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Efficacy of Combined PD-1 Inhibitor and Bevacizumab in Unresectable Liver Metastasis of MSI-H Colorectal Cancer: A Case Report

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Conflict of interest: None declared

Patient: Female, 25-year-old
Final Diagnosis: Colorectal cancer
Symptoms: Abdominal pain • anemia
Clinical Procedure: —
Specialty: Oncology
Objective: Unusual clinical course

Background: Programmed death 1 (PD-1) inhibitors have demonstrated limited effectiveness in patients with microsatellite instability-high (MSI-H) colorectal cancer (CRC). Recent studies suggest that their efficacy can be enhanced when combined with anti-angiogenic agents.

Case Report: We present a case of a 25-year-old woman with CRC harboring a KRAS mutation and MSI-H status, along with initially unresectable liver metastases. Despite receiving first-line chemotherapy combined with bevacizumab, her disease progressed. Subsequently, she was treated with a combination of a PD-1 inhibitor and bevacizumab as second-line therapy. This approach resulted in a partial response, ultimately leading to a pathological complete response after resection of the liver metastases. The patient continued with the combination therapy for over a year and showed no serious treatment-related adverse events. Postoperative follow-up imaging confirmed the absence of tumor recurrence or metastasis, and the patient remained in remission.

Conclusions: This case highlights the potential of combining immune checkpoint inhibitors with anti-angiogenic agents in treating patients with MSI-H metastatic CRC, particularly those with initially unresectable liver metastases. Although further research is warranted to validate this therapeutic strategy, our findings support the use of this combination as a viable option for achieving pathological complete response and improving outcomes in this patient population. Comprehensive clinical studies are needed to optimize conversion therapy regimens and enhance the likelihood of success in treating patients with MSI-H CRC with advanced disease.

Keywords: Angiogenesis Inhibitors • Colorectal Neoplasms • Immune Checkpoint Inhibitors • Microsatellite Instability

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/946757

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Introduction

Colorectal cancer (CRC) ranks as the second leading cause of cancer-related mortality globally [1], with approximately 30% to 50% of patients with CRC developing liver metastases, the most common site of metastasis, during their course of disease [2]. The 5-year overall survival rate for patients with unresected liver metastases is approximately 10% [3]. However, this rate can be increased to 40% to 60% following the resection of liver metastases [4]. Despite this, most patients with CRC present with liver metastases that are initially deemed unresectable. Advances in the development of antitumor therapies have enabled the conversion of initially unresectable liver metastases to resectable ones in some patients, with multimodal treatment leading to a state of no evidence of disease (NED).

There is currently no universally accepted standard for conversion therapy regimens, which permits the use of various treatment protocols aimed at reducing tumor burden. Conversion therapy typically involves a combination of chemotherapy and an appropriate biologic agent, with selection based on the patient's genetic profile. Microsatellite instability-high (MSI-H) has been identified as both a prognostic and predictive biomarker in CRC, as tumors with MSI-H status are generally more responsive to immune checkpoint inhibitors (ICIs), including programmed death 1 (PD-1) inhibitors [5]. The efficacy of PD-1 inhibitor monotherapy in patients with MSI-H CRC has been reported to range from 32% to 40% [6,7], with a substantial proportion of patients with MSI-H CRC not deriving benefit from ICI monotherapy. The combination of anti-angiogenic agents with ICIs has been shown to improve the efficacy of ICIs [8-10]. Anti-angiogenic drugs are a class of biological agents that function by normalizing tumor vasculature and alleviating tumor-associated hypoxia, thereby reducing immunosuppression within the tumor microenvironment and promoting immune activation [10]. Commonly used anti-vascular agents in CRC include bevacizumab, ramucirumab, regorafenib, and fruquintinib. Bevacizumab is an exogenous, humanized monoclonal antibody to human vascular endothelial growth factor that inhibits its biological activity, with combinations of bevacizumab and chemotherapy being the standard first-line therapy regimen in advanced CRC. Combinations of ICIs and bevacizumab have demonstrated promising efficacy in various types of tumors [11-13]. This report presents a case of a patient with CRC with a *KRAS* mutation and MSI-H status, for whom unresectable liver metastases was initially diagnosed. The patient achieved a pathological complete response (pCR) following treatment with a combination of immunotherapy and bevacizumab.

