ANTICANCER RESEARCH *40*: 4401-4404 (2020)
doi:10.21873/anticanres.14444

EGFR Mutated Lung Adenocarcinoma Metastasis to the Pancreas Mimicking Primary Pancreatic Ductal Carcinoma

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Abstract. *Background: The occurrence of lung adenocarcinoma metastasizing to the pancreas is overall rare and can histologically imitate primary pancreatic ductal carcinoma (PDAC). Case Report: This is a case report of a 70-year-old female with a history of surgically resected right lung adenocarcinoma presenting for routine follow up without symptoms. CT scans revealed a pancreatic cystic mass with ductal dilatation that was sampled via endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and thought to be a primary pancreatic mucinous neoplasm with high grade dysplasia suspicious for carcinoma based on smear cytology. On repeat EUS-FNA and biopsy (FNB) with additional immunohistochemical testing for lung adenocarcinoma markers thyroid transcription factor (TTF1) and Napsin A and molecular testing, the lesion was identified as a metastasis of lung adenocarcinoma with an epidermal growth factor receptor (EGFR L858R) mutation; subsequently, the patient underwent targeted therapy that yielded an almost complete response. Conclusion: To the best of our knowledge, this is the first documented case in English literature of a lung adenocarcinoma metastasis to the pancreas mimicking a pancreatic primary neoplasm and highlights the potential pitfalls of EUS-FNA for the diagnosis of certain metastases to the pancreas.*

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Key Words: Epidermal growth factor receptor (*EGFR*) mutation, lung adenocarcinoma, pancreatic ductal carcinoma, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and biopsy (FNB), immunohistochemistry.

In the USA, approximately a quarter-million new lung cancer cases occur annually, making it one of the most common cancer diagnoses (1, 2). Pancreatic cancer, typically occurring as pancreatic ductal carcinoma (PDAC), occurs much less frequently in comparison, with about 58,000 new cases per year (2). Rarer still than a primary pancreatic tumour is lung cancer metastasizing to the pancreas; previous literature suggests less than 1% of metastatic non-small cell lung cancers will involve the pancreas (3). The potential for misdiagnosis is thus high, given that a lung metastasis can appear morphologically similar to a primary pancreatic cancer. Herein, we report a case of a 70-year-old woman with a history of lung adenocarcinoma presenting with a pancreatic lesion initially suspected to be a pancreatic primary but was ultimately diagnosed as metastatic lung cancer. Diagnosis, treatment, and prognosis are discussed.

Case Report

A 70-year-old Asian-American female with a history of fully resected right lung adenocarcinoma, osteopenia, gastroesophageal reflux disease (GERD), and a family history of lymphoma, presented to a routine follow-up for lung cancer monitoring without major symptoms after completing surgery and chemotherapy. Subsequent computed tomography (CT) scans (Figure 1) identified a 0.6 cm hypodense pancreatic cystic mass with distal ductal dilation, suspicious of intraductal papillary mucinous neoplasm (IPMN) of the pancreas. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was performed on the lesion with smears (Figure 2) showing clusters of atypical epithelial cells in the background of normal pancreatic duct epithelium and thin mucinous material. Cytological features were compatible with a primary pancreatic mucinous neoplasm with high grade dysplasia and possible adenocarcinoma, implying a possible pancreatic ductal carcinoma could not be excluded.

Follow-up CT revealed that the pancreatic lesion was growing, prompting an additional endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB). The specimen was processed into cell blocks for hematoxylin and eosin (H&E) staining (Figure 3A and B) and immunostaining (Figure 3C and D). These stainings revealed that the tumor cells were positive for lung adenocarcinoma markers TTF1 (Figure 3C) and Napsin A (Figure 3D) and were morphologically similar to the patient's prior lung adenocarcinoma. These findings thus supported the diagnosis of metastatic lung adenocarcinoma involving the pancreas over a metachronous pancreatic primary tumor.

Molecular tests were also performed on the cell blocks and demonstrated a mutation in the epithelial growth factor receptor (*EGFR* L858R). Additional magnetic resonance imaging (MRI) and CT scans uncovered a solitary, peripherally-enhancing brain lesion measuring 5-6 mm that was suspicious for metastasis.

Based on the updated diagnosis and identification of the *EGFR* mutation, the patient began targeted oral therapy. Initially, the patient went on erlotinib as part of a study, but discontinued this therapy due to poor tolerance. The patient was then treated with osimeritinib (Tagrisso) 80 mg daily with more success. Follow-up imaging studies demonstrated that the brain lesion responded well to treatment, reducing in size from 5-6 mm to 2 mm. Positron emission tomography (PET)/CT scans of the pancreas showed no overtly suspicious lesions, implying the neoplasm regressed with the treatment. Interestingly, the imaging also revealed that the region of the previously identified pancreatic lesion had very low-grade background uptake in contrast to the patient's previous lung cancer, which was strongly hypermetabolic. Overall, the patient prognosis on targeted therapy has been positive.

