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Case Report

Primary pancreatic lymphoma: Report of 4 cases with literature review ☆,☆☆

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ABSTRACT

Pancreatic cancer (PC) is ranked as the 14th most common cancer and the 7th leading cause of cancer-related deaths. The most common histological type is adenocarcinoma, other type such as primary pancreatic lymphoma (PPL) still very rare. Due to the lack of specific clinical and imaging characteristics, the diagnostic of PPL remains challenging. We report 4 cases of PPL diagnosed and managed at our gastroenterology department between 2019 and 2023. *Case 1:* A 16-year-old male presented with abdominal pain, jaundice, and weight loss. Imaging revealed an 8 cm tumor in the pancreas, subsequent biopsies confirming Burkitt's lymphoma. Despite chemotherapy, the patient succumbed to the disease. *Case 2:* A 92-year-old female with no prior medical history presented with abdominal pain, jaundice, pruritus, and weight loss. Imaging revealed a large pancreatic mass, and biopsies identified large B-cell lymphoma. Unfortunately, the patient passed away before treatment initiation. *Case 3:* A 63-year-old male with a history of tobacco smoking presented with abdominal pain, weight loss, and anorexia. Imaging and biopsies confirmed diffuse large cell B-phenotype lymphoma. The patient achieved complete remission after rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone (R-CHOP) therapy. *Case 4:* A 67-year-old man with jaundice, abdominal pain, and weight loss was diagnosed with diffuse large cell B lymphoma through imaging and fine needle aspiration (FNA). The patient responded well to R-CHOP therapy. In conclusion, PPL is an uncommon tumor, with no specific clinical or radiological characteristics. A thorough evaluation of clinical, radiological, biological and histological data is necessary to consider it as a differential diagnosis and ensure accurate and timely management.

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Introduction

Pancreatic cancer (PC) is a highly aggressive malignancy with an unfavorable prognosis. It is the seventh leading cause of cancer death worldwide. The predominant type of PC is pancreatic ductal adenocarcinoma (PDAC), which constitutes over 95% of pancreatic tumors [1]. Other types of exocrine pancreatic cancers include squamous, adenosquamous, colloid carcinoma. Primary pancreatic lymphoma (PPL) is very rare, accounting for merely 0.1% of malignant lymphomas, 0.6% of extra nodal lymphomas, and only 0.2% of all pancreatic tumors [2] while secondary pancreatic involvement is more common in lymphomas, especially when there is extensive lymph node or extra nodal disease [3].

PPL can occur at any age and is more common in elderly patients, with a male predominance.

Furthermore, some factors may increase the risk of its occurrence including immunosuppression resulting from conditions like HIV infection or solid organ transplantation [3].

There is no typical clinical presentation of PPL, while vague symptoms such as abdominal pain, weight loss, nausea, and vomiting are prevalent [3], jaundice, acute pancreatitis, small bowel obstruction, and gastrointestinal bleeding are uncommon [4].

Differentiation PPL from pancreatic adenocarcinoma may be challenging. Importantly, the appearance of these 2 entities significantly overlaps on a variety of imaging modalities, however they have markedly different prognoses and management. Actually the success of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone (R-CHOP) therapy highlights the importance of early and accurate diagnosis of PPL. The combination of cross section imaging with Endoscopic Ultrasound-Guided (EUS) and FNA has significantly enhanced the diagnostic approach for pancreatic masses, including PPL

In this study we report 4 cases with PPL, and we provide valuable insights for the medical literature.

Case 1

A 16-year-old male suffering from abdominal pain was admitted to our department. The patient's vital signs were normal. His physical exam is positive for icteric sclera, jaundice and epigastric tenderness. The rest of his exam were otherwise normal. Laboratory test revealed hyperbilirubinemia at 179 mmol/L, lactate dehydrogenase (LDH) levels were elevated at 1020 UI/L as well as β2-microglobulin 35 mg/L, while carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) levels were within normal limits (Table 1).

