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Significant Radiologic Response of Pancreatic Metastasis After Targeted Therapy of Ceritinib (LDK378) for *ALK*-Rearranged Lung Adenocarcinoma Presenting With Hyperglycemia

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Pancreatic metastasis from non-small cell lung cancer (NSCLC) is usually asymptomatic or presents with abdominal pain, acute pancreatitis, or jaundice. A lung primary is associated with worse survival compared to pancreatic metastases from other organs. Surgical treatment of solitary metastasis to the pancreas from NSCLC has been reviewed in several studies, one of which had a notable disease-free interval. To our knowledge, there are no prior reports of targeted therapy of pancreatic metastasis of NSCLC followed by a significant response. Herein we report the case of a 31-year-old female with a solitary pancreatic metastasis from *ALK*-rearranged lung adenocarcinoma despite treatment with chemotherapy and crizotinib; she presented with symptoms of hyperglycemia. Targeted therapy with ceritinib (LDK378) led to symptomatic improvement and a significant radiologic response in the lung and pancreas, but not in the brain.

Key Words: Pancreatic metastasis; ALK; Lung cancer; Ceritinib; LDK378

INTRODUCTION

A series of retrospective research studies reported metastasis to the pancreas from other cancers including non-small cell lung cancer (NSCLC) (1–5). Secondary pancreatic cancer is usually asymptomatic or presents with abdominal pain, acute pancreatitis, or jaundice (3–9). NSCLC is a poor prognostic factor in metastatic tumors of the pancreas, with a worse survival compared to pancreatic metastases from other organs, including renal cell cancer (9). Surgical treatment of a solitary metastasis to the pancreas from NSCLC has been reviewed in several studies, some with a notable disease-free interval (8–10). To our knowledge, there are no prior reports of targeted therapy of pancreatic metastasis of NSCLC followed by a significant response. Herein we present the case of a patient with pancreatic metastasis from *ALK*-rearranged lung adenocarcinoma who presented with symptoms of hyperglycemia and received symptom improvement and a significant radiologic response in the lung and pancreas after targeted therapy with ceritinib (LDK378; Novartis Pharmaceuticals).

CASE REPORT

A 31-year-old female went to a local hospital for a persistent cough in January 2013. At this local hospital, she was evaluated with a chest computed tomography (CT) scan that revealed a lesion in the left lobe with multiple metastatic lesions on both sides and enlarged lymph nodes in the left hilum and mediastinum. An abdominal CT scan and a brain magnetic resonance imaging (MRI) were also performed, and both demonstrated no abnormalities. A bronchoscopic biopsy confirmed the pathological diagnosis of adenocarcinoma; however, targetable driver mutations were not tested due to the availability of limited biopsy tissue.

The patient initially received two chemotherapy regimens with GP (gemcitabine 1,250 mg/m^2 D1, 8; cisplatin 75 mg/m^2 divided into D1–2) in January 2013 and February 2013. In March 2013, her treatment was empirically changed to gefitinib, an *EGFR*-targeted drug for lung cancer, due to the presence of new metastatic brain lesions revealed by MRI. One month later, although the therapeutic response was assessed as stable disease (SD) according to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST1.1), the size of the lung tumors continued to increase. Considering the lack of *EGFR* mutation and other driver mutation tests, the treatment was changed to PP (pemetrexed 500 mg/m^2 D1; cisplatin 75 mg/m^2 divided into D1–2) chemotherapy in April 2013.

