CASE STUDY IN GASTROENTEROLOGY & HEPATOLOGY

Primary Pancreatic Lymphoma Presenting as Acute Pancreatitis

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Primary pancreatic lymphoma (PPL) is a rare extranodal manifestation of any histopathologic subtype of non-Hodgkin lymphoma that predominantly involves the pancreas. Fewer than 2% of extranodal malignant lymphomas and 0.5% of all pancreatic masses constitute PPL.[1] Common clinical manifestations include abdominal pain, jaundice, acute pancreatitis, small bowel obstruction, and diarrhea. The clinical and radiologic findings are not pathognomonic, and the diagnosis is established only after histopathologic and cytopathologic examination with confirmatory molecular testing. Although rare, this particular neoplasm is amenable to treatment even in very advanced stages.

It has been shown that diffuse large B-cell lymphoma with a gene expression profile similar to the profiles of germinal center (GC) B cells has a better prognosis than lymphoma with a gene expression profile that resembles activated B cells.[2] Therefore, GC immunohistochemical staining was adopted for all patients diagnosed with B-cell lymphoma. These cases can be divided into 3 expression patterns: a GC B-cell pattern expressing CD10 and/or BCL6 but without activation markers, an activated GC B-cell pattern expressing at least 1 GC B-cell marker and 1 activation marker, and an activated non-GC B-cell pattern expressing activation markers (MUM1/IRF4) but no GC B-cell markers.[2] These expression patterns represent distinct clinicopathologic subtypes of diffuse large B-cell lymphoma that impact disease prognosis and treatment.

Case Report

A 19-year-old African American woman with no history of illnesses presented to the emergency department with a 2-day history of dull aching bilateral upper quadrant abdominal pain and bilious vomiting. She had no fevers, chills, diarrhea, or constipation. She denied having dysuria and hematuria but did notice discoloration of her urine to dark brown. She had not taken any recent medications, including acetaminophen or herbal remedies. A physical examination was significant for mild right upper quadrant tenderness and a negative Murphy sign, but was otherwise normal. Laboratory testing identified a total bilirubin level of 4.9 mg/dL, aspartate transaminase level of 170 U/L, alanine aminotransferase level of 280 U/L, alkaline phosphatase level of 196 U/L, amylase level of 466 U/L, and lipase level of 393 U/L. Her complete blood count, renal biochemistries, and coagulation studies were within normal limits.

Multiaxial, multisequence abdominal magnetic resonance imaging with and without intravenous gadolinium revealed acute pancreatitis and 2 hypodense masses, both measuring 16 × 15 mm, within the head and tail of the pancreas (Figure 1). The masses were described as heterogeneous, T2 hyperintense with peripheral and progressive central enhancement consistent with malignancy. The main pancreatic duct was of normal caliber, and there was no connection between the masses and the pancreatic duct. No intra-abdominal or retroperitoneal lymphadenopathy was noted. The bile duct was compressed by the mass in the head of the pancreas, also resulting in gallbladder distention.

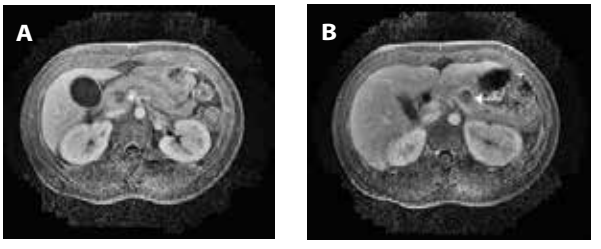

Figure 1. Multiaxial, multisequence abdominal magnetic resonance imaging with and without gadolinium revealing acute pancreatitis and 2 hypodense masses (both measuring 16 × 15 mm) within the head (**A**) and tail (**B**) of the pancreas.

