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【 CASE REPORT 】

Unresectable Ulcerative Colitis Associated Colon Cancer in a Young Japanese Patient

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Abstract:
We herein present the case of a 30-year-old Japanese male patient with ulcerative colitis (UC) who was admitted to our hospital because of significant ascites. Upon evaluation, the patient was diagnosed with unresectable UC-associated colon cancer (UCAC), localized in the transverse colon. Using gene profiling of the tumor tissue, anti-epidermal growth factor receptor (EGFR) antibody combination chemotherapy was selected. Subsequently, the patient exhibited a temporary response to this regimen, with an enhancement in his quality of life and he was able to survive for 12 months. This case underscores the potential benefits of aggressive chemotherapy tailored to the gene profile in UCAC treatment, offering insights into potential avenues for improving the patient prognosis.

Key words: ulcerative colitis, colitis associated cancer, colon cancer, RAS, anti-EGFR antibody agents

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Introduction

Colorectal cancer (CRC) is one of the most common human malignant neoplasms, with the third highest frequency occurring after breast and lung cancers (1). Ulcerative colitis (UC) is one of the strongest risk factors for CRC, and UC-associated colon cancer (UCAC) is classified as a CRC subtype (2). In chronic intestinal mucosal inflammation, carcinogenesis is thought to be caused by a variety of factors, including oxidative stress from cytokine exposure in the intestinal epithelium, changes in the intestinal microbiota, changes in mucus expression, and genetic mutations, although the details are still unknown (3). In the 2000s, with the development of various drugs for the treatment of UC, including biologics, the incidence of UCAC declined (4). However, the hazard ratio for the development of CRC in patients with UC was reported to be 1.66 and that for death was 1.59, thus indicating that a certain number of deaths still occur (1). Prevention and the early detection of UCAC are very important; however, once an unresectable advanced CRC develops, there is no established treatment, and the prognosis is very poor (5).

In this report, we describe a young Japanese patient with advanced UCAC who achieved a temporary response to anti-epidermal growth factor receptor (EGFR) antibody combination chemotherapy, an improved quality of life, and he was able to survive for 12 months.

Case Report

A 30-year-old Japanese male patient with a 12-year history of extensive UC was transferred to Asahikawa Medical University Hospital because of a significant volume of ascites. Notably, his father also had UC, but there was no family history of CRC. He had been receiving anti-tumor necro-

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sis factor-α antibody agents (infliximab; 5 mg/kg) and an immunomodulator (azathioprine; 75 mg/body) for four years due to refractory UC. Despite achieving clinical remission, colonoscopy was not performed during this period. However, one year prior to admission, he experienced a gradual exacerbation of abdominal discomfort and bloating, thus leading to immobility and urgent admission to a previous hospital. Computed tomography at that time revealed massive ascites and raised suspicion of UCAC development. Upon transfer to our hospital, physical examination revealed the following: a stature of 171.9 cm; weight of 73.9 kg; body temperature of 37.5°C, blood pressure of 123/77 mmHg, heart rate of 113 beats/min, indicative of sinus tachycardia, and peripheral capillary oxygen saturation of 97% on room air. He reported an 8 kg weight loss over three months with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 3. The laboratory values at the time of transfer are summarized in Table 1. The results showed a strong inflammatory response, mild anemia, hypoalbuminemia, and high tumor marker levesubstantial volume of ascites within the abdominal cavity (Fig. 1A-C), with contrast-enhanced thickening of the transverse colon wall (Fig. 1B). Although the wall continuity was partially disrupted, free air was not observed (yellow arrows in Fig. 1B. Additionally, suspicious findings of multiple peritoneal disseminations were noted (green arrows in Fig. 1B, C) with no evidence of either hepatic or pulmonary metastases (Fig. 1A, D)]. Colonoscopy revealed a large neoplasm with deep ulceration causing stenosis in the transverse colon (Fig. 2A, B), moderate-to-severe inflammation with active ulceration in the sigmoid colon (Fig. 2C), and an irregular flat elevated lesion with moderate active inflammation in the rectum (Fig. 2D). Radiographic imaging enhanced by amidotrizoate sodium meglumine showed complete stenosis of the transverse colon (yellow arrows in Fig. 2E). A pathological examination of the tumor tissue revealed positive p53 staining in adenocarcinoma cells and mucous lake forma-

Table 1. Blood Test Results.

