Internal Medicine
The Japanese Society of Internal Medicine

【 CASE REPORT 】

Synchronous Duodenal Cancer and Lung Cancer Harboring an Epidermal Growth Factor Receptor Mutation Treated with Erlotinib and Oral Fluoropyrimidine

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Abstract:

Chemotherapy for multiple primary cancers is challenging. We describe a case of synchronous duodenal cancer with lung cancer harboring an epidermal growth factor receptor (*EGFR*) mutation treated with erlotinib and S-1, an oral fluoropyrimidine agent. A 78-year-old woman with advanced *EGFR*-mutated lung adenocarcinoma was simultaneously diagnosed with duodenal adenocarcinoma. After the treatment with erlotinib, the lung cancer responded well, but her duodenal cancer showed no response. S-1 was added to erlotinib, and the duodenal cancer demonstrated a good response with tolerable toxicities. The concurrent use of erlotinib and S-1 was safe and efficacious for synchronous lung cancer harboring an *EGFR* mutation and duodenal cancer.

Key words: multiple primary cancers, duodenal cancer, lung cancer, epidermal growth factor, S-1, fluoropyrimidine

(Intern Med 56: 2367-2371, 2017)
(DOI: 10.2169/internalmedicine.8312-16)

Introduction

The development of diagnostic technology and a prolonged survival time have contributed to the increased frequency of multiple primary cancers (1-3). Multiple primary cancers are categorized into two groups: (a) synchronous, defined as cancers occurring within 2 months of each other; and (b) metachronous, defined as cancers that occur sequentially with an interval of longer than 2 months (3). Among 2 million cancer patients in the United States over 1973-2003, 8.8% patients had metachronous cancers, and 1.7% had synchronous cancers (2).

The treatment of synchronous multiple primary cancers is clinically difficult. Treatment of each cancer and/or the sequencing of their respective treatments are comprehensively determined by various factors, including the resectability, curativeness, or chemosensitivity of each cancer. When considering chemotherapy for two cancers at once, the treatment strategy is even more difficult. Furthermore, the concurrent use of two or more chemotherapeutic regimens can be highly toxic.

We herein present the first reported case of synchronous double cancers: lung cancer that harbored an epidermal growth factor receptor (*EGFR*) mutation (*EGFR*[Mut]) and duodenal cancer, which were concurrently treated with erlotinib and S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan), an oral fluoropyrimidine agent.

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Table. Laboratory Data on Admission.

WBCs	4.72×10^3 /μL	BUN	7.6 mg/dL
RBCs	362×10^4 /μL	Cr	0.39 mg/dL
Hb	6.9 g/dL	CRP	0.09 mg/dL
Hct	25.4 %	iron	8 g/dL
Plt	42.5×10^4 /μL	TIBC	372 μg/dL
TP	6.7 g/dL	UIBC	364 μg/dL
Alb	3.7 g/dL	ferritin	7 ng/mL
T.bil	0.7 mg/dL	CEA	42.6 ng/mL
AST	36 IU/L	SLX	51 U/mL
ALT	31 IU/L	CA19-9	<1 U/mL
LDH	245 IU/L		
ALP	422 IU/L		
γ-GTP	57 IU/L		

WBCs: white blood cells, RBCs: red blood cells, Hb: hemoglobin, Hct: hematocrit, Plt: platelets, TP: total protein, Alb: albumin, T.bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyltranspeptidase, BUN: blood urea nitrogen, Cr: creatinine, CRP: C-reactive protein, TIBC: total iron-binding capacity, UIBC: unsaturated iron-binding capacity, CEA: carcinoembryonic antigen, SLX: sialyl Lewis X antigen, CA 19-9: carbohydrate antigen 19-9

Case Report

A 78-year-old woman visited our hospital for the examination of a prolonged cough. A medical interview further revealed frequent episodes of tarry stools, and laboratory data indicated iron-deficiency anemia (hemoglobin 6.9 g/dL, serum iron 7 μg/dL, serum ferritin 7 ng/mL, and unsaturated iron binding capacity 384 μg/dL; Table). Chest computed tomography (CT) showed a mass shadow with a maximum diameter of 73 mm in the right upper lung lobe, and abdominal CT demonstrated a duodenal tumor with a maximum diameter of 54 mm (Fig. 1). Positron emission tomography-CT revealed a ^{18}F-fluorodeoxyglucose uptake in the duodenum, in addition to the lung tumor and supraclavicular, mediastinal, and abdominal lymph nodes, and multiple bone metastases (Fig. 2). A transbronchial biopsy of the lung tumor revealed an $EGFR^{Mut}$ adenocarcinoma with the deletion of $EGFR$ exon 19. Esophagogastroduodenoscopy (EGD) showed an ulcerous protrusion in the superior duodenal angle (SDA) with a diameter of approximately 2.5 cm but no tumorous lesion in the stomach (Fig. 3). Abdominal CT and magnetic resonance cholangiopancreatography showed a tumor in the SDA with a diameter of 4 cm without invasion of the pancreas. There were no abnormal findings in the hepatobiliary-pancreas area.

