American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e921269
DOI: 10.12659/AJCR.921269

Received: 2019.11.08
Accepted: 2020.01.08
Available online: 2020.02.05
Published: 2020.03.16

A Rare, Yet Treatable Pancreatic Tumor: Epstein-Barr Virus-Positive Diffuse Large B-Cell Lymphoma

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, 62-year-old
Final Diagnosis: Pancreatic lymphoma
Symptoms: Epigastric pain • unintentional weight loss
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Rare disease

Background: Epstein-Barr virus (EBV)-positive diffuse large B-cell lymphoma (DLBCL) is a rare subtype of B-cell neoplasm that can have diverse presentations. When it involves the pancreas (i.e., pancreatic lymphoma), it can mimic metastatic pancreatic adenocarcinoma. Pancreatic lymphoma and adenocarcinoma often have similar clinical, laboratory, and radiographic features making the distinction challenging without pathological tissue examination. The differentiation of these 2 entities is important as the prognosis of pancreatic lymphoma is certainly more favorable with a chance of cure with chemoimmunotherapy.

Case Report: We present an unusual case of EBV-positive DLBCL involving the pancreas that was initially believed to be metastatic pancreatic adenocarcinoma. The patient was treated with chemoimmunotherapy and had a remarkable response. This is the first known case of EBV-positive DLBCL involving the pancreas that was successfully treated with chemoimmunotherapy.

Conclusions: EBV-positive DLBCL can have diverse presentations, including a pancreatic mass with multi-organ involvement, which mimics metastatic pancreatic adenocarcinoma. The prognosis of EBV-positive DLBCL is thought to be worse than that of EBV-negative tumors. However, it remains certainly superior to that of its adenocarcinoma counterpart with conventional chemoimmunotherapy.

MeSH Keywords: Epstein-Barr Virus Infections • Lymphoma, Large B-Cell, Diffuse • Pancreatic Neoplasms

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/921269

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Background

Epstein-Barr virus (EBV)-positive diffuse large B-cell lymphoma (DLBCL) represents less than 5% of all DLBCL cases in the Western world [1]. It can be difficult to diagnose initially, as it commonly involves extra-nodal sites such as the kidney [2], liver [3], and stomach [4]. Herein, we present a case of EBV-positive DLBCL involving the pancreas that was initially thought to be metastatic pancreatic adenocarcinoma. Despite reports suggesting inferior outcomes compared to EBV-negative cases, EBV-positive DLBCL certainly has a more favorable prognosis than metastatic pancreatic adenocarcinoma. Therefore, it is imperative to recognize this entity and differentiate it from its adenocarcinoma counterpart.

Case Report

A 62-year-old male with an unknown past medical history was admitted to our hospital with a half-year of unintentional weight loss and epigastric pain. He had a significant cigarette smoking history of 1 pack-per-day for 40 years, and only quit smoking 3 months prior to this hospitalization. Computed tomography (CT) scans demonstrated a large pancreatic mass (9.4×12.2×12.4 cm) along with involvement of the spleen, liver, lung, and retroperitoneum (Figure 1A). Laboratory testing was significant for mild elevations in lactate dehydrogenase level (LDH) and carbohydrate antigen (CA) 19-9, while liver enzymes and blood counts were within normal limits. His hemoglobin A1c was 6.2 mmol/mol.

The patient's clinical presentation along with laboratory and radiographic findings were highly suggestive of metastatic pancreatic adenocarcinoma. The suspected diagnosis was communicated to the patient and the prognosis was briefly discussed. He was made aware that this is likely a terminal disease with no curative therapeutic options. A core needle liver biopsy was performed to confirm the diagnosis. Surprisingly, the pathology from the biopsy revealed extensive replacement of the hepatic parenchyma by a dense inflammatory infiltrate along with large cells with large nuclei and prominent nucleoli (Figure 2). Immunohistochemical stains were strongly positive for CD20, CD30, CD45, EBV (EBER), CD79a, PAX-5, and MUM-1, and negative for CD3, CD10, CD15, Bcl-2, Bcl-6, CD138, and ALK-1 (Figure 3). These findings were consistent with a diagnosis of EBV-positive DLBCL. Staging completion with a bone marrow aspiration and biopsy were negative.

