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Case Report

Surgical Resection for Local and Lateral Lymph Node Recurrence of MSI-high Cecal Cancer with the *BRAF* V600E Mutation

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An 84-year-old female underwent open right hemicolectomy with D3 lymph node dissection for cecal cancer, pathologically identified as pT4aN2M0 Stage IIIc and *BRAF* mutation-positive. Due to early recurrence of abdominal wall and right lateral lymph nodes, the patient was treated with FOLFOXIRI + Bevacizumab. Imaging after 5 courses of chemotherapy found tumor shrinkage and no new metastases. The patient did not tolerate chemotherapy well, and tumor resection was performed. Microsatellite instability (MSI) testing using multiplex polymerase chain reaction (PCR) fragment analysis revealed MSI-high status. The patient is currently recurrence-free without chemotherapy at 1 year postoperatively. *BRAF*-mutated colorectal cancer has a poor prognosis, and may require resection of the metastatic or recurrent tumor after comprehensive evaluation.

Key words: *BRAF* V600E mutation, cecal cancer, MSI-high

FOLFOXIRI (fluorouracil + leucovorin + oxaliplatin + irinotecan) + bevacizumab is the first-line systemic chemotherapy regimen for patients with unresectable advanced recurrent colorectal cancer with the *BRAF* V600E mutation [1, 2]. However, its prognosis is extremely poor [3]. In contrast, microsatellite instability (MSI)-high cases of *BRAF* mutation have been reported to have a better prognosis than microsatellite-stable cases [4, 5]. We herein report the case of a rare subtype of MSI-high cecal cancer with the *BRAF* V600E mutation whose abdominal wall and lateral lymph node recurrence responded to FOLFOXIRI + bevacizumab therapy and was surgically resected.

Case Presentation

An 84-year-old female was diagnosed with advanced cecal cancer with mild anemia, and underwent open right hemicolectomy with D3 lymph node dissection. Pathological examination showed poorly differentiated adenocarcinoma, pT4aN2aM0 pStage IIIc [6]. She was started on capecitabine plus oxaliplatin (CAPOX) as adjuvant chemotherapy. After one course of CAPOX, a follow-up abdominal computed tomography (CT) scan revealed a heterogeneous 2-cm mass in the right lower abdominal wall, suggesting local recurrence (Fig. 1), although both carcinoembryonic antigen (CEA) and CA19-9 tumor markers were within normal limits. Moreover, a positron emission tomography (PET)/CT scan showed fluorine-18 deoxyglucose (FDG) accumulation in the mass on the right lower abdominal wall,

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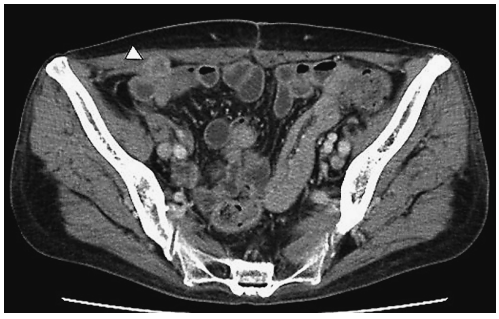

Fig. 1 Abdominal computed tomography finding. There was a heterogeneous 2-cm mass in the right lower abdominal wall.

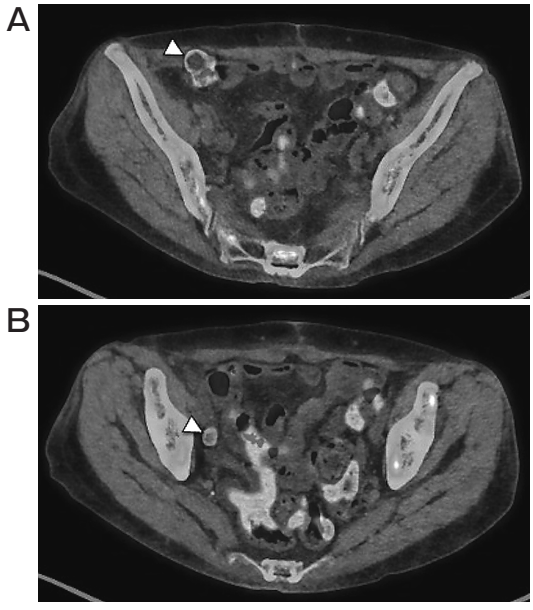

Fig. 2 PET/CT scan finding. A PET/CT scan revealed FDG accumulation in the 2-cm mass on the right lower abdominal wall (A), and a 1.5-cm enlarged right lateral lymph node (B).

