Primary pancreatic anaplastic large cell lymphoma, ALK negative: A case report

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Malignant tumors of the pancreas constitute about 15% of cancer patients and the most frequent of them is the adenocarcinoma of the pancreas[1]. Primary pancreatic lymphoma (PPL) is a very rare disease constituting less than 0.5% of all pancreatic malignancies and less than 2% of extranodal lymphomas[2]. Primary pancreatic anaplastic large cell lymphomas (PPALCL) are extremely rare. Only three cases of PPALCL have been reported in the literature[3,4]. Herein we report the fourth case of PPALCL which was diagnosed by duodenal and surgical biopsies.

CASE REPORT

An 80-year-old man, who was under evaluation of a fever of unknown origin in a Private Health Center, was admitted to our clinic for further investigation. He was complaining of an intermittent fever of 2 mo duration which stabilized during the last 3 wk. Anorexia, weight loss of about 10 kg in the last 6 mo and fatigue were also reported. Physical examination was unremarkable except for a leg edema. His hematological profile was as follows: Hct: 31%, Hb: 9.9 g/L, MCV: 92 fl, MCH: 30 pg/cell, reticulocytes: 1.6%, WBC: 10.6×109/L (neutrophils 80% -lymphocytes 11% - monocytes 6% -eosinophils 2.5% -basophils 0.5%), PLT: 389×109/L, ESR: 110 mm, CRP: 13 mg/dL (normal range: 0-0.8 mg/dL). Serum biochemistry showed a great elevation of LDH: 1880 U/L (normal range: 313-618 U/L), high levels of alkaline phosphatase, low levels of albumin and hypoalbuminemia: 7.1 g/L (normal range: 6.6-8.7 g/L) though. Elevated β2 microglobulin: 4.19 mg/L (normal range: 1.42-3.21 mg/L) was also found. Other biochemical, serologic and immunologic investigations were normal. Laboratory studies performed after the onset of the symptoms, with values similar to our findings, were available from the patient’s file. A chest and abdominal CT scan, also available to us, had demonstrated that the uncinate process and partially the head of the pancreas were blurred (Figure 1A); enlarged peripancreatic, mesenteric, para-aortic and inferior vena cava lymph nodes were found. At that time, he had undergone a gastrointestinal endoscopy without pathologic findings. In further imaging study with MRI scan, a soft tissue mass located in the head of the pancreas and especially the uncinate process had appeared (Figure 1B). A slow flow signal of inferior vena cava had been observed due to the mass compression. After his admission in our clinic a new endoscopy of the upper gastrointestinal tract revealed an ulcerated mass-like deformity of the duodenal bulb with a friable surface (Figure 2). Gastric and duodenal mucosal biopsy specimens were taken. Bone marrow biopsy was also performed. Glucocorticoids were administered...
as a second choice therapy after antibiotics treatment, based on FUO treatment’s protocol and on the high indication of a lympho-proliferative disorder. Temporary clinical and laboratory improvement was noticed (ESR declination: 55 mm). Explorative laparotomy confirmed a diffuse spread of a malignant mass of the pancreas extending to the adjacent organs. Because of the brittle consistency and necrotic surface of the pancreatic mass, the biopsy specimen was taken from the adhesion of pancreatic surface with gastric serosa. Hematoxylin-and-eosin-stained sections of the duodenal biopsy revealed a diffuse dense infiltration of duodenal mucosa by large pleomorphic cells with abundant eosinophilic cytoplasm, ovoidal or irregular nuclei with one or prominent nucleoli (Figure 3A). Rare cells with embryo-like, horseshoe-shaped nuclei or cells with multiple nuclei resembling Reed-Sternberg cells were found. The mitotic activity was intermediate and several atypical mitoses were observed. Scanty neoplastic cells infiltrated the epithelium of intestinal glands as well as the surface epithelium. Histologic sections from the second biopsy material showed loose connective tissue with numerous dilated vessels and lymphatics, most of them having tumor cell emboli with morphology similar to the neoplastic population of the duodenal mucosa (Figure 3B). The intravascular presence of neoplastic cells was confirmed by immunohistochemistry using the endothelial cell marker CD34 (Novocastra, Newcastle, UK). Immunohistochemical stains of both biopsies showed the following tumor-cell immunophenotype: CD45+, CD45RO+, EMA+, CD43+ (DakoCytomation, Glostrup, Denmark), CD30+ (Figure 4), Muc1+, Fascin+ (Novocastra, Newcastle, UK), CD20−, CD45RA−, CAM 5.2−, Anaplastic Lymphoma Kinase (ALK)1−(DakoCytomation, Glostrup, Denmark) and CD3− (Novocastra, Newcastle, UK). Cellular phenotype and immunophenotype support
the diagnosis of anaplastic large cell lymphoma (ALCL), of T-cell lineage, ALK negative. Fluorescent in situ hybridization (FISH) using LSI ALK dual color, break apart rearrangement probe (Abbott GmbH and Company, KG, Wiesbaden-Delkenheim, Germany) was performed in paraffin-embedded tissue sections from both specimens. Presence of two fused yellow signals or two adjacent (one orange and one green signals) in 200 non-overlapping tumor-cell nuclei showed lack of ALK gene rearrangement at 2p23 region. Bone marrow biopsy showed no evidence of lymphoma involvement. The patient died in the Intensive Care Unit 2 d later due to hemodynamic instability.

