

# Primary Pancreatic Follicle Center–Derived Lymphoma Masquerading as Carcinoma

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**P**Primary pancreatic lymphoma is a rare malignancy that accounts for approximately 0.5% of pancreatic neoplasms. Primary pancreatic lymphoma is typically a circumscribed, solitary tumor that affects the pancreatic head and periampullary region. The diagnosis of primary pancreatic lymphoma is often unsuspected because of the rarity of this condition and the overlap in clinical, radiologic, and laboratory features between primary pancreatic lymphoma and carcinoma, which is a more common malignancy to affect the region. Because the clinical management, therapy, and prognosis of primary pancreatic lymphoma hinge on its diagnosis and classification, tumor sampling for histologic and immunophenotypic evaluation is essential; tumor samples can be obtained by imaging-guided, endoscopic, or surgical means. Chemotherapy is the mainstay of treatment. The clinical benefits of surgical intervention in primary pancreatic lymphoma need reappraisal, given the improved outcomes associated with aggressive combination chemotherapeutic regimens that include rituximab (Rituxan, Genentech).

## Case Report

A 61-year-old white male, previously healthy and working, sought medical attention following 2–3 weeks of fatigue, weight loss, and jaundice. Pancreatic carcinoma was suspected clinically, and examination with transabdominal and endoscopic ultrasound detected a hypoechoic mass

involving the head of the pancreas that encased the gastroduodenal artery. The patient underwent endoscopic retrograde cholangiopancreatography (ERCP) with biliary stenting for symptomatic relief from his obstructive jaundice, but he developed post-ERCP pancreatitis. At presentation to our facility, his physical examination was unremarkable, and there was no abdominal tenderness, distension, or palpable mass. His serum liver enzyme levels were elevated: His total bilirubin level was 2.8 mg/dL (normal, 0–1 mg/dL), alkaline phosphatase level was 80 U/L (normal, 25–125 U/L), aspartate aminotransferase (AST) level was 197 U/L (normal, 15–41 U/L), and alanine aminotransferase (ALT) level was 220 U/L (normal, 0–45 U/L). His serum amylase level was normal (28 U/L; normal, 25–161 U/L). The patient's medical history included gastroesophageal reflux disease and prostate cancer status post–radical prostatectomy. He reported infrequent use of alcohol that was limited to social occasions and no history of smoking. His family history was significant for breast cancer, diabetes, gallstones, and coronary artery disease.

Abdominal computed tomography (CT) confirmed the presence of a 5-cm enhancing mass that effaced the pancreatic parenchyma and closely apposed the superior mesenteric vein near the portal vein confluence. The superior mesenteric artery, common hepatic artery, and celiac artery were uninvolved. There was no upstream dilatation of the pancreatic duct or intrahepatic bile duct. Several borderline to mildly enlarged peripancreatic and mesenteric lymph nodes were noted. A repeat endoscopic ultrasound visualized the mass, but fine-needle aspiration was not attempted due to intervening blood vessels between the mass and the ultrasound probe.

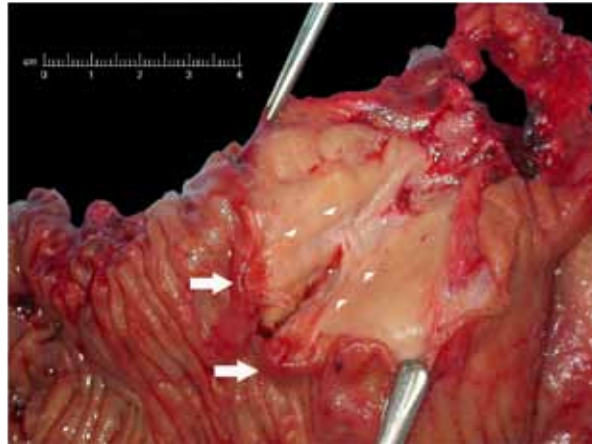
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One month later, following symptomatic resolution of his pancreatitis, the patient underwent a Whipple pancreaticoduodenectomy and segmental resection of the jejunum and its mesentery. The resected pancreas and duodenum revealed a 4.5-cm, well-circumscribed, rubbery, homogeneous, pink-to-tan mass involving the pancreatic head, ampulla, and periampullary duodenum with extension into the peripancreatic soft tissue (Figure 1). A focal area of tumor necrosis was present. The tumor surrounded the main pancreatic duct, distal common bile duct, and common ampullary channel but did not appear to obliterate the ductal architecture. Enlarged peripancreatic and mesenteric lymph nodes were readily identified.

