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Long-Term Survival of a Patient with Metastatic MSI-H Colorectal Cancer with Immunotherapy Combined with Chemotherapy Treatment: A Case Report and Review of Literature

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Abstract

Colorectal Cancer (CRC) is one of the most prevalent malignancies worldwide, accounting for a significant number of cancer-related deaths each year. However, therapeutic options for Colorectal Cancer (CRC) patients with defective DNA Mismatch Repair (dMMR)/high microsatellite instability the survival of dMMR/MSI-H CRC patients. To date, there are no case reports on the use of immunotherapy in combination with chemotherapy for the treatment of dMMR/MSI-H metastatic Colorectal Cancer (mCRC). Here, we report a unique case of a patient with advanced metastatic dMMR/MSI-H colon cancer showing MLH1(+); 2. MSH2(-); MSH6(-); PMS2(+) on colon biopsy demonstrating long-term stable survival under the treatment protocol of Immunotherapy combined with chemotherapy.

Keywords: Colon cancer; Stage IV, High microsatellite instability; Immunotherapy and chemotherapy

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Introduction

Colorectal Cancer (CRC) is the third most prevalent cancer worldwide. According to GLOBOCAN, it is an estimation of more than 1.9 million new cases of CRC and 930,000 deaths in 2020 [1]. CRC occurs as a result of multiple biochemical processes regulated by genetic mutations, microenvironmental factors and epigenetic alterations [2]. Metastatic colon cancer is a highly aggressive tumor type with a higher grade of malignancy among colon cancers and is characterized by poor treatment efficacy and poor prognosis [3]. Several predictive biomarkers have emerged to aid treatment decisions in metastatic colorectal cancer, such as KRAS (40%), NRAS (5%-10%), and BRAF (8%-10%) mutation status, tumor laterality, Microsatellite Instability (MSI) (5%-7%), and other less common alterations such as HER2 (2%), MET (2%), NTRK (0.2%-2.4%), ALK (0.2%-2.4%) and ROS1 (0.2%-2.4%) [4,5]. Chemotherapy combinations based on the inclusion of 5-Fluorouracil (5-FU) are the standard of care for metastatic Colorectal Cancer (mCRC). However, there is some proof that patients with DNA Mismatch Repair-deficient (dMMR)/Microsatellite Instability-High (MSI-H) mCRC respond to conventional chemotherapy less favorably and have a poorer prognosis than those with Mismatch Repair proficient (pMMR) or Microsatellite Stable (MSS) disease [6,7]. MSI is associated with high mutational and neo-antigenic loads and the immune system recognizes the tumor, hence the high response and survival observed with immunotherapy in MSI-H CRC, Programmed Death 1 (PD-1) blockade has emerged as a highly effective therapy for dMMR/MSI-H metastatic colorectal cancer [8-11]. Pembrolizumab (Keytruda) and nivolumab (Opdivo®) are the two recognized PD-1 inhibitors approved by the FDA for patients with dMMR or MSI-H metastatic CRC [12]. Data from the KEYNOTE-177 study found that pembrolizumab met the criterion of superiority for progression-free survival compared to chemotherapy, with longer progression-free survival for pembrolizumab (median 16.5 months, 95% CI 5.4-38.1) *vs.* chemotherapy (median 8.2 months, 95% CI 6.1-10.2) [13]. Despite significant advances in Immune Checkpoint Inhibitor (ICI) therapy, more than half of patients do not respond to immune monotherapy [14]. Multiple ongoing studies are currently investigating the benefit of adding chemotherapy to PD-4/PD-L1 inhibitors in patients with dMMR/MSI-H metastatic colorectal cancer, including the COMMIT (NCT02997228), CA209-8HW (NCT04008030) and MK-1308A-008 (NCT04895722) studies [13].

In this paper, we report just such a unique case study of a MSI-H CRC patient with a KRAS wild-type mutation, where we aimed to highlight the superior anti-tumor activity of combining PD-1 blockers with chemotherapeutic agents as a therapeutic option for MSI-H CRC.