Abdominal computed tomography (CT) revealed dilation of the common bile duct (CBD) upstream of a sizable 8 cm tumor located in the head of the pancreas. This lesion displayed irregular contours with poorly defined enhancement in a heterogeneous manner along with areas of necrosis. Additionally, the tumor involving the gastroduodenal region; infiltrated segments I, II, and IV of the liver with multiple mesenteric lymph, moderate ascites and thrombosis in the portal trunk (Fig. 1). There was no dilation of main pancreatic duct. The CT scan also revealed a gastric infiltration prompting the need of gastroscopy which revealed a bulbar ulcer with a whitish background (Fig. 1), biopsies were subsequently performed. Results confirmed the diagnosis of Burkitt's lymphoma, with immunohistochemical staining showing positive results for CD20, CD10, and BCL-6, as well as proliferative index of 100%, (Fig. 1).

The patient received 6 cycles of CHOP regimens including doxorubicin, cyclophosphamide, vincristine, and prednisolone. However, despite the treatment, the patient's condition deteriorated quickly resulting in death (Table 2).

Case 2

A 92-year-old female with no previous medical history was admitted for abdominal pain and progressive, jaundice, pruritus and 10 kg weight loss over 1 month. On clinical exam, the patient's vital signs were found to be within normal ranges, she had jaundice with a temperature of 39°, with no evident mass or peripheral adenopathy. Laboratory investigations confirmed abnormal liver function tests (Table 1) LDH levels were elevated at 452 UI/L, Serum levels of CA 19-9 and CEA were normal.

CT scan revealed a large mass of 11 cm in the pancreatic head and dilated common bile and pancreatic duct. This tumor was infiltrating the surrounding structures, such as the portal vein, and spléno mesenteric trunk.

Magnetic resonance imaging (MRI) revealed a heterogeneous pancreatic mass infiltrating the main retro pancreatic bile duct and the duodenum (Fig. 2).

Per endoscopic biopsies were performed and revealed large B-cell lymphoma, tumor cells are diffusely positive for CD20, BCL6 and BCL2, with an estimated tumor proliferation index of 85%.

The patient presented septic shock and, unfortunately, passed away before initiating specific treatment (Table 2).

Case 3

A 63-year-old male patient with history of chronic tobacco smocking was admitted in our department for diffuse abdominal pain associated with a deep weight loss of 20 kg over 2 months, anorexia, and asthenia. Physical exam revealed abdominal tenderness with no sign of jaundice or fever and no peripheral lymphadenopathy. Laboratory test showed an elevated ferritin level at 4598 ng/mL, Serum tumor markers CA 19-9 and CEA and the liver function were normal (Table 1). Abdominal CT scans showed an infiltrated and hypodense lesions in the body and tail of the pancreas (Fig. 3). EUS confirmed the tumor's presence in the tail and body of the pancreas (Fig. 3) and the FNA was performed confirming the diagnosis of a diffuse large cell B phenotype lymphoma, with

