Case Report

Paradigm shift from palliation to cure in metastatic microsatellite high colorectal carcinoma with immune checkpoint inhibitors

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ABSTRACT

Colorectal carcinoma (CRC) is one of the most frequently diagnosed malignancies worldwide with a high mortality rate. CRC is often plagued with significant treatment-related morbidity and mortality, and metastatic progression is common. With the advent of immunotherapy, inoperable and advanced cancers have shown favorable response. Immunotherapy has paved the way for survival of all those with advanced metastatic disease whose treatment was limited to palliative care. We explore the case of a 28-year-old female with advanced metastatic CRC refractory to chemotherapy and targeted therapy, managed with PD-1 inhibitor with complete clinical and pathological response in a relatively short period of time. The notion of upfront immunotherapy for advanced metastatic CRC with microsatellite instability is definitely reinforced by the favorable response seen in our case, and we hope that these findings would help reduce the dependence on chemotherapy as the mainstay therapeutic for advanced CRC.

KEY WORDS: Colorectal cancer, immunotherapy, microsatellite instability, nivolumab

INTRODUCTION

Colorectal carcinoma (CRC) is one of the leading causes of cancer-related death.[1] In spite of the advances in chemotherapy and targeted therapy, the recurring nature of the disease makes it virtually impossible to cure patients with advanced CRC.[2] Immunotherapy has made it possible to curtail the disease and achieve long-term disease-free survival.[3] We report a case with metastatic, microsatellite instability-high (MSI-H) CRC, refractory to chemotherapy and targeted therapy, managed with PD-1 inhibitor (nivolumab) with complete clinical and pathological response, without any toxicity in a relatively short period of time. A scenario is rarely seen in advanced colorectal carcinoma.

CASE

A 28-year-old female from Nigeria presented to us in January 2018 with severe perineal and supra pubic pain. She appeared cachectic, depressed, agitated and on examination had pallor, bipedal edema and tender hepatomegaly. She had no other co-morbidities. She initially presented with hematochezia at an outside hospital in December 2016. Computed tomography (CT) scan showed rectal tumor touching the uterus and the anterior cortex of S2 vertebra along with para-aortic and precaval region lymphadenopathy. A 4.2 cm liver mass in segment II and VI was also seen suggesting metastasis. She continued further management in the United States of America wherein MutL Homolog gene 1 (MLH) methylation study detected methylation of MLH-1 promoter region suggestive of MSI-H status. Biopsy confirmed the diagnosis of B-RAF Negative, MSI High adenocarcinoma of rectum with liver metastasis. K-RAS mutation study was not done. She underwent diversion colostomy in February 2017 to relieve obstruction and was started on palliative chemotherapy with 5-fluorouracil, folinate, oxaliplatin, and irinotecan (FOLFOXIRI) (day 1 and day 14 every 28 days) and targeted

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therapy with bevacizumab, of which she completed six cycles. This was followed by stereotactic body radiation therapy for the liver metastasis. Repeat imaging showed good response in the liver but progression in the primary lesion. She opted to continue six more cycles of FOLFOXIRI + bevacizumab in Nigeria, which she completed in October 2018.

Upon presentation to us, a positron emission tomography (PET)/CT was done which showed a metabolically active lesion in the rectum and sigmoid colon with severe narrowing in the lower sigmoid colon, multiple liver metastases, pelvic lymph nodes, left hydroureter, and hydronephrosis [Figure 1]. Repeat biopsy with immunohistochemistry (IHC) from rectum showed K Ras mutant, Her2neu (human epidermal growth factor receptor 2) negative adenocarcinoma [Figure 2]. She underwent S2 foraminal block and superior hypogastric plexus block in January 2018 for intolerable pain in the perianal region and bilateral groin with little improvement in pain. Her hydronephrosis was managed surgically with double-J stenting.

In view of inoperable disease, further treatment with oral regorafenib/luporal was discussed with the patient, which she refused as she was extremely discouraged with her prior experience with chemotherapy. Hence, an alternative treatment with immunotherapy was proposed with the possible low success rate, which she accepted. She was started on nivolumab 3 mg/kg intravenous every 2 weeks in February 2018. After receiving her first dose, to our surprise, she experienced complete disappearance of pain and a significant improvement in the appetite. Her pain medications were tapered and then stopped. She revisited us after completion of six cycles (3 months). She was symptomatically better, had significant weight gain, and was off her pain medications. A reassessment PET/CT scan showed near-complete resolution of the primary tumor with complete resolution of hepatic and lymph node metastasis [Figure 3]. As she had an excellent response to immunotherapy without any immune-related adverse effects, she was planned to receive further six cycles of immunotherapy.

