INTERNAL MEDICINE

□ CASE REPORT □

Synchronous Gastrointestinal Stromal Tumor and Primary Lung Adenocarcinoma

Yousuke Wada[1], Tomonobu Koizumi[2], Toshiki Yokoyama[1], Kazuhisa Urushihata[1], Hiroshi Yamamoto[1], Masayuki Hanaoka[1] and Keishi Kubo[1]

Abstract

Although rare, gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. The asynchronous occurrence of other malignancies in patients with GIST during the clinical course is relatively common. However, the synchronous coexistence of GIST and lung cancer has only rarely been reported. We experienced a case of coincidental primary lung adenocarcinoma and intestinal GIST. The present case is not only of interest due to the rare coincidence of GIST and lung cancer, but also because there was an epidermal growth factor receptor gene mutation in the lung cancer and a c-kit mutation in the GIST.

Key words: EGFR-gene mutation, c-kit mutation, gefitinib, lung cancer, metastatic intestinal tumor

(Intern Med 51: 2407-2410, 2012)
(DOI: 10.2169/internalmedicine.51.7888)

Introduction

Gastrointestinal stromal tumors (GIST) are uncommon mesenchymal neoplasms affecting the gastrointestinal tract (1, 2). The synchronous occurrence of GIST and other primary gastrointestinal malignancies has been reported previously (3-10). However, the synchronous existence of lung cancer and GIST seems to be extremely rare (7-10). We experienced a case of advanced stage lung adenocarcinoma associated with intestinal GIST. The GIST was found during an evaluation for lung cancer staging. Epidermal growth factor receptor (EGFR) and c-kit gene mutations were identified in the lung adenocarcinoma and GIST, respectively. To our knowledge, this is the first such case of coincidental lung cancer and GIST reported to date.

Case Report

A 54-year-old woman was admitted to a local hospital in July 2011 because of general malaise. As severe anemia and an abnormal mass on chest radiography were observed, she was referred to our hospital. Her physical examinations were unremarkable and there was no superficial lymph node swelling. Chest computed tomography (CT) revealed an abnormal mass in the left lower lobe and multiple nodules in both lung fields (Fig. 1). Bronchofiberscopy was performed, and the histological findings revealed an adenocarcinoma positive for EGFR mutation (exon 19 deletion) (Fig. 4A). Brain magnetic resonance imaging (MRI) showed multiple tumors, suggesting metastasis from lung cancer (Fig. 2A). The laboratory findings on admission included a hemoglobin level of 6.9 g/dL, CEA of 9.6 ng/mL, CA-125 of 87 U/mL and positive occult blood in the feces. ^{18}F-Fluorodeoxy glucose positron emission tomography (FDG-PET) revealed a mass showing an abnormal uptake in the left lower lung field (SUV max: 13.4) and multiple intrathoracic lesions (Fig. 3). Furthermore, the accumulated uptake of FDG-PET was also observed in the lower abdominal mass (SUV max: 15.8, Fig. 3). Abdominal CT showed an embryonate-prone nodular shadow in a small intestinal tumor (Fig. 2B). An ultrasound-guided needle biopsy of the small intestinal tumor was performed using colon fiberscopy. The histological findings indicated the lesion to be predominantly composed of spindle-shaped cells, which were diffusely positive for c-kit in an immunohistochemical analysis (Fig. 4B, C). In ad-

[1]The First Department of Internal Medicine, Shinshu University School of Medicine, Japan and [2]Comprehensive Cancer Center, Shinshu University School of Medicine, Japan
Received for publication April 4, 2012; Accepted for publication May 28, 2012
Correspondence to Dr. Tomonobu Koizumi, tomonobu@shinshu-u.ac.jp

