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Case Report

Successful Neoadjuvant Therapy with Pembrolizumab Monotherapy for Advanced Ascending Colon Cancer

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Abstract

Immune checkpoint inhibitors have emerged as an effective standard of care for deficient mismatch repair (dMMR)/high microsatellite instability (MSI-H) metastatic colorectal cancer (CRC). However, the role of immunotherapy in the neoadjuvant setting remains uncertain. We report a patient with advanced colon cancer who received curative surgery after successful treatment with pembrolizumab monotherapy. She remains in complete remission after 16 months following the first diagnosis without any immune-related adverse events. In conclusion, single-agent pembrolizumab has strong potential in neoadjuvant therapy for patients with dMMR/MSI-H advanced CRC.

Keywords: Colorectal cancer, deficient mismatch repair, immune checkpoint inhibitor, microsatellite instability, pembrolizumab

Introduction

Colorectal cancer (CRC) is the most common cancer of the digestive system. Deficient mismatch repair (dMMR) associated with high microsatellite instability (MSI-H) occurs in about 15%–20% of all cases of CRC.[1] Testing for MSI/MMR status is recommended for all patients with newly diagnosed CRC to identify gene-specific Lynch syndrome family and to guide the treatment of immune checkpoint inhibitors (ICIs).[2] Immunotherapy has emerged as an effective standard of care for dMMR/MSI-H metastatic CRC (mCRC). Several studies have evaluated the efficacy of ICIs in the neoadjuvant setting for CRC, such as the phase I/II NICHE-1 study and phase II NICHE-2 study.[3,4] However, the role of ICIs in the neoadjuvant setting for dMMR/MSI-H CRC remains uncertain and needs further studies given the lack of randomized controlled trials. Here, we report pembrolizumab monotherapy as successful neoadjuvant therapy in a patient with dMMR/MSI-H advanced colon cancer.

Case Report

A 64-year-old woman presented to our medical oncology outpatient clinic with a 1-month history of intermittent black stool, associated with dyspnea on exertion and weight loss of 3 kg in 1 month. She had a history of diabetes mellitus, hypertension, and immune thrombocytopenia postsplenectomy.

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She did not have a family history of malignancies. A blood test disclosed anemia, and colonoscopy revealed a huge ulcerative mass at the ascending colon with near-complete obstruction of the lumen [Figure 1]. Pathology of the colonoscopic biopsy confirmed Grade 2 adenocarcinoma. Immunohistochemistry and molecular testing showed wild-type *KRAS*/*NRAS*, negative for human epidermal growth factor receptor 2, positive for *BRAF* V600E mutation, and dMMR with loss of nuclear expression of MutL Homologue 1 (MLH1) and post-meiotic segregation increased 2 (PMS2). Abdominal computed tomography (CT) revealed ascending colon cancer with serosa infiltration, pericolic lymphadenopathies, and suspected left adrenal gland metastasis, consistent with cT3N1M1a, stage IVA.

She received two cycles of doublet chemotherapy with FOLFIRI (infusional 5-fluorouracil 2800 mg/m^2, leucovorin 400 mg/m^2, and irinotecan 180 mg/m^2) and in combination with bevacizumab 5 mg/kg on the second cycle. However, an adverse event of Grade 4 neutropenia developed after the first cycle of chemotherapy, followed by febrile neutropenia necessitating hospitalization after the second cycle. Given the status of MSI-H, immunotherapy with pembrolizumab 200 mg every 3 weeks was administered. After five cycles of pembrolizumab monotherapy, CT revealed marked shrinkage of the colonic tumor but no change in the left adrenal tumor [Figure 2]. She underwent laparoscopic right hemicolectomy 1 month later. The pathology revealed poorly differentiated adenocarcinoma with a partial response (tumor regression score 2) and final staging of ypT3N0, without lymphvascular or perineural invasion. R0 resection was achieved. Four more cycles of triweekly pembrolizumab were applied subsequently as adjuvant therapy. Follow-up positron emission tomography/CT revealed no evidence of locoregional recurrence but a left adrenal tumor with increased fluorodeoxyglucose uptake. Left laparoscopic adrenalectomy was performed, and the pathology disclosed adrenal cortical adenoma, excluding malignancy. Currently, she remains in complete remission after 16 months following the first diagnosis without any immune-related adverse events.

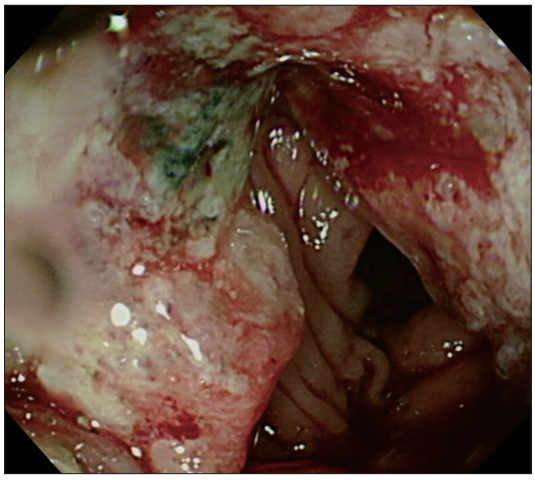

Figure 1: Colonoscopy revealed a huge ulcerative mass at the ascending colon with near-complete obstruction of the lumen

