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A case presentation of an Iranian patient with metastatic colon cancer caused by BRAF mutation

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Abstract

A 49-year-old patient presented to our clinic with significant weight loss and abdominal pain. She underwent a colonoscopy, which showed a tumor with a size of 10 cm in her transverse colon. The pathology report showed adenocarcinoma. Subsequently, partial right-sided colectomy and bilateral oophorectomy were performed. The repeated pathology evaluation confirmed adenocarcinoma of the colon with metastatic involvement of the right ovary. Upon further evaluation, she was positive for *BRAF* V600E mutation, which is rare in the Iranian population. She was negative for *KRAS* and *NRAS* mutations but was positive for microsatellite instability (MSI). Postoperative chemotherapy was initiated with folinic acid, fluorouracil, and oxaliplatin (FOLFOX). However, during her post-operation period, she developed metastasis to the abdominal wall. Our report highlights the importance of genetically analyzing the tissue samples from these patients to better understand the clinicopathologic features and behavior of these tumors.

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Introduction

Colorectal cancer (CRC) is the third most common cancer globally and the fourth most common cause of death due to cancer (1). CRCs have a homogeneous histologic pattern; however, each tumor may have distinctive molecular-causing mechanisms. The most common molecular mechanisms include microsatellite instability (MSI), chromosomal instability, and DNA mismatch repair (MMR) (2).

BRAF activating mutation (v-raf murine sarcoma viral oncogene homolog B1) is one of the signaling pathways that leads to the activation of MAPK (mitogen-activated protein kinase) resulting in tumorigenesis (2, 3).

BRAF V600E is found in 5-10% of metastatic CRCs (mCRCs) and is associated with a lower median overall survival (OS), progression-free survivals (PFS) rates, and inadequate response to standard therapies (3-5).

Furthermore, the V600 mutation of *BRAF* has a major role in the epigenetic activation of MLH1 and MSI phenotypes in patients with CRC (3, 6-8).

mCRCs with *BRAF* V600 mutations are associated with the female gender, right-sided primary tumor, older age, MSI, and uncommon metastasis patterns such as peritoneal and distant lymph node involvements (2, 7-11).

Key point

Here we presented a case report showed the clinical significance of molecular analysis in metastatic colon cancer in better understanding the clinicopathological features, tumor behavior, metastasis and dissemination pattern.

Herein, we present an Iranian case of metastatic colon cancer with a de novo *BRAF* V600 mutation and MSI.

Case Presentation

A 49-year-old woman was referred to our hematology clinic for further evaluation of her chronic abdominal pain and significant weight loss. Physical examination was unremarkable. She had no significant past medical or relevant family histories.

In July 2018, an ultrasound of the abdomen and pelvis revealed a cyst with a diameter of 11 mm in the left lobe of the liver. In addition, the patient underwent a colonoscopy which showed a large 10 cm length tumor in the transverse colon; therefore, multiple biopsies were taken. Surgical pathology evaluation reported neoplastic proliferation of the epithelial cells forming glands and tubules within fibrous stroma with hyperchromic nuclei. Nuclear

atypia and polymorphism were also seen. As a result, she was diagnosed with adenocarcinoma. Furthermore, spiral computed tomography (CT) scan of the abdomen and pelvis showed thickened left subphrenic wall and a short segment of the colon was associated with surrounding fat stranding, which was a differential diagnosis of focal infiltrative process.

Consequently, partial right-sided colectomy, splenectomy, and bilateral oophorectomy were performed. The pathology evaluation revealed colon adenocarcinoma with metastatic involvement of the right ovary. Moreover, the proximal and distal of the colon were free of involvement, but 2/4 of the resected lymph nodes were involved. The stage of the tumor was reported as C Duck.

