JOP. J Pancreas (Online) 2006; 7(3):262-273.

REVIEW

Primary Pancreatic Lymphomas

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Summary

Primary pancreatic lymphomas are extremely rare. Clinically, primary pancreatic lymphomas usually present with symptoms of carcinoma of the pancreatic head. Patients with primary pancreatic lymphomas are between 35 and 75 years of age and with a strong male predominance. Common clinical manifestations include abdominal pain, jaundice, acute pancreatitis, small bowel obstruction, and diarrhea. An accurate cytopathologic diagnosis by fine-needle aspiration (FNA) is imperative because the primary treatment is non-surgical. Cytomorphologic features include hypercellularity with discohesive cells with round nuclei, often prominent nucleoli, mitoses, and karyorrhexis. Flow cytometry analysis demonstrates a monoclonal pattern of immunoglobulin light chain expression. FNA coupled with flow cytometry analysis appears to be highly accurate in the diagnosis of primary pancreatic lymphomas. Fluorescence in-situ hybridisation technique has been established its role in the diagnosis of lymphoid malignancies, including primary pancreatic lymphomas. LDH and beta-2 microglobulin are important diagnostic and prognostic tumor markers. The differential diagnoses of primary pancreatic lymphomas include secondary lymphoma, pancreatic endocrine neoplasm, and florid chronic pancreatitis. The role of surgery is limited to the rare occasions when initial FNA and flow cytometry analysis are non-diagnostic. Treatment usually consists of a combination of chemotherapy and radiation therapy, or stem cell transplantation. Primary pancreatic lymphomas has a much better prognosis than adenocarcinoma of the pancreas.

Introduction

Extranodal non-Hodgkin's lymphomas (NHLs) represent up to 30-40% of all NHL cases. The gastrointestinal tract is the most commonly involved extranodal site; accounting for about half of such cases [1]. Stomach and the small intestine constitute the most common gastrointestinal sites. Secondary invasion of the pancreas from contiguous, retroperitoneal lymph node disease is the prevalent mode of involvement. Secondary involvement of the pancreas from the duodenum or adjacent peripancreatic lymphadenopathy is well-known. Primary pancreatic lymphoma (PPL) is an extremely rare disease [2]. PPL can present as an isolated mass mimicking pancreatic carcinoma. However, unlike carcinomas, PPL are potentially treatable [3].

Diagnostic Criteria

Diagnostic criteria for PPL, as defined by Dawson *et al.* [4] include:

1. neither superficial lymphadenopathy nor enlargement of mediastinal lymph nodes on chest radiography;

2. a normal leukocyte count in peripheral blood;

3. main mass in the pancreas with lymph-nodal involvement confined to the peripancreatic region; and

4. no hepatic or splenic involvement.

Incidence

The incidence of PPL is extremely rare. Fewer than 2% of extranodal malignant lymphomas and 0.5% of all pancreatic masses constitute PPL [1, 5, 6]. To date, fewer than 150 cases of PPL have been reported in the English medical literature.

Clinical Presentation

Studies done at different institutions after excluding secondary lymphomas, have suggested a strong male predominance (male-to-female ratio of 7:1). The patients range in age from 35 to 75 years (mean age: 55 years) [7]. In another study, there were 5 females and 2 males ranging in age from 60 to 86 years (mean age: 68 years). Most patients with PPL initially present with a pancreatic mass [8]. Although the clinical presentation of primary pancreatic lymphoma is nonspecific, some findings may strengthen the clinical suspicion of lymphoma rather than pancreatic cancer. 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%) (Table 1) [7, 8, 9, 10]. Other clinical symptoms may include anorexia, or early satiety. Obstructive jaundice seems to be less frequent than in pancreatic adenocarcinoma [8, 9]. The classic symptoms of nodal non-Hodgkin's lymphoma, such as fever, chills, and night sweats are uncommon, found in only 2% of patients [9, 10]. They certainly are not helpful signs in this diagnosis. A case with repeated episodes of unconsciousness as the presenting symptom has been reported [6]. The cause of unconsciousness here is related to low blood glucose levels (diabetic crisis) resulting from destruction of the pancreatic tissue by tumor infiltration [6]. It is of note that the review of literature suggested no significant difference regarding patient age or duration of symptoms between patients with non-Hodgkin's lymphoma primarily involving the pancreas and patients with pancreatic adenocarcinoma.

