Diagnosis of a Patient with Primary Pancreatic Lymphoma

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Primary pancreatic lymphoma (PPL) is a rare condition that represents 2% of extranodal malignant lymphomas and 0.5% of all pancreatic masses.[1] Diagnostic criteria for PPL include a lack of superficial lymphadenopathy or mediastinal lymphadenopathy on chest radiography, a normal peripheral leukocyte count, a mass in the pancreas with only peripancreatic nodal involvement, and a lack of hepatic or splenic involvement.[1] The presentation of patients with PPL can often mimic that of patients with pancreatic adenocarcinoma. Distinguishing between the 2 conditions continues to be imperative, as PPL responds well to chemotherapy, whereas pancreatic adenocarcinoma may require surgical excision.[2] To confirm the diagnosis of PPL, histologic analysis is required, and samples are commonly obtained by endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA). EUS has been shown to be an accurate tool for identifying, diagnosing, and staging pancreatic masses.[3] A review of the literature reveals limited descriptions of endoscopic PPL findings and few EUS images of the condition.[3-7]

Case Report

A 76-year-old woman was admitted with a 3-week history of jaundice, epigastric pain, and an 11-lb weight loss. She had a previously diagnosed 5-cm pancreatic head mass and had undergone an endoscopic retrograde cholangiopancreatography (ERCP) with cytology brushings as well as a computed tomography (CT)-guided biopsy, both with inconclusive pathology results. Her leukocyte count was 13,600/μL, which was attributed to a urinary tract infection. An abdominal CT scan showed a pancreatic head mass measuring 5–6 cm, peripancreatic lymphadenopathy, encasement of the portal vein confluence and superior mesenteric artery, and intrahepatic and common bile duct distention (Figure 1). No superficial adenopathy was noted, and a CT scan of the chest demonstrated no mediastinal adenopathy. The patient had a total bilirubin level of 15.8 mg/dL (normal, 0.2–1.2 mg/dL), a lactate dehydrogenase (LDH) level of 351 U/L (normal, 110–216 U/L), and a beta-2 microglobulin level of 4.2 mg/L (normal, 1.0–2.0 mg/L).

An ERCP showed a 3–4-cm irregular stricture in the middle to lower third of the common bile duct with postobstructive dilation, and a biliary stent was subsequently placed. An EUS revealed a 47 mm × 38 mm hypoechoic mass in the head and proximal body of the pancreas with lymph nodes around the head and body of the pancreas (Figure 2). No mediastinal or celiac

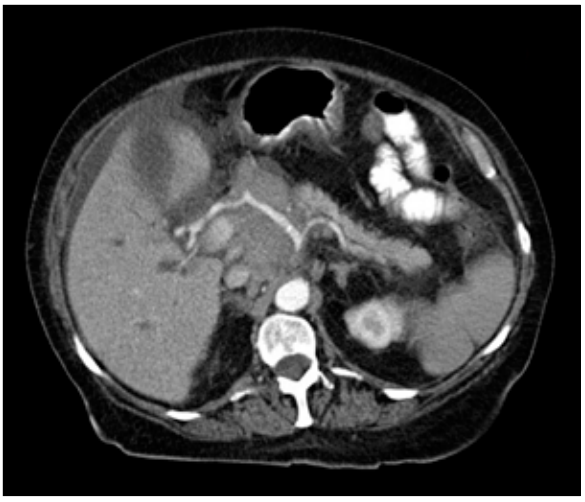

Figure 1. A contrast-enhanced computed tomography scan of the abdomen demonstrating a poorly marginated, heterogeneous pancreatic mass measuring 5–6 cm, encasement of the proximal superior mesenteric artery and portal vein confluence, multiple periaortic lymph nodes, and marked intrahepatic biliary dilation. No dorsal pancreatic duct dilation was seen.