Treatment was started immediately with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). After just 2 cycles of chemotherapy, a positron emission tomography (PET)/CT scan revealed the pancreatic mass had diminished from 12 cm to 3 cm, along with resolution of liver and splenic lesions (Figure 1B). At that time, the patient also reported improvement in appetite, weight gain of 15 pounds, and resolution of epigastric pain. He completed a total of 6 cycles of R-CHOP and tolerated it well overall. Central nervous system (CNS) analysis was also performed after each cycle and CNS prophylaxis with intrathecal methotrexate was administered. A CT scan done 4 weeks after completion of treatment showed further decrease in the pancreatic mass size, now measuring 2.2 cm x 1 cm, without metabolic activity and no lesions detected in the liver or spleen (Figure 1C). Deauville X was assigned. Finally, a CT scan done 9 months after completion of therapy showed no evidence of a pancreatic mass or metastatic disease (Figure 1D). He continued to be clinically asymptomatic 18 months after his initial diagnosis and over 12 months after completing chemoimmunotherapy. Our plan is to continue with surveillance with history and physical examination every 3 months and imaging every 6 months.

Discussion

Pancreatic lymphoma is a rare extra-nodal manifestation of non-Hodgkin's lymphoma, which includes DLBCL. Pancreatic lymphoma can be either primary (a dominant mass in the pancreas with lymph node involvement confined to the peri-pancreatic region, and no hepatic or splenic involvement) or secondary (systemic extra-pancreatic with secondary involvement of the pancreas). Both types can mimic pancreatic adenocarcinoma with or without metastases. Our case was classified as a secondary pancreatic lymphoma given the involvement of the liver and spleen. This case was extremely unusual since the lymphoma was EBV-related. EBV is classically associated with certain lymphomas, including Burkitt's lymphoma, Hodgkin's lymphoma, and DLBCL [5]. However, almost all case of pancreatic lymphomas reported in the literature are EBV-negative [2]. In our literature review, we found only one reported case of EBV-positive DLBCL of the pancreas. It was a case of a 68-year-old male patient who was first treated with a Whipple procedure and then 6 cycles of R-CHOP chemoimmunotherapy. He was reported to be in remission. However, as both surgery and chemotherapy were used, the authors of that case note that it was difficult to tell whether the Whipple procedure was truly needed, or if chemotherapy would have been sufficient by itself [6]. In our patient case report, we present a case of EBV-positive DLBCL involving the pancreas, which was treated with chemoimmunotherapy alone with complete response. According to a study of 44 patients by Sadot et al., chemotherapy alone for pancreatic lymphoma has been shown to have a 75% complete response rate, 18% relapse rate, and median overall survival of about 6 years [7].

Traditionally, EBV-positive DLBCL patients have worse outcomes relative to their EBV-negative counterparts [8]. This was

