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■ ORIGINAL ARTICLE ■

Aspiration Cytopathology of Peripancreatic Space: A Clinicoradiologic and Cytopathologic Analyses of 42 Cases

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Background: The pancreas is surrounded by soft tissue known as the peripancreatic space (PPS). Pathologic lesions of the PPS are infrequent and have only rarely been reported in the cytopathology literature. **Methods:** A retrospective review of cytopathology files at two large institutions revealed 42 cases of PPS lesions obtained by transabdominal fine needle aspiration (FNA) or endoscopic ultrasound-guided FNA over a 16-year period. Clinicoradiologic findings and follow-up information were also reviewed. **Results:** Patients ranged in age from 23-83 years (mean, 60 years) with an equal gender distribution. The major clinical presentations included pain, jaundice, nausea/vomiting, and abnormal liver enzymes. Radiographic characteristics included lymphadenopathy and cystic/solid soft tissue masses with a size range of 1.5 to 8 cm. Cytologically, 4 (9.5%) cases were nondiagnostic, 9 (21.5%) were diagnosed as benign, 4 (9.5%) were atypical or suspicious for cancer, and 25 (59.5%) were malignant. Six of 25 (24%) patients had metastasis of a prior known malignancy. **Conclusions:** FNA of PPS masses is a rare occurrence. The majority of lesions are metastatic carcinomas from a variety of primary sites. Flow cytometry and immunoperoxidase studies are useful adjuncts to determine the tumor origin. The sensitivity of PPS aspiration for a malignant diagnosis is 90% with a positive predictive value of 100%.

Key Words: Peripancreatic space; Cytopathology; Fine needle aspiration; Adenocarcinoma

The pancreas is surrounded by a zone of soft tissue referred to as the peripancreatic space (PPS), which contains lymph nodes and neurovascular structures. Solid or cystic space-occupying lesions of the PPS are rare and represent a variety of non-neoplastic and neoplastic processes. Current imaging studies such as computed tomography (CT), ultrasound, and endoscopic ultrasound (EUS) are highly sensitive in detecting masses but their ability to differentiate between benign and malignant diseases is limited.[1] In the face of an uncertain clinicoradiologic impression, or if the patient is considered a poor surgical candidate due to pre-existing medical conditions a definitive cytologic/tissue diagnosis is required to direct the appropriate clinical treatment of such cases.[2-6] Image-guided fine needle aspiration (FNA) of the pancreas is an established diagnostic procedure with high sensitivity, specificity, and lacking in serious complications.[7-10] However, to our knowledge, there has only been one previous dedicated series describing the cytopathologic findings of PPS masses.[8]

MATERIALS AND METHODS

A retrospective search of the cytopathology archives at The Johns Hopkins Hospital and University of Maryland Medical Center was carried out for a period of 16 years (1989 to 2005). The search revealed 42 FNAs obtained specifically from the peripancreatic space. Clinicoradiologic findings and follow-up information for each case were additionally reviewed and correlated with the morphologic findings.

In 33 cases the material was obtained transabdominally via ultrasound or computed tomograhphic guidance employing a 22-gauge fine needle. In 9 cases FNA was performed through a curvilinear echoendoscope with a 22-gauge needle. All cases had on-site evaluation performed by the cytopathology staff. A standard smear technique with air-drying and staining with Diff Quik was employed. Slides were also wet-fixed in 95% ethanol for subsequent Papanicolaou staining. Needle rinsed with balanced salt solution were subsequently made into paraffin cell blocks and 4 μm sections were stained with hematoxylin

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and eosin. Immunoperoxidase staining was performed in 10 cases for neuroendocrine and/or lymphoid markers employing the conventional methodology. In 7 cases suspicious for a lymphoproliferative process the aspirate was also sent for flow cytometric analysis.

RESULTS

Patients' demographics, clinical, and radiologic data (Table 1)

A total of 42 patients with a male to female ratio of 1:1 was included in the study. The ages of the patients ranged from 23-83 years (mean, 60 years; median, 64 years). Five cases were consults from outside institutions without detailed clinical or radiologic information. Of the remaining 37 cases, the major clinical presentations included upper gastrointestinal symptoms, jaundice, abdominal pain, and abnormal liver enzymes. Eleven patients (6 females and 5 males) had a prior history of malignancy including lymphoma and carcinomas of the lung, colon, breast, and kidney.

