

Primary pancreatic lymphoma. Report of five cases

Primary pancreatic lymphoma (PPL) is a very rare disease. We report five cases of PPL (4 men and 1 woman, mean age 65 years) diagnosed and treated at our Institution from 1987 to 1997. None of these patients had evidence of extrapancreatic disease and they were categorized as PPL involving pancreas only (stage IE, 3 patients) or pancreas and peripancreatic lymph nodes (stage IIE, 2 patients). The most common presenting symptoms were abdominal pain and weight loss. Imaging techniques showed a mass of the pancreatic head in all cases. The histological diagnosis (3 diffuse-large cell non-Hodgkin's lymphoma and 2 lymphoplasmacytic lymphoma/immunocytoma) was made by ultrasound-guided fine needle aspiration biopsy and tissue core fine-needle biopsy in three patients and by surgery in the remaining two patients. The 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. This study shows that: 1) imaging techniques can suggest the suspicion of PPL but are unable to distinguish PPL from pancreatic adenocarcinoma; 2) histological diagnosis can be easily obtained by percutaneous US-guided tissue core biopsy; 3) surgery can be avoided both for diagnosis and therapy but the treatment of choice of PPL may only be evaluated on a larger series of patients

Haematologica 2005; 90(3):e23-e26

Extranodal non-Hodgkin's lymphomas (NHL) represent up to 30-40% of all NHL cases. The gastrointestinal tract, especially the stomach and the small bowel, is the most commonly involved extranodal site, accounting for about half cases.¹ Although secondary involvement of the pancreas from the duodenum or adjacent peripancreatic lymphadenopathy is not uncommon and well documented,² primary pancreatic lymphoma (PPL) is an extremely rare disease, representing fewer than 2% of extranodal malignant lymphomas and 0,5% of all pancreatic masses.³ Fewer than 150 cases of PPL have been reported in the English literature.⁴ Diagnostic criteria of PPL, defined by Dawson *et al.*,⁵ 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; 4- no hepatic or splenic involvement. 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.⁶ Most cases are intermediate or high-grade NHL, with diffuse large cell lymphoma being the predominant (about 60%) histotype.^{4,7}

Presenting symptoms are non-specific, including abdominal pain, weight loss, nausea and vomiting. Obstructive jaundice seems to be less frequent than in pancreatic adenocarcinoma. Systemic symptoms such as fever, chills and night sweats are uncommon.^{4,7-9}

PPL is often described at imaging techniques as a large

homogeneous mass, frequently infiltrating extra-pancreatic surrounding tissues, with or without associated retroperitoneal and/or mesenteric lymphadenopathy. In most cases the pancreatic mass is located in the head of the gland; less common presentations are masses in the body or tail or diffuse pancreatic involvement. Some authors [10] have described a low incidence of significant dilatation of Wirsung's duct, patency of the major peripancreatic vessels in most patients and absence of calcifications or necrosis within the tumour mass. Lymph node involvement below the renal veins could be another finding not seen in pancreatic adenocarcinoma. Percutaneous ultrasound (US), endoscopic US and computed tomography (CT) scan are well-established procedures to evaluate pancreatic masses, however these imaging techniques alone cannot allow a pathologic diagnosis. A cyto-histological diagnosis of a pancreatic mass can be performed by CT or US-guided fine-needle aspiration biopsy (FNAB) and tissue core fine-needle biopsy (FNB).^{11,12}

We report five cases of PPL observed between 1987 and 1997 at our Medical Oncology and Haematology Department. The aim of this report is to describe the clinical presentation of this rare disease, the diagnostic procedures and treatment.