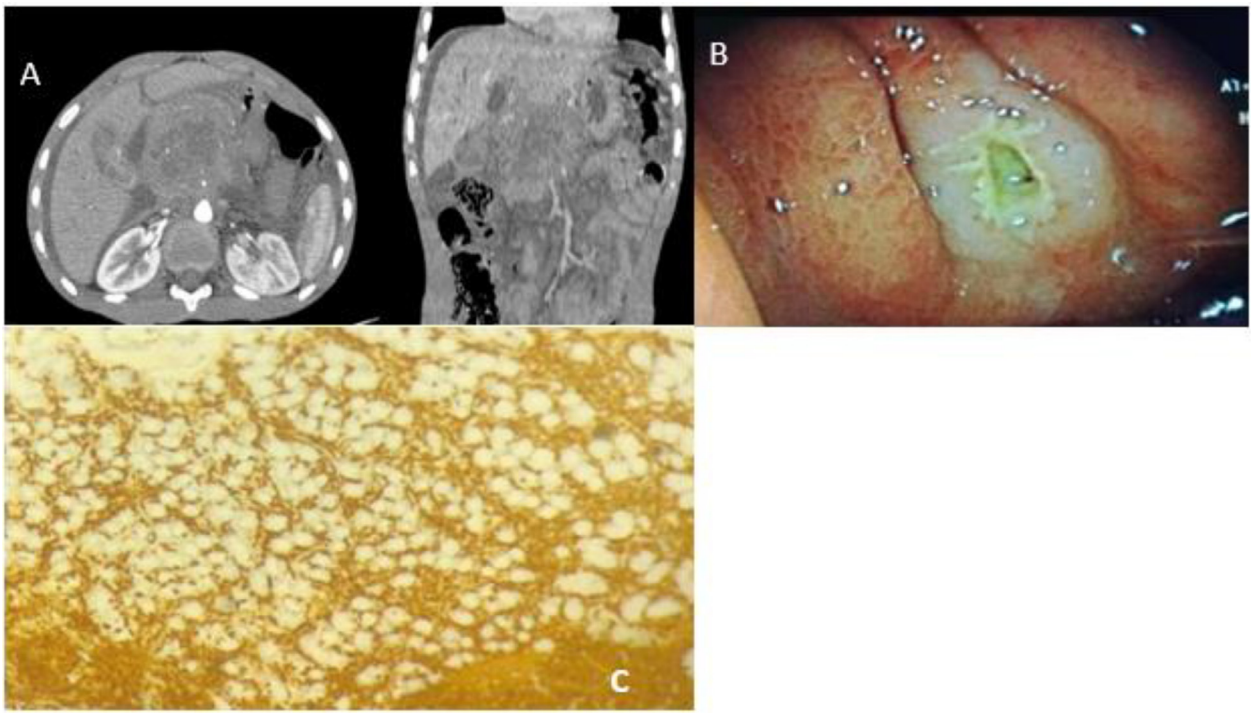

Fig. 1 – Case 1. (A) The CT scan of the first case showing the large irregular mass in the head of the pancreas responsible for dilation of the CBD, as well as invasion of the gastroduodenal region. (B) Gastroscopy showing a suspicious bulbar ulcer with a whitish background. (C) Immunohistochemical examination from the bulbar ulcer of the first clinical case showing Burkitt's lymphoma with positive CD10, CD20 and BCL-6 marking.

intense and diffuse labeling of the tumor cells by CD20, Bcl2, and Bcl6 (Fig. 3).

The patient received 6 courses of R-CHOP and achieved complete remission (Table 2).

Case 4

A 67-year-old man with 6 weeks history of jaundice, abdominal pain and weight loss, was admitted in our department. He had epigastric tenderness and jaundice with no fever. Laboratory test revealed hyperbilirubinemia at 172 mg/L, LDH levels were increased to 2275 IU/L as well as β2-microglobulin level at and CA 19-9 at 3560 IU/mL (Table 1).

Abdominal CT scan showed a lesion of the head and body of the pancreas, infiltrating the duodenum, and causing infiltration and stenosis CBD with upstream dilation. Additionally, there were bulky intraperitoneal lymphadenopathy (Fig. 4).

EUS showed a large >10 cm heterogeneous mass in the head of the pancreas, with an encasement of the portal vein and the superior mesenteric vein as well and multiple retroperitoneal lymph nodes. FNA was performed and the immunohistochemical staining found a robust expression of CD20 with a Ki67 estimated at 80% confirming the diagnosis of diffuse large cell B lymphoma (Fig. 4).

The patient received R-CHOP regimen, with favorable outcomes (Table 2).

Discussion

Lymphoma represents a diverse range of malignancies arising from the clonal proliferation of lymphocytes and constitutes approximately 5% of all malignancies. It can originate from the clonal expansion of B-cells, T-cells, and natural killer cell subsets of lymphocytes at various stages of their development [5].

