Case Reports in Gastroenterology

Case Rep Gastroenterol 2023;17:56–63
DOI: 10.1159/000529001
Received: June 8, 2022
Accepted: January 3, 2023
Published online: January 27, 2023

Single Case

A Patient with Transverse Colon Cancer Complicated by Cowden Syndrome Administered FOLFOXIRI + Bevacizumab Therapy

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Keywords
Cowden syndrome · Transverse colon cancer · Chemotherapy

Abstract
Cowden syndrome is characterized by several clinical features related to tumorous lesions primarily consisting of systemic hamartomas. The mutation of a tumor suppressor gene, the *PTEN* gene, is etiologically involved. As gastrointestinal lesions, polyps of all digestive tracts involving the esophagus to rectum develop. In patients with Cowden syndrome, the risk of colorectal cancer may increase. However, the characteristics of colorectal cancer in these patients remain to be clarified and sufficient findings regarding chemotherapy have not been obtained. A 39-year-old man was treated with a colonic stent for colitis obstructive due to circumferential transverse colon carcinoma. After decompression, elective extended laparoscopic right hemicolectomy was performed. Preoperative systemic detailed examination revealed characteristic dermal/mucosal findings, polyposis of the upper digestive tract, and a thyroid tumor. On *PTEN* gene sequencing, a mutation was detected at codon 130 of exon 5, leading to a diagnosis of Cowden syndrome. Postoperative adjuvant chemotherapy was performed for 6 months, but recurrent peritoneal dissemination was observed 1 month after its completion. FOLFOXIRI + bevacizumab therapy was started. Transiently, a partial response was achieved in peritoneally disseminated nodes according to the RECIST. There was no increase in the volume of cancerous ascites. However, an increase in the volume of ascites and local relapse were noted at the completion of the tenth course. The regimen was switched to

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FOLFIRI + panitumumab, but peritoneal dissemination exacerbated and the patient died 18 months after surgery.

Introduction

In patients with Cowden syndrome (CS), multiple hamartomatous lesions of the skin/mucosa, digestive tract, mammary gland, thyroid, central nerves, and urogenital organs develop. The disease is mediated by autosomal dominant inheritance. Germline pathogenic mutations of the tumor suppressor gene phosphatase and tensin homolog (*PTEN*) which is located on chromosome 10 q23.3 may be etiologically implicated. *PTEN* gene mutations are detected in approximately 80% of patients with CS [1]. Hamartomas become cancerous relatively frequently. Elevated standardized incidence ratios and estimated lifetime risks of malignant tumors, such as breast cancer, thyroid cancer, endometrial cancer, renal cancer, and colorectal cancer (CRC), in patients with CS are reportedly 25.4 and 85.2%, 51.1 and 35.2%, 42.9 and 28.2%, 30.6 and 33.6%, and 10.3 and 9.0%, respectively [2]. Concerning CRC, the incidence is significantly higher than that in healthy adults [2–4].

Diagnostic criteria for CS were proposed by the International Cowden Consortium in 2000 and revised by the National Comprehensive Cancer Network (NCCN) in 2008. In Japan, the Japanese Clinical Guidelines 2020 for Diagnosis and Treatment of Cowden Syndrome/*PTEN* Hamartoma Tumor Syndrome in Children and Adults were prepared by the Japanese Society for Hereditary Tumors (JSHT) in 2020 [3]. However, the characteristics of CRC in patients with CS remain to be clarified. No effective treatment method has been established. In this study, we report a patient with CS who underwent FOLFOXIRI + bevacizumab (BEV) therapy for transverse colon cancer.