Histologic examination of the pancreatic tumor showed neoplastic large cells with round-to-irregular nuclei, vesicular chromatin, small nucleoli, and moderate amounts of cytoplasm arranged in sheets and vague nodules (Figure 2A). Mitotic figures and apoptotic bodies were conspicuous. The neoplastic cells infiltrated and replaced the pancreatic parenchyma, permeated the muscularis propria, and extended into the ampullary and duodenal mucosa (Figure 2B). The neoplastic cells abutted the main pancreatic and distal common bile ducts, but no lymphoepithelial lesions were identified (Figure 2C). The peripancreatic and mesenteric lymph nodes showed a follicular neoplasm composed of small lymphocytes with cleaved nuclei intermixed with fewer than 15 centroblasts per high-power field (Figure 3). Immunophenotypic profiling on formalin-fixed, paraffin-embedded tissue showed that the neoplastic cells in the pancreas were positive for CD20 (Figure 4A), Pax-5, CD10 (Figure 4B), bcl-6, bcl-2, and MUM-1 in a subset; these cells were negative for cyclin D1, CD138, and the pan-T-cell marker CD3. In situ hybridization for Epstein-Barr virus–encoded small nuclear RNA was negative. The cell proliferation marker Ki-67 (MIB-1 antibody) was positive in approximately 70–80% of the neoplastic cells (Figure 5). Flow cytometric analysis showed a monoclonal B-cell population that coexpressed CD19, CD20, CD22, and CD10 with immunoglobulin  $\lambda$  light chain restriction. The overall findings were consistent with diffuse large B-cell lymphoma, follicular center derivation, in association with low-grade follicular lymphoma in the surrounding lymph nodes.

The patient had an unremarkable postoperative clinical course. Radiologic imaging showed no evidence of extra-abdominal disease, and a bone marrow trephine biopsy showed no signs of a lymphoproliferative disorder. The patient had stage II-AE disease based on the modified Ann Arbor staging criteria. The patient was treated with 6 cycles of cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab; his serum liver enzyme levels normalized within 2 months following surgery (total bilirubin, 0.4 mg/dL; alkaline phosphatase, 123 U/L; AST,



**Figure 1.** Gross image of a primary pancreatic lymphoma (diffuse large B-cell lymphoma, follicle center-derived); the arrows denote the ampulla, while the arrowheads denote the ampullary channel.

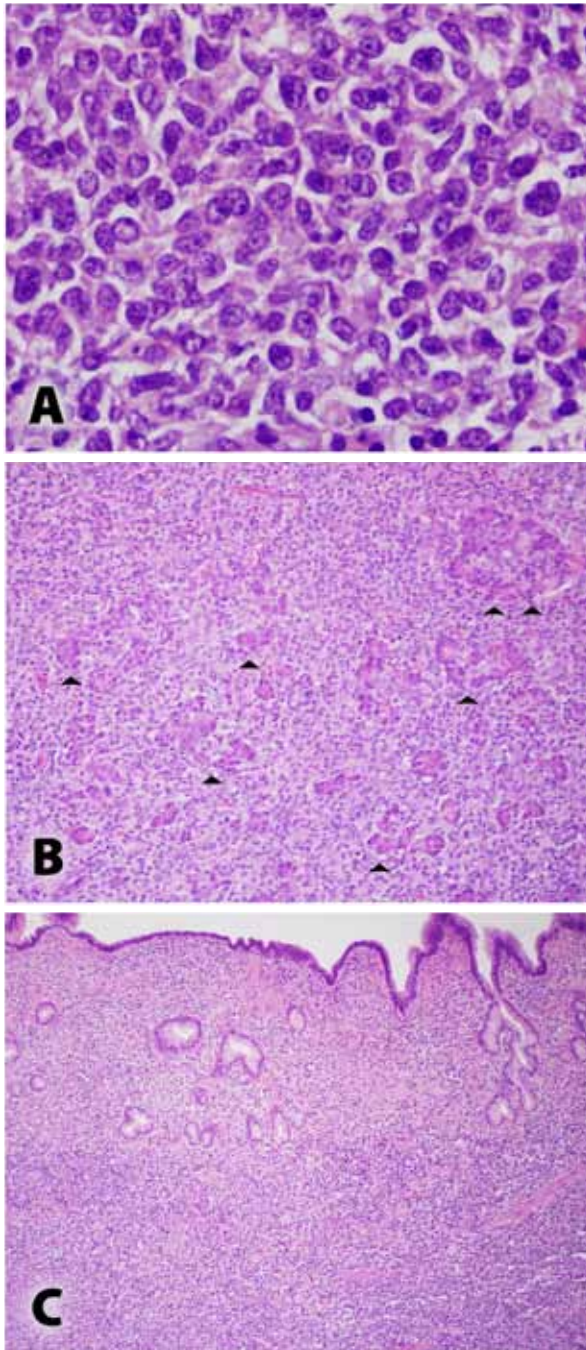
31 U/L; and ALT, 31 U/L). The patient showed no evidence of residual disease or lymphadenopathy after 1.5 years of follow-up.

