

Clinical, radiological and biological features of lung metastases in gastrointestinal stromal tumors (Case reports)

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Abstract. Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors that most frequently arise in the gastrointestinal tract. The liver and peritoneum are common sites of distant GIST lesions, whereas lung metastases are infrequent, accounting for 7% of all lesions. The clinical significance of these metastases remains unknown. Although lung metastases are relatively rare in the natural history of GIST, they may become more prevalent due to increased patient life expectancy. The present report describes four patients with GIST who had lung metastases. Two were female (54 and 28 years of age), and two were male (64 and 44 years of age). The primary GISTs were localized in the stomach in two patients and in the small intestine in the other two patients. Three patients presented with multiple lung lesions and one presented with one lung lesion. Lung metastases were present at the time of initial diagnosis in one patients, and were observed during the follow-up period in the other three. In this report we detail the clinical presentation and radiological features of the lung lesions as observed by computed tomography (CT) and computed tomography/positron emission tomography (CT/PET). We describe each patient's clinical history and treatment which included surgery and the tyrosine kinase inhibitors, imatinib and sunitinib, and the novel therapy, nilotinib. Moreover, we discuss some biological aspects of this relatively rare occurrence and the resulting clinical implications. These findings may help

clinicians to manage lung metastases arising from GISTs in future.

Introduction

Gastrointestinal stromal tumors (GISTs) are common mesenchymal tumors in the gastrointestinal tract which arise from the interstitial cells of Cajal (ICC). Specific abnormalities of the KIT and PDGFR- α (PGDFRA) receptors are the main oncogenic event in GISTs, and these receptors remain the most relevant therapeutic targets (1). Approximately 75-80% of GISTs harbor gain-of-function c-KIT mutations, 7-10% harbor gain-of-function PGDFRA mutations, and the remaining are defined as wild-type (WT) because they have no KIT or PDGFRA mutations (2,3). The mutational status of these genes affect disease progression and response to tyrosine kinase inhibitors (4,5). The liver and peritoneum are the most frequent sites of distant metastases from GISTs. but lung lesions are rare, comprising 7% of these metastases (6). To date, lung metastases have been reported as anecdotal findings, and few studies have examined the clinical significance of these lesions (7-12). We describe four patients with GIST treated at our institution who presented with lung metastases, focusing on the clinical, radiological and biological features of these lesions.

Case reports

Case 1. In 2003, a 64-year-old male underwent gastric resection for a high-risk GIST harboring a homozygous c-KIT deletion mutation (aa 550-555I, KPMYEV) in exon 11. In 2008, a follow-up CT scan revealed two lung lesions and a solid opaque region 14 mm in diameter in the parenchyma of the right lower lobe, which was confirmed by CT/PET (Fig. 1A and B). After 15 months of treatment with 400 mg daily imatinib (Glivec[®]/Gleevec[®], Novartis Pharmaceuticals Corp., East Hanover, NJ, USA), the patient achieved a complete metabolic response by PET and a partial response by CT of the lung lesion (7.8 vs. 14 mm) (Fig. 1C and D). He