Case Report

The patient was a 39-year-old man with colitis obstructive due to circumferential transverse colon carcinoma (Fig. 1a, b, yellow arrows). We chose the bridge to surgery policy and placed a colonic stent. Immediate bowel decompression was obtained and several characteristic clinical findings were confirmed before surgery. Upper gastrointestinal endoscopy revealed multiple areas of glycogenic acanthosis of the esophagus and several juvenile polyps in the stomach/duodenum (Fig. 1c, d). Regarding dermal/mucosal lesions, papilloma-like protrusions of the oral mucosa/lingual apex, and horny papules at the limb ends were observed (Fig. 1e, black arrow and f, white arrow). Computed tomography (CT) and ultrasonography revealed a tumor measuring 8 × 8 mm in the right lobe of the thyroid gland (Fig. 1g, red arrow). Aspiration biopsy cytology demonstrated no malignant findings. The Wechsler Adult Intelligence Scale (WAIS)-III score was 102 (near average). *PTEN* gene sequencing revealed a mutation in codon 130 of exon 5, leading to a diagnosis of CS [3]. Regarding family history, the patient's grandfather had CRC (the age at the time of onset was unclear), and his mother had uterine cancer (age at the time of onset: ≥40 years). The preoperative carcinoembryonic antigen and carbohydrate antigen 19-9 levels were 1.3 and 21.3 ng/mL, respectively. Laparoscopic right hemicolectomy was performed 4 weeks after colonic stent insertion. The final pathological diagnosis was

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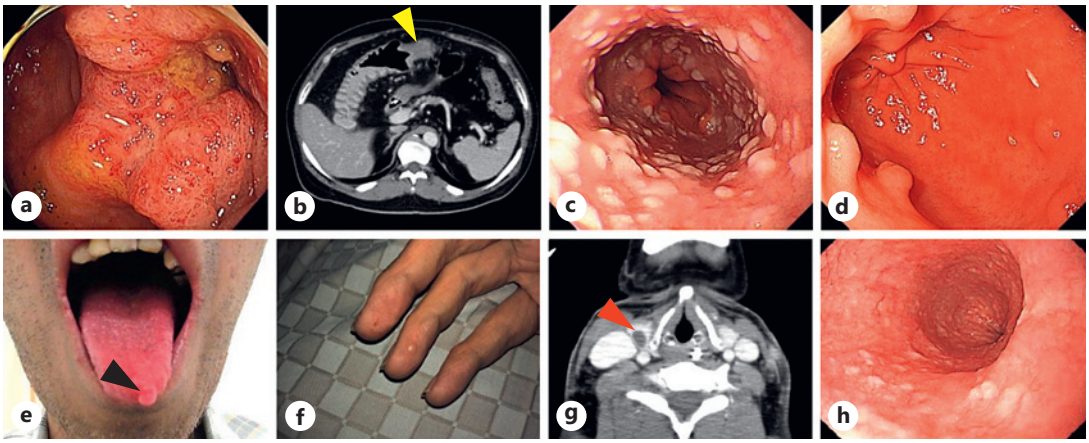

Fig. 1. Preoperative colonoscopy and contrast-enhanced abdominal computed tomography (CT) findings/characteristic clinical findings. **a** Colonoscopy revealed a type 3 lesion of the transverse colon. Circumferential stenosis was noted. **b** CT showed circumferential wall thickening (yellow arrow) of the transverse colon. **c**, **d** Upper gastrointestinal endoscopy showed multiple areas of glycogenic acanthosis of the esophagus and several juvenile polyps in the stomach/duodenum [3]. **e**, **f** Regarding dermal/mucosal lesions, papilloma-like protrusions of the oral mucosa/lingual apex (black arrow) and horny papules at the limb ends (white arrow) were observed [3]. **g** CT and ultrasonography revealed a tumor measuring 8 × 8 mm in the right lobe of the thyroid gland (red arrow). Aspiration biopsy cytology demonstrated no malignant findings [3]. **h** Upper gastrointestinal endoscopy 1 year after surgery showed a marked reduction in the glycogenic acanthosis of the esophagus.

pT4aN2bM0 stage IIIC transverse colon cancer according to the TNM classification. Based on genetic testing of the tumor tissue, both the RAS and BRAF genes were wild type. A microsatellite instability test indicated microsatellite stability.