Design and methods

A retrospective analysis of all NHL cases diagnosed and treated at Medical Oncology and Haematology Department, Hospital of Piacenza, Italy, between July 1987 and October 1997, was performed. The records of 630 patients with NHL were analysed. After a detailed examination of the available material, a group of five patients (0,8%) with confirmed diagnosis of PPL was identified. All cases satisfied the definition for PPL proposed by Dawson *et al.*⁵ Data concerning age, sex, clinical presentation, comorbidity, imaging findings, cyto-histological diagnosis, treatment modality and follow-up were retrospectively reviewed. Results of haematological and biochemical analyses including haemoglobin level, platelets count, total and differential white blood cell count, peripheral blood smears, erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), serum aspartate aminotransferase (SGOT), serum alanine aminotransferase (SGPT), total and direct bilirubin, alkaline phosphatase (ALP), serum protein electrophoresis, anti Hepatitis C Virus antibody (anti HCV-Ab) and Hepatitis B Virus surface antigen (HBs Ag) were available in all patients, as well as chest X-ray, abdominal US and CT scanning of the chest and the abdomen. For patients diagnosed before 1990 anti HCV-Ab was performed in their frozen sera. Serum amylase and the tumour marker CA 19.9 were available in three patients.

Two patients underwent exploratory laparotomy with resection of the pancreatic mass, while in three patients percutaneous US-guided FNAB and FNB were performed as previously reported.¹¹⁻¹⁴ Bone marrow trephine biopsy, liver biopsy and upper gastrointestinal endoscopy were performed in all patients.

Clinical staging was assigned using the Ann Arbor classification. All histological sections were reviewed and classified according to the Revised European American Lymphoma (REAL) classification.¹⁵

Results

From July 1987 to October 1997, five patients with PPL were diagnosed and treated at our Medical Oncology and Haematology Department. This group represents about 0,8% of all NHL patients (5 of 630) referred to our

Institute during the same period. Four men and one woman were identified. The mean age at diagnosis was 65 years (range 58-71 years). Abdominal pain and weight loss (>10% of body weight within 6 months before the diagnosis) were the most common presenting symptoms, observed in 4 of 5 patients (80%). Other B-symptoms such as fever, chills or night sweats were absent in all cases. Jaundice due to extra-hepatic biliary obstruction was present in 3 of 5 patients (60%) and required percutaneous stenting for biliary drainage in one case (patient n.4).

Laboratory results are summarized in Table 1.

Table 1. Primary pancreatic lymphoma. Laboratory data of the five reported patients

	mean values	range	n. of patients upper normal values
LDH (U/l)	446	148-993	2/5 (40%)
ESR (mm/h)	28	14-40	3/5 (60%)
Total bilirubin (mg/dl)	6.0	1.0-13.0	4/5 (80%)
Dir. bilirubin (mg/dl)	3.4	0.3-7.2	4/5 (80%)
ALP (U/l)352	141-559	3/5 (60%)	
SGOT (U/l)	68	19-137	3/5 (60%)
SGPT (U/l)	72	21-186	3/5 (60%)
Serum amylase (U/l)	271	108-492	3/3 (100%)
CA 19.9 (U/ml)	167.9	16.1-446.0	2/3 (67%)

LDH: lactate dehydrogenase (normal value: 220-450 U/l); ESR: erythrocyte sedimentation rate (normal value: 1-37 mm/h); total bilirubin (normal value: 0-1.1 mg/dl); direct bilirubin (normal value 0-0.3 mg/dl); ALP: alkaline phosphatase (normal value 64-300 U/l); SGOT: serum aspartate aminotransferase (normal value 10-37 U/l); SGPT: serum alanine aminotransferase (normal value 10-37 U/l); serum amylase (normal value < 100 U/l); CA 19.9 (normal value < 37 U/ml)

Haemoglobin level, total and differential white blood cell count and platelets were within normal limits in all cases. Microscopic evaluation of peripheral blood smears revealed normal leukocyte count, without atypical lymphoid cells. Two patients had associated hepatitis C virus chronic infection, one with clinical evidence of cirrhosis and the other one with chronic hepatitis. No patients had hepatitis B virus infection.

Diagnostic and staging procedures are summarized in Table 2. In three cases abdominal CT and US scans showed a bulky hypodense/hypoechoic homogeneous mass originating from pancreatic head and infiltrating retroperitoneal tissues; in two of them there was also encasement of mesenteric, splenic and portal vessels. Only in two cases (subsequently diagnosed as low grade NHL) there was a well-circumscribed pancreatic lesion. Dilatation of the common bile duct was present in two cases, while significant dilatation of Wirsung's duct was never found. In two cases peripancreatic lymphadenopathy were described, while none of the patients had superficial, thoracic or other abdominal lymph node enlargement. Figure 1 shows a CT abdominal scan in patient n. 4; it is possible to recognize a hypodense pancreatic head mass (diameter 5 cm) with compression of the common bile duct in the last tract and gall bladder dilatation.

