Case Report

A Pathological Complete Response after Nivolumab Therapy for Unresectable Sigmoid Colon Cancer with Microsatellite Instability-high Status and BRAF Mutation: A Case Report

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Key Words
Deficient mismatch repair/ microsatellite instability-high;
BRAF mutation;
Colorectal cancer;
Nivolumab;
Conversion therapy

Colorectal cancer (CRC) is the third most common malignancy worldwide and the second most common cause of cancer-related mortality. Radiotherapy, surgery, chemotherapy, and targeted therapy with monoclonal antibodies are among the multidisciplinary treatments. Immune checkpoint inhibitors paved the way for a new era in cancer therapy. Its efficacy is proven for metastatic and unresectable CRC with microsatellite instability-high status. However, limited information exists regarding immune checkpoint inhibitors in neoadjuvant and conversion settings for colorectal cancer.

CRC with BRAFV600E mutation is a marker of poor prognosis and resistance to chemotherapy. Targeted triplet therapy improved the overall survival in BRAF-mutated CRC; however, the side effects were daunting.

This study reports a case of a large, locally advanced sigmoid colon cancer with microsatellite instability-high status and BRAF mutation. A complete pathologic response was achieved after 12 cycles of nivolumab, even after the failure of initial chemotherapy and targeted triplet therapy.

Hence, this study suggests immunotherapy as a new first-line therapy in the conversion setting for patients with CRC who have microsatellite instability and BRAF mutations. However, further research on immunotherapy in conversion settings is required.

[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2023;34:97-101*]

Colorectal cancer (CRC) is one of the most common malignancies worldwide.[1] Complete radical resection remains an important treatment to cure CRC. However, detecting CRC in the early stage is difficult. As for patients with unresectable metastatic CRC (mCRC) or advanced cancer who are not candidates for curative surgery, a cytotoxic chemotherapy and molecular target agent combination, is now the standard treatment.[2]

A common mutation in CRC is in the BRAF gene (most commonly V600E substitution). Resistant to standard chemotherapies occurs in 10% of mCRC patients and is a marker of poor prognosis.[3,4]

Immune therapy heralds a new era of cancer ther-

Received: February 8, 2023. Accepted: February 16, 2023.
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apy. However, information regarding immune checkpoint inhibitors (ICI) as a neoadjuvant and conversion treatment for unresectable CRC is limited. Thus, this study aimed to report a case of unresectable sigmoid colon cancer with microsatellite instability-high (MSI-H) status and BRAF mutation. The patient underwent complete surgical resection with a complete pathologic response (pCR) after 12 cycles of nivolumab, even after the failure of conventional chemotherapy and triplet-targeted therapy.

Case Report

A 39-year-old male with an unremarkable medical history presented with abdominal fullness and abdominal pain. His family history of cancer was unremarkable. Initial contrast-enhanced computed tomography (CE CT) showed a 9 cm sigmoid colon tumor with suspected invasion to urinary bladder (Fig. 1A) and several enlarged lymph nodes. Colonoscopy revealed a bowel obstruction from an annular ulcerating cancer. The diagnosis of poorly differentiated adenocarcinoma, BRAF V600E mutation, and MSI-H status was confirmed by pathological diagnosis of biopsied specimen. Laboratory studies revealed a remarkable elevation in serum carcinoembryonic antigen (CEA) (727.2 ng/mL). Initially, the patient underwent colonic stent placement to resolve bowel obstruction symptoms. Furthermore, positron emission tomography revealed no evidence of distal metastasis and confirmed the initial diagnosis of cT4bN2M0.

Upfront radical surgery might be invasive and not curative, based on consideration the huge tumor size and urinary system invasion. The patient received systemic chemotherapy with 5-fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI) and bevacizumab. A follow-up colonoscopy and CT showed tumor progression (from 9 cm to 12 cm) after 12 cycles of treatment. Additionally, the CEA level increased to 2332.5 ng/mL.