Head of the pancreas is the most common location (more than 80%), though tumor can be found in the body and tail region [7, 11]. The tumors vary in size from 2 to 15 cm in greatest dimension, with the mean dimension of 8.0 cm as evaluated on the radiological scans [7].

Etiology

The cause of PPL, akin to most non-Hodgkin's lymphomas is unknown. It is known that lymphomas are more likely to develop in immunosuppressive people, such as following organ transplant or HIV or AIDS. However, despite the increased risk, NHL is still uncommon in these people. Certain viruses such as the Epstein Barr virus, which causes glandular fever, can contribute to the development of lymphomas. One rare type of lymphoma, which usually affects the stomach - mucosa-associated lymphoid tissue (MALT) lymphoma - is known to be caused by a type of bacterial infection known as *Helicobacter pylori*. No such association is known to date with PPL. Familial pancreatic lymphoma has also been reported [8].

Diagnosis

Percutaneous ultrasound (US), endoscopic ultrasound (EUS) and computed tomography

Table 1. Common manifestations of primary pancreatic lymphoma.

Symptom/sign	Incidence
Abdominal pain	83%
Abdominal mass	58%
Weight loss	50%
Jaundice	37%
Nausea	34%
Vomiting	18%
Diarrhea	12%
Pancreatitis	12%
Bowel obstruction	12%
Diarrhea	12%
Fatigue	9%
Fever, chills, night sweats	2-7%
Gastrointestinal bleeding	2%
Gastric outlet obstruction	2%

(CT) scan are well-established procedures to evaluate pancreatic masses. Imaging procedures can suggest a diagnosis of PPL, but a cytohistological diagnosis is mandatory for diagnosis and treatment planning of patients with suspected pancreatic mass. This cytohistological diagnosis can be performed by CT- or US-guided fine-needle aspiration biopsy (FNAB) and tissue core fine-needle biopsy (FNB) [12, 13].

Conventional Radiography

PPL does not contain calcifications, when untreated. Therefore, radiographs of the abdomen are of little value [14]. On the other hand, barium examination of the upper gastrointestinal tract may show duodenal effacement, reflecting a large tumor mass, but it is not commonly performed and is of limited value [14].

Angiography

The role of conventional angiography to evaluate vessel patency has been replaced by the CT imaging. We did not find any conventional angiographic that address PPL. However, literature review reveals patency of the peripancreatic vessels in most patients with PPL: encasement of the proximal superior mesenteric artery in 12% of patients, stenosis of the superior mesenteric vein or the confluence of the portal and superior mesenteric veins in 5%, and splenic vein occlusion in 4% [14]. These imaging findings differ from those found in patients with pancreatic adenocarcinoma, in whom vessel stenosis or occlusion is a very common finding and the most common reason for unresectability.

CT Scan

Imaging plays a key role in the diagnosis and staging of pancreatic masses. Lymphoma certainly falls into this group of diseases. CT is by far the most common imaging technique used in the detection and characterization of primary pancreatic lymphoma. Most lesions are less dense than muscle and appear homogeneous. Small heterogeneous areas within a tumor mass can be seen in isolated cases, and, therefore, do not allow exclusion of the diagnosis of primary pancreatic lymphoma. Enhancement after administration of i.v. contrast medium is usually poor yet homogeneous. Heterogeneous enhancement was reported in isolated cases, but this finding alone prevents differentiation from adeno-carcinoma [14, 15, 16].

Radiologists imaging the pancreas must be familiar with the imaging findings of pancreatic lymphoma and be able to differentiate it from pancreatic adeno-carcinoma because treatment and prognosis of the both differ significantly. Two different morphologic patterns of pancreatic involvement are seen in patients with PPL [14]:

i) a localized, well-circumscribed tumoral form; and

ii) a diffuse enlargement infiltrating or replacing most of the pancreatic gland.