WBC, /μL	12,660	BUN, mg/dL	9.2
RBC, $\times10^4$/μL	458	Cre, mg/dL	0.58
Hb, g/dL	12.8	eGFR, mL/min	132.6
Plt, $\times10^4$/μL	79.3	Na, mEq/L	138
PT-INR	1.10	K, mEq/L	4.5
APTT, s	30.8	Cl, mEq/L	98
Fib, mg/dL	533	CRP, mg/dL	13.35
FDP, μg/mL	11.8	Fe, μg/dL	11
TP, g/dL	6.8	UIBC, μg/dL	148
Alb, g/dL	2.4	Fer, ng/mL	67.4
T-Bil, mg/dL	0.3	CA19-9, U/mL	81
AST, U/L	12	CEA, ng/mL	18.3
ALT, U/L	6	HBs Ag, IU/mL	<0.01
LD, U/L	160	HBs Ab, mIU/mL	<2.5
γGTP, U/L	16	HCV Ab, S/CO	0.06
AMY, U/L	20	Anti-TP Ab, U/mL	<5.0

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Plt: platelet, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, Fib: fibrinogen, FDP: fibrin degradation products, TP: total protein, Alb: albumin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LD: lactate dehydrogenase, γGTP: γ-glutamyl trans peptidase, AMY: amylase, BUN: blood urea nitrogen, Cre: creatinine, eGFR : estimated glomerular filtration rate, Na: sodium, K: potassium, Cl: chlorine, CRP: C-reactive protein, Fe: ferrum, UIBC: unsaturated iron binding capacity, Fer: ferritin, CA19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, HBs Ag: hepatitis B surface antigen, HBs Ab: hepatitis B surface antibody, HCV Ab: hepatitis C virus antibody, Anti-TP Ab: anti-treponema pallidum antibody

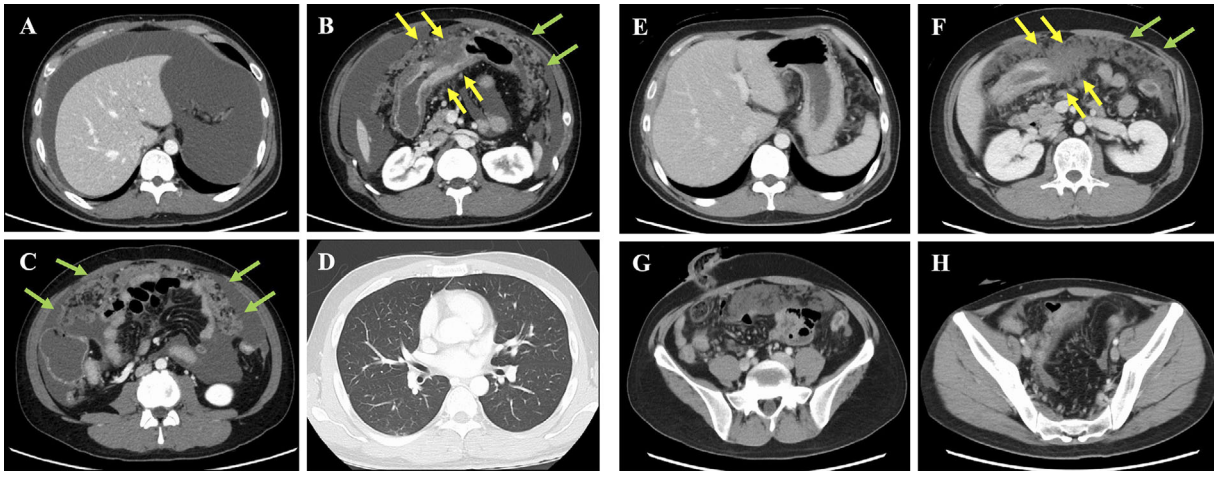

Figure 1. Computed tomography images before and after chemotherapy. Before chemotherapy, images depict massive ascites in the abdominal cavity (A-C), the primary lesion in the transverse colon (B, yellow arrows), multiple peritoneal disseminations (B, C, green arrows), and the absence of hepatic and pulmonary metastases (A, D). Following chemotherapy, there was a decrease in ascites (E-H), no significant changes in the primary lesion, and multiple peritoneal dissemination (F, yellow and green arrows).

