Case Report

Rare BRCA2 Mutation and MSI-H in Male Patient with Aggressive Stage III Colorectal Cancer, Case Report and Literature Review

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ABSTRACT: Colorectal cancer is the third most common malignancy worldwide. We report the case of a 66-year-old man diagnosed with stage III B colorectal cancer who underwent radical surgery, adjuvant chemotherapy and subsequently developed hepatic metastases. Two months following metastasectomy, PET-CT scan revealed liver metastases with metabolic activity. The patient was started on FOLFIRI chemotherapy regimen in combination with cetuximab, and achieved stable partial remission 7 weeks after starting the treatment. NGS and IHC testing of the surgically removed tumor revealed MSI-H/dMMR, and NRAS/KRAS wild type status, moderate positive (30%) expression of PD-L1 protein, along with BRCA2 mutation.

KEYWORDS: *Colorectal cancer, BRCA2, MSI-H.*

Introduction

Colorectal cancer (CRC) is a common malignancy and one of the primary causes of cancer-related mortality today [1].

Early stage CRC benefits from curative treatment consisting of either surgery (wide resection and lymphatic drainage) or surgery coupled with adjuvant chemotherapy (combination of oxaliplatin and fluoropyrimidine).

Metastatic CRC patients are rarely candidates for radical surgery.

Generally, the focus and the methods of the treatment for metastatic CRC cases shift to improve overall survival (OS) using chemotherapy, targeted agents, and immunotherapy.

However, surgical excision of metastases is a viable option in selected individuals, either upfront or subsequent to systemic therapy [2].

The pathogenesis of CRC is complex, involving genetic and environmental risk factors.

Molecular testing are used to diagnose hereditary disorders or to predict treatment response (RAS, BRAF, MSI, PD-L1).

Immunohistochemistry (IHC) analysis of expression loss of mismatch repair (MMR) proteins is a relevant clinical investigations in CRC, which along with clinical and family history, assists in establishing a Lynch syndrome (LS) diagnosis [3].

BRCA1 and BRCA2 (BReast CAncer gene 1 and BReast CAncer gene 2) are tumor suppressor genes that prevent tumor formation by controlling abnormal cell proliferation.

Carriers of the BRCA1 and/or BRCA2 mutations face a lifetime risk of up to 85% for breast cancer and a risk of 20-40% for ovarian cancer.

The influence of these mutations on the risk of colorectal cancer is less understood [4].

Case Report

A 66-year-old male, former smoker, with no previous medical history, no family history of cancer, on no medications, was admitted in October 2018 for acute abdominal pain and increased frequency of bowel dysfunction.

Patient underwent colonoscopy that revealed a vegetant, stenosing, and ulcerated mass in the transverse colon, with a diameter of approximately 7cm, located 45cm from the anal margin.

Endoscopic biopsies were performed and revealed moderately differentiated adenocarcinoma.

Tissue removed during biopsy was examined for the expression loss of MMR proteins (MLH1, PMS2, MSH2, MSH6) using immunohistochemistry.

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Nuclear expression was determined as follows: MLH1-, PMS2-, MSH2+, and MSH6+, indicating microsatellite instability-high (MSI-H) and mismatch repair deficiency (dMMR).

Contrast-enhanced computed tomography (CT) scanning of the thorax, abdomen, and pelvis showed a circumferential tumor in the transverse colon, without enlarged lymph nodes, with no evidence of metastatic disease (Figure 1).