**DISCUSSION**

PPL is an extremely rare neoplasm that may be confused with the most common pancreatic adenocarcinoma. The majority of PPL reported to date in literature have been classified as B-cell type, but several cases of T-cell pancreatic lymphomas have also been described[5]. Most cases are intermediate or high grade NHL with diffuse large B-cell lymphoma being the predominant type. Presenting symptoms are nonspecific, including abdominal pain, weight loss, nausea, vomiting. Systemic-B symptoms such as fever, chills and night sweats are uncommon. Imaging techniques such as CT, percutaneous U/S and recently endoscopic U/S are the most useful procedures to evaluate the staging of pancreatic masses, although they cannot identify their neoplastic nature. A cytostological diagnosis can be performed by U/S and CT guided techniques, endoscopy and explorative laparotomy[6]. Chemotherapy treatment with CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone) is usually administrated in patients with lymphomas[6-8]. The accurate distinction of ALCL from non-lymphoid malignancies is critical from the standpoint of patient’s management because primary ALCL responds to radically different chemotherapy than adenocarcinoma[5,6].

ALCL is an uncommon type of NHL, first described by Stein et al., in 1985 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[7]. In the latest World Health’s Organization (WHO) classification of NHLs, ALCL is a distinctive nature T-cell lymphoma subtype[5]. Clinical presentations of ALCL include a systemic form with nodal and/or extranodal involvement, primary cutaneous ALCL, HIV-related ALCL and ALCL occurring as a secondary event in patients with lymphomatoid papulosis, mycosis fungoides and rarely Hodgkin disease. The main histologic patterns accepted by WHO are the common variant, the lymphohistiocytic and the small cell variant[5]. In these lymphomas, the most frequent genetic alteration is the translocation t (2; 5) (p23; q35) between the 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 immunohistochemically using monoclonal or polyclonal antibodies, by RT-PCR and FISH[5,8]. ALK immunohistochemical expression is detected in 60-85% of ALCL cases[5]. ALK+ ALCL is most frequent in the first decades of life, shows a male predominance and often has advanced stage disease with frequent B-symptoms and extranodal involvement. It also tends to respond better to chemotherapy than ALK-systemic ALCL[5,9].

Our patient was considered to be affected by PPL according to Dawson et al., clinical criteria which include: (1) the absence of superficial lymphadenopathy or enlargement of mediastinal lymph nodes on chest radiography, (2) a normal leucocyte count in peripheral blood, (3) main mass in the pancreas with lymph-nodal involvement confined to the peripancreatic region, and (4) the absence of hepatic or splenic involvement[9]. The elevated values of LDH and β2 microglobulin in addition to the clinical characteristics of our patient, such as intermittent fever, anorexia, weight loss and fatigue, also suggested the lymphoproliferative nature of the mass. Moreover, the presence of the mass in the pancreas at imaging techniques while the duodenum was normal in the first endoscopy, proved that it originated in the pancreas and not in the duodenum which is an extremely rare location also.

Only three patients with primary pancreatic ALCL are reported in the literature. The first case described in 1997 in Japan by Maruyama et al., was diagnosed by both duodenal and surgical pancreatic biopsies[10]. The second case was published in 2003 in Israel by Cohen et al., and was diagnosed by operative pancreatic biopsy[11]. Chim et al., recently reported the third case and they supported the diagnosis on operative mesenteric lymph node material biopsy because the tumor resection was not possible[11]. In our case a pancreaticoduodenectomy, the “Whipple procedure” was not performed, as in the case of Chim et al., because of a friable tissue consistency and patient’s hemodynamic instability during surgery. Therefore, the diagnosis of our PPALCL was based on the biopsy material taken from duodenal mucosa (three small pieces) and the adhesion of pancreatic surface with gastric serosa.