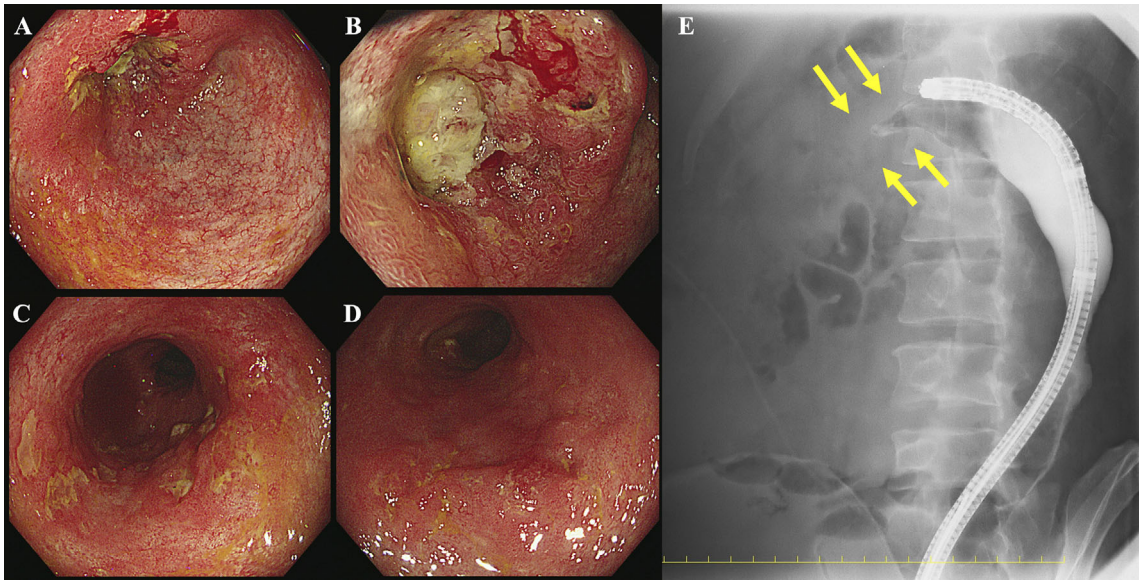

Figure 2. **Endoscopic findings and radiographic imaging. An endoscopic examination revealed a large neoplasm with a deep ulcer and mild inflammation in the transverse colon (A, B), moderate to severe inflammation with active ulceration in the sigmoid colon (C), and an irregular flat elevated lesion with moderate active inflammation in the rectum (D). A radiographic imaging demonstrating complete stenosis of the transverse colon (E, yellow arrows).**

