Metastases to the Pancreas Encountered on Endoscopic Ultrasound-Guided, Fine-Needle Aspiration

Judy C. Pang, MD; Michael H. Roh, MD, PhD

Metastatic lesions in the pancreas are very uncommon and may be difficult to differentiate from the more commonly encountered primary neoplasms derived from the exocrine and endocrine pancreas. Reported frequencies of intrapancreatic metastases vary considerably in the literature, from 4.5% in clinical series to 11% in autopsy series. Metastases to the pancreas can be seen in the context of widely disseminated disease; however, isolated solitary metastases to the pancreas are less frequently encountered (2%). The most commonly reported primary sites of malignancies responsible for these metastases are the kidney, lung, breast, colon, and skin (melanoma). Metastasis to the pancreas may occur years after treatment of the primary neoplasm and is often not considered on initial evaluation because of the rarity of such events. The possibility of a metastasis to the pancreas should be entertained in patients with any prior history of malignancy because a proper diagnosis is essential in identifying surgical candidates, or avoiding potentially unnecessary surgery and facilitating triage to more appropriate nonoperative therapy. Herein, we describe intrapancreatic metastases secondary to renal cell carcinoma, melanoma, and lung carcinoma, as documented by cytologic examination of endoscopic ultrasound-guided fine-needle aspiration of the pancreatic masses.

Accepted for publication May 22, 2015.
From the Department of Pathology, University of Michigan Health System, Ann Arbor.
The authors have no relevant financial interest in the products or companies described in this article.
Presented in part at the New Frontiers in Pathology: An Update for Practicing Pathologists meeting; University of Michigan; September 4–6, 2014; Ann Arbor, Michigan.
Reprints: Judy C. Pang, MD, Department of Pathology, University of Michigan Health System, 1500 E Medical Center Dr, 2G340, Ann Arbor, MI 48109-5054 (e-mail: jcpang@med.umich.edu).

Metastatic renal cell carcinoma represents one of the most common sources of metastasis to the pancreas, and this can be encountered as many as 10 or more years after the resection and diagnosis of the primary tumor; one patient was reported to have developed an intrapancreatic metastasis 28 years after the initial nephrectomy. Patients who present with isolated metastatic intrapancreatic lesions are amenable to surgical resection, with significant improvement in survival after aggressive surgery. Surgery remains an effective means of treatment for renal cell carcinoma—both the primary tumor and isolated metastases—because chemotherapy, radiotherapy, and hormonal therapy have generally proved ineffective. When compared with other tumors that metastasize to the pancreas, renal cell carcinoma appears to be the tumor most frequently treated with surgical resection. When the...
metastatic disease is limited to the pancreas, surgical resection can provide a 5-year survival rate of 43% to 88%.8

In general, FNAs of renal cell carcinoma are bloody because of the vascularity of these tumors. As a result, the samples can vary in cellularity, and it is not uncommon for samples to be hypocellular because of hemodilution.8 When the tumor cells are visualized, the cytomorphology of the malignant epithelial cells can mimic pancreatic adenocarcinoma.1 The subtype of renal cell carcinoma most commonly encountered as an intrapancreatic metastasis is the clear cell subtype.1,6 Figure 1 illustrates an example of an EUS-FNA of a 4.5-cm pancreatic body mass. The Diff-Quik–stained smears were significant for the presence of clusters of malignant epithelial cells displaying frothy, overtly vacuolated cytoplasm (Figure 1, A). These findings immediately raised concern for a metastatic renal cell carcinoma, clear cell type; nonetheless, a primary pancreatic adenocarcinoma still remained as a differential diagnostic consideration. The Papanicolaou-stained smear corroborated these findings (Figure 1, B). Immunohistochemistry for PAX8, a transcription factor typically expressed in carcinomas of renal, thyroid, and Müllerian origin,9,10 highlighted these tumor cells (Figure 1, C). The constellation of cytomorphic and immunophenotypic findings was consistent with a metastatic clear cell renal cell carcinoma.

Although the clear cell subtype is most likely to be encountered in the setting of metastatic renal cell carcinoma to the pancreas, occasionally other subtypes can be seen. An example of an EUS-FNA of a 2.2-cm metastatic chromophobe renal cell carcinoma in the head of the pancreas is illustrated in Figure 2. The Diff-Quik–stained smears demonstrated a cellular aspirate predominantly composed of a discohesive population of round epithelioid cells with low nucleus to cytoplasm ratios and finely granular cytoplasm (Figure 2, A). Some of the cells exhibited centrally placed nuclei, whereas others demonstrated eccentrically placed nuclei. These findings were recapitulated on the Papanicolaou-stained smears (Figure 2, B). In this context, differential diagnostic considerations included a pancreatic neuroendocrine tumor and an acinar cell carcinoma.

Metastatic renal cell carcinomas demonstrate features similar to those of pancreatic neuroendocrine tumors on computed tomography imaging studies because both are hypervascular and well circumscribed, as opposed to pancreatic adenocarcinomas, which are more commonly hypovascular and ill defined.8 In addition, octreotide scans can be positive in renal cell carcinoma. In one study, somatostatin receptors in renal cell carcinoma were detected by scintigraphy in 9 of 11 cases.11 Immunohistochemical workup was performed for this EUS-FNA specimen; the tumor cells were diffusely positive for PAX8, cytokeratin 7, and c-kit/CD117 (Figure 2, C through E), which are all expected to be expressed in chromophobe renal cell carcinomas.8 Based on the cytomorphology and immunophenotype, a diagnosis of metastatic renal cell carcinoma, consistent with the chromophobe subtype, was rendered. Figure 2, F, shows the histologic section from the prior nephrectomy surgical specimen.

