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# Obstructive jaundice as primary presentation of a stage IIE Non-Hodgkin lymphoma: A decision making process between advanced lymphoma and locally advanced/metastatic pancreatic adenocarcinoma

K. Blouhos, K.A. Boulas\*, A. Paraskeva, I. Kariotis, N. Baretas, A. Hatzigeorgiadis

Department of General Surgery, General Hospital of Drama, Drama, Greece

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## ABSTRACT

**INTRODUCTION:** Secondary pancreatic tumors are uncommon and account for 2–5% of pancreatic cancer. Tumors characterized most commonly with pancreatic involvement are lymphoma, renal cell and lung carcinomas.

**PRESENTATION OF CASE:** A 76-year-old female patient with obstructive jaundice as the primary symptom and inguinal lymphadenopathy is presented. Imaging revealed a bulky solitary solid pancreatic head mass along with paraaortic and mesenteric lymphadenopathy. The absence of a previous history of malignancy and the presence of a dominant pancreatic mass along with distal lymphadenopathy confined differential diagnosis to advanced secondary pancreatic lymphoma, which is the most common secondary pancreatic tumor, and locally advanced/metastatic pancreatic adenocarcinoma. Pathologic confirmation with excisional biopsy of an enlarged inguinal lymph node and EUS-FNB of the pancreatic head mass confirmed the diagnosis of secondary Non-Hodgkin pancreatic lymphoma allowing initiation of induction chemotherapy.

**DISCUSSION:** Secondary pancreatic lymphoma can be seen up to 30% of patients with advanced lymphoma; although the head of the pancreas is the most common location, obstructive jaundice is not the predominant symptom as obstruction of the common bile duct is usually absent. In the setting of a solitary nodular type pancreatic mass, key imaging findings highly suggestive of secondary pancreatic lymphoma and not of adenocarcinoma are the absence of vascular invasion, bile and pancreatic duct obstruction, and the presence of lymphadenopathy below the level of the left renal vein.

**CONCLUSION:** When a secondary pancreatic tumor is highly suspected pathologic confirmation is always needed before initiation of induction or palliative chemotherapy.

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## 1. Introduction

1.1. This work has been reported in line with the SCARE criteria [1]

Secondary pancreatic tumors are uncommon and account for 2–5% of pancreatic cancer. Tumors characterized most commonly with pancreatic involvement are lymphoma, renal cell and lung carcinomas. Secondary pancreatic lymphoma is far more common than other secondary pancreatic malignancies and primary pancreatic lymphoma [2]. Although the head of the pancreas is the most common location, obstructive jaundice is not the predominant

symptom. Key imaging findings highly suggestive of secondary pancreatic lymphoma are the absence of vascular invasion, bile and pancreatic duct obstruction, and the presence of lymphadenopathy below the level of the left renal vein. However, pathologic confirmation is always necessary for establishing the diagnosis before initiation of induction chemotherapy [3].

Herein, the case of an otherwise-healthy 76-year-old female patient with obstructive jaundice due to a dominant pancreatic head mass and distal lymphadenopathy diagnosed with a stage IIE Non-Hodgkin lymphoma with pancreatic head involvement is presented. The question, whether the present pancreatic mass represents a primary or secondary pancreatic neoplasm, inevitably arises. The present case report is educational as it describes the dynamic decision making process for differential diagnosis between pancreatic adenocarcinoma which represents the vast majority of pancreatic head masses and secondary pancreatic lymphoma.

\* Corresponding author.

E-mail addresses: [katerinantwna@hotmail.com](mailto:katerinantwna@hotmail.com), [boulaskonstantinos@gmail.com](mailto:boulaskonstantinos@gmail.com) (K.A. Boulas).

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phoma, and unique due to the unusual presentation with jaundice as the predominant symptom.