## Discussion

Pancreaticobiliary involvement by non-Hodgkin lymphoma is typically a manifestation of a systemic disease. In contrast, primary pancreatic lymphoma, or lymphoma localized to the pancreas with or without peripancreatic nodal involvement, is much rarer and accounts for only 0.5% of all pancreatic neoplasms and less than 1% of primary extranodal non-Hodgkin lymphoma.<sup>1-4</sup> Primary pancreatic lymphoma encompasses a heterogeneous group of B-cell and T-cell lymphoproliferative disorders, but the vast majority are of B-cell lineage; indeed, diffuse large B-cell lymphoma accounts for approximately 80% of cases. The remaining reported cases are predominantly low-grade B-cell lymphoproliferative disorders, including follicular lymphoma and small lymphocytic lymphoma; in rare instances, T-cell non-Hodgkin lymphoma and classic Hodgkin lymphoma may cause primary pancreatic lymphoma.<sup>3,5,6</sup> Familial pancreatic lymphoma, lymphoma associated with AIDS, and lymphoma associated with short gut syndrome have been described in case reports.<sup>7-9</sup>

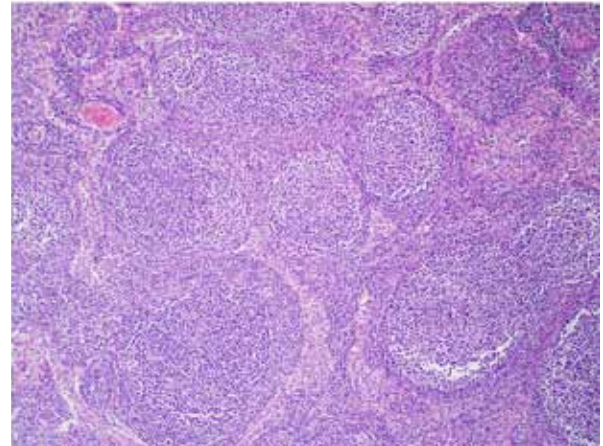
Primary pancreatic lymphoma typically affects patients in the sixth decade of life, and it has a slight male predominance. It usually presents as a circumscribed, solitary mass that involves the pancreatic head, with the body and tail of the pancreas being less often affected; in rare cases, the tumor may diffusely involve the pancreas.<sup>10</sup> At presentation, the tumor is usually large and may exceed 10 cm in the longest dimension. The neoplasm often extends into peripancreatic tissues and encroaches or surrounds adjacent vessels; in rare





**Figure 2.** The neoplasm was composed of large cells with vesicular chromatin and small nucleoli (hematoxylin and eosin stain; **A**); it infiltrated and replaced the pancreatic parenchyma (arrowheads mark residual pancreatic lobules; **B**) and encroached on the common bile duct (**C**).

instances, it may cause thrombosis or vascular occlusion.<sup>5,11,12</sup> Permeation into the duodenum or stomach is associated with early satiety and/or small bowel or gastric outlet obstruction. Mild alteration of the main pancreatic duct and elevation of serum amylase levels