A biopsy specimen of the duodenal tumor was diagnosed histologically as adenocarcinoma. The duodenal tumor did not express thyroid transcription factor (TTF-1) or napsin A on immunohistochemistry, in contrast to the positive expression of TTF-1 and napsin A in the lung adenocarcinoma (Fig. 4). The patient was therefore diagnosed with primary duodenal adenocarcinoma arisen independently of the lung cancer.

She demonstrated increased serum carcinoembryonic antigen (42.6 ng/mL) and sialyl Lewis X (51 U/mL) and negativity for carbohydrate antigen 19-9 (<1 U/mL; Table). Her Eastern Cooperative Oncology Group performance status was 1, and she had normal hematopoietic, renal and liver functions, except for iron-deficiency anemia due to the bleeding from the duodenal cancer (Table).

Determining which tumor was the origin of the multiple metastases to lymph nodes and bones was difficult. EGFR-tyrosine kinase inhibitor (EGFR-TKI) therapy has a rapid and definite effect on lung cancer with $EGFR^{Mut}$, which could help in the differential diagnosis of the multiple metastatic lesions. Therefore, the patient first received erlotinib (150 mg/day, daily), an oral EGFR-TKI, for her lung cancer. After 6 weeks of erlotinib treatment, the maximum diameter of the lung tumor had decreased from 73 to 36 mm on chest CT (Fig. 1). In addition, the supraclavicular, mediastinal, and abdominal lymph nodes metastases had shrunk dramatically, and the osteolytic bone metastases demonstrated osteosclerotic changes. These lesions were therefore considered to have the same origin as the lung cancer.

However, the duodenal cancer remained unchanged or had slightly increased from 54 to 58 mm on abdominal CT (Fig. 1). EGD revealed invasion of the duodenal cancer to the gastric antrum (Fig. 3). Sustained bleeding from the duodenal cancer required frequent blood transfusions, and the tumor was also thought to present a risk for bowel obstruction. We therefore administered S-1 (80 mg/m^2/day on days 1-28 in a 42-day cycle) for the duodenal cancer in addition to erlotinib. Surgery was proposed but not accepted by the patient, who was not willing to undergo invasive approaches. Two months after the administration of S-1, the maximum diameter of the duodenal tumor had decreased from 58 to 47 mm on abdominal CT (Fig. 1). EGD also demonstrated shrinkage of the duodenal cancer and improvement of the invasion in the gastric antrum (Fig. 3). Her gastrointestinal bleeding stopped. The efficacy was maintained for a further 18 months until progression of the duodenal cancer.