Case Report

A 25-year-old woman with anemia during pregnancy and abdominal pain after giving birth was admitted to our center in March 2018. Prior to admission, she had undergone a colonoscopy with biopsy at another hospital (**Figure 1**). Pathological examination of the biopsy specimen revealed a moderately to poorly differentiated adenocarcinoma. Amplification refractory mutation system polymerase chain reaction detected a *KRAS* G13D mutation. The family history included a father with CRC, a grandfather with gastric cancer, and a grandmother with lymphoma. Laboratory studies revealed a hemoglobin level of 77 g/L, CEA level of 344.2 µg/L, CA19-9 level of 2016 U/mL, and lactate dehydrogenase level of 973 U/L. Abdominal contrast-enhanced computed tomography (CT) revealed a large mass in the ascending colon with diffuse liver metastases (**Figure 2**). The patient developed increased abdominal pain the day after admission, raising suspicion for a potential intestinal perforation. An emergency palliative right hemicolectomy and liver biopsy were performed. Pathological examination indicated a moderately to poorly differentiated adenocarcinoma with perineural invasion. Her mesenteric lymph nodes were negative for metastatic carcinoma (0/2), and although 2 other tumor deposits were observed, her postoperative tumor, node, metastasis stage was determined to be pT4aN1cM1a.

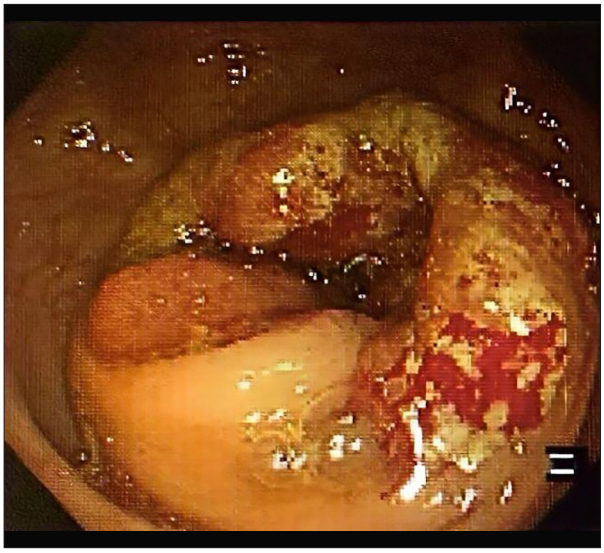

Figure 1. Preoperative colonoscopy indicated a circumferential irregularly elevated lesion near the hepatic region of the ascending colon, leading to luminal stenosis.

Her liver metastases were initially evaluated as unresectable; however, NED was considered achievable with conversion therapy. Her postoperative Karnofsky performance status score was 80. Subsequently, the patient received 3 courses of XELOX (capecitabine and oxaliplatin) in combination with bevacizumab. During treatment, the patient developed back pain, which persisted despite opioid analgesia, and her tumor markers continued to rise (**Figure 3**). She was subsequently deemed insensitive to and intolerant of chemotherapy. A post-treatment enhanced CT scan revealed the progression of liver metastases (**Figure 4A, 4B**).

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Figure 2. Contrast-enhanced computed tomography showed a large mass in the ascending colon of this patient, along with multiple liver metastases.