Certain radiological findings have been found to be beneficial to differentiate PPL from the more common pancreatic adenocarcinoma [14]:

a. the combination of a bulky localized tumor in the pancreatic head without significant dilatation of the main pancreatic duct strengthens a diagnosis of pancreatic lymphoma over adenocarcinoma;

b. enlarged lymph nodes below the level of the renal veins; and

c. invasive tumor growth not respecting anatomic boundaries and infiltrating retro-peritoneal or upper abdominal organs and the gastrointestinal tract are additional reliable signs for PPL.

Neither calcifications nor necrosis within the tumor mass have been described in any case of untreated PPL. Presence of calcification or necrosis is helpful findings for ruling out non-Hodgkin's lymphoma. Prayer *et al*. described invasive tumor growth not respecting anatomic boundaries and infiltrating retro-

peritoneal or upper abdominal organs and the gastrointestinal tract as an additional reliable sign for non-Hodgkin's lymphoma [17]. This conclusion was further supported by Van Beers *et al*., who also reported adjacent duodenal invasion in three of eight patients [16].
Performing a contrast-enhanced scan with current helical CT arterial phase techniques reliably assesses patency of the main pancreatic vessels and adjacent arteries and veins. Imaging findings show encasement of the superior mesenteric artery and stenosis or occlusion of the superior mesenteric, splenic, or portal vein in a minority of cases as described above.

MR Imaging

Merkle *et al*. reported two different morphologic patterns of pancreatic involvement seen on MR imaging that are similar to the CT appearance [14]:

i) the well-circumscribed tumoral type appears as a low-signal-intensity homogeneous mass within the pancreas on T1-weighted images with subtle enhancement after i.v. administration of gadolinium-containing contrast medium. On T2-weighted images, a tumoral mass shows a more heterogeneous character with a low to intermediate signal amplitude slightly higher than that of the residual gland but much lower than the signal intensity of fluid;

ii) the diffuse infiltrating type of pancreatic involvement shows similar characteristics of low signal intensity on unenhanced T1- and T2-weighted images, with mild to moderate enhancement after gadolinium injection. In the diffuse infiltrating type, enhancement is predominately homogeneous but may include small foci of little or no gadolinium uptake.

In general, bile and pancreatic ductal dilatation can be easily assessed with MR imaging using MR cholangiopancreatography. Only mild pancreatic ductal dilatation is visible on the MR imaging cases presented.
Furthermore, MR imaging is equivalent to CT regarding information about the peripancreatic vessels and enlarged lymph nodes. Additional information is obtained when MR angiography is used.

Endoscopic Retrograde Cholangiopancreatography (ERCP) and Percutaneous Transhepatic Choledochography (PTC)

The findings of ERCPs of Wirsung's duct appearance were also available in the literature:

a. 30 % showed a normal duct appearance;

b. 10% ductal displacement;

c. 50% mild duct stenosis;

d. 10% stricture of the main pancreatic duct; and

e. no severe distal dilatation of Wirsung's duct.

This is in contrast to pancreatic adenocarcinoma in which moderate to severe dilatation of Wirsung's duct is common [12, 18].
Bile duct dilatation from obstruction is seen more often because jaundice occurs in 42% of patients with non-Hodgkin's lymphoma primarily involving the pancreas.