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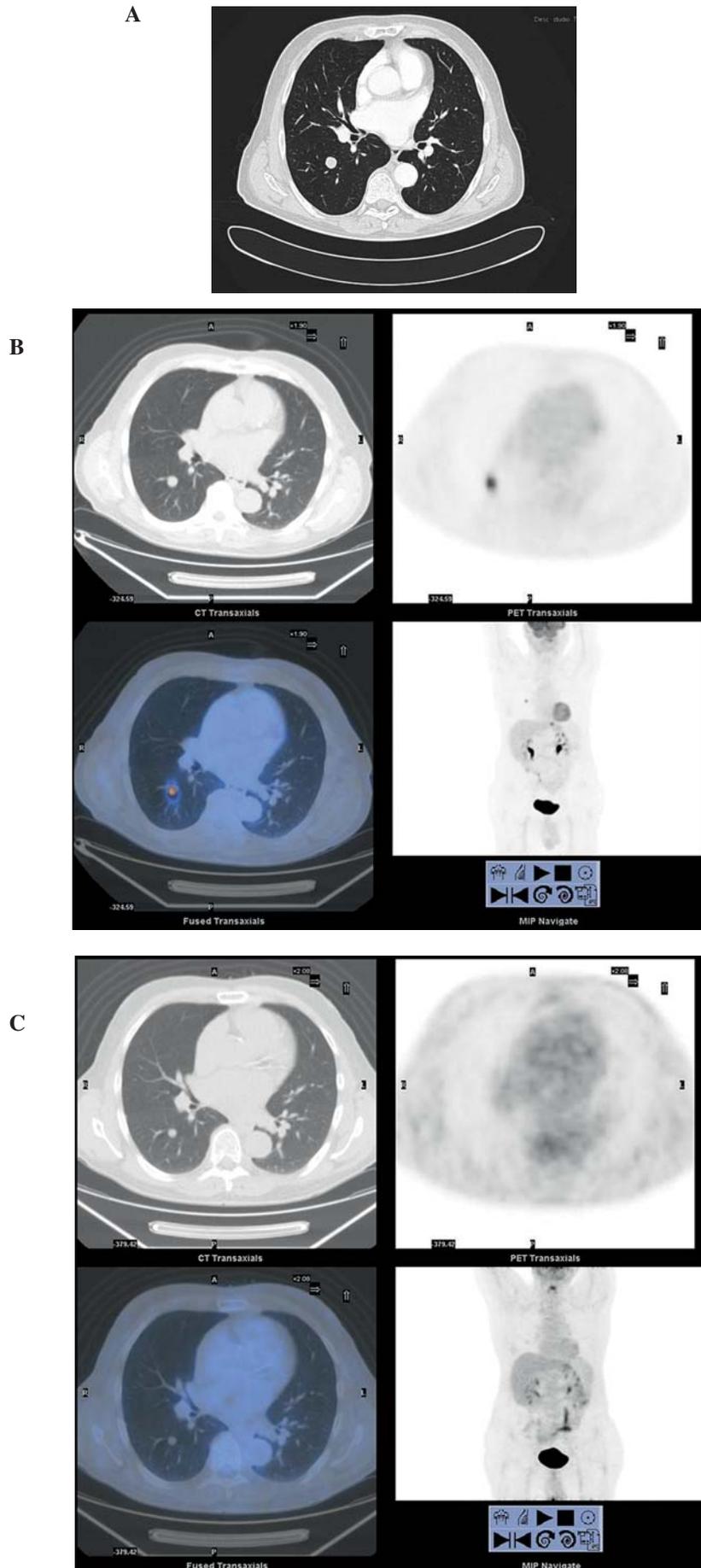


Figure 1. A, B and C. Computed tomography.

