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Case Report

Durable Clinical Benefit after Dual Checkpoint Inhibition and Single-agent Nivolumab Following Pembrolizumab Failure in Mismatch Repair-deficient Colon Cancer

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Abstract

Immunotherapy with immune checkpoint inhibitors (ICIs) is beneficial in treating tumors with high microsatellite instability or DNA mismatch repair deficiency (dMMR) tumors. However, the ideal therapy for patients with advanced dMMR cancer after the failure of the first ICI regimen remains unclear. This case report describes a patient with dMMR ascending colon cancer who later developed endometrial cancer. The patient underwent a sequence of immunotherapies, starting with pembrolizumab, followed by a combination of ipilimumab and nivolumab and finally single-agent nivolumab. This sequence led to a prolonged period of disease control exceeding 20 months. The case highlights the potential benefits of dual checkpoint inhibition and sequential ICI regimens in managing advanced dMMR tumors even after first-line ICI failure; this combination is a promising strategy to explore in future research.

Keywords: Colon cancer, endometrial cancer, ipilimumab, microsatellite instability, mismatch repair-deficient, nivolumab, pembrolizumab

Introduction

Among patients with colorectal cancer (CRC), high microsatellite instability (MSI-H) and DNA mismatch repair deficiency (dMMR) results in a high response rate to immune checkpoint inhibitors (ICIs).[1] The dMMR/MSI-H phenotype, present in approximately 15% of all CRC cases, is associated with right-sided primary tumors, mucinous composition, and poor differentiation. Approximately 20% of Stage II, 12% of Stage III, and 4% of Stage IV CRC tumors are diagnosed with the dMMR/MSI-H phenotype.[2] These tumors are hypermutated, generating abundant mutation-derived neoantigens that trigger a robust immune response within the tumor microenvironment (TME).[3] Given the findings from

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the Phase III KEYNOTE-177 and Phase II Checkmate-142 trials, the National Comprehensive Cancer Network guidelines recommend pembrolizumab and nivolumab – with or without ipilimumab – in both in the primary and secondary treatment contexts for patients with MSI-H/dMMR metastatic CRC (mCRC). However, standard therapeutic options beyond the initial ICI regimen for advanced dMMR cancer remain undefined. We present a case of a patient with dMMR ascending colon cancer and subsequent endometrial cancer who was effectively treated with a regimen comprising ipilimumab and nivolumab, followed by single-agent nivolumab after pembrolizumab failure.

Case Report

A 45-year-old woman received a diagnosis of poorly differentiated, Stage IIIB ascending colon cancer (pT3N2bcM0). The patient's immunohistochemistry revealed an absence of MLH1 and PMS2 expression, indicating dMMR, and testing for the BRAF V600E VE1 variant indicated wild-type BRAF [Figure 1a]. The patient underwent an open right hemicolectomy and duodenal serosa repair in 2019, followed by eight cycles of adjuvant chemotherapy with fluorouracil, leucovorin, and oxaliplatin (FOLFOX). However, abdominal computed tomography (CT) in 2020 revealed what was suspected to be metastatic mesenteric lymphadenopathy with peritoneal seeding [Figure 1b]. Subsequent positron emission tomography revealed no other distant metastases. Based on these results, a multidisciplinary team transitioned the patient to the FOLFIRI + Avastin regimen (5-fU, irinotecan, leucovorin, and bevacizumab) for six additional cycles [Figure 1c]. During this regimen, the patient experienced adhesion band-related jejunal strangulation necessitating enterolysis and segmental intestinal resection.

After six cycles of FOLFIRI + Avastin, doctors detected an incidental endometrial lesion. Subsequent biopsy and pathological examination confirmed endometrioid adenocarcinoma. In July 2020, the patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy,

