

A pathological complete response after nivolumab plus ipilimumab therapy for DNA mismatch repair-deficient/microsatellite instability-high metastatic colon cancer: A case report

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Abstract. The standard treatment for colorectal cancer has always been surgery and chemotherapy, which may be used in combination to treat patients. Immune checkpoint inhibitors have been a significant advancement in the standard treatment of metastatic, unresectable colorectal cancer with deficient mismatch repair. However, little information is available about their use in neoadjuvant and conversion settings with only a few case reports and only one phase 2 trial. The present study reports the case of a large, locally advanced right-sided metastatic deficient mismatch repair/microsatellite instability-high colon cancer, which showed a pathological complete response after combination treatment with nivolumab and ipilimumab. To the best of our knowledge, resected metastatic colon cancer with a pathological complete response after treatment using dual immune checkpoint inhibitors has not been previously reported. Overall, this case report suggests the use of immune checkpoint inhibitors before colorectal surgery.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related mortality worldwide with an increasing incidence (1,2). The incidence of CRC worldwide is predicted to increase to 2.5 million new cases in 2035 (3). Although complete surgical resection remains an important treatment option, 21% of patients newly diagnosed with CRC had distant metastases (4); further, multidisciplinary treatments, including

radiotherapy and chemotherapy, are important, especially in advanced cancer. The overall survival of patients with metastatic CRC (mCRC) has been improving mainly due to advances in systemic therapy. The overall survival of patients diagnosed with unresectable mCRC has increased from ~1 year during the era of fluoropyrimidine monotherapy to more than 30 months with the integration of multiple cytotoxic agents and targeted therapies, such as FOLFOX plus bevacizumab (5). A combination of cytotoxic and molecularly targeted agents is now the standard treatment for unresectable mCRC.

Recently, for deficient mismatch repair (dMMR)/microsatellite instability-high (MSI-H) tumors, which account for 4-5% of CRCs (6), immune checkpoint inhibitors (ICIs) that target cytotoxic T-lymphocyte antigen-4 and programmed cell death protein 1 (PD-1) and its ligand have changed the standard treatment for patients with unresectable CRC and mCRC (7). The randomized, phase 3 trial KEYNOTE-177, which compared first-line pembrolizumab to standard-of-care chemotherapy with or without bevacizumab for dMMR/MSI-H mCRC, found that pembrolizumab significantly increases progression-free survival compared with chemotherapy, with fewer treatment-related adverse events (8). The phase 2 study CHECKMATE-142 showed the improved efficacy of combination immunotherapy (nivolumab plus ipilimumab) compared with anti-PD-1 monotherapy (9). These studies compelled the United States Food and Drug Administration to approve single and dual ICIs as acceptable standard treatment options for dMMR/MSI-H mCRC. However, little has been reported about the use of ICIs in neoadjuvant or conversion settings. Here, we report a case of a large dMMR/MSI-H colon cancer, which showed a pathologic complete response after combination treatment with nivolumab and ipilimumab.

Case report

A 24-year-old man with no previous medical history had been diagnosed with right-sided colon cancer and was referred to our institution. He had recurrent constipation and diarrhea for 1 month. He had never smoked cigarettes and consumed

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alcohol only socially. Family history was remarkable for his mother with colorectal cancer and second-degree relatives with one gastric cancer, two hepatocellular carcinomas, one pharyngeal cancer, and one cervical cancer. Laboratory studies showed no elevation in serum CEA (1.1 ng/ml) and CA19-9 (<2.0 U/ml). Initial dynamic contrast-enhanced computed tomography (CE-CT) showed a huge mass (110x70 mm) in the ascending colon (Fig. 1A) with direct invasion of the right ureter and duodenum (Fig. 1B, C), which was a major concern for upfront surgical resection. This patient had double inferior vena cava (IVC), and the tumor had invaded the right IVC (Fig. 1D). Several enlarged lymph nodes around the tumor were observed, but no distant metastases were noted. The patient underwent colonoscopy, which revealed a circumferential ulcerating tumor in the ascending colon. Biopsy supported the pathological diagnosis of poorly differentiated adenocarcinoma (Fig. 2A).

