Synchronous Recto-Sigmoid Colorectal Carcinomas With Microsatellite Instability and an Activating PIK3CA Mutation

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Abstract
Synchronous colorectal cancer is a rare subtype of colorectal carcinoma defined by the presence of 2 or more primary tumors simultaneously or within 6 months of initial detection. The overall impact of a synchronous presentation on prognosis is not yet clear. Surgical resection is the primary treatment. However, higher rates of local recurrence and metastasis in synchronous colorectal cancer demand greater exploration of the role of adjuvant therapy. The increased frequency of microsatellite instability observed in synchronous colorectal cancer also affects therapy selection. Similarly, activating PIK3CA mutations are regularly noted in colorectal cancer, but their role in a synchronous presentation has not yet been described. We report a case of a young patient with a synchronous recto-sigmoid colorectal carcinoma complicated by microsatellite instability and an activating PIK3CA mutation—a presentation as of yet unreported in literature. We also review the impact of these molecular events on the efficacy of several chemotherapies and targeted therapies.

Keywords
synchronous colorectal carcinoma, microsatellite instability, immunotherapy

Introduction
Colorectal carcinoma is an exceedingly common malignancy with a global disease burden that is rising annually. It accounts for more than 800,000 deaths per year worldwide.同步性结肠癌是一种罕见类型的结肠癌，定义为同一时间段内存在两个或多个原发性肿瘤。同步性结肠癌的总体预后影响尚不明确。手术切除是主要的治疗方式。然而，同步性结肠癌的局部复发率和转移率更高，需要探索辅助治疗的作用。同步性结肠癌中观察到的微卫星不稳定性频率增加也影响了治疗选择。同样，激活的PIK3CA突变在结肠癌中定期被发现，但在同步性呈现中尚未被描述。我们报告了一例年轻患者同步性直肠-结肠癌伴微卫星不稳定性及激活性PIK3CA突变——一种尚未在文献中报告的呈现方式。我们还回顾了这些分子事件对几种化疗和靶向治疗的影响。

Case Presentation
A man in his early 40s with a history of recurrent diverticulitis presented to the emergency department due to a 2-month history of intermittent left lower quadrant abdominal pain and unintentional 20-pound weight loss. Gastrointestinal history consisted of recurring flares of severe abdominal pain and diarrhea occurring once every 12 to 16 months spanning a 4-year period. The patient was diagnosed with diverticulitis.

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Received July 9, 2022. Revised July 25, 2022. Accepted August 7, 2022.

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during each flare and was subsequently managed with antibiotics to complete resolution. On presentation, the patient reported 2 months of progressively worsening left-sided abdominal pain alongside an increased frequency of watery, non-bloody bowel movements without fevers, nausea, or emesis. He also denied rectal tenesmus, rashes, vision changes, or joint pain. He had no personal history of inflammatory bowel disease or cancer. Family history was similarly unremarkable with no reports of colorectal cancer, inflammatory bowel disease, or other colonic pathologies. He affirmed no history of tobacco use with occasional alcohol consumption.

The patient was afibrile with a blood pressure of 106/72 mm Hg, heart rate of 81 beats per minute, and oxygen saturation of 98% on room air. Physical examination was significant for a soft, non-distended abdomen with tenderness to palpation in the left lower quadrant. There were no overt masses distinguishable on palpation and no rebound tenderness or guarding. Laboratory tests revealed a normal leukocyte count of 9.7 × 10⁹/L (reference range: 3.50-11.50 × 10⁹/L) comprising 76.1% neutrophils (reference range: 40%-80%), a low hemoglobin level of 12.5 g/L (reference range: 13.5-17.5 g/L) with a mean corpuscular volume of 90.8 fL (78-100 fL), and a platelet count of 380 × 10⁹/L (reference range: 150-400 × 10⁹/L). A computed tomography (CT) of the abdomen and pelvis demonstrated a phlegmonous mass with central necrosis and an abscess formation across 18 cm of the distal descending colon as well as bladder inflammation without apparent fistula formation, raising concerns for local malignancy although advanced diverticular disease could not be completely excluded. The patient was discharged with suspected recurrent diverticulitis, prescribed repeat antibiotic treatment for 14 days, and instructed to pursue a follow-up colonoscopy after completion.