US- and CT-Guided Biopsy

An accurate fine needle aspiration (FNA) diagnosis of PPL is critical for timely, non-surgical management and obviates the need for an exploratory laparotomy [14]. FNA is considered a safe, rapid, and easy procedure with high diagnostic accuracy. Percutaneous or endoscopic core biopsy should be performed to establish the diagnosis. In early reports, because percutaneous imaging guided biopsy was not considered an accurate diagnostic tool, the correct diagnosis was rarely made. This attitude has changed significantly in the last decade. Recent literature shows US- and CT-guided biopsy techniques can easily provide sufficient diagnostic tissue [12, 13, 14, 18, 19, 20]. This technique is without major complications. In most patients, the diagnosis can be established

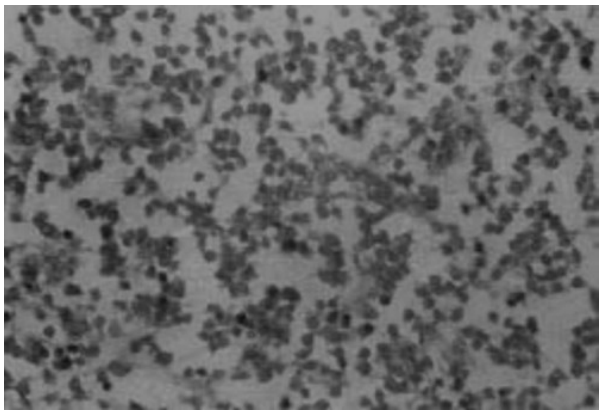

Figure 1. Fine needle aspiration biopsy of pancreatic mass showing small round cells in loose sheets consistent with the diagnosis of primary pancreatic lymphoma (PPL).

without surgery; this fact is a major reason to look for findings suggestive of pancreatic lymphoma.

The smears show variable degrees of cellularity, with the majority of the cases containing ample amounts of diagnostic material [7]. Cells can be present in a discohesive pattern with only rare intact fragments of the native non-neoplastic pancreas or fibroconnective tissue observed (Figure 1). Malignant lymphocytes have large nuclei (greater than three to four times the size of a mature lymphocytic nucleus) with single to multiple prominent nucleoli. The nuclei are predominantly naked in a background of abundant necrosis and karyorrhexis. Higher magnification can illustrate marked anisonucleosis, prominent nucleoli, deep nuclear indentations, scant to barely discernible cytoplasm, and karyorrhexis. Lymphoglandular bodies can be present in the slide background. A predominantly small lymphocytic population with deeply cleaved nuclei, whereas a monotonous population of small, mature-appearing lymphocytes can be found [7].

Endoscopic Ultrasonography (EUS)

Recently, EUS has also been used to evaluate pancreatic masses and surrounding structures. EUS can, in some cases, provide histological diagnosis of PPL [21]. Flamenbaum *et al*. described the typical endoscopic sonography findings as a strongly hypoechogenic appearance in the pancreas, hypertrophy in all its segments, a hyperechoic wall in the common pancreatic duct contrasting with the adjacent parenchyma, and multiple isoechogenic peripancreatic lymph nodes [22]. These authors concluded that the endoscopic sonography findings were highly specific and allowed distinction of lymphoma from all other pancreatic tumors.

Surgery

With the availability of these less invasive modalities, surgery should be reserved for the rare instance when percutaneous or endoscopic biopsies are not diagnostic. Another possible role for surgery in PPL was to by-pass biliary obstruction, but in recent years various non-operative strategies can provide a high rate of successful relief of this complication [23].

Flow Cytometry

Flow cytometry (FC) has significantly enhanced the diagnostic role of FNA, particularly in the case of hematolymphoid malignancies. FC is extremely sensitive in the detection of antigen expression and identifies small clonal populations. FC analysis distinguishes lymphomas from chronic pancreatitis through the detection of clonality based on surface Ig light chain expression studies. In lymphomas, Ig light chain expression is usually restricted to either kappa or lambda, whereas inflammatory processes reveal a mixed expression of kappa and lambda light chains. FC also has limited capability in classifying lymphomas into different, well recognized subcategories. This is made possible by studies of surface marker expression and is best applicable for low-grade lymphomas [7, 14, 24].