We considered upfront surgical resection as a feasible option, but the size and circumferential invasion would make the surgery highly invasive and possibly noncurative. Therefore, we decided to administer neoadjuvant treatment. Before the chemotherapy, an ileostomy and biopsy of the mesenteric lymph node were performed. The resected lymph node confirmed the pathological and molecular diagnosis of lymph node metastasis (Fig. 2B), with *KRAS* (codon 13) mutation, non-*BRAF* V600E, and MSI-H. Neoadjuvant chemotherapy with capecitabine and oxaliplatin (CAPEOX) plus bevacizumab was administered (10). During CAPEOX and bevacizumab treatment, the patient only developed grade 1 nausea. After three courses of this treatment, a follow-up CT scan revealed an enlarged tumor (112 x72 mm) and an appearance of multiple pulmonary metastases (Figs. 3A and 4). Since the first treatment was a failure given the disease progression, the combination therapy of nivolumab (240 mg) plus ipilimumab (1 mg/kg) every 3 weeks was performed as second-line systemic therapy, based on the result of high-MSI status. After three courses of such immunotherapy, the tumor had remarkably shrunk to 52x49 mm, and all the pulmonary metastases had almost disappeared. After an additional three courses of nivolumab (240 mg) monotherapy the tumor decreased to 49x46 mm, and all pulmonary metastases had become radiologically undetectable (Figs. 3B and 4). During these immunotherapies, the patient only developed grade-2 dermatitis. Eighteen weeks after nivolumab and ipilimumab combination therapy and four weeks after the last nivolumab infusion, surgical resection-including right hemicolectomy and resection of the right kidney, ureter, and right IVC-was performed. Because the tumor firmly adhered to the duodenum, resection and reconstruction of part of the third portion of the duodenum were also implemented. The operation lasted 10 h and 21 min, and the blood loss amounted to 9011 ml.

A gross examination of the surgical specimen showed a cut surface of a creamy yellow tumor (90x65x60 mm³) in the ascending mesocolon (Fig. 5A). Pathological examination demonstrated that the tumor was totally covered with granulation tissue with no viable cells. Thus, the treatment outcome was pronounced as pathologic complete response (pCR) (Fig. 5B and C). The patient presented a grade-B pancreatic fistula (International Study Group of Pancreatic Surgery pancreatic fistula classification) (11) after surgery but managed

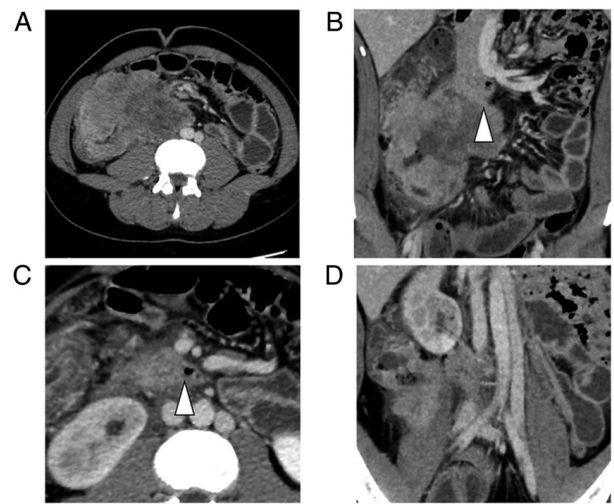


Figure 1. (A) Initial computed tomography scan showing a tumor (110x70 mm) in the ascending colon. (B) Coronal view showing direct invasion of the duodenum (arrowhead). (C) Axial view showing direct invasion of the duodenum (arrowhead). (D) The tumor had invaded the right inferior vena cava. Arrowheads indicate the third portion of the duodenum.

to recover and was discharged on postoperative day 19 with an open drainage tube, which was removed on postoperative day 93. Because Lynch syndrome was suspected from personal and familial history, genetic counseling and testing were performed, and a germline pathogenic variant was found in *MSH2*. The patient is alive and well 12 months after surgery and 22 months after the initial diagnosis.

