CASE REPORT

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Is the Combination of Pembrolizumab and Regorafenib the Beginning of a New Era in the Treatment of Metastatic Colorectal Cancer?

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ABSTRACT

Colorectal cancer is one of the most common lethal cancers worldwide. In the treatment of metastatic colorectal cancer (mCRC), survival rates have increased due to advancements in cytotoxic chemotherapy and targeted agents. However, the optimal use and sequence of these agents in multistage treatment protocols remain uncertain. Regorafenib, a multikinase inhibitor with immunomodulatory features, has been found to enhance antitumor activity in patients with gastric cancer and mCRC when combined with immunotherapy. Additionally, regorafenib treatment offers a manageable safety profile. In this study, we present the case of a patient with microsatellite instability-high mCRC who achieved a complete response to combination treatment with regorafenib and pembrolizumab. This case report aims to contribute to the literature on this novel combination therapy and provide guidance to clinicians in treatment practices and management.

Keywords: Regorafenib; multi-kinase inhibitor; colorectal cancer; anti-PD1 blockade; immune checkpoint inhibitor

INTRODUCTION

Metastatic colorectal cancer (mCRC) remains a major global health challenge despite significant advances in cytotoxic chemotherapy and targeted therapies, which have improved survival outcomes. Despite therapeutic advances, treatment sequencing and resistance management remain key challenges in mCRC.

Regorafenib, a potent inhibitor of angiogenic and oncogenic kinases, is a standard treatment option for CRC patients.[1] In microsatellite instability-high (MSI-H) tumors, which are characterized by high tumor mutational burden (TMB) and increased immune infiltration, immune checkpoint inhibitors (ICIs) such as pembrolizumab or nivolumab ± ipilimumab have demonstrated durable responses.[2] Despite being immunogenic, MSI-H tumors may benefit from further modulation of the microenvironment by anti-angiogenic agents. Regorafenib, a multikinase inhibitor with immunomodulatory properties, boosts antitumor effects in gastric cancer and CRC patients when combined with immunotherapy, while maintaining a manageable safety profile. While the combination of regorafenib with ICIs has been primarily explored in microsatellite stable (MSS) mCRC to overcome immune resistance by altering the tumor microenvironment, its use in MSI-H tumors remains limited and is not routinely adopted in clinical practice.

In this case report, we present a patient with MSI-H mCRC who achieved a complete response to the combination of pembrolizumab and regorafenib following persistent metabolic activity despite long-term pembrolizumab monotherapy. This case highlights the potential synergistic effect of regorafenib in enhancing immunotherapy efficacy and supports further investigation of this novel combination approach in MSI-H colorectal cancer.

CASE PRESENTATION

A 52-year-old male patient presented to the hospital in July 2019 with abdominal pain. Suspected of appendicitis, the patient

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underwent emergency surgery during which a tumoral mass, surpassing the serosa and adhering to the ileum anastomosis, was detected in the cecum. The patient underwent a right hemicolectomy with a lateral ileo-transversostomy. Pathological examination revealed a 10x10x4 cm grade 3 poorly differentiated mucinous adenocarcinoma in the cecum with infiltration into the ileum. The 15 resected lymph nodes were reactive. The tumor infiltrated the visceral peritoneum and ileum, and was noted at the radial surgical margin. The pathological stage was determined to be pT4bN0Mx. The patient exhibited loss of DNA mismatch repair (MMR) protein expression for MSH2 and MSH6, consistent with MSI-H status. Molecular analysis revealed a KRAS mutation, while NRAS and BRAF were wild-type. Human epidermal growth factor receptor 2 (CerbB2) expression was negative. Postoperative abdominal computed tomography (CT) demonstrated asymmetric thickening at the colonic anastomosis site, raising suspicion for local recurrence. Multiple newly developed nodular lesions, suggestive of peritoneal implants, were observed in the surrounding region. Compared to the prior imaging, several intraabdominal lesions had increased in size, while others represented newonset implants. Multiple lesions, primarily considered implants, have recently developed in the right lower quadrant along the incision line within the rectus muscle.