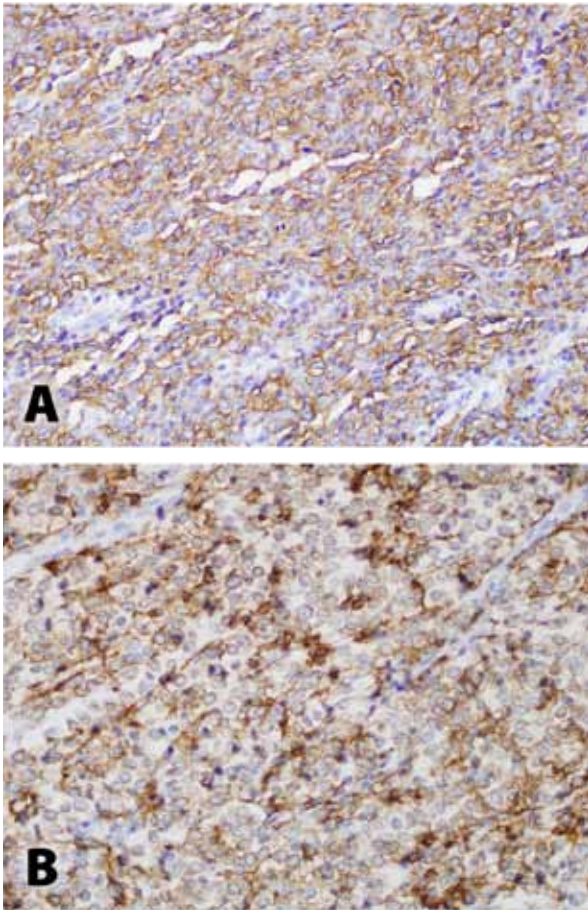
**Figure 3.** This was a low-grade follicular lymphoma, with back-to-back follicles, that involved a peripancreatic lymph node.

may be observed, but the clinical manifestation of pancreatitis is infrequent. Lymphomatous involvement of the ampullary channel and common bile duct may cause stenosis and strictures, which may result in obstructive jaundice and dilatation of the proximal bile duct; obstructive jaundice is reported in approximately 48% of cases.<sup>13-15</sup> Regional lymphadenopathy may be seen, including nodes below the renal vein. Abdominal pain and discomfort are the most common presenting symptoms, but referable pain to the back is rare. Other signs and symptoms associated with primary pancreatic lymphoma include abdominal distention, palpable mass, nausea, vomiting, anorexia, weight loss, diarrhea, upper gastrointestinal bleeding, and ascites.<sup>16,17</sup> B symptoms such as fever and night sweats have been documented in only 2% of cases.

Primary pancreatic lymphoma appears hypoechoic on endoscopic ultrasound and hypodense on CT, with relatively homogeneous but poor intravenous contrast enhancement.<sup>18,19</sup> When the tumor is associated with necrosis or pancreatitis, it may appear focally heterogeneous and irregularly enhancing with contrast. Calcifications have not been reported in primary pancreatic lymphoma. Contrast-enhanced incremental CT scans and arteriography typically show patency of peripancreatic and mesenteric vessels; stenosis and vascular occlusion have been reported in only a small subset of cases.<sup>18,19</sup>

In terms of laboratory findings, levels of the serum tumor marker carbohydrate antigen 19-9 may be elevated, particularly in the setting of biliary obstruction.<sup>12</sup> Elevated levels of soluble interleukin-2 receptor (sIL-2R) may occur in either lymphoma or carcinoma, but an extreme elevation is highly suggestive of a lymphoproliferative disorder.<sup>20</sup> Similarly, elevated levels of serum lactate dehydrogenase and  $\beta 2$  microglobulin in association with a bulky tumor favor a lymphoid neoplasm.<sup>12</sup>

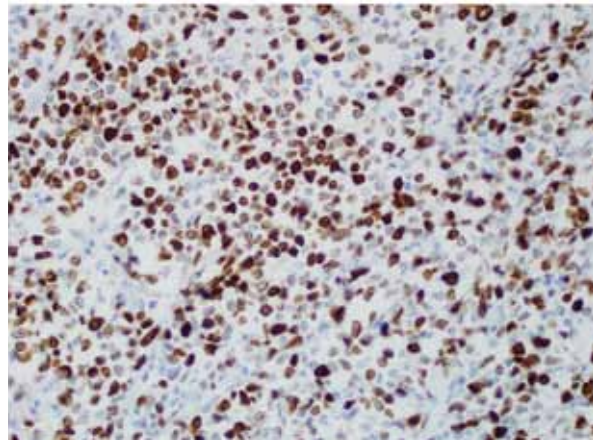




**Figure 4.** The neoplastic cells showed immunoreactivity for CD20 (A) and CD10 (B).

Because the clinical, laboratory, and radiologic features of primary pancreatic lymphoma overlap with those of carcinoma, tumor sampling is essential for diagnosis and classification. Tissue may be obtained by imaging-guided, endoscopic, or open biopsy or by fine-needle aspiration; when coupled with ancillary studies such as flow cytometry, tissue sampling is highly sensitive in establishing a diagnosis.<sup>3,10</sup>

