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A Case of Panitumumab-Responsive Metastatic Rectal Cancer Initially Refractory to Cetuximab

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Key Words
Cetuximab-resistant rectal cancer · Epidermal growth factor receptor mutation · Panitumumab

Abstract
A 64-year-old man was initially diagnosed with rectal cancer and liver metastasis. He underwent rectal amputation and partial hepatectomy. mFOLFOX6 was begun as first-line chemotherapy, but multiple pulmonary and right femoral lymph node metastases were found 1 year postoperatively. FOLFIRI plus bevacizumab was then started, but the tumors recurred after 2 years and 11 months. The regimen was changed to cetuximab with CPT-11. The lesions partially responded after 3 months, and the patient was free from progression for 1.5 years. Four years and 7 months after the adjuvant chemotherapy was started, the metastatic lesions gradually increased again, and the regimen was changed to panitumumab. After 2 months, the lesions had markedly decreased again and showed a partial response for 6 months. Although the pulmonary lesions became progressive again, the patient has been alive for 5 years and 8 months since the first operation.

Introduction

The development of cetuximab and panitumumab, antibodies to epidermal growth factor receptor (EGFR), has improved the survival of patients with metastatic colorectal cancer, and those agents are a standard component of therapy [1–3]. It is known that the *KRAS* mutation status predicts resistance to these antibodies [4–6], but patients with *KRAS*

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wild-type metastatic colorectal cancer who respond to EGFR antibodies ultimately acquire resistance to these agents.

Montagut et al. [7] reported that an EGFR ectodomain mutation was a possible factor in the mechanisms of acquired cetuximab resistance, and that panitumumab was able to bind and inhibit the growth of cells with this mutation. Clinically, however, these agents are likely to exhibit multiple mechanisms of resistance.

We herein report a case of panitumumab-responsive metastatic rectal cancer that was initially refractory to cetuximab.

Case Presentation

A 64-year-old man was initially diagnosed with rectal cancer and liver metastasis. He underwent rectal amputation and partial hepatectomy, and pelvic node metastasis was pathologically diagnosed. Two months after the resection, he received first-line adjuvant chemotherapy comprising 5-flurouracil, leucovorin and oxaliplatin (mFOLFOX6). One year and 9 months later, computed tomography with contrast enhancement revealed multiple pulmonary and right femoral lymph node metastases. Second-line chemotherapy comprising 5-flurouracil, leucovorin and irinotecan (FOLFIRI) plus bevacizumab was begun, and he was free from progression for 2 years and 11 months. At that point, imaging studies revealed progressive disease (PD) as evidenced by metastatic lesions. Third-line chemotherapy comprising cetuximab combined with CPT-11 was then begun. The lesions showed a partial response after 3 months, and the patient was free from progression for 1 year and 6 months.

The metastatic lesions then showed gradual growth and the patient again developed PD. He began to suffer from severe right femoral pain, and panitumumab therapy was begun. After 2 months, the femoral pain had diminished, the multiple pulmonary lesions had been markedly reduced and a portion of the lesions had disappeared (fig. 1).

The patient's partial response status was maintained for 6 months. Although the pulmonary lesions began to progress again, the patient has been alive for 5 years and 6 months since the first operation (fig. 2).

Discussion

We herein describe a case of panitumumab-responsive metastatic rectal cancer that was initially refractory to cetuximab. Both agents are EGFR monoclonal antibodies. We had administered a combination of CPT-11 plus cetuximab as third-line chemotherapy because no mutations of the *KRAS* or *BRAF* codons were revealed in initially resected tissues, and the patient had gained a partial response status. When the metastatic lesions showed evidence of PD again, panitumumab therapy was initiated because there were no other means of treatment. Two months after beginning this therapy, the multiple pulmonary lesions had markedly responded and the femoral pain had diminished.

A recent in vitro study suggested that resistance to cetuximab could result from a secondary EGFR mutation in the extracellular domain of the receptor. This mutation is a cytosine (C) to adenine (A) substitution at EGFR nucleotide 1,476, and it causes a substitution of serine to arginine at amino acid 492, which is within the EGFR ectodomain. The *S492R* mutation impairs cetuximab ligand binding, but not EGFR ligand binding. This implies that cetuximab-resistant cells retain sensitivity to panitumumab, and panitumumab may thus be clinically effective in some individuals with cetuximab resistance [7]. We obtained

the patient's consent to undergo EGFR mutation analysis and performed a two-part metastatic femoral lymph node biopsy. The nucleotide sequence revealed that EGFR genes from the 2 lymph nodes were identical to those of the initially resected tissues, and that there were no *S492R* mutations (fig. 3). These results suggested that the mechanism of resistance to anti-EGFR antibodies might involve more than has been previously reported.

