# Primary pancreatic lymphoma

## *Histopathological pattern of 8 cases*

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## ABSTRACT

**الأهداف**: سرطان الغدد الليمفاوية للبنكرياس الأولي (PPL) هو ورم نادر للغاية. تهدف هذه الدراسة إلى الإبلاغ عن النمط المرضي للمرض في مستشفيين من المستوى الثالث.

**المنهجية**: تمت مراجعة شرائح وتقارير علم الأمراض لجميع الحالات التي تم تشخيصها في أقسام علم الأمراض في اثنين من مستشفيات الإحالة. تم إجراء دراسة كيميائية مناعية إضافية لإعادة تصنيف الأورام اللمفاوية وفقًا للنظام الحالي.

**النتائج**: تم تحديد ثمانية مرضى يعانون من PPL. – تتراوح أعمارهم بين 36 إلى 71 عاماً. يشمل العرض السريري آلامًا في البطن وفقدان الوزن واليرقان وكتلة البطن والغثيان والقيء. كشف التقييم المرضي عن خمسة أورام لمفاوية كبيرة منتشرة في الخلايا البائية (DLBCL)، وسرطان الغدد الليمفاوية في الخلايا البائية عالي الدرجة، وسرطان الغدد الليمفاوية MALT، وسرطان الغدد الليمفاوية الجريبي من الدرجة واحد.

**الخلاصة**: PPL هو ورم نادر جدًا بدون اختبارات سريرية أو معملية أو نتائج إشعاعية محددة. ألم البطن هو العرض السريري الأكثر شيوعًا. DLBCL هو النوع الفرعي المرضي الأكثر شيوعًا. ينبغي أن تؤخذ PPL في الاعتبار عند تقييم كتلة البنكرياس لتجنب الاستئصال الجراحي غير الضروري.

**Objectives:** To report the histopathological pattern of primary pancreatic lymphoma (PPL) in 2 tertiary hospitals.

**Methods:** The pathology slides and reports of all the cases diagnosed in pathology departments in 2 referral hospitals were reviewed. An additional immunohistochemistry study was done to reclassify lymphomas according to the current system.

**Results:** Eight patients with PPL have been identified. The ages ranged from 36 to 71 years. Clinical presentation includes abdominal pain, weight loss, jaundice, abdominal mass, nausea, and vomiting. Pathological evaluation revealed 5 diffuse large B-cell lymphomas, one high-grade B-cell lymphoma, one MALT lymphoma, and one follicular lymphoma.

**Conclusion:** Primary pancreatic lymphoma is a very rare tumor without specific clinical, laboratory tests, or radiological findings. Abdominal pain is the most common clinical presentation. Diffuse large b-cell lymphoma is the most common pathological subtype. Primary pancreatic lymphoma should be taken into consideration when evaluating pancreatic mass to avoid unnecessary surgical resection.


**Keywords:** lymphomas, pancreas, Saudi Arabia

***Saudi Med J 2024; Vol. 45 (3): 307-312***
***doi: 10.15537/smj.2024.45.3.20230930***

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*Received 27th November 2023. Accepted 4th February 2024.*

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Primary pancreatic lymphoma (PPL) is defined by the World Health Organization (WHO) as extranodal lymphoma originating in the pancreas with the bulk of the tumor localized to this location. Contiguous and distant lymph node involvement could be present, but the primary clinical presentation is in the pancreas.[1] Primary pancreatic lymphoma is a very rare neoplasm and represents 0.6% of extranodal lymphomas and less than 0.5% of all pancreatic neoplasms.[1,2] On the other hand, secondary pancreatic involvement is relatively common, particularly in widespread lymphomas, and is detected in up to 30% of cases by some authors. Primary pancreatic lymphoma is more frequently seen in the elderly and more identified in men than women. According to the Surveillance, Epidemiology and End

Results [SEER] database, which included 835 patients, the median age was 67 years, and the median overall survival was 53 months in patients with PPL.[3] They also found that younger age is associated with better survival. Little is known on the pathological features of PPL in Saudi Arabia, and only 2 case reports from the Saudi community have been published.[4,5]

