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Urachal Carcinoma Shares Genomic Alterations with Colorectal Carcinoma and May Respond to Epidermal Growth Factor Inhibition

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Abstract

Metastatic urachal carcinoma is a rare, understudied, and aggressive malignancy with limited treatment options. Histologically, urachal carcinomas resemble enteric adenocarcinomas and anecdotally respond to systemic therapies utilized in colorectal cancer. Targeted exome sequencing of archival primary tumor tissue from a patient with metastatic urachal cancer revealed *EGFR* amplification and wild-type *KRAS*. The patient was treated with cetuximab, a monoclonal antibody directed against EGFR, as a single agent, and achieved a response lasting more than 8 mo. Subsequent whole-exome sequencing revealed no additional alterations likely to be associated with cetuximab sensitivity. Formalin-fixed, paraffin-embedded tumor specimens from nine additional urachal cancers were subjected to targeted exome sequencing. Mitogen-activated protein kinase (MAPK) pathway mutations were found in four of the nine samples, but no *EGFR* amplification was detected. Importantly, *APC* mutations were detected in two of the nine patients. To our knowledge, this is the first report of a response to single-agent cetuximab in a patient with metastatic urachal cancer and of molecular analysis to probe the basis for sensitivity. On the basis of these findings and the histologic, and now genomic, similarities with colorectal cancer, monoclonal antibodies directed at EGFR could be used in the treatment of metastatic urachal cancer.

Patient summary: Urachal cancers are morphologically and genomically similar to colon adenocarcinomas and may respond to drugs targeting the epidermal growth factor receptor.

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Urachal cancer is an aggressive bladder malignancy arising from a vestigial remnant. Patients with metastatic urachal cancer have poor prognosis, with median survival of ~1.3 yr [1]. Given the rarity of urachal cancer, prospective trials to guide the treatment of patients with metastatic disease are lacking, there are no standard chemotherapeutic regimens, and management strategies are empiric and highly institution-dependent. Histologically, urachal cancer resembles enteric adenocarcinoma and anecdotally may respond to chemotherapy used to treat colorectal cancer [1]. Comprehensive molecular analyses of urachal cancer are lacking; however, an analysis of *KRAS* and *BRAF* mutations in urachal cancer previously identified *KRAS* mutations in four out of seven specimens [2].

A 35-yr-old male presented with metastatic urachal cancer to the lungs. A partial cystectomy was performed as palliative treatment for severe hematuria. Pathological analysis confirmed the diagnosis of mucinous urachal carcinoma, and the possibility of colorectal adenocarcinoma invading the bladder was excluded. He was subsequently treated with two cycles of gemcitabine-FLP (5-fluorouracil, leucovorin, cisplatin) that resulted in transient disease stabilization. However, treatment was discontinued because of severe treatment-related toxicities including fatigue, nausea, vomiting, and diarrhea. Paclitaxel plus carboplatin was then administered but was discontinued owing to disease progression (Fig. 1A). Given the lack of treatment options, targeted exome sequencing was performed on archival tissue from the primary tumor (Foundation One; Foundation Medicine, Cambridge, MA, USA) and revealed *EGFR* amplification and wild-type *KRAS* (Table 1). On the basis of these findings, the patient was started on treatment with the anti-EGFR monoclonal antibody cetuximab, and experienced a 25% decrease in tumor burden that lasted for more than 8 mo (Fig. 1B). Treatment was generally well tolerated with the exception

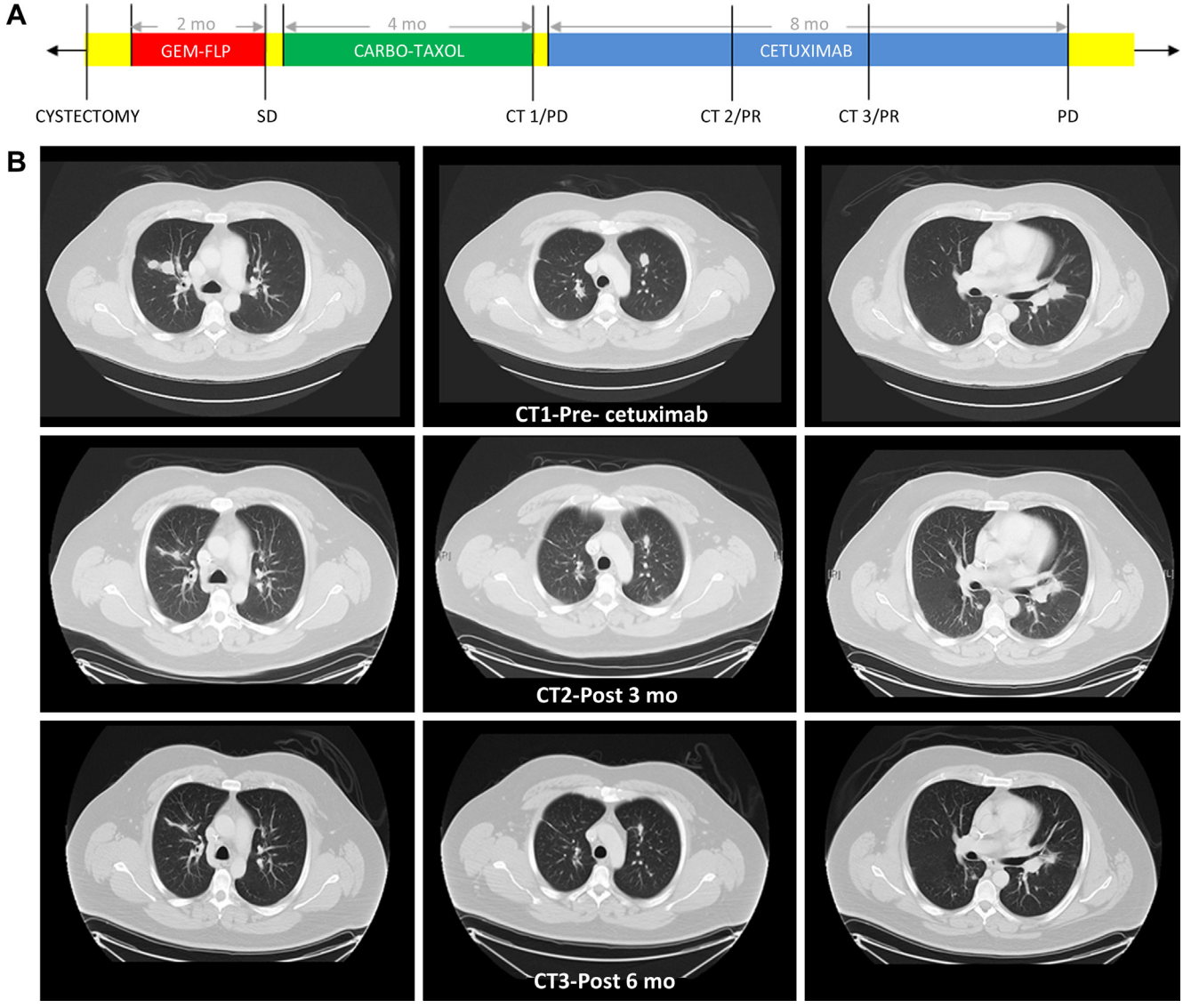

Fig. 1 – Clinical information for the index patient. (A) Timeline demonstrating treatment course. CT = computed tomography scan; SD = stable disease; PR = partial response; PD = progression of disease. Yellow represents periods without chemotherapy treatment. (B) CT images of lung metastases before and after 3 and 6 mo of cetuximab treatment.

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