Upper gastrointestinal endoscopy revealed duodenal ab extrinseco compression in one case (patient n.3), while was normal in the remaining four patients. Bone marrow trephine biopsy was negative in all cases. Liver biopsy (percutaneous US-guided in three patients and by laparotomy in two patients) showed no liver involvement.

In all cases a cyto-histological diagnosis was obtained: in three cases by percutaneous US-guided FNAB and FNB, in two cases by examination of the surgical pancreatic specimen after pancreaticoduodenectomy. Three cases were diffuse large-cell non-Hodgkin's lymphoma and two cases were low grade lymphoplasmacytic lymphoma/immunocytoma according to the REAL classification. Immunophenotypically all cases were of B-cell origin. Clinical stage at diagnosis according to the Ann Arbor classification was IE in three patients and IIE in two patients.

Radical resection of the tumour by pancreaticoduodenectomy was performed only in two patients (n. 2 and n. 5) initially referred to surgery departments for suspicion of pancreatic adenocarcinoma. Pancreaticoduodenectomy was followed by six courses of chemotherapy including cyclophosphamide, vincristine, prednisone (CVP) in one case and cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) in the other one. The

Table 2. Primary pancreatic lymphoma: diagnostic procedures and clinicopathological findings of the five reported patients

Case No	Imaging techniques	Diagnostic biopsies CT/US	Cytohistic findings	Ann Arbor Stage
1	hypodense/hypoechoic bulky pancreatic head mass infiltrating retroperitoneal tissues with encasement of mesenteric, splenic and portal vessels; diameter 5 cm; biliary dilatation; peripancreatic lymph nodes	FNAB + FNB	large B-cell	IIE
2	hypodense/hypoechoic well-circumscribed pancreatic head lesion; diameter 3 cm	surgery	lymphoplasmacytic	IE
3	hypodense/hypoechoic bulky pancreatic head mass infiltrating retroperitoneal tissues with encasement of mesenteric, splenic and portal vessels; diameter 6.5 cm; duodenal ab extrinseco compression, peripancreatic lymph nodes	FNAB + FNB	large B-cell	IIE
4	hypodense/hypoechoic bulky pancreatic head mass infiltrating retroperitoneal tissues; diameter 5.0 cm; biliary dilatation	FNAB + FNB	large B-cell	IE
5	hypodense/hypoechoic well-circumscribed pancreatic head lesion; diameter 3.5 cm	surgery	lymphoplasmacytic	IE

FNAB: fine-needle aspiration biopsy; FNB: fine-needle tissue core biopsy. CT: computed tomography; US: ultrasound.

remaining three patients (n. 1, n. 3, n. 4) were treated with chemotherapy, initially with non-hepatotoxic drugs (two cycles of CVP with dose reduction at 50%) and then, after the normalization of the bilirubin level, with CHOP regimen (four cycles). Two of them received also local radiotherapy (total 40 Gray) as consolidation. We did not observe therapy-related complication, except for a case of haemorrhagic post-attinic gastritis (patient n. 1). All patients achieved a complete remission. The mean follow-up was 78 months (range 8-160 months). Among the three cases treated with non-surgical therapy, one patient is still alive in complete remission at 69 months, one patient, affected by cirrhosis of the liver, died in complete remission of oesophageal variceal bleeding at 67 months and one relapsed at 80 months from treatment and, in spite of a second line of chemotherapy, died of lymphoma progression 8 months later. In one case, pancreaticoduodenectomy was complicated by recurrent cholangitis and the patient died 8 months after surgery in complete remission. The second patient treated with pancreaticoduodenectomy is still alive at 160 months of follow-up.

Discussion

PPL is a very rare neoplasm that may be confused with the more common pancreatic adenocarcinoma. The largest single study in Western countries involved 14 patients,¹⁶ while 19 cases were reported by a Japanese study.⁶ Most other reports described only isolated cases.