In a study performed at Johns Hopkins Hospital, six cases were classified by FC analysis, as large B-cell lymphomas (LBCL), all of which had Ig light chain restriction and CD20 expression. One case of LBCL also expressed CD10, which is a marker of follicular center cell differentiation and raised

the possibility of a large cell transformation from a follicular center cell lymphoma. FC data concerning another case revealed CD20 expression and kappa light chain restriction. The immunophenotype, along with the cytomorphologic findings of small lymphocytes with cleaved nuclei, favored a diagnosis of a low-grade follicular center cell lymphoma. FC for one case revealed a clonal population of small lymphocytes with coexpression of CD5 and CD23, a phenotype that is consistent with a diagnosis of small B-cell lymphocytic lymphoma (SLL) [7].

Fluorescence In-Situ Hybridisation

Cytogenetic analysis is now a routine part of the diagnosis and management of a significant number of lymphoid malignancies. Whilst conventional cytogenetics remains the most comprehensive method for assessing chromosome abnormalities, the technical difficulties associated with conventional cytogenetics in most lymphomas has resulted in increased use of fluorescence in situ hybridisation (FISH) to identify specific abnormalities that are useful in either the diagnosis or management of these disorders. FISH technique is useful to detect chromosome anomalies with high sensitivity and specificity in paraffin-embedded tissue and may provide important diagnostic and prognostic genetic information [25].

Hemathology

In general, patients with PPL have normal hemoglobin level, total and differential white blood cell counts and platelets. Microscopic evaluation of peripheral blood smears can reveal normal leukocyte count, without atypical lymphoid cells [7, 9, 18].

Serum Tumor Markers

Anecdotal case reports of elevated CA 19-9 levels in PPL have been reported [26]. Lactate dehydrogenase (LDH) and beta-2-micro-globulin are both essential serum markers for the diagnosis and differential diagnosis of PPL. Beta-2-microglobulin level greater than 2 mg/L and LDH level higher than normal are poor prognostic markers [27].

Bone Marrow Biopsy

Bone marrow (trephine) biopsy should done in all patients even with normal blood counts to complete the staging.

Types of PPL

All cases of PPL reported to date in Western countries are of the B-cell type, but some cases of T-cell pancreatic lymphoma have been described in Japanese series. Most cases are intermediate or high-grade NHL, with diffuse large cell lymphoma being the predominant (about 60%) histotype [7, 9, 28, 29, 30]. Low grade lymphoplasma cytic subtypes have also been reported. Approximately four cases of a anaplastic large cell (ALK-) PPL lymphoma (ALCL-PPL) have been reported. ALCL is an uncommon type of NHL, first described as a pleomorphic large cell lymphoma with strong membrane and Golgi associated CD30/Ki-1 antigen expression in a very high percentage of neoplastic lymphoid cells, with the involvement of paracortical region and sinuses of lymph nodes [31]. The main histologic patterns accepted by WHO are the common variant, the lymphohistiocytic and the small cell variant. In these lymphomas, the most frequent genetic alteration is the translocation t (2; 5) (p23; q35) between the anaplastic lymphoma kinase (ALK) gene on chromosome 2 and the nucleophosmin (NPM) gene on chromosome 5. As a result of this translocation, the hybrid (NPM-ALK) gene promotes the production of chimeric NPM-ALK protein. The NPM-ALK fusion chimeric protein can be detected immunohistochemic-ally using monoclonal or polyclonal antibodies, by RT-PCR and FISH [31].

Differential Diagnosis

Progressive painless jaundice associated with an aggressive pancreatic mass and a lack of

Table 2. Differential diagnosis of primary pancreatic lymphoma (PPL).