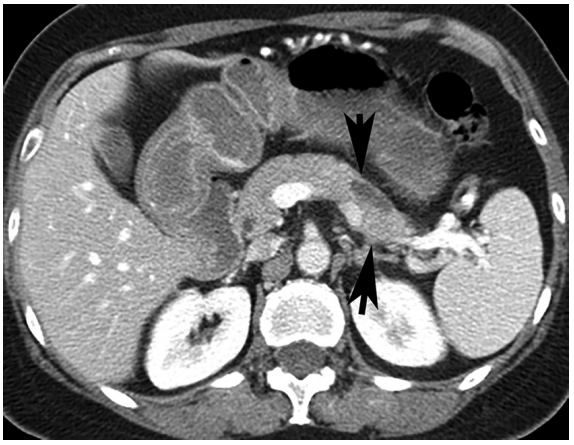

Figure 1. *Axial computed tomography scan showing a distal pancreatic lesion (arrows) with cystic changes and ductal dilatation.*

Discussion

In cases of surgically resected lung adenocarcinoma, metastatic lesions most often arise in the brain, bone, or liver; previous literature suggests that metastasis to other organ sites occurs in less than 5% of the cases, with less than 1% of cases involving the pancreas (3, 4). Thus, an important diagnostic challenge in patients with a history of lung cancer is differentiating metastatic disease in the pancreas from a pancreatic primary.

The majority of primary pancreatic cancers are PDAC, a ductal neoplasm associated with a strongly desmoplastic stroma histologically (5). EUS-FNA is commonly performed on pancreatic lesions pre-operatively to confirm cancer diagnoses, especially for PDAC (6). While highly sensitive for ruling out benign or low-grade pancreatic lesions, EUS-FNA without immunostain has limited ability to differentiate PDAC from metastatic lesions with similar cytologic features. As seen in this case, the patient's lesion was initially identified as a probable pancreatic primary, and since no cell block was made, the less common diagnosis of lung metastasis could not be made.

Accurately diagnosing pancreatic lesions has major implications for subsequent clinical management. In patients with PDAC, surgical resection is the primary consideration as it is the only curative treatment for this otherwise highly lethal tumor (7). For patients with metastatic lung adenocarcinomas, drug therapies are preferred to surgical intervention and molecular testing is especially important to determine if targeted therapies can be used (8).

In this case, the patient's growing pancreatic lesion and history of lung adenocarcinoma implied a lung metastasis could not be ruled out, prompting a second EUS-FNB so that immunohistochemical staining for TTF and Napsin A could be performed to obtain a differential diagnosis. Once metastasis was confirmed, molecular testing was done and showed an oncogenic mutation in *EGFR*, an epithelial cell membrane receptor whose downstream signaling regulates cell growth (8). This led to treatment with osimeritinib, a third generation TKI targeting the EGFR signaling pathway. After a month of therapy, PET/CT and MRI demonstrated that the pancreatic and brain lesions both regressed, demonstrating overall effectiveness of the non-surgical intervention in this patient.

In summary, this report documents a rare case of a fully resected lung adenocarcinoma later metastasizing to the pancreas and mimicking a primary pancreatic ductal carcinoma in a 70-year old female. While initially suspicious for a primary pancreatic mucinous neoplasm with high grade dysplasia suspicious for carcinoma based on imaging and the initial EUS-FNA without immunostaining, a subsequent EUS-FNB along with specific immunostaining for lung markers TTF and Napsin A confirmed lung metastasis.

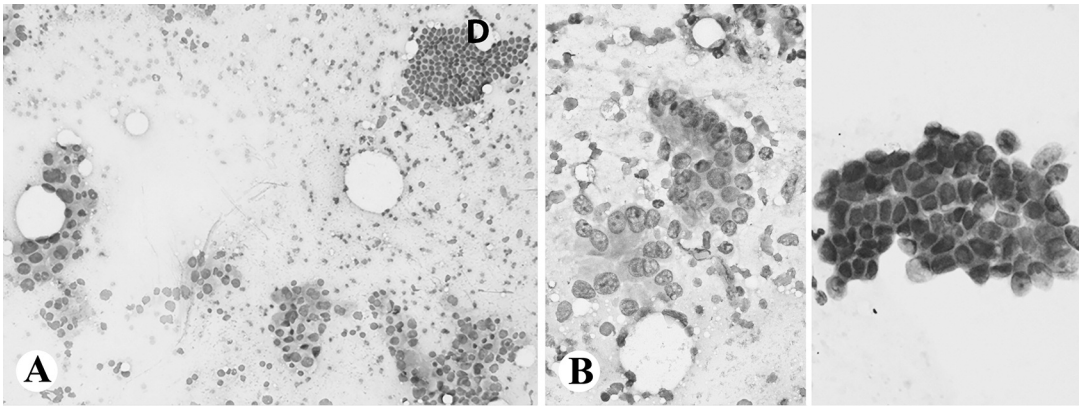

Figure 2. *Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) cytopathology of the pancreatic lesion showing normal pancreatic ductal epithelium (D) and clusters of atypical epithelial cells mimicking pancreatic ductal carcinoma (Diff-Quik stain, A and B left; Papanicolaou stain, B right) (A, 100×; B, 400×).*