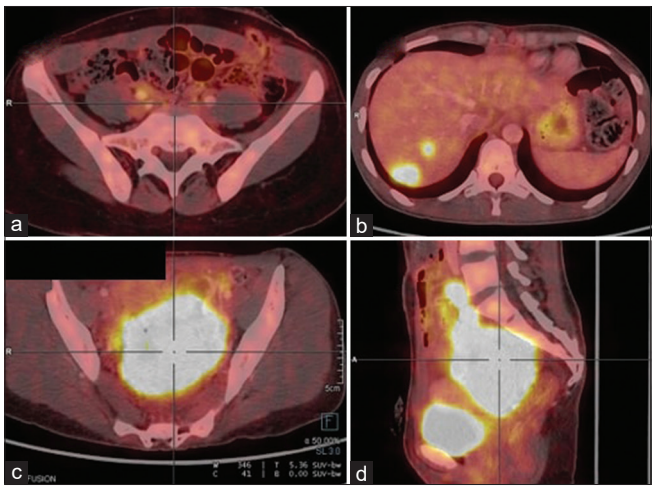

Figure 1: Positron emission tomography/computed tomography scan demonstrating (a) Pelvic lymph nodes, left hydroureter, and hydronephrosis, (b) multiple liver metastases, (c and d) metabolically active lesion in the rectum and sigmoid colon with severe narrowing in the lower sigmoid colon

She continued her nivolumab regimen for six more cycles and was reevaluated with PET/CT which showed no recurrence of disease. Colonoscopy showed no mass in the rectum but a small stricture at the rectosigmoid junction. Biopsy from the stricture site showed dense lymphoplasmacytic infiltrate and no evidence of disease. In view of excellent clinical response, a multidisciplinary discussion involving both medical and surgical oncology teams came to a consensus to stop further immunotherapy and operate on the primary tumor. She underwent laparoscopic anterior resection and closure of diversion colostomy in September 2018. Histopathology of the resected mass showed no evidence of malignancy [Figure 4]. Her last PET/CT (December 2020) shows the patient still in remission.

DISCUSSION

CRC is one of the most common cancers in developed countries with high mortality rate. In spite of increased awareness, screening, and early intervention, most cases (50%) present with metastatic disease.[2] Standard medical therapy for advanced CRC includes frontline systemic chemotherapy, comprising a fluoropyrimidine and either oxaliplatin or irinotecan, along with therapies targeted toward vascular endothelial growth factor and EGFR.[4] Despite the available options, up to 50% of the patients present with relapse.[5]

High-level mutations are often associated with mismatch repair deficiency (dMMR). Approximately 15% of all CRCs are dMMR–MSI-H.[6] Based on polymerase chain reaction or IHC, cases are interpreted as MSI-H, if two or more of the five microsatellite markers show instability.[7]

Immunotherapy is associated with a delayed antitumor response. It takes days to weeks for immune cell activation

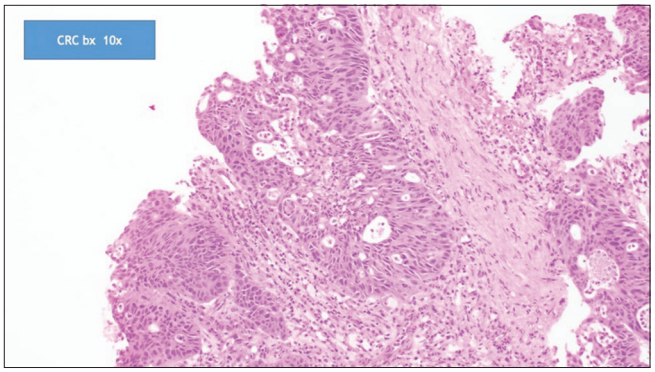

Figure 2: Pathological finding with hematoxylin and eosin staining showing colorectal carcinoma