Differential diagnoses	Differentiating features
Secondary lymphoma	‣ Imaging studies help to differentiate PPL (which are either organ confined or further involve the immediate peripancreatic lymph nodes) from secondary lymphomas.
Florid chronic pancreatitis	‣ Presence of calcification or necrosis is helpful findings for ruling out non-Hodgkin's lymphoma (NHL).
Pancreatic endocrine neoplasm (PEN)	‣ PEN could be identified by their distinctive cytomorpholgy, immunoperoxidase (IPOX) characteristics, and negative flow cytometry (FC) analysis. PEN usually express CD56 and are negative for lymphoma markers, findings that could be evaluated by both FC and IPOX analysis. ‣ PEN demonstrates relatively small uniform neoplastic cells with a well preserved rim of granular-appearing cytoplasm. ‣ Nuclei are most often eccentrically placed within the cell cytoplasm, giving a plasmacytoid appearance, with finely granular and evenly distributed chromatin. ‣ Rarely, a predominant population of tumor cells with naked nuclei is observed simulating NHL.
Acinar cell carcinoma	‣ Less often, acinar cell carcinoma can have a predominant population of discohesive single cells and may resemble an NHL. ‣ However, closer examination reveals fragile, basophilic, granular cytoplasm. ‣ Nuclei often have prominent nucleoli and the slide background shows distinctive finely vacuolated or foamy material derived from tumor cell cytoplasm.

significant lymphadenopathy creates diagnostic confusion with a primary ductal carcinoma [11]. Pancreatic lymphoma is often described as a large, homogeneous mass with extrapancreatic extension, with or without associated lymphadenopathy. Histologically, swollen mesenteric lymph nodes biopsied intraoperatively showed lymphoplasmacytic lymphoma findings. It is important to consider lymphoma in a patient with suspected adenocarcinoma showing atypical imaging findings no matter how minor they are [30]. Less common presentations are masses in the body or tail of the pancreas, or, more rarely, diffuse involvement of the entire organ [30]. Clinically, the differential diagnosis of primary pancreatic lymphoma from pancreatic carcinoma is most often extremely difficult, particularly when these masses are associated with an elevated CA 19-9 level [26]. Based on cytomorphology, the main differential diagnoses of PPL are secondary lymphomas, pancreatic endocrine neoplasms (PENs), acinar cell carcinoma, and florid chronic pancreatitis (Table 2).

Staging

As with many other cancers, NHL is categorized on the basis of tumor burden. The Ann Arbor Staging System is the most popular system for classifying NHL [32]. The Ann Arbor Staging categories are described in Table 3.

Table 3. The Ann Arbor Staging for non-Hodgkin's lymphoma (NHL) including primary pancreatic lymphoma (PPL).

Stage 1	NHL is limited to one lymph node group (e.g., neck, underarm, groin, etc.) above or below the diaphragm, or NHL is in an organ or site other than the lymph nodes (extranodal) but has not spread to other organs or lymph nodes.
Stage 2	NHL is limited to two lymph node groups on the same side of the diaphragm, or NHL is limited to one extranodal organ and has spread to one or more lymph node groups on the same side of the diaphragm.
Stage 3	NHL is in two lymph node groups, with/without partial involvement of an extranodal organ or site above and below the diaphragm.
Stage 4	NHL is extensive (diffuse) in one organ or site, with/without NHL in distant lymph nodes.

After an NHL patient has been assigned a stage, this categorization may be refined by adding the biologic grade of the disease, that is, "low", "intermediate", or "high" grade. Other descriptive terms - such as "bulky" versus "non-bulky" disease and the presence or absence of B symptoms - may be used to fully describe a particular case of lymphoma.

Additional Designations
(applicable to any of the stages of Hodgkin's disease or NHL)

- A: absent (no) symptoms;
- B: presence of any of the following B symptoms: fever (greater than 38.6 °C), drenching night sweats, unexplained weight loss of 10% or more within the last 6 months, severe itching (see the signs and symptoms of lymphoma reported in the "Clinical Presentation" section);
- E: involvement of a single extranodal (other than the lymph nodes) site that directly adjoins or is next to the known nodal group;
- X: Presence of "bulky" disease, that is, a nodal mass whose greatest dimension is more than 10 cm in size, and/or a widening of the mediastinum (middle chest) by more than one-third;
- CS: clinical stage as obtained by doctor's examinations and tests;
- PS: pathological stage as obtained by exploratory laparotomy (surgery performed through an abdominal incision) with splenectomy (surgical removal of the spleen).