Radiologically, 2 patients were found to have cystic lesions in the peripancreatic region. Eight patients had only peripancreatic lymphadenopathy, 17 patients had a mass or other abnormal radiologic appearance involving the pancreas and/or the peripancreatic space. Ten patients had both pancreatic involvement and diffuse peripancreatic lymphadenopathy. The sizes of the lesions ranged from 1.5 to 8.0 cm. The radiologic impressions ranged from benign lesions such as pseudocyst to metastatic malignancy.

Cytopathologic findings (Fig. 1)

Cytologic materials were obtained as mentioned above by either EUS-FNA or CT/ultrasound guided transabdominal FNA. The sites of aspiration included the peripancreatic lymph nodes (n = 12), peripancreatic soft tissue (n = 18, mass or cyst), and from both lymph nodes and soft tissue (n = 12).

Four cases did not obtain adequate diagnostic materials. In later surgical resection specimens 2 of them had moderately differentiated adenocarcinoma and the other 2 had only pancreatic intraepithelial neoplasias. Of the remaining 38 cases, 9 cases were diagnosed as negative for malignancy on cytology. Three of these turned out to be malignant (2 lymphomas and 1 carcinoma) on surgical pathology follow-up. The 3 cytologically negative cases that turned up positive on follow-up had sampling issues including a small tumor size that was not sampled by the FNA needle, a common problem at any anatomic site. None of these three cases were missed on cytology. Four cases were called atypical/suspicious for malignancy on cytology and two of them proved to be carcinoma on subsequent resection or biopsy.

The cytologic diagnoses of 25 cases called malignant on FNA included 5 metastatic adenocarcinomas of the pancreas, 5 non-Hodgkin lymphomas, 2 metastatic pancreatic endocrine (islet cell) tumors, 1 metastatic melanoma, and 12 metastatic carcinomas of a non-pancreatic origin (1 hepatocellular, 3 colon, 1 renal cell, and 7 carcinomas of unknown primary). Six of these patients had metastasis of a prior known malignancy (colon, kidney, liver, and skin). Flow cytometry was used to confirm the lymphoma cases. Five of the 10 metastatic cases were successfully analyzed by immunoperoxidase staining to identify the site of the primary tumors.

Cytomorphologic features

The smears of metastatic adenocarcinoma (Figs. 2, 3) generally showed tissue fragments of varying sizes admixed with single cells, often with an associated background tumor diathesis and/or lymphocytes. The fragments were three-dimensional with a frequent glandular architecture. The malignant cells were often quite pleomorphic and displayed loss of polarity with a haphazard architecture. The cells had round to oval nuclei and occasionally prominent nucleoli.

The cases of metastatic well-differentiated endocrine neoplasm (islet cell tumor) showed loosely cohesive fragments of monotonous cells with small round to oval uniform nuclei and speckled ("checker board") chromatin (Fig. 4). The cells displayed a rather flat monolayered architecture with lack of glandular differentiation. The one case of metastatic hepatocellular carcinoma actually turned out to be a fibrolamellar variant. It showed smears with moderate cellularity and singly dispersed malignant hepatocytes displaying frequent binucleation, prominent nucleoli, and abundant, granular, "oncocytic" cytoplasm associated with fragments of fibrous tissue (Fig. 5).

The one case of metastatic melanoma was hypercellular with tissue fragments as well as singly dispersed malignant cells (Fig. 6). The tumor cells were relatively monotonous with round to oval often binucleated nuclei, and resembling an epithelioid neoplasm. The cells displayed single, prominent, eosinopohilic ("cherry red") nucleoli. The patient's history of metastatic melanoma was known at the time of FNA. The cases of non-Hodgkin lymphomas displayed hypercellular smears with monotonous-appearing, large lymphocytes (Fig. 7). The malignant cells often showed prominent nucleoli with background smears containing abundant lymphoglandular bodies, occasional tangible-