Case Presentation

A 29-year-old young man in Dunhuang City Hospital because of no obvious cause of bloody stools in 2021.12. Notably, several of the patient's relatives had colon, stomach, pancreatic, rectal and bladder cancers. The patient performed colonoscopy found: colon mass. 2022.1.1, in Gansu Provincial People's Hospital, Department of Anus and Gastroenterology, chest, abdominal and pelvic CT examination showed: Sigmoid colon occupancy, more than the consideration of colorectal cancer (T3N2M1), localized with the small bowel, the bladder may be adhered to the MRI of the whole abdomen found that MRI of whole abdomen revealed multiple enhancing nodules along the peritoneum in the abdominal cavity, which was mostly considered as metastasis. The patient and his family requested conservative treatment, and after excluding the contraindications to chemotherapy, he was discharged from the hospital on 2022.1.9 after 1 cycle of intravenous oxaliplatin 250 mg d1, and oral Xiloda 2.0 g three times a day d1-14 chemotherapy. On 2022.02.18, the patient was readmitted to the hospital for thoracoabdominal-pelvic CT, which suggested that the sigmoid colon occupation had increased in extent compared with the CT findings on 2022.1.3, and the patient's disease progressed. We obtained the pathological tissue wax block of the patient from Dunhuang City Hospital and performed immunohistochemical staining to obtain the results of MLH1(+); MSH2(-); MSH6(-); PMS2(+), which suggested that the patient was MSI-H; at the same time, the immunohistochemical staining results showed: Tubular choriocarcinoma of the (colon), the glands with high-grade intraepithelial neoplasia, and some of the glands with carcinomatosis, as the tissue from the Dunhuang City Hospital, the tissue was superficial and fragmented, and the possibility of higher-level lesions could not be excluded. Then we improved the genetic testing: KRAS Exon-4 mutation was found. At this time, the patient was clearly diagnosed as sigmoid colon malignant tumor (T3N2M1 stage IV KRAS Exon-4 mutation MSI-H) with retroperitoneal lymph node metastasis. Transferred to Gansu Provincial People's Hospital,

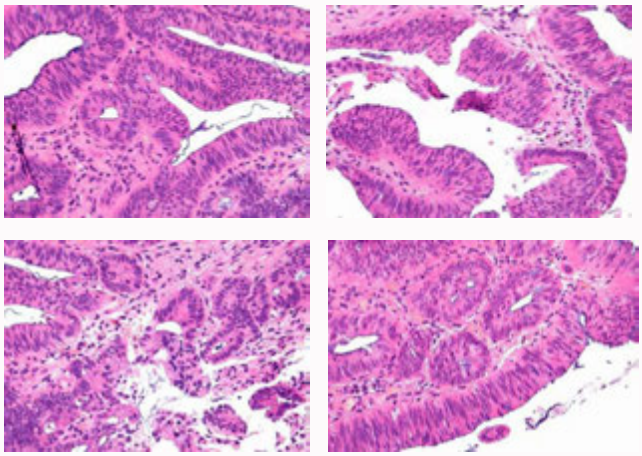

Figure 1: Immunohistochemical staining shows MLH1(+); MSH2(-); MSH6(-); PMS2(+), which suggested that the patient was MSI-H; Tubular choriocarcinoma of the colon, the glands with high-grade intraepithelial neoplasia, and some of the glands with carcinomatosis.

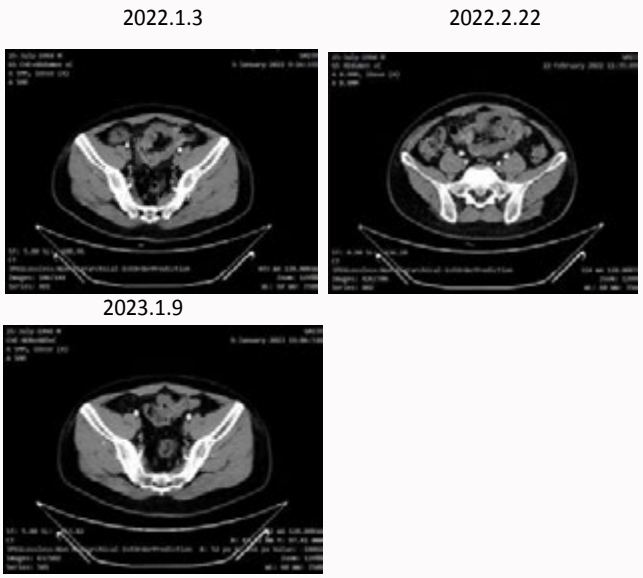

Figure 2: CT imaging of the patient during treatment. The tumor appeared enlarged and the disease progressed after chemotherapy, but after treatment with immune-combination chemotherapy the results showed that the tumor was significantly smaller.

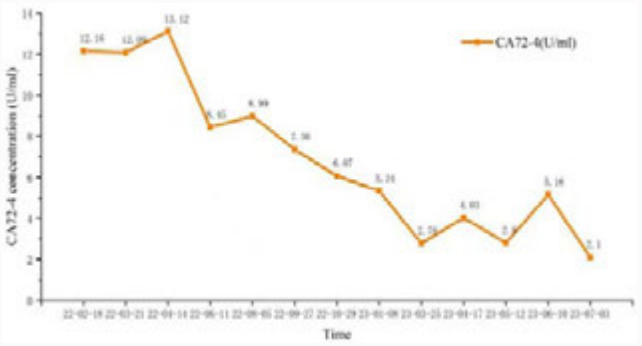

Figure 3: Changes in tumor marker CA72-4 during treatment. Decrease in tumor markers after immunotherapy combined with chemotherapy treatment.