The treatment of primary pancreatic lymphoma involves aggressive combination chemotherapy, particularly for intermediate-grade and high-grade lymphomas such as diffuse large B-cell lymphoma. With the recent addition of rituximab (an anti-CD20 chimeric monoclonal antibody) to standard chemotherapeutic regimens (such as combination therapy with doxorubicin, cyclophosphamide, vincristine, and prednisone), long-term remission is achievable.<sup>21</sup> Adjuvant radiotherapy carries a risk of postradiation biliary and duodenal strictures, and its use may be limited to treatment of bulky tumors and prevention of recurrence.<sup>22,23</sup> Surgical management such as biliary decompression and resection has been



**Figure 5.** The Ki-67 cell proliferation index was approximately 70–80%.

associated with improved clinical outcomes, including symptomatic relief and long-term survival.<sup>1,15,16,24</sup> However, many of the studies in this area were performed prior to the addition of rituximab to standard combination therapies; thus, the clinical benefits of surgery with curative and palliative intent for the treatment of primary pancreatic lymphoma require reappraisal.

### Summary

Primary pancreatic lymphoma is a rare neoplasm that clinically mimics pancreatic and periampullary carcinoma. This condition comprises a heterogeneous group of lymphoproliferative disorders, of which diffuse large B-cell lymphoma is the most common. The clinical, radiologic, and laboratory features of primary pancreatic lymphoma often overlap with those of carcinoma, but primary pancreatic lymphoma typically presents as a bulky tumor and lacks the features typically associated with pancreatic carcinoma, such as referable back pain, significant pancreatic and/or bile duct obstruction or alteration, obstructive jaundice, and peripancreatic vascular occlusion or thrombosis. Additional findings that favor a diagnosis of lymphoma include regional lymphadenopathy, particularly infrarenal nodes, and markedly elevated levels of sIL-2R. The clinicopathologic diagnosis and classification of primary pancreatic lymphoma are critical for appropriate treatment and clinical management; adequate tumor sampling for pathologic and flow cytometric evaluation can be obtained by imaging-guided, endoscopic, or surgical means. The treatment of primary pancreatic lymphoma consists of aggressive combination chemotherapy. Following the addition of rituximab to standard chemotherapeutic regimens, the role of surgery with curative and palliative intent needs further evaluation.

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## Review

### Pancreatic Tumor: When Is It Not Pancreatic Adenocarcinoma?

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Pancreatic adenocarcinoma (PC) is the third most common noncutaneous malignancy and the second most common gastrointestinal malignancy in the United States.<sup>1</sup> Up to 90% of all PCs are ductal in origin.<sup>2</sup> PC carries a dismal prognosis, with 5-year survival rates after potentially curative resection of only 10–25%.<sup>1,3,4</sup>

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The overall 5-year survival rate for PC is less than 5%, since only 15–20% of patients are deemed to be operative candidates on presentation.<sup>5</sup> Primary pancreatic lymphoma (PPL) is an exceedingly rare type of extranodal non-Hodgkin lymphoma (NHL) that comprises less than 0.5% of all pancreatic tumors.<sup>6</sup> PPL must be differentiated from NHL with secondary pancreatic involvement from retroperitoneal and/or paraortic lymphadenopathy, which can occur in 30–40% of NHL cases with extranodal disease. Compared to PC, PPL may not require operative intervention, carries a much better overall prognosis, and responds to combined chemotherapy and radiotherapy. In addition, new targeted immunotherapeutic agents can improve survival, and targeted radioimmunotherapy may be effective in refractory disease. As Alexander and coauthors illustrate, differentiating PPL from PC can be challenging because of the significant overlap in presenting symptoms.<sup>7</sup> However, differentiation of PPL from PC is of critical importance for appropriate therapeutic planning. Correct preoperative diagnosis of PPL in the case by Alexander and coauthors could have allowed the patient to avoid the morbidity of pancreatic surgery (and perhaps the morbidity of an endoscopic biliary stent) and could have allowed for earlier initiation of targeted therapy for this potentially curable disease.

