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Case Report

Conversion Therapy Using mFOLFOX6 With Panitumumab for Unresectable Liver Metastases From Multiple Colorectal Cancers With Familial Adenomatous Polyposis

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A 39-year-old man received a diagnosis of unresectable multiple liver metastases from multiple colorectal cancers with familial adenomatous polyposis. After construction of an ileostomy, modified FOLFOX6 (mFOLFOX6) with panitumumab was administrated because rectal cancer and sigmoid colon cancer are KRAS wild type. The 13 courses of chemotherapy resulted in a marked reduction in the size of liver metastases and sigmoid colon cancer. Consequently, curative resection with total colectomy, ileal pouch anal anastomosis, and liver metastasis resection with radiofrequency ablation was performed. Progression of KRAS wild-type rectal cancer after chemotherapy suggested that each clone from rectal and sigmoid colon cancer might have a different sensitivity to epidermal growth factor receptor antibody. Immunohistochemical analysis revealed loss of PTEN expression in rectal cancer compared with liver metastases from sigmoid colon cancer, showing that the difference of mFOLFOX6 with panitumumab might be related to activation of the PI3K-AKT pathway.

Key words: Panitumumab – mFOLFOX6 – Colorectal cancer – Liver metastases – Familial adenomatous polyposis

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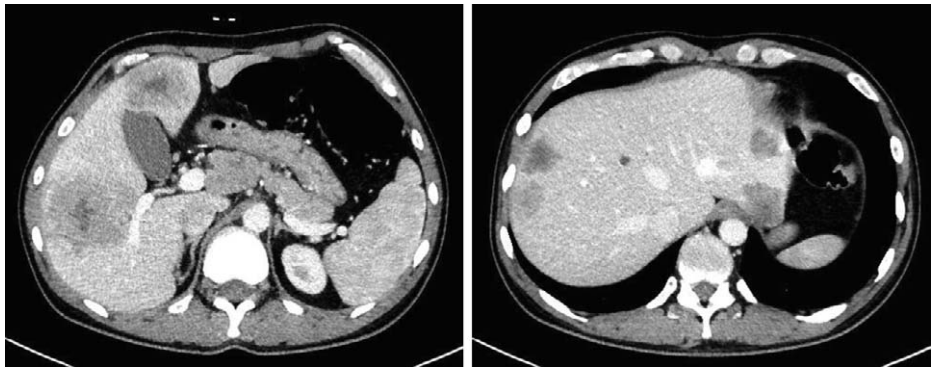

Fig. 1 CT revealed that multiple liver metastases were in both liver lobes and were diagnosed as unresectable.

The only available treatment associated with long-term survival in patients with liver metastases from colorectal cancer is complete liver tumor resection, with 5-year survival rates ranging from 25% to 57%.[1] However, only 40% to 50% of patients with colorectal metastasis to the liver are eligible for surgical resection.[2] Therefore, other liver metastasis patients undergo palliative chemotherapy to stabilize the disease and prolong their overall survival.

During the past decade, the biggest advance made regarding unresectable liver metastases from colorectal cancer has been the ability of oncologists to convert inoperable liver disease to resectable disease using various molecular targeting drugs.[3,4] Several clinical studies have shown that the association of chemotherapy with bevacizumab (vascular endothelial growth factor monoclonal antibody), or cetuximab [epidermal growth factor receptor (EGFR) monoclonal antibody] is particularly promising in improving the resectability rate and, ultimately, survival.[5]

Panitumumab is a fully human monoclonal antibody that binds specifically to the EGFR, and consequently, severe panitumumab-related infusion reactions are rare. Panitumumab, when added to FOLFOX4 (folinic acid, 5-fluorouracil, and oxaliplatin), increased response rate and improved progression-free survival in previously untreated metastatic colorectal cancer.[6] Retrospective analyses of phase 3 trials of anti-EGFR antibodies, including cetuximab and panitumumab, found KRAS status to be an important predictive marker of efficacy, with only wild-type patients benefiting from treatment.[7]

Here, we report a successful conversion therapy using modified FOLFOX6 (mFOLFOX6) plus panitumumab in a patient with familial adenomatous polyposis (FAP) who had unresectable multiple liver metastases from multiple colorectal cancers. To the best of our knowledge, we are the first researchers to demonstrate treatment of multiple target tumors derived from different clones with mFOLFOX6 and panitumumab, and to show differential panitumumab sensitivity for multiple primary tumors and liver metastases.