The patient underwent a second-line, triplet-targeted therapy with cetuximab, dabrafenib, and trametinib because the initial therapy failed. However, patient discontinued therapy after four cycles of therapy because of intolerable side effects with grade 4 skin necrosis.

Immunotherapy with nivolumab (3 mg/kg alone) was suggested and administrated every 3 weeks based on high MSI status. The patient developed grade 2 dermatitis during immunotherapy. After 12 cycles of nivolumab, CT showed remarkable tumor shrinkage to 5 cm (Fig. 1B), radiologically undetectable enlarged lymph nodes, and dramatically decreased CEA levels from 2332.5 ng/mL to 12.57 ng/mL after 12 cycles of nivolumab.

Surgical resection was performed, including low anterior resection, partial cystectomy, and soft tissue tumor adhesion excision, after a multidisciplinary team discussion. The specimen was friable and ulcerative with a colonic stent. Pathological examination demonstrated no visible cancer cell (ypT0N0, 0/13); compatible with pathological complete response. The patient recovered well postoperatively, with no evidence of local or distal recurrence at his 24-month follow-up.

Discussion

Immunotherapy is a proven treatment for several types of solid tumors.[4] MSI status was considered an important predicting factor for the clinical benefit of ICIs because an overall response rate of 40% was reported in patients with MSI-H mCRC, while 0% in the MSS group.[5]

The NICHE trial demonstrated that neoadjuvant immunotherapy leads to promising pathological re-

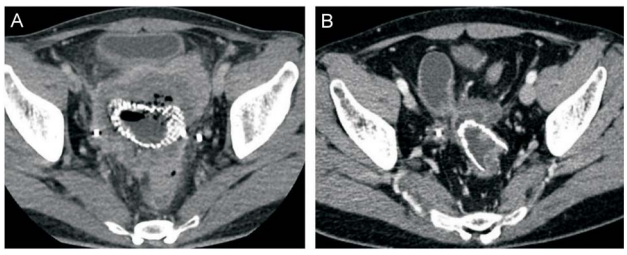

Fig. 1. (A) Initial contrast-enhanced computed tomography showed a large obstructive tumor at the sigmoid colon with direct urinary bladder invasion. A colonic stent was in placed. (B) Marked shrinkage of the main tumor after 12 courses of nivolumab immunotherapy.

sponses in MSI-H early-stage colon cancers.[6] Major pathological response (MPR, ≤ 10% viable residual tumor) and pCR occurred in 19 and 12 patients, respectively, among 20 patients with resectable MSI-H tumors who received nivolumab and ipilimumab. These data indicated the potential of neoadjuvant immunotherapy in CRC.

Case reports regarding immune therapy in neoadjuvant and conversion settings are rare, and no clinical trials have been published yet. We reported a case of a 39-year-old man with sigmoid colon cancer and urinary bladder invasion that was converted to pCR after 12 cycles of single immunotherapy with nivolumab with no evidence of local or distal recurrence at 24-month follow-up.

Conversion therapy is an obvious need for young patients with unresectable CRC because surgery remains its only curative therapy. The NCCN guideline recommends FOLFIRINOX and bevacizumab as one of the first-line therapy for unresectable CRC with BRAF mutation. However, triplet-targeted therapy for treating BRAF mutant CRC has decreased because of serious side effects.[7] Concerning the high pCR rate after immunotherapy, this will be the new first-line therapy for MSI-H mCRC, which was confirmed by the KEYNOTE-177 trial (11% vs. 3.9%).[8]

The CHECKMATE 142 trial revealed that nivolumab provided durable responses and disease control in pretreated patients with MSI-H mCRC.[9] Furthermore, the NICHE trial revealed the clinical benefit of combination treatment with nivolumab and ipilimumab, compared to nivolumab monotherapy.[6] Nivolumab and ipilimumab provide a synergic effect to promote T cell antitumor activity through complementary mechanisms of action.[10] Dual therapy, in neoadjuvant and conversion settings, provides a higher response rate and potentially higher conversion rate; however, side effects of dual therapy can potentially delay curative surgery. The optimal regimens, immunotherapy cycles, and surgery timing after ICI in conversion settings remain unknown. This patient underwent surgery 6 months after 12 cycles of immunotherapy. More clinical studies are required to determine the optimal time for surgery in conversion settings for continuous tumor shrinkage after immunotherapy, including the risk for regrowth and metastasis.