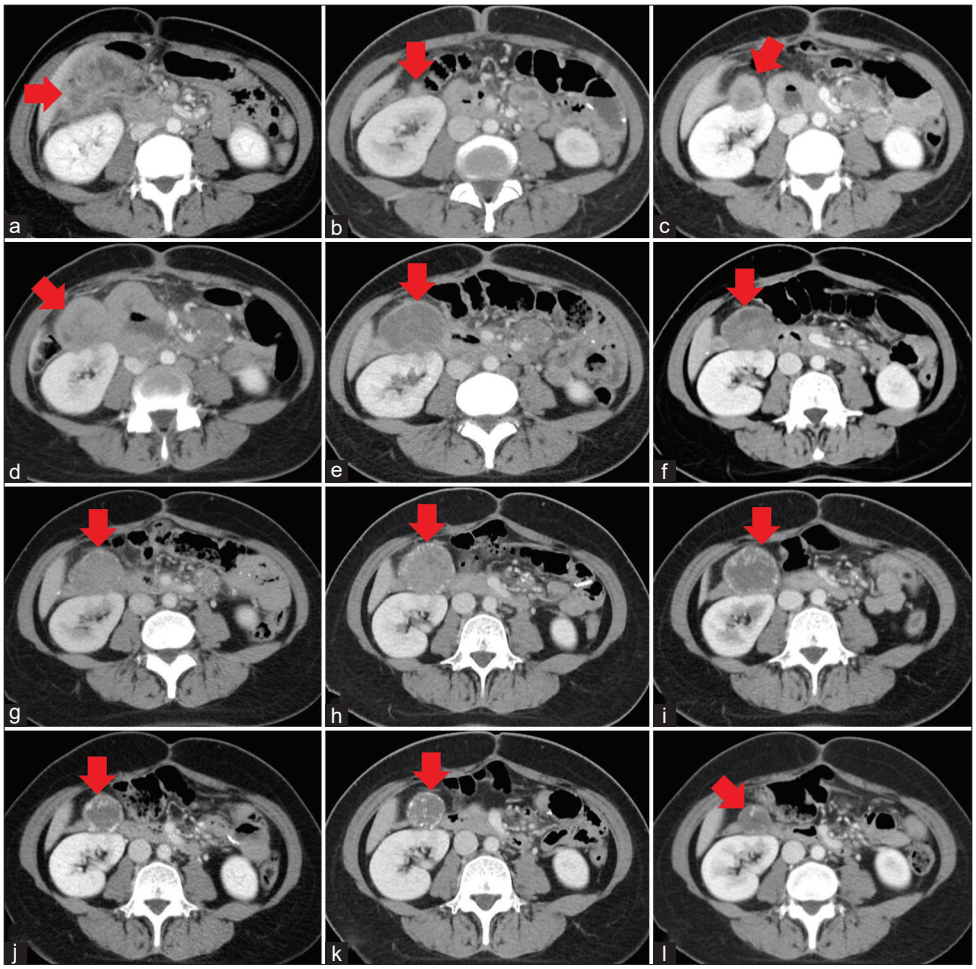

Figure 1: Computerized tomography showing (a) 8.9 cm lobulated mass lesion (arrow) with central necrosis and mottled air bubbles in the right middle abdomen before treatment; (b) no local recurrence at the right hemicolectomy site but evidence of tumor seeding (arrow) in the right perirenal region after fluorouracil, leucovorin, and oxaliplatin; (c) tumor growth to 2.5 cm (arrow) after FOLFIRI + Avastin; (d) tumor growth to 4.3 cm (arrow) after three cycles of pembrolizumab; (e) 4.7 cm necrotic tumor (arrow) after four cycles of nivolumab and ipilimumab; (f) tumor regression to 4.5 cm (arrow) after 4 months of nivolumab monotherapy; (g-i) stable tumor size of approximately 4.5 cm – 4.3 cm (arrow) under nivolumab; (j and k) stable tumor at 3.6 cm (arrow) under nivolumab; and (l) tumor regression to 2.6 cm (arrow) under nivolumab

and bilateral pelvic lymph node dissection. The endometrial cancer also demonstrated a lack of MLH1 and PMS2 expression in immunohistochemistry, mirroring the dMMR found in colon cancer. Consequently, the multidisciplinary team started the patient on a self-funded pembrolizumab regimen, initiated at a flat dose of 100 mg every 3 weeks. The patient underwent three courses of pembrolizumab from August 2020 to September 2020. However, abdominal CT in October 2020 indicated disease progression, with enlarged lymph nodes in the mesentery, para-aortic space, and retroperitoneum [Figure 1d].

