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Original Article

Primary Non-Hodgkin's Lymphoma of the Pancreas: How Can We Differentiate it from Pancreatic Adenocarcinomas?

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ABSTRACT

Background: Primary pancreatic lymphoma (PPL) is a rare condition and its differentiation from most commonly adenocarcinoma is very important because of different prognosis and treatment strategies. The aim of this study was presenting different aspects for differentiating PPL from pancreatic adenocarcinoma.

Materials and Methods: During 14 months, 5 patients who underwent endoscopic ultrasonography in our ward were recorded. Demographic characteristics, laboratory and imaging findings were evaluated. Literature review was done.

Results: The duration of symptoms was between one to two months. The primary presenting symptoms were abdominal pain, weight loss, jaundice and pruritus. All patient except one, diagnosed as primary pancreatic lymphoma by EUS-guided fine-needle aspiration. Occasional presence of B-symptoms, larger size of the lesion, less occurrence of invasion to the large vessels despite larger size, less occurrence of obstructive jaundice (in spite of greater frequency in the head of the pancreas) and normal or lower titer of CA19-9 may be useful keys for differentiating primary pancreatic lymphoma from pancreatic cancer.

Conclusion: Although cytology or tissue histology is fundamental for the diagnosis, clinical, laboratory and imaging findings may be valuable tools for differentiation PPL from pancreatic adenocarcinoma.

Keywords: Non-Hodgkin Lymphoma, Diagnosis, Histology

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INTRODUCTION

Despite Hodgkin's disease, non-Hodgkin's lymphoma frequently arises outside the lymphatic system. Among extranodal organs, gastrointestinal tract, particularly the stomach and small bowel are the most common sites of extra-nodal origin. Primary pancreatic lymphoma (PPL) is rare and accounts for less than 0.7% of all pancreatic malignancies and 1% of extranodal lymphomas (1, 4, 5). Volmar et al found 14 cases (1.3%) of PPL in biopsy of 1050 cases of pancreatic mass lesions (2). In 207 cases of malignant pancreatic tumors, only three (1.5%) cases of pancreatic lymphoma

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was found and most of the lesions were pancreatic adenocarcinoma (3). Thus, PPL is a rare condition. It is important to diagnose PPL because of its better prognosis and also a different management strategy in comparison with pancreatic adenocarcinoma. By suspecting PPL on clinical and imaging grounds, surgery and its associated complications can be avoided, since the mainstay of the treatment is non-surgical strategies including chemotherapy. The present article is a prospective review of five cases of PPL, based on the clinical presentation and imaging features of PPL, which were identified and treated in Digestive Disease Research Center at Shariati Hospital, Tehran-Iran. The issue is discussed in the context of the world literature in an attempt to heighten clinicians' awareness of the condition.

MATERIALS AND METHODS

Between July 2006 and May 2007, a total number of 5 patients with the diagnosis of PPL underwent endoscopic ultrasonography in our ward. Patients were excluded from the study if they had disseminated lymphoproliferative disorder (e.g., secondary pancreatic lymphoma). Literature review was done. We tried to compare studies with large number of patients with primary pancreas lymphoma with our study. Demographic characteristics, clinical presentations and imaging features of PPL were assessed.

RESULTS

All patients except one, diagnosed as PPL by EUS-guided fine-needle aspiration (EUS-FNA). The exception was a case who underwent surgery and Whipple procedure in spite of our recommendation for EUS-FNA. The five PPL patients included three males and two females with the mean age of 42 years (22 to 73 years). The duration of symptoms was between one to two months. The primary presenting symptoms were abdominal pain (3), weight loss (4), jaundice (1) and pruritus (1). The results of CBC tests were within normal limits in all five patients except for normochromic and normocytic anemia (Hb=11.5) in one. Hyperamylasemia was seen in one patient at presentation. LDH, ESR, CRP, Ca, P, serum protein electrophoresis and amylase were normal in other cases. In one patient aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct bilirubin and CA19-9 were 85 IU/L (normal: up to 37), 70 IU/L (normal: up to 37), 14.5 mg/dl and 137 micg/L (normal: up to 37), respectively. Liver function tests and CA 19-9 were otherwise normal in all other patients. Chest radiographies were normal. Abdominal CT scan revealed the location of the tumor at the head of pancreas in all cases. On EUS all tumors were hypoechoic and with almost homogenous echogenicity except for heterogeneous echo pattern in one. The tumors were larger than 4 cm in two cases, with regional lymphadenopathy in one case and portal vein invasion in one other. The specimens were obtained by EUS-FNA in four cases (figure 1) and by pancreatic resection in the remaining one case. All tumors were diffuse large B-cell lymphoma (DLBL) by histopathologic examination (Figures 2,3).