and a 1.5-cm enlarged right lateral lymph node with FDG accumulation (Fig. 2). Based on these findings, we diagnosed abdominal wall and right lateral lymph node recurrence. Genetic testing of the surgical specimen using a polymerase chain reaction (PCR)-based method revealed RAS wild-type and the *BRAF* V600E mutation, and FOLFOXIRI + bevacizumab was introduced as a second-line therapy following CAPOX therapy. After 5 courses without severe adverse events, a CT scan showed that the mass on the right lower abdominal wall had shrunk slightly to 1.5 cm (Fig. 3). Although there were no obvious new lesions on imaging, the patient experienced difficulty in tolerating the

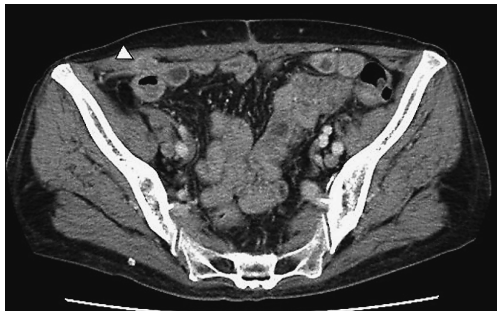

Fig. 3 Follow-up abdominal computed tomography finding. The recurrent mass in the right lower abdominal wall had shrunk to 1.5 cm after 5 courses of chemotherapy.

chemotherapy and underwent laparotomy to excise the abdominal wall mass and right pelvic lymph node. There were no intraoperative complications, the operative time was 1 hour and 53 minutes, and the estimated blood loss was 80 grams. The abdominal wall mass measured 2.8 × 1.5 cm, and the right lateral lymph node was 1.5 × 0.8 cm (Fig. 4A). Histopathologically, both tumors were diagnosed as metastasis of poorly differentiated adenocarcinoma from cecal carcinoma (Fig. 4B-D). No postoperative adjuvant chemotherapy was administered, and the patient is alive and recurrence-free one year after surgery. A later MSI test using multiplex PCR-fragment analysis revealed MSI-high status.

Discussion

BRAF mutations are found in 5-12% of patients with metastatic colorectal cancer, and *BRAF*-mutated colorectal cancer has been reported to have a poor prognosis, not only in patients with unresectable advanced recurrence but also in stage II/III patients after adjuvant chemotherapy [7]. According to the guidelines of the Japanese Society for Cancer of the Colon and Rectum and the European Society for Medical Oncology, the first-line systemic chemotherapy regimen for patients with unresectable advanced recurrent colorectal cancer with the *BRAF* V600E mutation is FOLFOXIRI + bevacizumab [1, 2]. In addition, the recommended second-line chemotherapy regimen consists of BRAF inhibitors: either triplet therapy with encorafenib, binimetinib and cetuximab, or doublet therapy with encorafenib and cetuximab [8].

Although it is accepted that aggressive resection improves the prognosis of liver metastases from col-