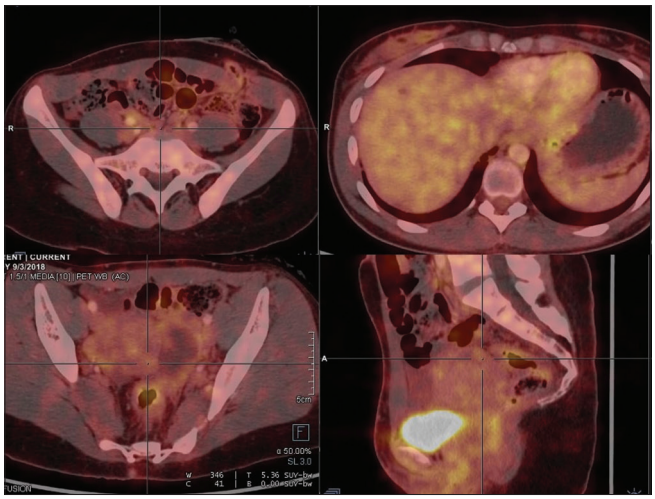

Figure 3: Interim positron emission tomography/computed tomography scan post 3 months immunotherapy with nivolumab showing near-complete resolution of the primary tumor with complete resolution of hepatic and lymph node metastasis

and T-cell proliferation, and a clinically significant immune response occurs over weeks to months.[8] During the interim, patients might present with initial progression. A Phase 2 clinical trial involving MSI-H CRC patients on immunotherapy demonstrated a median time of response of 2·8 months.[9] On the contrary, our patient showed immediate symptomatic response with first dose and a sustained clinical benefit with further cycles of nivolumab. We hypothesize that the immediate symptomatic response could be because of the change in the microenvironment of the tumor due to previous chemotherapy with FOLFOXIRI. Chemotherapy could have enhanced tumor antigen presentation by upregulating their expression on tumor cells or of the major histocompatibility Class 1 molecules to which they bind.[10] A similar response was seen in a patient, part of a Phase I study, initially refractory to chemotherapy who responded to PD1 inhibitor and was in remission for 21 months.[11]

A study comparing immunotherapy responses on MSI-H to those with MSI-stable CRC demonstrated significantly higher infiltration of lymphocytes in MSI-H cells when compared to MSI stable cells in the primary lesion biopsy.[12] A similar IHC picture was seen in our case postimmunotherapy indicating a possible direct immunogenic cell death.

Studies have shown that PD1 blockade can stimulate T-cells which have lost their function due to exhaustion, anergy, tolerance, or immunosuppressive effects of the tumor microenvironment.[13] A long-term durable immune response is observed due to the development of memory T-cells which help keep the tumor in check even after discontinuing immunotherapy.[14] This is further backed by the fact that our patient remains disease free in spite of discontinuing therapy for 2 years.

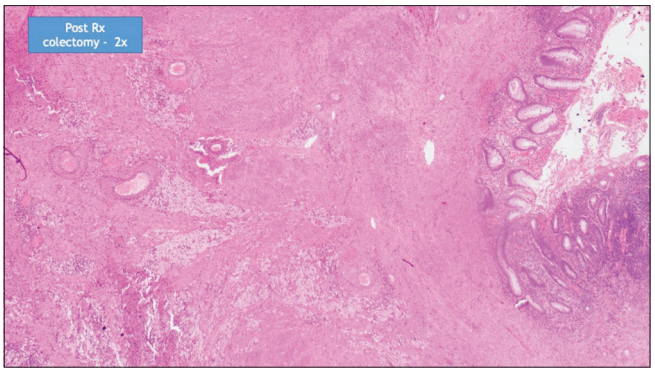

Figure 4: Hematoxylin and eosin staining of biopsy from the stricture at the sigmoidal junction showing extensive T-cell infiltration and normal mucosa with no tumor cells

Our case reinforces the Food and Drug Administration approval for using immunotherapy as a first-line treatment agent for patients with MSI-H/dMMR metastatic CRC.[15] There is a paradigm shift wherein metastatic CRC patients with MSI-H status can be offered upfront immunotherapy which boasts good tolerability with minimal toxicity. We feel the need for more prospective clinical trials with single-agent PDL-1 inhibitors as treatment of choice for MSI-H metastatic CRC.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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