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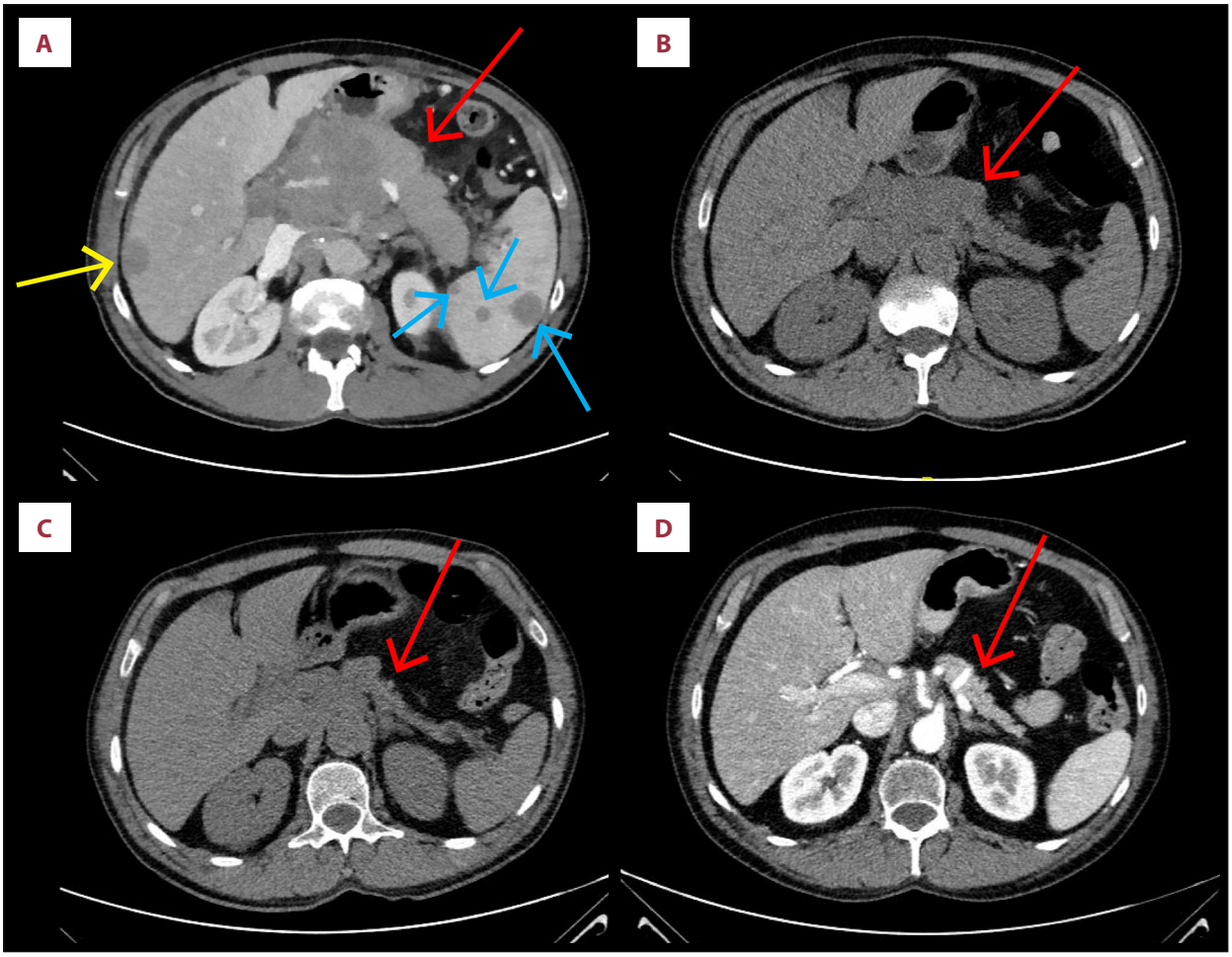

Figure 1. Abdominal Imaging on admission and after treatment. (**A**) Computed tomography (CT) on presentation: large 9.4×12.2×12.4 cm pancreatic mass (red arrow) with liver (yellow arrow) and splenic lesions (blue arrows). (**B**) CT after 2 cycles of R-CHOP: significantly decrease size of the pancreatic mass from 12 to 3 cm (red arrow), along with resolution of the ascites and lesions in the liver and spleen. (**C**) CT after 6 cycles of R-CHOP: smaller 2.2×1 cm pancreatic mass (red arrow) with no lesions in the liver or spleen; Deauville X was assigned. (**D**) CT: nine months after completion of therapy showed no evidence of a pancreatic mass or metastatic disease.