The mean age of the five patients in our report (65 years) was similar to that observed in the study by Tucek *et al.*,⁸ apparently older than in pancreatic adenocarcinoma. Similarly to previous reports,^{7,9} also in our experience the presenting symptoms and signs were non-specific: all patients were symptomatic, complaining epigastric pain, weight loss and/or jaundice. Elevation of transaminase, alkaline phosphatase and direct bilirubin were common findings, whereas only in two cases we observe elevation of CA 19.9.

Imaging techniques, such as US and CT scan, play a key role in the diagnosis and staging of pancreatic masses. Recently, Merkle *et al.*¹⁰ described imaging findings in pancreatic lymphoma and they concluded that on CT two different morphologic patterns of pancreatic involvement are seen: a localized, well-circumscribed tumoral form and a diffuse enlargement infiltrating or replacing most of the pancreatic gland. Some radiological findings have been reported to differentiate PPL from the more common pancreatic adenocarcinoma: the combination of a bulky localized tumour in the pancreatic head without significant dilatation of the main pancreatic duct strengthens a diagnosis of pancreatic lymphoma over adenocarcinoma; enlarged lymph nodes below the level of the renal veins and invasive tumour growth not respecting anatomic boundaries and infiltrating retroperitoneal or upper abdominal organs and the gastrointestinal tract are additional reliable signs for PPL. Neither calcifications nor necrosis within the tumour mass have been described in any case of untreated PPL.¹⁰

Imaging procedures can suggest a diagnosis of PPL but a cyto-histological examination is mandatory for diagnosis and treatment planning of patients with suspicious PPL.^{11, 12} US- and CT-guided biopsy techniques can easily provide sufficient diagnostic tissue. We achieved a definite diagnosis of PPL by percutaneous US-guided FNAB and FNB in all the three patients in which it was performed, thus avoiding unnecessary surgical intervention. This technique proved to be safe, without major compli-

cations, as previously reported in large series of patients with lymphoma.¹¹⁻¹⁴ In a recent report¹⁷ FNAB was coupled with flow cytometric analysis and proved to be highly accurate in the diagnosis of PPL. We underline the need of experienced cytopathologists as well as advanced immunoistochemical assays to obtain a correct diagnosis on a small amount of tissue. It must be emphasized that FNAB can suggest a cytological diagnosis of malignant lymphoma, but cytology alone may not be adequate in establishing a new definite diagnosis of NHL. Thus, US-guided core-needle biopsy should always be performed, as routinely done at our Institution.^{11, 13, 14} when FNAB of an abdominal lesion is suggestive for NHL. According to the literature, the majority of cases of PPL reported here were large B-cell NHL; however, also two cases of low-grade lymphoplasmacytic lymphoma were recorded and interestingly only these subtypes presented at imaging techniques as well-circumscribed pancreatic lesions.

Recently, endoscopic ultrasonography (EUS) has also been used to evaluate pancreatic masses and surrounding structures; biopsies taken from the duodenal area during EUS can provide in some cases a histological diagnosis of PPL.¹⁸ 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 bypass biliary obstruction, but in recent years various non-operative strategies can provide a high rate of successful relief of this complication. Total pancreatectomy is felt to have no impact on survival and, with its associated morbidity (as reported in our patient n. 2 who died of recurrent cholangitis), is now not recommended for diagnosis and treatment of PPL.⁷ Some authors have suggested a beneficial role for surgical resection only in stage I or early stage II PPL.⁴ The limited number of our series cannot permit a comparison between the outcome of surgical and non-surgical therapy. Larger series of patients are needed to evaluate if chemotherapy, eventually followed by involved-field radiation therapy, is the treatment of choice of PPL. Given the uncommon nature of this pathology, data should be collected in a large cooperative setting. In conclusion, the diagnosis of PPL is based on cyto-histological examination and the simplest way to obtain sufficient tissue is US-guided FNAB and FNB. 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.¹⁰

Arcari Annalisa, Anselmi Elisa, Bernuzzi Patrizia, Bertè Raffaella, Lazzaro Antonio, Moroni Carlo Filippo, Trabacchi Elena, Vallisa Daniele, Vercelli Andrea and Cavanna Luigi.
Department of Medical Oncology and Haematology, Hospital of Piacenza, Italy.