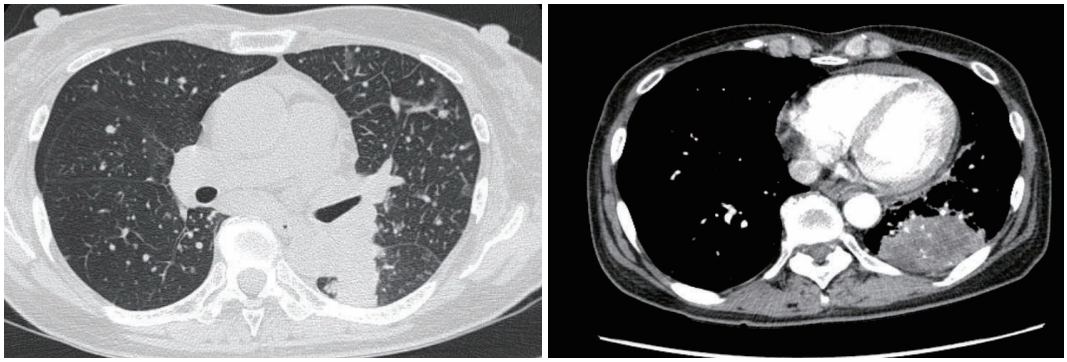

Figure 1. **A chest CT scan showed multiple nodular shadows in both lung fields and a mass in the left lower lung field.**

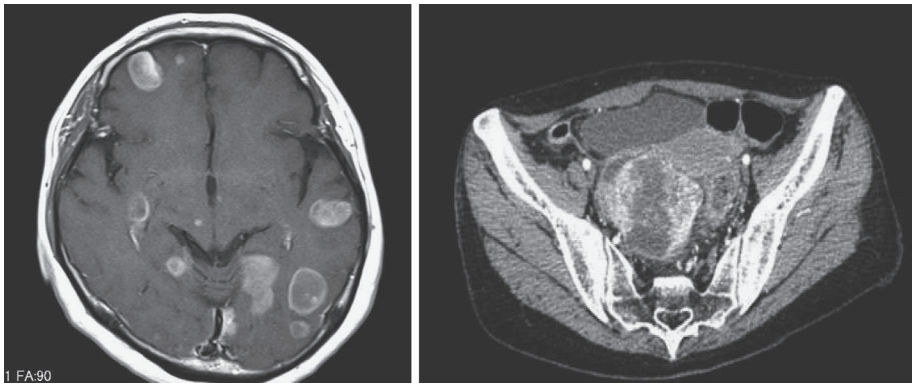

Figure 2. **A: Brain MRI showed multiple metastases in the brain. B: Abdominal CT showed a small intestinal tumor.**

dition, c-kit gene mutations were also observed in the specimen (exon 11 deletion).

Although the primary site remained to be determined, we speculated that the pulmonary and brain metastases were due to lung cancer in the patient. As a result, the patient was diagnosed with synchronous pulmonary adenocarcinoma (T2N3M1b) and GIST (high risk). In addition, we examined the specific gene mutations in both specimens and found that the GIST was negative for EGFR mutations and the lung tumor was negative for c-kit gene mutations.

The patient was treated with gefitinib (250 mg/day, orally) and whole-brain irradiation at a dose of 30 Gy/10 divisions was also administered. Chest radiography showed a tendency for an improvement of the abnormal findings after gefitinib therapy. However, the patient developed acute abdominal pain on the 20th day of gefitinib therapy. The patient underwent an emergency operation because of suspected diffuse peritonitis due to perforation from the GIST tumor. The tumor was removed, and the postoperative course was uneventful. Gefitinib therapy was thereafter restarted after recovery of the normal bowel movement functions. However, consciousness disturbance occurred due to the progression of brain metastases, and therefore the patient was started on palliative treatment.

Discussion

We herein reported a case of synchronous pulmonary adenocarcinoma and GIST. The GIST was found incidentally while evaluating the stage of the lung adenocarcinoma. The malignant cells in both tumors had specific gene mutations.