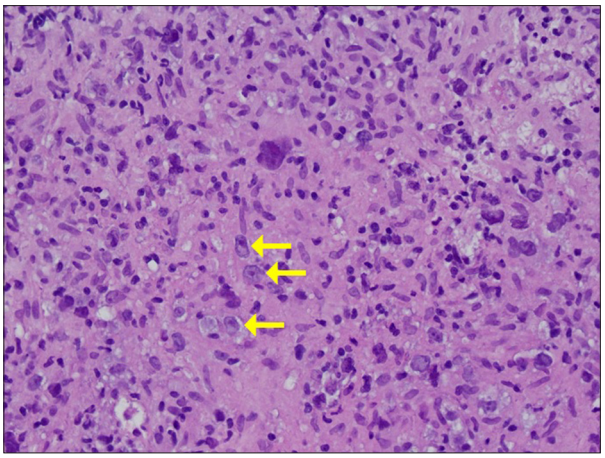

Figure 2. Hematoxylin and eosin (H&E) stained sections of liver core biopsy. Extensive replacement of the hepatic parenchyma by a dense inflammatory infiltrate composed predominantly of histiocytes and small lymphocytes. Scattered within this infiltrate are large cells with large, ovoid to irregular nuclei and prominent nucleoli (yellow arrows). Some large cells are multinucleated.

reported to be due to a variety of mechanisms, which include immune checkpoint molecules that increase cell viability and reduce apoptosis [9]. However, the majority of these early studies were done with an Asian cohort [10]. Recent data from North American patients with DLBCL suggests that EBV status does not change overall survival outcomes [11]. Regarding treatment, chemoimmunotherapy with R-CHOP is commonly

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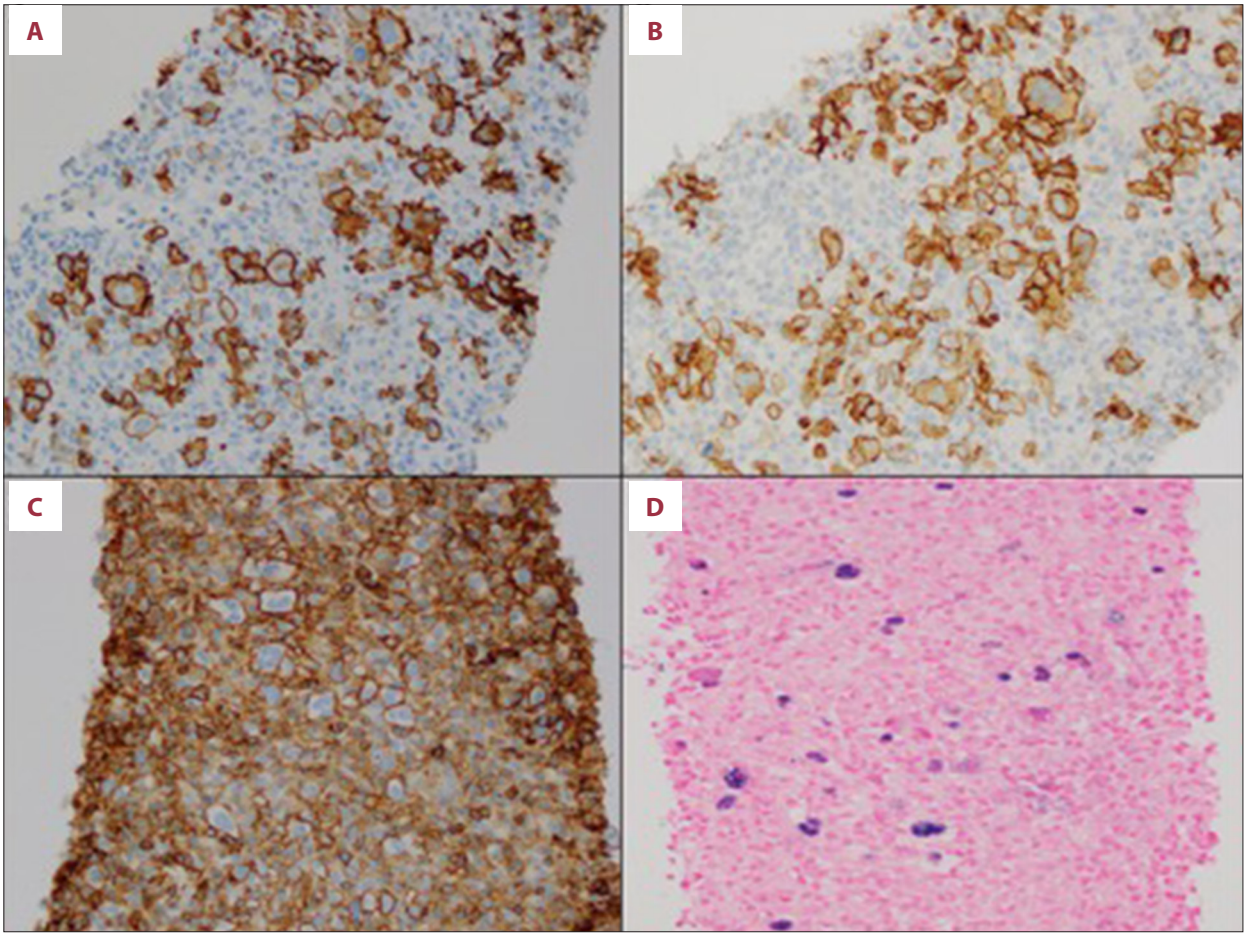

