Review Article

Primary pancreatic lymphoma: what we need to know

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Abstract: Hodgkin's lymphoma is a group of malignant lymphoid which involve various organs including gastrointestinal tract. Stomach and small intestine are commonly involved more; however, pancreas can be primarily involved as well. The secondary involvement of pancreas caused by Hodgkin's lymphoma is more prevalent than the primarily involvement (1 .25–2.2% *vs.* <1%). Primary pancreatic lymphomas (PPLs) consist of 1–2% of all lymphoma outside nods. The symptoms and findings of PPL imaging can be akin to that of pancreas adenocarcinoma and differentiating them is difficult without examining the tissue sample. The prognosis and treatment of PPL are different from those of adenocarcinoma and due to the superior prognosis of PPL compared to pancreas adenocarcinoma, the proper diagnosis of the disease is important.

Keywords: Pancreas; lymphoma; adenocarcinoma

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Introduction

Non-hodgkin's lymphoma (NHL) is a group of malignant lymphoids which can be seen at any age. It is often determined with enlarged lymph nodes, fever, and weight loss. NHL commonly affects extranodal organs while the involvement of pancreas is primarily rare and can be with or without the involvement of lymph nodes around the pancreas (1). Differentiation of primary pancreatic lymphoma (PPL) and adenocarcinoma is important due to different treatment and better prognosis; however, the symptoms of PPL are not specific and can mimic adenocarcinoma. PPL can often be seen as a mass larger than 5 cm in the pancreas while unlike adenocarcinoma, no vascular involvement is commonly observed. The definitive diagnosis of PPL is impossible based on imaging and it requires pathological examination. CT-guided biopsy and laparotomy have been proposed for obtaining tissue samples. Fine needle aspiration (FNA) through endoscopic ultrasound (EUS) (EUS-FNA) has been a good method to obtain tissue samples through endoscopic ultrasound in recent years (2).

Epidemiology

PPL consists of approximately 1% of all extranodal lymphomas and 5% of all pancreatic masses (1). PPLs are more common in males (58%) and are usually seen in the 5th or 6th decades of life.

The most histological type of PPL is diffuse large B cell lymphoma which forms 80% of all cases, however, other histologic types may rarely be seen (3).

Rad *et al.* (4) reported on patient with pancreatic mass and icter who had low grade B cell lymphoma in the histological examination (*Figures 1* and *2*).

Clinical symptoms

Clinical symptoms of PPL are not specific for the disease and include epigastric pain, abdominal mass, weight loss,

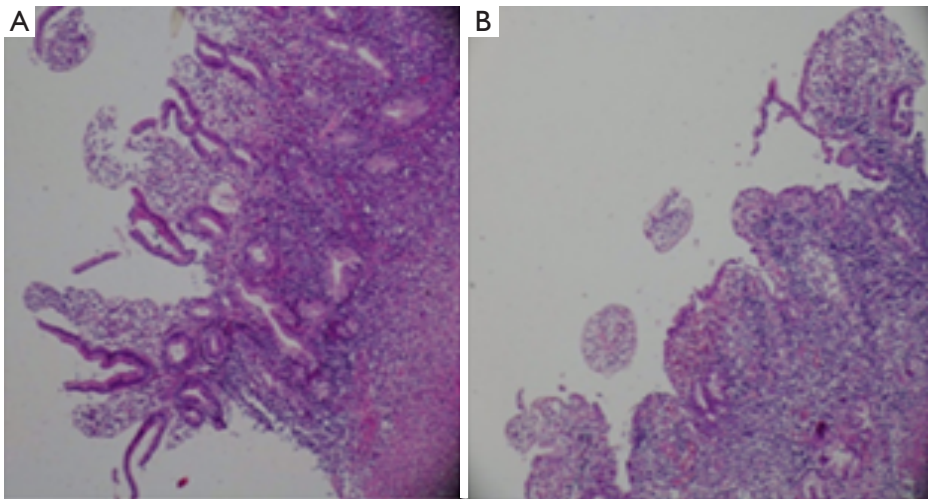

Figure 1 Low grade B cell lymphoma (hematoxylin-eosin stain; original magnification ×200).