The patient was started on first-line therapy with XELOX (oxaliplatin + capecitabine) and bevacizumab. After four cycles, abdominal CT revealed an increase in the size of the recurrence at the anastomosis site, and the implants in the anterior abdominal wall and adipose tissue. In particular, implants at the root of the mesentery showed moderate progression without central necrosis. Second-line therapy with FOLFIRI (5-fluorouracil, leucovorin, + irinotecan) and ziv-aflibercept was initiated. After seven cycles of treatment, positron emission tomography (PET)/CT revealed morphologic progression in the existing recurrent mass lesion adjacent to the anastomosis site, as well as in the peritoneal implants in the abdominopelvic region, as well as localization in the anterior abdominal wall. In August 2020, the patient, identified as having MSI-H disease, was started on third-line therapy with 200 mg intravenous pembrolizumab. Partial regression in the size of the nodular densities of the intraperitoneal serosal implants was observed and the and the patient went on to receive a total of 35 cycles of this treatment. Control PET/CT showed partial size regression in nodular densities near the anastomosis site and in the periduodenal area. The hypodense areas in the rectus abdominis muscle plane in the right lower quadrant of the abdomen, previously interpreted as implants, showed significant metabolic and partial morphologic regression.

Although the patient achieved a partial and sustained response after 35 cycles of pembrolizumab, the persistence of metabolically active fluorodeoxyglucose-avid lesions despite prolonged immunotherapy indicated the presence of residual active disease. Therefore, based on the potential immunomodulatory properties of regorafenib to boost the anti-tumor immune response the addition of regorafenib to pembrolizumab was considered. This combination was initiated following formal approval from the national health authority, which acknowledged the combination as an off-label but scientifically rational approach in the absence of progression. In July 2023, 160 mg/day of oral regorafenib was added to the pembrolizumab regimen.

After four months of combination therapy, follow-up PET/CT in November 2023 revealed stable disease without further regression in the reticulonodular densities near the anastomosis site or in the previously identified lesions in the rectus abdominis muscle plane, interpreted as implants. No adverse events were observed during the combination therapy. All biochemical parameters remained within normal limits throughout treatment, except for a marginally elevated baseline CEA level (5.4 µg/L; reference 0–5), which remained stable without significant fluctuation (Table 1). In the last PET/CT scan taken in April 2024, it was observed that the reticulonodular densities around the rectus abdominis muscle planes in the right lower quadrant had completely disappeared, lost their metabolic activity, and the patient was considered to have a complete response (Figure 1).

TABLE 1: Biochemistry and hemogram parameters of the patient before the start of treatment, at the 5th month of treatment and at the 10th month of treatment.

Laboratory values	Before starting regorafenib treatment (June 2023)	5th month of regorafenib+pembrolizumab treatment (November 2023)	10th month of regorafenib+pembrolizumab treatment (April 2024)	The reference range
AST (U/L)	29	20	29	<35
ALT (U/L)	40	40	41	<45
ALP (U/L)	97	103	117	40-129
GGT (U/L)	60	52	54	<55
Total bilirubin (mg/dL)	0.78	0.94	0.8	0.1-1

TABLE 1: Continued

Laboratory values	Before starting regorafenib treatment (June 2023)	5th month of regorafenib+pembrolizumab treatment (November 2023)	10th month of regorafenib+pembrolizumab treatment (April 2024)	The reference range
LDH (U/L)	169	175	211	135-225
Albumin (g/L)	45.7	46.7	47.7	35-52
CRP (mg/L)	2.64	1.2	1.65	0-5
Urea (mg/dL)	30	21	33	10-50
Creatinine (mg/dL)	1.18	1.02	1.02	0.7-1.3
CEA (µg/L)	5.4	4.9	5.41	0-5
WBC (10^3/µL)	11.63	9.81	9.62	4.5-11.0
Neutrophil(10^3/µL)	8.75	6.29	5.93	1.51-7.07
Hemoglobin (g/dL)	15.3	16.7	16	13.1-17.2
Platelet (10^3/µL)	247	259	269	150-450

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; CRP: C-reactive protein; LDH: Lactate dehydrogenase; CEA: Carcinoembryonic antigen; WBC: White blood cell count.

