Case Report

Two Months of Therapy: A Case of Pathologic Complete Response to Chemoimmunotherapy in a Patient With Metastatic Colorectal Cancer

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Clinical Practice Points

- Knowledge of the mutations responsible for CRC biology provides the opportunity for developing therapeutic targets.
- We report a complete pathologic response in a patient with dMMR CRC after only 2 months of chemoimmunotherapy.
- This case's results may affect the clinical role of chemotherapy to enhance responses to immune checkpoint inhibitors and the ideal duration of therapy.

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Introduction

Colorectal cancer (CRC) is the fourth most common cancer in the United States and the second leading cause of cancer-related deaths. In the past decade, targeted therapies have increased the median overall survival for metastatic CRC from 12 months to 30 months.[1] Recent data emerging from The Cancer Genome Atlas have identified subtypes of colon cancer associated with common oncogenic pathways.[2] One area of particular interest involves a subset of CRC with mismatch repair (MMR) deficiency associated with a hypermutated phenotype. This phenotype of CRC potentially results from thousands of mutations linked to inherited MMR mechanisms (eg, Lynch syndrome) or sporadic cancers associated with somatic mutations or epigenetic phenomenon, including gene promoter methylation, which leads to silencing of gene expression. Knowledge of the mutations responsible for CRC biology provides the opportunity for developing therapeutic targets.

Instability of microsatellites, both truncated and expanded, are observed in $\leq$ 20% of early-stage CRC cases and $\leq$ 5% of advanced-stage CRC cases.[3] High microsatellite instability (MSI) is often associated with a high mutation burden, in the range of thousands per megabase. MSI cancers increase recognition by the cytotoxic T lymphocytes and have a better prognosis compared with stable microsatellite tumors.[4,5] Most CRC cases arising from MMR are secondary to somatic mutations, with a few arising from germline mutations such as Lynch syndrome.[6] The 4 genes associated with Lynch syndrome are MLH1, MSH2, MSH6, and PMS2. Sporadic deficiencies in MMR result from MLH1 methylation, which produces complete loss of the MMR pathway.[6] Immune surveillance plays a role in CRC regulation, and tumor dysregulation of immune checkpoints might contribute to immune resistance mechanisms.[7] Therapeutic manipulation to promote CRC antitumor immunity has been studied. Two immune checkpoint inhibitors, CTLA4 and PD-1 antibodies, increase the immune response in CRC tumors with high MSI.[8] Although most patients with advanced CRC will not benefit from single-agent immune checkpoint inhibitors, the results from phase II studies have suggested a disease control rate of 70% in patients treated with single-agent nivolumab or pembrolizumab.[9,10] Pembrolizumab has been approved for patients with MMR deficient (dMMR) tumors, irrespective of the site of disease. Immunotherapy for CRC could involve 5-fluorouracil (5-FU) to enhance antitumor immunity by elimination of

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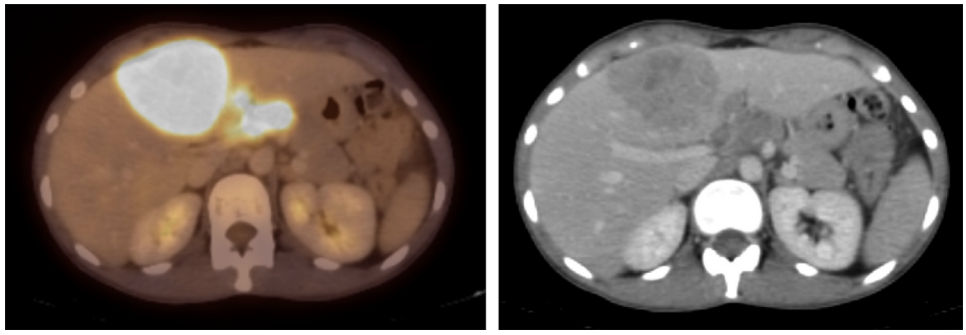
Figure 1 Positron Emission Tomography/Computed Tomography Scan Demonstrating a Large Hepatic Mass, a Large Sigmoid Colon Mass, and Extrahepatic Extensive Lymphadenopathy in the Porta Hepatis