As adjuvant chemotherapy, CAPOX therapy was started. A total of 7 courses were administered in 6 months. However, abdominal distension rapidly developed 1 month after the completion of the adjuvant chemotherapy, and the patient was emergently admitted. CT revealed large-volume ascites retention. Cytodiagnosis of the ascites confirmed adenocarcinoma. CT identified peritoneal disseminated nodes, leading to a diagnosis of recurrent peritoneal dissemination (Fig. 2a, yellow arrow). For ascites control, diuretic administration and cell-free and concentrated ascites reinfusion therapy were performed. Subsequently, FOLFOXIRI + BEV therapy was started. At the completion of the eighth course, a partial response (PR) was achieved in peritoneal disseminated nodes measurable on CT according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Fig. 2b, red arrow). Transiently, there was no increase in the volume of cancerous ascites. However, abdominal distension was exacerbated at the completion of the tenth course, and CT revealed an increase in the volume of ascites and wall thickening at the anastomotic site. Colonoscopy demonstrated tumor infiltration from the extramural area at the anastomotic site. Biopsy findings suggested poorly differentiated adenocarcinoma, leading to a diagnosis of local relapse. The chemotherapeutic regimen was switched to FOLFIRI + panitumumab (PANI) therapy, but the patient's general condition rapidly deteriorated due to the exacerbation of the peritoneal dissemination after the completion of the fourth course. Chemotherapy was discontinued. The patient died 18 months after surgery (Fig. 3). The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529001).

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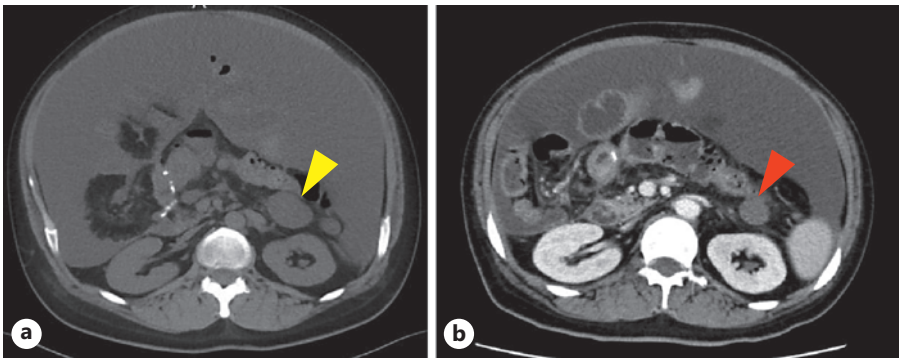

Fig. 2. CT findings. **a** Peritoneal disseminated nodes (yellow arrow) were observed before the start of FOLFOXIRI + BEV therapy. **b** Their size decreased at the completion of the eighth course (red arrow). A partial response (PR) was achieved according to RECIST.