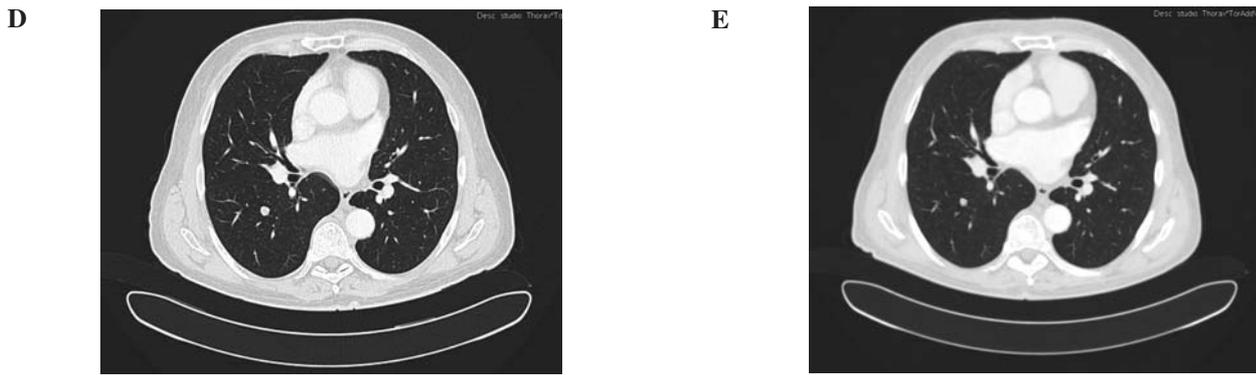


Figure 1. (A) Computed tomography (CT) taken in August 2008 revealed a 14-mm solid opaque region in the parenchyma of the lower right lobe of the lung. (B) Computed tomography/positron emission tomography (CT/PET) evaluation in September 2008 confirmed the presence of an hypermetabolic nodule in the lower region of the right lobe of the lung. (C) October 2008: early CT/PET taken after one month of imatinib treatment showed a complete metabolic response. (D) December 2008: CT evaluation after three months of treatment showed a partial response, with a reduction in lesion diameter (7.8 vs. 14 mm). (E) CT taken at the most recent evaluation (December 2009) showed stable disease.

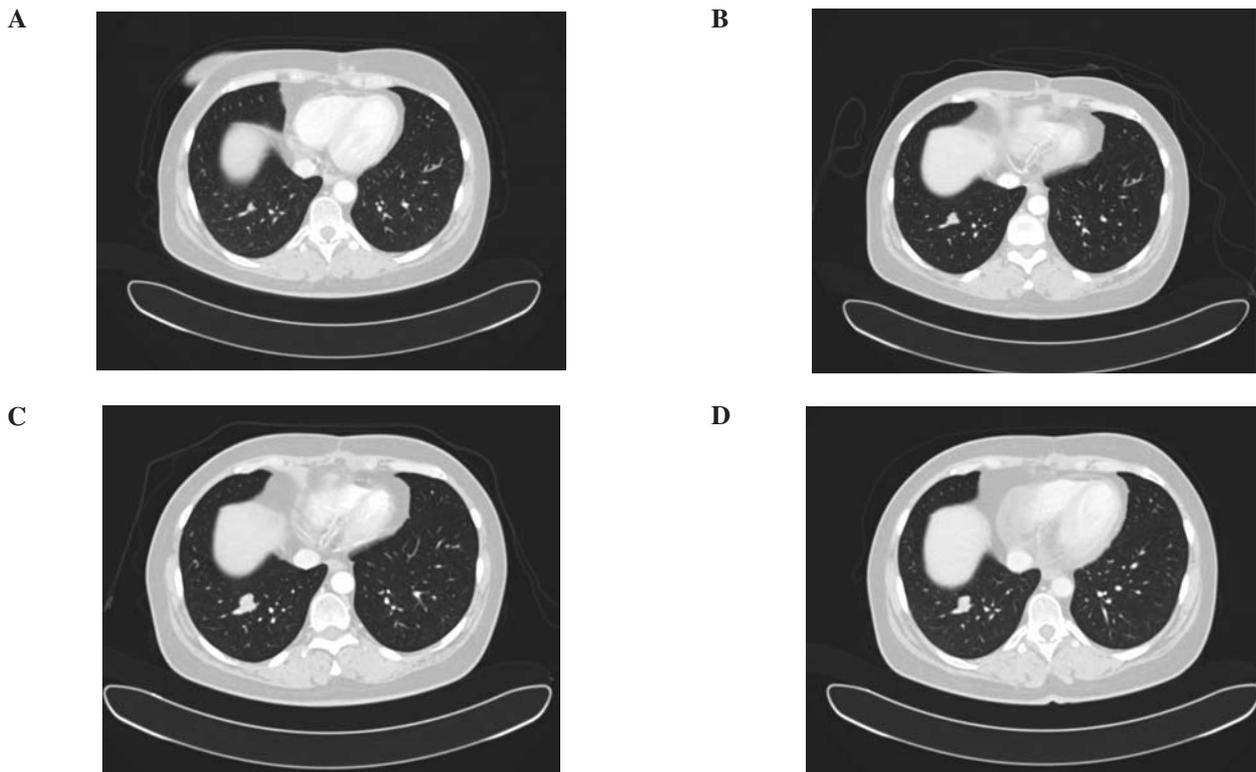


Figure 2. (A) February 2009: a nodular image at the right low lobe was observed, but was not suspected to be a lung lesion because of the small tumor diameter (5 mm). (B) July 2009: a mild dimensional increase of the known lung nodule was observed (9 vs. 5 mm). (C) November 2009: an additional increase in the lung lesion diameter was observed (13 vs. 9 mm). (D) February 2010: at the last computed tomography evaluation, the patient was found to have stable disease.

continued on imatinib and his most recent CT evaluation showed stable disease (Fig. 1E).