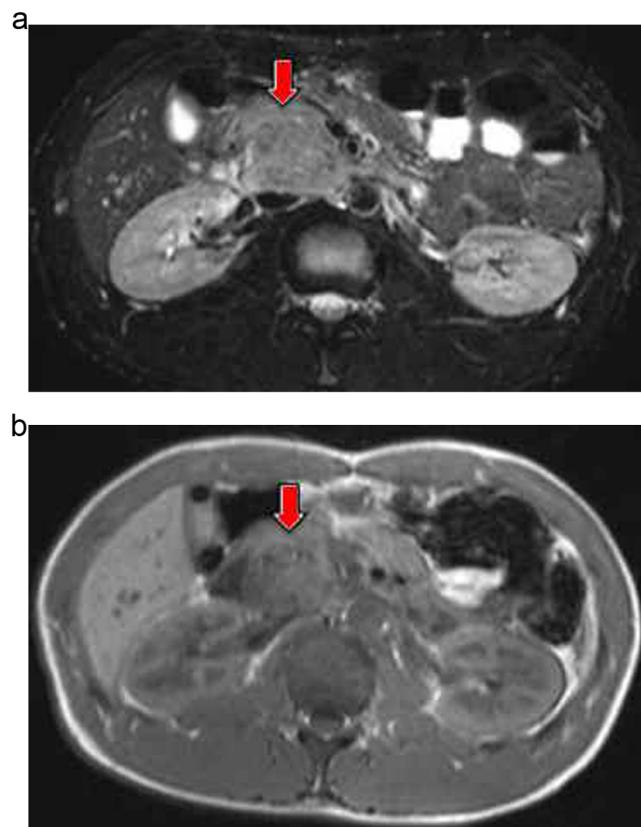
## 2. Presentation of case

An otherwise-healthy, obese class I (BMI 31.5 kg/m<sup>2</sup>, BSA 2.0 m<sup>2</sup>), non-smoking, 76 year-old housewife patient referred to our surgical department owing to progressive jaundice associated with darkening of the urine and pruritus over the preceding 40 days. Direct questioning revealed a history of vague abdominal pain, abdominal distention, fatigue and weight loss of approximately 12 kg over the last 2 months. There was no other previous medical, surgical and relevant family history. At initial presentation jaundice, palpable spleen and palpable firm and fixed bilateral inguinal lymph nodes were present on physical examination. Laboratory studies revealed a significant increase in serum total bilirubin (27.10 mg/dl), alkaline phosphatase (294 U/l),  $\gamma$ -glutamyl transferase (113 U/l) and LDH (856 U/l). Regarding tumor markers, level of CA 19-9 (147 U/ml) was elevated. Serum amylase (55 U/l), IgG (929 mg/dl), IgG4 (48 mg/dl) and  $\beta$ 2-microglobulin (1.82 mcg/ml) were normal.

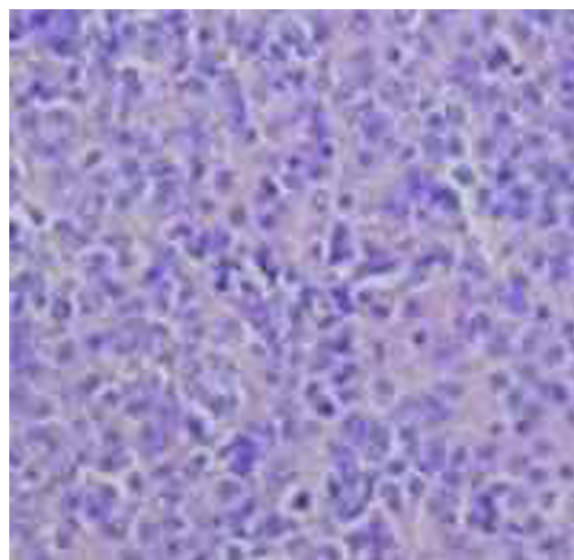
Initial abdominal CT demonstrated an ill defined pancreatic head mass along with mesenteric and paraaortic lymph nodes enlargement. Dynamic-enhanced pancreatic CT examination with a 16-multidetector row scanner according to a dual-phase pancreatic protocol revealed a bulky, nodular type, solitary, homogenous, hypoattenuating 4 × 5 cm pancreatic head mass with pancreatic and common bile duct dilatation and pancreatic body and tail atrophy. No evidence of local structures tumor invasion was present. Gadolinium-enhanced dynamic MRI examination with arterial, venous and delayed phase fat-saturated T1-weighted images demonstrated a bulky circumscribed poorly enhanced mass in the pancreatic head with normally enhanced adjacent pancreatic parenchyma (Fig. 1 a and b). Diagnostic ERCP depicted an irregular interruption of the pancreatic duct and narrowing in the distal common bile duct with upstream dilation. A plastic stent was placed across the biliary obstruction.

