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Clues for Diagnosing Primary Pancreatic Lymphoma

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Key Words

Primary pancreatic lymphoma · Endoscopic ultrasound

Abstract

Primary pancreatic lymphoma (PPL), a localized lymphoma in the pancreas, accounts for <0.5% of all pancreatic masses and presents with symptoms favoring the more common adenocarcinoma. It is important to differentiate PPL from adenocarcinoma since treatment and prognosis differ considerably. PPL is potentially curable with chemotherapy, especially if it is diagnosed at early stages. A definitive diagnosis can only be based on histopathological findings. Endoscopic ultrasound-guided fine needle aspiration (EUS-guided FNA) is a reliable, minimally invasive and cost-effective method for this purpose. Even though there are neither typical clinical features nor specific biomarker for the diagnosis of PPL, certain common presentations have been observed which may indicate PPL. We herein present the case of a 43-year-old man who was successfully diagnosed with PPL by EUS-guided FNA. His clinical, laboratory and radiographic findings supported PPL over adenocarcinoma as well. This case demonstrates that high clinical suspicion based on clinical, laboratory and imaging features is critical in PPL diagnosis and management.

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoid malignancies which can occur at any age. Most often it is marked by enlarged lymph nodes associated to symptoms such as fever and weight loss. Although NHL frequently involves extranodal organs or arises outside the lymphatic system, primary pancreatic lymphoma (PPL), a lymphoma localized to the pancreas with or without peripancreatic nodal involvement, is an exceedingly rare entity. PPL accounts for only 1% of extranodal lymphomas and for 0.5% of all pancreatic masses [1]. Compared to PPL, NHL with secondary involvement of the pancreas is more common and can occur in 30–40% of NHL cases with extranodal disease. Behrns' diagnostic criteria are well accepted to define and distinguish PPL from secondary involvement of the pancreas by

NHL and include: (1) a mass predominantly located in the pancreas; (2) involved lymph nodes confined to the peripancreatic region, no palpable superficial lymphadenopathy, no mediastinal nodal enlargement on chest radiograph; (3) no hepatic or splenic involvement; (4) normal white cell count [2].

PPL shows a slight male predominance (58%) and is usually seen in the 5th or 6th decade of life. The most common histological subtype of PPL is diffuse large B cell lymphoma, accounting for 80% of all patients [2]. In rare cases, PPL can also present as follicular lymphoma, small lymphocytic lymphoma and T cell lymphoma either of NHL or of Hodgkin lymphoma. Interestingly, PPL rarely presents with the typical B symptoms seen in lymphoma, i.e. fever, weight loss or night sweats. The common presentations of PPL are vague abdominal complaints such as dyspepsia, pain, nausea, vomiting, flatulence, an abdominal mass and weight loss. CT scans usually demonstrate a circumscribed, solitary tumor that most commonly involves the pancreatic head. It appears hypoechoic and hypodense on endoscopic ultrasound (EUS) and CT, respectively. It is crucial to differentiate PPL from pancreatic adenocarcinoma since PPL is potentially treatable and its prognosis is better even if it is found at a late stage. However, due to its rarity and nonspecific clinical presentations and radiographic findings, differentiating PPL from the more common pancreatic adenocarcinoma is often a very difficult task without the aid of a cytopathological diagnosis. Tissue sampling can be obtained by US/CT-guided fine needle aspiration (FNA), EUS-guided FNA or surgical means. Diagnosis by imaging-guided or EUS-guided FNA is preferred since it will avoid surgery and its associated complications.

The treatment of choice for PPL is chemotherapy. Especially with the aggressive combination chemotherapeutic regimens including rituximab, long-term remission is achievable. Even though there are significant overlaps of clinical features of PPL with those of carcinoma, literature reviews have found some clinical, laboratory as well as imaging features favoring a diagnosis of PPL. Here we present a case of PPL which presented with several clinical, laboratory and imaging findings that supported PPL over adenocarcinoma. The patient was successfully diagnosed with PPL using EUS-guided FNA and responded well to R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone). This case demonstrated that even though the clinical, laboratory and radiologic features of PPL overlap with those of pancreatic adenocarcinoma, high clinical suspicion and tumor sampling, especially by EUS-guided FNA, to achieve clinicopathologic diagnosis and classification of PPL is essential to proper patient management.

Case Report

A 43-year-old man presented to the outpatient practice with a 1-week history of right upper quadrant abdominal pain, nausea, weight loss and an epigastric mass. The patient had been seen 6 months earlier for evaluation of a 2-year history of recurrent abdominal discomfort. He had described intermittent left upper quadrant abdominal distress associated to complaints of reflux and constipation. Physical examination at that time was unremarkable. He underwent both upper endoscopy and colonoscopy, the results of which were unremarkable except for the finding of mild gastritis. His symptoms initially resolved with oral treatment with esomeprazole.