Idylla™ NRAS-BRAF mutation test was performed to genetically analyze the tissue sample. The evaluation was negative for mutations in the *NRAS* codons 12,13,59,61,117,146 (negative, wild type) but a mutation in the *BRAF* codon 600 (mutation V600E/D) was detected. In addition, the assessment of *KRAS* mutation with the Biocartis system showed no mutation in the *KRAS* codons 12,13,59,61,117,146. Further immunohistochemistry test demonstrated loss of *MLH1* and *PMS2* with normal *MSH2* and *MSH6*; and, was positive for MSI.

Mammography of the breasts showed round calcified foci at the supra-medial area of the right breast and the supralateral of the left breast. A breast imaging report and detection score of 0 (BI-RADS) was reported which required further evaluation. Therefore, additional breast sonography was performed that revealed benign findings (BI-RADS 2).

Postoperative therapy with FOLFOX (folinic acid, fluorouracil, oxaliplatin) regimen was initiated. However, in October 2018, during the post-operation period after six rounds of chemotherapy, the patient noticed a mass in her abdominal wall (Figure 1). Thoracic CT scan reported evidence of peritoneal carcinomatosis in the left sub-diaphragmatic region. Ultrasound evaluation of that specific area showed three hypoechoic masses with diameters of 21, 27, and 26 mm in the abdominal wall under the surgery scar suggesting metastasis to the abdominal wall.

In December 2018, the patient was referred to a clinical geneticist for consultation. The result was; "Pathologic description of tumor is highly suggestive for Lynch syndrome, although positive *BRAF* has known to be the marker for MLH methylation, it can be seen in sporadic cases and does not usually accompany with Lynch syndrome. Taking into consideration that an individual *BRAF* result is not reliable for the final diagnosis".

Subsequently, resection of the abdominal wall mass was performed, and histological analysis reported metastatic carcinoma. The immunohistochemical specimen result of the wall mass was in favor of metastatic carcinoma (of colon origin), and CD125 and CDK20 were positive, CDX2 was strongly positive, and CDK7, WT1, ER, and vimentin were negative in the tumoral cells.

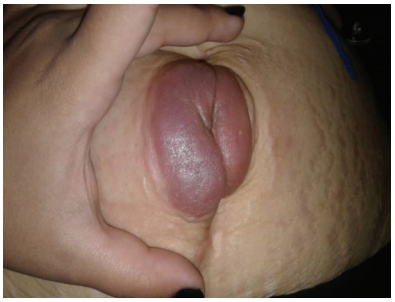

Figure 1. The image of the abdominal wall lesion that appeared after the patient's surgery.

As mentioned above, after the first surgery the patient was treated with FOLFOX, but following the appearance of the abdominal wall mass, irinotecan was added, and the regimen was changed to FOLFIRINOX. Then, the patient was a candidate for treatment with cetuximab, an anti-epidermal growth factor receptor (EGFR), due to the presence of wild-type mutations of *KRAS* and *NRAS,* but considering the *BRAF* V600 mutation, the treatment with cetuximab was canceled and Avestin (bevacizumab) was initiated. Therefore, her therapy was continued with FOLFIRINOX and Avestin. Recent studies have stated better outcomes with cetuximab administration in *BRAF* positive patients. Therefore, further therapy protocols will be considered and decided for our case based on these results.

After three rounds of treatment with FOLFIRINOX and Avestin, the abdominal lesions disappeared, but the patient discontinued the treatment and did not follow up at the clinic.

Discussion

Studies have evaluated the association of various molecular markers with the prognosis of CRC. MMR testing is recommended for clinical assessment and management of CRC. However, testing for *RAS* mutation (*KRAS* and *NRAS* codons) is another predictive marker, and *BRAF* mutations also have potential prognostic and predictive abilities (12, 13).

BRAF and *RAS* mutations are 'driver mutations' and are among the first occurrences in colorectal carcinogenesis. However, they have differences in the stimulation of tumor cell transformation, oncogenic signaling, functional roles during cancer progression and metastasis as well as the different impact they have on the diagnosis, prognosis, and clinical outcome of the diseases, and therapeutic options (14, 15).