Excisional biopsy of an enlarged left superficial inguinal lymph node revealed a diffuse growth pattern and large lymphocytes without follicular structures (Fig. 2). Immunohistologic findings showed lymphocytes that were strongly positive for CD20, CD79a and Bcl-2 and negative for CD3, CD5, CD10, CD23, CD30, and Bcl-6. These results supported the diagnosis of diffuse large B cell lymphoma. EUS-FNB with 22G needle of the pancreatic head mass performed in order to allow us to complete the pathologic diagnosis. Hematoxylin and eosin staining of tissue specimens showed that tumor cells were medium sized atypical lymphocytes with diffuse proliferation and without follicular structures (Fig. 3). Bone marrow aspiration and biopsy samples demonstrated no infiltration by lymphoma cells. All the above clinical, imaging and pathologic results were strongly suggestive with the diagnosis of a stage IIE Non-Hodgkin lymphoma with secondary pancreatic head involvement.

The patient submitted to the above diagnostic interventions during a two weeks hospital stay and referred to a tertiary hospital for hematology and oncology specialty care. The patient treated with 8 cycles repeated every 21 days of the Cyclophosphamide (750 mg/m<sup>2</sup> by intravenous infusion on day 1)-Vincristine (1.4 mg/m<sup>2</sup> by intravenous infusion on day 1)-Prednisolone (100 mg by oral administration days 1–5) regimen. Interval abdominal CT for response assessment after 2 and 8 cycles demonstrated partial and complete response of the targeted pancreatic head lesion and mesenteric and paraaortic lymph nodes according to the RECIST 1.1 criteria. Jaundice and inguinal lymphadenopathy progressively resolved within 3 months from initiation of therapy. The

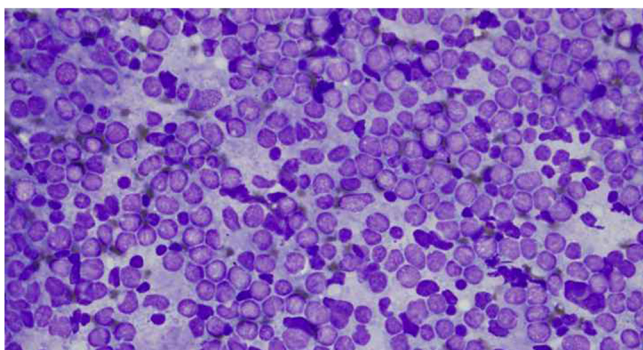


**Fig. 1.** (a) Fat-suppressed T2-weighted MR image shows a bulky circumscribed homogeneously hyperintense mass in the pancreatic head (red arrow) and (b) Fat-suppressed T1-weighted MR image shows a hypointense mass in the pancreatic head (red arrow) relative to adjoining normal pancreatic parenchyma.



**Fig. 2.** Hematoxylin-eosin-stained histologic section (magnification × 400) revealed a diffuse growth pattern and atypical large lymphocytes without follicular structures.

patient experienced mild nausea, soreness, scattered skin rash with mild itching within 24–48 h after treatment without other short and long term side effects. Follow up at the first year including biannual abdominal CT showed no evidence of lymphoma remission.



**Fig. 3.** Fine-needle aspiration cytology is consistent with B-cell lymphoma. High power view ( $\times 40$ ) shows numerous large monotonous lymphocytes with open chromatin admixed with small, dark, round, mature lymphocytes.

