

Case Report

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# Immunotherapy as a promising treatment strategy for dMMR colorectal cancer with brain metastasis: a case report

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## Abstract

Brain metastasis in colorectal cancer is a rare occurrence with poor prognosis and limited treatment options. This case report presents a unique and previously unreported case of brain metastasis in a patient with dMMR (DNA mismatch repair-deficient) colorectal cancer. The patient, a 70-year-old male, initially presented with abdominal pain and was diagnosed with moderately differentiated adenocarcinoma of the right colon. Following surgical resection and adjuvant chemotherapy, the patient developed cognitive decline and was found to have a metastatic lesion in the left temporal lobe. Immunohistochemical analysis revealed MSH2 positivity and MSH6, MLH1, and PMS2 negativity, indicating dMMR status. Further genetic testing showed wild-type Kras, Nras, and Braf, and high tumor mutational burden (TMB). The patient was subsequently treated with pembrolizumab immunotherapy, resulting in a significant improvement of symptoms and a reduction in the size of brain metastasis. This case highlights the rarity and challenging management of brain metastasis in colorectal cancer, particularly in the context of dMMR tumors. The successful use of immunotherapy in this case provides valuable insights into the



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potential efficacy of immune-based treatments for dMMR colorectal cancer with brain metastasis, underscoring the need for further research in this field.

**Keywords:** Brain metastasis, colorectal cancer (CRC), dMMR/MSI-H, immunotherapy

## INTRODUCTION

Colorectal cancer (CRC) is a significant global health concern and a leading cause of morbidity and mortality<sup>[1]</sup>. Despite advances in treatment, the occurrence of metastasis remains a major challenge<sup>[2]</sup>. Brain metastases from CRC are relatively rare, accounting for only 3%-5% of cases, and are associated with poor prognosis and diminished quality of life<sup>[3]</sup>. Recent studies have highlighted the predictive value of microsatellite instability (MSI) and mismatch repair (MMR) status in CRC patients undergoing immunotherapy. Approximately 15% of CRC cases exhibit MSI or deficient MMR (dMMR), which have been linked to improved responses to immune checkpoint inhibitors<sup>[4]</sup>. Notably, the KEYNOTE-016 and CheckMate-142 trials demonstrated promising outcomes with pembrolizumab and nivolumab, respectively, in patients with MSI/dMMR-positive CRC<sup>[5-8]</sup>. Moreover, the KEYNOTE-177 trial demonstrated that pembrolizumab monotherapy improved progression-free survival compared to standard chemotherapy in patients with advanced MSI/dMMR-positive CRC<sup>[9]</sup>.

The significance of early-stage testing in guiding the management of metastatic colorectal carcinoma (mCRC) and identifying patients who may benefit from immunotherapy cannot be overstated. Utilizing both immunohistochemistry (IHC) and microsatellite instability-polymerase chain reaction (MSI-PCR) methods is crucial for accurate identification of patients who are eligible for immunotherapy<sup>[10,11]</sup>. IHC testing is commonly used to screen for mismatch repair (MMR) protein status, while MSI-PCR and MMR IHC testing are particularly important for the clinical management of colorectal cancer (CRC)<sup>[11]</sup>. However, it is important to note that the results of IHC testing can be influenced by somatic mutations, which may lead to discrepancies in test results and affect the identification of deficient MMR (dMMR) in Lynch syndrome<sup>[10,12]</sup>. To ensure accurate assessment of microsatellite instability, it is recommended to perform both immunohistochemistry testing for MMR protein expression and polymerase chain reaction studies for microsatellite instability<sup>[13]</sup>. The detection of microsatellite instability status can also rely on the assessment of MMR proteins through immunohistochemistry and molecular methods through multiplex PCR<sup>[14]</sup>.

Despite these advances, the clinical significance of MSI/MMR in CRC patients with brain metastases remains unclear, and there are currently no reports on the use of immunotherapy in this specific population. Herein, we present a unique case of a 70-year-old male patient with CRC who developed brain metastases one year after surgery and was found to be dMMR. The patient received pembrolizumab immunotherapy and exhibited a favorable response, experiencing significant improvements in quality of life. This case highlights the potential of immunotherapy in treating CRC patients with brain metastases and MSI-H/dMMR. Further investigation is warranted to explore the therapeutic implications and efficacy of immunotherapy in this specific patient population.