Case Report

A 39-year-old man was admitted to our hospital for investigation of melena that had started 1 year before. Among his family members, his mother had died of colorectal cancer at the age of 62 years. He already had received a diagnosis of FAP at age 31 years; however, no scheduled surveillance by colonoscopy had been undertaken in the intervening 8 years. Results for his hematologic and biochemical tests were within the normal range, except for signs of anemia (hemoglobin, 9.9 mg/dL) and high levels of tumor markers (carcinoembryonic antigen, 13.9 ng/mL; cancer antigen 19-9, 111.0 ng/mL). Colonoscopy revealed the presence of a voluminous tumor in the sigmoid colon, occupying a half-circumference of large bowel. More than 100 polyps were found in the colorectum, most of which measured ~5 mm at the greatest diameter. Biopsies from 2 tumor lesions established the diagnosis of adenocarcinoma with KRAS wild type. Abdominal computed tomography (CT) revealed multiple liver metastases (7 lesions, with 10 cm as the largest dimension; Fig. 1).

Based on these findings, the patient received a diagnosis of FAP complicated with unresectable liver metastases from multiple colorectal cancers. After construction of an ileostomy to prevent obstruction due to advanced colorectal cancers, the

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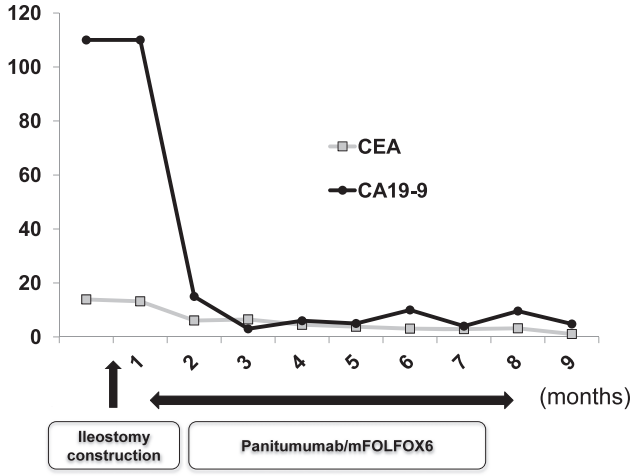

Fig. 2 Changes in serum carcinoembryonic antigen and cancer antigen 19-9 levels after starting panitumumab and mFOLFOX6.

patient was treated with chemotherapy with mFOLFOX6 plus panitumumab. After the second course of chemotherapy, both tumor markers decreased markedly and were within the normal range (Fig. 2). Although the patient experienced grade 1 neutropenia and eczema, which were controllable, drug doses were maintained as initially planned. CT was performed after 13 courses of chemotherapy, and they revealed a marked decrease in the size of multiple liver metastases (3 lesions, with 2 cm as the largest dimension) and sigmoid colon cancer, resulting in a partial response according to Response Evaluation Criteria in Solid Tumor (RECIST). The response rates for liver metastases and sigmoid colon cancer were 78% and 25%, respectively (Fig. 3A and 3B). In contrast, rectal cancer was evaluated as stable disease because of a 10% increase in size (Fig. 3C).

The patient was evaluated as eligible for curative resection of liver metastases. He underwent total proctocolectomy with ileal pouch anal anastomosis and resection of liver metastases in S5 and S8, and microwave coagulation of S4. At laparotomy, there were no macroscopic signs of hepatotoxicity, such as steatohepatitis and blue liver. Histopathologic analysis of resected specimens demonstrated that sigmoid colon cancer was moderately differentiated adenocarcinoma with lymph node metastasis (pT3, pN1) and severe tumor invasion to lymphatic duct and vessel (ply3, pv1). Pathologic tumor regression grade (pTRG) was 2 (Fig. 4A and 4B). Rectal cancer was diagnosed as moderately differentiated adenocarcinoma without lymph node metastasis (pT2, pN0), tumor invasion to lymphatic duct and vessel (ply0, pv0). The pTRG was 1a (Fig. 4C and 4D). In contrast, in resected liver metastases, only a few viable cancer cells were recognized, and almost all cancer cells were replaced with fibroblasts (pTRG 2; Fig. 4E and 4F). Collectively, the pathologic findings strongly suggested that the liver metastases originated from sigmoid colon cancer because there was no apparent evidence of cancer cell detachment from rectal cancer (pN0, ply0, and pv0). Repeated genome analysis from sigmoid colon cancer, rectal cancer, and liver metastases showed that all surgical specimens had KRAS and BRAF wild types.