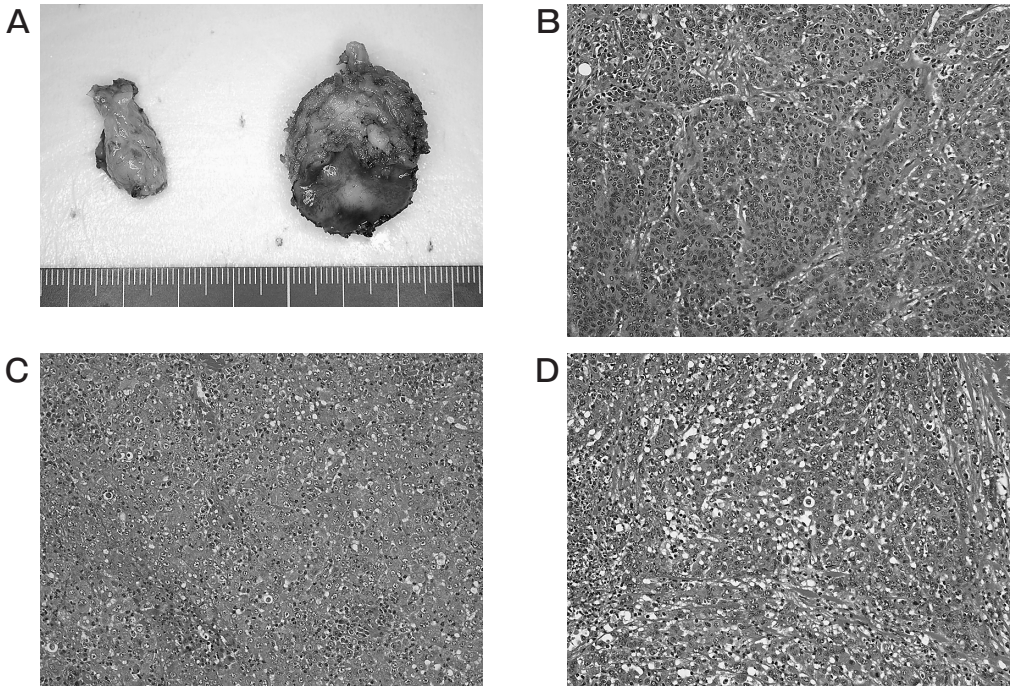

Fig. 4 Specimen extraction and histopathological finding. The abdominal wall mass measured 2.8 × 1.5 cm (**A**, ***right***), and the right lateral lymph node was 1.5 × 0.8 cm (**A**, ***left***). The primary tumor (**B**), abdominal wall recurrence (**C**), and right lateral lymph node recurrence (**D**) were all diagnosed histopathologically as poorly differentiated adenocarcinoma (hematoxylin and eosin staining).

orectal cancer, the indication for surgery in patients with the *BRAF* V600E mutation remains controversial [9,10]. In our case, FOLFOXIRI + bevacizumab therapy was introduced because of early local recurrence and right lateral lymph node recurrence during adjuvant chemotherapy with CAPOX for Stage IIIc cecal cancer. Although no new lesions were found during the 5 months of chemotherapy, the patient's performance status would decrease with continued chemotherapy. Therefore, we decided to perform surgical resection because the proposed surgery was less invasive. Though it has been only one year since the surgery, the patient is now recurrence-free without chemotherapy. Even if a patient has the *BRAF* V600E mutation, if systemic control is possible, resection of the metastases should be considered regardless of *BRAF* status. Previous reports have shown that among *BRAF* mutation-positive patients, overall survival and recurrence-free survival were significantly better in MSI-high patients compared with microsatellite-stable patients [4,5,11]. In addition, a case of *BRAF* V600E-mutated and MSI-high transverse colon cancer with recurrent cervical lymph node metastasis that responded well to secondary therapy and could be surgically resected has been reported, suggesting that resection of metastases is worth considering if systemic control is possible [12].

Conclusions

We report the case of a patient with *BRAF* mutation-positive cecal cancer with abdominal wall and right lateral lymph node recurrence, who underwent tumor resection after FOLFOXIRI + bevacizumab therapy. Even in *BRAF*-mutated colorectal cancer, which is considered to have a poor prognosis, it is worthwhile to consider resection of metastatic or recurrent tumors after a comprehensive evaluation of the patient's general condition and tumor factors. MSI-high status might be a prognostic factor for a favorable response to treatment, including surgery, in *BRAF*-mutated colorectal cancer.