PPL is a very rare disease, representing only 0.1% of malignant lymphomas, 0.6% of extranodal lymphomas, and 0.2% of all pancreatic cancers and the most common type of PPL is diffuse B-cell lymphoma accounting for approximately 80% of all cases [6].

Although PPL can occur at any age, it predominantly affects elderly patients, especially males. The most reported risk factor is Immunosuppression, whether associated with HIV infection or solid organ transplantation [6]

The results from our 4 cases align with the existing literature, out of the 4 patients, 3 were aged 50 or older with a male a predominance (3 males to 1 female). Moreover, the most prevalent histological type was diffuse large B-cell lymphoma. However, none of our patients were immunocompromised.

Like our patients, PPL manifests with a variety of nonspecific symptoms such as abdominal pain, jaundice, pancreatitis, and/or obstruction of the gastric or duodenal region. Additionally, some other symptoms like fever, night sweats, and weight loss are commonly observed. Those clinical manifesta-

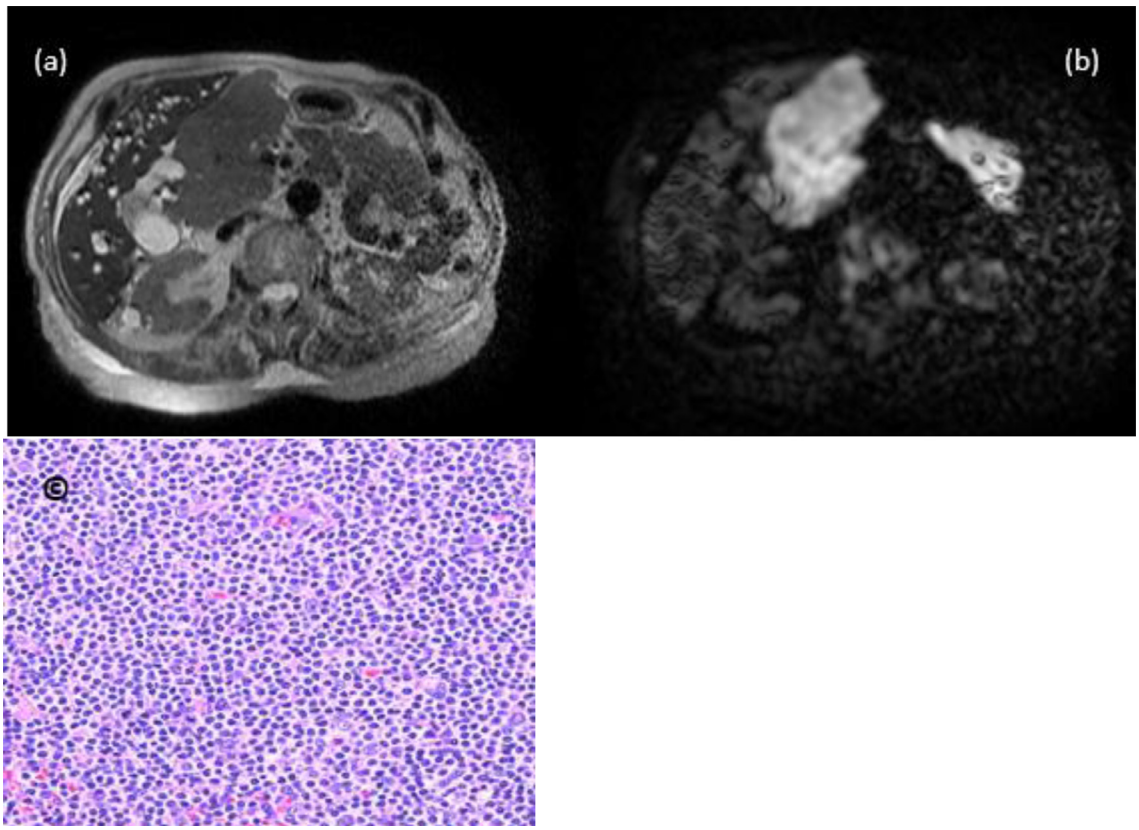

Fig. 2 – Case 2. (A) The abdominal MRI of the second case showing a large mass in the head and body of the pancreas causing dilation of the CBD and the MPD, as well as vascular invasion. (B) The lesion was hyperintense on diffusion-weighted imaging. (C) Histologically, the sample shows lymphomatous proliferation arranged in layers, the tumor cells are large and show clear cytonuclear atypia.