The patient's postoperative course was uncomplicated, and postoperative chemotherapy was started using mFOLFOX6. A follow-up CT scan 1 year later showed no recurrence.

Paraffin sections were stained with hematoxylin-eosin (H&E). Immunostaining was performed using anti-EGFR (Santa Cruz Biotechnology, Santa Cruz, California), anti-PTEN antibody (D4.3) XP (1:50 dilution; Cell Signaling Technology, Boston, Massachusetts), and anti-pAKT (monoclonal mouse antibody; 1:200 dilution; BD Biosciences, Franklin Lakes, New Jersey) antibodies. For each immunohistochemical procedure, antigen retrieval was performed in citrate buffer, and detection was amplified by the Dako EnVision system (Dako, Glostrup, Denmark). The immunohistochemistry results are shown in Fig. 5. Indeed, EGFR was expressed at the same level in rectal cancer, sigmoid colon cancer, and liver metastases (S5 and S8; Fig. 5A). PTEN expression was absent in rectal cancer, compared with sigmoid colon cancer and liver metastases (S5 and S8; Fig. 5B). In contrast, pAKT in rectal cancer was diffusely expressed; however, no staining in sigmoid colon cancer and liver metastases (S5 and S8) was recognized (Fig. 5C).

Discussion

The PRIME study (Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) was the first study to evaluate the benefits of adding panitumumab treatment to first-line FOLFOX chemotherapy for metastatic colorectal cancer.[6] In addition, it prospectively evaluated KRAS status. The study indicated that addition of panitumumab to oxaliplatin-based chemotherapy results in significantly increased progression-free survival in patients with metastatic colorectal cancer with KRAS wild-type tumors. The results of the PRIME study

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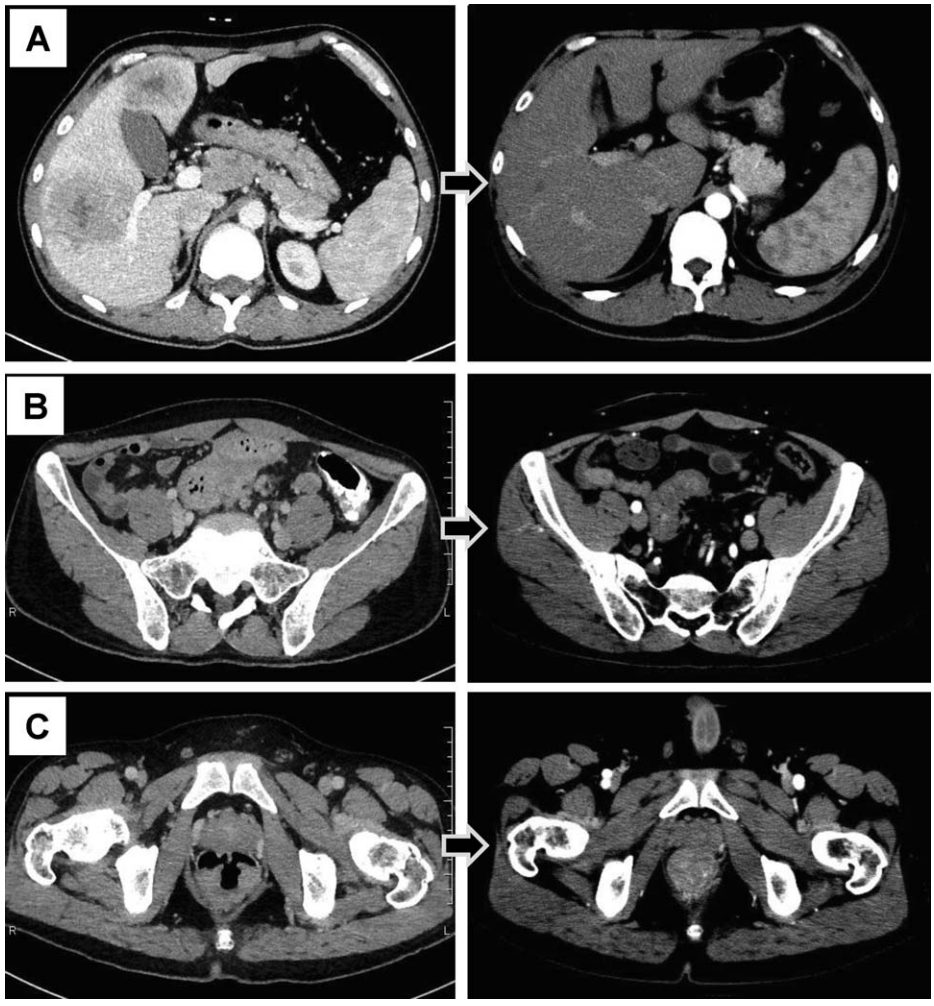