**Figure 1.** Endoscopic ultrasound-guided fine-needle aspiration of a metastatic clear cell renal cell carcinoma to the pancreas. The Diff-Quik–stained (A) and Papanicolaou-stained (B) smears demonstrate the presence of cohesive malignant epithelial cell clusters exhibiting finely to overtly vacuolated cytoplasm. Immunohistochemistry for PAX8 (C) highlights scattered tumor cells in the cell block preparation (original magnifications ×400 [A], ×600 [B], and ×200 [C]).

**METASTATIC MELANOMA**

Melanoma is one of the most common malignancies that metastasize to the gastrointestinal tract. Although autopsies reveal gastrointestinal tract involvement in 50% to 60% of patients with melanoma, the clinical diagnosis is only made in 1.5% to 4.4% of all patients with melanoma.12 Solitary organ involvement, specifically that
of the pancreas, is extremely rare (<1%),13 with fewer than 200 cases reported in the literature,14 thus making resections of intrapancreatic metastases exceedingly rare. Sperti et al,15 in a review of the literature, looked at a total of 32 patients who underwent pancreatic resection. The median time between the treatment of the primary melanoma and the detection of pancreatic metastases was 6 years (range, 14 months to 34 years). Simultaneous resection of an extrapancreatic organ was performed in 5 patients. A total of 15 patients had detailed follow-up: 7 patients died of metastatic disease (median survival, 12 months; range, 2–25 months), 1 patient was alive with disease 8 months after surgery, and 7 patients were alive and free of recurrence (median survival, 20 months; range, 6–108 months).15 The only factor that seemed to be associated with improved survival in patients with intrapancreatic metastases was a long disease-free interval after treatment of the primary melanoma, specifically, an interval of more than 2 years.15

Aspirates of melanoma are cellular and consist of discohesive malignant-appearing cells with nuclear pleomorphism and prominent nucleoli. The admixture of malignant epithelioid and spindle-shaped cells and the presence of melanin pigment are helpful clues to establishing the diagnosis. Confirmatory immunostains demonstrating immunoreactivity for some or all of the melanoma markers, such as S100, HMB-45, Melan-A/Mart-1, and MITF, can be used to clinch the diagnosis of metastatic melanoma. An accurate diagnosis of metastatic melanoma is crucial, especially in the current era of precision medicine, because 29% to 66% of cases are positive for activating mutations in \textit{BRAF}.16 The most common \textit{BRAF} mutation in this context is the V600E substitution; patients with advanced melanomas harboring this mutation are eligible to receive targeted therapy with the \textit{BRAF} antagonist, vemurafenib.16

Figure 3 illustrates an example of an EUS-FNA of a metastatic melanoma in the pancreatic body. The Diff-Quik–stained and Papanicolaou-stained smears demonstrated a highly cellular population of discohesive to loosely cohesive epithelioid and spindle cells (Figure 3, A through C) displaying nuclear pleomorphism and conspicuous nucleoli. Focally, in one of the Papanicolaou-stained smears, coarse brown granular pigment consistent with melanin pigment could be appreciated within a few tumor cells (Figure 3, C). Confirmatory immunohistochemistry revealed that the tumor cells were positive for S100 (Figure 3, D). Scattered tumor cells also exhibited immunoreactivity for HMB-45 and Melan-A/Mart-1 (Figure 3, E and F, respectively).

**METASTATIC LUNG CARCINOMA**

Lung cancer frequently metastasizes to distant organs, with the most common intra-abdominal sites being the adrenal glands (44%) and liver (43%). Metastasis to the pancreas is reported to occur in 14% of patients examined at autopsy.17,18 The most common histologic type encountered in this setting is small cell carcinoma (10%), followed by adenocarcinoma (2.4%), large cell carcinoma (1.9%), and squamous cell carcinoma (1.1%).19 Most cases of metastatic lung cancer to the pancreas are found incidentally on radiologic imaging and staging in patients with widely disseminated disease.20 Thus, it is rare to encounter disease limited to the pancreas that is amenable to surgical resection, and treatment options...
are mainly palliative. In a small series by Hiotis and colleagues, 21 3 patients with metastatic non–small cell lung carcinoma to the pancreas underwent pancreatic resection, and recurrence of the disease after surgery was observed in all three.

Figure 4 illustrates an example of metastatic lung carcinoma, which was encountered in an EUS-FNA of a 1.0-cm pancreatic tail mass. The pancreatic aspirate consisted of cohesive clusters of malignant epithelial cells; the cells were arranged in a streaming fashion, the nuclei were hyperchromatic with coarse chromatin, and keratinization was evident on the Papanicolaou-stained smear (Figure 4). In addition, the absence of glandular features in this aspirate was important because a malignant glandular component could have suggested a de novo pancreatic adenosquamous carcinoma. Although metastatic squamous cell carcinoma of the lung to the pancreas is rare (1.1%), primary squamous cell carcinoma of the pancreas is also rare (reported incidence, 0.5%–2%). 22 To our knowledge, ancillary immunohistochemical markers permitting the distinction between squamous cell carcinomas of primary lung versus pancreatic origin are unknown. Clinical and radiologic correlation is essential in these cases.

CONCLUSIONS

Isolated metastatic lesions to the pancreas are rare, but they should be considered in any patient with a history of a prior malignancy. Ancillary immunocytochemical stains can be helpful in confirming the diagnosis of a metastasis. Accurate diagnoses along with clinic-radiologic correlation are essential, given the management and treatment implications. Although aggressive surgery (ie, Whipple pancreatoduodenectomy) for patients with metastatic renal cell carcinoma can be advocated in certain clinical scenarios, the role of resection of intrapancreatic metastases secondary to other primary tumors is less clear and may not offer much benefit.
References