Synchronous and asynchronous cases of GIST and other malignancies have been studied in several series (3-9). Based on these reports, GIST associated with other primary malignancies occurs at incidence rates ranging from 2.9% to 32.6%. The most common accompanying neoplasms were colorectal and gastric adenocarcinoma, as well as pancreatic tumors (3-5). Therefore, cases of synchronous and asynchronous GIST and other gastrointestinal malignancies are relatively common. The high prevalence of other gastrointestinal malignancies with GIST is likely due to the use of investigative or therapeutic surgery for other malignancies. Concomitant GIST is thus usually discovered incidentally during surgery performed for another malignancy. Indeed, Kawanowa et al. (6) reported that microscopic GIST can be found in 35% of stomach-resected patients with gastric cancer.

However, synchronous GIST has been rarely reported in

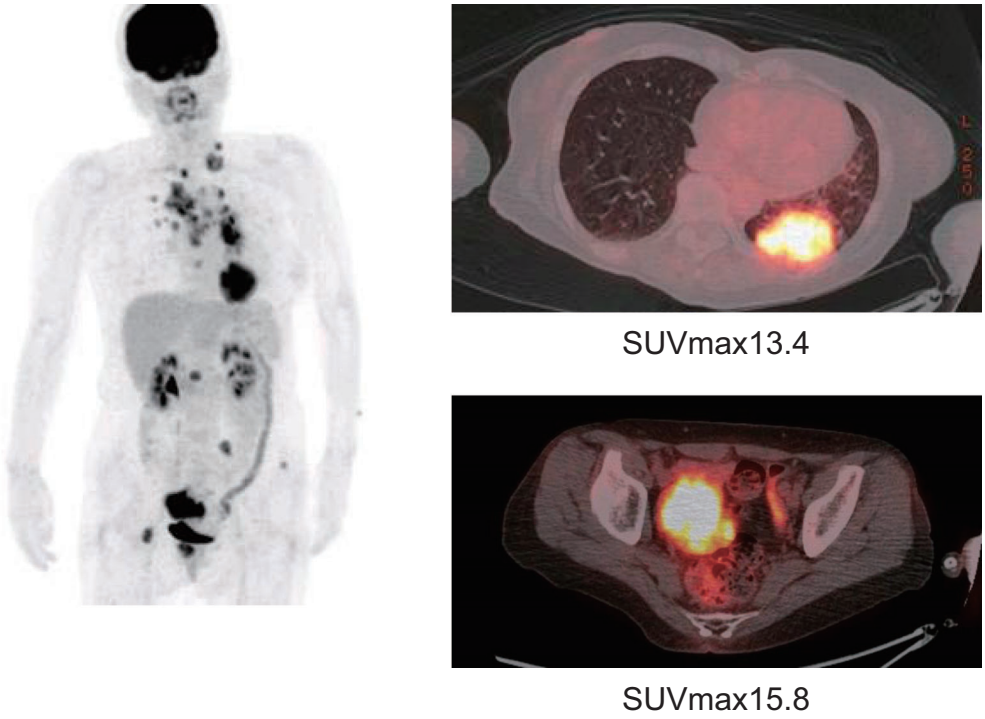

Figure 3. **^{18}F-Fluorodeoxy glucose positron emission tomography (FDG-PET) revealed a mass showing abnormal uptake in the left lower lung field (SUVmax: 13.4), multiple intrathoracic lesions, and a lower abdominal mass (SUVmax: 15.8).**