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References

1. Japanese Society for Cancer of the Colon and Rectum: Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol (2020) 25: 1–42.
2. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A and Arnold D: ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol (2016) 27: 1386–1422.
3. Yokota T, Ura T, Shibara N, Takahashi D, Shitara K, Nomura M, Kondo C, Mizota A, Utsunomiya S, Muro K and Yatabe Y: BRAF mutation is a powerful prognostic factor in advanced and recurrent colorectal cancer. Br J Cancer (2011) 104: 856–862.
4. Hamilton SR: BRAF mutation and microsatellite instability status in colonic and rectal carcinoma: context really does matter. J Natl Cancer Inst (2013) 105: 1075–1077.
5. Seppälä TT, Böhm JP, Friman M, Lahtinen L, Väyrynen VMJ, Liipo TKE, Ristimäki AP, Kairaluoma MVJ, Kellokumpu IH, Kuopio THI and Mecklin J-P: Combination of microsatellite instability and BRAF mutation status for subtyping colorectal cancer. Br J Cancer (2015) 112: 1966–1975.
6. Japanese Society for Cancer of the Colon and Rectum: Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3d English Edition. J Anus Rectum Colon (2019) 3: 175–195.
7. Sorbye H, Dragomir A, Sundström M, Pfeiffer P, Thunberg U, Bergfors M, Aasebø K, Eide GE, Ponten F, Qvortrup C and Glimelius B: High BRAF mutation frequency and marked survival differences in subgroups according to KRAS/BRAF mutation status and tumor tissue availability in a prospective population-based metastatic colorectal cancer cohort. PLoS ONE (2015) 10: e0131046.
8. Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, Wasan H, Ciardiello F, Loupakis F, Hong YS, Steeghs N, Guren TK, Arkenau HT, Garcia-Alfonso P, Pfeiffer P, Orlov S, Lonardi S, Elez E, Kim TW, Schellens JHM, Guo C, Krishnan A, Dekervel J, Morris V, Calvo Ferrandiz A, Tarpgaard LS, Braun M, Gollerkeri A, Keir C, Maharry K, Pickard M, Christy-Bittel J, Anderson L, Sandor V and Tabernero J: Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-mutated colorectal cancer. N Engl J Med (2019) 381: 1632–1643.
9. Schirripa M, Bergamo F, Cremolini C, Casagrande M, Lonardi S, Aprile G, Yang D, Marmorino F, Pasquini G, Sensi E, Lupi C, Maglio GDe, Borrelli N, Pizzolitto S, Fasola G, Bertorelle R, Rugge M, Fontanini G, Zagonel V, Loupakis F and Falcon A: BRAF and RAS mutations as prognostic factors in metastatic colorectal cancer patients undergoing liver resection. Br J Cancer (2015) 112: 1921–1928.
10. Yaeger R, Cercek A, Chou JF, Sylvester BE, Kemeny NE, Hechtman JF, Ladanyi M, Rosen N, Weiser MR, Capanu M, Solit DB, D'Angelica MI, Vakiani E and Saltz LB: BRAF mutation predicts for poor outcomes after metastasectomy in patients with metastatic colorectal cancer. Cancer (2014) 120: 2316–2324.
11. Phipps AI, Alwers E, Harrison T, Banbury B, Brenner H, Campbell PT, Jenny Chang-Claude J, Buchanan D, Chan AT, Farris AB, Figueiredo JC, Gallinger S, Giles GG, Jenkins M, Milne RL, Newcomb PA, Slattery ML, Song M, Ogino S, Zaidi SH, Hoffmeister M and Peters U: Association Between Molecular Subtypes of Colorectal Tumors and Patient Survival, Based on Pooled Analysis of 7 International Studies. Gastroenterology (2020) 158: 2158–2168.
12. Murata Y, Uehara K, Aiba T, Ogura A, Fukaya M, Miyata K, Tanaka A, Ohara Y, Jinno T and Ebata T: Pathological Complete Response to Second Line Chemotherapy in a Patient with Cervical Lymph Node Metastasis from Transverse Colon Cancer with RAS and BRAF V600E Mutations: A Case Report. Nihon Shokaki Gekagakkai Zasshi (Jpn J Gastroenterol Surg) (2021) 54: 278–284 (in Japanese).