**Methods.** This retrospective study was carried out at King Abdulaziz University Hospital (KAU) and King Faisal Specialist Hospital and Research Centre (KFSH&RC), Jeddah, Western region, Saudi Arabia. The inclusion criteria included all PPLs found to fit the WHO criteria and covered the period between April 2002 and March 2023. The pathology slides and reports of all the cases were reviewed. An additional immunohistochemistry study for the reclassification of diffuse large b-cell lymphoma (DLBCL) was added. Diffuse large b-cell lymphomas were subcategorized using the Hans algorithm.[c] Diffuse large b-cell lymphomas were subclassified to germinal center B-cells (GCB) and non-germinal center B-cells (non-GCB) according to the immunohistochemistry expression profile using CD10, MUM-1, and BCL-6 markers. Ethical approval was obtained from the biomedical research committee at KAU (Reference No. 34-22). Informed consent was waived by the committee as the research project used archived material. The study was performed according to the principles of Helsinki Declaration. A pathological review and additional immunohistochemical study enable recategorization of lymphomas to be included in the currently accepted pathological classification.

*Statistical analysis*. Chi-square test was used to assess the gender difference tumor location and lymphoma pathological types.

**Results.** Eight patients with PPL have been identified. A summary of the clinicopathological features is shown in Table 1. The 8 PPL patients included 5 males and 3 females. The ages ranged between 36 to 71 years. The patients presented with abdominal pain (7), weight loss (7), jaundice (2), nausea (5), vomiting (2), fever (2), night sweats (2), abdominal mass (1), and back pain (2). The characteristic features of lymphoma such as fever and night sweats have been seen in only 2 cases.

**Disclosure.** Authors have no conflict of interests, and the work was not supported or funded by any drug company.

One of the patients in this series was HIV positive. The patient had CNS involvement, received high-dose methotrexate, finally developed cytomegalovirus viremia, severe pneumonia, and sepsis, and died before the initiation of chemotherapy. No significant immunodeficiency was identified in the other cases.

The radiological findings included the presence of pancreatic masses. In 5 cases there was an associated lymph node enlargement in the upper abdomen. The specimens were obtained from percutaneous CT-guided biopsy (4 cases) and endoscopic core biopsy (2 cases), pancreatic resection (1 case), and excisional biopsy of frozen section (1 case). In the case of the resection, the patient had distal pancreatectomy and splenectomy. In the case of excisional biopsy, the clinical and radiological diagnosis was pancreatic carcinoma. The patient had a laparotomy, revealing a pancreatic head tumor. Pathological examination of a frozen section of the lesion confirmed the presence of atypical lymphoid infiltrate suggestive of lymphoma. An excisional biopsy of the mass was performed instead of the Whipple procedure surgery, and pathological examination of the permanent excisional material confirmed the diagnosis of lymphoma.

Primary pancreatic lymphoma had a median size of 7.1 cm (range 4.2–10). Tumors have been localized in the pancreatic head in 75% of cases. Pathological evaluation revealed 5 DLBCLs, one high-grade B-cell lymphoma, one mucosa-associated lymphoid tissue (MALT) lymphoma, and one follicular lymphoma (Figure 1). The DLBCLs showed a diffuse infiltrate of large, atypical B lymphoid cells with vesicular chromatin and prominent nucleoli. Three of the DLBCLs showed immunoprofile of a non-GCB subtype with one DLBCL of the Germinal center B cell (GCB) subtype. In one case there was no available material for subtyping. Ki-67 ranged between 60 and 90% in the DLBCL cases. In patient number 5, the initial pathology slides of CT-guided biopsy have been interpreted as suggestive of a neuroendocrine tumor. A review of the slides revealed normal pancreatic tissue with no evidence of malignancy. A repeat CT-guided biopsy revealed DLBCL.

For the patient with high-grade lymphoma, a biopsy showed diffuse infiltration of medium to large nuclei-sized lymphocytes with high mitotic rate and numerous apoptosis. An immunohistochemistry study showed positive staining for LCA, CD20, CD79a, PAX5, CD10, MUM1, and BCL-6. They were negative for CD3, CD5, CD10, CD138, and cyclin-D1. Ki67 was positive in more than 90% of the cells. No classic

**Table 1 -** Summary of the primary pancreatic lymphoma cases from 2 referral hospitals in the Western regions of Saudi Arabia.