The patient’s symptoms of abdominal pain and diarrhea did not alleviate with routine antibiotics and left lower quadrant swelling progressively worsened. Three weeks later, he underwent a colonoscopy which revealed a partially obstructing tumor in the recto-sigmoid colon. Three small, non-bleeding polyps were also seen in the ascending colon and 1 polyp was seen in the transverse colon, all which were resected and retrieved. Pathology of indistinct recto-sigmoid mass demonstrated an invasive, moderately differentiated adenocarcinoma arising from a tubulovillous adenoma. Polymerase chain reaction of the biopsy tissue was positive for microsatellite instability (MSI) in greater than 30% of microsatellites indicating MSI-high (MSI-H) cancer status. Molecular analysis revealed a gain of function variant of the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) gene. Specifically, a c.3140A>G p.H1047R mutation indicated an adenine to guanine substitution in nucleotide position 3140, resulting in a missense mutation from histidine to arginine in codon 1047 of coding exon 20 (based on DNA reference sequence NM_006218.4). Immunohistochemical stain confirmed deficient mismatch repair (dMMR) with a loss of PMS2 protein expression in cancer cells and intact expression of the MLH1, MSH2, and MSH6 proteins. Pathology of resected polyps showed fragments of tubular adenoma. Of note, sequencing noted no relevant mutations of BRAF, TP53, KRAS, or NRAS genes.

Due to highly concerning tissue analysis, the patient was scheduled for subsequent imaging for staging. CT of the abdomen and pelvis exhibited marked wall thickening of the descending colon and sigmoid, consistent with chronic diverticulitis and superimposed known adenocarcinoma (Figure 1). There was also evidence of chronic perforation with inflammatory changes in the lower left retroperitoneum. A laparoscopic partial colectomy was performed with mobilization of the splenic flexure, low anterior resection, and diverting loop ileostomy. Notably, pathology of the resected tissue revealed 2 separate masses—a 4.2 cm pT3 sigmoid invasive adenocarcinoma with 0/38 nodes positive and a 2.2 cm pT3 rectal invasive adenocarcinoma. No lymphovascular or perineural invasion was seen in either tumor site and margins on both resections were negative. Macroscopic perforation was also noted. A postoperative carcinoembryonic antigen (CEA) level was collected and resulted at 3.3 ng/mL (reference range: 0.0-4.3 ng/mL). Under the setting of clinical presentation, biopsy results, and radiographic findings, the patient was diagnosed with stage IIA (pT3N0M0, based on the 7th edition of The American Joint Committee on Cancer staging manual) colorectal cancer with 2 synchronous primary tumors in the sigmoid and rectum. Subsequent genetic testing indicated no known inherited cancer syndromes.

The patient was evaluated by gastrointestinal oncology. CT of chest and magnetic resonance imaging (MRI) of the pelvis and liver demonstrated no areas of concern for metastatic disease. While the FOLFOX (folinic acid, 5-fluorouracil, and oxaliplatin) chemotherapy regimen was initially considered for treatment, the biggest risk of relapse was deemed to be local due to noted macroscopic perforation. Therefore, he was treated with radiation therapy to the pelvis for a total dose of 50.4 Gy over 28 days (1.8 Gy per day) to the postoperative tumor bed. He subsequently underwent ileostomy reversal with no complications.

Three weeks following completion of radiotherapy, a positron emission tomography (PET) and CT of the abdomen and pelvis were performed to reevaluate tumor burden. Imaging revealed persistent disease with increased fluorodeoxylucose uptake in the left iliopsoas muscle. The patient was monitored, and repeat imaging was performed 3 months later which confirmed disease progression. A CT-guided biopsy of the reactive iliopsoas tumor bed was performed, and pathology confirmed metastatic adenocarcinoma of colorectal origin. CEA levels steadily increased to 7.2 ng/mL from the baseline 3.3 ng/mL 5 months earlier. The patient was subsequently enrolled in a clinical trial as part of the standard of care arm where he received 36 cycles of FOLFOX as well as bevacizumab over the course of 18 months with
discontinuation of oxaliplatin after cycle 6 due to worsening tinnitus. Due to disease progression on routine surveillance imaging, he was transitioned to pembrolizumab for a total of 6 cycles over 1 year with intermittent cessation secondary to decompensated liver function and transaminitis with aspartate transferase of 166 IU/L (reference range: 0-37 IU/L) and alanine transaminase of 53 IU/L (reference range: 0-50 IU/L). Although initially concerning for metastatic progression, subsequent biopsy of the patient’s liver demonstrated significant cirrhosis, most likely secondary to longstanding increased alcohol consumption. Hepatic function was stabilized, and repeat imaging indicated progressive disease. The patient was trialed again on FOLFOX with the addition of panitumumab. The patient subsequently decompensated after 2 cycles with worsening fatigue. Upon discussion with family members, this young gentleman discontinued all treatment, returned home, and passed shortly after, slightly over 3 years following initial diagnosis of synchronous sigmoid and rectal adenocarcinoma.