Table 1 – Summary of the biological results of the 4 PPL cases.

	Case 1	Case 2	Case 3	Case 4	Normal range
Bilirubin	105	74	15	172	2-12 mg/L
AST	125	83	21	129	5-34 UI/L
ALT	187	59	14	148	0-55 UI/L
Gamma-glutamyl transferase	217	355	19	160	M 0-64 UI/L F 0-36 UI/L
PAL	315	315	195	330	<150 UI/L
LDH	1020	452	243	2275	120-243 UI/L
B2 -microglobulin	35	-	73	111	0.97-2.64 mg/L
CRP	18.8	109	21	47	0-5 mg/L
WBC	6860	8630	5510	12,470	4000-10,000/uL
HB	11.3	8.2	14.9	12	M 13-18g/dL F 12-16 g/dL
Platelet Count	249,000	270,000	121,000	120,000	150,000-400,000/uL
LYM	80	510	550	180	1500-4000/uL
Creatinine	5	11.2	8.9	9.3	7-11 mg/L
Urea	0.25	0.68	0.32	0.64	0.15-0.45 g/L
Albumin	27	24	24	30	35-50 g/L
Ferritin	-	119	4598	2756	20-200 ng/mL
Ca 19-9	25.52	4.5	3.08	3560	<37 UI/mL
CEA	3.4	3.15	1.57	2.58	<5 ng/mL