In addition to a pre-existing grade 2 skin rash due to erlotinib, the patient developed grade 2 fatigue and appetite loss after starting S-1 treatment; however, these were tolerable. After 20 months of S-1 treatment, the treatment was discontinued because of progression of the duodenal cancer. Two months after stopping S-1 treatment (and after 23 months of erlotinib treatment), the erlotinib treatment was also discontinued because of progression of the lung cancer and deterioration of the patient's health status. Twenty-four months after being diagnosed with synchronous double cancers, she died due to bleeding induced by the duodenal cancer.
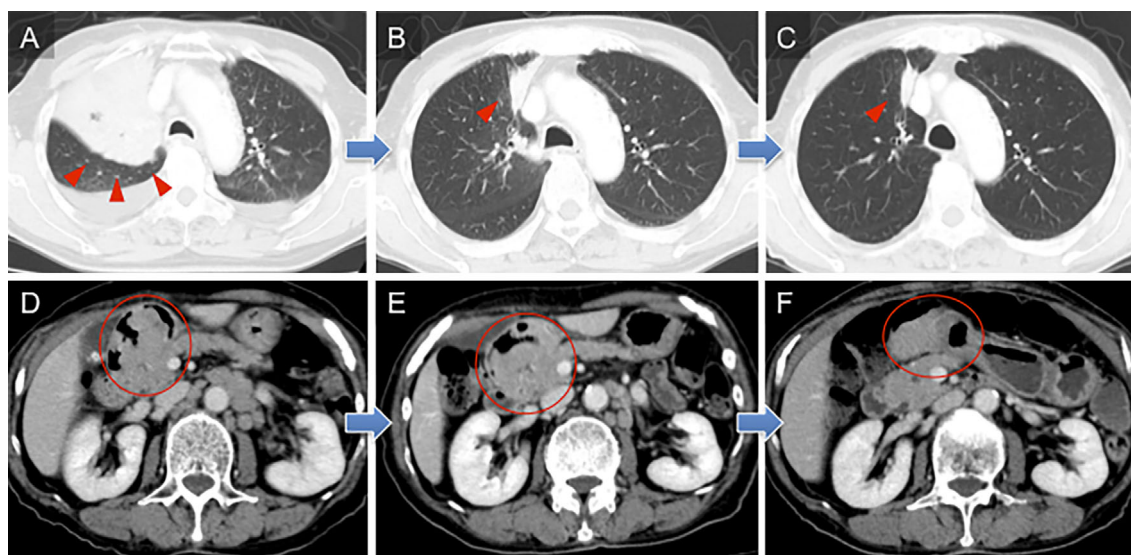
Figure 1. The clinical courses of lung cancer (arrowhead; A, B, and C) and duodenal cancer (circle; D, E, and F) on CT. The initial CT examination demonstrated a lung tumor in the right upper pulmonary lobe (A) and duodenal tumor (D). Six weeks after erlotinib monotherapy, the lung cancer had decreased (B), but the duodenal cancer showed no obvious change (E). Two months after adding S-1 therapy to erlotinib regimen, the duodenal cancer had decreased (F), and the lung cancer remained decreased (C).
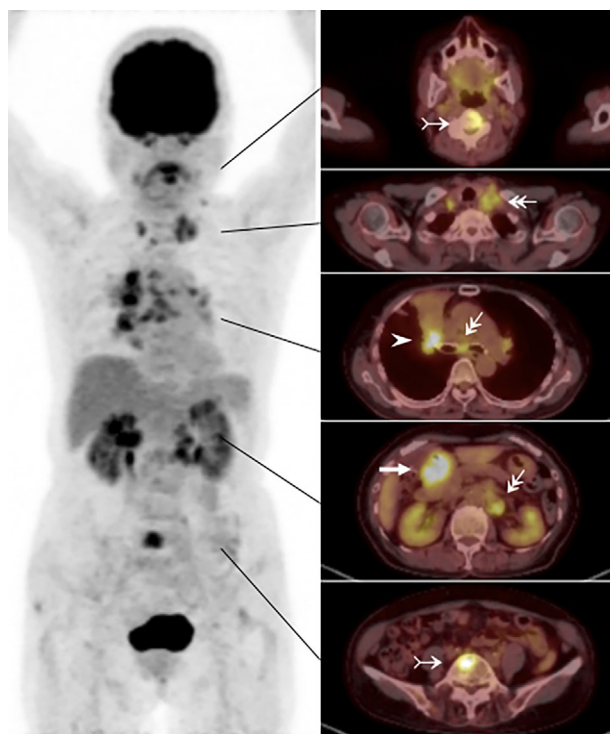

Figure 2. Positron emission tomography imaging shows the ^{18}F-fluorodeoxyglucose uptake in the tumor at the right upper pulmonary lobe (arrowhead), duodenum (arrow), cervical and lumber vertebra (arrows with tails), and the supraclavicular, mediastinal, and abdominal lymph nodes (two-headed arrows).

Discussion

The concurrent use of erlotinib and S-1 was safe and effi-cacious for synchronous primary $EGFR^{Mut}$ lung cancer plus primary duodenal cancer. Although duodenal cancer is a rare disease, S-1 is widely used for various tumors sensitive to fluoropyrimidine agents, and this combination may be applicable for other multiple tumors concomitant with $EGFR^{Mut}$ lung cancer.