This study was approved by the Ethics Committee of Ibaraki Prefectural Central Hospital, Ibaraki Cancer Center. Written informed consent for publication was obtained from the patient.

Discussion

Immunotherapy has changed the standard treatment for metastatic and unresectable dMMR CRC; however, little information and experience are available on its use before colorectal surgery.

Neoadjuvant immunotherapy exhibited a high pathological response rate in trials in melanoma, glioblastoma, and colon cancer with small numbers of patients (12-15). As for CRC, one exploratory clinical phase-2 trial and some case reports provided some information. In the exploratory NICHE trial, among 20 patients with resectable dMMR/MSI-H tumors who received nivolumab and ipilimumab, a major pathological response (MPR, $\leq 10\%$ residual viable tumor) was observed in 19/20 patients, and pCR was observed in 12/20 patients (16). One course of the combination immunotherapy with ipilimumab (1 mg/kg) was administered on day 1 and nivolumab (3 mg/kg) on days 1 and 15 in the NICHE trial. A case report on resected colon cancer after dual immunotherapy by Kinney and Khalil (17) has described the resection case of a 52-year-old man with right-sided colon cancer who presented pCR after three courses of combination immunotherapy (ipilimumab 1 mg/kg on day 1 and nivolumab 240 mg on days 1, 15 and 29) every 6 weeks. These studies suggest the potential benefit of immunotherapy in neoadjuvant settings.

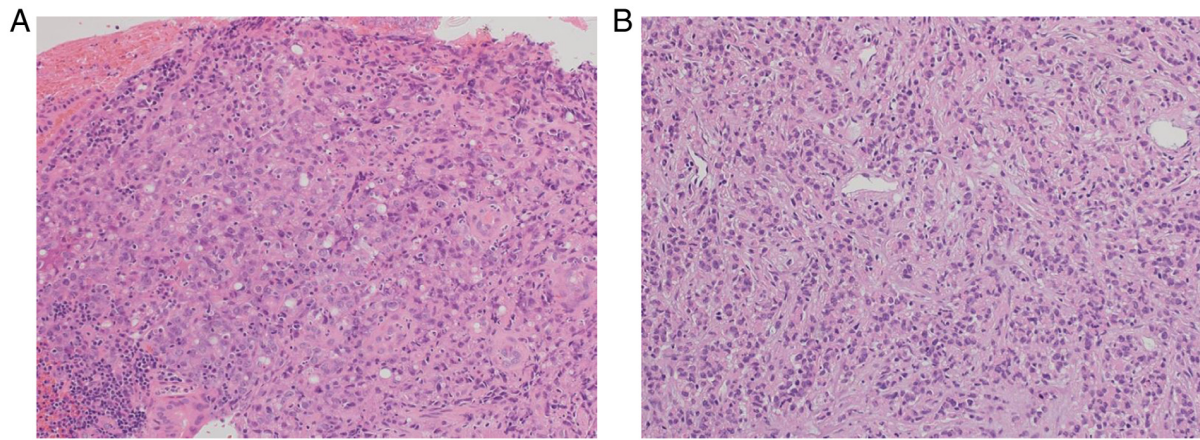


Figure 2. (A) Hematoxylin-eosin staining of the biopsy specimen revealing poorly differentiated adenocarcinoma (magnification, 200x). (B) A pathological examination of the resected lymph node showed poorly differentiated adenocarcinoma and confirmed the lymph node metastasis (magnification, 200x).