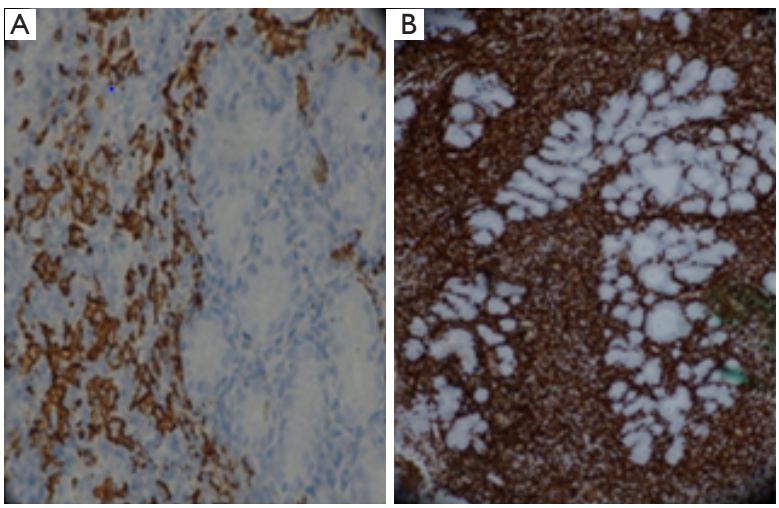

Figure 2 CD20-BCL2-CD10-CD43-CD3 positive atypical lymphocytic cells (immunohistochemistry; magnification, ×25).

jaundice, nausea, vomiting, diarrhea, pancreatitis, and intestinal obstruction (5,6).

PPLs rarely represent B symptoms which are often seen in other lymphoma and include fever, night sweats, and weight loss. The most symptoms of PPLs are with vague abdominal discomforts such as dyspepsia, pain, nausea, vomiting, feeling of fullness, and body weight loss (7).

Dawson *et al.* proposed five criteria for the diagnosis of PPL (8):

(I) Lack of peripheral lymphadenopathy;
(II) Lack of involvement of mediastinal lymph node;
(III) Counting normal peripheral white blood cells;
(IV) Pancreatic mass specified in surgery with the involvement of lymph nodes confined to the pancreas;
(V) Lack of involvement of liver or spleen.

Imaging techniques

Transabdominal ultrasound (TUS)

TUS is a technique dependent on the accuracy of operator and has a low precision to see small masses in the head of the pancreas. TUS can indicate dilatation and obstruction of the bile ducts and liver metastases (9). Using new methods of

ultrasound such as Color-power Doppler us, 3 dimensional (3D) US, and harmonic imaging, contrast-enhanced us, the diagnosis of pancreatic masses has significantly enhanced (10). Using contrast enhanced us, vascular involvement can be investigated in the pancreas masses that can help the differentiation of pancreatic masses (11).

Abdominal CT scan

To examine pancreas masses and liver metastases, CT scan which is an accessible and noninvasive method can be used and based on the results of CT scan, decisions can be made on sampling to prove the diagnosis. The quality of CT scan images has been improved using multiple detector CT which creates images with high resolution 3-D imaging and multiplanar ones. Rapid injection of iodine-containing contrast and images that are immediately taken after injection are among the methods to increase the sensitivity of CT in the evaluation of pancreatic masses (11). CT sensitivity is low for lesions less than 2 cm (12-14).

CT scan guide can be used for the biopsy of pancreatic lesions with the sensitivity about 95% (15,16). Radiological results from the previous studies in which the secondary lymphoma of the pancreas was similar to primary lymphoma include nodular, diffuse and multinodular (6,17,18). Most masses have been recognized through intravenous injection by CT scan well and sometimes are bulky and infiltrated. Lesions with the homogeneous low attenuation are along with a slight enhancement of pancreatic parenchyma (5).

