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CLINICAL CASE REPORT

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Metachronous Primary Adenocarcinoma of Lung During Adjuvant Imatinib Mesylate Therapy for Gastrointestinal Stromal Tumor of Stomach

A Case Report

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Abstract: Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor in gastrointestinal tracts; however, the synchronous or metachronous coexistence of GIST with additional primary malignancy is not common.

Here, we present an unusual case of gastric GIST with metachronous primary lung adenocarcinoma diagnosed during his adjuvant treatment with oral receptor tyrosine kinase inhibitor imatinib mesylate (400 mg daily). After 6-month use of imatinib, the patient suffered from dry cough and dyspnea. Subsequent lung biopsy demonstrated adenocarcinoma with diffuse interstitial changes.

Our research emphasizes the possibility of an additional primary tumor with GIST, and reminds the clinicians to strengthen the surveillance of the additional cancer during the follow-up of GIST patients.

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Abbreviations: GIST = gastrointestinal stromal tumor, CT = computed tomography.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common gastrointestinal mesenchymal tumor with an annual incidence of 0.68 to 2/100,000 worldwide, accounting for 1% to 2% of all gastric malignancies.[1–4] GISTs have been documented in all parts of the gastrointestinal tract but are most common in the stomach and small intestine, followed by colorectum, mesentery, and esophagus. Based on the size and mitosis count of primary tumor, it is stratified into 4 risk groups from very low risk to high risk.[5] Surgery is the primary treatment for resectable GIST, and complete excision of the tumor is the most significant prognostic factor. The 5-year survival rates have been reported to be 42% and 8% to 9% for patients underwent complete and incomplete resection, respectively.[6,7] Even in the patients underwent radical resection, 40% to 90% would suffer from recurrence or metastasis.[8–10] Before the availability of imatinib, treatment options other than surgery were chemotherapy and radiotherapy, both with relatively poor efficacy. The imatinib, a kind of signal transduction inhibitor, exerts its activity in GIST through blockade the tyrosine kinases associated with the KIT-protein (stem cell factor receptor). Currently, it has been approved that imatinib could be used in patients with metastatic or unresectable GISTs as well as in high-risk patients after radical resection.

The synchronous or metachronous occurrence of additional primary malignancy in GIST patient is deemed to be an uncommon entity, mainly noted in case studies previously.[11–14] It was reported that GIST patients had a much higher frequency of accompanying with additional malignancies than clinical practice[15–19] and such occurrence often brings diagnostic and therapeutic challenges. The incidence of GIST patients with additional malignancies was reported to be 9% to 27%, and primary lung cancer in GIST patients was rather rare, with an incidence of 0.5% to 1.2%.[15,17,18] To the best of our knowledge, this is the first case study describing the metachronous primary lung adenocarcinoma in GIST patient who are undergoing adjuvant therapy.

Herein, we present the case of a patient who exhibited gastric GIST with metachronous lung adenocarcinoma after the use of imatinib mesylate (400 mg orally daily) for 6 months. Written informed consent was obtained from the patient and the patients' relatives for publication of this case study.

Case Report

A 50-year-old Chinese policeman came to our hospital in March 2014, complaining of a right abdominal mass found accidently for 1-month duration, without symptoms of abdominal pain, vomit, melena, or loss of weight. The patient had a smoking and drinking history for >30 years. His medical, family, or psychosocial histories were all unremarkable. Abdominal computed tomography (CT) scan revealed a huge

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M-JJ, S-SW, and YY were significantly involved in medical care, radiological investigations, analysis and data interpretation, and drafting of the article. YC and X-FL participated in medical care and critical review of the article. L-HW read the imaging data and J-HX made the pathological diagnosis and did the immunohistochemical staining of the patient. All authors have read and approved the final article.

