CASE REPORT

AIDS-Related Pancreatic Burkitt´S Lymphoma. EUS-FNA Enhanced Diagnosis With Fluorescence In Situ Hybridization (FISH)

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ABSTRACT

Context Non-Hodgkin's lymphoma is a common complication in HIV-patients that most frequently affects the gastrointestinal tract. Primary pancreatic lymphomas and Burkitt Lymphoma involving the pancreas are uncommon. It is important to recognize them because can mimic an adenocarcinoma or pancreatitis, but their management is completely different. **Case report** We report a case of a forty-seven-year-old man who presented with an AIDS-related Burkitt Lymphoma with acute pancreatitis as initial manifestation. Initially patient was admitted with abdominal pain and high amylase levels. Computed tomography imaging was suggestive of acute pancreatitis. Later was found to be human immunodeficiency virus seropositive. 4-weeks later, a control computed tomography scan revealed growth of a well-defined large pancreatic mass, with diffuse enlargement of the gland, and a normal-appearing pancreatic duct. Consequently an endoscopic ultrasound-guided fine needle aspiration was performed with a 19-gauge needle and revealed a proliferation of medium lymphocytes, inconspicuous cytoplasm and frequent mitosis. The lymphocytes were positive for CD20 and CD10. The Ki-67 labeling index was almost 80%. BCL-2 and MYC FISH molecular analysis was performed and confirmed t(8;14)(q24;q32). On the basis of these results, pancreatic Burkitt's lymphoma was diagnosed. Positive emission tomography scan completed staging and showed uptake in the pancreas and multiple metastasis. Accordingly patient received chemotherapy by PHETEMA BURKIMAB protocol, obtaining complete remission. **Conclusion** Pancreatic Lymphoma should be considered in differential diagnosis of pancreatic masses. EUS-FNA including flow cytometry and molecular analysis are useful techniques that may help to establish early diagnosis and prompt treatment avoiding unnecessary surgery.

INTRODUCTION

Burkitt lymphoma of the pancreas is a Non-Hodgkin's lymphoma, a rare disease that constitutes less than 0.5% of all pancreatic tumors and accounts for less than 2% of extranodal lymphomas [1-3]. Non-Hodgkin's lymphoma is a common complication in human immunodeficiency virus (HIV)-seropositive patients that most frequently affects the gastrointestinal tract [4].

Acute pancreatitis associated with pancreatic lymphoma is extremely uncommon. This entity usually presents with abdominal pain, jaundice, or weight loss. Clinically, is most likely to be misdiagnosed as pancreatic cancer [5, 6].

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Abbreviation EUS-FNA Endoscopic Ultrasound-Guided Fine Needle Aspiration; CT Computed Tomography
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Patients with HIV can develop acute pancreatitis from HIV infection and related causes or from factors independent of HIV [7].

Pancreatic lymphoma and adenocarcinoma can be difficult to differentiate without histopathological diagnosis. Correct diagnosis is essential since treatment and prognosis are completely different [4-6]. Currently diagnosis of lymphoma is based upon the evaluation of histological, immunophenotypic and genetic studies. Therefore a correct diagnosis and classification is mandatory before initiating treatment.

Endoscopic ultrasound (EUS) is considered as the most accurate method for the diagnosis of pancreatic tumors [8]. EUS-guided fine needle aspiration cytology (EUS-FNAC) and biopsy (EUS-FNAB) are excellent, minimally invasive and cost-effective techniques for obtaining adequate material for diagnosis pancreatic tumors [9].

Traditionally diagnosing lymphomas with FNA has been difficult, however some studies have shown that FNA with combined cytology and immunophenotyping by flow cytometry and FISH molecular analysis can be used to make the diagnosis [10-19]. These complementary techniques may help in the differential diagnosis of solid

pancreatic masses, especially on those cases with atypical presentation [10].