| | Age/ gender | Site in pancreas | Procedure | Clinical | Radiology | Diagnosis | Treatment | Follow-up |
|---|---|---|---|---|---|---|---|---|
| 1 | 37/F | head | EUS-needle core | Abdominal and back pain, nausea, weight loss | Solid mass (10x7.5 cm | DLBCL | R-CHOP | Died after 6 months |
| 2 | 52/M | head | Excisional biopsy after frozen section | Abdominal pain, weight loss | Solid mass (5x4.5 cm | DLBCL | R-CHOP | Died after 14 months |
| 3 | 57/F | head | EUS-needle core | Abdominal pain, jaundice | Solid mass involving the whole pancreas (6x5.3 cm) | Follicular lymphoma, Grade 1 | Not available | Not available |
| 4 | 47/M | head | CT guided Core biopsy | Abdominal pain, nausea, vomiting, weight loss, fever, night sweats | Solid mass (8.6x6.5 cm | DLBCL | R-CHOP | 3 months. Lost follow up |
| 5 | 36/M | head | CT guided Core biopsy | HIV +, Abdominal pain, jaundice, nausea, vomiting, weight loss. | Solid mass involving the whole pancreas (9.6x8 cm) | DLBCL | R-CHOP | disease progression, sepsis, CMV viremia and died 5 months after diagnosis |
| 6 | 71/M | Tail | CT guided Core biopsy | Abdominal pain, nausea, weight loss. | Solid mass involving tail of the pancreas (9x 6.1 cm) | High-grade b cell lymphoma | R-CHOP | 2 months follow up |
| 7 | 60/F | Tail | Distal pancreatectomy resection | fever, weight loss, nausea, night sweat | Distal pancreas and splenomegaly (4.2x 3.1cm) | MALT | Surgical resection and splenectomy | 16 months follow up |
| 8 | 61/ M | head | CT guided Core biopsy | Abdominal pain, loss of weight | Solid mass (4.5 x4 cm) | DLBCL | R-CHOP | 23 months follow up |

EUS: Endoscopic ultrasound, CT: Computed tomography , DLBCL: diffuse large b-cell lymphoma, MALT: Mucosa-associated lymphoid tissue, R-CHOP: rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone, CMV: Cytomegalovirus

features of Burkett's lymphoma could be identified. The diagnosis was high-grade B-cell lymphoma; no material was available for double-hit lymphoma assessment by fluorescence in situ hybridization. In the patient with MALT lymphoma, the tumor showed diffuse infiltrate of small lymphocytes, some with irregular nuclear contours associated with plasmacytic differentiation. The tumor cells were positive for CD20, CD43, and BCL-2. They were negative for CD10, CD3, CD23, Cylin-D1, and CD5. Ki-67 showed positive staining in approximately 30% of tumor cells. The features were consistent with low-grade MALT lymphoma and against the other differential diagnoses, which include immunoglobulin G (IgG4)4-related disease. There was no storiform fibrosis, phlebitis, or increased IgG4/ IgG ratio by immunohistochemistry staining. The last case shows infiltration with small lymphocytes with a low mitotic rate. The tumor cells expressed CD20, PAX-5, CD10, BCL-2, and BCL-6 They were negative for CD3, CD5, CD23, and cyclin-D1. Ki-67 was detected in approximately 10% of tumor cells. The overall morphology and immunohistochemical profiles were consistent with low-grade follicular lymphoma (grade 1).

There was no statistically significant gender difference regarding the tumor location ($p$-value of 1) or lymphoma pathological type ($p$-value of 1).

**Discussion.** In Saudi Arabia, like other countries, PPL is extremely rare and represents less than 0.6% of extranodal non-Hodgkin's lymphomas.[7] Patients represents a diagnostic challenge due to the propensity to be misdiagnosed at the clinical and radiological levels as pancreatic adenocarcinoma. The clinical presentation may mimic pancreatic carcinoma or acute pancreatitis. The most common symptoms of PPL are abdominal pain. The patients may present with abdominal mass, nausea, loss of weight, and jaundice. The characteristic clinical manifestations of lymphoma, like fever, chills, and night sweats, are infrequently seen and present in only 2% of patients, according to some authors. In this study, 2 (25%) patients showed fever