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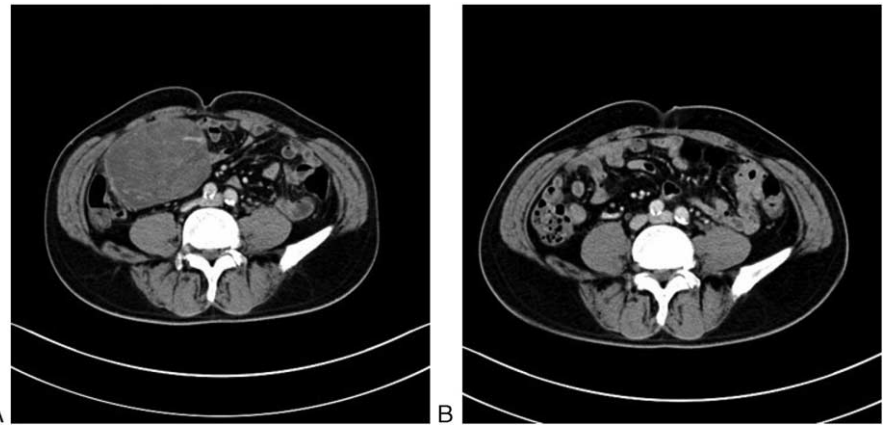

FIGURE 1. Abdominal CT. A, Enhanced total abdomen computed tomography scan found a huge gastric GIST in antrum of stomach before operation, in March, 2014. B, Enhanced total abdomen CT scan found no signs of recurrence or metastasis for GIST 6 months after operation, in October, 2014. CT = computed tomography, GIST = gastrointestinal stromal tumor.

mass in antrum of stomach (Figure 1A) and chest high-resolution computed tomography scan showed normal (Figure 2A). Routine blood, urine, stool examinations had no obvious abnormity. The functions of both liver and kidney were normal. The serum level of glycoprotein CA125 was 67.4 U/mL, above the upper limitation of detection (35 U/mL) and the level of carcinoembryonic antigen was within limitation. The patient received tumor resection on March 10, 2014. Neither ascites nor metastasis in liver, peritoneum, or pelvic cavity was documented in the operation. The tumor originated from the greater gastric curvature and was exophytic toward the abdominal cavity, with varicose blood vessels and omentum majus wrapped around it.

The histologic examination confirmed gastric GIST, 16 cm × 8.5 cm × 7 cm in size, mitotic figure >10 per 50 HPF. Immunohistochemical staining demonstrated a strong positivity for c-kit (CD117), CD34, and DOG-1 (Figure 3). According to the improved National Institute of Health risk classification criteria, the patient was classified into the high-risk group.[5,20] Therefore, the patient started to take imatinib (Glivec is Novartis Pharmaceuticals Corporation, Switzerland) 400 mg/day as an adjuvant therapy after operation.

In October 2014, he came to our hospital again for dry cough and gradually progressive dyspnea, especially on exertion for >1 month, without fever or hemoptysis. Routine blood, urine, stool examinations and liver and kidney function tests had no obvious abnormity. The serum level of carcinoembryonic antigen, glycoprotein CA125, and squamous cell carcinoma antigen were elevated to 5.7, 164, and 5.0 U/ml, respectively. The chest-enhanced CT scan showed latticed shadows and interstitial changes like ground-glass opacities diffusely distributed in bilateral pulmonary and hydropneumothorax in the right lung. Combining with clinical symptoms, the CT signs listed above may be considered as carcinomatous lymphangitis accompanied with interstitial changes (Figure 2B). Both transbronchial and percutaneous lung biopsy specimens were proved to be primary lung adenocarcinoma by pathology. Immunohistochemical staining of the lung tissues demonstrated to be negative for both CD117 and DOG-1, positive for TTF-1 and weak positive for anaplastic lymphoma kinase (ALK) (Figure 4). The epidermal growth factor receptor gene was wild-type in exons 18–21. Based on the pathologic and immunohistochemical examinations, the lung tumor was totally