We report a 47 years-old case of massive pancreatic involvement caused by a Burkitt Lymphoma in a HIV-infected patient, presenting as acute pancreatitis that was successfully diagnosed by EUS-guided FNA.

CASE REPORT

A forty-seven-year-old male with drug addiction 20 years ago, ethanol abuser and chronic liver disease HBV and HCV treated with Interferon and Ribavirin in 1998 with SVR. Presented with acute abdominal pain and fullness after alcohol ingestion. Physical examination revealed no jaundice or lymphadenopathy, but upper abdominal tenderness and hepatomegaly were evident. No peritoneal signs were present. The rest of his physical examination was normal. Laboratory studies showed hemoglobin 13.7g/dL (Reference Range:13.5-17.5g/dL), total leucocyte count 8.6x109/L (RR:4-11.0 x109/L) with 80% neutrophil (40-70%), (lymphocytes 938 (RR: 900-5200)); platelets 140x109/L (RR:150-425 x109/L); SGOT:14U/L (RR: 0-40U/L); SGPT:13U/L (RR: 0-40U/L); serum amylase:718U/L (RR: 10-100U/L); lipase: 814U/L (RR: 13-60U/L); CRP 6.8 mg / dl (RR: 0-10). The other biochemical parameters were within normal limits. HIV Serology: positive. The patient did not have a history of either AIDS or undergoing blood transfusion. He had no available data concerning HIV seropositivity. Abdominal CT-scan (**Figure 1**) showed a slightly increased pancreatic volume and density of peripancreatic fat, without bounded collections. The patient was diagnosed as having acute pancreatitis. He improved clinically and was sent home. Subsequently, in sucessive controls a HIV infection (stage A2) was confirmed and started antiretroviral treatment.

Two-months later, a control CT-scan (**Figure 2**) observed a large mass in the pancreatic head, up to 9.5 cm, with duodenum infiltration and superior mesenteric vein thrombosis, suggested to be a neoplasia. Splenomegaly (14.5 cm), spleen and hepatic hilum lymphadenopathy (3.8 cm in diameter) were also present. A EUS-guided FNA cytology and biopsy with 19G core needle was performed (**Figure 3**). Cytology on site showed multiple lymphoid cells (**Figure 4**). Biopsy revealed a fragment of tissue diffusely involved by medium size lymphocytes inconspicuous cytoplasm and frequent mitosis (**Figure 5**). Immunohistochemical studies resulted positive for CD10, CD20 and negative for CD30, CD99, BCL-2 TDT, ALK. Ki-67 proliferative index was positive in almost 80% of tumor cells (**Figures 6-7**). Flow cytometry showed monoclonal B immunophenotype population (**Figure 8**).

Finally a molecular study using FISH with probes Split signal (DAKO) was negative for BCL2 rearrangement and demonstrated C-MYC IGH-positive t(8; 14) (q24;q32) (**Figure 9**). These findings confirmed a primary pancreatic Burkitt lymphoma.

A complete staging includying PET, CT scan of chest were subsecuently performed, showing increased uptake only in the pancreas and multiple paravertebral thoracic metastases. Bone marrow infiltration was confirmed. The lymphoma was classified as Non-Hodgkin Burkitt lymphoma, stage IVB. Patient underwent chemotherapy by PHETEMA BURKIMAB protocol plus triple intrathecal prophylactic therapy. During treatment analytical tests and imaging studies, includying a new Endoscopic-ultrasound and CT-PET scan, demonstrated progressive improvement until complete remission. Thirty-six months later, the patient is disease-free.