Figure 3. Immunohistochemical stains on the liver lesion biopsy. (**A**) CD20, 40×; (**B**) CD30, 40×; (**C**) CD45, 40×; (**D**) EBER, 40×. Immunohistochemical stains demonstrate that the large cells are strongly and diffusely positive for CD20 (brown stain in **A**), CD30 (brown stain in **B**), CD45 (brown stain in **C**), EBV DNA or EBER (pink stain in **D**), CD79a, PAX-5, and Mum-1. They are negative for CD3, CD10, CD15, Bcl-2, Bcl-6, CD138, and ALK-1.

used [12]. One recent retrospective analysis found that the addition of rituximab to standard chemotherapy (CHOP) in EBV-positive DLBCL was associated with higher likelihood of complete response and overall survival compared to CHOP alone [13]. Furthermore, the EBV status did not seem to affect response or survival in DLBCL patients treated with R-CHOP.

Besides chemotherapy, other therapeutic options for pancreatic lymphoma include surgery and radiotherapy. The use of surgery for pancreatic lymphoma can be effective in certain situations. Surgery often can provide the specimen needed for diagnosis of pancreatic lymphoma [14]. This was not required in our case, as we were able to biopsy the liver metastasis. One study reported that surgical resection of localized disease had superior cure rates to chemotherapy alone [15], and another study concluded that combination of surgical intervention and chemotherapy improved the 5-year survival rate compared to chemotherapy alone [16]. However, it is important to note that these surgeries were done on early stage, localized pancreatic lymphomas, which did not apply to our patient's case. In addition, these studies did not include rituximab as part of the chemotherapy regimen. Although surgical techniques have improved, the increased efficacy of chemotherapy regimens involving rituximab has lessened the role of surgery in pancreatic lymphomas. Surgery in the adjuvant setting for pancreatic lymphoma is also noted to be controversial. Per our literature review, many cases of adjuvant surgery occurred due to persistent symptoms, such as a choledochojejunostomy for jaundice [14,17]. As our patient exhibited no symptoms after his chemotherapy, we decided against surgical intervention after weighing the risks and benefits.