Physical examination at the time of his recurrent complaints revealed a well-nourished male complaining of epigastric tenderness and a 6 × 3 cm epigastric mass. There was no evidence of peripheral lymphadenopathy or hepatosplenomegaly. Laboratory data revealed a normal complete

blood count, serum transaminase as well as carbohydrate antigen 19-9 (CA19-9) level. He did however have an elevated amylase of 297 (reference range 20–104), lipase of 264 (reference range 5.6–51.3) and LDH of 24 (reference range 8–20). CT scan of the abdomen performed under pancreatic protocol revealed a 14.3 cm right upper quadrant mass ([fig. 1](#)) with obliteration of the fat planes between the stomach, duodenum, colon and pancreas. There was also a mass effect evident on the inferior vena cava, and there was no indication of pancreatic ductal dilatation; other findings noted consisted of scattered enlarged mesenteric and retroperitoneal lymph nodes. He subsequently underwent EUS which revealed a pancreatic mass within the pancreatic head ([fig. 2](#)) as well as extrinsic compression of the duodenum with ulceration. EUS-guided FNA of the pancreas was performed along with biopsies of the duodenal mucosa. The pathology demonstrated large atypical lymphoid cells ([fig. 3](#)) which stained positive for pan B cell markers: CD20 and PAX5 with co-expression of CD10, BCL-2 and BCL-6 on immunohistochemistry staining ([fig. 4](#)). Flow cytometry analysis was performed which also demonstrated a monoclonal kappa CD10 positive large B cell population ([fig. 5](#)). Further workup consisting of PET scan did not reveal any other pathological site apart from the pancreatic mass. Bone marrow biopsy was performed and revealed normal cellularity. The above findings are indicative of PPL by Behrns' diagnostic criteria. A repeated PET scan 1 month after R-CHOP chemotherapy showed resolution of the mass, although some hazy residual infiltration of the fat in the region anterior to the pancreatic head did persist.

Discussion

Adenocarcinoma of the pancreas ranks as the fourth leading cause of cancer death in the United States and is the second leading cause of death with respect to gastrointestinal carcinomas. Its prevalence continues to rise within the United States especially as the population ages. Most patients with pancreatic cancer typically present late in their course and have either locally extensive or metastatic disease. Overall, only up to 20% of these patients end up being candidates for resection and have a potential for curative surgery. This late presentation is therefore the result of a combination of delays related to patient presentation, misdiagnoses, and lack of sufficiently sensitive screening and diagnostic techniques that would help identify truly localized disease. An additional contributing factor is the rather unfavorable natural history of these tumors in which widespread dissemination of malignant cells exists that typically occurs early and usually during the preclinical phase of the disease. Being able to differentiate the possible etiology of the pancreatic mass is paramount, as this would lead to less morbidity and mortality.

PPL often mimics adenocarcinoma of the pancreas in many aspects. It is important therefore to differentiate them, given the fact that the treatment and prognosis will differ considerably. Although the final diagnosis is based on cytohistological evidence, literature reviews so far have described several clinical, laboratory as well as imaging features that can help substantiate the possible diagnosis of PPL.

Battula et al. [3] performed the largest case review consisting of 89 PPL cases. They demonstrated that PPL typically has a less frequent presentation of painless obstructive jaundice or abdominal pain even though it is commonly located in the pancreatic head. This was further corroborated and is consistent with Du et al.'s clinical observation [4]. Unfortunately there does not exist any specific biochemical marker for PPL. Discussion has circulated around the use of LDH as a possible screening tool. Elevated levels of both LDH and β 2-microglobulin have been noted and these may actually help in diagnosing PPL, but remain controversial as these are rather nonspecific. Today there exists consensus that the CA19-9 levels will remain normal unless biliary involvement is present. CA19-9 is the most useful marker in

patients with suspected pancreatic tumors as its level correlates with both tumor burden and the level of cancer expression. A level >200 U/ml is strongly suggestive of pancreatic adenocarcinoma [5] as this carries a positive predictive value of 100%. Unfortunately, only half of patient with tumors <2 cm in size have elevated levels. Also normal values may occur in some pancreatic tumors that do not express CA19-9. Approximately 50% of individuals cannot synthesize this antigen and are therefore regarded as Lewis a–b negative. Certain findings on imaging may support the diagnosis of PPL. These are the combination of a bulky localized tumor in the pancreatic head without significant dilatation of the main pancreatic duct or enlarged lymph nodes below the level of the renal veins. Other less specific findings would be the lack of invasion into vascularity surrounding the pancreas as well as the presence of calcifications or necrosis within the tumor, which seem to suggest a possible diagnosis of PPL [4, 6].