Discussion
Observational studies have generally characterized overall presentation of synchronous colorectal cancer with an emphasis on postsurgical outcomes. There is currently no data to guide adjuvant management of synchronous colorectal cancer, including those in recto-sigmoid distributions. Although survival in patients with synchronous colorectal carcinoma relative to solitary colorectal carcinoma is undetermined, several notable factors influencing overall clinical outcomes have been identified. Synchronous colorectal carcinoma is more likely in the male gender and in older age. The pathologic stage, particularly of the index lesion, also affects postoperative survival. The majority of presenting cases involve 2 primary tumors; however, up to 7 independent primary tumors have been identified. Compared with the number of primary tumors, tumor location maintains greater impact on outcomes. This is likely due to the fact that location directly informs the subsequent surgical procedure. Studies investigating the relative distribution of primary tumors located in the same colonic segment compared with separate segments have yielded mixed results. Nonetheless, synchronous colorectal carcinoma in the same segment is typically treated with regional resection. When tumors are in separate segments, surgical approaches include 2 regional resections or one extensive resection, generally depending on the length between the 2 masses.

Studies exploring postsurgical outcomes in patients with synchronous colorectal carcinoma typically emphasize rates of postoperative complications, but data regarding disease persistence and the use of adjuvant therapy are not readily available. Treatments would include modalities typically employed in solitary colorectal cancer, including chemotherapy and targeted therapy. In the case of rectal involvement, radiation therapy may also be utilized. This is particularly important as distant metastasis is more frequently noted in synchronous presentations. Naturally, this is likely due to the presence of additional primary tumors with metastatic potential. However, the potential for macroscopic colonic perforation should also be considered. Although uncommon, perforation secondary to malignancy is most often seen in the sigmoid colon and is implicated in sequelae such as

Figure 1. Computed tomography (CT) of abdomen and pelvis with (a) coronal and (b) axial views demonstrating diffuse marked thickening of the wall of the distal descending and proximal sigmoid colon associated with pericolonic inflammatory soft tissue changes and nodular density.
peritonitis, local recurrence, and metastatic disease. While pathologic stage is a significant risk factor for perforation, increasing local colonic burden in synchronous colorectal carcinoma, particularly recto-sigmoid presentations, could likely also contribute.

In the realm of solitary colorectal cancer, molecular discoveries and identification of targetable pathways have played an increasing role in therapy. In synchronous colorectal carcinoma, studies have generally emphasized higher rates of MSI than those observed in patients with solitary colorectal cancer. MSI-positive colorectal carcinoma can manifest in familial cancer syndromes as well as sporadically through epigenetic inactivation of mismatch repair genes. An MSI-positive status has interestingly been associated with better stage-adjusted survival, of which the underlying biomolecular mechanism is not yet entirely clear. Some studies suggest the high mutational load observed in MSI-positive colorectal carcinoma may promote neoantigens that foster a more robust immune microenvironment. Mutations in TP53 and KRAS have also been observed in synchronous colorectal cancer, though there is a large degree of discordance in presentation. In addition, mutations in PIK3CA, the catalytic subunit of the PI3K enzyme, have not been preferentially associated with synchronous colorectal cancer but are observed in 10% to 20% of all colorectal cancer, although impact on prognosis is unclear. The PI3K enzyme is a protein kinase and member of the PI3K/AKT/mTOR pathway involved in cellular proliferation and survival. Notably, the vast majority of PIK3CA-activating mutations are detected in the helicase domain in exon 9 or the kinase domain in exon 20.