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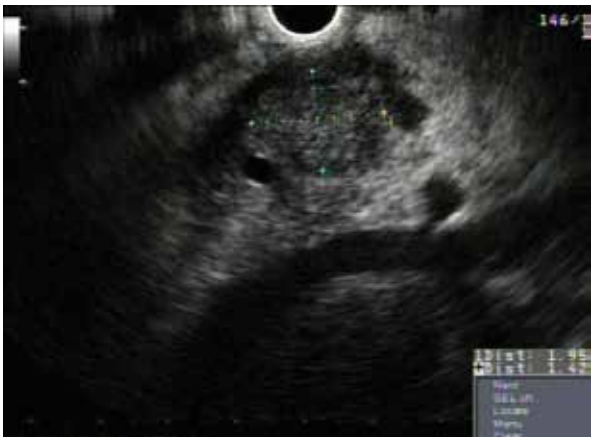

Figure 2. An endoscopic ultrasound showing 2 isoechoic masses with a small cystic appearance suggestive of a multifocal solid pseudopapillary tumor. The differential diagnosis included autoimmune pancreatitis, pancreatic sarcoidosis, and lymphoma.

An endoscopic ultrasound was performed for further characterization and tissue sampling (Figure 2). Endosonographic findings included isoechoic masses with small cystic spaces within a larger mass, which is most consistent with a solid pseudopapillary tumor. Fine-needle aspiration was nondiagnostic. The patient's symptoms resolved, and her pancreatic and liver function enzymes improved. A second endosonographic biopsy performed at a later date was again nondiagnostic. The patient returned with symptomatic biliary obstruction, and an exploratory laparotomy was performed. An intraoperative frozen section revealed atypical cells that were concerning for epithelial malignancy; thus, a resection with extended pancreaticoduodenectomy was performed. Postoperative flow cytometry was diagnostic of a large B-cell lymphoma (Figure 3).

On pathologic examination, the patient's samples were described as large atypical lymphoid cells (Figure 3A) that stained negative for CD10 (Figure 3B) and were immunoreactive for CD20 (Figure 3C), supporting a diagnosis of diffuse B-cell lymphoma. Additional immunohistochemical stains revealed positivity for BCL2 and BCL6. Stains for CD3 and cytokeratin AE1/3 were negative in tumor cells. Stains for MUM1 were positive in tumor cells, whereas the tumor was immunonegative for CD138. The immunoprofile of MUM1, BCL6, and CD10 immunoreactivity was consistent with that of a large B-cell lymphoma with a GC-activated phenotype. In addition, the assessment of margins and lymph node involvement was based upon hematoxylin and eosin histology. The margins of resection were negative for lymphoma. The patient has not had any recurrence of disease based upon cross-sectional imaging and fluorodeoxyglucose–positron emission tomography scans.