## CASE DESCRIPTION

The patient, a 70-year-old male, was admitted on April 14, 2021, with a chief complaint of recurrent epigastric pain for the past 2 weeks. Colonoscopy revealed a cauliflower-like circumferential mass in the hepatic flexure, causing luminal obstruction and making it difficult for the colonoscope to pass through. Histopathological examination of the biopsy specimen indicated moderately differentiated adenocarcinoma. Further investigations revealed mild anemia with a hemoglobin level of 99 g/L. Tumor markers showed an

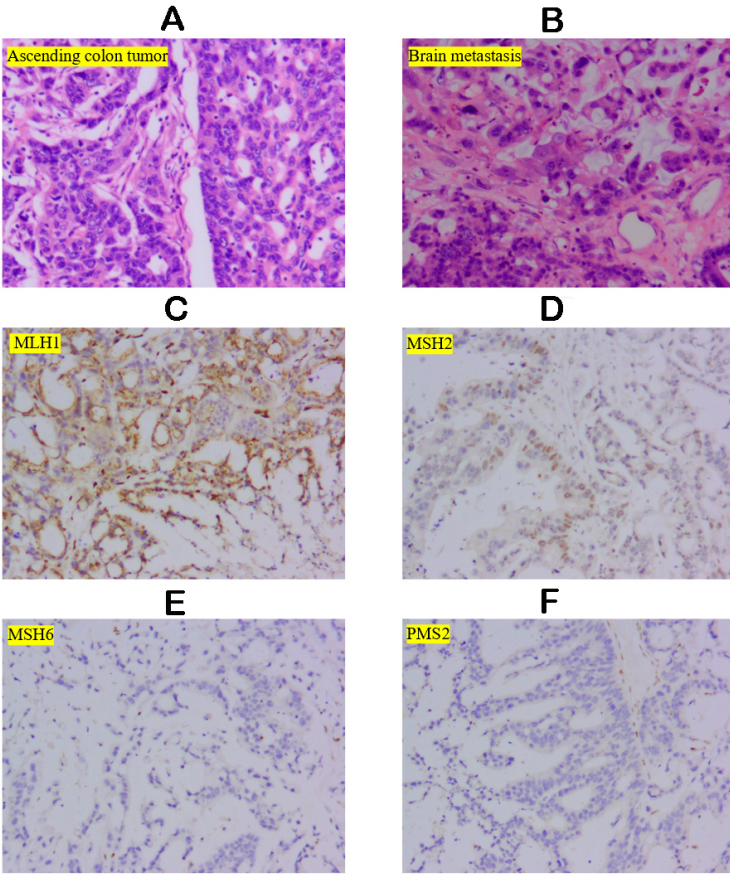
elevated carcinoembryonic antigen (CEA) level of 26.4 ng/mL, while cancer antigen 199 (CA199) was within the normal range. Chest and abdominal computed tomography (CT) confirmed a mass in the hepatic flexure of the colon without evidence of metastasis to other sites. After ruling out contraindications, the patient underwent laparoscopic right hemicolectomy. The postoperative pathology report revealed a protruding, moderately to poorly differentiated adenocarcinoma of the right colon [Figure 1A], measuring 14 cm × 8 cm × 4 cm, infiltrating into the subserosal layer, with evidence of neural and vascular invasion, and one out of twenty-seven harvested pericolic lymph nodes showing metastasis. The pathological stage of the patient's colorectal cancer was stage III (pT3N1M0) according to the American Joint Committee on Cancer (AJCC) staging system, 8th edition. The immunohistochemical results for DNA mismatch repair (MMR) status were as follows: MSH2 (present), MSH6 (present), MLH1 (not present), and PMS2 (not present). Following surgery, the CEA level returned to normal [Figure 2], and the patient received four cycles of adjuvant chemotherapy with the XELOX regimen, followed by regular follow-up every three months.