Table 1. Patients' demographics, clinical and radiological findings

Case No.	Age (yr)	Gender	History of previous malignancy	Clinical presentation	Radiological finding	Radiological differential diagnosis
1	23	F	Yes	Cancer follow-up	Mass of the pancreatic head, lymphadenopathy	Recurrent HCC
2	38	F	No	Abdominal pain	Lesion of the pancreatic body	Benign
3	43	F	Yes	Jaundice	Soft tissue density at the SMA	Primary vs metastatic neoplasm
4	56	F	No	Abdominal pain, vomiting	Peripancreatic cysts	Peripancreatitis
5	59	F	Yes	Pancreatic mass	Mass of the pancreatic head, diffuse lymphadenopathy	Lymphoma
6	60	F	No	Abdominal pain	Pancreatic mass, peripancreatic lymphadenopathy	Pancreatic primary neoplasm
7	62	F	No	Weight loss	Lymphadenopathy, suspicious pancreatic mass	Post surgery changes
8	64	F	No	Abdominal pain, abnormal LFTs	Diffuse abdominal lymphadenopathy, soft tissue mass in the peripancreas	Lymphoma
9	64	F	No	Not specified	No specific radiologic findings	
10	67	F	No	Abdominal pain	Peripancreatic lymphadenopathy, numerous liver masses	Carcinoma
11	67	F	Yes	Abdominal pain	Enlarged pancreatic head	Pancreatitis vs neoplasm
12	67	F	Yes	Jaundice	Mass of the pancreatic uncinate	Pancreatic primary neoplasm
13	71	F	No	Jaundice	Small periampullary mass	No evidence of malignancy
14	71	F	No	Abdominal pain, abnormal LFT	Pancreatic uncinate mass	Pancreatic adenocarcinoma
15	72	F	Yes	Guaiac+stool	Mass of the pancreatic head	Pancreatic primary neoplasm
16	73	F	Yes	Anemia	Peripancreatic mass	C/w metastatic RCC
17	74	F	No	Jaundice	Pancreatic mass, lymphadenopathy	Pancreatic primary neoplasm
18	76	F	No	Abdominal pain, weight loss	Duodenal mass involving the pancreas	Duodenal neoplasm
19	78	F	No	Abdominal pain	Pseudocyst	Pseudocyst
20	80	F	No	Weight loss	Mass of the pancreatic body	Lymphoma vs adenocarcinoma
21	81	F	No	Unstable angina	Pancreatic mass	Pancreatic primary neoplasm
22	31	M	No	Scrotal swelling, HIV positive, disseminated TB	Extensive peripancreatic lymphadenopathy with calcification, hepatomegaly	Lymphoma vs extensive TB
23	31	M	Yes	Lymphadenopathy	Peripancreatic lymphadenopathy	Recurrent lymphoma
24	35	M	No	Nausea, hepatosplenomegaly	Extensive peripancreatic lymphadenopathy, hepatosplenomegaly	Suspicious for lymphoma
25	35	M	Yes	Nausea, back pain	Peripancreatic fluid/mass, liver masses	Metastatic neoplasm
26	43	M	No	Not specified	No specific radiologic findings	
27	47	M	No	Abdominal pain	Retroperitoneal masses	Lymphoma vs sarcoma
28	48	M	No	Jaundice, back pain	Pancreatic mass, liver mass, peripancreatic lymphadenopathy	Pancreatic primary neoplasm
29	51	M	Yes	Lower extremity weakness, abnormal LFTs	Pancreatic head mass	Pancreatic primary neoplasm
30	55	M	No	Abdominal pain, weight loss	Abnormal appearance of pancreatic head and body, peripancreatic lymphadenopathy	Carcinoma
31	55	M	No	Abdominal pain, night sweats	Peripancreatic lymphadenopathy	
32	57	M	No	Abdominal pain	Pancreatic mass, peripancreatic lymphadenopathy	Pancreatic neoplasm
33	58	M	No	Jaundice	Liver mass, peripancreatic lymphadenopathy	Suspicious for metastatic HCC
34	64	M	No	Jaundice	Mass of the pancreatic head	Chronic pancreatitis
35	64	M	No	Nonspecific	Peripancreatic lymphadenopathy	Lymphoma
36	65	M	No	ESRD for transplant	Pancreatic mass	Suspicious for pancreatic primary
37	65	M	Yes	Hematuria	Pancreatic mass, lymphadenopathy	Pancreatic adenocarcinoma
38	66	M	No	Not specified	No detailed radiologic findings	
39	73	M	No	Not specified	No detailed radiologic findings	
40	78	M	Yes	Cancer follow-up	Peripancreatic lymphadenopathy	Lymphoma vs metastasis
41	81	M	No	Not specified	No detailed radiologic findings	
42	83	M	No	Abdominal pain	Peripancreatic mass	Lymphoma vs carcinoid vs sclerosing mesenteritis