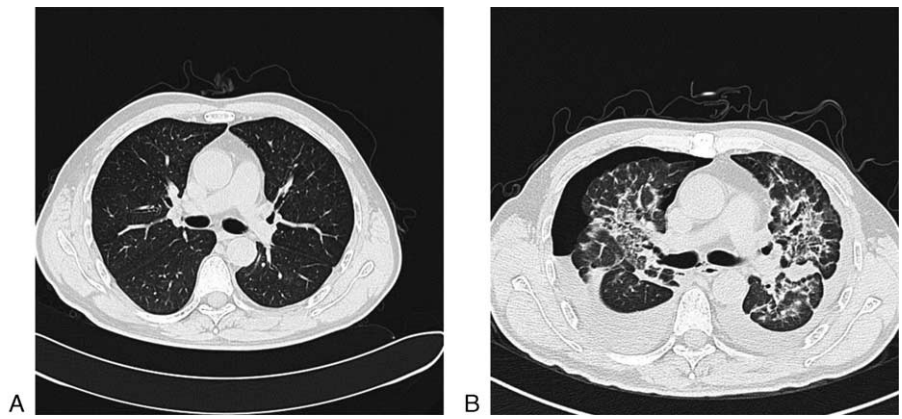

FIGURE 2. Chest CT. A, Chest high-resolution CT scan showed normal before GIST operation, in March, 2014. B, Chest-enhanced CT scan showed latticed shadows and interstitial changes like ground-glass opacities diffusely distributed in bilateral pulmonary and hydropneumothorax in the right lung 6 months after operation, in October, 2014. CT = computed tomography, GIST = gastrointestinal stromal tumor.

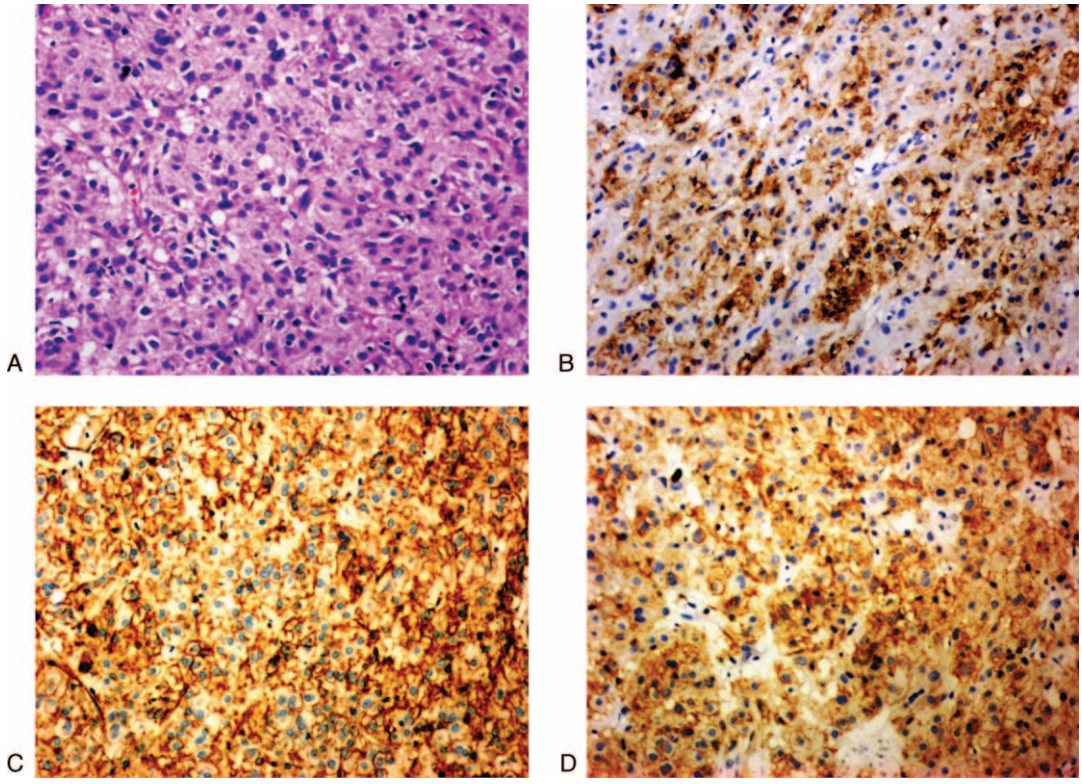

FIGURE 3. Pathology of gastric stromal tumor (GIST). A, high-grade GIST cells composed of spindle cells with ovoid nuclei arranged in short fascicles (nuclear palisading)—100 ×. B, Immunohistochemical stainings of GIST (all 100 ×) showed positive of c-KIT/CD117 (tyrosine kinase growth factor receptor), C, CD34, and D, DOG-1. GIST = gastrointestinal stromal tumor.

different from the GIST operated 6 months ago, which was considered to be a secondary malignancy. Neither enhanced CT scan of the total abdomen (Figure 1B) nor positron emission tomography-CT showed signs of malignance outside lungs. Since the diagnosis of lung cancer, this patient stopped taking imatinib and underwent 4 courses of chemotherapy consisting of pemetrexed and carboplatin, which was well tolerated without obvious adverse effects. The pulmonary lesions shrank slightly after chemotherapy and were evaluated to be stable disease. Now the patient was under a regular follow-up.