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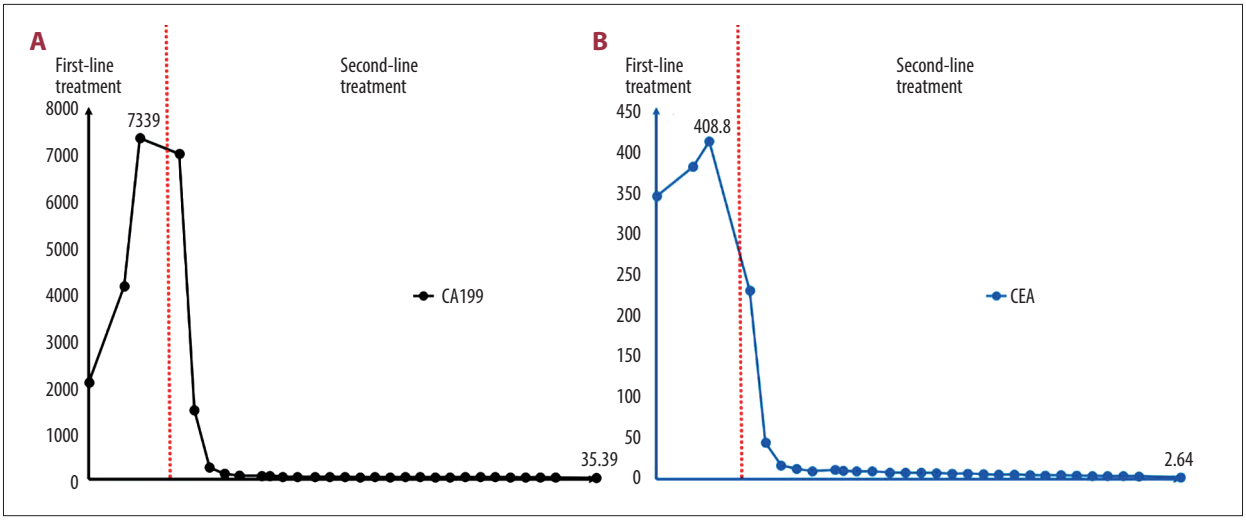

Figure 3. Serum concentrations of (**A**) CA19-9 and (**B**) CEA during first-line and second-line treatment of this patient.

DNA extracted from tumor tissue obtained during surgery was analyzed using next-generation sequencing, and microsatellite status was evaluated by polymerase chain reaction, with both indicating MSI-H. The results of mismatch repair analysis are presented in **Figure 5**. Given the sensitivity of MSI-H CRC to ICIs, the patient received a combined regimen of pembrolizumab and bevacizumab as second-line treatment. A post-treatment enhanced CT scan performed 2 months later revealed a partial response (**Figure 4C**). Subsequently, the patient received a total of 11 courses of this treatment regimen. Due to financial constraints, the patient was subsequently treated with 14 courses of toripalimab plus bevacizumab, followed by 2 courses of toripalimab alone, until February 2020. No serious treatment-related adverse events were observed during the treatment.

A follow-up CT scan in June 2019, one year after treatment, revealed multiple punctate hyperdense shadows around the liver metastases (**Figure 4D**). Enhanced CT and magnetic resonance imaging (MRI) in March 2020 suggested a possible complete response (**Figure 4E**). Based on these findings, her liver metastases were resected on March 18, 2020 (**Figure 4F**). A cholecystectomy was also performed due to intraoperative exploration of the gallbladder fossa, which revealed multiple fused tumors in a mass. Pathological examination revealed a large area of coagulative necrosis and granulomatous inflammation, with no definite tumor cell remnants, leading to a pathologic diagnosis of pCR. Three months after surgery, the patient received 6 courses of treatment with a combination of toripalimab and bevacizumab from June to September 2020.

A CT scan in March 2021 revealed that an enlarged lymph node adjacent to the right external iliac vessel had increased in size to 3.2 cm (**Figure 6**). As it could not be determined whether the enlarged lymph node represented a metastatic lesion, mass aspiration was considered necessary for further evaluation. Pathological examination revealed coagulated necrotic tissue, with no evidence of tumor cells. At the time of this report, the patient was still alive, with no signs of recurrence or metastasis, as confirmed by the last postoperative follow-up CT and MRI in November 2023.