Recent advances in molecular-targeted agents have changed cancer therapy (4). The EGFR-TKIs, one of the most successful targeted therapies, have dramatically prolonged the survival of patients with $EGFR^{Mut}$ non-small-cell lung cancer (NSCLC) (5). EGFR-TKIs are not only efficacious but also produce fewer hematologic toxicities, which are common in conventional cytotoxic chemotherapy (5). The non-overlapping toxicities of EGFR-TKIs allow for its combination with cytotoxic agents. In addition, EGFR-TKIs can enhance the antitumor activity of cytotoxic agents (6, 7). The combined use of EGFR-TKIs and cytotoxic agents are now expected to be a new treatment strategy for lung cancer (8, 9). Despite limited evidence, the combination of fluoropyrimidine-based chemotherapy and the EGFR-TKI gefitinib has demonstrated an acceptable safety profile in lung cancer (10, 11) and colon cancer (12) and may also be applicable to S-1 and erlotinib for the treatment of multiple primary cancers.

S-1 is an oral anticancer agent that comprises tegafur, gimeracil, and oteracil potassium. Tegafur is a prodrug of 5-fluorouracil (5-FU), and gimeracil increases the concentration of 5-FU by inhibiting its metabolism. Oteracil potassium reduces gastrointestinal toxicity by inhibiting the phosphorylation of 5-FU (13). S-1 has demonstrated safety and efficacy for various solid tumors, including lung cancer and gastrointestinal cancer (14-16). Its convenient oral admini-
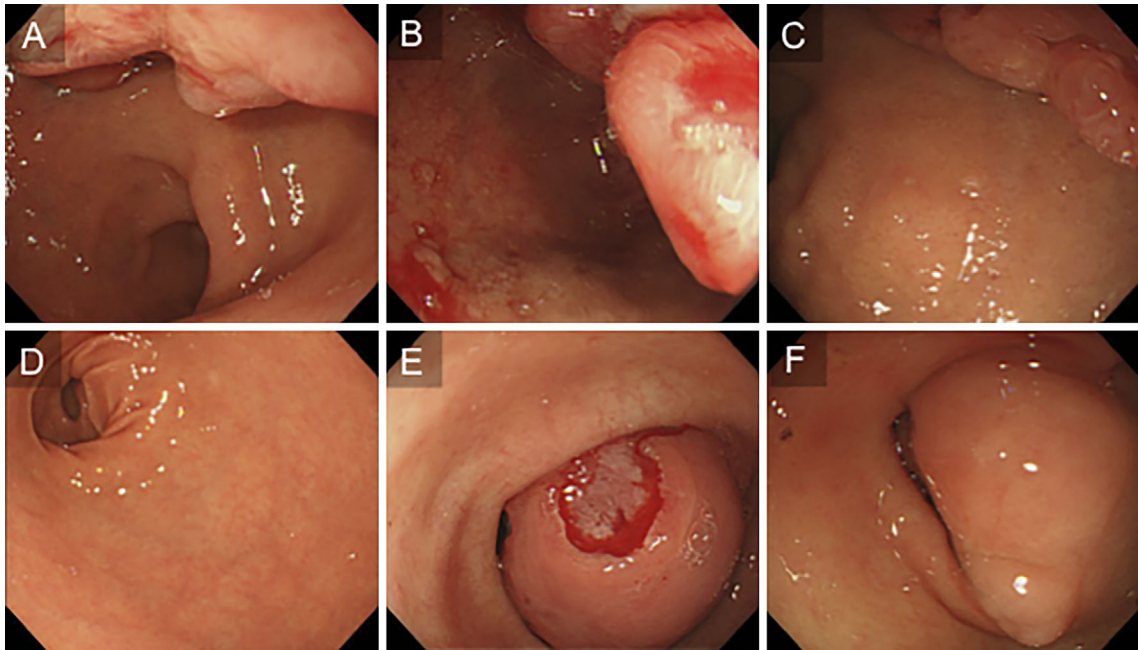
Figure 3. Endoscopic findings of the superior duodenal angle (A, B, and C) and the gastric antrum (D, E, and F) on esophagogastroduodenoscopy. On admission, a protrusion with an ulcer was detected at the superior duodenal angle (A) with normal gastric antrum (D). Six weeks after erlotinib monotherapy, the duodenal tumor was slightly enlarged (B) and had invaded the gastric antrum (E). Two months after adding S-1 therapy to erlotinib, the duodenal tumor had decreased (C), and the invading lesion in the gastric antrum had also improved (F).
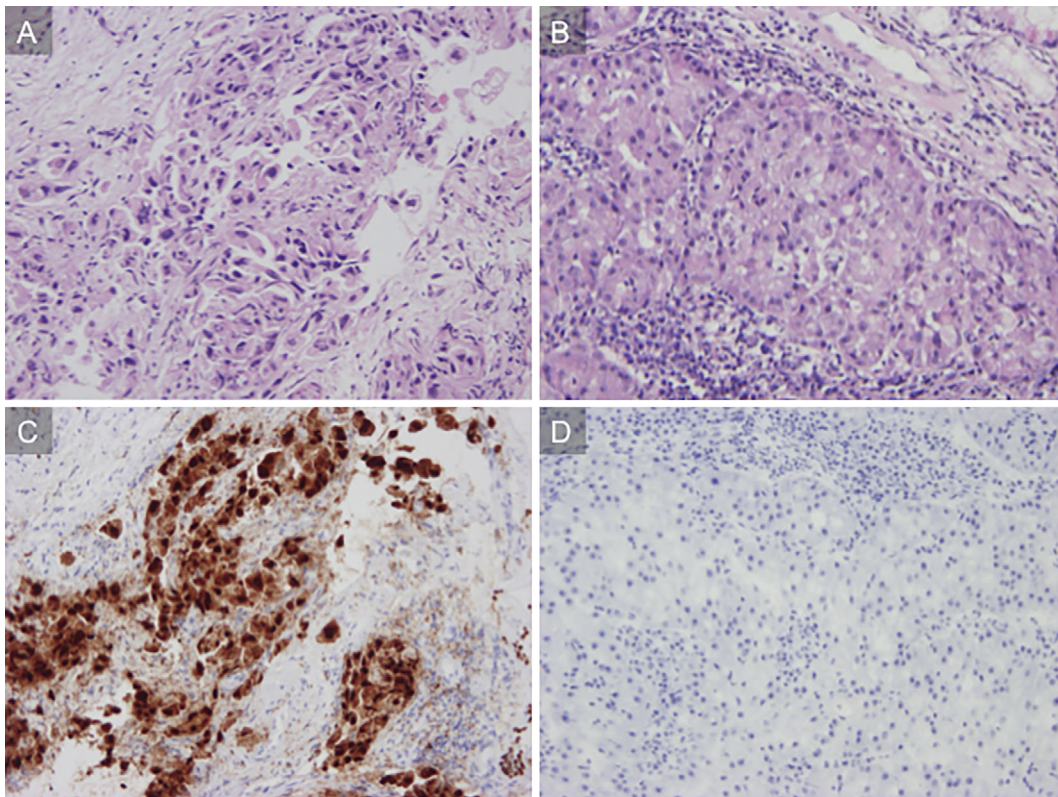