Case 2. In 2004, a 54-year-old female underwent ileal resection for a high-risk ileal GIST associated with limited peritoneal carcinomatosis. The kinase genotyping revealed a deletion mutation (c.1657_1674del p.Y553_K558del) in exon 11 of c-KIT. The patient underwent multidisciplinary treatment with surgery and several tyrosine kinase inhibitors. In December 2008, CT/PET revealed pelvic relapse. Two months later, a small nodular image in the right lower lobe

was observed by CT evaluation, but was not suggestive of lung metastasis due to its small size (Fig. 2A). In July 2009, while the patient was being treated with sunitinib (Sutent®, Pfizer, Inc., New York, NY, USA), a slight increase in lung nodule size was measured (9 mm compared to 5 mm). In November 2009, a further increase (13 vs. 9 mm) was noted, concurrent with pelvic lesions (Fig. 2B and C). Therefore, the patient began third-line treatment with the novel agent nilotinib, (AMN107; Tasigna®, Novartis Pharmaceuticals Corp.) and exhibited stable disease at the time of the most recent CT scan (Fig. 2D).

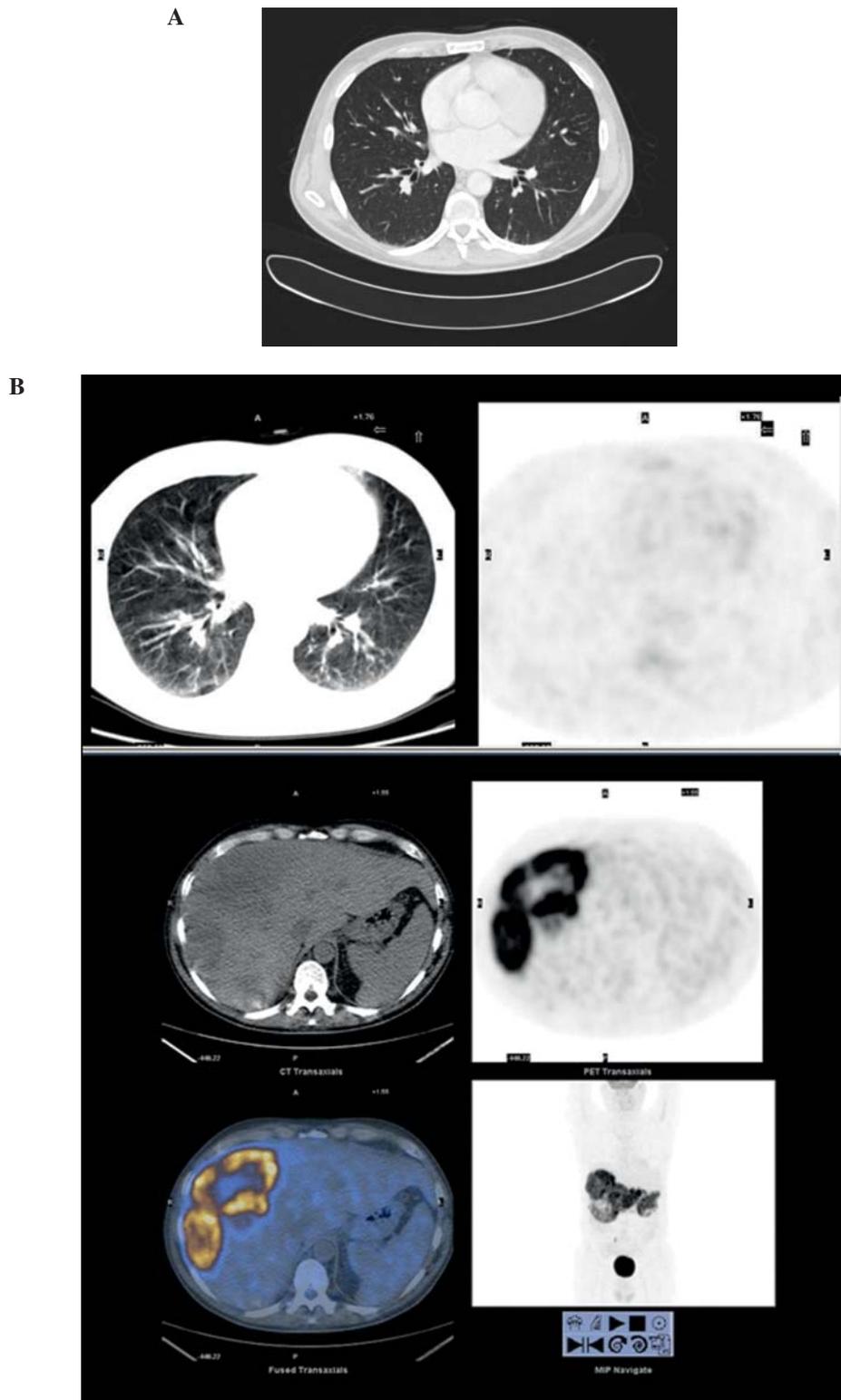


Figure 3. A and B. Computed tomography.

Case 3. In July 2008, a 44-year-old male underwent digiunal resection of a high-risk GIST. The kinase genotype revealed no c-KIT or PDGFRA mutations (WT). The patient was not treated with adjuvant imatinib because the disease was initially diagnosed as leiomyoma. In March 2009, a multifocal liver relapse occurred, and he underwent treatment with 400 mg daily imatinib, which was increased to 800 mg after disease progression. Six months later, CT revealed stable

hepatic disease with a millimetric micronodule in the middle lobe, which was not believed to be pathologic due its small size (Fig. 3A). Subsequent CT/PET confirmed the metabolic stability of the hepatic lesions, which displayed no ^{18}F -fluorodeoxyglucose (FDG) uptake in the pulmonary region (Fig. 3B). In November 2009, CT revealed an increased lung nodule diameter (6 vs. 2 mm), but the CT/PET findings remained negative (Fig. 3C). Due to clinical disease progres-