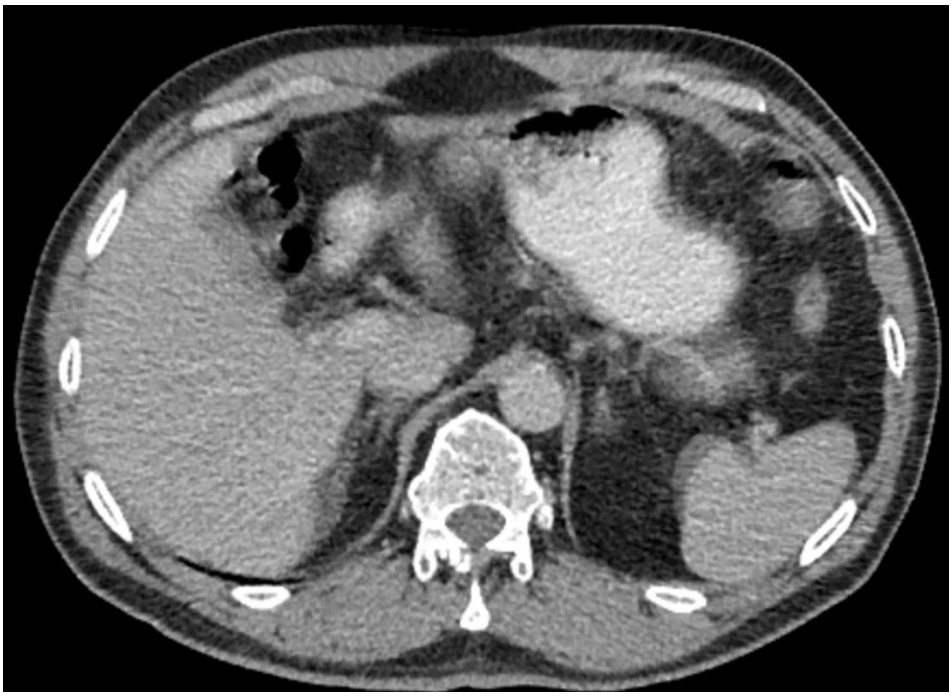

Figure 1. Contrast-enhanced axial CT scan taken in the portal venous phase shows normal hepatic parenchyma with homogeneous density-April, 2018.

Under the preoperative diagnosis of transverse colon cancer, an open extended right hemicolectomy was performed, with ileal anastomosis and adequate nodal resection (16 regional lymph nodes) in April, 2019.

Postoperative pathological examination showed moderately differentiated adenocarcinoma, invasive through the muscularis propria, with areas of medullary carcinoma (pT3), lymphovascular invasion (LVI+), perineural invasion (PNI+), tumor-negative resection margins (R0), one positive regional lymph node (pN1a), and tumor deposits (TD+).

Next-generation sequencing (NGS) performed on the surgically removed formalin-fixed, paraffin-embedded (FFPE) tissue block revealed the following gene alterations: BRCA2, PTCH1, ARID1A, CTNNB1, ERRFI1, SMARCB1, along with MSI-H status.

Further results showed three disease relevant genes with no reportable alterations: BRAF, KRAS, NRAS.

Notably, the NGS assay identified numerous gene alterations with no reportable therapeutic or clinical trial alternatives: ACVR1B, BCORL1, CASP8, CREBBP, MLL2, MSH3, MUTYH, NOTCH1, RARA, and SDHA. IHC staining exhibited moderate positive (30%) expression of the programmed death-1 (PD-1) ligand 1 (PD-L1), and lack of expression of c-erbB-2 oncoprotein.

Following the diagnosis of stage III B colon cancer, the patient was started on the standard of care in the adjuvant setting: 6 months of FOLFOX (combination of fluoropyrimidine and oxaliplatin).

Subsequent imaging studies detected two hepatic metastatic lesions located in segments VII and VIII, with no evidence of metastatic disease at other sites (Figure 2).