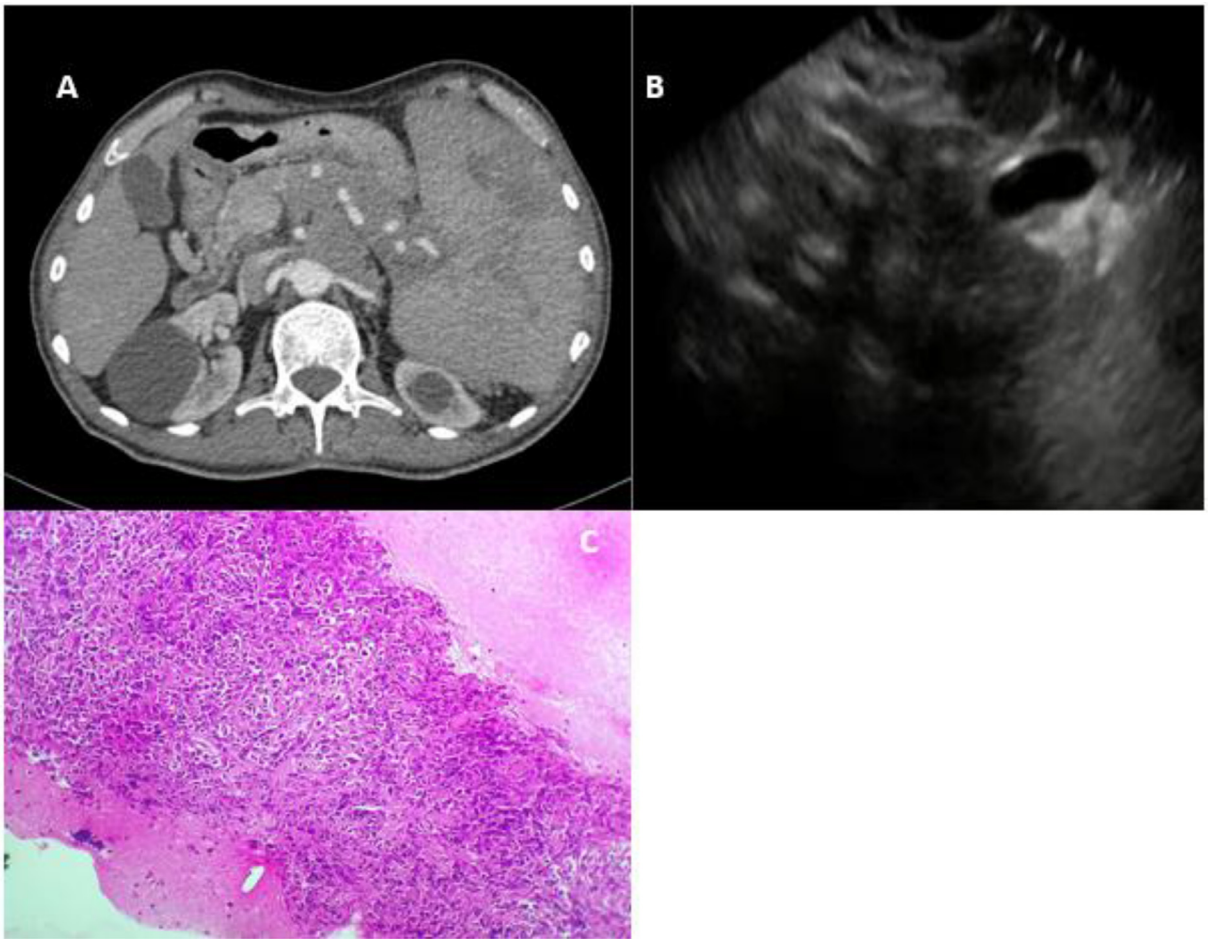

Fig. 3 – Case 3. (A) Abdominal CT scans showed an infiltrated and hypodense lesions in the body and tail of the pancreas. (B) EUS image of the third clinical case showing an irregular mass occupying the body and tail of the pancreas. (C) The cytological results of the FNA of the third case confirming the diagnosis of a diffuse large cell B lymphoma.

Table 2 – Summary of clinical, imaging, histological, treatment regimens and outcomes of the 4 PPL cases.

	Case 1	Case 2	Case 3	Case 4
Age	M	F	M	M
Sex	16	92	63	67
Presenting symptoms	Jaundice and abdominal pain Weight loss	Jaundice and abdominal pain Weight loss	Abdominal pain, weight loss	Jaundice and abdominal pain, weight loss
Delay until diagnosis	4 wk	2 wk	8 wk	6 wk
Method of diagnosis	Gastroscopy	Duodenoscopy with biopsy	EUS + FNA	EUS + FNA
CT appearance	Dilation of CBD + tumor located in the head of the pancreas.	Voluminous pancreatic process + infiltration of CBD	Hypodense lesion in the body and tail of the pancreas	Process of the head and body of the pancreas, infiltrating the duodenum, and CBD
Histological type	Burkitt's lymphoma	Diffuse large cell B lymphoma	Diffuse large cell B lymphoma	Diffuse large cell B lymphoma
Treatment	CHOP	-	R-CHOP	R-CHOP
Outcomes	Death	Death	Remission	Remission