Fig. 3 Changes in tumor volume in the liver, sigmoid colon cancer, and rectal cancer after panitumumab and mFOLFOX6. (A) Liver metastases (response rate, 78%; partial response). (B) Sigmoid colon cancer (response rate, 25%; partial response). (C) Rectal cancer (stable disease).

are consistent with those seen in 2 other first-line studies examining cetuximab chemotherapy.[8,9] To date, both EGFR antibodies (cetuximab and panitumumab) in combination with chemotherapy have a similar clinical benefit in the treatment of metastatic colorectal cancer.

In contrast, the 4.2-month benefit in median overall survival observed in the PRIME study in the KRAS wild-type population is similar to the 3.5-month benefit in the CRYSTAL trial (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer), in which cetuximab was added to first-line irinotecan-based chemotherapy.[10] In contrast, addition of cetuximab to first-line oxaliplatin-based chemotherapy does not improve overall survival or progression-free survival,[11] suggesting that panitumumab instead of cetuximab should be considered for first-line metastatic colorectal cancer patients with KRAS wild-type tumors.

Recently, panitumumab has also been studied in the perioperative setting prior to liver metastasis resection in patients with advanced colorectal cancer. A preliminary report suggested that 15% of unselected patients with KRAS wild type and 7% of KRAS mutant primary tumors were eligible for colorectal liver metastasis resection after treatment with panitumumab. R0 resection was achieved in 8% and 5% of patients in the KRAS wild-type and mutant groups, respectively. Furthermore, among the patients with liver-only metastases, 92% of those with KRAS wild type and 50% of those with KRAS mutant tumors underwent surgery.[12] Based on these