F, female; HCC, hepatocellular carcinoma; SMA, superior mesenteric artery; LFTs, liver function tests; RCC, renal cell carcinoma; M, male; HIV, human immunodeficiency virus; TB, tuberculosis; ESRD, end stage renal disease; vs, versus; c/w, consistent with.

body macrophages and karyorrhectic debris. A few cases displayed brisk mitotic activity.

Follow-up clinical/histopathologic data

Of those cases with surgical resection follow-up, one case di-

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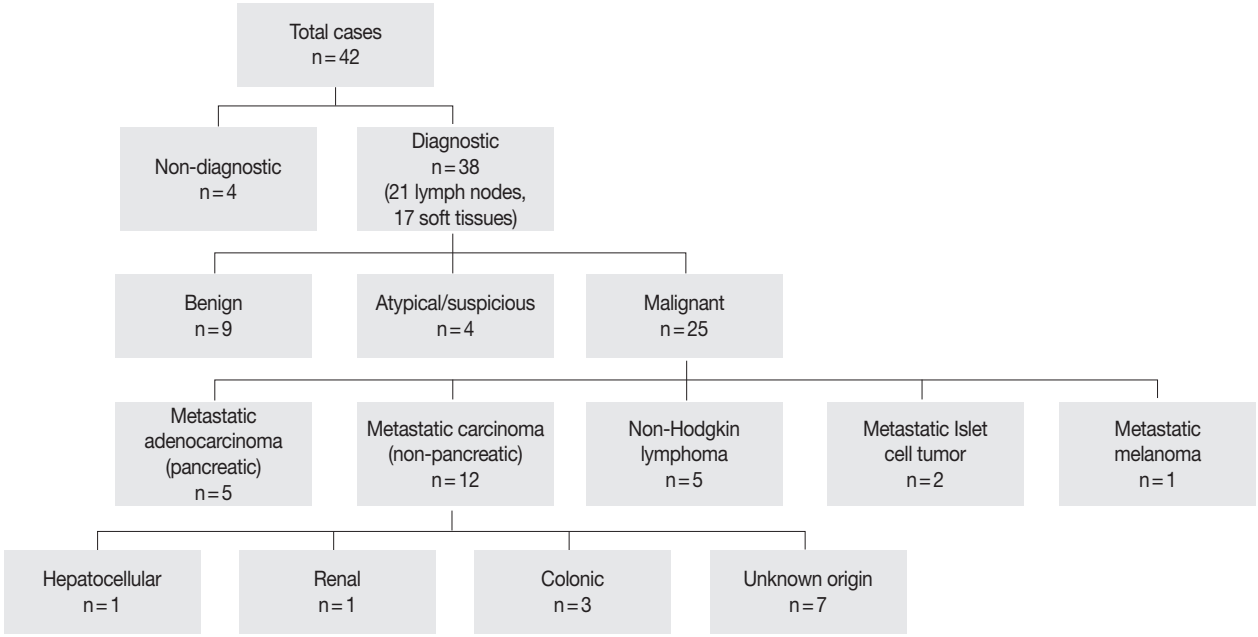

Fig. 1. Cytopathologic data on the 42 cases. The diagnostic yield is high with only four cases deemed inadequate for analysis. Most common pathologic lesion is a metastatic carcinoma.