Pancreatic lymphoma with a lower incidence may show the symptoms of acute pancreatitis on CT scan which appears as diffuse pancreatic enlargement while the results of typical pancreatitis in CT including inflammation around the pancreas or fat stranding do not exist; otherwise, they can be seen usually minimal. Fluid accumulation around the pancreas, pancreatic fat necrosis and rupture of the pancreatic duct are not seen in lymphoma. Vascular involvement by tumor can rarely be seen in lymphoma (5). Although pressure may be observed on vessels due to the effect of the mass, there are no changes resulting from the conflict involvement of tumor including a change in caliber and irregularity (19).

MRI

MRI is a good diagnostic method for pancreatic masses and is superior to CT in terms of tissue contrast. Pancreatic lymphoma can be seen as homogeneous, low signal intensity and focal nodular in T1W1 images and high or low signal intensity in T2W1 images. In DCE-MRI, low enhanced area surrounded by parenchyma is usually observed (5,18). Unlike CT, the lesions of pancreatic lymphoma are mildly heterogeneous in MRI, especially in T2W images. Tumors of Islet cell have more hyper intensity than lymphoma in T2w images.

Whole body DW1 had formerly a significant role in diagnosing and staging the disease in lymphoma patients. By receiving intravenous gadolinium contrast, lymphoma is homogeneously enhanced in a less degree than normal parenchyma. A number of lymphomas appear softly inhomogeneous in MRI. Due to the desmoplastic content, the pancreas adenocarcinoma is less enhanced and after receiving gadolinium, they are typically inhomogeneous. Due to the difference in the treatment and prognosis of pancreatic lymphoma, its differentiation from similar lesions such as pancreatic autoimmune and autoimmune pancreatitis seems to be of great significance (20).

Merkle *et al.* (5) offered the following criteria for distinguishing lymphoma from pancreatic autoimmune:

(I) Huge homogeneous mass without cystic-necrosis lesions or MPD involvement;
(II) Adjacent arteries involvement without obstruction;
(III) If there were lymphadenopathy under the left renal vein, it would be limited to the area around the pancreas.

However, despite the above criteria, CT-guided biopsy or EUS FNA is important for an accurate diagnosis in most cases.

EUS

Although EUS is dependent on operator, it is more sensitive than CT or MRI to detect suspicious pancreatic lesions or lesions less than 2 cm on CT if it is done by an experienced person (12,14,21-23). Tissue sampling by EUS can be done in two ways: either by EUS guided FNA (EUS-FNA) or EUS guided fine-needle core biopsy (EUS-FNB). The sensitivity of EUSFNA is 95% and its specificity is 100% (24-27). It is the preferred method for sampling the pancreatic tissue, especially when the biopsy results of other methods are negative or ambiguous for malignancy (28,29). Although EUSFNA along with cytopathology are usually suitable for the diagnosis of adenocarcinoma and neuroendocrine tumors, it may not well obtain the tissue required for the full tissue examination in order for the diagnosis of lymphoma-pancreatitis cancer and autoimmune