The only cancer samples obtained from biopsy by colonoscopy were reviewed. The PDL-1 expression on cancer cells is less than 1% (Fig. 2). PD-L1 expression in colon cancer positively correlates with TNM stage.[11] As for immunotherapy, PD-L1 expression was reportedly related to a better response to PD-1 inhibitors.[12] No clear-cut value for estimating PD-L1 expression exists with various PD-L1 expression results of CRC through biopsy.

This case report successfully demonstrated a pathological complete response after surgical resection of an initially unresectable and pretreated sigmoid colon cancer with MSI-H status and BRAF mutation.

Ethical Considerations

Ethical approval to conduct the study was obtained from the ethics review committee of MacKay Memorial Hospital before the commencement of the study.

Acknowledgments

The authors thank all surgeons and doctors who

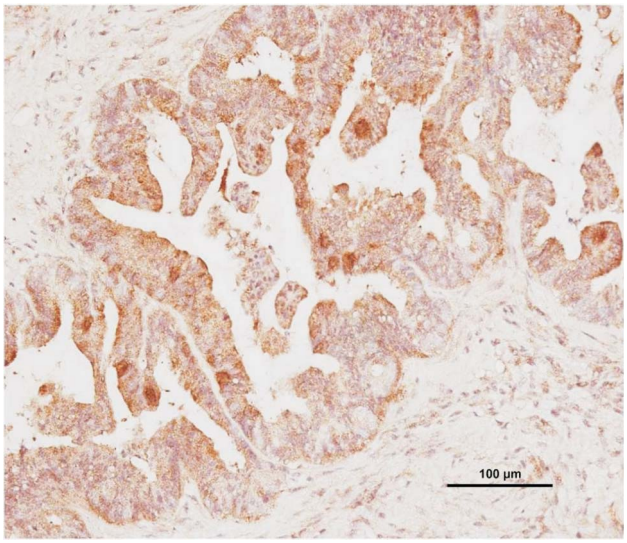

Fig. 2. Pretreated cancer biopsy showed PD-L1 expression of < 1%. The tumor cells only express cytoplasmic staining. Distinct plasma membrane staining is not observed (IHC stain, 200X).

cooperated in this study. The authors also would like to thank Enago (www.enago.tw) for the English language review.

Conflicts of Interest

The authors declare no conflicts of interest.

Funding

The authors declare that they have not receive funding.

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病例報告

帶有高度微衛星體不穩定狀態和 BRAF 突變的無法切除之乙狀結腸癌，使用 Nivolumab 單株抗體治療後達到病理完全緩解：病例報告

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結直腸癌是全球第三大常見惡性腫瘤。放療、手術、化療和標靶治療屬於目前標準的多面向治療。免疫檢查點抑製劑的出現開創了嶄新的道路。它的療效已被證明於具有高度微衛星體不穩定狀態的轉移性和不可切除的結直腸癌。然而，目前關於使用免疫檢查點抑製劑做為結直腸癌前輔助性化學治療和轉化治療的角色仍然沒有明確定論。

本研究報告了一例同時帶有高度微衛星體不穩定狀態和 BRAF 突變的局部晚期乙狀結腸癌病例。病人在化學治療和標靶治療相繼失敗後，在接受 12 次的 Nivolumab 單株抗體療程後達到了病理完全緩解。

因此，這項研究建議將免疫療法用於帶有高度微衛星體不穩定狀態和 BRAF 突變的結直腸癌患者作為一種新的一線轉化治療。

關鍵詞 錯配修復缺乏/高度微衛星體不穩定狀態、BRAF 突變、結直腸癌、Nivolumab 單株抗體、轉化治療。