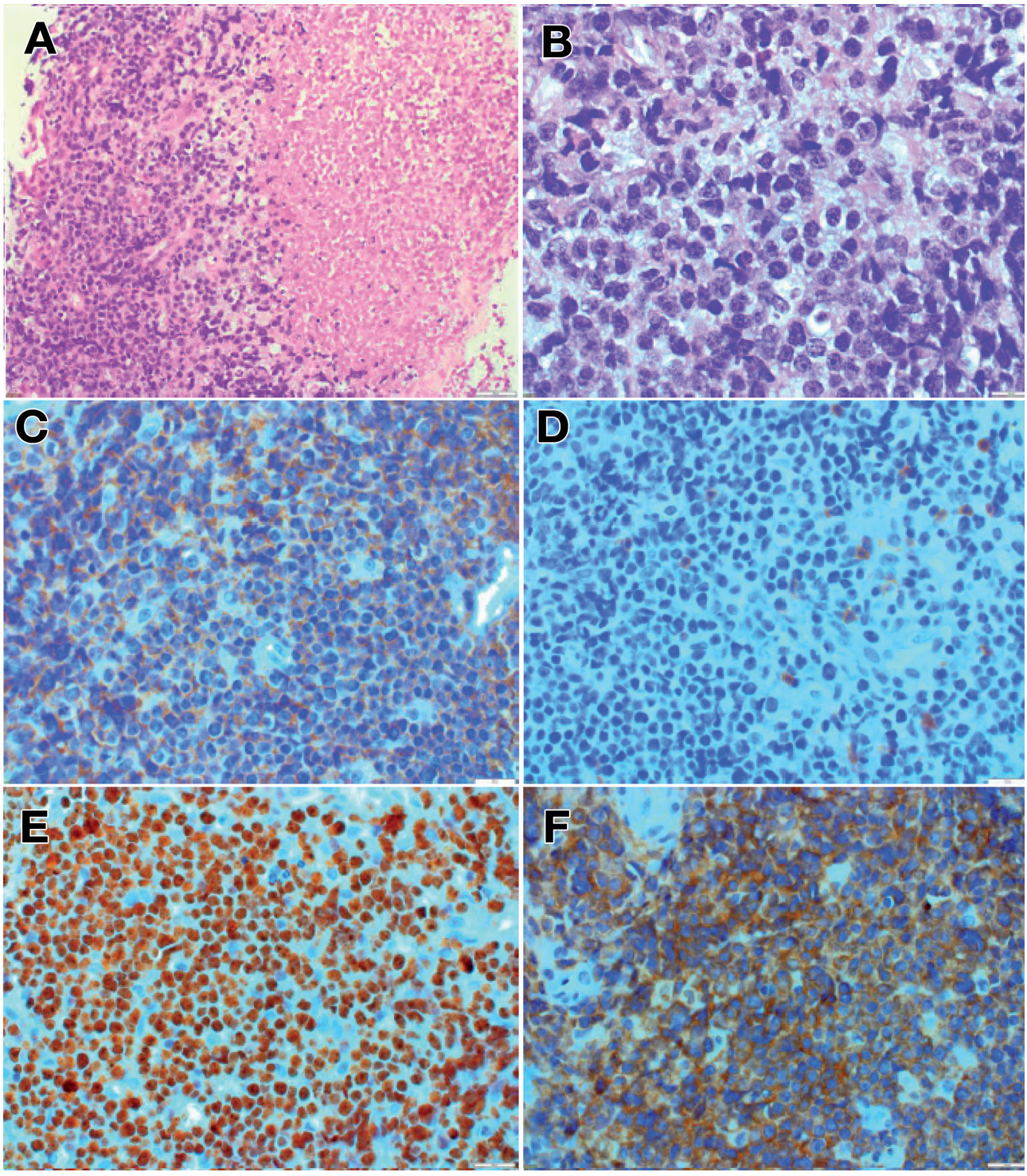


**Figure 1 -** Histopathological and immunohistochemical features of pancreatic diffuse large b-cell lymphoma. **A**) Section of pancreatic neoplasm tumor showing diffuse infiltration of large lymphoid cells with areas of necrosis (Hematoxylin and eosin, 200×). **B**) Higher power of the same case reveals large lymphoma cell infiltration (Hematoxylin and eosin, 400×). **C**) large lymphoid cells expressing CD20 (Immunohistochemistry stain, 200×). **D**: large lymphoid cells are negative for CD3 (Immunohistochemistry stain, 200×). **E**) High proliferation index by Ki-67, approximately 90% of tumor cells expressing KI-67 (Immunohistochemistry stain, 200×). **F**: large lymphoid cells expressing CD10 (Immunohistochemistry stain, 200×).

and night sweats. The final diagnosis of pancreatic lymphoma depends entirely on pathologic evaluation. Determination of primary versus secondary type will depend on the clinical and radiological assessment. The aetiology of PPL is not very clear; however, PPL may be associated with immunodeficiencies, such as in the case of HIV infection or iatrogenic following solid organ transplantation. PPL has also been reported in patients with short-bowel syndrome and hepatitis C virus (HCV) infection.[8]