Correspondence: Arcari Annalisa
Department of Medical Oncology and Haematology, Hospital of Piacenza, Piacenza, Italy

Tel: +39 0523 302254 Fax: +39 0523 302295

E-mail: aarcari2002@yahoo.com

Keywords: Primary pancreatic lymphoma, fine needle aspiration biopsy.

No competing interests declared

References

- Zucca E, Roggero E, Bertoni F, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 1: Gastrointestinal, cuta-

- neous, and genitourinary lymphomas. *Ann Oncol* 1997; 8, 727-37.
- Salvatore JR, Cooper B, Shah I, Kummert T. Primary pancreatic lymphoma: a case report, literature review, and proposal for nomenclature. *Med Oncol* 2000; 17 (3), 237-47.
 - Baylor SM, Berg JW. Cross classification and survival characteristics of 5,000 cases of cancer of the pancreas. *J Surg Oncol* 1973; 5, 335-8.
 - Koniaris LG, Lillemoe KD, Yeo CJ, Abrams RA, Colemann J, Nakeeb A et al. Is there a role for surgical resection in the treatment of early stage pancreatic lymphoma?. *J Am Coll Surg* 2000; 190 (3), 319-30.
 - Dawson IM, Cornes JS, Morson BC. Primary lymphoid tumors of the intestinal tract: report of 37 cases with a study of factors influencing prognosis. *Br J Surg* 1961; 49, 80-9.
 - Nishimura R, Takakuwa T, Hoshida Y, Tsujimoto M, Aozasa K. Primary pancreatic lymphoma: clinicopathological analysis of 19 cases from Japan and review of the literature. *Oncol* 2001; 60 (4), 322-9.
 - Behrns KE, Sarr MG, Strikler JG. Pancreatic lymphoma: is it a surgical disease?. *Pancreas* 1994; 9, 662-7.
 - Tuchek JM, De Jong SA, Pickleman J. Diagnosis, surgical intervention, and prognosis of primary pancreatic lymphoma. *Am Surg* 1993; 59, 513-8.
 - Islam S, Callery MP. Primary pancreatic lymphoma- a diagnosis to remember. *Surgery* 2001; 129 (3), 380-3.
 - Merkle EM, Bender GN, Brambs HJ. Imaging findings in pancreatic lymphoma: differential aspects. *Am J Roentgenol* 2000; 174 (3), 671-5.
 - Di Stasi M, Lencioni R, Solmi L., Magnolfi F, Caturelli E, De Sio I et al. Ultrasound-guided fine needle biopsy of pancreatic masses: results of a multicenter study. *Am J Gastroenterol* 1998; 93, 1329-33.
 - Faulkner JE, Gaba CE, Powers JD, Yam LT. Diagnosis of primary pancreatic lymphoma by fine needle aspiration. *Acta Cytol* 1998; 42 (3), 834-6.
 - Civardi G, Vallisa D, Berte R, Giorgio A, Filice C, Caremani M, et al. Ultrasound-guided fine needle biopsy of the spleen: high clinical efficacy and low risk in a multicenter Italian study. *Am J Hematol* 2001; 67 (2), 93-9.
 - Buscarini L, Cavanna L. Ultrasound and ultrasonically guided biopsy in oncohematology- review- *Haematologica* 1991; 76, 53-64.
 - Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML et al. A revised European American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; 84, 1361-92.
 - Hart MJ, White TT, Brown PC, Freeny PC. Potentially curable masses in the pancreas. *Am J Surg* 1987; 154, 134-6.
 - Nayer H, Weir EG, Sheth S, Ali SZ. Primary pancreatic lymphoma. *Cancer* 2004; 102 (5), 315-21
 - Harrison JL, Millikan KW, Prinz RA, Zaidi S. Endoscopic ultrasound for diagnosis and staging of pancreatic tumors. *Am Surg* 1999; 65, 659-64.