One year after the surgery, the patient started experiencing symptoms of memory loss and declining cognitive abilities. Concurrently, the CEA level began to rise, reaching 8.2 ng/mL [Figure 2]. Magnetic resonance imaging (MRI) of the brain revealed a lesion in the left temporal lobe consistent with metastasis from colon cancer [Figure 3A]. Following the exclusion of other metastatic sites through positron emission tomography-computed tomography (PET-CT), the patient underwent surgical resection of the brain metastasis in July 2022. Pathological examination of the resected brain tissue confirmed the presence of colonic adenocarcinoma with necrosis [Figure 1B], which was consistent with the patient's medical history, morphology, and immunohistochemistry profile. Immunohistochemistry analysis of the fourth slide showed MSH2 present with weak positivity and not present for MSH6, MLH1, and PMS2 [Figure 1C-F].

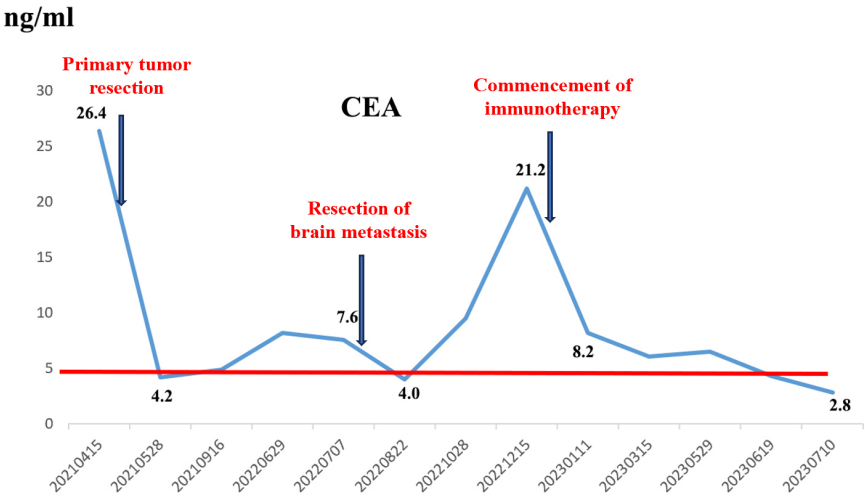
Postoperatively, the patient underwent another four cycles of adjuvant chemotherapy with the XELOX regimen. However, after five months of the brain metastasis resection, the patient exhibited recurrent symptoms of memory loss and declining attention, accompanied by a re-elevation of CEA levels [Figure 2]. MRI of the brain indicated a recurrence of brain metastasis [Figure 3B]. Following multidisciplinary team discussion, genetic testing on the brain metastasis specimen revealed wild-type Kras, Nras, and Braf genes, and the patient was found to be MSI-H. MSI-H was defined using the next-generation sequencing (NGS) method. Additionally, the patient had a high tumor mutational burden (TMB) of 77.7 muts/mb, suggesting potential benefits from immunotherapy. Subsequently, the patient commenced treatment with pembrolizumab 200 mg q3w for immunotherapy. After the third cycle, the patient's symptoms gradually improved. Follow-up MRI scans in February and June 2023 showed a significant reduction in brain metastasis [Figure 3C and D]. Currently, the patient is under maintenance therapy with pembrolizumab, and the CEA level has returned to normal [Figure 2]. The patient's overall condition is stable and favorable.