The FOLFOX regimen is considered standard-of-care adjuvant chemotherapy for colorectal cancer; however, MSI-positive status presents unique challenges in management. Studies indicate relative resistance of colorectal cancer cells to 5-fluorouracil-based therapy in patients with dMMR stage II colorectal cancer. Other investigations have demonstrated no significant difference in overall response rate to 5-fluorouracil-based therapy between MSI-stable and MSI-positive colorectal cancer, although higher dosages of the FOLFOX regimen may be required. Regarding targeted therapy, studies have demonstrated survival benefit in patients with dMMR stage II or III colorectal cancer who received bevacizumab, a vascular endothelial growth factor A inhibitor, in addition to FOLFOX chemotherapy. Because MSI-positive colorectal carcinoma expresses numerous neoantigens with elevated levels of multiple checkpoint proteins, current research has also emphasized the utility of immune checkpoint inhibitor therapy. The Food and Drug Administration has approved pembrolizumab, a programmed cell death protein 1 antibody, for metastatic dMMR/MSI-H colorectal cancer. Anti-epidermal growth factor receptor (EGFR) targeted therapy, such as cetuximab and panitumumab, is also employed in metastatic colorectal cancer with non-mutated KRAS, but its role in dMMR/MSI colorectal cancer has not been well established. However, colorectal cancer with activating PIK3CA mutations has demonstrated clinical resistance to anti-EGFR targeted therapy, likely due to the role of the PI3K enzyme as a downstream effector of EGFR.

Our patient presented with early-stage synchronous recto-sigmoid colorectal carcinoma with an activating PIK3CA mutation and MSI-H status and no clinically significant medical history or genetic predisposition. Despite regional surgical resection with negative margins, he progressed to metastatic disease. Importantly, while MSI-positive status is a frequently observed finding in synchronous presentations, literature regarding associated PIK3CA mutations is limited; one study examining tumor samples from synchronous colorectal carcinomas observed frequent alterations in PIK3CA, although further characterization was not performed. Following surgical resection, local radiation therapy was pursued in our patient due to the lack of efficacy of 5-fluorouracil-based therapy in MSI-H colorectal carcinoma noted at the time as well as the primary concern of local recurrence. Following disease progression, the following regimens were employed: FOLFOX and bevacizumab with 18 months of progression-free survival, pembrolizumab with 1 year of progression-free survival, and FOLFOX and panitumumab with subsequent decompensation. While these results cannot adequately support the use of any one therapy, the efficacy of bevacizumab and pembrolizumab aligns with current understanding of MSI-H positive colorectal cancer. It must also be noted that results from therapy, especially FOLFOX and panitumumab, were complicated by the patient’s increasing alcohol consumption compromising liver function. Nonetheless, this gentleman’s disease course contributes to our current understanding of synchronous colorectal cancer. In particular, the patient’s recurring diagnosis of diverticulitis emphasizes a well-documented difficulty in differentiating chronic diverticulitis from colorectal cancer. This underlines the need for greater physician awareness and suspicion, especially in the case of a synchronous recto-sigmoid presentation that may further complicate imaging and the diagnosis.

**Conclusion**

The primary treatment of synchronous colorectal cancer is surgical resection, but higher tendency of local recurrence and metastatic disease demands exploration of effective adjuvant therapy. Microsatellite instability is more frequently observed in synchronous colorectal cancer than in solitary presentation, which affects the efficacy of select adjuvant chemotherapies and targeted therapies. The genetic profile can affect therapy selection. PIK3CA-activating mutations are commonly seen in colorectal cancer and their role in synchronous tumors is not yet clear; however, they are associated with higher resistance to anti-EGFR therapy. The presented case of synchronous...
colorectal tumors with an activating PIK3CA mutation has not been reported in literature thus far. The resulting clinical course offers important insight into presumed resistance to anti-EGFR therapy and the efficacy of other targeted agents.

**Data Availability Statement**
All data generated or analyzed during this study are included in this published article and referenced articles are listed in the References section.

**Declaration of Conflicting Interests**
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**
The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Ethics Approval**
Our institution does not require ethical approval for the reporting of an individual case.

**Informed Consent**
Written informed consent was obtained from the patient’s next-of-kin for anonymized information to be published in this article.

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