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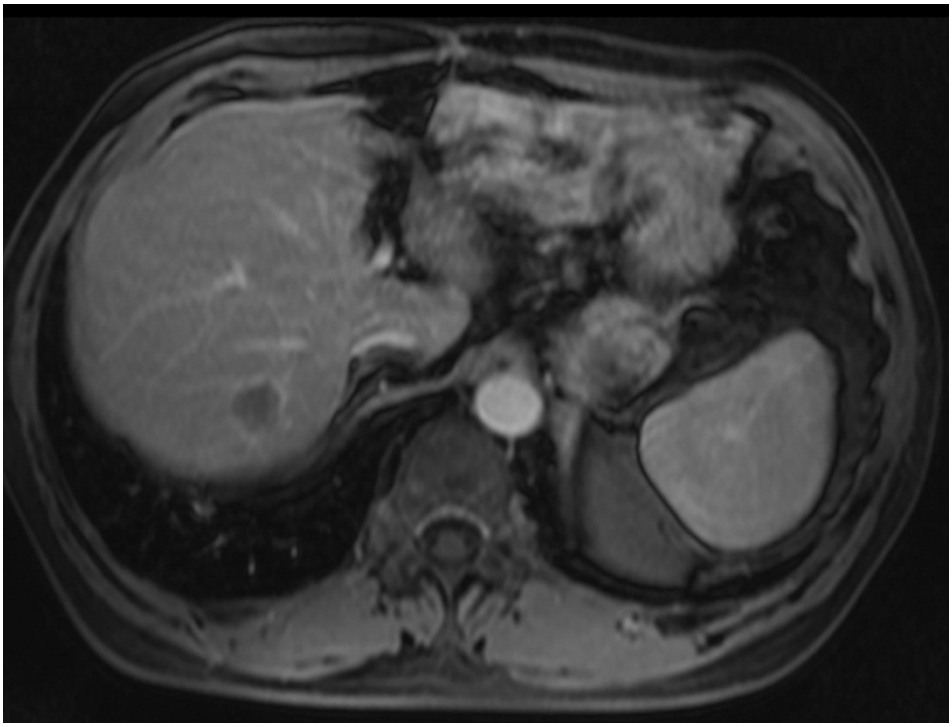

Figure 2. Axial gadolinium-enhanced T1-weighted MR image during the portal venous phase demonstrates a peripherally enhancing lesion (metastasis) measuring 23.8/26.4mm in the right hepatic lobe (segment VII)-April, 2019.

Patient underwent hepatic metastasectomy in May, 2019.

Pathological report confirmed colorectal metastasis.

Positron emission tomography (PET) scan revealed liver metastases with metabolic activity two months following hepatic surgery (Figure 3).

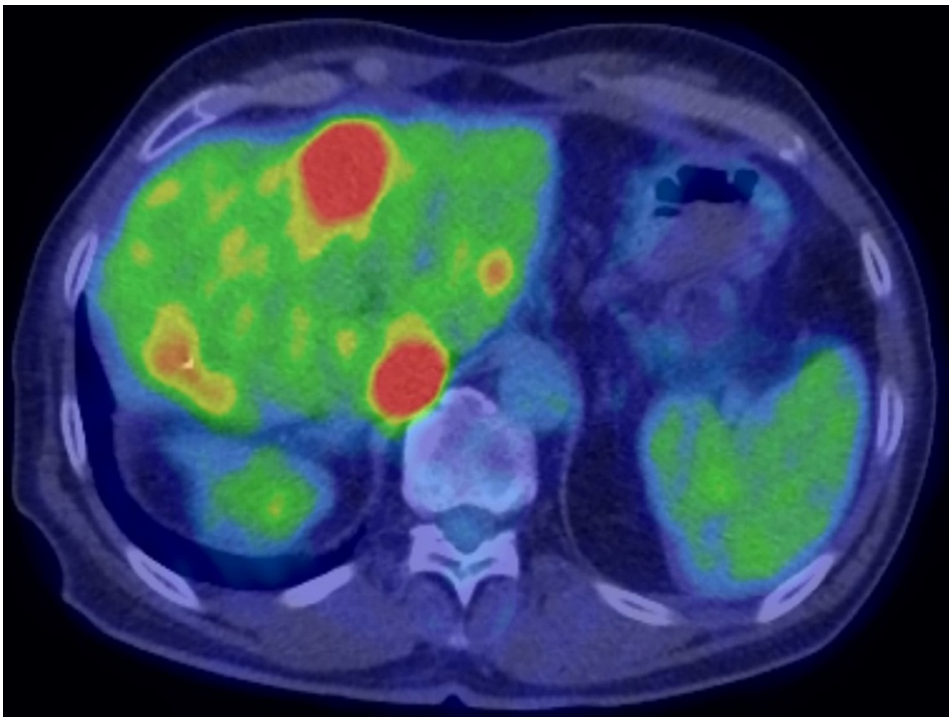

Figure 3. Axial image of the FDG PET scan shows pathological FDG uptake of hepatic metastatic lesions of a 66-year-old patient with a history of segmentectomy-June, 2019.