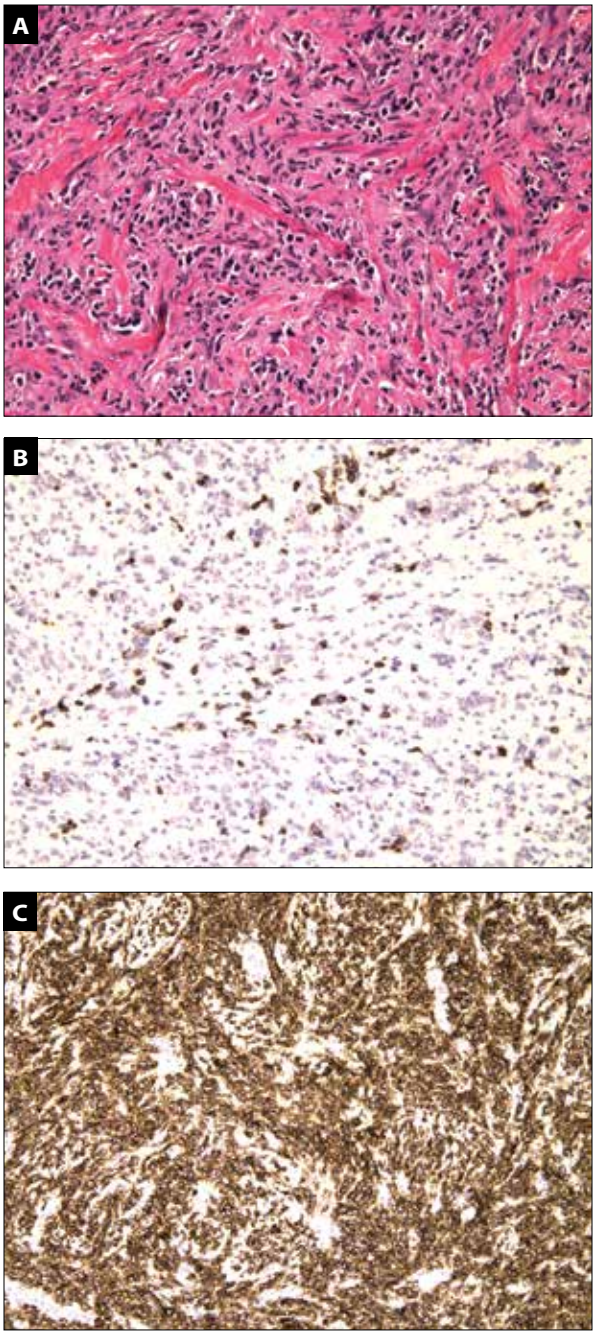

Figure 3. Medium-power magnification of paraffin-embedded pancreatic tissue samples. Hematoxylin and eosin staining reveals large atypical lymphoid cells (**A**). CD3 (specific T-cell antibody) immunoglobulin staining is negative for the presence of T cells (**B**). CD20 (specific B-cell antibody) phosphoprotein staining is positive for the presence of B cells (**C**).

Discussion

Extranodal non-Hodgkin lymphomas represent up to 30% to 40% of all cases of non-Hodgkin lymphoma. The gastrointestinal tract is the most commonly involved

extranodal site, accounting for approximately half of such cases. Secondary involvement of the pancreas from the duodenum or adjacent peripancreatic lymphadenopathy has been well described; however, PPL is extremely rare.[3,4] Fewer than 2% of extranodal malignant lymphomas and 0.5% of all pancreatic masses constitute PPL. Fewer than 150 cases of PPL have been reported in the English language medical literature.[4] Diagnostic criteria for PPL, as defined by Dawson and colleagues,[4] include a dominant mass in the pancreas, the absence of superficial or mediastinal lymphadenopathy on chest imaging, a normal leukocyte count in peripheral blood, and the absence of hepatic or splenic involvement.

Several case series report a strong male preponderance of PPL, with a male-to-female ratio of 7:1. Ages range from 35 to 75 years (mean age, 55 years).[5] Abdominal pain is the most common presenting symptom (83%), followed by abdominal mass (58%), weight loss (50%), jaundice (37%), acute pancreatitis (12%), small bowel obstruction (12%), and diarrhea (12%). Other clinical symptoms may include anorexia or early satiety. Obstructive jaundice is less frequent than in pancreatic adenocarcinoma.[6] The classic systemic symptoms of nodal non-Hodgkin lymphoma, such as fever, chills, and night sweats, are uncommon, found in only 2% of patients. The head of the pancreas is the most common location for PPL (>80% of cases), although tumors may occur elsewhere in the gland. PPL is diagnosed more commonly in immunosuppressed individuals, such as transplant recipients or people with HIV.[4,6]