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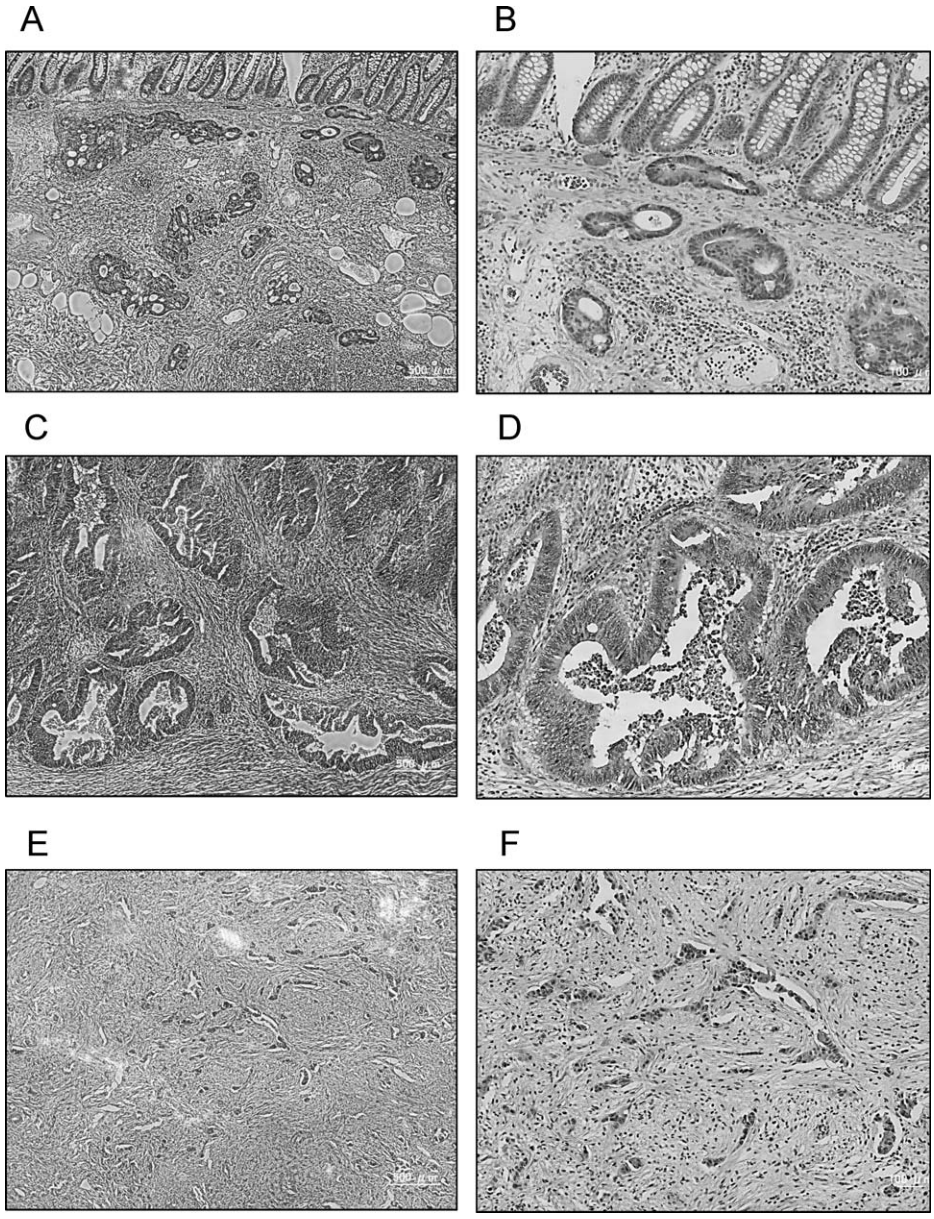

Fig. 4 Pathologic findings of surgical specimens. H&E [×40 (A) and ×100 (B)] staining of sigmoid colon cancer (pTRG 2). H&E [×40 (C) and ×100 (D)] staining of rectal cancer (pTRG 1a). H&E [×40 (E) and ×100 (F)] staining of liver metastasis (pTRG 2).

previous studies, we chose combination therapy with panitumumab and oxaliplatin-based chemotherapy as the first-line therapy for our patients with KRAS wild-type tumors (sigmoid colon cancer and rectal cancer). As expected, after 12 courses of this regimen, multiple liver metastases were markedly reduced in size (response rate was 78% in liver metastases), resulting in conversion therapy with complete resection.

The present case report showed a particularly interesting phenomenon. Panitumumab plus mFOLFOX6 was not effective against advanced rectal cancer, which showed a 10% increase in size (pTRG 1a). In contrast, this regimen was effective against multiple liver metastases from advanced sigmoid colon cancer (pTRG 2). KRAS mutation is the first established molecular marker that precludes responsiveness to EGFR-targeted treatment with