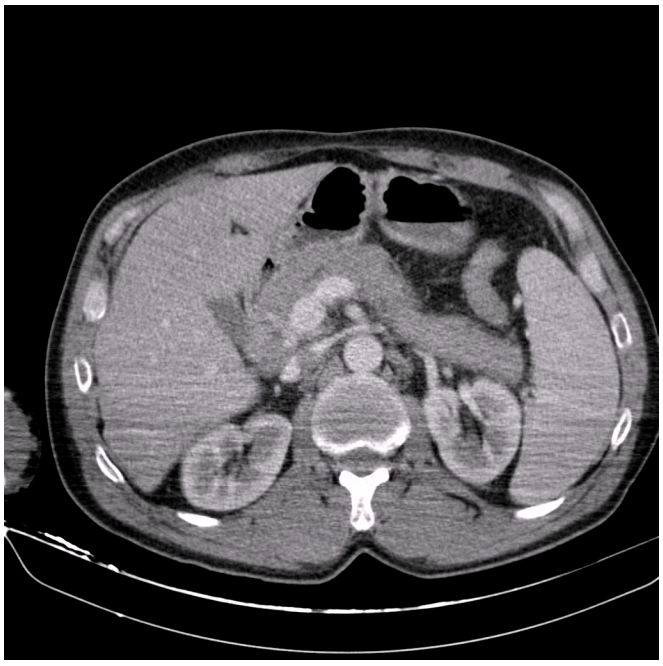

Figure 1. Initial CT scan compatible with acute pancreatitis

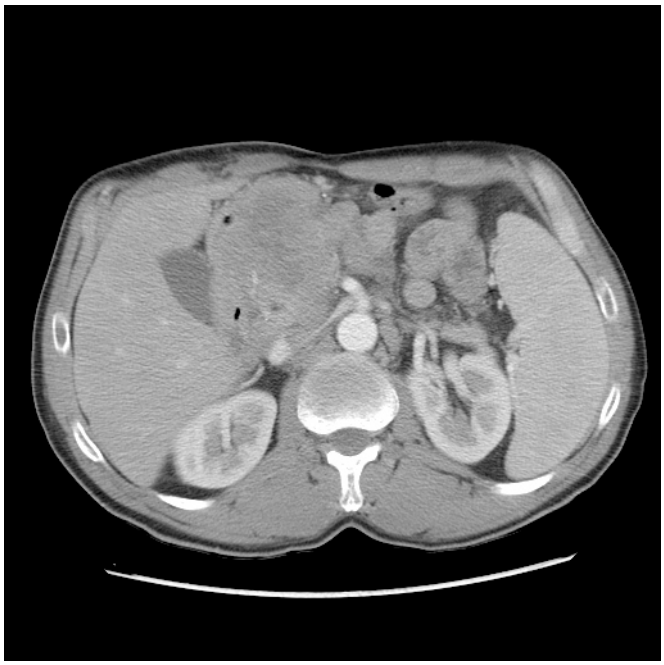

Figure 2. Control CT scan revealing large mass in the pancreatic head, up to 9.5 cm, with duodenum infiltration and superior mesenteric vein thrombosis, suggested to be a neoplasia

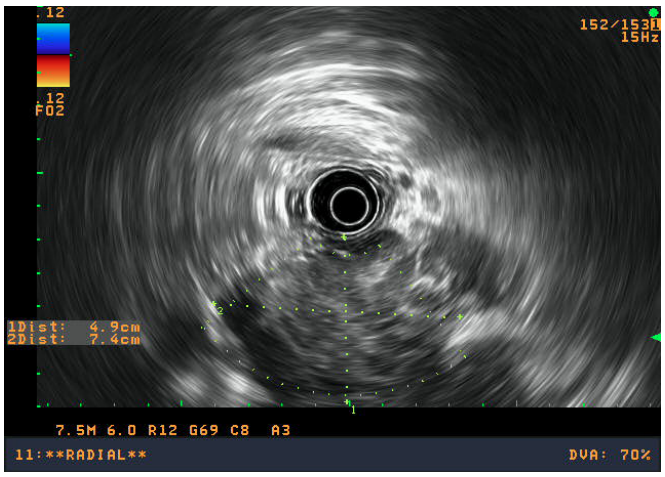

Figure 3. EUS demostrated a large hypoechoic and heterogeneous mass with irregular margins and vascular invasion