Due to multiple changes in the patient's treatment plan, which involved various therapeutic approaches, including chemotherapy, immunotherapy, and surgical interventions, a simplified timeline has been created to provide a clearer review of the patient's treatment (**Figure 7**).

Discussion

The liver is the most common site of metastasis in patients with CRC. Conversion therapy should be considered for patients with initially unresectable CRC with liver-only metastases, as it can lead to NED following tumor shrinkage. No standard regimen has been established for conversion therapy, indicating that all treatment options capable of reducing tumor size can be effective. Combinations of monoclonal antibodies targeting the epidermal growth factor receptor and chemotherapy have been shown to be more effective than chemotherapy alone in patients with CRC and liver metastases harboring wild-type *RAS*. This approach is associated with higher rates of NED, objective response, secondary resection, and improved survival [3,14-16]. Two phase III clinical trials are currently underway to evaluate the effectiveness of bevacizumab and cetuximab in combination with chemotherapy for the conversion treatment of patients with metastatic CRC and wild-type RAS [17,18]. Moreover, The BECOME trial demonstrated that the combination of bevacizumab and mFOLFOX6 was superior to mFOLFOX6 alone in increasing the resectability of liver

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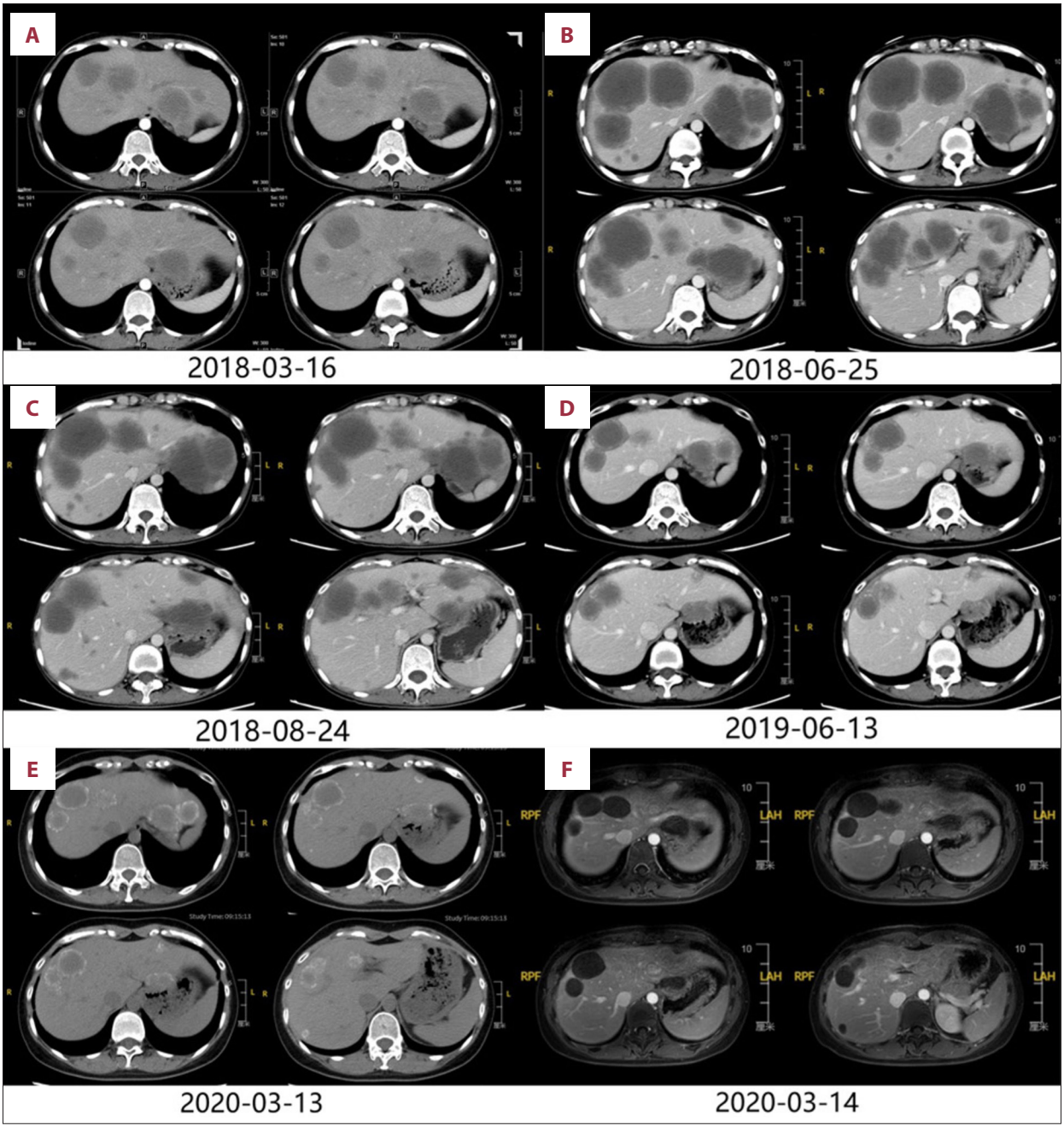