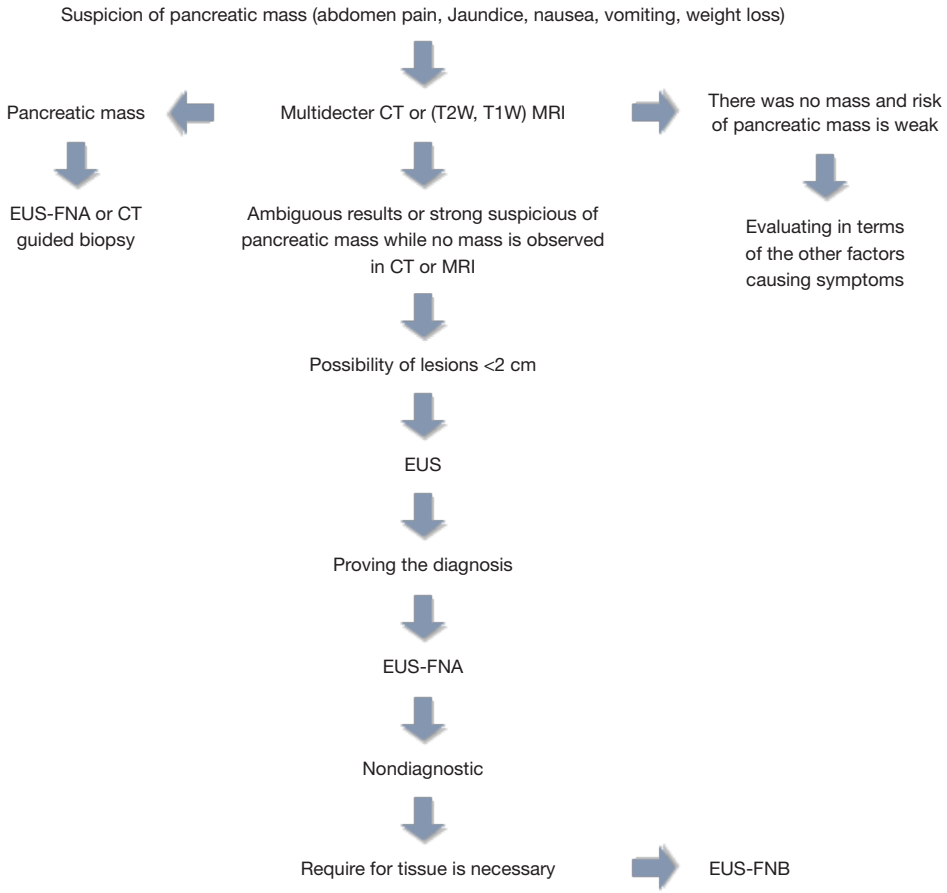

Figure 3 Evaluating pancreatic mass. EUS-FNA, endoscopic ultrasound guided fine needle aspiration; FNB, fine-needle core biopsy.

(30,31). EUS-FNB is not superior to EUS-FNA for the diagnosis of pancreatic masses. However, it is used in the events where EUS-FNA does not help make a diagnosis and tissue samples are needed (32-37). Due to the rigidity of the needle and angle of the endoscope for sampling, obtaining a sample of pancreatic masses by EUS-FNB is hard (38). We have designed an algorithm for evaluating patients with suspected pancreatic mass (*Figure 3*).

The complications of EUS-guided sampling of the masses of pancreas include hemorrhage (0.5–2% of the cases) (24,26,27,39,40) and tumor seeding in other parts of the abdomen whose risk is very low (41-43). The study conducted by Khashab *et al.* (44) indicated that EUS-FNA by flow cytometry was preferred to EUSFNA without flow cytometry in the assessment of 16 patients suspected to primary pancreas lymphoma.

In another study, Ramesh *et al.* (45) showed that from 2,397 patients undergoing EUS-FNA due to the solid mass of pancreas, 12 patients had PPL and the mean of the largest diameter of the mass was 47.5 mm (SD =21) and over 80% of the cases were in the head of pancreas. Echo image was heterogeneous in 75% of cases, while the rest were hypoechoic.

Abedi *et al.* (46) reported on a case report who was a 38-year-old man with the history of smoking, Intravenous Drug Using (IVDU), and hepatitis B and C and was admitted due to the nausea, vomiting, RUQ pain, and epigastric pain. EUSFNA performed for the patient and indicated a mixed echo mass in the pancreatic head invading the portal vein and SMA (superior mesenteric artery) and SMV (*Figures 4,5*). In the pathobiological examination of tumor tissue, small round cells which were a sign of lymph proliferative disorder was seen and the examination of IHC proved the diagnosis of lymphoma.