Cytohistologic diagnosis is mandatory for diagnosis and treatment planning of patients with suspected pancreatic masses. Percutaneous ultrasound, endoscopic ultrasound, and computed tomography are well-established procedures to evaluate pancreatic masses.[4] An accurate fine-needle aspiration diagnosis of PPL is critical for timely, nonsurgical management. Flow cytometry has significantly enhanced the diagnostic role of fine-needle aspiration, particularly in the case of hematolymphoid malignancies. Flow cytometry is extremely sensitive in the detection of antigen expression and identifies small clonal populations.[6] It is imperative to differentiate lymphoma from adenocarcinoma when a pancreatic mass is diagnosed, as the type of mass affects both treatment options as well as outcomes. There are imaging features that suggest a diagnosis of lymphoma rather than adenocarcinoma for pancreatic masses. Specifically, the findings of a bulky localized tumor in the pancreatic head without significant dilatation of the main pancreatic duct, invasive tumor growth not respecting anatomic boundaries, and the absence of calcifications and necrosis within the tumor mass are all seen more commonly in lymphoma.[6,7]

Patients with a confirmed diagnosis of PPL are managed without surgery, and long-term disease remission can be achieved with chemotherapy alone.[8] Histology along with molecular analysis provides for a tailored chemotherapy regimen. The role of surgery is limited to rare occasions when fine-needle aspiration along with flow cytometry is nondiagnostic and a question remains regarding the true nature of the neoplasm.[8,9] Pancreaticoduodenectomy does not impact survival in patients with PPL and, with its associated morbidity, is not generally indicated for PPL.[9,10] Chemotherapy alone is the most common treatment for patients with PPL. The most common regimen includes cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone.[3] The role of radiation therapy in the management of PPL is not yet defined. A study by Behrns and colleagues identified 10 patients with PPL and compared their mean survival with treatment: 13 months for patients who received chemotherapy alone (n=2), 22 months for patients treated with radiation therapy only (n=5), and 26 months for patients receiving combined radiation therapy and chemotherapy (n=3).[11] Using comprehensive treatment approaches, cure rates of up to 30% are reported for patients with PPL, a prognosis that is better than the dismal 5% 5-year survival rate in patients with pancreatic adenocarcinoma.[4,8]

The authors have no relevant conflicts of interest to disclose.

References

1. Saif MW. Primary pancreatic lymphomas. *JOP*. 2006;7(3):262-273.

2. Chang CC, McClintock S, Cleveland RP, et al. Immunohistochemical expression patterns of germinal center and activation B-cell markers correlate with prognosis in diffuse large B-cell lymphoma. *Am J Surg Pathol*. 2004;28(4):464-470.

3. Zucca E, Roggero E, Bertoni F, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 1: gastrointestinal, cutaneous and genitourinary lymphomas. *Ann Oncol*. 1997;8(8):727-737.

4. Dawson IM, Cornes JS, Morson BC. Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. *Br J Surg*. 1961;49:80-89.

5. Nayer H, Weir EG, Sheth S, Ali SZ. Primary pancreatic lymphomas: a cytopathologic analysis of a rare malignancy. *Cancer*. 2004;102(5):315-321.

6. Merkle EM, Bender GN, Brambs HJ. Imaging findings in pancreatic lymphoma: differential aspects. *AJR Am J Roentgenol*. 2000;174(3):671-675.

7. Anand D, Lall C, Bhosale P, Ganeshan D, Qayyuum A. Current update on primary pancreatic lymphoma. *Abdom Radiol (NY)*. 2016;41(2):347-355.

8. Tuchek JM, De Jong SA, Pickleman J. Diagnosis, surgical intervention, and prognosis of primary pancreatic lymphoma. *Am Surg*. 1993;59(8):513-518.

9. Brown PC, Hart MJ, White TT. Pancreatic lymphoma, diagnosis and management. *Int J Pancreatol*. 1987;2(2):93-99.

10. Liakakos T, Misiakos EP, Tsapralis D, Nikolaou I, Karatzas G, Macheras A. A role for surgery in primary pancreatic B-cell lymphoma: a case report. *J Med Case Rep*. 2008;2:167.

11. Behrns KE, Sarr MG, Strickler JG. Pancreatic lymphoma: is it a surgical disease? *Pancreas*. 1994;9(5):662-667.