### 3. Discussion

Secondary pancreatic tumors are uncommon and account for 2–5% of pancreatic cancer. Tumors that are characterized most commonly with pancreatic involvement are lymphoma, renal cell, lung, breast and colorectal carcinoma followed by melanoma and leiomyosarcoma [4]. Secondary pancreatic lymphoma can be seen up to 30% of patients with advanced lymphoma and it is far more common than primary pancreatic lymphoma, which accounts for less than 0.5% of pancreatic malignancies, and other secondary pancreatic malignancies [5]. In the present case, the presence of a dominant pancreatic mass with distal lymphadenopathy such as paraaortic, mesenteric and inguinal lymphadenopathy confines differential diagnosis to secondary pancreatic lymphoma and advanced pancreatic adenocarcinoma.

#### 3.1. Secondary pancreatic lymphoma or pancreatic adenocarcinoma

Secondary pancreatic lymphoma is the most prominent diagnosis, as it is more common than other secondary pancreatic malignancies and primary pancreatic lymphoma. At first, the patient had no previous history of malignancy and staging did not reveal a synchronous cancer. Secondly, the present pancreatic mass does not fulfill the criteria of primary pancreatic lymphoma, which are: a) no evidence of palpable superficial lymphadenopathy; b) no enlargement of mediastinal lymph nodes; c) normal leukocyte count; d) dominant pancreatic mass peripancreatic involved lymph nodes; and e) no hepatic or splenic involvement [6].

#### 3.2. Clinical aspects

Pancreatic lymphoma affects patients in the 5th and 6th decade of life and has a slight male predominance. Clinical symptoms are generally nonspecific; abdominal pain, mass and weight loss are the most common symptoms followed by jaundice, nausea, vomiting, pancreatitis and bowel obstruction. Although the head of the pancreas is the most common location accounting for more than 80% of pancreatic lymphomas, jaundice is not the predominant symptom [7]. The classic symptoms of Non-Hodgkin lymphoma such as fever, chills and night sweats are common presentation in secondary but are rarely present in primary pancreatic lymphoma. In patients with pancreatic lymphoma CA 19.9 level is normal, unless a biliary obstruction is presented, and LDH and  $\beta 2$ -microglobulin levels are usually elevated [8].

Pancreatic ductal adenocarcinoma accounts for 80% of all pancreatic cancers. It usually arises in elderly patients with an age at onset of 71 years for men and 75 years for women. Approximately

60%–70% of pancreatic cancer arises in the head of the pancreas. For tumors of the head, jaundice is an early and predominant symptom as it results from a mass effect leading to obstruction of the common bile duct. Moreover, 80% of patients with pancreatic adenocarcinoma have a high CA 19.9 level [9]. In the present case, the patient was a female in the 7th decade of her life. Jaundice was the predominant symptom and level of CA 19.9 was elevated. Initial CT revealed a dominant pancreatic head mass with distal paraaortic and mesenteric lymphadenopathy. The above clinical and imaging characteristics account more for pancreatic adenocarcinoma. However, the presence of inguinal and distal mesenteric lymphadenopathy could not be explained by an advanced pancreatic cancer but could fit together perfectly with the diagnosis of secondary pancreatic lymphoma.