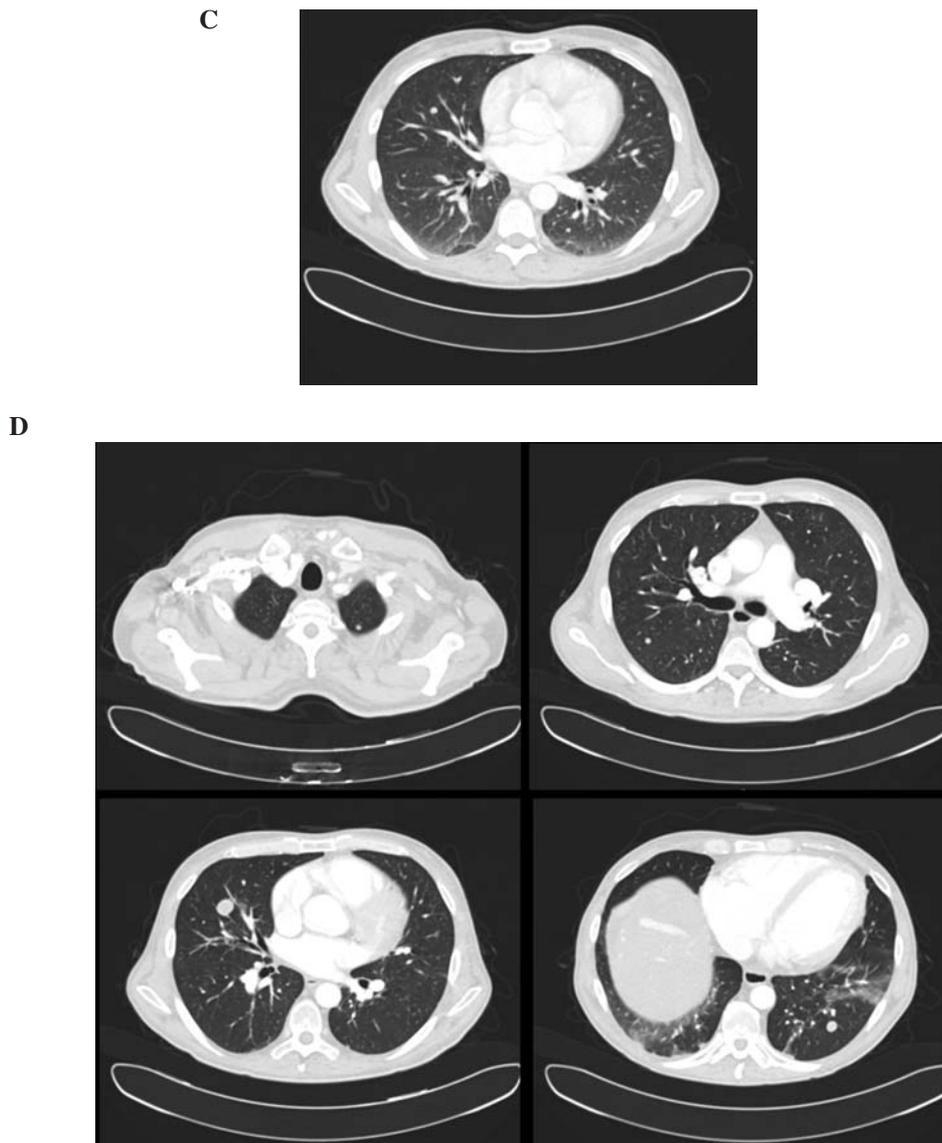


Figure 3. (A) Computed tomography (CT) taken in September 2009 revealed a micronodule at the middle lobe, which was not believed to be pathologic due to the small diameter of the tumor (2 mm). (B) September 2009: computed tomography/positron emission tomography (CT/PET) confirmed the metabolic stability of the hepatic lesions, revealing minimal ^{18}F -fluorodeoxyglucose uptake in the pulmonary region. (C) November 2009: CT revealed an increase in the lung nodule diameter (6 vs. 2 mm). (D) March 2010: CT evaluation showed an increase in the number and diameter of the lung lesions.

sion, the patient began second-line therapy with 37.5 mg daily sunitinib, but after three months of treatment the CT evaluation showed an increase in the number and diameter of the lung lesions (Fig. 3D). He is scheduled to begin third-line treatment with nilotinib.

Case 4. In 2005 a 28-year-old female was diagnosed with GIST of the stomach with liver and lung metastases, and was sequentially treated with imatinib and sunitinib. In 2007, she underwent total gastrectomy due to bleeding of the primary lesion. Histological examination confirmed that the metastases were WT and were derived from the primary lesion. The bilateral lung lesions and the liver metastases remained stable for five years, as monitored by CT and CT/PET (Fig. 4A-C). The patient was being treated with nilotinib and exhibited stable disease at the most recent CT evaluation (Fig. 4C).

Discussion

The liver and peritoneum are the most frequent metastatic sites of gastrointestinal stromal tumors (GISTs) (6), but lung metastases from GISTs are relatively rare. The aim of the present case study was to describe the clinical, radiological, and molecular aspects of lung metastases arising from GISTs.

Clinically, lung metastases are asymptomatic due to their small size and intra-parenchymal distribution, and are frequently diagnosed as occasional findings. These lesions form as micronodules without initial pathologic significance, and may grow slowly (cases 2 and 3) or remain stable over longer periods (cases 1 and 4). In addition, these lung metastases do not appear to be associated with pathological mediastinal or hilar lymph nodes, as evidenced by the low frequency of GIST dissemination to the lymph nodes. Furthermore, there appeared to be no correlation between the

