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A Stage II Colorectal Adenocarcinoma Patient with Multiple Driver Gene Mutations, High TMB and High MSI

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1. Abstract

Colorectal cancer (CRC) is a common malignant tumor of the digestive tract, which is a serious threat to human health. Mutations in key driver genes have great relationship with the occurrence, development, treatment and prognosis of CRC. The targeted therapy and immunotherapy have become effective burgeoning tumor treatment strategy. A 45-year-old Chinese woman with multiple driver gene mutations with CRC was reported. This report indicated the clinical features, surgical treatment, pathological diagnosis, immunohistochemical and gene sequencing results. The patient had 6 driver gene mutations that have clear or potential clinical significance with corresponding treatment regimens and can lead to activation of multiple oncogenic pathways. These genes were *CHEK2*, *NTRK1*, *FGFR3*, *FBXW7*, *FANCM* and *CD274*. Larotrectinib is the first approved broad-spectrum anticancer drug for *NTRK1* fusions, and might be an option for subsequent treatment. In addition, high TMB and high MSI indicated that the patient is sensitive to immunotherapy. However, because the patient had just undergone surgery, the corresponding treatment was not performed according to the results of gene detection. We reported a case of CRC patient with multiple driver gene mutations, and developed a follow-up treatment strategy based on the gene detection results, which has certain clinical guiding significance.

2. Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors in the clinic. According to the latest report, in 2020, the United States is expected to have 147,950 new cases of CRC and 53,200 deaths, ranking third in tumor morbidity and mortality, respectively [1]. The disease mostly occurs in middle-aged people, of which patients over 45 years old account for 93.5% of the total affected population. The incidence of CRC is influenced by many factors, such as living environment, living habits, and family history [2]. In addition, more and more studies have shown that the occurrence and development of CRC is also closely related to the mutation of multiple genes. Common mutations in CRC mainly occurred in *KRAS*, *PIK3CA*, *PTEN*, *BRAF* and *NRAS* genes [3]. The treatments of CRC primarily include conventional surgical treatment, radiotherapy and chemotherapy, as well as targeted therapy and immunotherapy. The effectiveness of various treatments is also affected by gene mutations. Related researches showed that gene mutation can not only provide a basis for early screening of CRC, but also evaluate the efficacy of chemotherapy drugs. Xu et al. [4] demonstrated that there was a certain relationship between UGT1A1 gene polymorphism and toxicity and clinical efficacy of irinotecan-based chemotherapy in patients with advanced CRC. Additionally, gene mutation also can guide the use of targeted drugs and immunotherapy and provide optimization for treatment options. For instance, Khan et al. [5] indicated that EGFR gene amplification and KRAS mutations could as the predictive markers for metastatic CRC patients receiving combination biologic therapy of cetuximab plus bevacizumab. Tong et al. [6] demonstrated FBW7 mutational status is a pivotal genetic determinant of CRC response to targeted therapies. Currently, the Food and Drug Administration (FDA) has approved a number of CRC targeting and immunotherapy drugs, such as cetuximab, bevacizumab, pembrolizumab and nivolumab. CRC patient with multiple driver gene mutations is greatly infrequent. In this current report,

we introduced such a infrequent case of a 45-year-old Chinese female, and the customized treatment strategy based on the results of gene detection. We present the following case in accordance with the CARE Guideline [7].