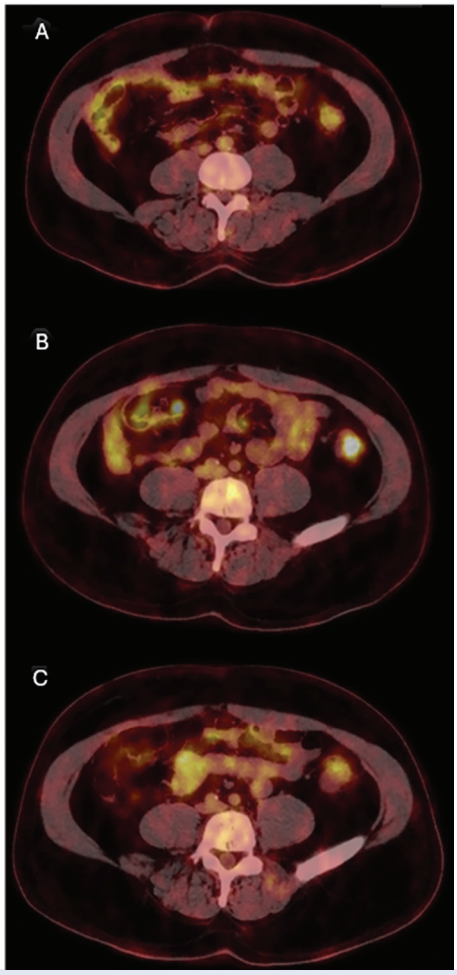

FIGURE 1: PET/CT images showing metabolic response of peritoneal and rectus muscle implants before regorafenib initiation (A), at 5 months (B), and at 10 months (C) of pembrolizumab + regorafenib therapy.

PET: Positron emission tomography; CT: Computed tomography

The patient, who showed a stable and significant response, continues on the current treatment.

The patient received pembrolizumab for 2 years, followed by 1 year of pembrolizumab plus regorafenib. As the complete response persisted, treatment was discontinued in June 2024 and the patient was transitioned to surveillance. He is currently being followed without therapy, and the complete response is ongoing.

DISCUSSION

ICIs such as anti-programmed cell death 1 (PD-1) or programmed death-ligand 1 monoclonal antibodies have improved overall survival in patients with various types of cancer. CRC with deficient MMR or MSI-H status is associated with a high TMB, increased infiltration of lymphocytes into the tumor, and high expression of checkpoints such as PD-1, cytotoxic T-lymphocyte-associated protein 4, and lymphocyte activation gene 3. Despite their inherent immunogenicity, MSI-H tumors may occasionally demonstrate suboptimal responses to ICIs alone, underscoring the need for strategies that further amplify anti-tumor immunity such as combining ICIs with agents such as regorafenib.

The small-molecule tyrosine kinase inhibitor regorafenib has inhibitory efficacy against a number of targets related to tumor angiogenesis and oncogenesis. Regorafenib is used as a second-line and subsequent monotherapy in patients with mCRC. Preclinical studies have shown that the concurrent antitumor activity of regorafenib and anti-PD-1 is enhanced *in vivo* CRC models.[5] Regorafenib's immunomodulatory effect has been explained by a number of mechanisms, including decreased tumor-infiltrating

macrophages, enrichment of the M1 macrophage phenotype, increased activation of T-cells, decreased infiltration of regulatory T-cells, and decreased expression of inhibitory checkpoints like indoleamine 2,3-dioxygenase.[6,7] In murine models such as CT26 and MC38, the combination of regorafenib and anti-PD-1 antibody was shown to inhibit tumor growth more effectively than either agent alone. This improved therapeutic effect was associated with reduced tumor-infiltrating macrophages and Tregs, increased M1 macrophage polarization, and elevated interferon-γ production, indicating a shift toward an inflamed "hot" tumor microenvironment.[8]

