

CASE REPORT

Efficacy of erlotinib and imatinib in a patient with a rectal gastrointestinal stromal tumor and synchronous pulmonary adenocarcinoma : A case report

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Abstract : The synchronous existence of lung cancer and gastrointestinal stromal tumors (GIST) is considered to be extremely rare. To the best of our knowledge, this is the first report about the treatment of lung cancer and GIST with two kinds of molecular targeting drugs. An 83-year-old woman with a rectal GIST, which carried a c-kit mutation, and pulmonary adenocarcinoma, which exhibited an epidermal growth factor receptor (EGFR) mutation, was treated alternately with imatinib and erlotinib. Good control over both diseases was achieved for two years. The present case is not only of interest due to the rare co-occurrence of GIST and lung cancer, but also because it involved two tumors carrying different gene mutations, and both tumors were brought under control using different molecular targeting drugs. *J. Med. Invest.* 63 : 144-148, February, 2016

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INTRODUCTION

Gastrointestinal stromal tumors (GIST) are rare mesenchymal neoplasms of the digestive tract (1-3). Most GIST are initiated by oncogenic mutations involving the receptor tyrosine kinase proto-oncogene c-kit gene or the platelet-derived growth factor receptor alpha (PDGFRA) gene (4). The synchronous occurrence of GIST and other primary gastrointestinal malignancies has been reported previously (5-13). However, the synchronous occurrence of lung cancer and GIST seems to be extremely rare (6-8). We experienced a case of advanced stage pulmonary adenocarcinoma associated with a rectal GIST. Epidermal growth factor receptor (EGFR) and c-kit gene mutations were identified in the pulmonary adenocarcinoma and GIST, respectively. To the best of our knowledge, this is the first report about the treatment of lung cancer and GIST via the alternating administration of two kinds of molecular targeting drugs.

CASE REPORT

An 83-year-old woman was admitted to a local clinic because of lower abdominal pain. As an abnormal rectal mass was observed on abdominal computed tomography (CT), she was referred to our hospital. A physical examination produced unremarkable results, and no superficial lymph node swelling was detected. Abdominal CT revealed an abnormal mass in the ventral rectum (Fig. 1A, B). Colon fiberoscopy was performed, and the abdominal mass was found to be a rectal submucosal tumor (Fig. 2). An ultrasound-guided needle biopsy of the rectal submucosal tumor was performed via the perineum. A histological examination indicated that

the lesion was predominantly composed of spindle-shaped cells, which were found to be diffusely positive for c-kit in a subsequent immunohistochemical analysis (Fig. 3A, B). In addition, a c-kit gene mutation (exon 11 deletion) was also detected in the specimen. The patient's laboratory findings on admission included a hemoglobin level of 10.7 g/dL, a carcinoembryonic antigen (CEA) level of 3.5 ng/mg, and a cancer antigen 19-9 (CA19-9) level of 5.0 U/ml. The patient did not exhibit severe anemia or elevated tumor marker levels. The possibility of rectal resection had been mentioned to the patient and her relatives, but they did not want to take this option. The patient and her relatives understood that if the tumor increased in size then the patient might develop ileus and that this would require a colostomy to be performed. The patient was treated with imatinib (400 mg/day, orally), but the dose of imatinib was reduced after one week (300 mg/day, orally) as the patient suffered severe nausea and diarrhea. After that, the patient's side effects improved. An abdominal CT scan performed at one month after the start of treatment showed that the patient's abnormal findings had improved (a partial response (PR) according to the RECIST criteria), and chest and abdominal CT scans performed at three months after the start of treatment indicated that the patient's abnormal findings continued to exhibit a PR, but left-sided pleural effusion was detected (Fig. 4A, B). As the patient complained of dyspnea, she underwent a thoracic cavity puncture, and a cytological examination revealed an adenocarcinoma, which was positive for an EGFR mutation (exon 19 deletion) (Fig. 5). A chest CT scan performed after the pleural effusion had been drained revealed a tumor (diameter : 22×20 mm) in the left lower lobe (Fig. 4C). The patient did not wish to undergo ¹⁸F-fluorodeoxy glucose positron emission tomography. Brain magnetic resonance imaging did not detect any metastases. As a result, the patient was diagnosed with synchronous pulmonary adenocarcinoma (T1bNxM1a, Stage IV) and GIST (high risk).