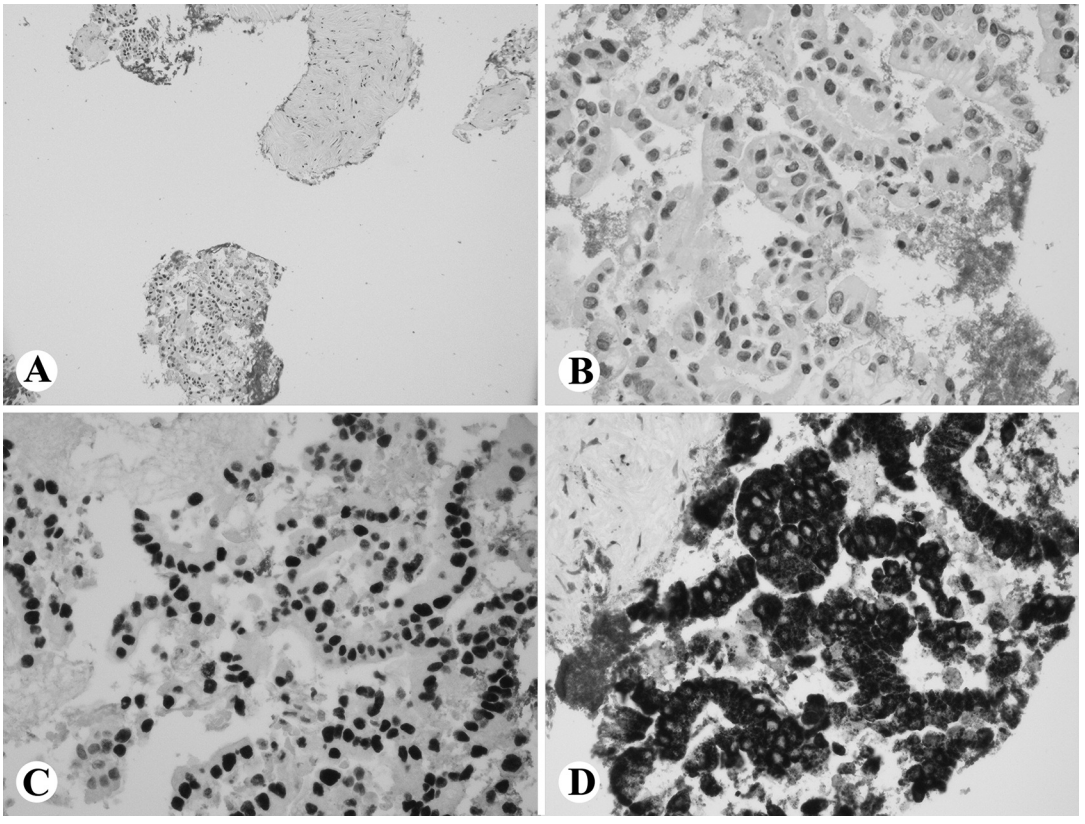

Figure 3. *Endoscopic ultrasound guided fine needle aspiration and biopsy (EUS-FNAB) showing clusters of atypical epithelial proliferation in a background of fibrotic tissue (A and B, H&E stain). Immunohistochemistry: the atypical epithelial cells are positive for TTF1 (C) and Napsin A (D) (A, 40×; B-D, 400×).*

Additional molecular studies further revealed the tumor's *EGFR* mutation, leading to precise targeted therapy. Overall, this case demonstrates a potential diagnostic pitfall of EUS-FNA in differentiating primary and metastatic pancreatic lesions with similar cytology. Careful review of the patient's cancer history was thus critical for determining the correct diagnostic testing, ultimately leading to improved treatment precision and positive patient outcomes.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this case report.

Author's Contributions

CC wrote the article; MXK and MK made the pathologic diagnoses; KM and AA performed the biopsies; QS reviewed the article; and JL made the diagnoses, collected and analyzed the data and finalized the manuscript. All Authors reviewed and approved the final article.

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Received June 13, 2020
Revised July 6, 2020
Accepted July 9, 2020