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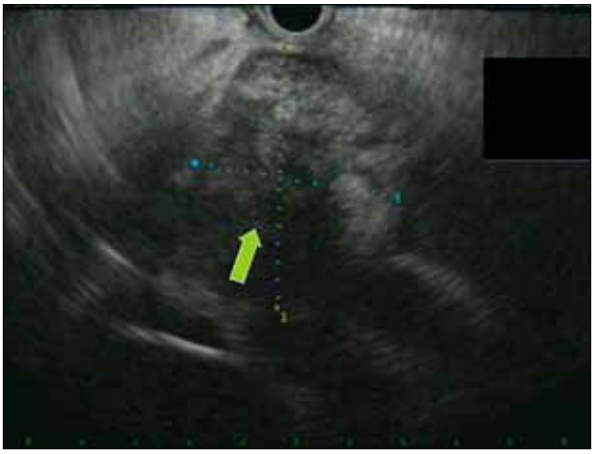

Figure 2. An endoscopic ultrasound of a hypoechoic mass measuring approximately 47 mm × 38 mm (arrow) in the head and proximal body of the pancreas.

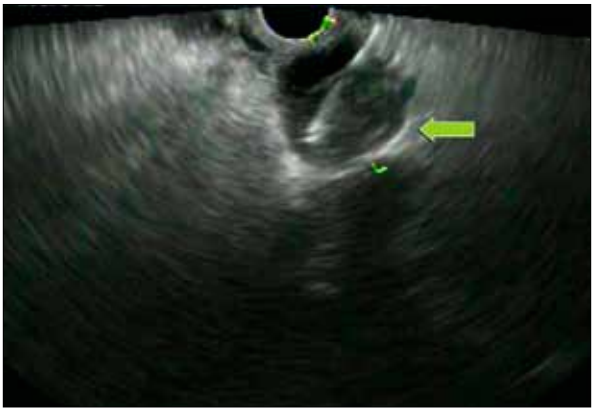

Figure 4. An endoscopic ultrasound fine-needle aspiration of a peripancreatic lymph node (arrow).

nodes were seen. FNA was performed with 4 passes of a 22-gauge needle into the pancreatic head mass and 4 passes of a 25-gauge needle into a lymph node (Figures 3 and 4). Cytologic analysis showed a monoclonal CD19-positive B-cell population with kappa light chain restriction that was suggestive of non-Hodgkin lymphoma. Flow cytometry was diagnostic for B-cell lymphoma. The patient received chemotherapy, and there was a significant reduction in the size of the mass on follow-up imaging. An ERCP performed 7 months after the initial testing demonstrated normal-caliber bile ducts and no extrinsic compression. There was no evidence of residual strictures, and the stent was not replaced.

Discussion

Clinical diagnostic criteria for PPL are well established, whereas there is a lack of consensus regarding radiographic and ultrasonographic characteristics due to the

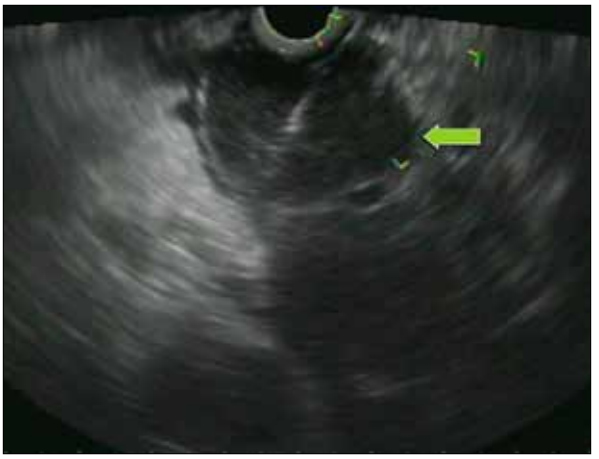

Figure 3. An endoscopic ultrasound fine-needle aspiration of the mass seen in Figure 2 (arrow).