Recent studies have identified signaling pathways that bypass EGFR and mediate cetuximab resistance. These include amplification of the closely related ERBB2 receptor and increased levels of the EGFR ligand heregulin. Some cancers remain co-dependent on EGFR and ERBB2, and it is thus necessary to combine both an EGFR inhibitor and an ERBB2 inhibitor for those types of resistance [8, 9]. However, it is unknown whether this mechanism is common to panitumumab. We did not examine the ERBB2 receptor expression of our patient, but considering the fact that a good response was obtained by the panitumumab alone, the resistance mechanism seems to differ from that to panitumumab.

Some reports have demonstrated differences in immunological responses between cetuximab and panitumumab. Cetuximab is a chimeric IgG1 antibody capable of mediating antibody-dependent cellular cytotoxicity both in vitro and in vivo. In contrast, panitumumab is unable to induce the classical immune response, natural killer cell-mediated antibody-dependent cellular cytotoxicity, because of its IgG2 isotype [10, 11]. This difference in immunological responses is likely to produce differences in the clinical effect of each antibody.

Indeed, Montagut et al. [7] identified the *S492R* mutation in 2 out of 10 tumors from patients with cetuximab resistance, and those 2 tumors showed good response to panitumumab. The *S492R* mutation was not found in our patient; it seems that the expression of the mutation does not occur at a high frequency. Validation of the available evidence and clarification of its clinical significance through clinical studies is anticipated.

In summary, the present case implies that there are likely to be multiple or unknown mechanisms of drug resistance of EGFR-targeting antibodies, including panitumumab. It will thus be important to understand the mechanisms of drug resistance through both in vitro models and those using human tumor tissue, and to consider the use of panitumumab after a tumor has been shown to be refractory to cetuximab.

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Disclosure Statement

We declare that the authors have no conflict of interest.

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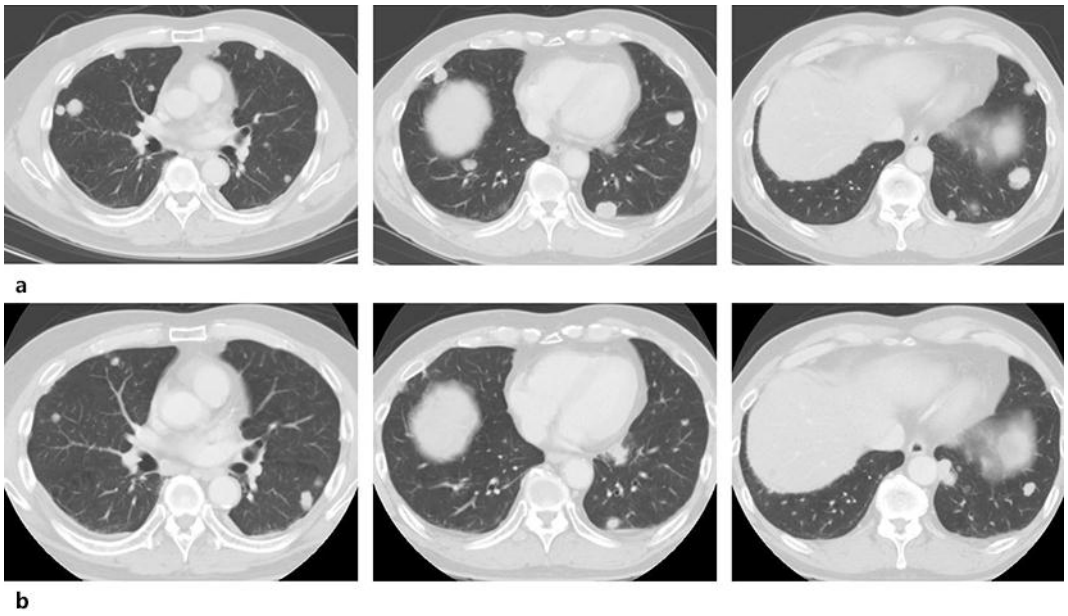

Fig. 1. Chest computed tomography image before starting panitumumab (**a**) shows multiple pulmonary metastatic lesions in the bilateral lungs. **b** After 2 months of panitumumab treatment, the pulmonary lesions had been markedly reduced and a portion of the lesions had disappeared.