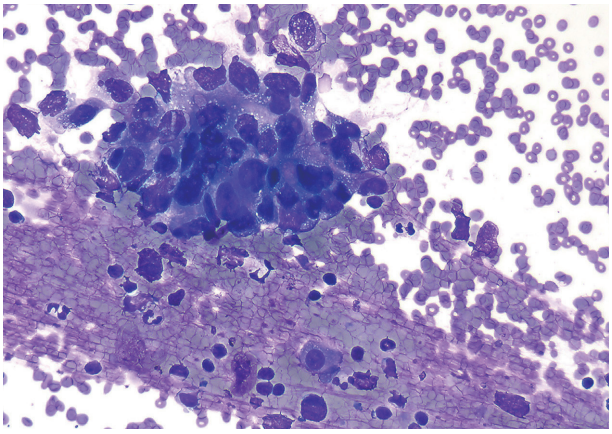

Fig. 2. Metastatic pancreatic adenocarcinoma, peripancreatic space, fine needle aspiration. A three-dimensional fragment of malignant epithelium with significant pleomorphism, nuclear overlap and finely vacuolated cytoplasm. A few discohesive tumor cells are also noted in the background (Diff Quik stain).

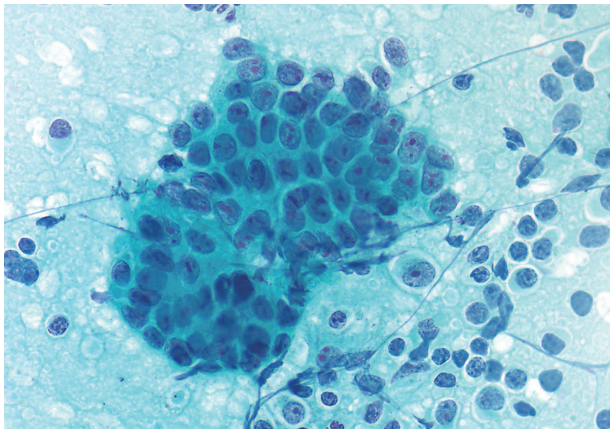

Fig. 3. Metastatic colonic adenocarcinoma, peripancreatic space, fine needle aspiration. A flat sheet of malignant epithelium with enlarged crowded nuclei and single prominent nucleoli. Background lymphocytes are consistent with a lymph node aspiration (Papanicolaou stain).

agnosed as metastatic pancreatic adenocarcinoma on FNA was later found to be of colonic origin. One of the metastatic carcinomas of unknown origin was proved to be a primary gynecologic malignancy and another case turned out to be a metastatic pancreatic endocrine tumor.

The follow-up results are summarized in Table 2. Two of 4 cases called "atypical/suspicious for malignancy" on FNA and later confirmed by tissue studies to be malignant were included in the positive cytology group. The sensitivity, specificity, positive predictive value and negative predictive value in our study is 90%, 100%, 100%, and 75%, respectively.

DISCUSSION

The pancreas is a retroperitoneal organ with close proximity to the duodenum, common bile duct, superior mesenteric artery, portal vein, transverse colon, spleen, stomach, and left lobe of the liver. The PPS is a zone of soft tissue between the pancre-

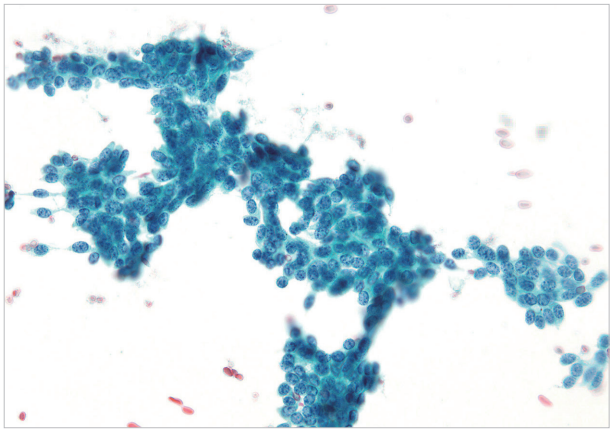

Fig. 4. Metastatic well-differentiated endocrine neoplasm (islet cell tumor), peripancreatic space, fine needle aspiration. Loosely cohesive fragments of neuroendocrine cells with small round to oval uniform nuclei and speckled chromatin (Papanicolaou stain).