## Presentation and Work-up

The case by Alexander and coauthors describes a 61-year-old white man with a history of localized prostate cancer who presented with 2–3 weeks of fatigue, weight loss, and painless jaundice.<sup>7</sup> He had elevated liver enzyme levels. Cross-sectional imaging revealed a 5-cm enhancing pancreatic mass in the head of the gland without evidence of pancreatic duct dilation, which would be unusual for a large adenocarcinoma of the pancreas. The mass closely apposed the superior mesenteric vein and was associated with several borderline to mildly enlarged peripancreatic and mesenteric lymph nodes. Cross-sectional imaging did not reveal distant metastatic disease to the liver or other organs.

While suspicion for PC must be at the top of the list in any patient over 40 years of age who has a mass in the head of the pancreas, carefully reviewing all data and having a broad differential in the work-up of patients with such a presentation are of critical importance. Between 10% and 15% of solid pancreatic tumors are not PC, and consideration should be given to other lesions, such as pancreatic neuroendocrine tumor (PNET), chronic pancreatitis, lymphoplasmacytic sclerosing pancreatitis (LPSP), metastatic disease to the pancreas, and unusual lesions (including tuberculoma, sarcoidosis, and pancreatic lymphoma).<sup>2,8-10</sup>

The absence of pancreatic duct dilation in a patient with a large symptomatic pancreatic-head lesion should raise questions about the diagnosis of PC. Other adjunct markers, such as carbohydrate antigen 19-9 (CA19-9; which was not reported for this patient), can be suggestive of PC when markedly elevated. Decision making based on CA19-9 levels should be contingent on the knowledge that this test is imperfect, and falsely elevated results can occur in cholangitis and other benign pancreaticobiliary conditions. (Likewise, falsely normal values can occur in PC among the 5–10% of the population who do not express the Lewis antigen). PNETs are usually well-circumscribed hypervascular tumors, some of which are functional and can present with or without symptoms, but typically they do not present with jaundice in the absence of metastatic disease to the liver. Somatostatin receptor scintigraphy could be helpful in establishing this diagnosis. The absence of chronic abdominal pain or pancreatic calcifications makes chronic pancreatitis unlikely. Focal autoimmune pancreatitis or LPSP can have a presentation similar to that described for this patient. Supporting laboratory data—including elevated levels of immunoglobulin G4 and positive antinuclear antibody test results—along with radiographic findings of sausage-shaped pancreas, halo sign, and retroperitoneal fibrosis could further support this diagnosis.

Isolated metastatic disease to the pancreas is seen in 2–3% of all pancreatic tumors.<sup>11</sup> The most common primary tumors that metastasize to the pancreas include renal cell

carcinoma, lung cancer, breast cancer, colon cancer, gastric cancer, melanoma, and ovarian cancer.<sup>12</sup> Metastatic prostate cancer to the pancreas has been reported; however, it is less likely in the case presented by Alexander and colleagues since the patient had no other sites of metastatic spread.<sup>13</sup> The presence of a pancreatic tuberculoma would be exceedingly unusual in patients who lack risk factors for tuberculosis and are not from areas where tuberculosis is endemic. The absence of a history of sarcoidosis makes isolated pancreatic sarcoidosis also very unlikely. The diagnosis of primary pancreatic lymphoma in this patient is supported by the presence of infrarenal mesenteric lymphadenopathy; absence of pancreatic atrophy, calcifications, and ductal dilation; and lack of vascular encasement in the setting of a large pancreatic-head mass.<sup>14</sup> Other laboratory findings that could potentially support a diagnosis of PPL, which were not reported in the case by Alexander and coauthors, include elevations in lactate dehydrogenase and  $\beta$ 2 microglobulin levels.