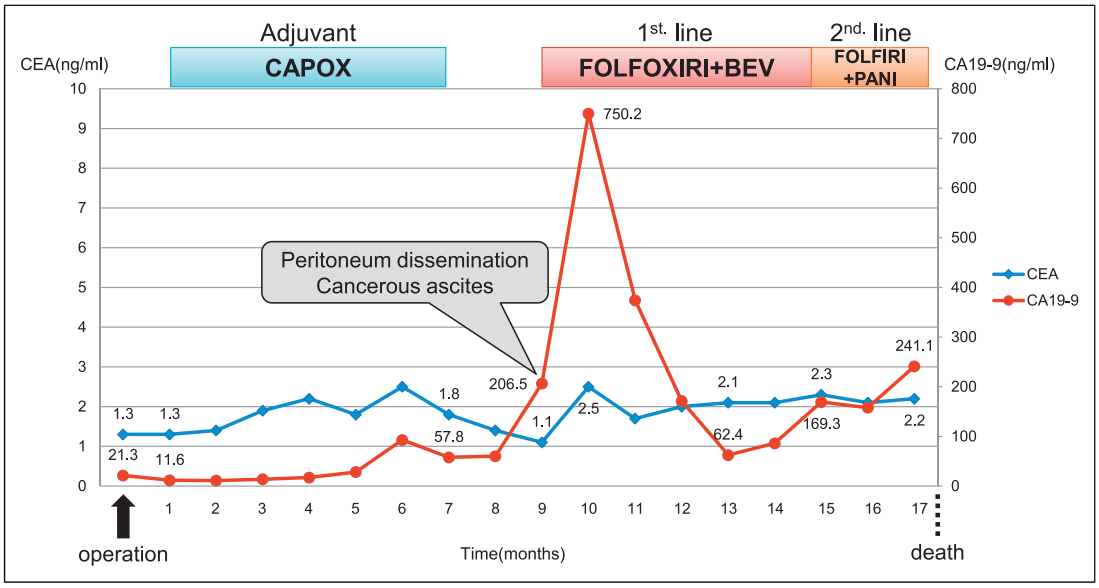

Fig. 3. Clinical course of the patient. To treat peritoneal dissemination and cancerous peritonitis, FOLFOXIRI + bevacizumab (BEV) therapy was administered as the primary treatment, and FOLFIRI + panitumumab (PANI) therapy was administered as the secondary treatment. However, the patient died 18 months after surgery. CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Discussion

In patients with CS, polyps may develop throughout the entire digestive tract (running from the esophagus to rectum). The histological type varies: hyperplastic, inflammatory, hamartomatous, and adenomatous. In CS patients, the risk of CRC related to hamartomatous or mixed-type gastrointestinal polyps may be increased [1, 2, 4]. Since CS has a high risk of complications with cancer, it is important to conduct appropriate surveillance and detect it at a curable stage. The NCCN clinical practice guidelines suggest "total colonoscopy every 5 years after the age of 35 (if a close relative has a CRC patient under 40 years of age, it should be performed 5–10 years earlier than the age of onset of CRC at the youngest age, depending on symptoms and the presence or absence of polyps)." Therefore, genetic testing of *PTEN* is important for the definitive diagnosis

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of this syndrome, understanding of carcinogenesis risk, and appropriate surveillance. It is also recommended from the viewpoint of diagnosis of this syndrome in blood relatives, carcinogenesis risk, and appropriate surveillance [1, 3]. However, when performing genetic testing for *PTEN*, correct information such as the sensitivity and limitations of the test should be provided, appropriate genetic counseling should be performed, and informed consent should be obtained to determine whether or not to take the test.

The *PTEN* gene, which is a causative gene of CS, is a known tumor suppressor gene. *PTEN* is an enzyme that catalyzes the dephosphorylation reaction of phosphoinositide 3-kinase (PI3K). In many human cancer cells, the loss of *PTEN* function through gene mutation results in the activation of the PI3K/AKT/mTOR pathway as a result of a reduction in *PTEN* expression, promoting tumor proliferation [1, 2, 5]. AKT, a downstream target of the PI3K signaling pathway, was shown to be overexpressed in most intestinal adenomas, indicating an early role for the PI3K signaling pathway in carcinogenesis of CRC. Also, activation of the PI3K signaling pathway correlates with a high risk of local recurrence. In accordance with this, *PTEN* expression in the nucleus has been shown to gradually decrease during the normal adenoma-adenocarcinoma-metastatic sequence. There is a decrease in *PTEN* expression in approximately 19–42% of patients with CRC [6, 7].