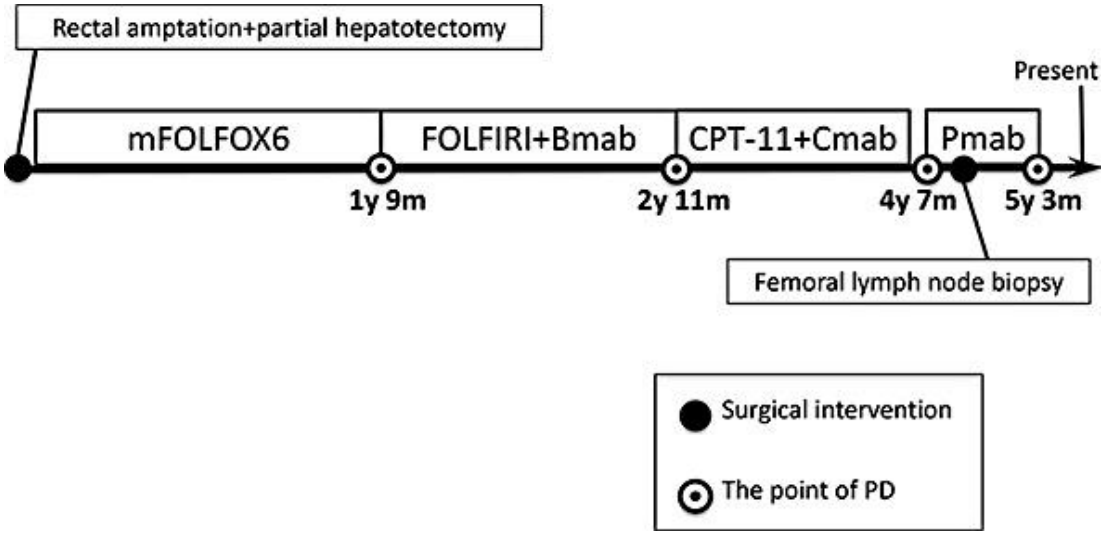

Fig. 2. Progression table shows the chemotherapy regimens; the horizontal line represents time. y = Year(s); m = months; Bmab = bevacizumab; Cmab = cetuximab; Pmab = panitumumab.

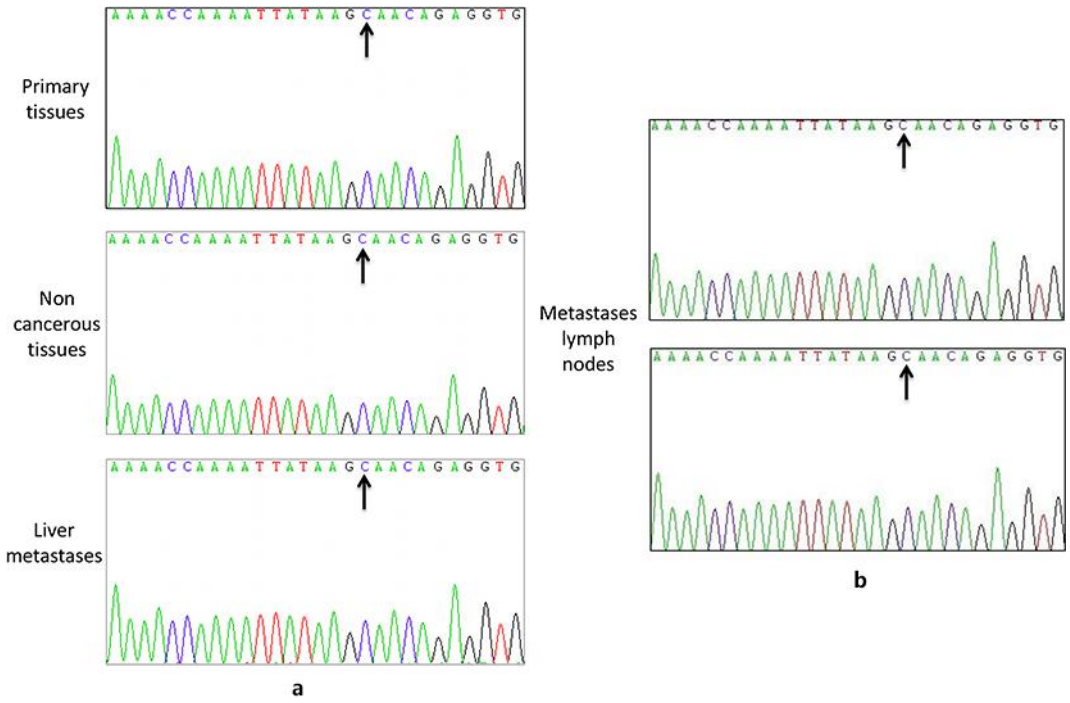

Fig. 3. EGFR nucleotide sequences. **a** Nucleotide 1,476 was cytosine (C, arrow) in all of the initially resected tissues (primary tissue, noncancerous tissues and liver metastases). **b** Nucleotide 1,467 was cytosine (C, arrow) in the 2 resected metastatic femoral lymph nodes, and the EGFR nucleotide was identical to that in the genes of the initially resected tissues. There were no *S492R* mutations.