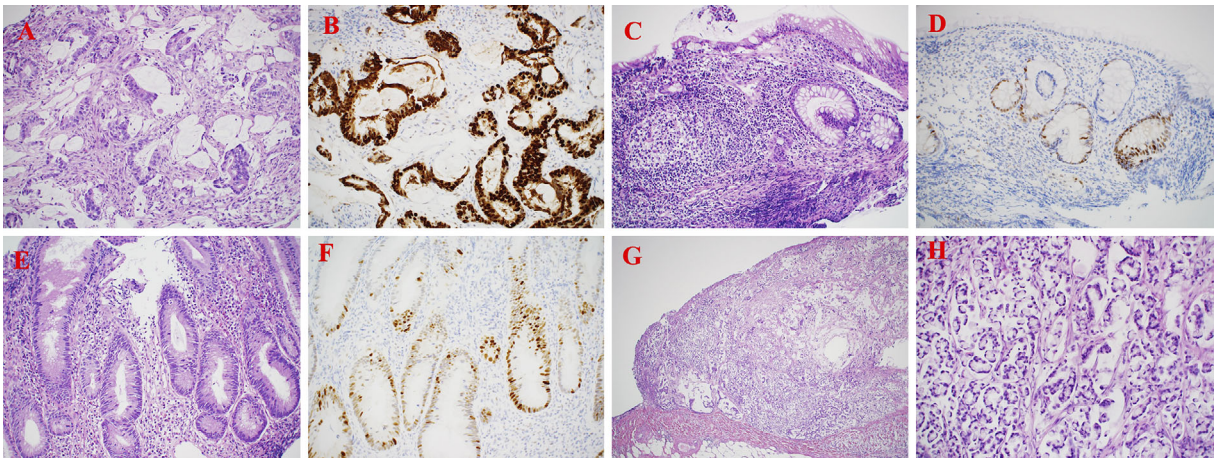

Figure 3. **Pathological findings. A pathological analysis revealed p53 stain-positive mucinous adenocarcinoma from the tumor tissue (A, B), absence of dysplasia from the anorectal side of the tumor (C, D), dysplasia from the rectal irregular flat elevated lesion (E, F), and signet-ring cell carcinoma from the peritoneal seeding lesion (G, H). A, C, E, and G show Hematoxylin and Eosin staining, and B, D, F, and H show p53 staining.**

tion, leading to a diagnosis of mucinous adenocarcinoma (Fig. 3A, B). A biopsy from the anorectal side of the tumor revealed no dysplasia (Fig. 3C, D), whereas dysplasia was confirmed in the rectal irregular flat elevated lesion (Fig. 3E, F). Despite concerns regarding chemotherapy-induced intestinal perforation due to inadequate UC disease control, peritoneal dissemination, and significant ascites, the patient strongly requested aggressive treatment. Consequently, a central vein catheter with port insertion was inserted, and an ileostomy was initially created at the ileum end. A pathological examination of a partially resected peritoneal seeding lesion revealed numerous adenocarcinoma cells floating in a mucus lake, consistent with metastasis from the transverse colon cancer. More than half of the adenocarcinoma cells exhibited indurated signet-ring morphology with compressed nuclei (Fig. 3G, H). Genomic profiling of the peritoneal seeding lesion was conducted through gene capture hybridization combined with high-throughput sequencing technology (FoundationOne CDx, Chugai Pharmaceutical). Mutations in 12 genes (*TP53*, *ERBB3*, *SMAD4*, *ERBB4*, *HGF*, *IKBKE*, *LTK*, *MST1R*, *NTRK1*, *RBM10*, *SDHD*, *TIPARP*) and copy number changes in six genes

Table 2. Genetic Test Results.

Biomarker findings			
Microsatellite status	MS-stable		
Tumor mutation burden	6 Muts/Mb		
Gene	**Genomic findings**	**Abundance (%)**	**cDNA**
KRAS	Wild		
NRAS	Wild		
BRAF	Wild		
TP53	R248Q	39.25	c.743G>A
ERBB3	V104L	38.31	c.310G>T
SMAD4	R361H	28.36	c.1,082G>A
ERBB4	R1,275W	43.9	c.3,823C>T
HGF	R134H	14.22	c.401G>A
IKBKE	G660E	35.95	c.1,979G>A
LTK	G276S	39.51	c.826G>A
MST1R	G806W	17.76	c.2,416G>T
NTRK1	R682P	14.76	c.2,045G>C
RBM10	R853Q	18.18	c.2,558G>A
SDHD	V111L	61.62	c.331G>A
TIPARP	D21G	52.01	c.62A>G
AURKA	amplification CN7		
MYC	amplification CN36		
RICTOR	amplification CN8		
FGF10	amplification CN8		
GNAS	amplification CN7		
ZNF217	amplification CN7		

(*AURKA*, *MYC*, *RICTOR*, *FGF10*, *GNAS*, *ZNF217*) were identified. Notably, both *RAS/BRAF* genes were wild-type and microsatellite instability was stable (Table 2). Remarkably, no mutations were observed in *APC*. Consequently, CRC diagnosis strongly suggested UCAC based on endoscopic, pathological, and genetic findings. Ultimately, the patient was diagnosed with unresectable UCAC in the transverse colon at clinical stage IV (cT4aNXM1c, UICC-TNM classification, 8th edition).