Figure 4. (**A-E**) Contrast-enhanced computed tomography (CT) showing multiple liver metastases at different times: (**A**) baseline (2018-03-16); (**B**) after first-line treatment (2018-06-25); (**C**) after 2 courses of second-line treatment (2018-08-24); (**D**) after about 1 year of second-line treatment (2019-06-13); (**E**) CT before liver tumor resection (2020-03-13); and (**F**) contrast-enhanced magnetic resonance imaging showing multiple liver metastases (2020-03-14).

metastases, as well as improving response and survival rates in patients with CRC with initially unresectable liver metastases harboring *RAS* mutants [19]. Additionally, FOLFOXIRI combined with bevacizumab has been shown to be a viable treatment option, irrespective of baseline clinical characteristics and *RAS* or *BRAF* mutational status [20-22].

Given that this patient had a Karnofsky performance status score of 80 and harbored a *KRAS* G13D mutation, she was treated with first-line bevacizumab in combination with XELOX chemotherapy. Nevertheless, her tumor progressed rapidly while on treatment, suggesting that her poor response to chemotherapy may have been associated with the *KRAS* G13D mutation and MSI-H status. The selection of conversion therapy

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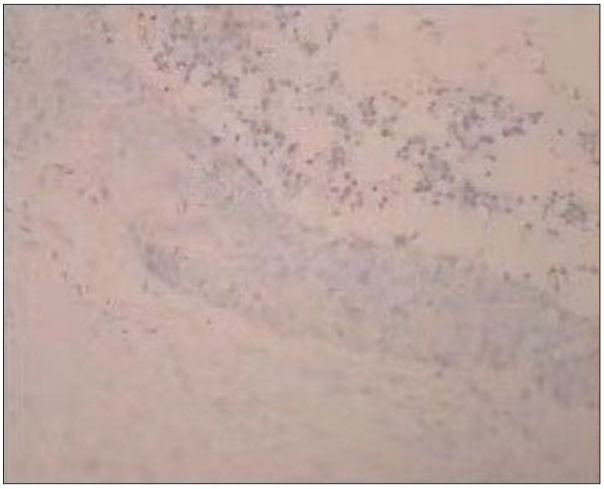

Figure 5. Immunohistochemistry of tumor tissue, suggesting deficient mismatch repair status: PMS2 (-), MSH2 (+), MSH6 (+), MLH1 (-).

Figure 6. An enlarged lymph node next to the right external iliac vessel.