Although it was necessary to treat both the patient's lung cancer and GIST, it was considered that administering both erlotinib (for the lung tumor) and imatinib (for the GIST) simultaneously would result in strong side effects. Thus, we decided to administer them

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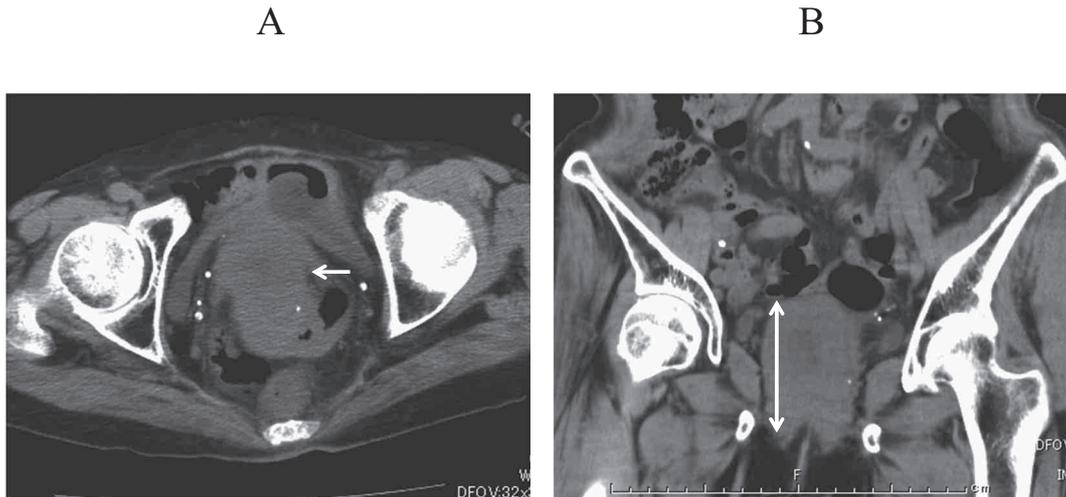


Figure 1. An abdominal CT scan detected a tumor in the ventral rectum (arrows).
A : axial view, B : coronal view

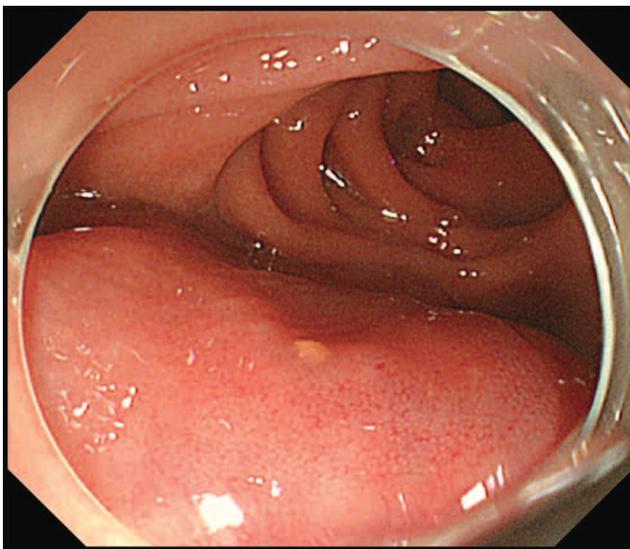


Figure 2. Colon fiberoptic showed a tumor in the rectal submucosa

alternately. As we considered that the patient's lung cancer was more serious than her GIST, we decided to administer the lung cancer treatment for longer periods than the GIST treatment. The patient was treated with imatinib for two weeks (300 mg/day, orally) and erlotinib (100 mg/day, orally) for four weeks in an alternating manner. Since side effects were expected, erlotinib was administered at a reduced dose from the beginning. The only side effect of this treatment was a mild rash (Grade 1). Good control of the lung cancer and the GIST was achieved (Fig. 6A, B), and the patient's CEA level fell from 6.6 ng/ml to 3.3 ng/ml. The patient demonstrated a PR according to the RECIST criteria, but passed away two years after the start of therapy at another hospital. The patient's lung cancer and rectal GIST did not worsen at the other hospital. The patient died of a urinary tract infection, but the above-mentioned therapy improved her quality of life (QOL) during the two-year treatment period.