In response to the progression of the disease, doctors adjusted the patient's treatment to a self-funded regimen of nivolumab combined with ipilimumab. The initial dosing was 3 mg/kg nivolumab and 1 mg/kg ipilimumab. Because combined progressive disease (PD)-1 and CTLA-4 blockade has high efficacy for MSI-H tumors, the regimen was adjusted to 100 mg of nivolumab and 50 mg of ipilimumab every 3 weeks. The patient underwent four courses of this combination therapy from October to December 2020. Subsequent abdominal CT revealed a reduction in the size of the retroperitoneal and para-aortic lymph nodes and a hypodense lesion with central necrosis invading the right kidney [Figure 1e]. The patient continued with single-agent nivolumab at a dose of 100 mg every 3 weeks, managing to sustain disease control for 20 months [Figure 1f-j]. From November 2022 until the time of writing, the treatment frequency was adjusted to nivolumab 100 mg every 4 weeks. At the time of writing, the patient had maintained disease control on this regimen [Figure 1k-l].

Discussion

Our case report highlights the efficacy of dual checkpoint inhibition and subsequent ICI regimens as a potent rescue strategy, which maintained disease control after progression following the first ICI regimen. Two case studies and a small case series have reported the use of CTLA-4 rescue following anti-PD-1 monotherapy in MSI-H/dMMR CRC.[4-6] Nevertheless, prospective data supporting the use of nivolumab plus ipilimumab for advanced MSI-H/dMMR CRC following progression after a prior ICI therapy line remains scarce.[1]

The objective response rate (ORR) of MSI-H CRC to immunotherapy ranges from 31.7% to 62.5%,[7] indicating substantial heterogeneity in patient response. A meta-analysis encompassing seven clinical trials sought to elucidate this primary resistance to MSI-H CRC immunotherapy. The ORRs to anti-PD-1, anti-PD-L1, and anti-CTLA-4 therapy were 38%, 54%, and 57%, respectively, with 25% of patients with MSI-H CRC exhibiting PD as their best-observed response. This evidence suggests intrinsic resistance to ICIs in a subset of patients with MSI-H CRC, limiting the effectiveness of immunotherapy. However, the incidence of intrinsic resistance was reduced from 31% to 12% under dual–drug immunotherapy. For first- and third-line therapies, the ORR to ICIs is 56% and 32%, respectively. Yet, the incidences of intrinsic resistance to first-line and second-line or subsequent therapies remain high, at 29% and 26%, respectively.[7]

Established predictive biomarkers for resistance to anti-PD-1 or anti-CTLA-4 therapy in MSI/dMMR mCRC are lacking. Notably, traditional markers such as PD-L1 expression level and RAS/BRAF mutation status have been unable to reliably predict the outcomes of ICI treatment. Interestingly, patients with dMMR mCRC experience similar outcomes from ICIs, whether the dMMR originates from a hereditary or sporadic factor.[3]

Resistance mechanisms in dMMR mCRC consist of tumor-intrinsic genetic defects that affect IFN-γ signaling and antigen presentation, in conjunction with oncogenic signaling pathways that alter these processes or induce the production of immunosuppressive factors in the TME. Strategies employed to overcome resistance include combination immunotherapies and rechallenge with ICIs. Experimentation with novel approaches is ongoing, including the use of antibodies and small molecules targeting other immune checkpoints such as lymphocyte-activation gene 3, T-cell immunoglobulin and mucin-domain containing-3, and T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains, along with the implementation of antitumor vaccines and adoptive cellular therapies.[3]

In summary, we detail the case of a patient with dMMR mCRC who experienced sustained clinical improvement from dual checkpoint inhibition and subsequent single-agent nivolumab after progression on pembrolizumab. This case suggests the potential of dual checkpoint inhibition and sequential ICI regimens, which warrant further investigation. Furthermore, we herein summarize the clinical response rates to ICIs, the mechanisms underlying intrinsic resistance, and strategies to overcome it. Future research is warranted to determine the optimal ICI therapy and predictive biomarkers for resistance in patients with dMMR mCRC.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given 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 due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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