Approximately 10 % CRCs are caused by mutations in the *BRAF* gene, mostly the V600E mutation (16). The prevalence of CRC caused by *BRAF* mutation has been reported to be approximately 0.7%-11.4% in Eastern Asian countries which is lower compared to Western countries that have a prevalence ranging from 3.7% to 20.6% (9).

There has been a significant increase in the prevalence of CRC in the Iranian population over the last three decades and it is now the fourth most common malignancy among the Iranian community (17, 18).

There are progressive and ongoing studies that evaluate the prevalence and characteristics of mutations in Iranian patients with CRC. For example, a study by Koochak et al reported that *KRAS* mutation occurred in approximately 33.6% of the Iranian patients diagnosed with CRC. They did not detect any *BRAF* mutation but reported that *BRAF* mutations rarely occur in mCRC in Iran (19). In addition, Naghibalhossaini et al found no V600E mutation of the *BRAF* gene in the Iranian population (20). Therefore, our case of CRC that has *BRAF* mutation is rarely observed in Iran.

CRCs with *BRAF* mutation are associated with unique and distinctive clinicopathological features including the female gender, older age, poor differentiation, mucinous histology, lymphovascular invasion, and proximal right-sided location. Additionally, *BRAF* V600E mutation has been reported to be strongly correlated with MSI (8-11). Moreover, the *BRAF* V600E mutated patients usually have a distinctive metastatic pattern which is associated with the aggressiveness and rapid progression of the disease as well as peritoneal and non-regional lymph node metastasis (8, 11).

Although gene expression profiling studies have expanded our knowledge of CRC the treatment of patients that have advanced CRC with *BRAF* mutation is still challenging. *BRAF* mutation is correlated with an aggressive phenotype, shorter OS and progression-free survival (PFS), and poor prognosis (21-23). Tol et al reported that shorter PFS in patients with mCRC that were treated with chemotherapy, bevacizumab, and cetuximab compared to those that were treated with chemotherapy and bevacizumab only (24).

Recently, abundant insights have linked molecular features of the tumor to the efficacy of target therapies. Increased knowledge about the *BRAF* and *KRAS* mutations help in choosing the most effective treatment. For example, *KRAS* mutation is predictive of the efficacy of anti-EGFR therapies in patients with CRC (25, 26). It is estimated that the responsiveness to anti-EGFR therapy in the *KRAS* wild-type tumors is only around 35% (27).

Some studies have investigated the efficacy of EGFR antibody therapies in patients with *RAS* wild-type/*BRAF* V600E mutated tumors. For example, Pietrantonio et al reported that the addition of an anti-EGFR monoclonal antibody to the treatment of patients with *RAS* wild-type/*BRAF* V600E mutant tumors did not significantly improve the PFS, OS, or overall response rates compared to the group that received control regimens (28). Another meta-analysis by Rowland et al reported no significant OS benefit from adding an anti-EGFR monoclonal antibody to the therapy of patients with *RAS* wild-type/*BRAF* V600E mutant mCRCs. However, they showed that OS was significantly higher in patients with *RAS* wild-type/*BRAF* wild-type tumors. Nevertheless, the comparison of the OS benefit of *BRAF* V600E and *BRAF* wild-type mutant tumors was not statistically significant. Therefore, the authors concluded that the different effects of anti-EGFR monoclonal antibodies on the OS rate that were observed by different mutations of *BRAF* V600E could have been coincidental (29).

Conclusion

In conclusion, this case report suggests the clinical significance of molecular analysis in metastatic colon cancer in better understanding the clinicopathological features, tumor behavior, metastasis, and dissemination pattern.

Authors' contribution

MRKF handling the patient. PN conducted the primary draft. SH conducted the secondary edit. All authors read and signed the final paper.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

The authors have entirely observed ethical issues (including plagiarism, data fabrication, double publication). The patient has given his informed consent regarding the publication of this case report.

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