rarity of the condition. The most common clinical manifestations seen on presentation include abdominal pain (83%), an abdominal mass (58%), weight loss (50%), and jaundice (37%). Interestingly, the classic symptoms of fever, chills, and night sweats seen in patients with non-Hodgkin lymphoma are seen in only 2% of patients with PPL.[1] Additional findings can include nausea, vomiting, diarrhea, pancreatitis, and small bowel obstruction.[1] Serologic testing (including markers for lymphoma and other tumors) can provide additional support for a diagnosis of PPL. LDH and beta-2 microglobulin continue to be useful markers in the diagnosis of lymphoma. CA 19-9 has been found to be a useful marker for pancreatic adenocarcinoma, but it may fail to narrow the differential diagnosis, as elevations have also been seen in patients with PPL or upper gastrointestinal tract malignancies.[1-2] Although the clinical presentation and serologic testing may raise suspicion of PPL, these findings are not specific for the diagnosis.

Imaging plays a key role in the diagnosis and staging of all pancreatic masses, including PPL. CT is by far the most common imaging technique used to diagnose and characterize PPL.[1,8] Two different morphologic patterns can be seen on a CT scan of PPL: a localized, well-circumscribed tumoral form and a diffuse enlargement with infiltration or replacement of the majority of the pancreas.[1,8] The diffuse infiltrating type of PPL can appear similar to acute pancreatitis on a CT scan, but these patients do not demonstrate typical clinical signs and symptoms of acute pancreatitis even when their serum amylase levels are elevated.[8] The well-circumscribed tumoral form of PPL can often appear similar to pancreatic adenocarcinoma. Clues to help distinguish PPL from pancreatic adenocarcinoma include a lack of pancreatic duct dilation despite ductal invasion, lymph

node involvement below the renal veins, a bulky homogeneous tumor with no alteration to the Wirsung duct or peripancreatic vessels, and invasive tumor growth that does not respect anatomic boundaries and infiltrates retroperitoneal or upper abdominal organs and the gastrointestinal tract.[8] Calcification or necrosis within the tumor mass can be helpful for ruling out lymphoma and has not been described in cases of untreated PPL.[1] Magnetic resonance imaging findings of PPL are similar to CT findings of the condition. Well-circumscribed tumoral types of PPL appear as homogeneous masses with low signal intensity on T1-weighted images and show subtle enhancement after the administration of gadolinium. These masses show a more heterogeneous character with a low-to-intermediate signal amplitude on T2-weighted imaging.[8] The diffuse infiltrating mass shows similar findings of low signal intensity on unenhanced T1- and T2-weighted images and mild-to-moderate enhancement after the administration of gadolinium.[8] Magnetic resonance cholangiopancreatography is helpful in the evaluation of bile and pancreatic duct dilation, with reports showing only mild pancreatic duct dilation in patients with PPL.[1,8]

ERCP or percutaneous transhepatic choledochography is usually performed as a preliminary therapeutic procedure when stenting of the biliary tree is necessary in the setting of obstruction. Bile duct dilation from obstruction is commonly seen in the setting of PPL, and jaundice occurs in 42% of patients.[8] The appearance of the Wirsung duct on pancreatography can also be useful for differentiating PPL from pancreatic adenocarcinoma. ERCP findings of the Wirsung duct have revealed mild duct stenosis (50%), a normal duct appearance (30%), ductal displacement (10%), or a stricture of the main pancreatic duct (10%).[1,8] As opposed to pancreatic adenocarcinoma—in which moderate-to-severe ductal dilation is often seen—severe distal dilation has not been reported in patients with PPL.[8]

EUS has emerged as a valuable tool in the diagnosis of PPL patients. EUS findings in patients with PPL include a strongly hypoechogenic pancreatic appearance, hypertrophy in all segments, a hyperechoic pancreatic duct wall contrasted with the pancreatic parenchyma, and isoechogenic peripancreatic lymph nodes.[4] Although additional reports have demonstrated large hypoechoic tumors involving the entire pancreas, morphologic features noted on EUS alone have not been shown to reliably differentiate PPL from other pancreatic malignancies.[3] When combined with flow cytometry results, EUS-guided FNA has been shown to improve diagnostic accuracy in several studies compared to FNA with standard cytology results. The diagnostic accuracy of these methods allows clinicians to avoid the need for surgical biopsy when making a diagnosis of PPL.[7] The sensitivity of diagnosing PPL ranged from 73% to 86% in 3 studies, which was a significant increase compared to the sensitivity of FNA alone.[3,6,7] Furthermore, the specificity was 100% in 2 of the studies.[3,9]