In the case by Alexander and colleagues, the patient underwent endoscopic retrograde cholangiopancreatography for obstructive jaundice and had stenting for biliary decompression. While patients with PPL can present with jaundice, the tumor usually does not invade the ductal walls, as seen in PC. Rather, patients present with obstructive jaundice secondary to extrinsic compression, and they are frequently found to have smooth long ductal narrowing on a cholangiogram.<sup>15</sup> Pancreatic ductal dilation is almost never found in PPL and is a critical sign that should prompt consideration of alternative diagnoses to PC.

The patient in the case by Alexander and coauthors underwent 2 endoscopic ultrasound (EUS) examinations. Fine-needle aspiration (FNA) was not performed on the second examination due to intervening vascular structures. Given the size of the mass and the presence of peripancreatic lymphadenopathy, it seems unusual that FNA could not be performed. If there was concern about EUS-FNA because of nearby vascular structures, perhaps one of the associated abnormal lymph nodes could have been sampled during EUS or by interventional radiology using computed tomography guidance. Endosonographic features of PPL alone (hypoechoic irregular pancreatic mass lesion) can be quite insensitive and indistinguishable from PC. The abundance of abnormal lymphocytes on rapid cytologic review of FNA should prompt the endosonographer to consider the possibility of lymphoma. Flow cytometry is very specific for clinching the diagnosis of PPL.<sup>16</sup>

A Whipple procedure was performed in the case by Alexander and colleagues because the diagnosis of PPL was not established preoperatively. This procedure revealed a 4.5-cm, well-circumscribed, rubbery, homogeneous mass with a focal area of tumor necrosis involving the head of the pancreas, ampulla, and duodenum and extending into the peripancreatic space. There was no invasion into ductal structures or obliteration of the architecture, which



is consistent with typical pathology of PPL.<sup>15,17</sup> Histologic and immunophenotypic examination, along with flow cytometric analysis, confirmed the diagnosis of diffuse large B-cell lymphoma (DLBCL), follicular center derivation, in association with low-grade follicular lymphoma in the surrounding lymph nodes.

## Management

Management and prognosis of PPL depend on the stage and grade of the tumor. The majority of PPLs are of diffuse large B-cell lineage. A chemotherapeutic regimen involving cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has become the first-line therapy for this condition and is predicted to yield complete remission rates of 63–77%.<sup>18</sup> Addition of the anti-CD20 antibody rituximab (Rituxan, Genentech) to the regimen (R-CHOP) has been shown to increase complete remission rates in limited-stage DLBCL to 85%, with improvements in long-term survival.<sup>18,19</sup> Combined radiation and chemotherapy has shown the greatest impact on long-term survival in early-stage disease.<sup>19,20</sup> New targeted radioimmunotherapy with 90-Y-Ibritumomab and 131-I-Tositumomab can be used for relapsed or refractory NHL.<sup>21–23</sup> In the past, surgical management has been touted as a treatment option, especially for early-stage PPL. Small, nonrandomized, prospective studies have suggested improved long-term outcomes with surgery in stage I disease.<sup>24</sup> Other studies have shown no incremental benefit.<sup>20</sup> All of the surgical literature on PPL was published prior to the addition of rituximab to the chemotherapy regimen; given currently expected rates of complete remission and long-term survival with combined R-CHOP and radiation therapy, surgical resection does not seem to offer a survival advantage. Therefore, operative intervention should be limited to cases where EUS or image-guided FNA cannot be obtained or where PC cannot be excluded as the etiology of the pancreatic lesion—as in the current case.

## Summary

The case by Alexander and colleagues described a 61-year-old man who presented with painless jaundice and signs and symptoms that were suspicious for PC. Work-up revealed a pancreatic-head mass, but tissue diagnosis could not be established. The patient was taken to the operating room for a pancreaticoduodenectomy, which led to an unexpected finding of PPL. The clinical presentation of the patient was typical of both PC and PPL. Imaging by computed tomography and EUS could not definitively discriminate between the 2 diagnoses, and operative intervention was required.

Key aspects of the case by Alexander and coauthors include the need for a broad differential when evaluat-

ing pancreatic mass lesions, as 10–15% of these cases are not PC and, thus, require vastly different therapeutic approaches and differ remarkably in their prognosis. PC must be differentiated from PPL, which is a unique pancreatic malignancy that is associated with good long-term survival and can be cured without surgical resection. Having a high index of suspicion should lead to suspicion of PPL; in many cases, this suspicion can be confirmed preoperatively by flow cytometry after EUS-guided-FNA biopsy.

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