Figure 4. Pathology of lung cancer (A, C) and duodenal cancer (B, D). Adenocarcinoma of the lung (A) and duodenum (B) on Hematoxylin and Eosin staining section. Lung adenocarcinoma showed positive immunostaining for thyroid transcription factor-1 (TTF-1) and napsin A (C), whereas the duodenal adenocarcinoma was negative for TTF-1 and napsin A (D).

stration route and tolerability due to reduced gastrointestinal toxicities are advantages of S-1, which make it suitable for fragile patients (e.g., older patients with comorbidities); for these reasons, S-1 was selected in the current case.

Primary duodenal cancer is a rare disease, accounting for 0.3% of gastrointestinal cancers (17); it currently has no standard chemotherapy (18). Combination therapy with capecitabine, a prodrug of 5-fluorouracil, and oxaliplatin demonstrated a 10% complete response and 50% overall response in a phase II study for 30 patients with advanced small bowel cancer, including 7 (23%) with duodenal cancer (19). In a retrospective analysis of 80 patients with metastatic small bowel adenocarcinoma, including 30 with (38%) duodenal cancers, chemotherapy with 5-fluorouracil and platinum agents had a response rate of 41% (20). Limited evidence suggests fluoropyrimidine agents are effective in treating duodenal cancers; this may be also the case for S-1.

In lung cancer, 1.3% and 4.3% of patients are reported to have synchronous and metachronous cancers, respectively (2). Reportedly, the most common tumors that accompany lung cancer are gastrointestinal tumors (21). Although the current case was a rare case of lung cancer and duodenal cancer, the concurrent use of erlotinib and S-1 may be also applicable for multiple primary cancers with $EGFR^{Mut}$ lung carcinoma and other gastrointestinal tumors for which S-1 therapy is indicated.

The authors state that they have no Conflict of Interest (COI).

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