department of medical oncology, assessed the patient's condition, excluded contraindications to treatment on 2022.2.25, 2022.3.22, 2022.4.14, 2022.5.12, given pembrolizumab 200 mg IV dO+XELOX regimen: Oxaliplatin 240 mg IV d1, hirudinumab 1.5 g po bid d1-14 immune-combined Chemotherapy treatment was given for 4 cycles. Tirilizumab combined with XELOX regimen was given for 1 cycle on 2022.06.11, and the chemotherapy process went well. The patient was treated with intravenous pembrolizumab 200 mg and oral capecitabine tablets 1.5 g on 2022.08.8, 2022.09.2, 2022.09.20, 22.10.29, 2023.1.10, 2023.3.4, 2023.3.25, 2023.4.17, 2023.5.12, 2023.6.10 in our department. Completed 13 cycles of immunotherapy combined with chemotherapy treatment (Figures 1-3).

Discussion and Conclusion

Immunotherapy, as an innovative anti-cancer strategy, activates the body's immune response by intervening in the signaling pathways between tumor cells and the host immune system, enabling the body's immune cells to recognize and attack tumor cells. In MSI-H colon cancer patients, inhibitors targeting immune checkpoints (e.g., PD-1 or PD-L1 inhibitors) have been shown to be effective, which bring significant therapeutic effects by restoring the anti-tumor immune

response and promote prolonged survival in a subset of patients. It has been reported in the literature that MSI-H/dMMR stage IV colorectal cancer patients represent approximately 4% to 5% of all colorectal cancer patients [15]. A pooled analysis of 13 clinical studies of first-line treatment for metastatic colorectal cancer showed that the median Overall Survival (OS) was 6.16 months for dMMR patients and 8.1 months for pMMR patients (HR=35.95; 1% CI: 13.1-61.0; P=001.27 [16]. MSI-H/dMMR mCRC patients have a poorer prognosis, especially patients with the BRAF V28E mutation [17]. ICIs targeting the PD-1 protein are highly effective and are now the first-line standard of care for patients with dMMR/MSI-H metastatic colorectal cancer [18]. Although ICI therapy has made progress in colorectal cancer treatment, >50% of dMMR/MSI-H metastatic colorectal cancer patients are non-responders [19]. Therefore, it is particularly significant to go in search of new strategies to extend the benefits of PD-1 immunotherapy to improve the prognosis of patients with dMMR/MSI-H mCRC. It was reported at 2022 ASCO ANNUAL MEETING that 12.3% of patients in the chemotherapy group progressed compared to 29.4% in the pembrolizumab group, and that these MSI-H patients may be primary resistant to immunotherapy, and whether they are better suited for chemotherapy or whether they are suited for the immune-combination chemotherapy, mFOLFOX6/ evacizumab +Atezolizum combination regimen is underway in in the NRG-GI004/ SWOG-S1610 COMMIT study. It is also worthwhile to reflect on the fact that MSI-H patients with K-RAS mutations do not benefit from immunotherapy in the same way that KRAS wild-type patients do. There is no research data on primary immune resistance, and various clinical attempts are underway, such as double immunotherapy, immunotherapy combined with conventional chemotherapy, or immunotherapy combined with antiangiogenic therapy, etc. The CheckMate-142 study showed that the ORR of PD-1 antibody combined with CTLA-4 antibody was significantly higher than that of PD-1 monoclonal antibody monotherapy in the backline treatment (51% *vs.* 31%); and the first-line treatment with dual immunotherapy had an ORR of up to 69% and a complete remission rate of 13%, which was significantly higher than other studies of PD-1 antibody monotherapy. In addition, it has been reported in the literature that patients with metastatic colorectal cancer got a complete pathological response after concurrent use of pembrolizumab and radiotherapy, which suggests that the combination of PD-1 blockade and radiotherapy may be a potential therapeutic strategy for metastatic colorectal cancer [20]. Chemotherapy in combination with immunotherapy is another common clinical attempt to treat some patients with very high tumor loads, where there is a risk of tumor progression prior to the onset of immunotherapy alone. Therefore, combination chemotherapy has the potential to help or reduce the risk of early tumor progression, buying valuable time for immunotherapy to take effect. Unfortunately, no clinical studies have yet demonstrated that chemotherapy in combination with a PD-1 antibody significantly improves the efficacy of immunotherapy compared to immunotherapy alone. In the case of the patient reported here, it was the combination of chemotherapy and immunotherapy that enabled the patient to survive for nearly two years or more.

In conclusion, although immune checkpoint inhibitors have fundamentally changed the clinical management of MSI/dMMR CRC patients, some MSI/dMMR CRC patients may develop primary resistance to immune checkpoint inhibitors, and finding new ways to improve the prognosis and prolong the survival of patients in these patients is an issue that deserves in-depth study now. Therefore, even though the booming precision medicine and immunotherapy are at the forefront and hold great promise for the treatment of cancer, we still have to work hard to select the right patients, find the right targets, and give the best treatment to the patients.

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