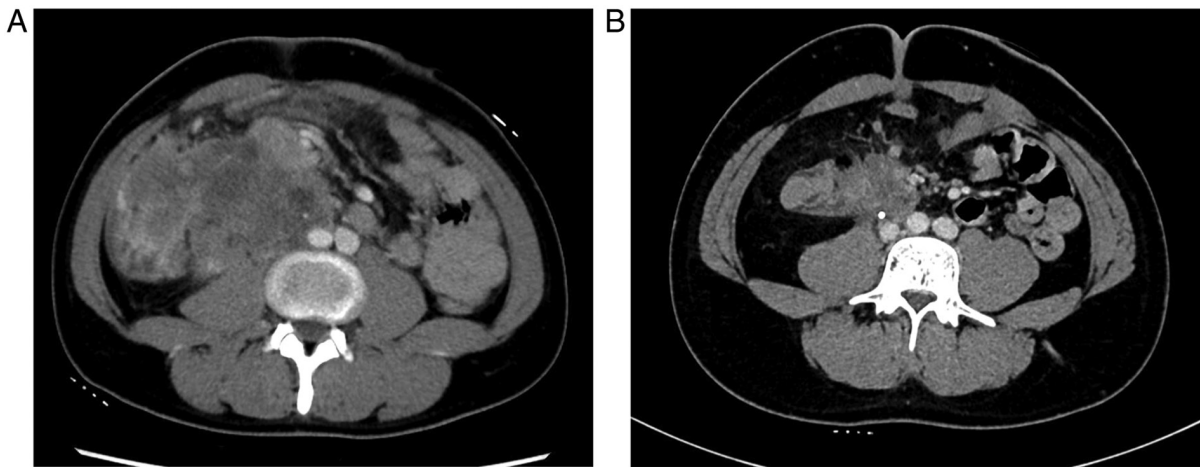


Figure 3. (A) Computed tomography scan performed after three courses of capecitabine and oxaliplatin showed tumor enlargement (112x72 mm) in the ascending colon compared with the initial examination (110x70 mm). (B) The shrunken tumor (49x46 mm) after the combination therapy of nivolumab and ipilimumab.

For patients with unresectable metastases, there is an obvious need for effective conversion therapy. The advancements in effective chemotherapy yielded higher response and resection rates (18,19). A study has reported that robust chemotherapy, such as modified FOLFOXIRI with cetuximab, improved the objective response rate, and this could be an option for conversion regimen (20). Case reports on immunotherapy in the conversion setting are rare, and so far, no clinical trial of immunotherapy in conversion settings has been conducted.

To the best of our knowledge, only one case report has been published on resected colon cancer with distant metastases achieving pCR after immunotherapy. Yang *et al* (21) have reported a case of dMMR/MSI-H ascending colon cancer initially showing multiple mesenteric and retroperitoneal lymph node metastasis and invasion to the IVC, ureter, and right kidney vessels, which was successfully converted to pCR after immunotherapy and radiotherapy (4 cycles of pembrolizumab 200 mg every 3 weeks and radiotherapy). The present case is the first report on advanced-stage CRC presenting similar locoregional extension plus distant pulmonary metastases and converted to pCR after dual immunotherapy.

Little is known about the choice of therapeutic agents for mCRC in the conversion setting. The clinical course of the present case demonstrates that we should have chosen immunotherapy as a first-line treatment before the surgery. This idea is supported by the high CR rate reported for pembrolizumab (8) as a first-line treatment in patients with dMMR/MIC-H mCRC in KEYNOTE-177 (11% vs. 3.9%). The final analysis of OS in KEYNOTE-177 was presented at the 2021 ASCO annual meeting and confirmed pembrolizumab as a new first-line standard-of-care for patients with MSI-H/dMMR mCRC. The next question is the best option for immunotherapy. In the abovementioned studies, immunotherapy was applied in various ways (16,17,21). The NICHE and CHECKMATE-142 trials showed the clinical benefit of combination ICI therapy relative to nivolumab monotherapy. Nivolumab and ipilimumab act synergistically to promote T-cell antitumor activity through complementary mechanisms of action (22,23). Nivolumab plus ipilimumab is suspected to demonstrate a high response rate in various cancers, including CRC (9,24). However, in neoadjuvant or conversion settings, the high toxicity of dual therapy can potentially delay curative