Radiotherapy was another option that was considered for our patient. Radiotherapy has been used for pancreatic lymphomas [14,18], with one literature review by Grimson et al. finding that radiotherapy was administered in 33 of 105 cases (31%) of pancreatic lymphoma [19]. Typical regimens involve up to 45 Gray of field radiotherapy (in 25 fractions) and has

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been reported to be well tolerated [19]. However, its role remains poorly defined, both in neoadjuvant and adjuvant settings [17]. With respect to outcomes, one study found that chemotherapy with CHOP plus adjuvant radiotherapy was superior to chemotherapy alone for localized intermediate and high-grade non-Hodgkin's lymphoma [20]. However, this study did not address the use of R-CHOP or more intensive chemotherapy regimens. Despite these limitations, some studies have suggested the use of combined chemotherapy and radiotherapy for pancreatic lymphomas [19]. Radiotherapy would have been a valid option for our patient if he had residual disease.

EBV-positive DLBCL is a morphologically heterogeneous disease category, with several distinct histologic patterns [21,22]. Some cases have a rich background of small lymphocytes and histiocytes which may resemble T-cell/histiocyte-rich large B-cell lymphoma, as with our patient. Histologic features can also mimic those of classic Hodgkin's lymphoma with scattered large cells within a mixed reactive background, while other cases tend to be more monomorphic with substantial similarities to EBV-negative DLBCL. Therefore, judicious use of ancillary studies, particularly immunohistochemistry, is necessary for accurate diagnosis.

Clinically, pancreatic lymphoma and adenocarcinoma are often indistinguishable. In fact, the presenting symptoms of pancreatic lymphoma are usually nonspecific and include abdominal pain (most common symptom), abdominal mass, weight loss, obstructive jaundice and acute pancreatitis. These symptoms are also commonly seen with pancreatic adenocarcinoma. Other constitutional symptoms such as fever, chills and night sweats, which are traditionally present in other lymphomas subtypes, appear to be much less common in pancreatic lymphomas [23].

While pancreatic lymphoma and adenocarcinoma seem to be indistinguishable clinically, other biochemical and radiographic findings can oftentimes be helpful. As such, abnormal blood counts, elevated lactate dehydrogenase or beta-2 microglobulin levels would favor pancreatic lymphoma, while an elevated serum CA 19-9 level would suggest an adenocarcinoma. However, there are few cases in the literature of elevated CA 19-9 in the setting of malignant lymphoma, similar to the case we reported, which could be due to increased bile duct proliferation [3]. With respect to imaging, the absence of pancreatic duct dilation and/or the presence of enlarged lymph nodes below the renal veins on CT scan are suggestive of lymphoma [24]. In addition, the size of the mass itself can be an important clue in some cases. It is estimated that 60% of pancreatic lymphomas are greater than 6 cm, while adenocarcinomas are unlikely to be larger than 10 cm [25]. Lastly, peritoneal involvement suggests an underlying adenocarcinoma (peritoneal carcinomatosis), as the peritoneal folds consist of fatty tissue without lymphoid tissue. However, lymphoid involvement of the peritoneum (peritoneal lymphomatosis) can also be seen in rare cases, such as with our patient, and is usually associated with aggressive histological lymphoma subtypes [26].

Conclusions

In summary, pancreatic lymphoma and adenocarcinoma can have overlapping clinical, laboratory, and radiographic features that make the diagnosis challenging. Pancreatic lymphoma, despite being less common than its adenocarcinoma counterpart, should be a consideration for any pancreatic malignancy, even if the peritoneum is involved and/or the Ca 19-9 level is elevated. The prognosis of EBV-positive DLBCL of the pancreas is thought to be worse than that of EBV-negative tumors. However, it remains certainly superior to that of its adenocarcinoma counterpart with conventional chemoimmunotherapy. Conventional systemic chemoimmunotherapy with R-CHOP is commonly used and associated with good outcome. This observation was reproducible in our case where the patient who presented with widespread disease and multi-organ involvement demonstrated a complete response to chemoimmunotherapy alone.

Conflicts of interest

None.

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