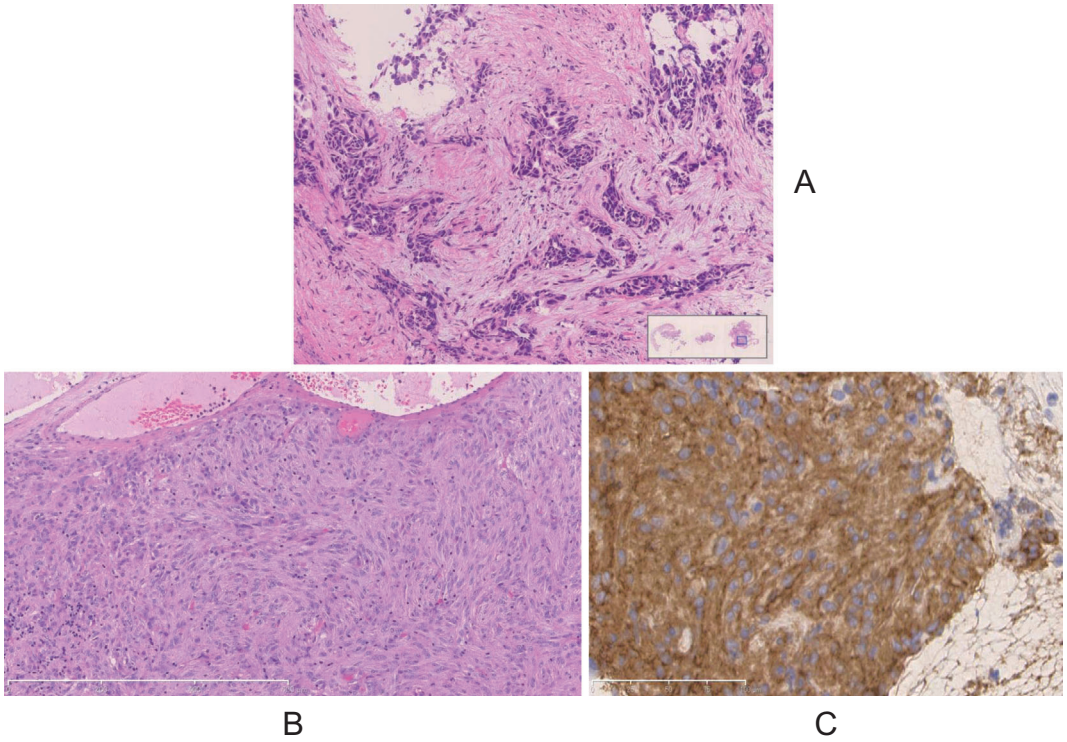

Figure 4. **The histological analysis revealed adenocarcinoma in the lung (A: Hematoxylin and Eosin (HE) staining ×400) and GIST (B: HE staining ×400) that was immunopositive for c-kit (C: ×400).**

patients with lung cancer. Pandurengan et al. (7) summarized the clinical courses of 783 GIST patients and found only 10 cases of lung cancer (1.3%) before and after the clinical course of GIST. Agaimy et al. (8) reported an occurrence rate of 5% (26 cases) of lung cancer in patients with GIST (486 cases). Furthermore, Ponti et al. (9) and Ruka et

al. (10) summarized 141 and 180 cases of GIST, respectively, and identified one and two cases, respectively, that developed non-small cell lung cancer after the diagnosis of GIST. Therefore, the development of lung cancer in patients with GIST is not necessarily rare. However, these cases of lung cancer were asynchronously observed. To our knowledge, ours is the first proven case of synchronous lung adenocarcinoma and GIST at the time of diagnosis.

As a differential diagnosis for the abdominal tumor in the present case, it was necessary to consider the possibility of small bowel metastases from lung adenocarcinoma. Our case presented with melena, but without the development of bowel obstruction before the perforation. The radiographic examinations, including CT and FDG-PET, showed a single giant mass in the lower abdominal cavity. These clinical manifestations in the present case seemed to be different from those in small bowel metastases, in which small and multiple lesions are common (11). As described above, GIST is often discovered incidentally during investigative or therapeutic procedures for unrelated diseases (11, 12). In addition, it was reported that second or multiple primary tumors were common in patients with non-small cell lung cancer (NSCLC), either preceding or following its clinical course (13). As a result, when apparent abdominal lymphadenopathy or a mass is observed in patients with NSCLC, it is necessary to consider the possibility of GIST as well as of that of metastasis. In particular, if the lesion is atypical in appearance and can be approached, a histological biopsy should be considered.

We found an EGFR mutation in the lung adenocarcinoma and c-kit mutations in the GIST in the present case. The detection of these gene mutations was useful for selecting strategies using molecular targeting agents that could provide a beneficial clinical outcome for both tumors. The patient was initially treated with gefitinib, but the interval of treatment was insufficient (20 days) because of the need to perform an emergency operation for GIST. During the recovery from abdominal surgery, the brain metastasis deteriorated in spite of whole brain radiation. We therefore failed to improve the clinical outcome in the present patient.