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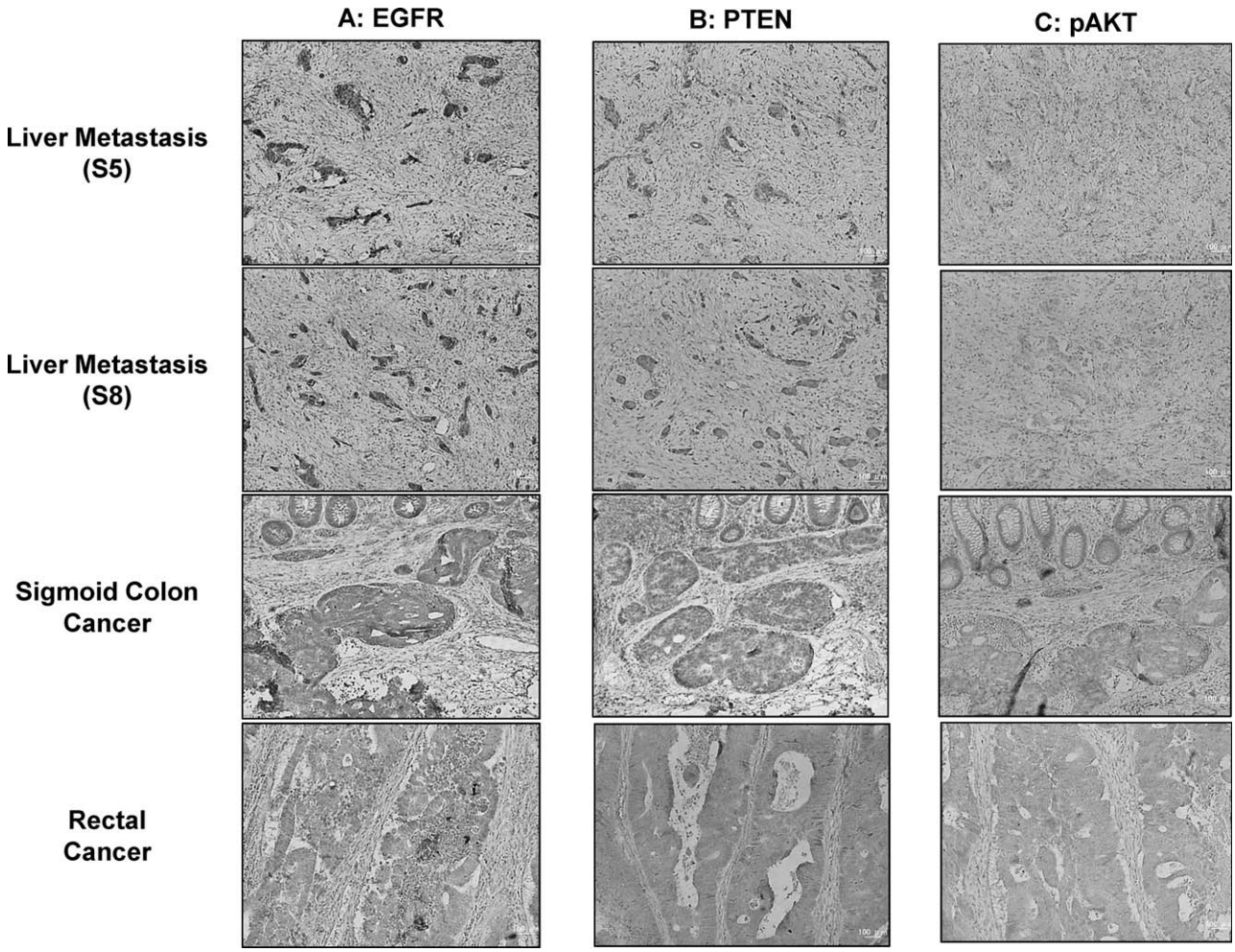

Fig. 5 Immunohistochemistry of EGFR, pAKT, and PTEN in surgical specimens. (A) EGFR (×100) staining in liver metastases (S5 and S8), sigmoid colon cancer, and rectal cancer. (B) PTEN (×100) staining in liver metastases (S5 and S8), sigmoid colon cancer, and rectal cancer. (C) Staining for pAKT (×100) in liver metastases (S5 and S8), sigmoid colon cancer, and rectal cancer.

cetuximab and panitumumab.[7,13,14] In addition, among wild-type KRAS colorectal cancers, resistance to anti-EGFR therapy may be associated with EGFR gene copy number and mutations of BRAF related to the RAS-RAF-MAPK pathway, or PIK3 cancer antigen mutation and loss of PTEN expression related to the PI3K-AKT pathway.[15–17] However, these additional biomarkers require further validation before incorporation into clinical practice. Our immunohistochemistry analysis revealed that loss of PTEN intensity in rectal cancer but not in liver metastases from sigmoid colon cancer suggests that resistance of the former to panitumumab and mFOLFOX6 is associated with activation of the PI3K-AKT pathway. Therefore, in the future it might be important to evaluate several predictive factors for EGFR antibody treatment of multiple advanced colorectal cancers with unresectable liver metastases, which we sometimes encounter in FAP patients, since multiple advanced colorectal cancers in a patient are completely different clones.

In conclusion, we reported successful conversion therapy with addition of panitumumab to mFOLFOX6 for unresectable liver metastases from multiple colorectal cancers in a patient with FAP. In the present case, the differential treatment response of the target tumors, which were all KRAS and BRAF wild type, could have been dependent on activation of the PI3K-AKT pathway.

Acknowledgments

The authors have no conflicts of interest to disclose.

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