The clinical and radiological differential diagnoses of pancreatic mass always include epithelial neoplasm and pancreatic adenocarcinoma. Although it is rare, PPL has been reported in association with pancreatic carcinoma. Retroperitoneal lymphadenopathy in patients with pancreatic carcinoma is usually managed as an incurable disease. The coexistence of PPL in the enlarged retroperitoneal lymph nodes of pancreatic carcinoma patients has been reported and considered one of the non-metastatic causes of lymphadenopathy, which should be considered in the differential diagnosis of those patients.[9]

Primary pancreatic lymphoma mainly occurs in the pancreatic head; however, it can also be found in the body and tail. The biochemical laboratory study is nonspecific for diagnosis of PPL. Usually, the serum carbohydrate antigen 19-9 (CA19-9) level is normal in patients with PPL in contrast to the elevated level that is classically found in adenocarcinoma of the pancreas. Primary pancreatic lymphoma is typically of the non-Hodgkin's b-cell histological type. Diffuse large b-cell lymphoma is the most common histological type in adults, and Burkett's lymphoma is the most common histological type in the pediatric age group. The histopathological differential diagnosis of lymphoma depends on the lymphoma pathological type. Diffuse large b-cell lymphoma should be differentiated from diffuse poorly differentiated carcinoma. Immunohistochemistry study is helpful for differentiation. In low-grade B-cell lymphoma, the differential diagnosis includes autoimmune pancreatitis. The differentiation between autoimmune pancreatitis (IgG 4-related disease) and low-grade MALT lymphoma is sometimes challenging because both can be associated with dense lymphoplasmacytic infiltrate. However, autoimmune pancreatitis usually shows storiform fibrosis and obliterative phlebitis and reveals an increased IgG4/IgG ratio by immunohistochemistry, which will help establish the diagnosis. The distention of pancreatic lymphoma from carcinoma is critical for management. While the usual management approach for pancreatic carcinoma is surgical resection, PPL is usually treated by chemotherapy. Therefore, diagnosis before surgical resection is important to avoid unnecessary surgery. This can be achieved by fine needle aspiration or core biopsy either percutaneously or through endoscopy. The diagnosis usually requires supportive ancillary tests, including immunohistochemistry and molecular study. The distinction between lymphoma and carcinoma is also important for the patient's prognosis. While pancreatic carcinoma carries a dismal prognosis, PPL is associated with a much better prognosis and can be curable even in patients with high-stage disease. Two previously reported cases are from Saudi Arabia.[4,5] The first one was a patient with an uncinate process mass tumor. The patient presented with epigastric pain and jaundice, diagnosed as non-Hodgkin lymphoma, and was treated with R-CHOP with no recurrence after one year of clinical follow-up.[4] The second patient was a transplant recipient who developed non-Hodgkin lymphoma and was treated with chemotherapy and radiation.[5]

Pancreatic endoscopic ultrasound-guided fine-needle aspiration combined with immunohistochemical assays, flow cytometry and molecular study can help in the final diagnosis of a small amount of tissue.[10,11] Primary pancreatic lymphoma can be misdiagnosed as pancreatic carcinoma. Frozen section evaluation is helpful for intraoperative diagnosis to avoid major surgery. Collision tumor of adenocarcinoma and lymphoma has been described.[12,13] The median overall survival was 53 months in patients with PPL. The 5-year survival rate of pancreatic MALT lymphoma has been reported to be as high as 89%; however, the prognosis is worse for high-grade lymphomas.[14]

***Study limitations.*** The study covered the PPL in only 2 tertiary institutions and the number of cases is limited. National-wide multicentre studies will be more suitable to shed more light on the disease pattern in the Saudi Artabia.

In conclusion, primary pancreatic lymphoma is a very rare tumor disease without specific symptoms, laboratory tests, or radiological findings. Abdominal pain and weight loss were the most common clinical presentation, involving 88% of patients. It is almost always non-Hodgkin lymphoma of B-cell immunophenotype, and DLBCL is the most common pathological subtype. Primary pancreatic lymphoma should be considered when evaluating pancreatic mass, especially when there is extensive lymphadenopathy localized to the peripancreatic region. Tissue biopsy, either through endoscopy or CT-guided and

histopathological examination, is important for final diagnosis and to avoid unnecessary surgical resection.

**Acknowledgment.** *The author acknowledges with thank Gladys Harder, Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital, Jeddah, Saudi Arabia, for technical support. The author gratefully acknowledges American Manuscript Editors (www.americanmanuscripteditors.com) for the English language editing.*

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