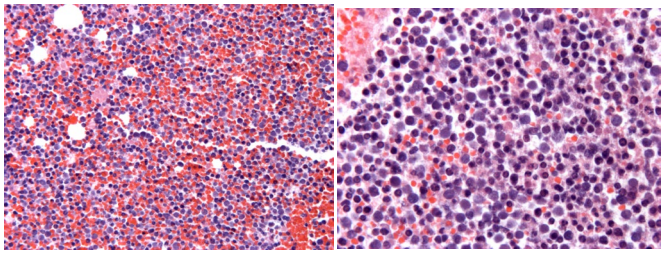

Figure 4. FNA-C. Citology (H&E 20X, 40X): showed multiple lymphoid cells

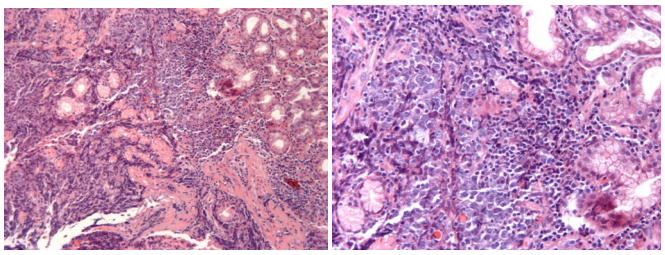

Figure 5. FNA-B: Biopsy (H&E 5X, 20X): revealed a fragment of tissue diffusely involved by medium size lymphocytes, inconspicuous cytoplasm and frequent mitosis

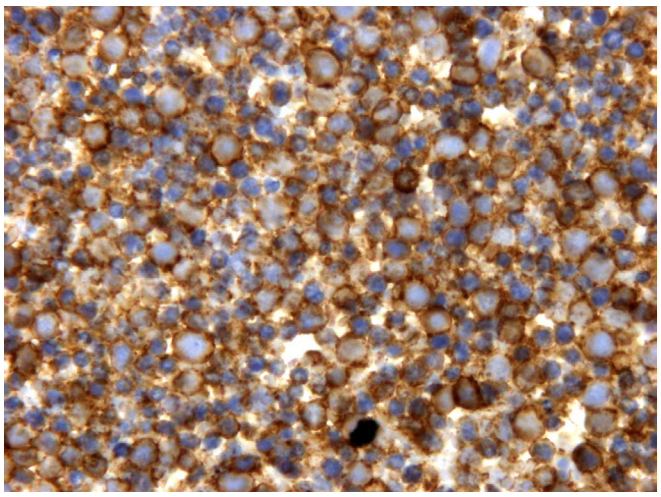

Figure 6. Immunohistochemical studies resulted positive for CD20

DISCUSSION

Lymphoma is the second most common neoplasm in patients with human immunodeficiency virus. Non-Hodgkin's lymphoma accounts for approximately 3% of the AIDS-related illnesses. Most primary pancreatic lymphomas are non-Hodgkin's Lymphomas and more than 25 percent of non-Hodgkin's lymphomas originate from extra-lymphatic organs [20, 21].

Primary pancreatic lymphoma represents 0.5% of pancreatic tumors, and less than 2% of extranodal malignant lymphomas. About a 30% of Non-Hodgkin's lymphoma may involve the pancreas, although less than 1% are considered primary pancreatic lymphomas [22, 23].

Burkitt's lymphoma is a subtype of B-cell non-Hodgkin lymphoma with aggressive clinical course that occur most commonly in patients with HIV infection [24].

Diagnostic criteria include: neither palpable superficial lymphadenopathy nor enlargement of mediastinal nodal on chest radiograph; normal white cell count, mass predominantly within the pancreas with lymph nodal involvement confined to the peri-pancreatic region, no hepatic or splenic involvement [25].