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At this time, a CT-guided lung biopsy was conducted, and *ALK* rearrangements were confirmed in the biopsy tissue by fluorescence in situ hybridization (FISH). After two cycles of PP, she was found to have progressive disease (PD) given the presence of enlarged brain lesions and multiple new metastatic lesions in the liver. The patient was then treated with *ALK*-targeted therapy with crizotinib (250 mg oral BID), which was available from Hong Kong since June 2013. The tumor assessment in December 2013 was PD due to enlargement of tumor size in both the lung and brain. However, because of chemotherapy intolerance, the patient continued crizotinib therapy, and she received whole-brain radiotherapy in December 2013. The fasting plasma glucose and the carcinoembryonic antigen (CEA) levels were tested several times, and both were in the normal range since the time of diagnosis. In April 2014, the patient was admitted to our hospital for progressive symptoms of fatigue, cough, dyspnea, and occasional blood-tinged sputum. At the time of admission, her fasting plasma glucose was 14.0 mmol/L, and HbA1c was 9.4% (normal range: 4.2%–6.2%), and the patient noted symptoms of persistent thirst and polyuria. A contrast CT scan of the abdomen demonstrated a solitary hypodense mass compared to the normal enhanced pancreas in the body of the pancreas with contraction of the pancreatic tail and expansion of the pancreatic duct (Fig. 1a–d). An abdominal CT revealed multiple low-density foci in the liver and multiple soft tissue density lesions around the mesentery and ovaries bilaterally. Multiple lesions in the lung and brain were also seen on a chest CT scan (Fig. 2a–d) and brain MRI scan (Fig. 3a and b), respectively. The patient was diagnosed with PD involving the brain, liver, and pancreas. In consideration of the patient's drug resistance to crizotinib and unsuitability for surgery, she was enrolled in a clinical trial of ceritinib (LDK378, CLDK378A2109), which is another *ALK*-targeted medicine; she received the treatment with LDK378 (750 mg oral QD) beginning in April 2014. The therapeutic response after 12 weeks of treatment was assessed as a partial response (PR) because of

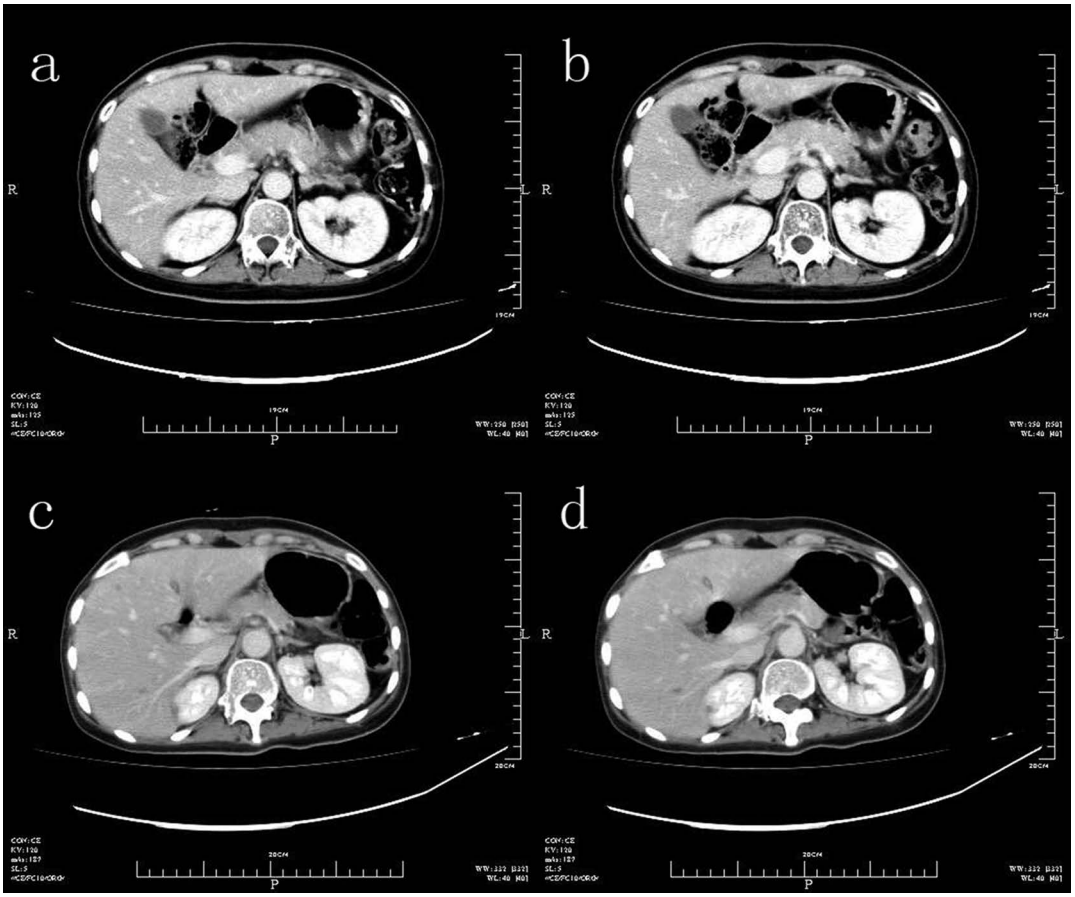

Figure 1. Computed tomography (CT) scan of abdomen revealed a solitary hypodensity area compared to the normal enhanced pancreas in the body of the pancreas. Before treatment with ceritinib (a, b) the metastatic lesion was 2.5×1.5 cm, while after 12 weeks of treatment with ceritinib it was about 0.8 cm (c, d).

