The tail of neuroendocrine tumors from lung to pancreas: Two rare case reports

Ashwin Soni a, Epameinondas Dogeas a, Krishna R. Juluri a, Christopher L. Wolfgang a, Ralph H. Hruban b, Matthew J. Weiss c,∗

a Department of Surgery, The Johns Hopkins Hospital, Baltimore, MD, USA
b Department of Pathology, Sol Goodman Pancreatic Research Center, The Johns Hopkins Hospital, Baltimore, MD, USA

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A B S T R A C T
INTRODUCTION: Primary pancreatic neuroendocrine tumors are a well-established disease entity, however, neuroendocrine metastases to the pancreas from other sites have been scarcely documented. Specifically, pancreatic metastases from a pulmonary carcinoid tumor have only previously been described in a single case report.

PRESENTATION OF CASE: We sought to outline our institutional experience of two patients with pulmonary neuroendocrine tumors that developed metastases to the pancreas, confirmed by gross pathology and immunohistochemistry. In both cases, the pancreatic metastases were surgically resected and their pulmonary origin were discovered post-operatively.

DISCUSSION: Our findings should raise awareness to the possibility of metastatic disease when evaluating a pancreatic mass in a patient with a clinical history of pulmonary carcinoid tumor. Expert opinion on immunohistochimically differentiating a primary pancreatic neuroendocrine malignancy from a metastasis should be employed in these cases.

CONCLUSION: Establishing this diagnosis pre-operatively could affect the decision to proceed with surgical resection, given the morbidity of pancreatectomy and the unknown long-term clinical outcome of patients with pulmonary carcinoid tumors metastatic to the pancreas.

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1. Introduction

Neuroendocrine tumors (NETs) of the pancreas are rare, comprising 1–2% of all pancreatic malignancies.1 The vast majority of these are primary pancreatic malignancies, as metastases to the pancreas are rare, and metastases of neuroendocrine tumors from other primary sources to the pancreas are even rarer.

Pulmonary neuroendocrine tumors comprise 20–30% of all NETs and 11–14% of all lung cancers and are classified into four subtypes, typical and atypical carcinoid, small cell lung carcinoma and large cell neuroendocrine carcinoma.2,3 Depending on their degree of differentiation, these tumors have been well-documented to metastasize to intrathoracic lymph nodes, liver, central nervous system (CNS), skeletal bones, adrenals, and mammary glands.3 There are reports of pulmonary NETs rarely metastasizing to other rare locations. For example, Birker et al.4 published a case report of a metastasis to the testis from a primary NET of the lung. Choi et al.5 showed in a case report that atypical lung NETs in an asymptomatic patient can metastasize to the breast. We have only found one other case of metastatic NET to the pancreas arising from the lung in the literature.6

Similarly, in studies of carcinomas metastatic to the pancreas, pulmonary origin is rare. In an autopsy study of 1740 Japanese patients with 690 malignant tumors of non–primary pancreatic origin, Nakamura et al.7 found only 103 secondary pancreatic tumors, 17% of which originated from the lung, and none of which were NETs. Kim et al.8 performed a review of 371 patients with NETs from various sites, in which none of the pancreatic NETs had their origin in the lung.

2. Presentation of cases

2.1. Case report 1

A 58-year-old female presented to our clinic in June 2013 with an incidentally diagnosed pancreatic neuroendocrine tumor. She was previously enrolled in a clinical trial in 2011 for low dose Computed Tomography (CT) surveillance protocol for lung cancer. At that time, she was found to have a 1.4 cm carcinoid tumor of the right lung. She denied having carcinoid symptoms at the time, with the exception of occasional diarrhea. Reportedly, her urine
5-hydroxyindoleacetic acid (5-HIAA) was within normal limits. Of note, a somatostatin receptor scintigraphy performed at the time was negative. She underwent a thoracotomy with lobar resection of the carcinoid tumor, with post-operative follow-up CT scans at 6-month intervals. On the last scheduled surveillance in June 2013, an incidental 1 cm pancreatic tail mass was discovered. Endoscopic ultrasound (EUS) with biopsy of the tumor was performed with findings consistent with a pancreatic neuroendocrine tumor. The patient denied any symptoms suggestive of hormonal secretion by the tumor. A gallium scan was negative, though a positron emission tomography (PET) scan demonstrated increased uptake in the tumor area. A CT scan in our institution revealed a 3.4 cm × 2.1 cm area of hypotenuation in the pancreatic tail, best visualized on the arterial phase images, corresponding to the patient’s recent EUS and biopsy proven neuroendocrine tumor in the pancreatic tail (Fig. 1). Interestingly, the mass itself demonstrated no appreciable internal hypervascularity on the arterial phase, and moreover, it was relatively poorly defined. In addition, there was no evidence of distant metastatic disease or any suspicious lymphadenopathy.

The patient’s medical history was otherwise notable for breast cancer in 2001 and hypertriglyceridemia. The decision was made with the patient’s involvement, to have this mass surgically resected, and a distal pancreatectomy and splenectomy was performed.

The surgical pathology results demonstrated a neuroendocrine carcinoma (WHO grade 3), 1.9 cm in size, involving the pancreas and the peripancreatic tissue (Fig. 2). Multiple foci of vascular and perineural invasion were identified. Background pancreas showed pancreatic intraepithelial neoplasia, and twenty-three lymph nodes that were taken were negative for tumor. This neuroendocrine tumor in the pancreas was morphologically similar to the patient’s previous lung tumor. The neoplastic cells in the pancreas immunolabeled with antibodies to synaptophysin and chromogranin and were negative for TTF1 and PAX8, with a high Ki67 index of nearly 25%.