According to the World Health Organization classification Immunodeficiency-associated Burkitt lymphoma occurs mainly in patients infected with HIV and it is frequently seen in patients with CD4+ counts greater than 200 mm-3 unlike other HIV-related lymphomas [26]. AIDS diagnosis precedes the onset of lymphoma in approximately 57% of patients, but the 30% diagnosis of AIDS is made at the time of diagnosis of the lymphoma and HIV positive reaction [23].

Non-Hodgkin's lymphoma is a common complication infection in patients with HIV that most frequently affects the gastrointestinal tract [27]. Although the gastrointestinal tract is the site most commonly involved in HIV-related lymphoma, pancreatic involvement is extremely rare [28].

Lymphoma involving the GI tract frequently produces nonspecific symptoms and signs. Patients usually present with upper abdominal pain, nausea, vomiting, distension, weight loss, jaundice or abdominal mass. Jaundice is less common than in pancreatic adenocarcinoma. Presence of palpable abdominal mass, size mass more than 6 cm and a shorter duration of symptoms were proposed to be

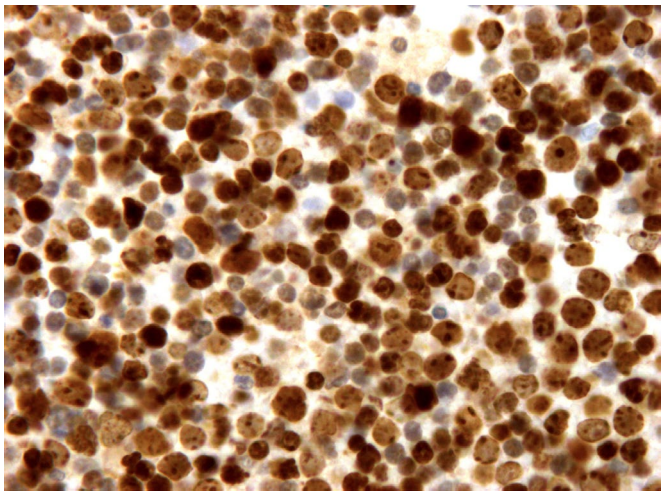

Figure 7. Ki-67 proliferative index was positive in almost 80% of tumor cells

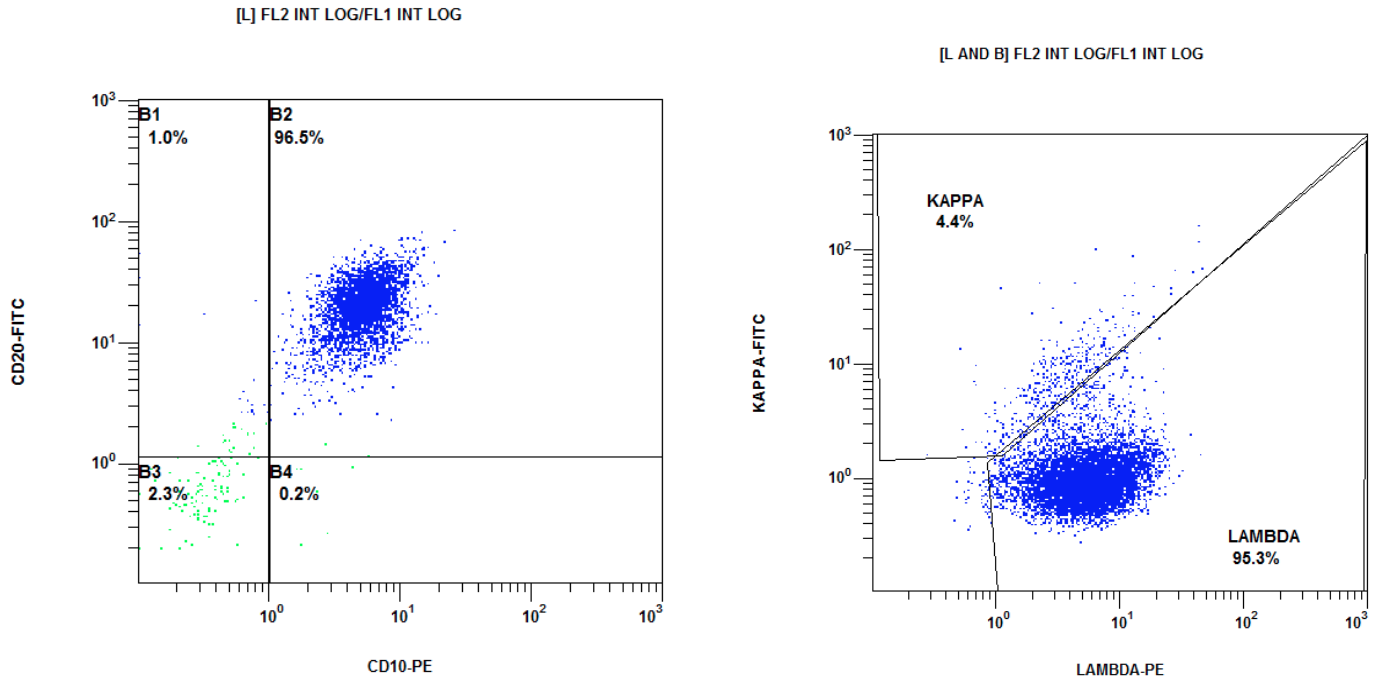

Figure 8. FLOW CYTOMETRY results CD19+CD20+CD10+CD22+CD79a+ IgG lambda+ IgG kappa- TdT-CD5-CD23

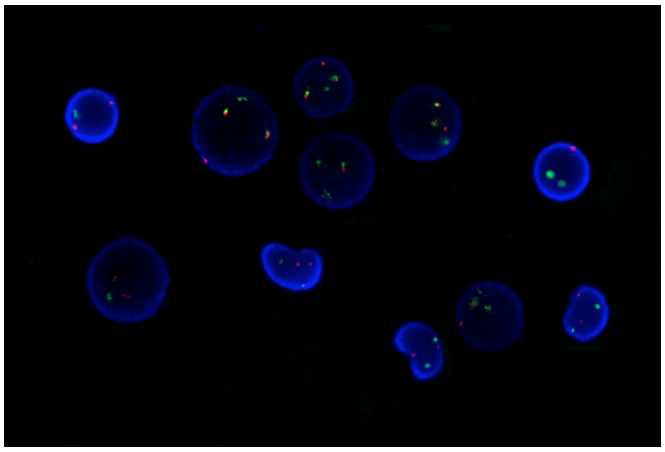