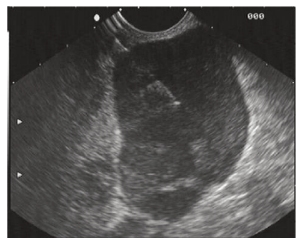

Figure 1: EUS-FNA from pancreas head mass

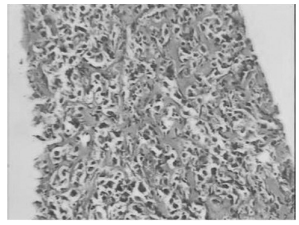

Figure 2: histology of malignant lymphoma infltrative the pancreas

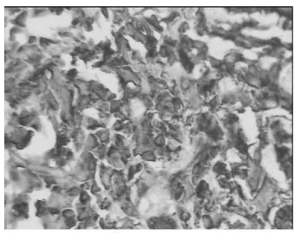

Figure 3:immunohistochemistry staining of mailgnant lymphoma

According to Ann Arbor classification, two cases belonged to IE stage, and the remaining three cases to IIE stage. All five patients underwent chemotherapy; one patient (73 y/o man) died 1.5 years after diagnosis (because of myocardial infarction) and the remaining four cases are in good condition on follow ups (mean duration of follow up of 12 months) (Table 1).

Table 1: Comparison of age, gender, FNA findings, cell types, and stages

Patient	Age(yr)	Gender	FNA-Aspiration	Stage
1	73	M	Diagnostic	I E
2	53	M	Diagnostic	I E
3	32	F	Diagnostic	II E
4	22	M	*	II E
5	50	F	Diagnostic	II E

*underwent surgery

Results of literature review has been summarized in table 2. In this table we compare the different aspects of patients characteristics with those of our results.

Table 2:Comparison of different characteristics of patients in other studies with those of our results

Reference No	Ours	15	2	22	23	12	24	6
Number of patients	5	4	14	9	12	8	7	6
Weight loss	4	4	-	7	6	-	3	3
Obstructive Jaundice	1	2	-	5	4	3	4	2
Methods of diagnosis (needle biopsy)*	4	1	7	5	6	8	2	2
Abdominal pain	3	2	-	5	10	6	5	2
Mean Size (Cm)	4	5	6.5	6	8	8	6.4	6
LDH (Elevated)	0	2	-**	-	-	-	-	-
Ca19-9 (Range)	25-137	50-500	-	-	-	-	-	-
Mean age	46	62.7	64.7	63.2	50	55	56	46
Sex (M)	3	4	7	4	8	7	6	5
Stage	3IIE / 2IE	II-E	-	5IV/2II/2III	8I / 4II	-	6IIE,1IE	4IIE,2IE
Location (head)	5	3	8	-	6	8	5	3

* remaining cases underwent surgery for diagnosis

**Not identified

DISCUSSION

The importance of PPL is its differentiation from pancreatic cancer considering their similarities in clinical manifestations and imaging results. In addition, PPLs are potentially treatable and their prognoses are better than those of pancreatic carcinomas even if not found at early stage. The previous data (6, 12, 15, 23, 24) showed a strong male predominance, which is similar to that in our study, but it usually presents in the 5th to 6th decade of life, one to two decades later than those in our cases. The clinical manifestations of PPL are various; abdominal pain and abdominal mass are two major symptoms which present in up to 83% and 58% of PPL cases, respectively (7, 12, 15, 23, 24). However, none of our patients had abdominal mass but two of them had abdominal pain. Weight loss, nausea, and vomiting are the other presenting symptoms. Diarrhea, jaundice, gastric outlet obstruction, pancreatitis and small bowel obstruction have been other reported symptoms (6, 8-12).