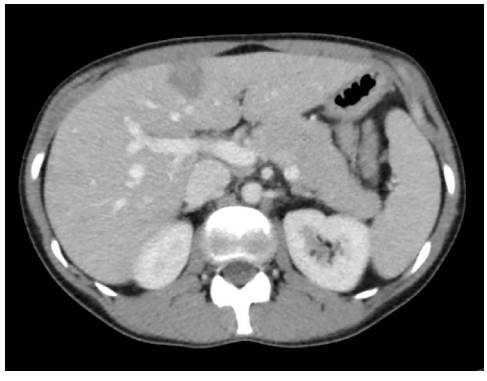
myeloid-derived tumor suppressive cells and increased interferon-γ production by tumor-specific $CD8^+$ cells. Preclinical studies have established the role of chemotherapy drugs as immune modulating agents that could be synergistic with immune checkpoint inhibitors against CRC. In mouse models, oxaliplatin has been reported to induce immunogenic cell death, leading to release of neoantigens, which are engulfed by dendritic cells and presented to tumor-specific $CD8^+$ T cells.[11,12]

Based on previously reported data, a clinical trial was designed to evaluate the safety and efficacy of mFOLFOX6 (5-FU, leucovorin, oxaliplatin) combined with pembrolizumab for patients with advanced, unresectable CRC, irrespective of their MMR status. In the present study, we report a complete pathologic response in a patient with dMMR CRC who had received mFOLFOX6 with pembrolizumab after only 2 months of therapy as observed at surgical resection.

Case Report

A 28-year-old woman presented with diarrhea and hematochezia of several months' duration. Colonoscopy demonstrated evidence of a large sigmoid colon mass. The biopsy results revealed a poorly differentiated adenocarcinoma of the colon. A 3-generation pedigree with emphasis on cancers and tumors was obtained during genetic counselling, which revealed her paternal grandfather had died of colorectal cancer at the age of 32. Immunohistochemical stains with working controls were performed on the specimen. The cancer cells were strongly and diffusely positive for keratin cocktail and CDX2, with negative staining for CK7, CK20, synaptophysin, chromogranin, and PAX-8. Immunohistochemical stains for the MMR proteins MLH1, MSH2, MSH6, and PMS2 were performed, with evidence of loss of expression of MLH1 and PMS2 and normal expression of MSH2 and MSH6. The patient received genetic counseling to discuss confirmation of Lynch syndrome, and her father was recommended to be tested for MLH1 mutation given the paternal history of early CRC.

Figure 2 Computed Tomography Scan After 2 months of Therapy Showing Radiographic Response



Further molecular studies showed *BRAF V600E* wild-type and *KRAS G12D* mutations. Her tumor was evaluated using FoundationOne, and evidence of *BRCA2*, *CDK12*, *PIK3CA*, *PTEN*, *APC*, *ARID1A*, *ARID2*, *CIC*, *CREBBP*, *FAT1*, *MLH1*, *MSH2*, *SPTA1*, and *TP53* mutations and a high tumor mutation burden of 48.71 muts/Mb were found. Despite the retained expression of MSH2 and loss of PMS2 on immunohistochemistry, the findings from the FoundationOne next-generation sequencing identified a mutation in *MSH2*. The patient underwent positron emission tomography, which demonstrating evidence of large central hepatic mass with extrahepatic extensive lymphadenopathy in the porta hepatis and para-aortic region (Figure 1).

She was enrolled in a clinical trial (ClinicalTrial.gov identifier, NCT02375672) and was treated with mFOLFOX6 every 2 weeks and pembrolizumab 200 mg intravenously every 3 weeks. After 2 months of therapy, she had experienced an excellent clinical response and a partial immune Response Evaluation Criteria in Solid Tumors and Response Evaluation Criteria in Solid Tumors response (Figure 2). Operative resection of the tumor required rectosigmoidectomy, partial cystectomy, left partial hepatectomy, and portocaval lymph node dissection. The final pathologic examination (Figure 3) revealed only acellular mucin and complete necrosis with associated necrotizing granuloma, clusters of foamy macrophages, and microcalcifications present in the pericolonic region consistent with a pathologic complete response. No viable