Summary

Various imaging modalities have been used in the evaluation of pancreatic mass lesions. Distinguishing PPL from pancreatic adenocarcinoma continues to be important due to the response of PPL patients to chemotherapy and the desire to avoid the risks of surgical staging and Whipple procedures when possible. Certain clinical and imaging characteristics may help to suggest a diagnosis of PPL but are not specific for differentiating between these 2 conditions; thus, tissue sampling is necessary to confirm the diagnosis. When combined with flow cytometry results, EUS-guided FNA has been shown to be a valuable tool in the diagnosis of PPL patients.[5] The use of EUS can be important in the initial evaluation of pancreatic mass lesions, confirmation of a lymphoma diagnosis, and prevention of surgical intervention. EUS may also prove valuable as a tool for monitoring PPL patients after treatment.[10]

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Review

Solid Pancreatic Masses: Not Always Adenocarcinoma

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Primary pancreatic lymphoma (PPL) is a rare disease that comprises 0.5% of pancreatic neoplasms. It is difficult to differentiate PPL from pancreatic adenocarcinoma (PC). As both conditions have similar clinical presentations and radiologic findings, PPL is frequently misdiagnosed as PC. As PPL is associated with a better prognosis than PC, a timely diagnosis may obviate the need for aggressive surgery (with attendant high morbidity) and may lead to early initiation of targeted therapy.

Wallace and colleagues present a typical case of PPL and provide a review of lymphoma diagnosis and management.[1] This case report describes an elderly woman who presented with abdominal pain, jaundice, and weight loss. A computed tomography (CT) scan revealed a pancreatic head mass with intrahepatic and extrahepatic biliary tree dilation. With this classic presentation, there is no doubt that PC must be one of the top differential diagnoses. However, 10% of solid pancreatic neoplasms are not PC. Other differential diagnoses to consider include pancreatic neuroendocrine tumor (PNET), autoimmune pancreatitis (AIP), metastasis from other primary sites, and rare diseases such as pancreatic tuberculosis or pancreatic sarcoidosis. All of these pathologies can masquerade as PC. The typical morphologic appearance of PNET includes well-circumscribed lesions that do not classically cause obstructive jaundice unless they coexist with hepatic metastasis. Functional PNETs may present with a variety of symptoms. A diagnosis of AIP is supported by elevated levels of immunoglobulin G4 in addition to CT findings of diffuse or focal pancreatic enlargement with or without a peripheral gland "halo."[2] Isolated metastatic disease to the pancreas can be seen in a variety of cancers, most commonly in melanoma, renal cell, lung, colon, gastric, breast, and ovarian cancers and rarely in prostate cancer.[3,4]

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In the case report by Wallace and coworkers, prior brushings obtained by endoscopic retrograde cholangiopancreatography (ERCP) and CT-guided biopsies yielded inconclusive findings.[1] Subsequently, fine-needle aspiration (FNA) obtained by endoscopic ultrasound (EUS) as well as analysis of flow cytometry confirmed a B-cell lymphoma. The patient responded well to chemotherapy. An unnecessary major surgical intervention with potential morbidity and/or mortality was avoided.