Few studies have examined chemotherapy as a treatment for CRC with *PTEN* gene mutations. Preclinical data suggested that the PTEN/PI3K/AKT pathway is important in determining the sensitivity of CRC cell lines to cetuximab, and that loss of *PTEN* expression may contribute to cetuximab resistance [6, 8]. However, in a meta-analysis of the correlation between the results of monotherapy with an anti-EGFR antibody and *PTEN* expression, the progression-free survival (PFS) and overall survival (OS) of patients with wild-type KRAS without *PTEN* expression were poorer than those of patients with wild-type KRAS with *PTEN* expression [8]. On the other hand, anti-EGFR antibody drugs may be effective in comparison with the best supportive care in wild-type KRAS patients regardless of *PTEN* expression [9, 10]. The most recent comprehensive study did not confirm that *PTEN* alterations are beneficial in predicting anti-EGFR in CRC. Regarding anti-angiogenesis, BEV-based therapy may be more effective in patients with metastatic CRC with loss of *PTEN* expression. The PI3K/AKT/mTOR signaling pathway has a potential role in modulating the effects of BEV. The mammalian target of rapamycin complex 1 regulates hypoxia-inducible factor 1 alpha transcription, which increases vascular endothelial growth factor expression. It was shown that the loss of *PTEN* expression in secondary tumor tissue samples of metastatic CRC patients who received BEV-containing combination therapy in first-line or second-line therapy was significantly associated with treatment response [6].

Recently, a meta-analysis of 6 randomized controlled trials (the FIRE-3 trial, CALGB/SWOG80405 trial, PEAK trial, CRYSTAL trial, PRIME trial, and 20050181 trial) assessing patients with wild-type RAS reported that the therapeutic effects of targeted drugs were different between patients in whom the primary focus was present on the right side (cecum, ascending colon, or transverse colon) and those in whom it was present on the left side (descending colon, sigmoid colon, or rectum). In patients with wild-type RAS/BRAF-related left-sided colon cancer, anti-EGFR antibody drugs produced effects as first-line therapy, and both the PFS and OS were favorable. However, in those with wild-type RAS/BRAF-related right-sided colon cancer, the effects of anti-EGFR antibody drugs were not marked [11]. Therefore, when administering first-line therapy for wild-type RAS/BRAF-related CRC, combination therapy with anti-EGFR antibody drugs is recommended for left-sided colon cancer patients, and combination therapy with BEV is recommended for right-sided colon cancer patients [11]. In those with wild-type RAS/BRAF-related right-sided colon cancer, as demonstrated in the present case, doublet therapy (FOLFOX, CAPOX, SOX, FOLFIRI, or S-1+IRI), in which a pyrimidine fluoride is combined with oxaliplatin or irinotecan, + BEV or

triplet therapy (FOLFOXIRI) + BEV combinations are considered [11]. In our patient with right-sided colon cancer, FOLFOXIRI + BEV therapy was selected as the first-line therapy after confirming the general condition, considering that relapse was detected in a short period after the completion of postoperative adjuvant chemotherapy. PR was transiently achieved, and the therapeutic effects of FOLFOXIRI + BEV therapy were confirmed. Upper gastrointestinal endoscopy 1 year after surgery demonstrated a marked reduction in the glycogenic acanthosis of the esophagus. It should be emphasized that the chemotherapy reduced a finding characteristic of glycogenic acanthosis of the esophagus (Fig. 1h, compared with Fig. 1c).