Patient was started on first-line metastatic regimen consisting of FOLFIRI (5-FU/LV and irinotecan) in combination with cetuximab and achieved partial remission 7 weeks after starting the treatment.

The subsequent PET scan performed in June 2019 displayed pathological FDG uptake of hepatic metastatic, along with metabolically active subdiaphragmatic lymphadenopathy.

In February 2020, the patient was started on immunotherapy consisting of a combination of nivolumab with ipilimumab, every three weeks for 4 cycles, followed by monotherapy with nivolumab, 480mg every 4 weeks.

In April 2020, a significant regression of hepatic metastases is observed with no progression detected until present time (Figure 4).

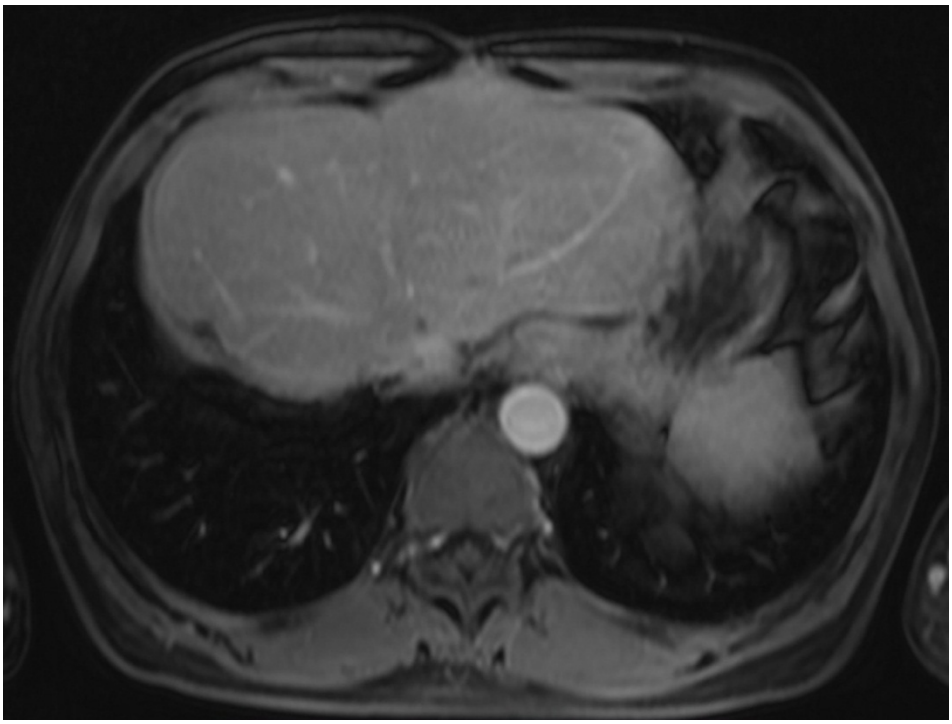

Figure 4. Axial gadolinium-enhanced T1-weighted MR image during the portal venous phase displays no measurable secondary hepatic lesions-April, 2020.

Discussion

Colorectal cancer-the third most common malignancy worldwide, continues to be a leading cause of cancer-related mortality.

The absolute risk appears to increase with age, the incidence being 15 times greater in people over the age of 50 as compared to those under the age of 50.

Despite screening programs and early detection procedures, the incidence of CRC has not decreased among young adults, possibly due to a distinct molecular profile [5].

Approximately 15% of CRC cases are MSI positive.

Three percent of MSI-H patients carry germline mutations in one of the MMR genes (a condition known as Lynch syndrome), while the remaining MSI-H tumors display acquired somatic mutations induced by aberrant promoter methylation of a gene encoding a DNA MMR protein (MLH1).