Treatment

Treatment of PPL consists of surgery, chemotherapy, radiotherapy or a combination of the above. The majority of patients with PPL can be managed without surgery and long-term disease remission can be obtained with chemotherapy alone [14, 23]. The role of surgery in this setting is limited to rare occasions when FNA plus FC are non-diagnostic, and tissue diagnosis therefore is required [23]. Furthermore the size of the local lymphoma mass in pancreas is important for the choice of therapy: surgery *vs*. chemotherapy *vs*. radiation *vs*. combination. Larger series of patients are needed to evaluate whether chemotherapy, eventually followed by involved-field radiation therapy, is the treatment of choice of PPL (Table 4) [7, 10]. Given the uncommon nature of this pathology, data should be collected in a large co-operative setting.

I. Surgery

Total pancreatectomy (Whipple procedure) is considered to have no impact on survival in a patient with PPL and, with its associated morbidity, is not generally recommended for diagnosis and treatment of PPL [12]. Some investigators have suggested a beneficial role for surgical resection only in stage I or early stage II PPL. Unfortunately, the limited number of cases in the literature does not permit a comparison between the outcome of surgical and non-surgical therapy. With the availability of these less invasive modalities, surgery should be reserved for the rare instance when percutaneous or endoscopic biopsies are not diagnostic [23, 33, 34].
Another possible role for surgery in PPL was to by-pass biliary obstruction, but in recent years various non-operative strategies can provide a high rate of successful relief of this complication [35].

Table 4. Treatment options for primary pancreatic lymphoma (PPL).

Modality	Indication	Comment
Surgery	1. Stage I 2. Stage II 3. FNA + flow cytometry (FC) non-diagnostic and tissue diagnosis is needed	Limited role
Chemotherapy	1. Primary treatment after tissue diagnosis 2. Adjuvant following surgery	Primary treatment
Radiotherapy	1. Adjunct to chemotherapy	Role poorly defined

Table 5. Most commonly used chemotherapy regimens in the treatment of primary pancreatic lymphoma (PPL).

Regimen	Agent
CVP	C: cyclophosphamide V: vincristine P: prednisone
CHOP	C: cyclophosphamide H: doxorubicin O: vincristine P: prednisone
MACOP-B	M:methotrexate A: adriamycin C: cyclophosphamide O: vincristine P: prednisone B: bleomycin

Adjuvant surgery discussed in the literature is controversial. Some surgeons advocate a choledochojejunostomy in patients with jaundice as a fast and permanent treatment option. Other groups perform transient endoscopic or percutaneous stenting for biliary drainage. Only technical information about pancreatic stenting is provided in the current literature.
Surgical tumor debulking is not generally accepted and is suggested in only one report.

II. Adjuvant Chemotherapy

Pancreaticoduodenectomy followed by chemotherapy regimens, such as cyclophosphamide, vincristine, prednisone (CVP) and cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) have been reported. Mostly, six cycles were administered [10].

III. Chemotherapy

Chemotherapy is the treatment of choice for most patients with pancreatic lymphoma. The most common regimen includes cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone: CVP; CHOP; MACOP-B (methotrexate, adriamycin, cyclophosphamide, vincristine, prednisone, bleomycin) (Table 5). In cases of hepatic dysfunction, non-hepatotoxic agents (CVP) has been administered with 50% reduction and promising outcome [14, 18, 30, 31, 36].

Rituximab, a chimeric monoclonal antibody against the CD20 B-cell antigen, has therapeutic activity in diffuse large-B-cell lymphoma. The addition of rituximab to the CHOP regimen increases the complete-response rate and prolongs event-free and overall survival in patients with diffuse large-B-cell lymphoma, without a clinically significant increase in toxicity [37].

IV. Radiotherapy

The role of radiation therapy in the management of PPL is also not yet defined [7, 14]. The role of radiation therapy as an adjunct to chemotherapy for the treatment of this disease is also poorly defined. Local radiotherapy up to total 40 Gray has been used as consolidation. No unexpected therapy-related complications have been reported, except for a case of hemorrhagic post-attinic gastritis [38].