Discussion

Mismatch-repair deficiency is found in patients with Lynch syndrome and 15%–20% of patients with sporadic CRC.[1] ICIs, such as anti-programmed cell death-1 (PD-1) and anti-cytotoxic T-lymphocyte-associated protein 4, have shown promise in the treatment of dMMR/MSI-H mCRC. Based on the results of the KEYNOTE-177 trial,[5] first-line pembrolizumab monotherapy is recommended rather than conventional chemotherapy for patients with dMMR/MSI-H mCRC in the latest guidelines published by the American Society of Clinical Oncology, National Comprehensive Cancer Network, and European Society of Medical Oncology (ESMO) in 2022.[2,6,7] An alternative option is nivolumab with or without low-dose ipilimumab according to data from the phase II CheckMate 142 trial.[8] However, the evidence remains limited in terms of neoadjuvant or perioperative immunotherapy for patient with dMMR/MSI-H advanced CRC.

While there is no prospective study supporting neoadjuvant immunotherapy in dMMR/MSI-H mCRC, a few case studies have reported notable responses. Ludford *et al*. conducted a retrospective study of 121 patients with initially unresectable stage III–IV dMMR colon cancer, of whom 11.6% (14/121) were converted to resectable status and underwent surgery after neoadjuvant single or dual ICIs for 2–28 months. Moreover, 92% (13/14) of the patients achieved a pathologic complete response (pCR), and none of the patients had disease relapse or progression after a median follow-up period of 22 months.[9] These data highlight the emerging role of immunotherapy as conversion therapy in dMMR/MSI-H mCRC. Large prospective studies are required to determine the optimal treatment duration and survival benefit.

In our patient, a remarkable response in dMMR/MSI-H advanced colon cancer was observed after a total of five cycles of neoadjuvant immunotherapy with pembrolizumab. The time from first dose to curative surgery was 4 months. Despite a pathologic partial response, R0 resection was achieved. She remains alive without disease relapse after 16 months following the first diagnosis.

In the setting of dMMR/MSI-H locally advanced CRC, several prospective studies have demonstrated the beneficial effects of neoadjuvant immunotherapy. The phase I/II NICHE-1 study from the Netherlands Cancer Institute revealed

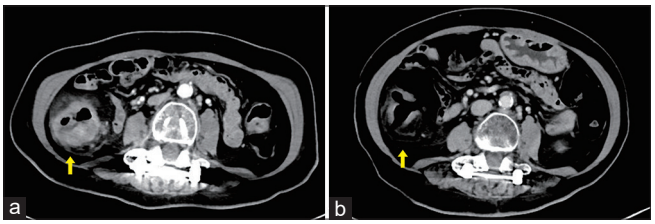

Figure 2: (a) Abdominal CT at the initial presentation showed ascending colon cancer with serosa infiltration and pericolic lymphadenopathies, (b) Abdominal CT showed a marked regressive change of the ascending colon cancer after five cycles of pembrolizumab. CT: Computed tomography

major pathological responses (MPRs) in 95% (19/20) of patients with dMMR stage I-III colon cancer after receiving neoadjuvant nivolumab (3 mg/kg on day 1, 15) combined with low-dose ipilimumab (1 mg/kg on day 1).[3] This dual ICI protocol was applied to a larger cohort in the phase II NICHE-2 study, reported as an abstract at the ESMO Congress 2022.[4] The NICHE-2 study enrolled 112 patients with dMMR nonmetastatic colon cancer, including 89% with stage III tumors, and the results showed an MPR rate of 95% and pCR rate of 67%. At a median follow-up of 13.1 months, none of the patients had disease recurrence. Grade 3–4 immune-related adverse events were observed in 3% of the patients. Another phase II study investigated neoadjuvant PD-1 blockade with dostarlimab (500 mg every 3 weeks for 6 months) in patients with dMMR stage II–III rectal cancer.[10] All 12 patients achieved a clinical complete response and were spared from subsequent chemoradiotherapy or surgery. Despite the lack of randomized controlled trials, the above data suggest the strong potential of neoadjuvant immunotherapy in dMMR/MSI-H locally advanced CRC.

In terms of adjuvant therapy for dMMR/MSI-H CRC, patients with stage II disease do not require any adjuvant therapy given the lower recurrence rate and limited benefit from fluoropyrimidine-based adjuvant chemotherapy.[11-13] In patients with resectable stage III dMMR/MSI-H CRC, consistent with proficient MMR tumors, oxaliplatin-based adjuvant chemotherapy was reported to improve disease-free survival and overall survival in the ACCENT pooled analysis of 12 adjuvant trials.[14] There are no available data supporting the use of ICIs as adjuvant therapy in resectable dMMR/MSI-H CRC. To determine the potential efficacy of ICIs in the adjuvant setting, a randomized phase III trial (NCT02912559) is ongoing in which adjuvant chemotherapy with or without atezolizumab is being evaluated in the treatment of stage III dMMR/MSI-H CRC.[15]

In conclusion, we present a patient with dMMR/MSI-H advanced colon cancer who achieved a durable response through perioperative pembrolizumab monotherapy and curative surgery. Our results are consistent with previous studies and indicate that ICIs can play an important role in neoadjuvant, conversion therapy, and organ-preservation strategies for patients with dMMR/MSI-H advanced CRC.

Ethics statement

Ethical approval to report this case was obtained from the Institutional Review Board of Kaohsiung Medical University Hospital (approval number: KMUHIRB-E(II)-20220250, approval date on November 22, 2022).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient gave her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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