Figure 9. Fluorescence in situ hybridization (FISH) with probes Split signal (DAKO) was negative for BCL2 and C-MYC IGH-positive: t(8; 14) (q24;q32)

signs and symptoms suggestive of pancreatic lymphoma. B-symptoms, fever and night sweats are uncommon in patients with pancreatic lymphoma. Sometimes clinical presentation can mimics acute pancreatitis in more than 10% of patients but the etiopathogenesis of acute pancreatitis in this field remain unknown. Proposed mechanisms include ductal obstruction, tumor vascular occlusion or ductal rupture. [5, 29-32].

Thus, differential diagnosis of pancreatic mass is established with other solid lesions, as pancreatic adenocarcinoma, metastases, neuroendocrine tumors, pseudopapilar tumor and lymphoma. Even though lymphoma is a rare malignant tumor, the correct diagnosis is essential since management is considerably different from other pancreatic tumors, with better prognosis and survival rates than adenocarcinoma.

Laboratory investigations and radiological studies cannot differentiate this entity from pancreatic adenocarcinoma. Presence on CT scan of bulky mass, rapid invasive growth and retroperitoneal lymphadenopathy below level of the renal veins supports diagnosis of lymphoma. However, there are fewer signs of invaded large vessel and metastasis of the liver and spleen [20, 28]. Histopathological examination is necessary for an accurate diagnosis in order to perform detailed analysis of tissue architecture and special stains for adequate classification.