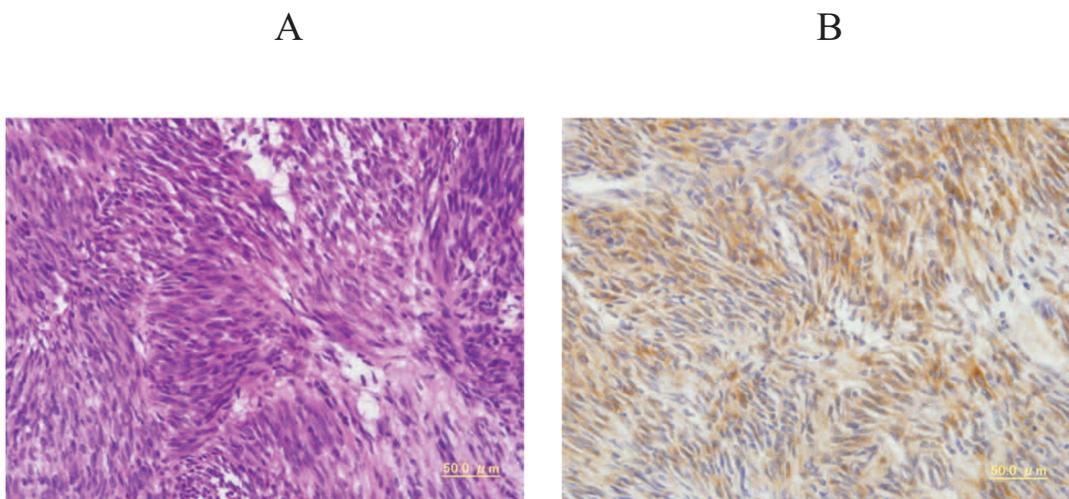


Figure 3. A histological analysis demonstrated the dense proliferation of spindle-shaped cells (A : Hematoxylin and eosin (HE) staining $\times 400$) The positive immunohistochemical staining of c-kit (CD117) was consistent with a diagnosis of GIST (B : $\times 400$).