This case highlights several of these important points. The patient presented with a large bulky pancreatic mass that did not demonstrate any significant dilatation of the main pancreatic duct or invasion of the large vessels. Furthermore he lacked any vascular, hepatic or splenic involvement as well as obstructive jaundice and presented with a normal CA19-9. All of these findings in conjunction would favor a diagnosis of PPL over adenocarcinoma. EUS combined with guided FNA can be used to establish a tissue diagnosis in patients who are suspected of having pancreatic lymphoma or are nonoperative candidates. FNA of the pancreas has an established sensitivity of >80% and a specificity of 95%. However it does carry a false-negative rate of 20%. Submitting the specimen to flow cytometry is a valuable and cost-effective method for the diagnosis of a pancreatic mass as demonstrated in this case, since the goal is to individualize the appropriate therapy leading to minimal risks and to be able to differentiate those patients who have potentially resectable disease from those who have unresectable or metastatic disease. Every effort should be made to have an accurate cytologic and histologic diagnosis by FNA technique, especially when clinical, laboratory and imaging findings support PPL.

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Fig. 1. CT scan of the abdomen with contrast: heterogeneous mass measuring 12.0 × 9.7 × 14.3 cm in the right upper quadrant with loss of fat planes between the stomach, duodenum, colon and pancreas.

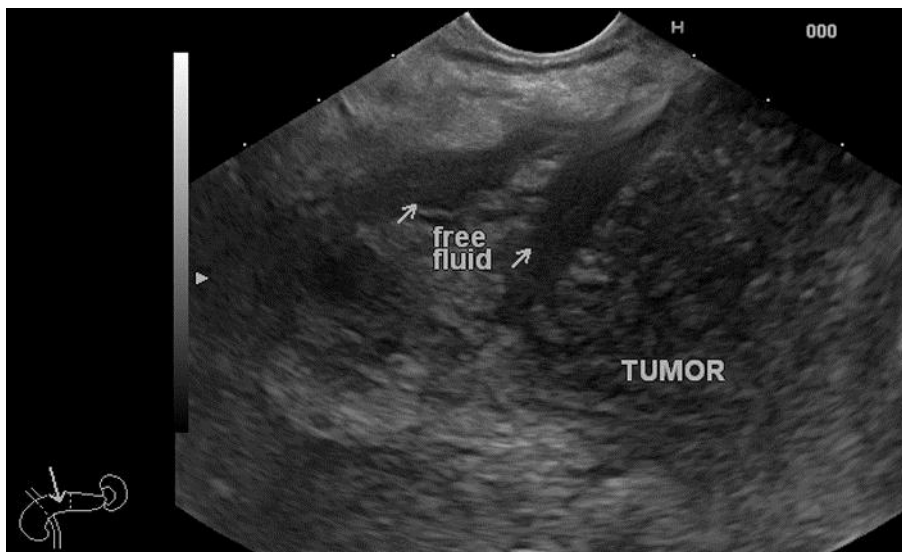


Fig. 2. EUS: heterogeneous mass in the head of the pancreas with surrounding free fluid and multiple collateral vessels.

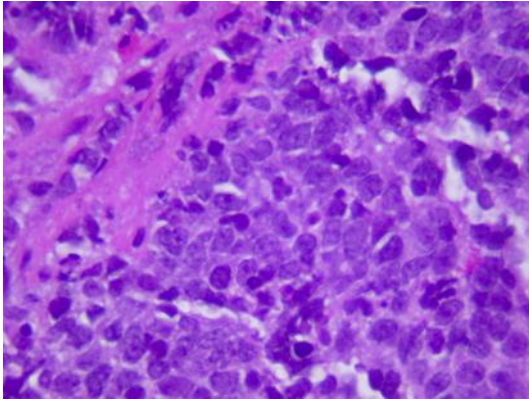


Fig. 3. EUS-guided FNA biopsy of the pancreatic head mass: atypical lymphoid cells with condensed chromatin and larger lymphomatous cells (40×).