The occurrence of MSI-H varies according to the stage of the tumor, with a high incidence (22%) in stage II CRC and a substantially reduced incidence (12%) in stage III and stage IV CRC (3.5%) [2].

MSI-H CRCs have a better prognosis than MSI-low (MSI-L) or microsatellite stable (MSS) cancers, as stated by several studies.

Poor differentiation, right-sided and mucinous tumors, increased numbers of tumors, and a reasonably high incidence of BRAF mutations are associated with MSI-H CRC on a pathologic and molecular level [6].

Noticeably, the BRAF gene mutation was not found in our patient's tumor.

A number of genetic and environmental risk factors are involved in the development of colorectal cancer.

The heritable contribution for developing CRC ranges from 18% to 35% [7] and includes conditions such as Lynch syndrome and familial adenomatous polyposis (FAP), MUTYH-

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associated polyposis (MAP), and the hamartomatous polyposis syndromes [8].

These syndromes are linked to various manifestations in addition to CRC, some of which include extracolonic malignancies.

LS is associated with an estimated 66% lifetime risk for males and a 43% lifetime risk for women, with cancer emerging 25 to 30 years earlier than the median age of the general population [9].

Through the process of homologous recombination (HR), tumor suppressor genes BRCA1 and BRCA2 contributes significantly to cellular homeostasis by promoting DNA replication and DNA double-strand breaks (DSBs) repair [10].

BRCA1 and BRCA2 mutations enhanced susceptibility to breast and ovarian cancers, as well as other malignancies, however the risk of colon cancer linked with these mutations is unclear.

The Ashkenazi Jewish community, whose BRCA1/2 mutations are as common as 1 in 40, deserves special attention [11].

Despite the great incidence, there is no data supporting the notion that BRCA1 or BRCA2 mutations pose a risk of CRC that is worth considering.

The main conclusion of a systematic review of 18 researches and a meta-analysis of 14 studies is that BRCA1 mutant carriers had a moderately increased risk (1.49-fold) of developing colorectal cancer, but not BRCA2 mutation carriers [12].

Another qualitative study found that women under the age of 50 who had the BRCA1 mutation have a higher chance of developing colorectal cancer at a younger age [13].

Both BRCA1 and BRCA2 are involved in a genome-protection mechanism.

However, in the BRCA1 and BRCA2 mediated homologous recombination pathways, the two proteins act at distinct phases.

Since BRCA1 operates upstream of BRCA2, BRCA2's function is reliant on BRCA1.

Furthermore, BRCA1 is involved in both checkpoint activation and DNA repair, while BRCA2 is an intermediary of the homologous recombination core mechanism [14].

Moreover, mutations in BRCA1 or BRCA2 are mutually exclusive.

Although the connections between the two proteins are unclear, the variation in mechanism might explain why BRCA1 but not BRCA2 is linked to an elevated risk for colorectal cancer.

The link between BRCA mutations and breast and ovarian cancer is widely recognized, and testing for BRCA mutations has long been standard practice.

Studies examining the connection of BRCA mutations with the risk of developing different malignancies, such as CRC, prostate cancer, and pancreatic cancer, have shown conflicting results since the risks are comparatively smaller and the data is inconsistent.

PARP inhibitors (PARPi) can cause synthetic lethality in cells with defective HR systems by promoting the development of single-strand breaks (SSBs) into DSBs, causing irreversible DNA damage and subsequent cell death.

Four PARP inhibitors (olaparib, rucaparib, talazoparib, and niraparib) have been approved for the treatment of ovarian, breast and pancreatic cancer with BRCA mutations [15].

Thus, we can hypothesize on the benefit of PARPi therapy for BRCA-mutated colorectal cancer based on the approval of the first PARPi used to treat a digestive system malignancy.

MSI and associated increased mutational burden seem to predict sensitivity to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors.

In 2013, a case study reported a complete response in a patient with MSI-H colorectal cancer treated with nivolumab, response that was lasting 3 years off therapy [16].

Conclusions

Based on the information we currently possess, the incidence of BRCA2 mutations in colorectal cancer is remarkably low, especially in men, and its relationship to colorectal cancer is still being investigated in depth.

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