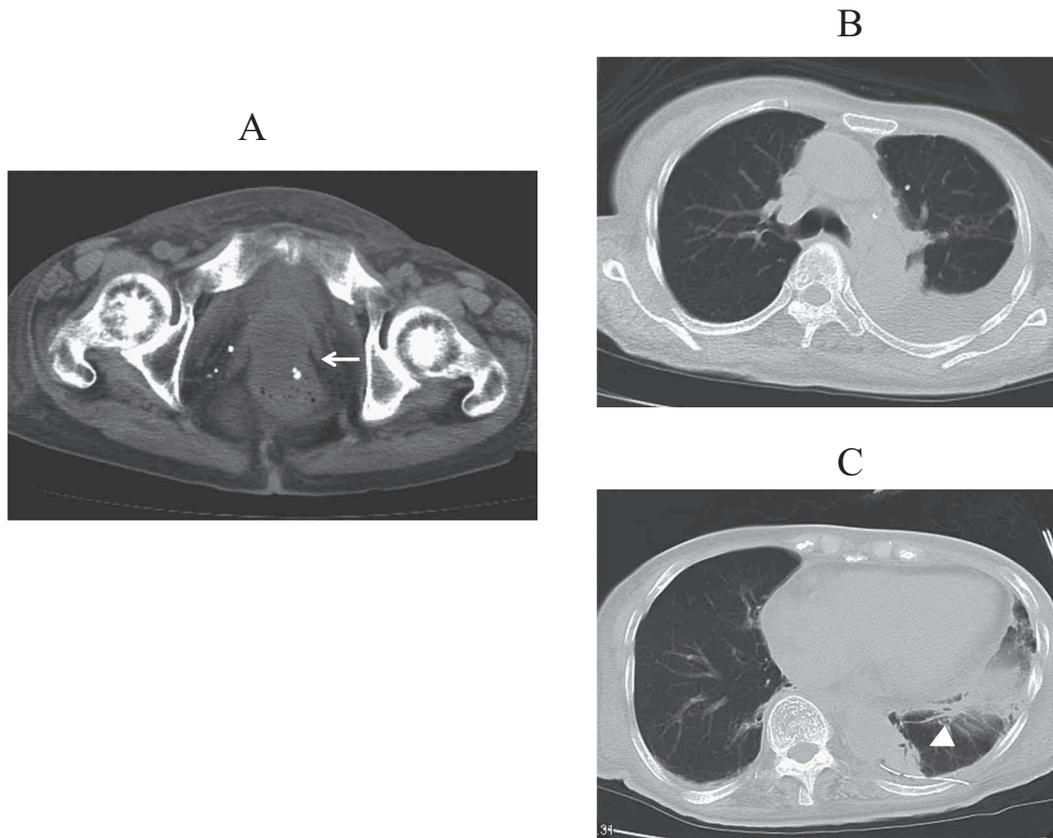


Figure 4. Patient's CT findings at 3 months after the start of treatment

A : An abdominal CT scan revealed that the patient's abnormal findings had improved slightly after 3 months' imatinib therapy (arrow). B : A chest CT scan detected left-sided pleural effusion. C : Chest CT detected a tumor in the left lower lobe after pleural effusion drainage (arrowhead).

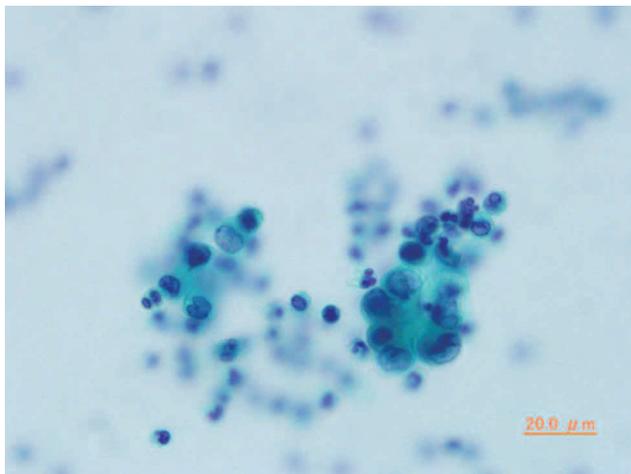


Figure 5. A cytological analysis resulted in a diagnosis of pulmonary adenocarcinoma ($\times 100$)

DISCUSSION

This case highlighted two important clinical issues : 1) There have only been a few reports about synchronous cases of GIST and lung cancer ; and 2) the administration of two kinds of molecular targeting drugs in an alternating manner brought both the lung cancer and GIST under control.

Regarding the first issue, GIST is a rare neoplasm that represents

about 0.1-1.0% of all malignant neoplasms of the gastrointestinal tract. Most GIST arise from the stomach (50-62%), small intestine (20-30%), colon (11%), or rectum (7%), while the esophagus is rarely affected (0.6-1%) (3, 11, 19, 20). GIST have been reported to occur synchronously, mostly with gastrointestinal carcinomas (21), but there are few reports about them occurring synchronously with lung cancer. Herein, we reported a case of synchronous pulmonary adenocarcinoma and GIST. The lung cancer was found incidentally during the treatment of the GIST with imatinib. The malignant cells in both tumors had specific gene mutations. Synchronous and asynchronous cases of GIST and other malignancies have been studied in several case series (5-12). Based on these reports, GIST associated with other primary malignancies occur at incidence rates ranging from 2.9% to 32.6%. The most common accompanying neoplasms are colorectal and gastric adenocarcinoma, and pancreatic tumors (5, 9, 10). Therefore, cases in which GIST occur synchronously or asynchronously with other gastrointestinal malignancies are relatively common. The high prevalence of other gastrointestinal malignancies in GIST patients is probably due to the frequent use of investigative or therapeutic surgery to treat/investigate other malignancies. Concomitant GIST are thus usually discovered incidentally during surgery performed for other malignancies. Indeed, Kawanowa *et al.* (11) reported that microscopic GIST were found in 35% of gastric cancer patients that underwent stomach resections. However, synchronous GIST have rarely been detected in patients with lung cancer. Pandurengan *et al.* (6) summarized the clinical courses of 783 GIST patients and found only 10 cases in which lung cancer (1.3%) occurred before or after the GIST. Agaimy *et al.* (12) reported that lung cancer exhibited a frequency of 5% (26 cases) in GIST patients (486 cases). Furthermore,