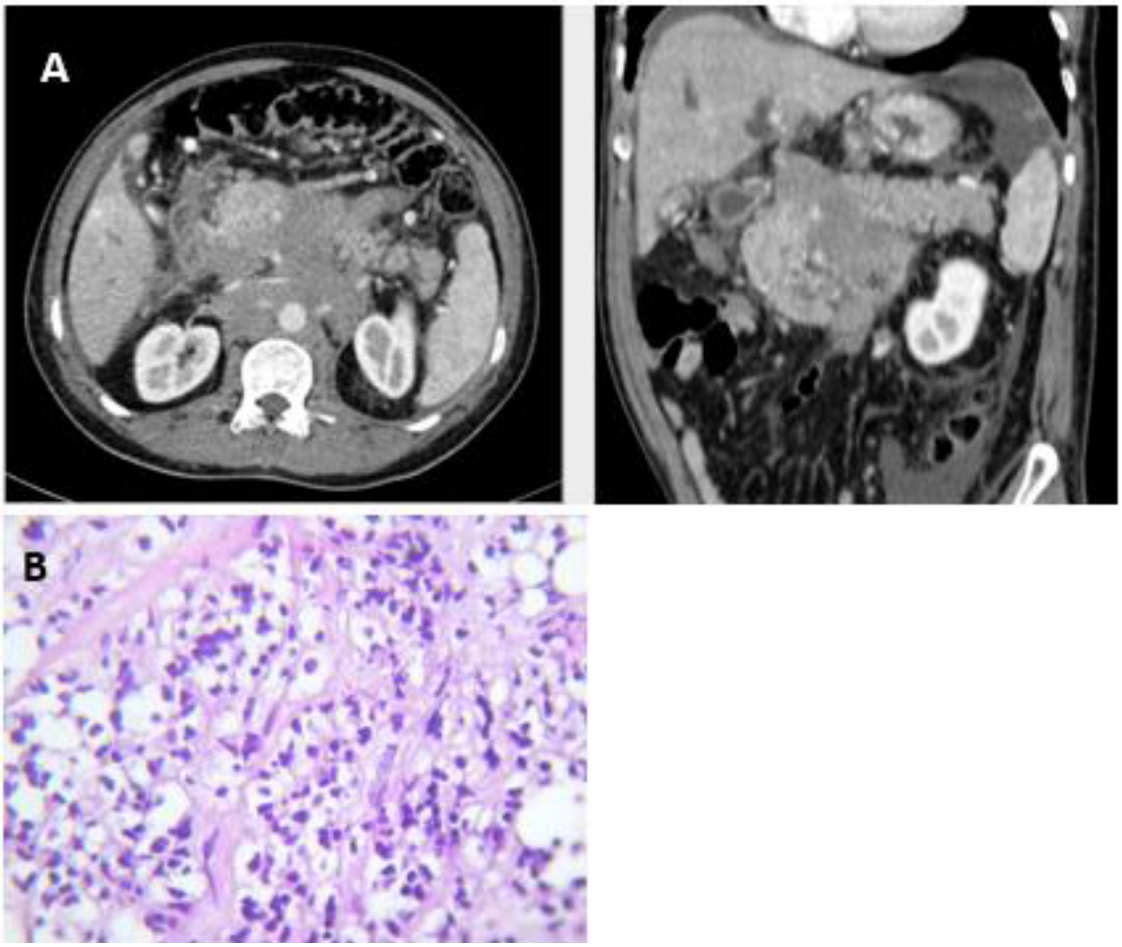

Fig. 4 – (A) Abdominal CT scan showed a lesion of the head and body of the pancreas, infiltrating the duodenum. (B) Cytological results of the fourth case confirming the diagnosis of diffuse large cell B lymphoma.

tions may overlap with those of the other pancreatic cancers [6].

The median time between the onsets of symptoms to diagnosis is around 4-5 weeks [3], same for our 4 patients. Regarding laboratory tests, although nonspecific, some biochemical markers can be helpful in suspecting the diagnosis of PPL. The CA 19-9 marker is typically elevated in patients with pancreatic adenocarcinoma [7], but it is seldom increased in patients with PPL as well as in other hepatobiliary and pancreatic diseases [8]. Additionally, while LDH and β2-microglobulin levels are known to be elevated in lymphoproliferative disorders, they may not necessarily be elevated in PPL [9]. Nonetheless, higher levels of β2-microglobulin and LDH have been linked to a poorer prognosis in PPL [6] In our study, CA19-9 levels were elevated in only 1 case, which unfortunately had a delayed diagnosis and resulted in a fatal prognosis. On the other hand, LDH and B2 microglobulin levels were elevated in 3 patients in our series.