Tumor markers

Serum carbohydrate antigen 9-19 (CA19-9) level increases

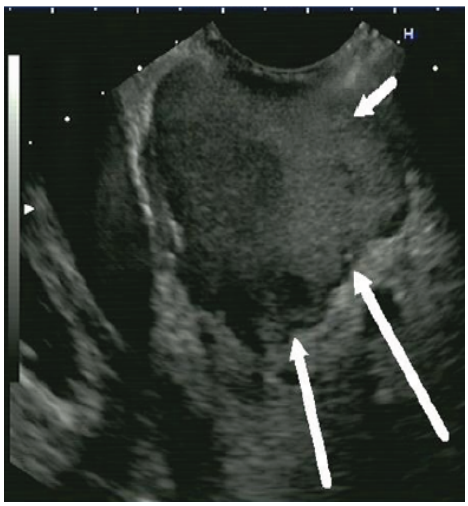

Figure 4 Diffusely enlarged of pancreas and echoic mass lesion 37–50 mm at the head of pancreas with adhesion to portal vein and SMV. SMV, superior mesenteric vein.

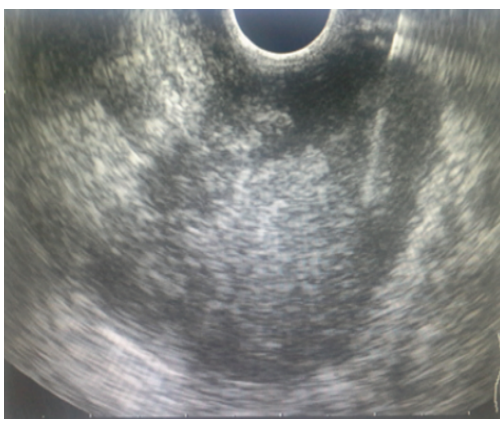

Figure 5 EUS-FNA indicated echoic lesion adhered to head of pancreas with invasion to portal vein, SMA and SMV. EUS-FNA, endoscopic ultrasound guided fine needle aspiration; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

rarely in patients with PPL (47). In contrast to patients with adenocarcinoma which is high in 80% of cases, CA19-9 is sometimes increased modestly in patients with PPL due to biliary obstruction (48). LDH serum can enhance in Lymphoproliferative disorders such as NHL; however, an increase in LDH is not required for the diagnosis of PPL (49).

Differential diagnoses

PPL is a rare disorder which can be present as a focal or diffuse mass and imitate the properties of common pancreas tumors such as adenocarcinoma or inflammatory process such as pancreatitis (47,50,51).

Table 1 Comparing PPL and adenocarcinoma

Diagnostic criteria	PPL	Adenocarcinoma
Vague abdominal symptoms	Common	Common
Symptoms B (fever-night sweats, weight loss)	Rare	Rare
Common result of imaging	Pancreatic mass	Pancreatic mass
Vascular involvement	Rarely	Common
Increasing CA19-9	Rarely	Often
Increasing LDH	Common	Rarely
Preferred treatment	Chemotherapy	Surgery

PPL, primary pancreatic lymphoma.

(I) Adenocarcinoma: pancreatic adenocarcinoma includes most pancreatic tumors; however, approximately 10–15% of masses are for other reasons such as cystic neoplasms and neuroendocrine tumors (52).

Differentiation PPL from adenocarcinoma is important since PPL has better prognosis even in advanced cases and can potentially be better treated. Due to the rarity of PPL and nonspecific clinical symptoms and imaging, differentiation of PPL from adenocarcinoma is very difficult without cytopathology. The tissue sampling can be performed through FNA under CT, EUS guides or sampling within surgery. Sampling by EUS or CT is preferred because it avoids unnecessary surgery and complications (7). *Table 1* shows a comparison of PPL and adenocarcinoma.