DISCUSSION

GIST represents the most common mesenchymal tumor of the gastrointestinal tracts. In clinical practice, synchronous or metachronous occurrence of additional malignancy in GIST patient is uncommon; however, previous studies showed that GIST patients always have a significantly higher incidence of an additional malignancy than observed in clinical practice, ranging from 9% to 27%.[21] According to analysis of the 783 GIST registered in University of Texas MD Anderson Cancer Center from 1995 to 2007, Pandurengan et al[18] demonstrated that 154

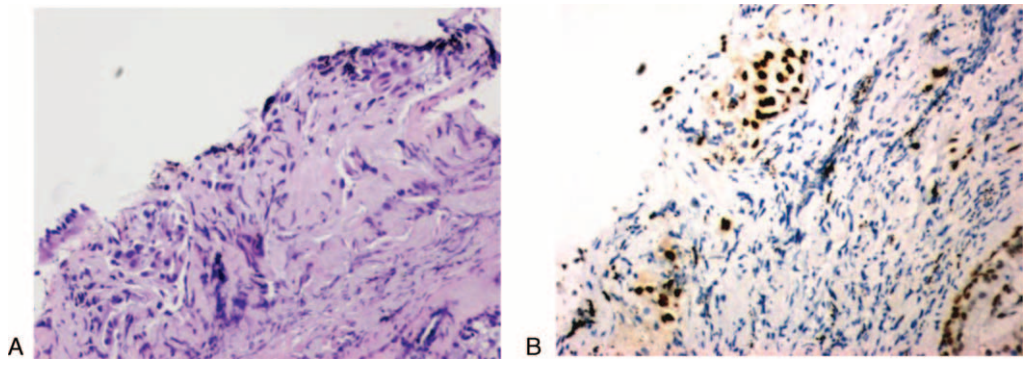

FIGURE 4. Pathology of lung adenocarcinoma. A, Epithelioid cells with obvious heteromorphosis; B, immunohistochemical staining of thyroid transcription factor—100 ×.

of 783 (20%) GIST patients developed other types of cancer, and some were even concomitant with ≥2 additional cancers. More additional primaries were diagnosed before (134) than after (52) GIST. Primaries observed before GIST were cancers of the prostate (25), breast (12), esophagus (9), kidney (7), and melanoma (6), and cancers of the lung (5) and kidney (5) were the most frequent malignancies after GIST. The incidence of metachronous GIST and lung cancer was about 1.2% in their study. Murphy et al[17] collected 6112 GIST patients through the Surveillance, Epidemiology, and End Results database, and 1047 (17.1%) had additional cancers. Similar to the result of Pandurengan et al, Murphy et al found that more patients had other cancers diagnosed before than after GIST. The most common cancer types were genitourinary cancers, gastrointestinal cancers, and breast cancers.[17] Agaimy et al[22] conducted a review of literature and found 486 (10%) GIST patients associated with additional malignancies among 4813 cases. The most common types of GIST-associated malignancies were gastrointestinal carcinomas (n = 228, 47%), followed by carcinomas of prostate (n = 43, 9%), lymphoma/ leukemia (n = 36, 7%), breast (n = 34, 7%), kidney (n = 27, 6%), and lung (n = 26, 5%).[22] Therefore, based on the above published data, we could conclude that the incidence rate of GIST-associated lung cancer was 0.5% to 1.2%.[15,17,18] The incidence of the additional primary malignancies with GIST reported in literatures appeared to be much higher than that experienced in clinical practice, which may be caused by long-term follow-up, various biases and disunity of diagnostic criteria. In addition, the underestimate of the GIST in general population may lead to the inconsistence. The average interval time for patients with GIST diagnosed before second malignancy was 4.7 years, and 1.4 years for patients with GIST diagnosed after another malignancy.[18] In our case, the lung cancer occurred 6 months after the GIST operation, which developed quickly.

