can have major negative effects on health. BRAF mutations can be found in ovarian tumors, thyroid cancer, colorectal cancer, melanoma, and other cancers. Rectal cancer patients who have a BRAF gene mutation at the V600E site are not as likely to survive as those whose mutations do not occur.

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Two out of every sixty-six cases of BRAF gene mutation V600E with early-stage lymph node metastases were seen at Hue Central Hospital. The NCCN guideline version 6.2023 is currently being actively used in the treatment of these two situations. They continue to have fulfilling lives, and the illness is currently under control.

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Disclosure statement

The authors have stated that they do not have any conflicts of interest.

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Authors' contributions

The authors have the same contribution to the stage in editing the paper and are responsible for all aspects of this work.

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Figure 1. Magnetic resonance reporting of patient DO VAN M. (case 2) who has high rectal cancer cT4aN2aMx; A and B. High rectum mass demonstrates heterogeneous enhancement; C. There is involvement of the mesorectum (red arrow), i.e. MRF (+); D. Tumor invasion of the peritoneum (blue arrow), i.e. T4a tumor; E. Perirectal abscesses associated with fistula development (green arrow); F. Lymph node metastasis (white arrow).

Figure 2. MRI at 3-Month follow-up of patient Do Van M. (case 2): Tumor size reduction after the first chemotherapy-course. Magnetic resonance imaging tumor regression grade 3(moderate).