3. Case Presentation

A 45-year-old Chinese woman presented abdominal dull pain without obvious inducement before 2 months, accompanied by difficulty in defecating, incomplete feeling of stool and thinning shape of stool, and was admitted to other hospital. A colonoscopy was performed to detect an ulcerative mass 70 cm from the anal margin, but the colonoscopy could not pass. The pathological results of bite examination were adenocarcinoma. The patient came to Tianjin Medical University Cancer Institute and Hospital for further treatment, and was admitted to the hospital as colon cancer on July 31, 2019. Radical resection of ascending colon cancer was performed on August 8, 2019, and the right hemicolonectomy specimen was submitted for examination. The vital signs of the patient were stable after the operation, and anti-inflammatory rehydration treatment was given. The pathological diagnosis was (right hemicolon) poorly differentiated adenocarcinoma, partly signet-ring cell carcinoma, and pathological stage was $pT_3N_0M_0$ (II stage). In addition, the results also included (right) ovarian mucinous cystadenomas and (right) chronic inflammation of the fallopian tubes. Immunohistochemical staining of tumor cells demonstrated: CDX2 (-), CK20 (portion+), CgA (-), Syn (-), Ki-67 (50%+), Villin (+), CK8/18 (+), MLH1 (-), PMS2 (-), and MSH6 (+). Loss of expression of mismatch repair proteins MLH1 and PMS2 indicated that the tumor had a high frequency of microsatellite instability (MSI-H) phenotype. Patients were recommended to perform MLH1 promoter methylation and BRAF V600E mutation detection to distinguish primary CRC or Lynch syndrome-related CRC. The fresh tumor tissue was sequenced by targeted next generation sequencing (NGS) of the 483 gene panel, while paracancerous tissue was used as controls. A total of 65 somatic gene mutations were detected in this patient, among which 6 had specific or potential clinical significance, namely *CHEK2*, *NTRK1*, *FGFR3*, *FBXW7*, *FANCM* and *CD274* (Table 1). The mutations of *CHEK2*, *FGFR3* and *FBXW7* happened on exons. Nevertheless, The mutation of *FANCM* occurred on the intron. Fusion mutation and amplification mutation occurred in *NTRK1* and *CD274*, respectively. The mutation frequency of *NTRK1*, *FGFR3*, *FBXW7* and *FANCM* were all greater than 20%. Except for *CHEK2*, the other five genes are associated with targeted drugs. Based on the sequencing data, it was found that the patient had the tumor mutation burden (TMB) of 60.39 Mut/Mb, which belongs to high TMB (TMB-H), and had the MSI-H. Multiple indicators of gene detection indicated that the patient was sensitive to targeted therapy and immunotherapy. So this patient can receive appropriate targeted therapy and immunotherapy. However, because the patient had just experienced surgery, she had not yet agreed to receive treatment strategy based on the results of genetic testing.

Table 1: The driver gene mutations that have clear or potential clinical significance

Gene	Targeted drug information				Targeted drug information		
	exon	site	type	Frequency (%)	Approved for this cancer species	Approved for other cancer types	Clinical drug
CHEK2	6	c.729dupT	---	heterozygous mutation	---	---	---
NTRK1	---	(TPM3-NTRK1)-(T7:N8)	fusion	21.80%	Larotrectinib, Entrectinib	---	---
FGFR3	13	c.1663G>A	point mutation	34.84%	---	Pazopanib, Ponatinib, Erdafitinib	AZD4547, BGJ398, Dovitinib
FBXW7	9	c.1394G>A	point mutation	32.86%	---	Everolimus, Sirolimus, Temsirolimus	---
FANCM	intron17	c.4515+2delT	deletion mutation	29.17%	---	Olaparib, Rucaparib, Niraparib, Talazoparib	---
CD274	---	---	amplification	3.17X	Nivolumab, Pembrolizumab	Atezolizumab	---