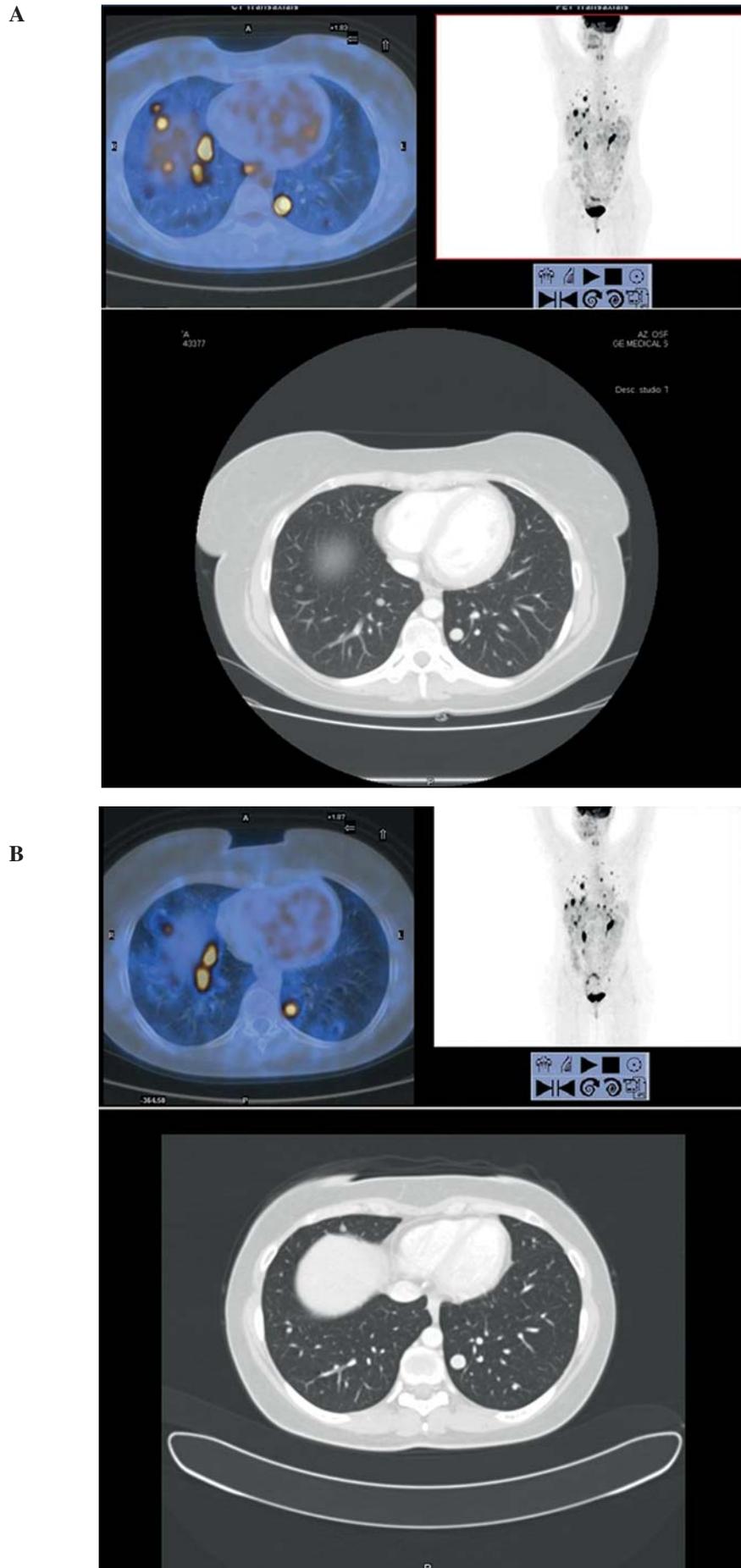


Figure 4. A and B. Bilateral lung lesions and liver metastases were observed at the time of patient diagnosis exhibiting positive computed tomography/positron emission tomography.

C



Figure 4. (A) Bilateral lung lesions and liver metastases were observed at the time of patient diagnosis exhibiting positive computed tomography/positron emission tomography (CT/PET) findings. (B) The lung lesions remained stable for five years as monitored by CT, and exhibited persistent CT/PET positivity, even throughout treatment. (C) At the time of the most recent CT evaluation, stable disease was observed.

risk of lung metastases and the site of the primary tumor, and lung metastases were frequently associated with other more common sites of relapse.