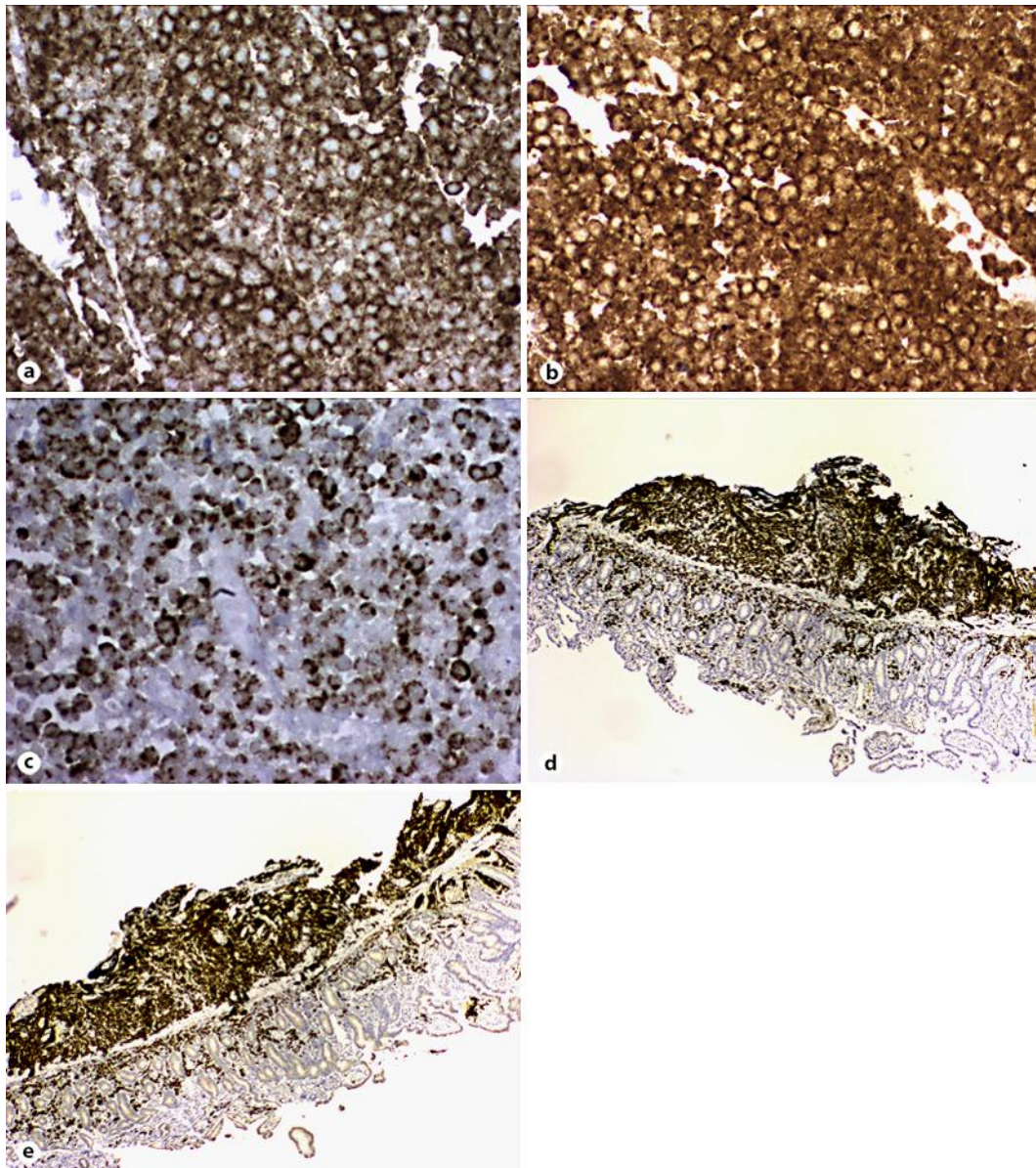


Fig. 4. Immunohistochemistry studies. **a** CD20 positive (40×). **b** CD10 positive (40×). **c** BCL-2 positive (40×). **d** BCL-6 positive (duodenum, 4×). **e** PAX5 positive (duodenum, 4×).

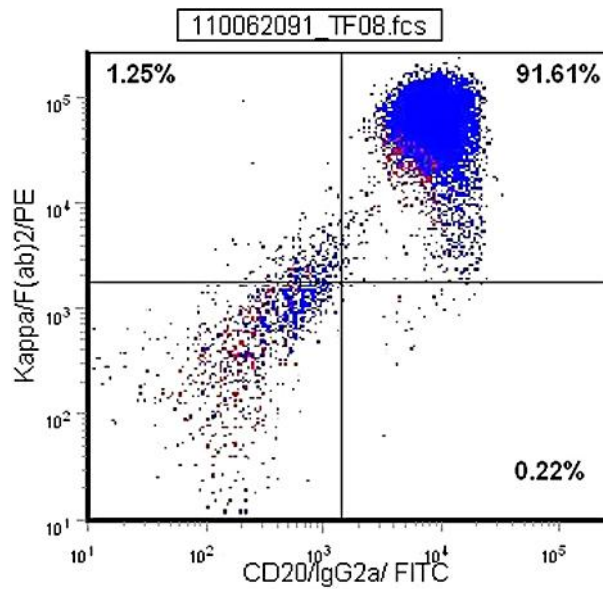


Fig. 5. Cytometry: CD10 positive B cell lymphoma.

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