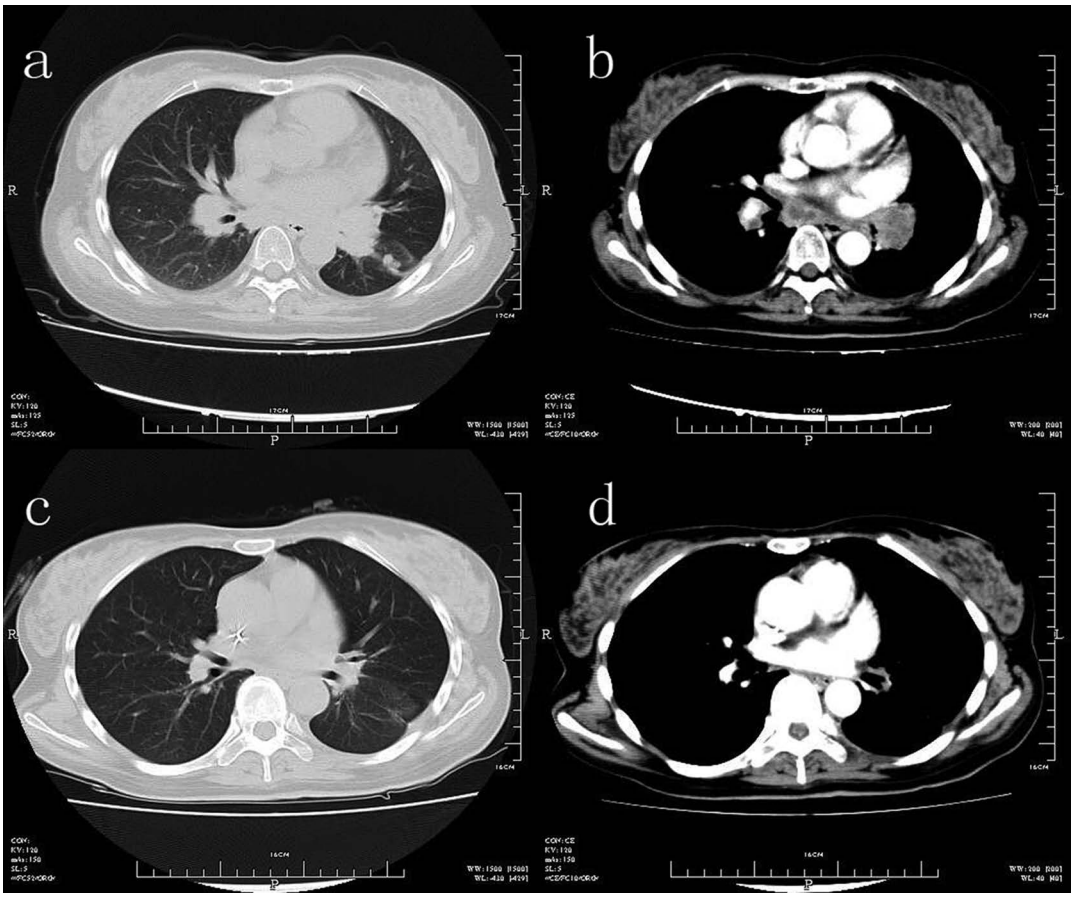

Figure 2. CT scan of the chest revealed a lobulated nodular lesion in the left lobe with enlargement of mediastinal lymph nodes (a, b); both the nodular lesion and the lymph nodes were reduced in size after 12 weeks of treatment with ceritinib (c, d).