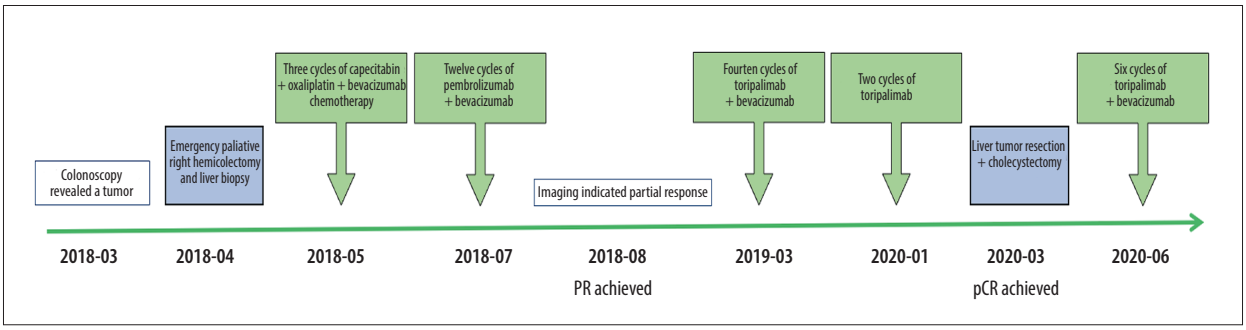

Figure 7. Timeline of the patient's treatment plan.

for patients with *KRAS* mutations should be guided by the molecular characteristics of their tumors.

MSI-H is a prognostic predictor in patients with advanced CRC and is associated with resistance to chemotherapy [23]. Patients with this subtype, however, can benefit from ICI therapy, with objective response rates (ORRs) to first-line pembrolizumab monotherapy being 45% [24], 32.8% to later-line pembrolizumab use [25], and 34% to later-line nivolumab monotherapy [7]. In contrast, the ORR of patients with MSI-H metastatic CRC to first-line treatment with nivolumab plus ipilimumab was found to be as high as 69% [26], with the ORR to later-line treatment reaching 65% [27]. These findings indicate that, although response rates to a single immunotherapy agent are relatively low, the combination of 2 immunotherapy agents results in significantly higher response rates. A previous report described a patient with initially unresectable liver metastases from CRC who achieved pCR following combined treatment with 2 immunotherapy agents [28].

Although anti-angiogenic agents have been reported to enhance the antitumor efficacy of ICIs, even in patients with stable microsatellites [8,9,29-31], the efficacy of various drug combinations differs significantly. This underscores the need to assess the effects of new drug combinations in large sample populations. Bevacizumab, an anti-angiogenic inhibitor targeting vascular endothelial growth factor, is widely used in the first-line treatment of metastatic CRC. It has been shown to enhance the efficacy of ICIs by improving the function of effector immune cells and inhibiting the activity of immunosuppressive cells [32]. The combination of bevacizumab and a PD-1 inhibitor resulted in a progression-free survival exceeding 17 months in a patient with metastatic CRC with a *BRAF* V600E mutation [33]. Moreover, a phase 1b trial involving patients with unresectable hepatocellular carcinoma found that the combination of atezolizumab and bevacizumab demonstrated promising antitumor activity and safety, with improved overall survival and progression-free survival rates, compared with that of sorafenib [34].

The patient in the present study, who had MSI-H status, was treated with a combination of bevacizumab and 2 PD-1 inhibitors as second-line conversion therapy, resulting in a pCR. Although no clinical trials to date have assessed outcomes of treatment with bevacizumab and a PD-1 inhibitor in patients

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with metastatic CRC, the NIVACOR trial, a phase II study of first-line nivolumab, bevacizumab, and FOLFOXIRI in patients with metastatic CRC, found that the ORR in patients with *RAS* or *BRAF* mutants was 76.7% [18]. In addition, a study evaluating the efficacy of a PD-1 inhibitor combined with targeted agents and chemotherapy in conversion therapy is currently ongoing [35]. Patients with unresectable advanced CRC have a poor prognosis, highlighting the need to identify effective conversion therapies to improve their chances of achieving NED and prolonged survival.