Considering the absence of guidelines for chemotherapy in unresectable UCAC, anti-EGFR antibody combination chemotherapy (FOLFOX+PANI; 85 mg/m^2 oxaliplatin, 200 mg/m^2 leucovorin, 400 mg/m^2 and 2400 mg/m^2 5-fluorouracil modified, and 6 mg/kg panitumumab) was initiated, guided by the European Society for Medical Oncology (ESMO) guidelines for sporadic CRC (6). The clinical course of the patient is shown in Fig. 4. Following three courses of FOLFOX+PANI, a marked reduction in ascites volume (Fig. 1E-H) and a significant decrease in tumor marker carcinoenbryonic antigen levels were observed. Additionally, the patient's ECOG PS performance status improved to 0 without either any severe adverse events or UC relapse, thus allowing him to be discharged from the hospital on day 25. Although no significant changes were noted in the primary lesion and multiple peritoneal disseminations (yellow and green arrows in Fig. 1F), the patient continued ten courses of FOLFOX+PANI as an outpatient. However, the ascites began to increase, prompting a switch to chemotherapy. Second-line chemotherapy comprised anti-VEGF antibody combination chemotherapy (FOLFIRI + RAM; 150 mg/m^2 irinotecan, 200 mg/m^2 leucovorin, 2400 mg/m^2 5-fluorouracil modified, and 8 mg/kg ramucirumab). Despite gradual increases in tumor markers and worsening general condition associated with ascites accumulation, chemotherapy was continued with ascites drainage for nine courses of FOLFIRI+RAM. Subsequently, PANI monotherapy was reinitiated as third-line chemotherapy; however, the patient died on day 375 without a clinical response to chemotherapy. Despite an overall survival of 12 months, aggressive treatment temporarily improved the patient's quality of life, thus allowing him to be temporarily discharged from the hospital. In addition, no symptoms of UC flare-ups appeared until death, probably because of the effect of the ileostomy.

Discussion

We herein present a case of a young UC patient with advanced UCAC who exhibited a temporary response to anti-EGFR antibody combination chemotherapy, thereby contributing to his survival. To our knowledge, this represents an inaugural instance wherein a combination anti-EGFR antibody regimen was tailored based on genetic profile information, resulting in a notable albeit temporary response, despite the absence of an established treatment paradigm for advanced UCAC. Given the dismal prognosis associated with UCAC, as exemplified in this case, emphasis on pre-

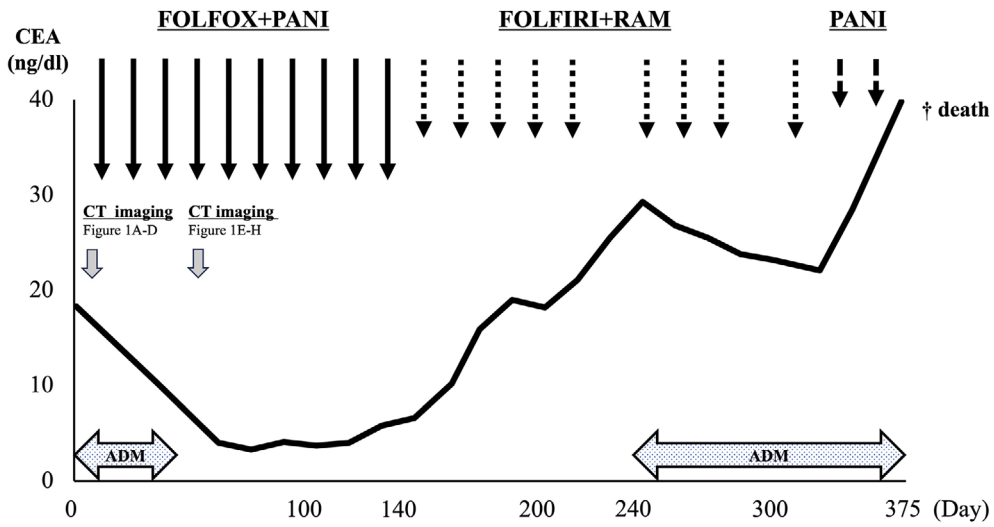

Figure 4. Clinical course in the present case. FOLFOX+PANI: oxaliplatin, leucovorin, 5-flurouracilmodified, and panitumumab, FOLFIRI+RAM, irinotecan, leucovorin, 5-flurouracilmodified and ramucirumab; PANI: panitumumab, CEA: carcinoembryonic antigen, CT: computed tomography, ADM: admission

vention and early detection is paramount. Thus, a comprehensive understanding of the endoscopic, pathological, and genetic attributes is imperative for both diagnosis and therapeutic decision-making in UCAC.