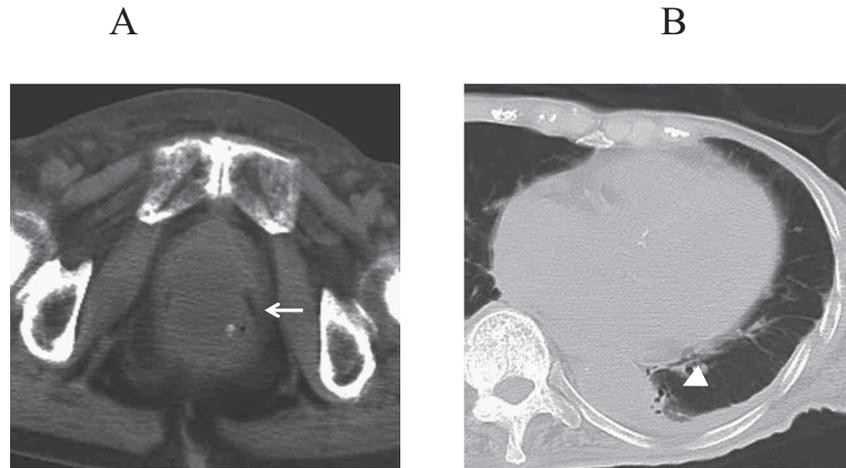


Figure 6. Patient's CT findings at 6 months after the start of treatment
 A : An abdominal CT scan revealed that the patient's abnormal findings had improved slightly after 6 months' imatinib therapy (arrow). B : A chest CT scan showed that the tumor in the left lower lobe had disappeared (arrowhead).

Ponti *et al.* (7) and Ruka *et al.* (13) summarized 141 and 180 cases of GIST, respectively, and identified one and two patients, respectively, that developed non-small cell lung cancer after being diagnosed with GIST. Therefore, the development of lung cancer in patients with GIST is not necessarily rare.

As for the second issue, in the present case two kinds of molecular targeting drugs were administered in an alternating manner to treat the patient's lung cancer and GIST, and these treatments were effective at bringing the tumors under control. The patient was treated with imatinib for two weeks and erlotinib for four weeks on an alternating basis. In the present case, we determined the optimal treatment strategy based on the expected side effects. The patient was initially treated with imatinib (400 mg/day, orally), but the dose was subsequently reduced to 300 mg/day (orally) since severe nausea and diarrhea appeared. After that, the patient's side effects improved. Since side effects were expected, erlotinib was administered at a reduced dose from the beginning. Although it was necessary to treat both the patient's lung cancer and GIST, it was considered that administering both drugs at the same time would result in strong side effects. Therefore, we decided to administer them alternately. As we considered that the patient's lung cancer was more serious than her GIST, we administered erlotinib for longer periods than imatinib. Good control of both the lung cancer and the GIST was achieved (the patient exhibited a PR according to the RECIST criteria), but the patient died of a urinary tract infection at two years after the start of therapy. Despite this, no pleural effusion or ileus occurred, which would have been indicative of the progression of the lung cancer and GIST, respectively, and the patient did not develop any treatment-related side effects. In addition, the abovementioned therapy improved the patient's QOL during the two-year treatment period.

We found an EGFR mutation in the pulmonary adenocarcinoma and c-kit mutation in the GIST in the present case. The detection of these gene mutations helped us to select treatment strategies involving molecular targeting agents that would have beneficial clinical effects on both tumors. The patient was initially treated with imatinib and erlotinib. Previous studies have attempted to detect EGFR and c-kit mutations in biphasic malignant lung tumors composed of primitive mesenchymal and epithelial components (17, 18). However, no coexisting mutations were found in these studies (17, 18). In the present case, the EGFR mutation status of the GIST and the c-kit mutation status of the lung tumor were not analyzed. It is therefore difficult to speculate on the interactions between the

EGFR and c-kit gene mutations and their etiological effects in the present case. Although the oncogenic interactions between the detected mutations remain to be determined, the coexistence of two different malignancies harboring specific EGFR and c-kit mutations in a single patient might represent useful information for future studies.

In summary, the present case is not only of interest due to the rare co-occurrence of a GIST and lung cancer, but also because it involved two tumors carrying different gene mutations, and both tumors were brought under control using different molecular targeting drugs.

CONFLICTS OF INTEREST STATEMENT

The authors' state that they have no conflicts of interest.

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