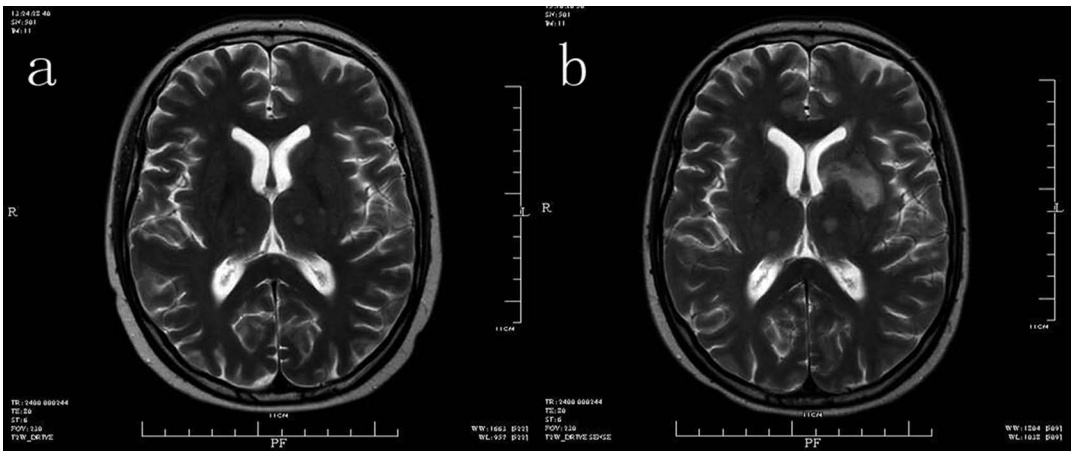

Figure 3. MRI scan of the brain revealed multiple hyperintense metastatic lesions on T2WI (a); the metastatic lesions were significantly enlarged after 24 weeks of treatment with ceritinib (b).

the significantly diminished lesions in the lung and pancreas (Figs. 1 and 2), but stable in the brain lesions. After 24 weeks of treatment with ceritinib (LDK378), she was assessed as having PD due to the increasing number of lesions in the brain (Fig. 3). From October 2014, because of headache secondary to the brain metastases, the patient was unable to return to the hospital for further follow-up and treatment, and she passed away in November 2014.

DISCUSSION

Herein we present a rare case of a woman with pancreatic metastasis from *ALK*-rearranged lung adenocarcinoma who presented with hyperglycemia symptoms and received significant radiologic response after *ALK*-targeted therapy with ceritinib (LDK378). On the basis of a series of retrospective studies that reported metastasis to the pancreas from other cancers including lung cancer, metastatic NSCLC to the pancreas is not as rare as one might think (1–5). Early in 1985, Cubilla and Fitzgerald reported that NSCLC was the primary source of metastatic disease in the pancreas, accounting for 18.8% (49/261) of all metastases (1). This was second in frequency only to breast cancer (19.5%, 51/261). Another review of 1,740 cases from Japan examined 103 cases of secondary pancreatic malignancies, 17.4% (18/103) of these cases had spread from the lung, which ranked second in frequency to metastases from stomach cancer (20.4%, 21/103) (2). In addition, several studies demonstrated the clinical, radiological, and pathological characteristics and the prognosis of secondary pancreatic malignancies, including those from lung cancer (2–5).

In this particular case, the patient experienced symptoms of hyperglycemia that were ignored at first; in fact, symptoms of pancreatic metastases are often nonspecific and subtle. In the review by Mourra et al. (6), 8 of 12 patients were asymptomatic, and metastases were found by routine surveillance imaging for primary lesions. A review of isolated metastases to the pancreas revealed that 43% of patients, which account for the largest group, were asymptomatic at the time of diagnosis (7). For patients with symptoms, the most common symptoms are abdominal pain (24%), jaundice (22%), and gastrointestinal bleeding (10%). In reported cases of pancreatic metastases from the lung, asymptomatic patients were also the most common (3,5–6,10–12). Patients with lung cancer also presented with acute pancreatitis (13–15) or abdominal pain (6,16) as the symptoms of metastasis to the pancreas in some other reports.