Nowadays Endoscopic ultrasound (EUS) is considered the most accurate method for diagnosis and staging pancreatic lesions [33]. EUS is a minimally invasive technique that provides detailed, high-resolution images of the pancreas. However, whether a lesion is malignant or benign cannot be diagnosed solely from its imaging features on EUS. The introduction of EUS-guided fine needle aspiration (EUS-FNA) offers the possibility to obtain in real time a cytological or histological diagnosis of pancreatic lesions with a high sensitivity (64-98%) and specificity (80-100%) [33, 34]. The advantages of EUS over other imaging techniques include real-time puncture, reduced risk of complications due to the proximity of the needle to the lesion, and the ability to sample small lesions that might be hard to sample using other methods.

Lymphoma traditionally required examination of tissue architecture and cytomorphology to make an accurate diagnosis, therefore, limiting the value of FNA as a diagnostic modality. Recently, the World Health Organization classification system of lymphomas introduces a new criteria based on a combination of information derived from immunophenotype, genotype, and histological features [33-35].

Moreover, EUS have incorporated the use of immunocytochemistry, flow cytometry and cytogenetic analysis, to increase the diagnostic yield with FNA in the

diagnosis and the classification of all types of lymphoma [10-19].

Flow cytometry only requires a small sample and is more sensitive and faster than immunohistological staining. Therefore, both flow cytometry and histology provide complementary information. Several studies have proven the usefulness of flow cytometry in diagnosis with samples obtained by EUS-guided FNA [10-19].

Immunophenotyping is a fundamental step in the diagnosis of lymphoma. In addition to the histomorphological assessment, immunohistological staining is generally used simultaneously for diagnosis and classification of lymphoma.

Cytogenetic analysis is also helpful for diagnosis and subclassification of lymphoma. Several lymphomas have characteristic genetic abnormalities that are important in determining their biological features and that can be useful in differential diagnosis. Eighty percent of Burkitt lymphoma cases harbor t(8;14) translocation, resulting in the juxtaposition of the *c-myc* gene on chromosome 8 with *IgH* enhancer elements on chromosome 14. In the remaining 20% of cases, t(2;8) or t(8;22) are observed placing the *c-myc* gene adjacent to either the kappa or lambda light chain (IgL), respectively [26].

Fluorescence In Situ Hybridization (FISH) a cytogenetic technique, uses fluorescently labeled DNA probes to chromosomal centromeres or unique loci to detect and localize the presence or absence of specific DNA sequences on chromosomes. Several studies have shown the usefulness of FISH, for the subtyping of non-Hodgkin lymphoma in cytological samples obtained by percutaneous FNA [36, 37], and Levy et al confirmed its application to EUS-FNA [38] as showed in our case.

In conclusion, primary pancreatic lymphoma is an uncommon tumor which can mimic pancreatic adenocarcinoma in appearance. Burkitt's lymphoma is a subtype of B-cell non-Hodgkin lymphoma that occurs most commonly in patients with HIV infection. Even though is a rare malignant tumor, must be suspected in HIV-patients.

The correct diagnosis is essential since management and prognosis is considerably different from other pancreatic tumors. EUS-FNA can be used to make a diagnosis but should be combined with flow cytometry and immunocytochemistry to increase the sensitivity and specificity.

Lymphoma subclassification is generally possible by immunophenotyping of immunohistological staining and flow cytometry in addition to histomorphological assessment. Moreover, cytogenetic abnormalities can be assessed by use of FISH. These ancillary techniques enhance the diagnostic potential of EUS-FNA and can avoid the need for invasive surgical biopsies and prompt treatment.

Conflict of Interest

The authors declare that they have no conflict of interest

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