LDH and β2 microglobulin are considered to be tumor markers in lymphoproliferative disorders and have an important prognostic value[10,11]. According to the textbook of Sleisenger and Fordtran’s, whenever a large mass is identified in the pancreas without biliary obstruction or pain the diagnosis of pancreatic lymphoma should be contemplated, particularly in the presence of an elevated serum LDH level[12]. A high LDH level was found in our patient in contrast to the three previously reported cases of PPALCL. The LDH values were normal in the cases of Chim et al., and Cohen et al., and non-recorded in the case of Maruyama et al. In addition, an elevated β2 microglobulin level was noticed in our case such as reported in ALCL, either ALK+ or ALK-in the study of Rassidakis et al.[13].

After chemotherapy administration, a remission of disease for 30 mo in the case reported by Cohen et al., and for 18 mo in the case reported by Maruyama et al., were achieved respectively, whereas in the recently reported case by Chim et al., a partial remission of 6 mo duration was noticed because the patient died of disease progression. Our patient did not receive a postoperative chemotherapy because unfortunately he died 2 d after the explorative
Table 1 Clinical and pathologic data of primary pancreatic ALCL reported cases in chronological order

| Maruyama et al.[1] | Cohen et al.[2] | Chim et al.[3] | Present study |
|-------------------|----------------|--------------|--------------|
| A/G               | 46/F           | 22/M         | 27/F         | 80/M         |
| Clinical symptoms | Back pain, anorexia | Upper abdominal pain, upper GI bleeding | Upper abdominal pain, weight loss | Leg edema |
| Physical examination | Icteric conjunctivae, flat and soft abdomen with mild tenderness | Pallor, epigastric mass | Epigastric mass | |
| Radiological findings | CT: mass in pancreatic head, ER: without pathologic changes in MPD | CT: mass in pancreatic head | CT: mass in pancreatic head and uncinate process, MRI: CT findings + IVC compression | |
| Endoscopy | Submucosal protrusion with erosion of the second portion of the duodenum | Duodenal bleeding near to Vater’s papilla | Bleeding ulceration of the first portion of the duodenum | Ulcerated mass-like deformity of the duodenum bulb |
| Laboratory findings | ALT, AST, ALP, total, and direct bilirubin elevated, serum amylase decreased, LDH: ND | Peripherial eosinophilia, LDH: in normal range | LDH: elevated, β2 microglobulin: elevated | |
| Surgical operation | Whipple’s | Whipple’s | Not performed | Not performed |
| Pathologic (IHC) findings | CD30+, CD45+, CD45RO+, EMA, ALK-ND | CD30+, CD45+, CD45RO+, EMA+, ALK- | CD30+, CD45+, CD45RO+, ALKND | Glucocorticoids (symptomatic) |
| Treatment | MACOP-P | CHOP | Not performed | Died due to hemodynamic instability |
| Follow up | NED at 18 mo | NED at 30 mo | 6 mo, died of disease progression | 2 d after explorative laparotomy |

A/C: age/gender, ALK: anaplastic lymphoma kinase, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, EMA: epithelial membrane antigen, ER: endoscopic retrograde pancreatography, F: female, FUO: fever of unknown origin, GI: gastrointestinal, IHC: immunohistochemistry, IVC: inferior vena cava, LDH: lactate dehydrogenase, M: male, MACOP-P: chemotherapy regimen consisting of cyclophosphamide, adriamycin, vincristine and prednisolone, EMA: epithelial membrane antigen, ALK: anaplastic lymphoma kinase, ALK-: ALK negative, ALK+: ALK positive.

l laparotomy.

The clinical information, laboratory and pathologic findings of the present case and the previously reported ones, are summarized in Table 1.

In conclusion, our case - added to the three published cases - is the fourth one of primary pancreatic ALCL, ALK-.

From the clinical point of view, since most clinicians do not consider PPL in the differential diagnosis of a pancreatic mass, our case indicates that PPL should be suspected in a patient with pancreatic mass and elevated serum markers, particularly LDH and β2 microglobulin. Biopsy specimens’ results from either the mass or the adjacent infiltrated organs, such as the duodenum in our case, confirm the diagnosis and identify the lymphoma. Thus, an earlier diagnosis leads to an appropriate and timeable treatment and finally, a better prognosis.

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