Shi et al. analyzed the CT features of seven pancreatic metastases from lung cancer and revealed that solitary lesions (6/7), located in the pancreatic tail (4/7) and small in size (1.1–3.0 cm), were often seen. The study also highlighted the CT imaging spectrum of pancreatic metastases from lung cancer; small, hypodense, or isodense masses were seen on unenhanced CT, and in terms of the enhancement pattern, the lesions had a hypoattenuated appearance compared to the normal enhanced pancreas (5). Furthermore, local pancreatic infiltration with mild enhancement instead of a focal mass was seen in one lesion, and peripheral rim enhancement was seen in two lesions of pancreatic metastases from lung cancer in their study (5). The patient in our study presented with a solitary hypodense area in the body of the pancreas compared to the normal enhanced pancreas, which was partly consistent with the study by Shi et al.

There is a case report of a patient who underwent resection of solitary pancreatic metastatic lesions from lung cancer and had a disease-free interval for nearly 2 years (8). However, in a review of prognostic factors of metastatic tumors of the pancreas, metastasis from lung cancer ($p = 0.002$) was associated with worse survival compared with pancreatic metastasis from renal cell cancer (9). In that review, the median survival of patients with metastatic lung cancer to the pancreas was approximately 5 months, compared with 12 months or longer for those with renal cell carcinoma (9). To our knowledge, there are no reports concerning the efficacy of targeted therapy on pancreatic metastasis from lung cancer.

The development of epidermal growth factor receptor (EGFR)-targeted tyrosine kinase (TKI) inhibitors has led to targeted therapies for NSCLC. It was reported that patients harboring EGFR-activating mutations and administered TKI therapy had better objective response rate (ORR) and longer progression-free survival (PFS) (17). The *ALK* rearrangement was discovered in NSCLC in 2007 (18). Crizotinib (Xalkori; Pfizer) is a first-in-class ALK inhibitor that works by competing with adenosine triphosphate (ATP) for binding to the tyrosine kinase pocket of ALK resulting in its anticancer effect (19–21). In the clinical trials of crizotinib in *ALK*-rearranged NSCLC, the median PFS was 7.7–8.1 months, which was significantly prolonged compared to the PFS associated with chemotherapy (21,22). However, approximately one third of patients treated with crizotinib inevitably relapse within 12 months (23,24). Furthermore, crizotinib cannot penetrate the blood–brain barrier in patients with central nervous system (CNS) metastasis (25,26). Ceritinib (LDK378) is a novel, selective small-molecule ATP-competitive second-generation ALK inhibitor, which acts not only in crizotinib-sensitive tumors but also in crizotinib-resistant tumors in xenograft models of *ALK*-rearranged NSCLC (27). Ceritinib (LDK378) can penetrate the blood–brain barrier to overcome the CNS resistance observed with crizotinib. In the phase I clinical trial of ceritinib (LDK378) in patients with *ALK* rearrangement, the median PFS was 6.9 months (95% CI, 5.3–8.8) for 80 patients who had previously received crizotinib, and the median PFS was 10.4 months (95% CI,

4.6 to could not be estimated) for 34 patients who had not previously received crizotinib (28). A pronounced response to ceritinib (LDK378) was also observed in 64 patients with CNS metastases at baseline. Tumor shrinkage was seen in patients with brain metastases with (50%; 95% CI, 39.7–60.3%) and without (69.2%; 95% CI, 48.2%–85.7%) prior ALK-TKI treatment (28). In a multi-institutional study, patients with brain metastases from ALK-rearranged NSCLC treated with radiotherapy and TKIs have significant prolonged survival (29). In our report, the patient with pancreatic and brain metastases from the lung showed a distinct response to ceritinib in the pancreas and lung, but the CNS disease continued to progress after brain radiotherapy. We believe the mechanism of CNS resistance to ceritinib (LDK378) may be related to issues of the blood–brain barrier or the genetic status of the brain metastases.

CONCLUSION

It is important to note that symptoms of pancreatic metastases from NSCLC are often nonspecific. As such, clinicians need to pay closer attention to subtle symptoms, such as those of hyperglycemia, and routine surveillance CT scan imaging for primary and secondary lesions needs to be performed. Second, surgical resection of metastatic lesions is uncommon, especially in patients with multiple-organ metastases. Our case illustrates the importance of targeted therapy. If a patient is diagnosed with NSCLC, the detection of driver mutations such as *EGFR*, *ALK*, and *ROS1* is necessary in tissues of the primary or secondary lesions for proceeding with treatment. This approach can result in an unexpected significant response of not only the primary disease but also metastases, thus possibly prolonging patient survival.

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