#### 3.3. Imaging aspects

Secondary pancreatic lymphoma may present as: 1) well circumscribed nodular type with solitary pancreatic mass. On dynamic pancreatic CT, pancreatic lymphoma typically presents as a well defined, circumscribed, homogeneous, low attenuated mass. On MRI, pancreatic lymphoma typically appears as a well defined, circumscribed, homogeneous, low signal intensity on T1WI and high signal intensity on T2WI mass. On dynamic MRI, lymphoma enhance homogeneously but to a lesser degree than normal pancreatic parenchyma. Lesions less well circumscribed, as in the present case, may be misdiagnosed as pancreatic cancer. Key-findings for differential diagnosis include: a) pancreatic lymphoma are better marginated and demarkated compared to normal parenchyma than adenocarcinoma which enhance less due to the desmoplastic reaction, b) vascular encasement and invasion, common bile and pancreatic duct obstruction with proximal dilation, which were absent in the present case, are signs highly suggestive of adenocarcinoma, and c) lymphadenopathy below the level of the left renal vein, which was present in the present case, is highly suggestive of secondary pancreatic lymphoma; 2) less commonly, it may present as diffuse enlargement of the gland that could mimic acute and autoimmune pancreatitis. However, typical features of acute pancreatitis, including peripancreatic fat stranding, peripancreatic inflammation and fluid collections are typically absent in the infiltrating pattern. Differential diagnosis with autoimmune pancreatitis should be based on histology, imaging, serology, other organ involvement and response to therapy (HISORT criteria); 3) rarely it may present as multinodular type, which mimics metastases from hypovascular tumors, such as gallbladder, lung, ovarian cancer; and 4) rarely it may present as invasion from an adjacent peri-pancreatic lymphomatous lesion [10].

#### 3.4. Pathologic aspects

The consensus statement of the International Study Group of Pancreatic Surgery clearly suggested that in the presence of a solid pancreatic mass suspicious for malignancy, biopsy proof is not required before proceeding with resection. However, confirmation of malignancy is mandatory, when: a) a borderline resectable disease is to be treated with neoadjuvant therapy; b) a diagnosis of autoimmune pancreatitis is highly suspected [11]. Moreover, pathologic confirmation is necessary when a secondary pancreatic tumor is highly suspected before initiation of induction or palliative chemotherapy in the setting of pancreatic lymphoma and other secondary pancreatic tumors, respectively [12]. When pathologic confirmation is needed, EUS-FNA and FNB is the first line diagnostic tool in the work-up. EUS-FNA is highly sensitive and specific for solid pancreatic lesions, with sensitivities as high as 80%–95% and specificity as high as 75%–100% [13]. Regarding secondary pancreatic tumors, EUS-FNA can facilitate an accurate diagnosis. Alomari



et al. in a retrospective study of 31 cases with secondary pancreatic tumors showed that correct diagnosis made in 29 cases (94%) [14]. Regarding pancreatic lymphoma, Ramesh et al. in a retrospective study of 2397 cases with solid pancreatic masses revealed that EUS-FNA facilitated the correct diagnosis in 9 (75%) among 12 cases with pancreatic lymphoma. Diagnosis in 3 patients was made by surgical biopsy due to high suspicion of malignancy and inconclusive EUS-FNA results. Diffuse large B cell lymphoma was the most common lymphoma variant that affected the pancreas accounting for 67% of all pancreatic lymphoma cases [15].

Conclusively, in the present case the presence of a dominant pancreatic mass with paraaortic, mesenteric and inguinal lymphadenopathy confined differential diagnosis to secondary pancreatic lymphoma and advanced pancreatic adenocarcinoma. The present pancreatic mass did not fulfill the criteria of primary pancreatic lymphoma and the diagnosis of other secondary pancreatic neoplasm was excluded by history and staging. Clinical characteristics, especially the presence of jaundice, accounted more for pancreatic adenocarcinoma. Imaging characteristics, especially the presence of lymphadenopathy below the level of the left renal vein, accounted more for secondary pancreatic lymphoma. Pathology results confirmed the radiological diagnosis of a stage IIE Non-Hodgkin lymphoma with secondary pancreatic head involvement allowing initiation of induction chemotherapy.

#### Conflicts of interest

There are no conflicts of interests

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#### Ethical approval

The authors declare that ethical approval has been exempted by their institution for this case report.

#### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

#### Author contribution

Boulas K was responsible for the study concept and design. Paraskeva A, Kariotis I and Baretas N equally contributed in writing

the paper. Blouhos K and Hatzigeorgiadis A had the final approval of the paper.

#### Guarantor

Hatzigeorgiadis A.

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