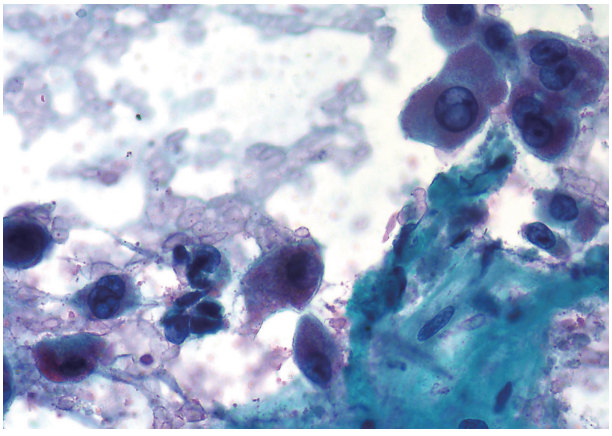

Fig. 5. Metastatic fibrolamellar hepatocellular carcinoma, peripancreatic space, fine needle aspiration. Singly dispersed malignant hepatocytes with binucleation, prominent nucleoli, and a granular cytoplasm associated with a fragment of fibrous tissue. Because of the well-differentiated nature of these cells, it is imperative to exclude the possibility of an inadvertent sampling of normal liver by the traversing needle (Papanicolaou stain).

Table 2. Cytologic-histologic and follow-up correlation

	Follow-up Positive	Follow-up Negative	Total	
Cytology positive	26	0	26	PPV 100%
Cytology negative	3	9	12	NPV 75%
Total	29	9	38	
	Sensitivity 90%	Specificity 100%		

PPV, positive predictive value; NPV, negative predictive value.

as and those aforementioned structures and contains lymph nodes, blood vessels, and nerves. Lesions of the PPS are rare but, when present, may lead to a mass effect causing clinical symptoms

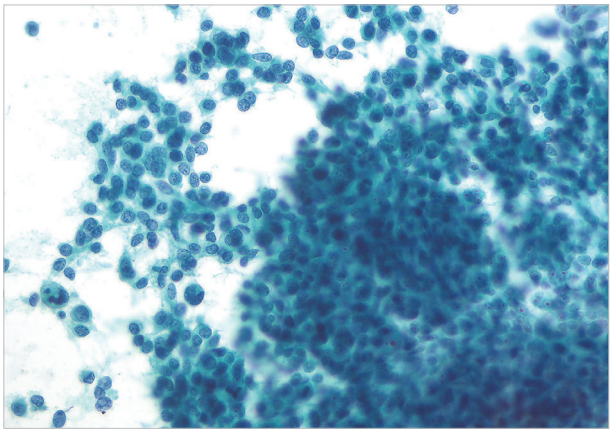

Fig. 6. Metastatic malignant melanoma, peripancreatic space, fine needle aspiration. Sheets and fragments of relatively uniform and cohesive cells that have prominent "cherry-red" nucleoli. In this case, the patient has a known history of a cutaneous malignant melanoma (Papanicolaou stain).

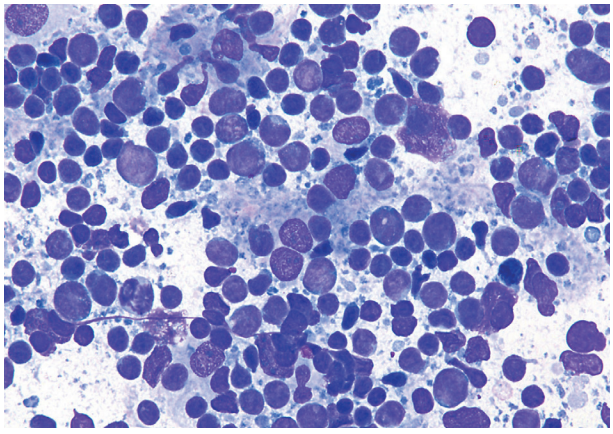

Fig. 7. Non-Hodgkin lymphoma, peripancreatic space, fine needle aspiration. The smear is hypercellular with a diffuse population of large, discohesive and mitotically active lymphoid cells. Numerous lymphoglandular bodies are present in the background (Diff Quik stain).

such as jaundice and abdominal pain. Current imaging modalities such as CT, ultrasound, and echoendoscopy are highly sensitive in detecting PPS lesions. However, they are limited in distinguishing between benign and malignant disease or primary pancreatic carcinomatous extension and metastatic disease. It is, therefore, important to have a tissue diagnosis to guide the appropriate clinical management. FNA is ideally suited to approach lesions in this anatomically difficult to access location of the retroperitoneum. It eliminates the need for open surgical biopsy or even radical resection with its associated morbidity and mortality.