Radiologically, lung metastases have a well-defined CT pattern at the time of patient presentation. Lung lesions in all of the present patients were nodules characterized by a regular profile, were extremely hyperdense after contrast uptake, and had no intralesional areas of necrosis, even in patients with more a durable response to treatment. While the features of lung metastases were homogeneous on CT, CT/PET findings varied between patients and between metastatic lesions in the same patient. CT/PET revealed FDG uptake in lung and liver lesions in patient 1. However, patients 2 and 3 exhibited consistently negative FDG uptake in lung lesions and positive uptake by the liver metastases. This suggests that CT/PET scans may not be the optimal method to diagnose and stage GISTs (13,14). The lack of FDG uptake may be related to the slow growth rate and small size of the lesions, suggesting that GIST lung metastases have a low intrinsic metabolism and a low biologic aggressiveness compared with the primary tumor or metastases at other sites. There is a positive relationship between FDG uptake and the Ki-67 proliferation index in non-small cell lung cancer, suggesting that differences in tumor cell proliferation are consistent with differences in tumor glucose metabolism (15). We found that the difference in FDG uptake between the primary tumor and the lung metastases (standardized uptake volume, $SUV_{max} = 55.1$ vs. 9.0, respectively) in patient 4 correlated with the difference in the Ki-67 proliferation index for these two lesions (12.5 and 5%, respectively). Because of potential limitations of FDG-CT/PET for the diagnosis of GIST lung metastases due to variations in tumor size or biological limits, other PET tracers that specifically target cell proliferation, such as 18F-fluorodeoxythymidine (FLT), may have higher diagnostic sensitivity (16).

Lung metastases appear to respond differently to treatment than liver and peritoneal metastases, regardless of primary tumor c-KIT- and PDGFRA molecular status. The radiological hallmark of the metastatic lesions after tyrosine kinase inhibitors in our patients was hyperdensity without necrotic areas. Patient 1 had a pulmonary partial response after three months of treatment with imatinib, but the lung lesion was reduced in size and maintained a consistent radio-

logical pattern without the typical signs of intralesional tumor response. This finding is inconsistent with the consolidated concept of response evaluation to target therapies. Non-cytotoxic drugs do not initially cause reduction in tumor volume, and in fact can lead to a paradoxical size increase due to necrosis. Therefore, tumor response evaluation is based both on intralesional density variation and changes in tumor diameter. The lack of observed density variation is inconsistent with the Choi criteria for the evaluation of response to TK-inhibitors (17,18). Patient 1 exhibited predictable CT/PET density findings during imatinib therapy due to reduced FDG uptake, whereas patient 4 showed a longer-term positivity of lung metastases, even during treatment. In general, lung metastases were more stable throughout tyrosine kinase inhibitor treatment, which was most likely due to the indolent behavior of these tumors. We do not yet have sufficient data to correlate KIT and PDGFRA genotypes to clinical responses to tyrosine kinase inhibitors. Two patients had a primary GIST with a WT mutational status, and the remaining two patients exhibited c-KIT exon 11 mutations. Kinase genotyping could only be performed in patient 4, whose primary and metastatic tumors were classified as WT for KIT and PDGFRA.

Recently, the presence of lung metastases in the absence of liver metastases was suggested to be an independent predictor of initial resistance to imatinib in patients with GIST (19). However, lung metastases did not affect the initial tumor response in patients with an external confirmation of GIST diagnosis, with the exception of misdiagnosed sarcomas that are notoriously unresponsive to imatinib (19). Although none of our patients presented with GIST metastases only to the lung, the small number of patients, the long natural history (cases 2 and 4), and the WT molecular profile (cases 3 and 4) may explain the limited clinical response to standard tyrosine kinase inhibitors. No conclusions may be drawn regarding secondary resistance, which appears to be a late event. The management of GIST lung metastases remains difficult because of multiple, bilateral and other associated non-resectable metastases. However, the low aggressiveness and lack of concomitant lymphatic spread suggest that surgery or other loco-regional treatments could be considered in cases of lesions confined to the lung, or in cases of resectable and responsive metastatic disease.

Although lung metastases are relatively rare in patients with GIST, they may become more prevalent due to the increase in patient life expectancy. It remains unclear whether there is a specific molecular profile that can predict whether a patient is at risk for these lung metastases. Novel molecular technologies and larger retrospective multicenter studies are needed to determine the best treatment for patients with lung metastases derived from primary GISTs.

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