## DISCUSSION

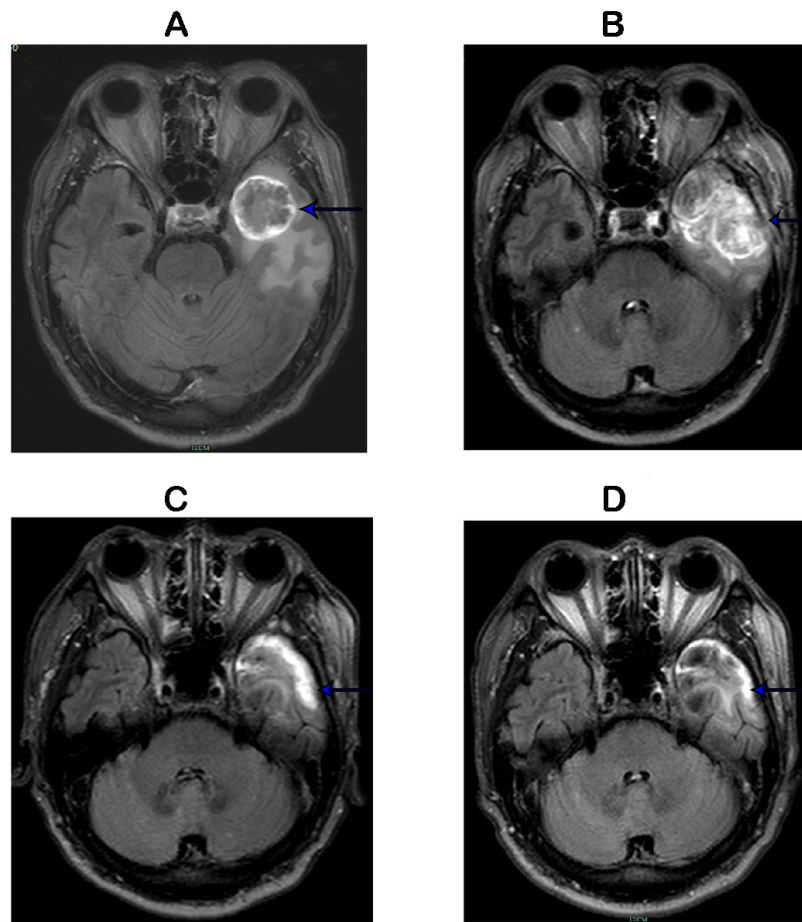
In this case report, we presented a rare case of colorectal cancer with brain metastases that was treated using a multimodal approach involving surgical resection, chemotherapy, and immunotherapy. The patient's poor prognosis was influenced by the low incidence of brain metastases in colorectal cancer, limited treatment options due to poor chemotherapy response, and the presence of the blood-brain barrier<sup>[9]</sup>. While immunotherapy has demonstrated significant efficacy in various cancer types, its application in colorectal cancer with brain metastases remains relatively unexplored due to limited available data on its effectiveness. This case highlights the potential benefits of incorporating immunotherapy as an adjunct therapy in managing brain metastases from colorectal cancer. By showcasing a successful outcome with immunotherapy in this rare case, we aim to stimulate further investigation and utilization of this treatment modality in similar scenarios.



**Figure 1.** This figure provides histological images of the primary ascending colon tumor and the brain metastasis. Subfigures include (A) (HE stain of the ascending colon tumor), (B) (HE stain of the brain metastasis), and (C-F) illustrating the immunohistochemical status of MMR proteins in the brain metastasis.



**Figure 2.** This figure depicts the expression of CEA over time, including changes before and after the resection of the primary lesion, before and after resection of the brain metastasis, and before and after immunotherapy.



**Figure 3.** This figure displays the patient's head MRI images, with (A) showing the left temporal lobe lesion, (B) showing the recurrence after resection, and (C and D) demonstrating the significant reduction in brain metastasis after immunotherapy.

Brain metastasis in colorectal cancer is a rare and severe complication associated with poor prognosis, limited treatment options, and a high risk of recurrence<sup>[15,16]</sup>. The incidence of brain metastases from colorectal cancer is comparatively lower than that of other solid tumors such as lung, breast, and melanoma<sup>[17]</sup>. Conventional treatments for brain metastases, including surgery, radiotherapy, and chemotherapy, often face challenges due to the blood-brain barrier's restrictive nature in delivering therapeutic agents<sup>[18]</sup>. Despite notable advances in immunotherapy for cancer, the efficacy of immunotherapy for brain metastases from colorectal cancer remains inadequately explored.

Immunotherapy has shown efficacy in the treatment of MSI-H/dMMR cancers, including CRC<sup>[19]</sup>. Pembrolizumab, an anti-programmed death-1 (PD-1) monoclonal antibody, has demonstrated antitumor activity against MSI-H/dMMR cancer<sup>[20]</sup>. The response rates of MSI-H solid tumors to immune checkpoint inhibitors (ICIs) are approximately 40% in the pan-cancer setting, with some responses showing long-term durability<sup>[21]</sup>. Tumor mutational burden (TMB) has also been explored as a predictive biomarker for immunotherapy response, and high TMB in MSI-H/dMMR tumors has been associated with increased and durable responses to ICIs<sup>[22]</sup>. In gastrointestinal cancers, including those with MSI-H/dMMR, a TMB-high status may further refine the efficacy of immunotherapy<sup>[23]</sup>. While the literature provides evidence of the efficacy of immunotherapy in MSI-H/dMMR cancers, including CRC, there is limited data specifically addressing the use of immunotherapy for brain metastases from pan-cancers with MSI-H/dMMR or high

TMB. Further research is needed to determine the effectiveness of immunotherapy in treating brain metastases in this specific patient population. However, the success of immunotherapy in other MSI-H/dMMR cancers suggests that it may have potential in the treatment of brain metastases as well.