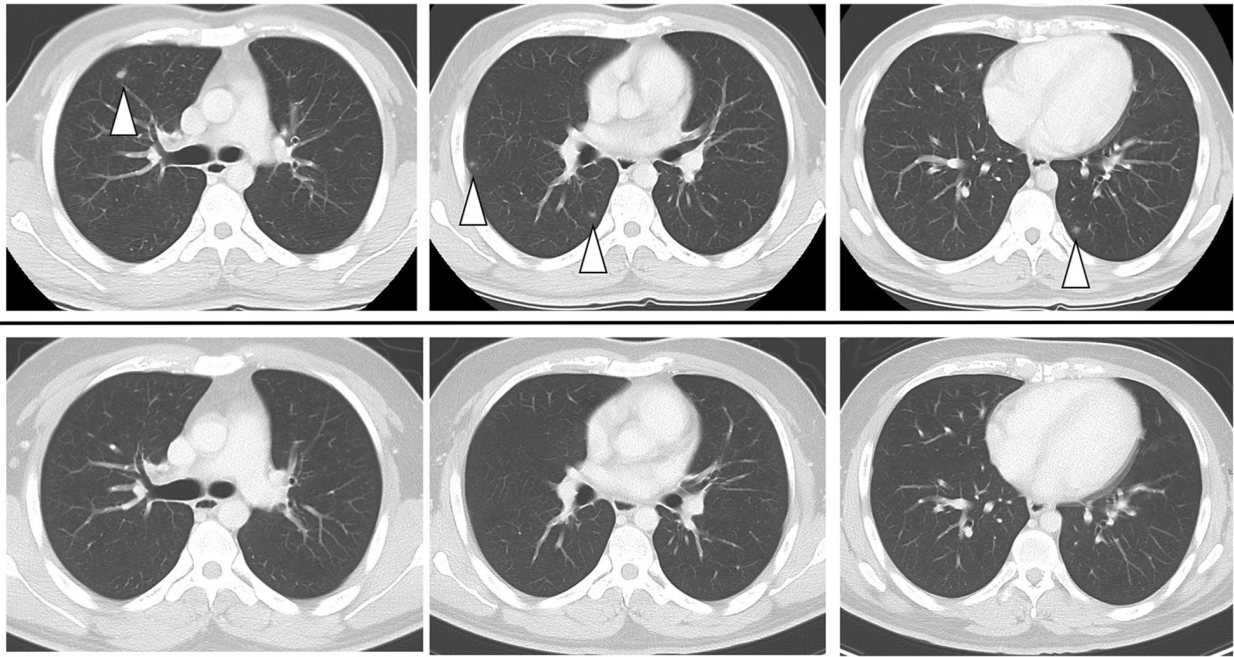


Figure 4. Computed tomography images after capecitabine and oxaliplatin show multiple pulmonary metastases (arrowheads; upper row images), which disappeared after the combination therapy of nivolumab and ipilimumab (lower row images).