The use of modern CT scan techniques, which involve multi-phase imaging in arterial and portal venous phases, enhances visualization of pancreatic neoplasms and the vascular involvement [10]. PPL can present in different ways, such as a sizable bulky mass, a focal nodular lesion, or a poorly defined, infiltrative mass showing uniform contrast enhancement [11].

The absence of pancreatic ductal dilatation, vascular invasion/occlusion, necrosis, and calcification, despite the tumor's significant size, should raise suspicion for PPL, which indicates further evaluation with EUS [12]. Regarding our patients, all of them had vascular invasion without total occlusion or deformation of the contours. However, dilation of the main pancreatic duct was observed in only 1 patient.

MRI may be used as an alternative when CT results are inconclusive or to reduce radiation exposure, particularly in younger patients. In PPL the mass have usually a reduced signal intensity on T1-weighted images and increased signal intensity on T2-weighted images. Additionally, diffusion-weighted sequences offer high sensitivity in visualizing lymphomatous tissue and lymph nodes [3]. In our study, only 1 patient underwent an MRI.

Depending solely on symptoms, imaging, and tumor markers without a definitive pathological diagnosis of suspected pancreatic mass may lead to the misdiagnosis of a small number of potentially curable patients because the prognosis and management of PPL is significantly different from that of adenocarcinoma [13,14]. Actually, a precise diagnosis of PPL

hinges on the use of a tissue sampling method that is highly sensitive and specific and minimally invasive. Some case reports utilized CT-assisted percutaneous biopsy but this technic have lower success rates and severe complications [6].

EUS is a diagnostic tool for identifying and characterizing pancreatic masses. Certain EUS features, such as large tumor size, heterogeneity, the lack of vascular invasion despite the tumor's large size, the absence of dilation in the pancreatic duct, and the presence of malignant peripancreatic adenopathy, are more indicative of PPL rather than adenocarcinoma [3]. EUS also offers the advantage of dynamic and real-time tumor observations [15]. EUS-FNA, when combined with rapid onsite evaluation, immunohistochemistry, and flow cytometry, proves to be a valuable diagnostic approach for accurately diagnosing and subtyping PPL [2].

In certain situations, it is necessary to choose the least invasive approach, such as biopsy of gastric or duodenal involvement during a gastroscopy or duodenoscopy. Biopsy per classic Endoscopy were helpful in 2 of our patients.

Regarding the treatment, according to the guidelines [16] chemotherapy is the established standard of care for management of PPL, with a high complete response rate. The most common treatment regimen includes R-CHOP. Other regimens include CVP (cyclophosphamide, vincristine, and prednisone), and MACOP-B (methotrexate, Adriamycin, cyclophosphamide, vincristine, prednisone, bleomycin).

PPL have a more favorable prognosis when compared to other tumors. While the 5-year overall survival rate for pancreatic cancer is 5%, the cure rates of up to 30% have been documented in PPL. Nevertheless, the prognosis in PPL is influenced by various factors such as the type of lymphoma, time to diagnosis, and the promptness of treatment [17,18]. In our 4 cases, the delay in diagnosis was tragically responsible of 2 deaths.

Conclusion

As demonstrated in our study, PPL represents a rare and challenging disease with nonspecific clinical signs. Several biological markers, as well as radiological findings can guide the diagnosis, however, histological confirmation is indispensable and requires urgent attention in order to start an early treatment. Delay in managing the condition can have a negative impact on the prognosis, as seen in the cases of 2 of our patients.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contribution

Writing and analysts: Lamrani FZ, Amri F, Correction & Data source: Koulali H, Bennani A, Ismaili Z, Kharasse G

Patient consent

Informed consent was obtained from each patient partaking in the study. The research carried no inherent risks for the participants, and all the information amassed was treated with the utmost confidentiality.

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