Several studies have attempted to find EGFR and c-kit mutations in biphasic malignant tumors composed of primitive mesenchymal and epithelial components in the lungs (14, 15). However, there were no coexisting mutations in these studies (14, 15). In the present case, there were no overlapping gene mutations between both tumors. It is therefore difficult to speculate on the interactions between EGFR and c-kit gene activation and the etiological associations in the present case. Although the ontogenetic interaction remains to be determined, the coexistence of two different malignancies harboring specific mutations of EGFR and c-kit in a single patient may represent useful information for future studies.

In summary, the present case is not only of interest due to the rare coincidence of GIST and lung cancer, but it also showed specific gene mutations of the tumors that might have been useful for molecular targeting therapy if the tumors had been detected earlier. It is necessary to be aware of the presence of GIST in patients with lung cancer who show an abdominal mass during the clinical course.

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

References

1. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol **33**: 459-465, 2002.
2. Miettinen M, Majidi M, Lasota J. Pathology and diagnostic criteria of gastrointestinal stromal tumors (GISTs): a review. Eur J Cancer **38** (Suppl 5): S39-S51, 2002.
3. Wronski M, Ziarkiewicz-Wroblewska B, Gornicka B, et al. Synchronous occurrence of gastrointestinal stromal tumors and other primary gastrointestinal neoplasms. World J Gastroenterol **12**: 5360-5362, 2006.
4. Liu YJ, Yang Z, Hao LS, Xia L, Jia QB, Wu XT. Synchronous incidental gastrointestinal stromal and epithelial malignant tumors. World J Gastroenterol **15**: 2027-2031, 2009.
5. Liszka Ł, Zielińska-Pajak E, Pajak J, Gołka D, Huszno J. Coexistence of gastrointestinal stromal tumors with other neoplasms. J Gastroenterol **42**: 641-649, 2007.
6. Kawanowa K, Sakuma Y, Sakurai S, et al. High incidence of microscopic gastrointestinal stromal tumors in the stomach. Hum Pathol **37**: 1527-1535, 2006.
7. Pandurengan RK, Dumont AG, Araujo DM, et al. Survival of patients with multiple primary malignancies: a study of 783 patients with gastrointestinal stromal tumor. Ann Oncol **21**: 2107-2111, 2010.
8. Agaimy A, Wünsch PH, Sobin LH, Lasota J, Miettinen M. Occurrence of other malignancies in patients with gastrointestinal stromal tumors. Semin Diagn Pathol **23**: 120-129, 2006.
9. Ponti G, Luppi G, Martorana D, et al. Gastrointestinal stromal tumor and other primary metachronous or synchronous neoplasms as a suspicion criterion for syndromic setting. Oncol Rep **23**: 437-444, 2010.
10. Ruka W, Rutkowski P, Nowecki Z, Nasierowska-Guttmejer A, Debiec-Rychter M. Other malignant neoplasms in patients with gastrointestinal stromal tumors (GIST). Med Sci Monit **10**: LE13-LE14, 2004.
11. Antler AS, Ough Y, Pitchumoni CS, Davidian M, Thelmo W. Gastrointestinal metastases from malignant tumors of the lung. Cancer **49**: 170-172, 1982.
12. Nilsson B, Bümming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era: a population-based study in western Sweden. Cancer **103**: 821-829, 2005.
13. Duchateau CS, Stokkel MP. Second primary tumors involving non-small cell lung cancer: prevalence and its influence on survival. Chest **127**: 1152-1158, 2005.
14. Macher-Goeppinger S, Penzel R, Roth W, et al. Expression and mutation analysis of EGFR, c-KIT, and β-catenin in pulmonary blastoma. J Clin Pathol **64**: 349-353, 2011.
15. Bergmann F, Moldenhauer G, Herpel E, et al. Expression of L1 CAM, COX-2, EGFR, c-KIT and Her2/neu in anaplastic pancreatic cancer: putative therapeutic targets? Histopathology **56**: 440-448, 2010.