In a phase 1b study, the combination of regorafenib and pembrolizumab as a first-line treatment for advanced HCC demonstrated promising antitumor activity.[9] Although MSS mCRC is generally resistant to ICIs, combining regorafenib with ICIs has shown modest benefit in selected MSS patients, particularly in the absence of liver metastases.[10,11] In contrast, MSI-H tumors, characterized by high TMB and immune cell infiltration, typically respond well to ICIs, and the addition of regorafenib may further boost this response through modulation of the tumor microenvironment.[12] The addition of regorafenib is thought to potentiate the efficacy of immunotherapy in selected tumor types by modulating the tumor microenvironment. Preclinical data indicate that MSI-H colorectal tumors exhibit heightened vascular endothelial growth factor pathway activity compared to MSS tumors, supporting the use of anti-angiogenic agents like regorafenib to modulate the tumor microenvironment. In our case, the addition of regorafenib to pembrolizumab may have augmented treatment effectiveness through simultaneous modulation of angiogenesis and immune response.[13,14]

MSI-H tumors exhibit significantly higher TMB compared to MSS tumors. This elevated mutational load promotes neoantigen presentation and facilitates immune cell infiltration, contributing to improved responses to ICIs. Although there is limited evidence suggesting that regorafenib directly increases TMB, its immunomodulatory effects may further amplify anti-tumor immunity in the already immunogenic MSI-H setting.[15] Moreover, retrospective analyses indicate higher response rates to regorafenib in MSIH, versus MSS CRC. An ongoing phase II trial (NCT06006923) is evaluating the safety and efficacy of regorafenib combined with pembrolizumab in MSIH colorectal cancer, featuring a lead-in regorafenib dose-escalation followed by randomization to either pembrolizumab alone or the combined therapy.[16]

Preclinical and clinical data suggest that lower doses of regorafenib may be sufficient to sensitize tumors to ICIs. For example, in mouse models, a dose of 5 mg/kg has been shown to modulate macrophage polarization and enhance T-cell activation, thereby increasing anti-PD-1 efficacy. Similarly, in clinical settings, 80 mg/day of regorafenib has been reported to retain immunomodulatory activity while minimizing toxicity, particularly dermatologic side effects. In contrast, higher doses may reduce $CD8^+$ effector T-cells and fail to confer additional immunologic benefit, highlighting the importance of optimal dosing in combination regimens.[17,18] However, in the absence of established guideline recommendations, we opted to initiate treatment with a standard oral dose of 160 mg/day. Notably, our patient tolerated standard-dose regorafenib without dermatologic or systemic toxicity, supporting its feasibility even in prolonged ICI exposure.

This case underscores the promising synergy between regorafenib and pembrolizumab in MSI-H colorectal cancer, reinforcing the need for personalized therapeutic strategies. In our patient, the addition of regorafenib to ongoing pembrolizumab therapy led to a complete metabolic response without notable adverse effects, suggesting potential benefit in cases with suboptimal response to immunotherapy alone. Although supporting data remain limited to small studies and case reports, our experience contributes to the growing body of evidence for this off-label combination. Prospective clinical trials are warranted to confirm its safety and efficacy and to clarify its place in the treatment landscape of MSI-H mCRC.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.G., F.P.A., O.Ö., E.G., Concept: A.G., F.P.A., O.Ö., E.G., Design: A.G., F.P.A., O.Ö., E.G., Data Collection or Processing: A.G., F.P.A., O.Ö., E.G., Analysis or Interpretation: A.G., F.P.A., O.Ö., E.G., Literature Search: A.G., F.P.A., O.Ö., E.G., Writing: A.G., F.P.A., O.Ö., E.G.

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