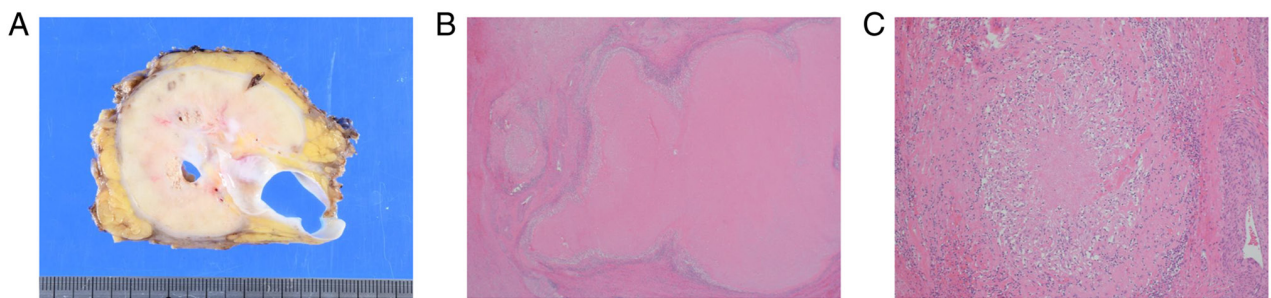


Figure 5. (A) Gross examination of the surgical specimen showing the cut surface of a creamy yellow tumor ($90 \times 65 \times 60 \text{ mm}^3$) in the ascending mesocolon. The ruler scale is in millimeters. (B and C) The tumor was totally covered with granulation tissue and contained no viable cells [(B) magnification, 20x; (C) magnification, 100x].

surgery, which needs further investigation. We provided a longer ICI therapy than that in the study by Yang *et al* (21), which totaled 18 weeks. The optimal duration required for ICI therapy in conversion settings remains unknown. This patient underwent surgery 4 weeks after immunotherapy. Determining the timing of surgical resection is difficult given the scarcity of information regarding ICI treatment for mCRC metastatic colorectal cancers in the conversion setting. There was a risk of local regrowth and distant metastases, and the patient was eager to undergo complete resection.

Radiological assessment of the tumor response to immunotherapy is difficult (16). Pseudoprogression is the initial tumor growth followed by latent or delayed response (25). Ten percent of patients with dMMR/MSI-H mCRC exhibited such a phenomenon during the first 3 months into immunotherapy (26). Such a phenomenon may pose a quandary on whether immunotherapy should be continued or switched to another regimen or surgery, especially when surgical resection is intended. The response assessment by radiology and histopathology reportedly showed poor correspondence

with a previous study on immunotherapy for colorectal cancer (8). Biomedical imaging of tumor progression is still mainly designed to determine lesion size alone, which is reflected in the Response Evaluation Criteria in Solid Tumors. Conventional assessment of treatment effect using the tumor size on CT is not appropriate in some cases; the refinement or innovation of new imaging modalities or new biomarkers that provide a more accurate assessment of ICI treatment effects is needed (27). Notably, at the initial assessment in the present case, the tumor showed a late enhanced marginal area on CE-CT, which suggests viable tumor cells. Gadoteric acid-enhanced magnetic resonance imaging before preoperative immunotherapy revealed the same enhancement pattern as CE-CT and showed high-signal intensity in diffusion-weighted imaging. Such an enhanced area was not observed after immunotherapy. Positron emission tomography (PET) imaging was found useful in distinguishing pseudoprogression in melanoma brain metastases, wherein an enlarged tumor exhibited a low tracer uptake, from true tumor progression, which presents

an intense tracer uptake (28). In the present case, we did not perform PET-CT before immunotherapy. However, PET-CT after immunotherapy showed no elevation of fluorodeoxyglucose uptake in the tumor. CE-CT and PET-CT may prove to be useful in detecting viable cells in tumors and in assessing the treatment effect of ICIs (29).

The present case report demonstrates the successful resection of an initially unresectable metastatic colon cancer obtaining pCR after dual ICI therapy. The case findings suggest methods of using immunotherapy in conversion setting. Initial immunotherapy could be considered as the standard management protocol for dMMR/MSI-H mCRC in conversion setting, however, further research is needed to confirm this suggestion.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SI, TO, HI and JY are responsible for the conception of the study, development of the study design, and writing of the paper. SI, TO, HI, MN, MH and HK were involved in the clinical and therapeutic management of the patient. SI, TO, MN, MH and HK acquired the data, and MN, MH and HK contributed clinical advice. JY contributed to the critical revision of the manuscript and provided important intellectual content. HS, MS and KA contributed to the interpretation of the pathological findings. SI and TO confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Ibaraki Prefectural Central Hospital, Ibaraki Cancer Center (approval no. 1040).

Patient consent for publication

Written informed consent for publication of clinical details and images was obtained from the patient.

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Competing interests

The authors declare that they have no competing interests.

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