The majority of previous case studies describe that GISTs were discovered during surgical procedures or the endoscopic surveillance for another primary malignancy. More patients had another malignancy diagnosed before than after GIST, but the overall survival seemed to be of no significant difference between 2 groups.[18] Additionally, no difference was found in the overall survival whether patients had GIST alone or GIST concomitant with 1 other cancer,[18] which may be due to the early stage of the second primary malignancy when diagnosed. This reminds us that during the follow-up of GIST, surveillances for recurrence and second malignancies are equally important. The current GIST guidelines recommend chest imaging only during the staging workup. Although in this case, we should also consider to use chest CT to monitor the patient during the follow-up. What is more, it is important to be aware that imaging-atypical metastatic lesions could be a potential second primary malignancy, which needs a biopsy for final diagnosis.

So far, limited data are available concerning long-term results of imatinib therapy in GIST patients. The reason for the high percentage of additional malignancies accompanied with GIST is not yet clear. Someone posit the hypothesis that an underlying genetic instability or mismatch repair may lead to the KIT-mutation resulting in GIST and also activate oncogenes that resulting in other malignancies.[18] According to a prospective, observational study of imatinib therapy for unresectable and metastatic GIST conducted in a Japanese institution,[23] 7 of 70 (10%) patients suffered from additional malignancies. Although no evidence at the moment supports that the imatinib therapy increases the risk of additional malignancies,[24–26] some researchers have their doubts. Some studies found that GIST patients in the imatinib era tended to show a higher incidence of additional malignancy than pre-imatinib era.[21] And in our case, after reviewing literatures, we still failed to find any information to explain the possible causes of the additional primary lung cancer. The improvement of the survival of GIST by imatinib, and the increasing high incidence of lung cancer in the general population might be the possible reasons.

Imatinib is a small molecule tyrosine kinase inhibitor administered to patients with chronic myelogenous leukemia and GIST. On February 1, 2001, imatinib mesylate was approved by the US Food and Drug Administration for the treatment of metastatic and unresectable GISTs. A randomized, double-blind, placebo-controlled, multicenter phase III trial[27] enrolled 713 high-risk patients who had complete resection of primary GIST tumors (≥3 cm). The patients were randomly assigned to receive imatinib 400 mg daily or placebo daily for 1 year as adjuvant therapy. Imatinib group had a significantly prolonged recurrence-free survival compared with placebo group (98% [95% confidence interval 96–100] vs 83% [78–88]; hazard ratio 0.35 [0.22–0.53]; $P < 0.0001$). Thus, they drew a conclusion that adjuvant imatinib therapy could prolong recurrence-free survival following the resection of high-risk GIST patients. So far, there existed no adequate clinical trial evidence to support the use of adjuvant imatinib in low-risk GIST tumor. In the current study, the patient received complete resection of a huge high-risk GIST tumor. According to the results of existing researches, adjuvant imatinib for 1 year is necessary for patients who are deemed at intermediate-to-high risk of recurrence after resection of primary GIST.[20] Therefore, our patient took imatinib (400 mg orally daily) for prevention of relapse and metastasis.

This drug is generally well tolerated; however, it has still been associated with various adverse effects, such as superficial edema, nausea, and muscle cramp. The incidence of pulmonary toxicity is rare. According to the study by Ohnishi et al,[28] among 5500 patients administered imatinib, there were 27 (0.5%) cases of interstitial pneumonia with the symptom of dry cough and dyspnea on exertion. In our case, after 6 months use of imatinib, images of interstitial changes occurred bilateral lungs, although the diagnosis of interstitial lung disease had not been adequately established. Therefore, clinicians should pay attention and process timely when the patients complain of dry cough and dyspnea, despite the low-incidence of imatinib-related interstitial pneumonia.

In conclusion, here we reported an unusual GIST patient who developed a lung adenocarcinoma with bilateral interstitial changes, after 6 months adjuvant use of imatinib mesylate. Although no obvious correlation could be concluded between the development of pulmonary adenocarcinoma and the usage of imatinib, this case reminded the clinicians to strengthen the surveillance of the additional cancer during the follow-up of GIST patients. In addition, despite the low-incidence of imatinib-related interstitial pneumonia, clinicians should pay attention and process timely when the patients complain of dry cough and dyspnea.

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