V. Autologous Peripheral Blood Stem Cell Transplantation

Limited data exists for the role of autologous peripheral blood stem cell transplantation in patients with PPL. We found one patient who underwent bone marrow transplantation and had no evidence of disease at 7 months [7].

VI. Palliation

Bile duct dilatation from obstruction is seen more often because jaundice occurs in 42% of patients with non-Hodgkin's lymphoma primarily involving the pancreas. Usually, endoscopic or percutaneous stent insertion is performed as a preliminary treatment procedure [14].

Prognosis

The Milan Cancer Institute reported that tumor burden and LDH levels represented the most important prognostic factors affecting outcome primary gastrointestinal non-Hodgkin's lymphoma [39].
Using complex treatment approaches, cure rates of up to 30% are reported for patients with primary pancreatic lymphoma. This prognosis is much better than the dismal 5% 5-year survival rate in patients with pancreatic adenocarcinoma [14].

Table 6. Prognosis of primary pancreatic lymphoma (PPL) with different modalities of treatment.

Reference	Type of Treatment	Outcome
Arcari *et al*. [10]	Surgery plus chemotherapy	5-8 months
	Chemotherapy	69-80 months
Behrns *et al*. [33]	Chemotherapy	13 months
	External radiation therapy	22 months
	Chemotherapy plus external radiation therapy	36 months

In one study of 10 patients with PPL, the mean survival was 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) (Table 6) [30].

In a report by Arcari *et al*., three patients diagnosed by percutaneous biopsy were treated with chemotherapy as front-line therapy and two of them received also local radiotherapy; one of these patients is still alive in complete remission at 69 months, one died of an unrelated disease at 67 months and one died of lymphoma relapse at 88 months. Two patients underwent pancreaticoduodenectomy plus adjuvant chemotherapy; one of them died of recurrent cholangitis 8 months after surgery while the other one is still alive in complete remission after 160 months [10].

Late recurrence as late as 18 years after treatment achieving complete remission for PPL has been reported [40].

In a Japanese study [9], immunophenotypic differences in outcome were observed. It was found that the 1-year actuarial survival rate for B-cell lymphomas (51.9%) was better than that of T-cell lymphomas (0%). However, in Japan the incidence of T-cell PPLs was higher, and, partly as a consequence of this, prognosis was poorer than in Western countries [9].

Conclusions

In summary, PPL is a rare form of extranodal lymphoma comprising less than 0.5% of pancreatic tumors originating from the pancreatic parenchyma. Although rare, this particular neoplasm is amenable to treatment even in very advanced stages. The clinical and radiological findings are not pathognomonic and the diagnosis is established only after histopathologic examination. Imaging procedures can suggest a diagnosis of PPL, but a cytohistological examination is mandatory for diagnosis and treatment planning of patients with suspicious PPL. Since patients with PPL require a non-surgical, chemotherapy-based treatment and have a much better prognosis than those with adenocarcinoma, percutaneous FNAB and FNB should be considered in all patients with pancreatic masses suspected to be of lymphomatous nature at imaging studies. Since most of the case reports in literature mention a favorable outcome following treatment, it is important to establish a definitive diagnosis for this disease. However, involvement of an experienced cytopathologist and immunohistochemical assays are necessary to obtain a correct diagnosis on a small amount of tissue.

Received February 7th, 2006 - Accepted March 29th, 2006

Keywords Lymphoma; Lymphoma, Non-Hodgkin; Pancreas; Pancreatic Diseases; Pancreatic Neoplasms

Abbreviations ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; CVP: cyclophosphamide, vincristine, and prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; FC: flow cytometry; FISH: fluorescence in situ hybridization; FNA: fine needle aspiration; FNAB: fine-needle aspiration biopsy; FNB: fine-needle biopsy; IPOX: immuno-peroxidase; LBCL: large B-cell lymphomas; NHL: non-Hodgkin's lymphoma; NPM: nucleophosmin; PEN: pancreatic endocrine

neoplasm; PPL: primary pancreatic lymphoma

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