Although the head of the pancreas is the most common location for PPL but in comparison with pancreatic adenocarcinomas, obstructive jaundice was found to be less frequent in isolated PPL (12, 13). Similarly in our series, all tumors located within the head of the pancreas but only one patient presented with obstructive jaundice despite the large size of the tumors in all five

cases (medium size of 4 cm). Indeed, one of the diagnostic clues to identify a pancreatic lymphoma is the presence of a large tumor at the head of the pancreas without obstructive effect on the adjacent biliary duct. In addition, pancreas lymphoma masses are usually larger than 6 cm at the time of diagnosis and may be as large as 30 cm (2, 6, 12, 15, 21-24).

Almost 12% of PPLs could mimic acute pancreatitis. One of our patients presented with acute pancreatitis. The constitutional symptoms such as fever, chills and night sweating (B-symptoms) which are common in other types of NHL are rare in PPL, making it difficult to diagnose only depending on these symptoms (14). Other symptoms include gastrointestinal bleeding, ascites and weight loss (8, 12). Among other presenting symptoms in our series, weight loss has been the most common one, presented in 4/5 of our cases. The laboratory findings are nonspecific for the diagnosis of PPL. Serum levels of lactate dehydrogenase (LDH) may be elevated in up to 50% of patients, and occasionally increases in serum level of CA 19-9 may be seen (6, 15). In our study, serum cancer antigen 19-9 (CA19-9) level in PPL patients was normal except in one patient. This is different from pancreatic adenocarcinoma, in which almost eighty percent of patients have a higher CA19-9 level. Imaging results play a role in the diagnosis of PPL. Transabdominal ultrasound (US), computed tomography (CT), endoscopic ultrasonography (EUS) and MRI are usual imaging modalities for pancreatic masses (4, 16). CT-scan is the most common imaging modality used in the detection of pancreatic tumors. However, the feature of PPL on CT is similar to pancreatic adenocarcinoma, including enlargement of pancreatic head and changes in density of the lesion. However, invasion to large vessels and liver are rarely seen in PPL. In addition, enlargement of abdominal lymph nodes below the level of renal veins is more commonly seen in PPL (11). However, the final diagnosis of PPL depends on histopathologic examination. In our study, the tissue was obtained by EUS- FNA in four patients and by surgery in one case. Compared with surgery, it is difficult to obtain enough specimens by FNA to perform immuno-histochemical analysis. This may lead to false negative results (10). However, because EUS-FNA technique is dynamic and relatively safe, real-time tissue sampling of pancreatic masses by this method seems to be advantageous. In addition, this modality is safer by avoiding damage to adjacent vessels (17, 18). Totally, one in five of our patients underwent operation. This patient was treated with Whipple surgery because the definitive diagnosis was not made before surgery and both patient and surgeon were not satisfied for doing EUS-FNA. Other four cases diagnosed by EUS-FNA. Although adenocarcinoma is the most common form of pancreatic neoplasm but malignant pancreatic tumors may be lymphomas, endocrine carcinomas, or metastases in 5–10% of the cases. All these lesions can be diagnosed by EUS-guided FNA (19, 20). Obviously, the management and sometimes the prognosis of these malignancies are different from those of adenocarcinomas, and thus, obtaining a histological confirmation of every solid lesion of pancreas may be necessary.

CONCLUSION

Although differentiation of adenocarcinoma from PPL is difficult but occasional presence of B-symptoms, larger size of the lesion, less occurrence of invasion to large vessels despite larger size, less occurrence of obstructive jaundice (in spite of greater frequency in the head of the pancreas) and normal or lower titer of CA19-9 may be useful keys for differentiating PPL from pancreatic cancer. However, cytology or tissue histology is fundamental for the diagnosis before chemo- or radiotherapy and

treatment decision making. FNA technique is recommended as a routine examination, while total pancreatectomy is considered to have no impact on survival and with its associated morbidities, is not generally recommended for diagnosis and treatment of PPL. PPL will not be such a disease with poor prognosis and with newer systemic agents, the potential benefits of surgery are likely to be quite modest.

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