Although the present patient showed a promising outcome, to provide a better understanding of the results and limitations of this study, several aspects warrant further investigation and deeper exploration.

First, this patient received a second-line treatment regimen for over 1 year before meeting the criteria for operability, thereby slightly increasing the likelihood of adverse events. The duration of second-line treatment may have been influenced by the extensive liver metastases and high tumor burden of this patient. More than 10 liver metastases and a high tumor burden have been reported as risk factors for failure of conversion therapy [36,37]. Her initial abdominal enhanced CT scan revealed more than 10 diffusely distributed liver metastases and a high tumor burden in this patient. A partial response was achieved after second-line treatment with the combination of a PD-1 inhibitor and bevacizumab. The optimum duration of immunotherapy remains unclear, although National Comprehensive Cancer Network guidelines recommend that patients undergoing conversion therapy proceed to surgery as soon as the tumor becomes operable [38]. While imaging showed no further regression during second-line treatment, CT scans revealed foci suggestive of premetastatic enhancement. MRI and additional imaging techniques revealed conversion of the liver metastases to coagulated necrotic tissue, indicating a clinical complete response. Imaging findings alone may not accurately assess the degree of tumor regression, highlighting the need for more precise modalities, such as combining ctDNA testing with artificial intelligence analysis of imaging results, to evaluate treatment response and determine the optimal timing for surgery in patients undergoing conversion therapy.

Second, this patient developed an enlarged lymph node in the pelvis 1 year after discontinuing immunotherapy. At that time, it was not possible to determine whether the enlarged lymph node was metastatic, without relying on pathologic diagnosis. Pseudoprogression after immunotherapy, potentially associated with immune activation, has been reported in other patients [39-41]. Accurate diagnoses in clinical practice are often based on imaging results, changes in tumor markers, pathological findings, and patient symptoms.

Third, the present patient did not undergo MSI testing before first-line treatment, possibly due to the availability of this test and her preferences at that time. According to current international guidelines, MSI testing should be conducted in all patients with CRC with a suspected hereditary component, such as those with a family history or meeting the criteria for Lynch syndrome, and can be considered for other patients based on clinical judgment. Future research is needed to assess whether first-line immunotherapy in patients with MSI-H can improve the likelihood of successful conversion therapy and to explore more effective options for conversion treatment.

Fourth, this patient was a young woman with MSI-H CRC and a family history of cancer. While the tumor status of her other family members remains unknown, the presence of multiple cancers in her family raises the possibility of Lynch syndrome, a hereditary condition associated with an increased risk of colorectal and other cancers. Lynch syndrome is characterized by germline mutations in mismatch repair genes, leading to microsatellite instability and a higher likelihood of developing MSI-H CRC. Given the potential genetic implications, it is crucial to investigate the genetic background of this patient further. Since her family history may indicate an inherited predisposition to cancer, close follow-up is warranted, both for early detection of any other malignancies and to monitor the progression or recurrence of her CRC.

Conclusions

This case report highlights the promising potential of combining ICIs, such as PD-1 inhibitors, with anti-angiogenic agents like bevacizumab in treating patients with MSI-H CRC, particularly those with initially unresectable liver metastases. The patient achieved a pCR following this combination therapy, and postoperative follow-up confirmed the absence of tumor recurrence or metastasis, with no significant treatment-related adverse events. However, given that these findings are based on a single case, further validation through large-scale, multi-center, randomized controlled trials is essential to confirm the therapeutic efficacy and safety of this combination in a broader patient population. Future studies should focus not only on optimizing treatment regimens and assessing long-term outcomes but should also explore potential biomarkers for predicting patient response, enabling more personalized therapeutic strategies. Additionally, comparative studies with existing standard therapies are necessary to establish the relative benefit of this combination approach. Ultimately, while this case offers encouraging preliminary evidence, more comprehensive clinical trials are required to provide robust scientific data, validate the treatment's effectiveness, and improve therapeutic options for patients with advanced MSI-H CRC.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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