5. Discussion

In the present research, this CRC patient was detected to carry six genetic mutations with definite or potential clinical significance. These six gene included *CHEK2*, *NTRK1*, *FGFR3*, *FBXW7*, *FANCM* and *CD274*. Cell-cycle-chekpoint kinase gene (*CHEK2*) is a tumor suppressor gene that encodes cell cycle checkpoint kinase2 (CHEK2). CHEK2 kinase is an important signal transduction protein in DNA double-strand break injury, which is involved in the arrest of cell cycle G1, S or G2/M phase and promotes cell repair of damage. After the *CHEK2* gene happened mutation, the kinases it encodes become inactive and unable to repair DNA damage [8]. The damaged DNA constantly replicates, producing a large number of abnormal cells, which in turn leads to canceration. The neurotrophic tyrosine kinase receptor type 1 (*NTRK1*) gene is a proto-oncogene that encodes the protein TrkA, which often has fusion mutations in a variety of tumors. *NTRK1* fusions occur in less than 1% of CRC patients. The NCCN guidelines for colon cancer indicate that larotrectinib is recommended for patients with *NTRK1* fusions [9]. Larotrectinib is the first broad-spectrum anticancer drug for *NTRK* fusions regardless of cancer species. The protein FGFR3 encoded by the fibroblast growth factor receptor 3 (*FGFR3*) gene is a tyrosine kinase receptor that plays an important role in the occurrence of cell mitosis, promotion of angiogenesis, wound healing and tumor formation. *FGFR3* can simultaneously initiate Ras-MAPK-mediated mitogen signaling transduction pathway and STAT signaling transduction pathway that inhibits cell growth. During normal development, cells grow and differentiate under the action of these two signaling systems. When *FGFR3* is mutated, the function of the receptor is abnormally activated, which disrupts the normal growth and development of tissues, leading to tumor formation [10]. Multiple studies have shown that *FGFR3* is an oncogene that causes the development of malignancies such as bladder cancer [11] and cervical cancer. F-box and WD-40 domain protein 7 (*FBXW7*) gene, also known as *FBW7* or *hCDC4*, is one of the important recognition factors of ubiquitin-proteasome degradation pathway and an important tumor suppressor gene discovered in recent years [12]. *FBXW7* gene is regulated by its upstream factors and plays a role in cell proliferation, differentiation, cell cycle progression, apoptosis, canceration and other biological processes [13]. Recent studies have found that *FBXW7* was mutated or reduced in a variety of tumors. Fanconi anaemia complementation group M (*FANCM*) is a tumor suppressor gene that encodes FANCM protein, the most conserved protein within the FA pathway [14]. *FANCM* has the activity of translocase and endonuclease, and its functions are necessary for facilitating branch migration of Holliday junctions and DNA repair structures at replication forks. It was found that the biallele inactivation of *FANCM* in CRC patients might indicate that the gene is a tumor suppressor gene [15]. The cluster of differentiation 274 gene (*CD274*), also known as PD-L1 or B7-H1, is a newly identified member of the B7 family. *CD274* gene can promote the development of CRC by directly influencing the proliferation, invasion and metastasis of CRC cells [16]. Expression of *CD274* in tumor-infiltrating immune cells was an independent factor in improving prognosis of CRC patients [17]. These 6 driver genes have specific or potential clinical significance and rarely mutate at the same time. In this article, we firstly reported a case of CRC patient carried mutations located in these 6 driver genes simultaneously. Among them, *NTRK1*, *FGFR3*, *FBXW7*, *FANCM* and *CD274* are related to targeted drugs, indicating that targeted therapy could be used as one of the subsequent treatment options for this patient. Tumor immunotherapy has become an effective burgeoning tumor treatment method in addition to surgery, chemotherapy, radiotherapy due to its significant survival benefits. As one of the methods of tumor immunotherapy, immune checkpoint inhibitor has been approved for the treatment of multiple advanced tumors. Although some cancer patients can benefit from it, the immune-related adverse reactions, primary drug resistance and secondary drug resistance have limited its widespread clinical application. The research of biomarkers related to the efficacy of immune checkpoint inhibitors is helpful for screening patient and individualized treatment, and it is of great significance to standardize monotherapy or combination therapy of immunosuppressants. The expression of programmed death-ligand 1 (PD-L1), TMB and MSI are currently the most studied tumor immunotherapy markers [18]. Tumor mutation burd (TMB) is defined as the number of mutations per Mb in the tumor genome. In theory, the higher the TMB, the more new tumor-associated antigens are produced, the more likely it is to stimulate the immune response, and the better the therapeutic effect will be with the elimination of inhibitory immune signals. Related studies have also identified that among CRC patients with MSI-H, patients with high TMB (TMB-H) can benefit more from PD-1/PD-L1 antibody treatment than patients with low TMB (TMB-L) [19]. The study indicated that patients with high level of TMB responded better to immune checkpoint inhibitor therapy [20]. Like TMB, the study of MSI as a prognostic marker of CRC has also received increasing consideration. MSI is caused by the DNA mismatch repair deficient (dMMR), which is manifested as the unstable state of microsatellites caused by the repetition of simple DNA sequences. MSI has important pathological and clinical significance in the pathological detection of CRC, and is also one of the important markers for the prognosis and the prediction of therapeutic effect. In the pembrolizumab study, MSI-H and MSS mCRCs had objective response to PD-1 inhibitor of 40% and 0%, respectively [21]. Immunotherapy has potential benefit for immunogenic MSI-H CRCs. In this present report, the TMB of this patient was 60.39 Mut/Mb and MSI belonged to MSI-H. These two indicators demonstrated that the patient was sensitive to immunotherapy, so immunotherapy could be used as one of the therapeutic regimens in the following treatment.

6. Conclusion

In conclusion, targeted therapy and immunotherapy were reasonable therapeutic option for CRC patients with multiple driver gene mutations, TMB-H and MSI-H. We will further explore the therapeutic effect of targeted therapy and immunotherapy on this CRC patient in the follow-up study.

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