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FNA of PPS is a rare specimen for cytopathologic interpretation. In a 16-year period from two large tertiary care institutions only 42 cases were located from thousands of abdominal aspirations. One reason might be the radiologic difficulty in separating peripancreatic lesions from true pancreatic masses.[10] The pancreatic FNAs are mostly performed to rule out tumors, whereas the peripancreatic FNAs are done for preoperative staging of suspected pancreatic cancers to guide the proper management plan.[8]

The differential diagnosis of a PPS lesion includes a broad spectrum of pathologic entities. Most of the lesions in our series were metastatic carcinomas (18/38, 47.4%). Primary pancreatic ductal adenocarcinoma represented nearly 1/3 of all metastatic cancers and 13.2% (5/18) of all PPS lesions in our series. Therefore, as expected, ductal adenocarcinoma of the pancreas is still the most likely diagnosis in a PPS FNA. Cancers developing in organs surrounding the PPS like the liver, kidneys and colon may also metastasize to the PPS, cytologically mimicking primary pancreatic carcinoma. Using EUS FNA for peripancreatic masses, Frazee *et al.*[8] reported a variety of non-pancreatic tumors including cholangiocarcinoma, lymphoma, gastric adenocarcinoma, gallbladder carcinoma, paraganglioma, breast carcinoma, and leiomyosarcoma. In their series 57% of the results were pancreatic adenocarcinoma.[9] An accurate clinical history of any known previous neoplasm often helps tremendously to narrow the list of possible diagnoses. In our series 11 patients had a prior history of malignancy and 6 of them had metastasis of the same cancer to the PPS. In doubtful cases, it is easier to compare the cytomorphology of possible metastasis to the original tumor to make the diagnosis. Additionally, it helps to select an appropriate immunoperoxidase panel to confirm the cytopathologic diagnosis.

Peripancreatic lymph node involvement by lymphoma can be difficult to interpret, particularly when smears are composed of a mixed population of small and large lymphocytes mimicking a reactive process. Also, low-grade lymphoproliferative disorders composed of small lymphocytes cannot be reliably diagnosed by cytomorphology alone. Flow cytometry and immunoperoxidase studies are important adjuncts to establish an accurate diagnosis in these difficult specimens.[11-14] Five non-Hodgkin lymphoma cases in our series had no prior history, and the PPS FNA was the initial diagnosis of lymphomatous involvement which was later confirmed by flow cytometry.

Uncommonly, a PPS lesion is the initial presentation of an occult cancer. Seven of the 25 (28%) malignant cases in our study presented as occult metastasis. The cytomorphology of these cases was mostly poorly differentiated carcinoma. Employing immunoperoxidase studies can be very useful to confirm the cytomorphologic impression of the cancer origin. This is often tremendously helpful in guiding the clinicoradiologic search for the primary site of the tumor, especially when there is no radiological evidence of a primary tumor. In 5 of 10 cases when immunoperoxidase studies were performed in our series we were able to identify the primary site of metastatic cancers in the PPS. The often helpful immunoperoxidase stains in this regard are cytokeratins 7 and 20,[15] DPC4 (expression is lost in 55% of pancreatic adenocarcinomas),[16] CDX-2 and/or villin (usually positive in intestinal carcinomas, especially colonic),[15] and markers like HMB-45/S-100 protein,[15] TTF-1/napsin-A,[17] Hep-Par-1,[15] RCC/PAX-2,[15] and inhibin (relatively specific for melanoma, carcinomas of the lung, liver, kidney, and the adrenals, respectively).[15]

In conclusion, FNA of PPS masses is a rare occurrence. The majority of lesions are metastatic carcinomas from a variety of primary sites. Flow cytometry and immunoperoxidase studies are useful adjuncts to determine the tumor origin. The sensitivity of PPS aspiration for a malignant diagnosis is 90% with a positive predictive value of 100%.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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