In the present case, the peritoneal dissemination rapidly exacerbated after the completion of the tenth course. It was difficult to select a regimen for second-line therapy. Regarding the use of targeted drugs for second-line therapy after first-line therapy with BEV, phase III clinical trials have revealed that continuous BEV administration (BEV beyond progression) (the ML18147 trial [12]), FOLFIRI + ramucirumab (RAM) therapy (the RAISE trial [13]), and FOLFIRI + aflibercept beta (AFL) therapy (the VELOUR trial [14]) can significantly prolong OS as a first-line therapy [11]. On the other hand, no phase III study has investigated the effects of combination therapy with anti-EGFR antibody drugs as second-line therapy after first-line therapy of patients with wild-type RAS-related CRC with BEV. In phase II clinical trials (the SPIRITT [13]), combination therapy with anti-EGFR antibody drugs was compared with BEV-combined therapy, and the response rate was higher in the former group. However, there were no significant differences in PFS or OS. Therefore, as second-line therapy after BEV administration for first-line therapy, a combination of chemotherapy, which prolongs OS, with BEV/RAM/AFL is recommended. Combination therapy with anti-EGFR antibody drugs is believed to induce tumor-reducing effects in patients in whom continuation until tertiary treatment is difficult [13].

In the present case, FOLFIRI + PANI therapy was selected after careful consultation with the patient and his family, taking into consideration the general condition at the start of second-line therapy. There was no increase in the volume of ascites for a few months, and the general condition of the patient was stable. The levels of tumor markers peaked. However, the general condition rapidly deteriorated, leading to a fatal outcome. If one of BEV/RAM/AFL had been combined for second-line therapy after first-line therapy with BEV, the outcome may have differed.

The present case suggests that FOLFOXIRI + BEV therapy is effective to some extent for recurrent wild-type RAS/BRAF-related transverse colon cancer in the presence of CS. It should also be emphasized that this therapy influenced glycogenic acanthosis of the esophagus, which is characteristic of CS. Regarding CRC complicated by CS, the rates of proliferation and metastasis/infiltration and drug susceptibility remain to be clarified. Enhancement of *PTEN* transcription is expected to improve *PTEN* function. *PTEN* transcription can be achieved by removing epigenetic blocks or altering (increase/decrease) exposure to transcription factor activation or inhibition. Epigenetic silencing of *PTEN* transcription is due to the methylation of a gene promoter or the histone. DNA methyltransferase inhibitors remove methyl groups from DNA, causing DNA demethylation. Some of these transcription factors can be stimulated pharmacologically [14]. At the post-transcriptional level, *PTEN* expression can be impaired by microRNAs (miRNAs) or RNA-binding proteins (RBPs). miRNAs are short noncoding RNAs that bind to mRNA and cause translational inhibition or transcript degradation, ultimately finally leading to loss of *PTEN* expression and activation of the PI3K/AKT signaling cascade. Complexes of several miRNAs and RBPs that target *PTEN* in CRC have been identified [15]. Modulation of these regulatory RNAs and RBPs thus restores *PTEN* translation and expression, exploits its anti-tumor activity, and increases cellular drug sensitivity. Restoring *PTEN* expression and eventual activity may eventually lead to inhibition of the PI3K/AKT pathway and have implications for treatment of CRC patients [6]. Targeting *PTEN* is an interesting area of research to explore CRC therapeutic strategies, but more studies are required.

Statement of Ethics

This report of a case followed the principles of the Declaration of Helsinki and was approved by the ethics review board of Juntendo University Urayasu Hospital, approval number 3-008. Written informed consent was obtained from the patient's family for publication of this case report and any accompanying images. After the patients' death, the authors consulted with the patients' father and sister regarding the publication of this case report and any accompanying images. They agreed and signed the consent form.

Conflict of Interest Statement

The authors have no conflicts of interest to declare to this manuscript.

Funding Sources

The authors received no funding for this research.

Author Contributions

Kazuhiro Takehara reported the case and wrote the manuscript. Yoichi Ishizaki and Kazuhiro Sakamoto assisted in the drafting of the manuscript and reviewed the article. Yoichi Ishizaki, Kunihiko Nagakari, Masakazu Ohuchi, and Masaki Fukunaga participated in treating the patient. Yoichi Ishizaki, Kunihiko Nagakari, Masakazu Ohuchi, Masaki Fukunaga, and Kazuhiro Sakamoto critically revised the manuscript. All authors declare that they contributed to this article and that they have read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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