Diagnosis

Diagnosing PPL remains challenging. This condition must be differentiated from PC as well as from secondary involvement of the pancreas by non-Hodgkin lymphoma. Laboratory tests are nonspecific for the diagnosis of PPL. The most commonly used diagnostic investigations in a symptomatic patient include CT scans and/or magnetic resonance imaging scans. Radiologic studies alone are usually not sufficient for definitively differentiating between PPL and PC. One finding not reported by Wallace and colleagues is the caliber of the pancreatic duct.[1] A large symptomatic pancreatic head mass in the absence of pancreatic duct dilation makes a diagnosis of PC uncertain.[5] Calcifications have not been reported in PPL patients. Diffuse intra-abdominal lymphadenopathy is not commonly a feature of PC. It is also important to note that lymph node metastases from PC generally occur proximal to the level of the renal vein.[6] Therefore, lymph node involvement below the renal veins argues against a diagnosis of PC. ERCP findings in PPL patients may show a spectrum of changes, ranging from a completely normal duct to evidence of strictures without any significant distal dilation. Criteria established by Behrns and associates can help to differentiate PPL from secondary involvement of the pancreas.[7] These criteria include a lymphoma localized to the pancreas with lymph nodes confined to the peripancreatic region, the absence of mediastinal nodal enlargement, no hepatic or splenic involvement, and a normal white blood cell count.

The Role of Endoscopic Ultrasound

Flamenbaum and colleagues reported that EUS findings of PPL patients include a hypoechoic pancreas with a hyperechoic pancreatic duct wall and isoechoic peripancreatic lymph nodes.[8] Although endosonographic features may provide some clues for diagnosing PPL patients, it is imperative to obtain cytopathologic analysis for diagnosis and classification. Tissue may be obtained by CT guidance, EUS-guided FNA, or open biopsy. EUS-guided FNA of pancreatic masses is a safe, accurate, and preferred method because it is dynamic and performed in real time.[9]

O'Toole and associates reported EUS-FNA complication rates of 0% for solid pancreatic lesions and 1.2% for cystic pancreatic lesions.[10] The high sensitivity and specificity of EUS-FNA for PC has been demonstrated in earlier studies.[11-13] If FNA is not diagnostic, then an EUS-guided Tru-Cut biopsy may be useful as a rescue intervention.[14] When used in combination with additional studies such as flow cytometry, tissue sampling is very sensitive for establishing a diagnosis of PPL.[15,16]

Treatment Options

There is still some controversy regarding the treatment of PPL. The study of PPL treatment has been limited by the rarity of the condition and, therefore, a lack of randomized trials and large case series. Chemotherapy is generally accepted as the mainstay of treatment for non-Hodgkin lymphoma patients. The majority of PPL cases are of diffuse large B-cell lineage. The most common chemotherapeutic regimen consists of cyclophosphamide, doxorubicin, vincristine, and prednisone. With this regimen, complete remission has been achieved in a majority of patients. More recently, the addition of rituximab (Rituxan, Genentech) to the regimen has been shown to further improve the response rates of patients with diffuse large B-cell lymphoma.[17] New targeted radioimmunotherapy with 131-I-tositumomab (Bexxar, GlaxoSmithKline) is being used for refractory non-Hodgkin lymphoma.[18,19]

The role of surgery is limited in the management of PPL patients because of the high morbidity and mortality rates associated with traditional pancreatic resections. Surgery is difficult in the setting of PPL because these tumors are generally bulky and are often associated with an otherwise histologically normal pancreas, which carries a high risk of postoperative pancreatic fistulae. However, a few reports have been published on the potential benefits of surgery in patients with PPL. Koniaris and associates reviewed 122 cases of PPL and reported that 58 cases were treated medically (with a 46% cure rate) and 15 patients underwent surgical resection of localized disease (with a 94% cure rate).[20] The researchers argued that technical improvements in pancreatic surgery can lead to reduced perioperative morbidity and mortality and that pancreatectomy should therefore be re-evaluated as a treatment method. Battula and colleagues reported that the 5-year survival rate of PPL patients treated with the current chemotherapy regimens was less than 50%, which was inferior to the rate associated with a combination of surgical intervention and chemotherapy; therefore, the researchers concluded that pancreaticoduodenectomy may have a therapeutic role in association with chemotherapy.[21] However, with recent increases in chemotherapy efficacy, the potential benefit of surgical treatment for PPL patients remains questionable.

The case report by Wallace and coworkers highlights the differential for solid pancreatic lesions and the importance of careful consideration, which may reveal an alternative diagnosis that may obviate the need for invasive surgical intervention.[1]

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