UC-associated dysplasia (UCAD) serves as the precursor lesion for UCAC, underscoring the preference for endoscopic identification at this stage of dysplasia. While UCAD typically manifests as an elevation termed as a dysplasia-associated lesion or mass (DALM), numerous flat lesions evade detection via conventional endoscopic methods. The SCENIC consensus categorizes endoscopic DALM findings into pedunculated, sessile, superficial elevated, flat, and depressed lesions (7). Despite being commonly depicted as raised, UCAC exhibits a diverse array of presentations, often complicating the diagnosis of the lesion extent and depth. A targeted biopsy has been heralded for its diagnostic utility (8), with meticulous observation through dye spraying being recommended for early detection (7, 9). Furthermore, upon identification of invasive carcinoma, the incidence of carcinoma or dysplasia at distant sites has been reported to be 35% internationally and 15% in Japan (10, 11). Pathologically, UCAC predominantly manifests as mucinous adenocarcinoma and poorly differentiated adenocarcinoma with ambiguous tumor spread. UCAD is frequently encountered in the contiguous intestinal mucosa with UCAC. Missense mutated p53 protein overexpression, akin to sporadic CRC, is common, with early mutations often discernible and aiding in dysmorphic epithelial differentiation (3, 12). In recent years, there has been a surge in the genetic analyses of UCAC. While sporadic CRC and UCAC share genetic mutation similarities in carcinogenesis, disparities exist in the timing of *TP53* and *APC* inactivation and *KRAS* activation (13). A comprehensive genetic analysis of colitis-associated colon cancer in 90 Japanese patients with inflammatry bowel disease revealed mutations in *TP53* and *RNF 43*, with fewer mutations in *APC, KRAS*, and *SMAD4* commonly observed in sporadic CRC (14). In our case, the primary lesion in the transverse colon exhibited a circumscribed, relatively gently elevated appearance, with indistinct borders. Additionally, irregular flattened elevation and rectal dysplasia distant from the primary site were observed. A pathological examination revealed a p53 stain-positive mucinous adenocarcinoma in the primary lesion and signet-ring cells in the peritoneal seeding lesion. Notably, gene mutations, including *TP53*, and the absence of mutations in *APC* and *KRAS* were consistent with inflammatory carcinogenesis. These endoscopic, pathological, and genetic findings collectively support a diagnosis of UCAC in sporadic CRC.

A primary challenge in our case was the absence of surveillance endoscopy for approximately four years, which was partially attributed to the COVID-19 pandemic. Timely detection at the dysplasia stage could potentially significantly alter patient prognosis. Given the grim prognosis associated with advanced UCAC and lack of established treatment guidelines, the clinical trajectory of our case strongly underscores the criticality of early detection via endoscopic surveillance. In addition to surveillance endoscopy, aggressive colonoscopy is warranted in patients with UC, particularly in the presence of subjective changes in symptoms. The current management of unresectable sporadic CRC entails molecular-targeted drug selection along with chemotherapy, guided by tumor localization and gene profiling (6). In the absence of established evidence for molecular-targeted drug selection in unresectable UCAC, we opted for molecularly targeted drugs based on sporadic CRC gene profiling. Consequently, the patient's discharge from the hospital following a notable response to primary treatment with anti-EGFR antibody combination chemotherapy markedly enhanced quality of life. Notably, genetic mutations affecting anti-EGFR antibody therapeutic efficacy, including *RAS*,

RAF, and *PI3K* gene mutations, *ERBB2, MET*, and *IGF-1R* activation, and microsatellite instability, have been documented (15, 16). However, none of these gene profiles were evident in our case, thus underscoring the significance of gene profile-based molecular-targeted drug selection in UCAC, akin to sporadic CRC. Future studies are warranted to delineate a therapeutic strategy for appropriate molecular-targeted drug selection, based on extensive UCAC case analyses.

In conclusion, this case report highlights a young Japanese patient with UCAC who exhibited a temporary response to anti-EGFR antibody combination chemotherapy, thereby enhancing his QOL and achieving a 12-month long survival. Comprehensive evaluation of endoscopic, pathological, and genetic data strongly supports the diagnosis of UCAC. Additionally, this case underscores the potential benefit of aggressive chemotherapy tailored to the individual's genetic profile in primary treatment, suggesting the prospect of a prolonged prognosis, even among patients with a compromised performance status, given the frequent occurrence of UCAC in younger individuals.

Author's disclosure of potential Conflicts of Interest (COI).
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