

Case Report

# BRAF Non-V600E Mutated Metastatic Colorectal Cancer in a Young Patient: Discussion from a Case Report

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## Keywords

Metastatic colorectal cancer · BRAF mutation · Prognosis · Molecular characterization

## Abstract

We report the case of a 32-year-old man with a caecal adenocarcinoma with major lymph node extension and peritoneal carcinomatosis, presenting a BRAF-K601E mutation. A triplet (5FU plus oxaliplatin plus irinotecan) combination with bevacizumab achieved tumor control but the disease progressed immediately after cessation and the patient died 8 months after the diagnosis. A short review of BRAF non-V600E mutations shows that outcome and clinical features depend on the mutation.

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## Introduction

Metastatic colorectal cancer (mCRC) is common and 25% of patients present with metastases at diagnosis. Over the last two decades the prognosis of metastatic cases has improved and is more than double that of 20 years ago. This is related to new and efficient systemic therapies and to biomarker-based selection, particularly RAS and BRAF testing [1]. RAS

mutational status is predictive of efficacy of anti-EGFR monoclonal antibodies. BRAF mutations [2], found in 8 to 12% of patients with mCRC, are considered as a negative prognostic marker with a median overall survival (mOS) for patients with BRAF-mutant (BRAF-mt) mCRC which is far shorter (less than 12 months) than for patients with BRAF-wild type (BRAF-wt) mCRC (more than 30 months) [1]. This is related to activation of the MEK-ERK pathway stimulating cell proliferation and survival. BRAF mutations are very frequent in melanoma (>50% of the cases) and have led to the development of specific therapies. Many BRAF-mt alleles have been found but the most common is BRAF-mt V600E. The clinical and prognostic significance of BRAF-mt non-V600E mutations is not well known but this is evolving.

### Case Presentation

Here we report the case of a 32-year-old man who died from a BRAF-mt K601E tumor. This patient, with no familial or personal history (apart from obesity, BMI = 37 kg/m<sup>2</sup>), had a cholecystectomy in March 2018 due to right upper quadrant pain and vomiting with enlarged gallbladder on US exam. Nothing was noted during laparoscopic cholecystectomy but pain persisted. Several weeks later a CT scan revealed multiple enlarged retroperitoneal and mediastinal lymph nodes with a right colon mass and regional adenomegalies. Biopsy of a supraclavicular node revealed a poorly differentiated adenocarcinoma; colonoscopy disclosed a large caecal tumor, tumor markers (CEA and CA 19–9) were normal. In May 2018 the patient underwent surgery (right colectomy) because of a subocclusion. A peritoneal carcinomatosis was found. Pathological exam of the right colectomy revealed a large (11 cm) caecal tumor which histologically corresponded to a poorly differentiated adenocarcinoma invading the serosa with a colloid component of 10%; 34 of the 35 resected lymph nodes were invaded. The tumor was classified pT4aN2b with nodal and peritoneal metastases. The tumor was MMR proficient, with no mutation of RAS, but a BRAF mutation on codon 601 (nucleotide substitution c.1801 A>G; BRAF-mt K601E) was identified; this mutation was considered as activating. Following the usual guidelines, a first-line chemotherapy combining 5FU, folinic acid, irinotecan and oxaliplatin associated with bevacizumab [3] was introduced. After 6 cycles the general status improved and pain disappeared, but CT scan showed only a 10% decrease in tumor size. Therefore, the same regimen was proposed for 6 other cycles. After 9 cycles the patient presented mild neuropathy and oxaliplatin was stopped. A few days later a pulmonary embolism led to withdrawal of bevacizumab. In mid-December, after 12 cycles, the patient reported no pain. He was tired (PS 1), but physical examination was normal. The CT scan images remained stable. It was decided to give him time off from chemotherapy during the 2 last weeks of December but when he came back in early January, pain had recurred and his performance status had worsened to PS 2. Despite medical palliative care, PS worsened and the patient died in mid-February, 8 months after colonic surgery. He never developed liver or lung metastases.

### Discussion

In melanoma, BRAF-mt K601E mutations were observed in 1–5% of cases [4] and their prognosis does not seem unusual. The incidence of BRAF-mt non-V600E mutations reported in different series of mCRC patients ranges from 1.6% [5] to 5.4% [6]. A large retrospective cohort (nearly 10,000 mCRC patients) from three US reference laboratories focused on BRAF-

mt non-V600E mutations in mCRC [7]. These mutations represented 22% of all BRAF-mt and were observed in 2.2% of all patients. When compared with BRAF-mt V600E, these non-V600E mutations were found in younger patients, more frequently females, with fewer high grade and right-sided tumors and less frequent peritoneal carcinomatosis. These patients with BRAF-mt non-V600E mutations were less likely to have MSI (6% vs. 30%). Surprisingly, their mOS (analyzed in a subgroup) was significantly longer; in this large series, mOS of BRAF wt ( $n = 249$ ) was 43.0 months, versus 11.4 months for BRAF-mt V600E ( $n = 99$ ) and 60.7 months for BRAF-mt non-V600E ( $n = 101$ )! Among their series of 208 patients with BRAF-mt non-V600E, the codon mutation distribution showed that 93 mutations were on codon 594, 29 on 469, 23 on 466 and 16 on 601 [8]. In melanoma, mutations in codons 594 and 596 were associated with a better prognosis than V600E mutations [9]. A small series of 7 BRAF-mt non-V600E mCRC was reported but their phenotype and prognosis seemed close to that observed in BRAF-mt V600E [10]. Cremolini et al. reported 10 cases of BRAF-mt on codons 594 and 596 and found that their prognosis was better and that these cancers were left-sided [5].

BRAF mutations are currently grouped into 3 classes: activating RAS-independent signaling as monomer (class 1: V600E) or as dimers (class 2: codon 597/601), and RAS-dependent with impaired kinase activity (class 3: codons 594/596) [11]. In this series, class 3 BRAF-mutated mCRC were more frequently left-sided, with no peritoneal deposits and had a better prognosis, close to BRAF-wt mCRC. This aggressive phenotype of BRAF-mt non-V600E was observed in our patient. In the database of our genetic laboratory we found 2 other cases of mCRC BRAF-mt K601E; both cases occurred in elderly women and both had peritoneal carcinomatosis of a right-sided colon cancer and survived less than 8 months.

## Conclusion

In conclusion, this case of a young patient with mCRC harboring a BRAF-mt K601E mutation is of interest. The tumor did not respond to the usual triplet combination plus bevacizumab used in such cases and the patient died within a few months without any liver or lung metastases but only lymph node invasion and peritoneal carcinomatosis. BRAF-mt non-V600E mutations are detected by NGS-based testing and are not so uncommon. Moreover, we have to know that these mutations are diverse and that some are associated with a less aggressive phenotype and a better prognosis; then it is of paramount importance not to consider all these patients as “usual BRAF-mt patients” and to adapt treatment strategy to the molecular characterization.

## Statement of Ethics

The authors have no ethical conflicts to declare.

## Disclosure Statement

The authors have no conflicts of interest to declare.

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