Several clinical trials have evaluated the efficacy of immunotherapy in metastatic colorectal cancer, including KEYNOTE-028, KEYNOTE-016, and CheckMate-142. The KEYNOTE-028 trial, a phase Ib study, investigated the safety and efficacy of pembrolizumab in patients with PD-L1-positive advanced solid tumors, including colorectal cancer. The ORR and disease control rate (DCR) were 17% and 33%, respectively<sup>[24]</sup>. The KEYNOTE-016 trial, another phase Ib study, assessed the safety and efficacy of pembrolizumab in patients with PD-L1-positive advanced solid tumors, including colorectal cancer. The ORR and DCR were 21% and 33%, respectively<sup>[5]</sup>. The CheckMate-142 trial, a phase II study, examined the safety and efficacy of nivolumab plus ipilimumab in patients with dMMR or MSI-H metastatic colorectal cancer. The ORR and DCR were 55% and 80%, respectively<sup>[7,8]</sup>.

More recently, the phase III KEYNOTE-177 trial compared the efficacy of pembrolizumab versus chemotherapy as a first-line treatment for dMMR or MSI-H metastatic colorectal cancer<sup>[25]</sup>. The study demonstrated a significant improvement in progression-free survival (PFS) in the pembrolizumab group compared to the chemotherapy group, with a median PFS of 16.5 months versus 8.2 months, respectively<sup>[26]</sup>. The overall survival (OS) data were not mature at the time of the study's publication<sup>[9]</sup>.

Although evidence regarding the efficacy of immunotherapy in colorectal cancer brain metastasis is limited, studies have emphasized the crucial role of immune status in determining its effectiveness. Consequently, early initiation of immunotherapy may lead to improved outcomes, particularly in patients with dMMR or MSI-H metastatic colorectal cancer<sup>[27,28]</sup>. Future research should focus on assessing the efficacy of immunotherapy in this patient population and identifying biomarkers that can predict treatment response. In addition to MMR status and TMB, other biomarkers and factors in the tumor microenvironment have been implicated in immunotherapy response in CRC. For example, the immune microenvironment, including the presence of tumor-infiltrating lymphocytes, can influence the efficacy of immunotherapy<sup>[29]</sup>. Furthermore, the expression of certain immune-related genes, such as DDR1, has been found to play a role in immunotherapy response in CRC<sup>[30]</sup>. It is important to note that while biomarkers can provide valuable information for predicting immunotherapy response, their clinical utility is still being explored. Validation of biomarkers and consideration of regulatory aspects are necessary for their incorporation into clinical practice<sup>[31]</sup>. Additionally, the tumor microenvironment, including factors such as the presence of stromal cells and immune cell infiltration, can impact the efficacy of immunotherapy and should be taken into account when assessing treatment response<sup>[32]</sup>.

Limitations of this study include its retrospective nature, being a single case report, and the lack of long-term follow-up data. Additionally, using a single-agent immune checkpoint inhibitor may not fully reflect the potential benefits of combination therapies. Moving forward, further studies are required to evaluate the efficacy and safety of immune checkpoint inhibitors in the treatment of dMMR metastatic colon cancer with brain metastasis. Future research should also concentrate on identifying biomarkers that can predict response to immunotherapy and selecting appropriate combination therapies to enhance treatment outcomes.

In conclusion, this case report underscores the potential of immune checkpoint inhibitors in the treatment of dMMR metastatic colon cancer with brain metastasis. While further investigation is warranted, this approach holds promise as a therapeutic option for patients with this rare and challenging-to-treat disease.

## DECLARATIONS

### Author contributions

Design of the study: Cheng X, Wu G

Acquisition of data: He W, Zhong W, Tong C

Analysis and interpretation of data: He W, Cheng X

Writing and revision of the manuscript: Cheng X, Wu G

Review was done by all authors

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

The study protocol was approved by the institutional review board for the First Affiliated Hospital, Zhejiang University School of Medicine. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient. The approval number is IIT20231005A.

### Consent for publication

The authors have obtained consent to publish from the participants to report individual patient data.

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