The pathology from the patient’s right lower lobe lung mass was reviewed, and it demonstrated atypical carcinoid (Grade 2 well-differentiated neuroendocrine neoplasm) measuring 1.4 cm with lymphovascular invasion. Focal necrosis was observed and up to five mitoses per 10 high power fields were identified. Resection margins were negative for the tumor. Submitted immunostains showed the neoplastic cells to be focally positive for TTF-1 and negative for CDX-2 and PAX-8, and a Ki-67 proliferation index of 8%.

To ensure that the lung was the primary source for the pancreatic NET, we had to rule out a metastasis from the patient’s previous breast cancer. A panel of breast cancer immunomarkers applied to the tumor in the pancreas demonstrated positive immunostaining for CK7, while stains for ER, PR, CK20, GATA-3, GCDFP and mammoglobin were all negative. This pattern suggests against a breast primary. Given the similar morphology and otherwise identical immunolabeling profiles, we would strongly favor that the lesion in the pancreas is a metastasis from the patient’s previous lung atypical carcinoid tumor.

2.2. Case report 2

The second case is a 59-year-old female of Ashkenazi descent, who was diagnosed with small cell lung cancer in 2003. Of note, the patient is germline BRCA2 mutation carrier. At that time, she was treated with a cisplatin-based chemotherapy regimen, lung irradiation, and partial prophylactic radiation to the brain at another hospital. In 2006, she was also diagnosed with Stage IIIC serous adenocarcinoma of the ovary, which was surgically managed and followed with 6 cycles of taxol and carboplatin chemotherapy. In subsequent follow-up, a rise in her CA-125 was noted, however, imaging studies have failed to demonstrate a definitive ovarian cancer recurrence. Imaging revealed an abnormality in the tail of the pancreas, and a positron emission tomography (PET) scan demonstrated uptake in this area. An endoscopic ultrasound and biopsy of this pancreatic tail lesion demonstrated neoplastic cells consistent with either a new primary or possibly metastatic disease from the lung.

A distal pancreatectomy, splenectomy, and paraortic lymphadenectomy were performed. Surgical pathology showed atypical neuroendocrine neoplasm, most consistent with a metastatic atypical carcinoid tumor, 2.5 cm in size, involving the parenchyma of the pancreas. Metastatic atypical neuroendocrine neoplasm was present in three of seventeen lymph nodes. Spleen and all margins were negative for tumor. The lesion was composed of spindle shaped neuroendocrine cells with an increased mitotic rate, which focally reached the threshold for atypical carcinoid (5–20 mitoses per 20 hpf). A panel of immunostains was performed, and the neoplasm in the pancreas was strongly positive for cytokeratin AE1/AE3, synaptophysin and chromogranin. While it was also positive labeling for somatostatin, this stain is known to have a very high background and it is challenging to identify how much of this labeling is specific. The neoplasm also weakly immunolabelled for TTF-1 and demonstrated a sustentacular pattern of labeling for S-100 protein. Stains for Ki-67 labeled approximately 5% of the neoplastic cells. Stains for insulin and glucagon were negative. This pattern
of labeling is most certainly consistent with an atypical carcinoid tumor of the lung metastatic to the pancreas.

3. Discussion

Our two cases establish the possibility of lung neuroendocrine tumors metastasizing to the pancreas, even years after the diagnosis of the primary lung tumor. Clinicians should consider this possibility when evaluating newly discovered pancreatic masses in patients with a history of lung neuroendocrine neoplasms. In our experience, endoscopic ultrasound with fine needle aspiration should be instrumental in the diagnostic evaluation of these patients, when technically feasible. Obtaining tissue diagnosis enables the comparison of the pancreatic mass’s morphologic characteristics and immunohistochemical profile to those of the previous lung NET. In particular, immunohistochemistry plays a vital role in differentiating primary pancreatic NET versus neuroendocrine metastasis and expert opinion on choosing and interpreting immunohistochemical markers should be sought. While the management of primary pancreatic neuroendocrine tumors is well outlined, there is scarcity of data on long-term outcomes of pancreatic neuroendocrine metastases from the lung.

Therefore, establishing this diagnosis pre-operatively could be instrumental in the treatment decision-making. Although surgical resection of the metastases was feasible in both of our cases and is likely to be technically feasible in the majority of similar cases in the absence of widespread disease, there are no published data describing long-term outcomes following resection of pulmonary neuroendocrine metastases to the pancreas. By definition, patients with lung NET metastases to the pancreas have systemic disease with likely micro-metastases present, but not yet clinically evident, in other organs. Therefore, the benefit of metastasectomy via pancreatectomy in this setting remains to be defined. Furthermore, the timing and choice of chemotherapy in this patient population is unclear.

4. Conclusion

In conclusion, these two cases highlight that metastases to the pancreas from lung NET are possible, although they remain very rare. Clinicians should be aware of this possibility during the follow-up of patients with a history of lung NET. Furthermore, our case reports identifies the subtleties of diagnosis and management in those patients and highlights that expert opinion should be sought.

Conflict of interest

None.

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Ethical approval

Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Ashwin Soni: writing, study design. Epameinondas Dogeas: writing. Krishna Juluri: writing. Christopher Wolfgang: data analysis. Ralph Hruban: data analysis, writing. Matthew Weiss: study design, data analysis, writing.

Key learning points

• Neuroendocrine tumors of the lung can metastasize to the pancreas.
• Tissue biopsy by EUS and immunohistochemical staining is paramount in differentiating primary neuroendocrine tumors of the pancreas from neuroendocrine metastasis.
• Expert opinion should be sought if neuroendocrine metastasis to the pancreas is suspected.
• The value of pancreatectomy for neuroendocrine metastasis to the pancreas remains unclear.

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