(II) Pancreatic neuroendocrine tumors: most pancreatic neuroendocrine tumors are sporadic; however, they may be associated with inherited genetic syndromes such as Multiple Endocrine Neoplasia (MEN) type 1 and 2.

They are without function in 45–91% of cases. Most tumors of functional neuroendocrine are insulinoma and then, glucagonoma, gastrinoma (Zollinger-Ellison syndrome), and somatostatinoma (53).

EUS-FNA has a sensitivity of over 90% for the diagnosis (54,55) and is useful to obtain tissue samples to examine the expression of Ki-67 so that prognostic factor is in the pancreatic endocrine tumors of the pancreas (53).

(III) Inflammatory process: PPL is a controversial

diagnosis as its radiological and clinical results are common to other pancreatic disorders such as AIP (an inflammatory disease of the pancreas which is usually determined by painless jaundice of pancreatic mass or enlargement and response to corticosteroids).

AIP diagnostic criteria include typical imaging findings of CT or MRI dynamics, increasing the level of IgG4, involvement of other organs (renal mass, tubulointerstitial nephritis, sclerosing cholangitis, retroperitoneal fibrosis, and submandibular mass), response to steroids and if available, examination of histology and immunostaining. Type 1 AIP is diagnosed without histological confirmation. In the cases that CT or MRI findings are typical for AIP and there are serum elevation of IgG4 or the involvement of other organs and in cases where diagnosis is not decisive based on other examinations, histological cytology is need (56).

Anderloni *et al.* (57) reported a case of primary pancreas lymphoma in a young woman with jaundice, fever, and abdominal pain that the patient's symptoms were Similar to autoimmune pancreatitis. Clinical examination by CT scan of abdomen and an endoscopy of upper GI showed a large duodenal mass. Endoscopic biopsy was done and the results were consistent with the primary lymphoma of the pancreas.

Abdi *et al.* (46) also reported a case of PPL presented with acute pancreatitis (Nausea, vomiting, RUQ and epigastric pain, high level of amylase 480 U/L, and lipase 326 U/L).

(IV) Metastatic diseases: metastasis to the pancreas is rare and no area of the pancreas is preferred (58). Most metastasis to pancreas is from renal cell carcinoma; however, metastasis has also been seen from other tumors including breast, lung, and colorectal tumors. There is usually a long delay between initial diagnosis of tumor and the presence of metastatic pancreas and multiple metastases may exist at the time of diagnosis (59). Metastasis to pancreas can result in the obstruction of bile duct or pancreatic duct, pain, and pancreatitis (60,61). The history of previous malignancy raises the possibility of metastatic lesion for pancreas. Thus, the examination for immunostains or core biopsy should be considered. EUSFNA by 22 gauge needle with immunostaining is a good diagnostic method in patients with unusual neuroendocrine or metastatic lesions (61).

Treatment

Treatment and prognosis of PPL depends on the stage and grade of the disease. Most PPLs are of diffuse large B cell type. According to recent reports, there have been a prolong remission in several cases of PPL with chemotherapy (62). The first-line of chemotherapy regimen is with prednisolone-vincristine-doxorubicin-cyclophosphamide (6,49). In some case of diffuse large B cell with positive CD20, rituximab is added to the above regimen and increases the rate of remission (3). The combination of radiotherapy and chemotherapy has been used in some cases; however, its effect has not been proven yet (63). In PPL, surgery is difficult because the tumor is large and along with the normal histology of other parts of pancreas and there is a high risk of pancreatic fistula after surgery as well (64).

Conclusions

PPL are rare lesions but potentially treatable by chemotherapy and have symptoms similar to other pancreatic malignancies and inflammatory lesions. Correct diagnosis of PPL is important to avoid unnecessary surgery. EUSFNA is a preferred method to obtain tissue sample for the diagnosis of PPL.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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