Primary hepatic peripheral T-cell lymphoma associated with Epstein-Barr viral infection

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Abstract

Primary hepatic peripheral T-cell lymphoma (H-PTCL) is one of the rarest forms of non-Hodgkin lymphoma. We report a patient who presented with worsening jaundice, abdominal pain, and vomiting. Laboratory values were significant for elevated total bilirubin, alkaline phosphatase, and liver aminotransferases. Following a liver biopsy, histopathology revealed several large dense clusters of atypical T-lymphocytes which were CD2+, CD3+, CD5+, CD7-, CD4+, CD8-, CD56-, CD57-, CD30+ by immunohistochemistry. The proliferation index was approximately 70% by labeling for ki67/mib1. The above histological profile was consistent with peripheral T-cell lymphoma of the liver. Epstein-Barr viral serology indicated a remote infection, a likely risk factor for PTCL. Bone marrow biopsy was negative for malignancy, further supporting hepatic origin.

Key words: Primary lymphoma; Liver cancer; Non-Hodgkin's lymphoma; T-cell lymphoma

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orign. Our patient’s medical history reported a prior Epstein-Barr viral infection, a risk factor for H-PTCL. In the setting of risk factors, H-PTCL should be born in mind when a patient presents with symptoms of malignancy, and an enlarged and infiltrating liver.

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INTRODUCTION

Peripheral T-cell lymphoma (PTCL) is the rarest of all cases of non-Hodgkin lymphoma (NHL). It constitutes approximately 0.0016% of all extranodal lymphomas1-3. PTCL not otherwise specified (NOS) is a heterogeneous subset of nodal T-cell lymphomas which does not satisfy the criteria for the other subtypes of PTCLs, namely, angioimmunoblastic T-cell lymphoma, and follicular T-cell lymphoma4. The annual incidence rate for PTCL is 1.56 per 100000 persons in non-Hispanic Whites, 1.32 per 100000 in Blacks, 0.89 per 100000 in Asians/Pacific Islanders, 0.63 per 100000 in American Indians/Alaskan natives, and 0.96 per 100000 in Hispanic Whites5. The distribution of PTCL NOS among racial groups is reported to be highest amongst non-Hispanic Whites (2689), followed by Blacks (661), Hispanic Whites (418), Asian/Pacific Islanders (322), and lowest in American Indians/Alaskan natives (20)5. When the lesion is localized or arises from the liver, it may also be referred as primary hepatic peripheral T-cell lymphoma (H-PTCL). We present a 37-year-old male with worsening jaundice, abdominal pain, and vomiting who was diagnosed with hepatic peripheral T-cell lymphoma with a Ki-67 of 70%.

CASE REPORT

A 37-year-old male with a past medical history of Epstein-Barr Virus (EBV) infection was admitted for jaundice and right upper quadrant abdominal pain. He reported having worsening symptoms for one month duration. The patient was a non-smoker and non-alcohol drinker. Review of systems was positive for decreased appetite and weight loss of 10 lbs. over the past two months. His family history was unknown. Physical examination was significant for mild scleral icterus and abdominal distension. Heart rate was 92/min, blood pressure was 107/67 mm Hg, respiratory rate was 20/min, oxygen saturation was 94% on room air, and temperature was 98.1 °F. Laboratory results were within normal limits with a white blood cell count (WBC) of 11.4/μL, hemoglobin of 12.2 g/dL, hematocrit of 37%, and platelet count of 291 k/cmm. Total bilirubin was 5.7 mg/dL, alkaline phosphatase (ALP) was 1005 U/L, LDH was 830 U/L, albumin was 3.2 g/dL, aspartate aminotransferase (AST) was 257 U/L and alanine aminotransferase (ALT) was 239 U/L. EBV serology was negative for IgM, and positive for IgG and EBV nuclear antigen, consistent with prior infection.

Abdominal magnetic resonance imaging (MRI) showed mild intrahepatic ductal dilatation, peripheral areas of arterial enhancement in liver felt to be related to vascular shunting, periportal edema, a cut off in the course of the biliary tree at the bifurcation, a simple liver cyst, and enlarged left retroperitoneal nodes. Upper endoscopy showed gastropathy in the gastric fundus and body. Endoscopic ultrasound was unrewarding. Following a liver biopsy, histopathology showed several large dense clusters of atypical T-lymphocytes, which appeared to be centered in the portal areas. The atypical lymphocytes were medium to large in size and were CD2+, CD3+, CD4+, CD5+, CD7-, CD8-, CD56-, CD57-, CD30+, by immunohistochemistry (Figure 1).

The proliferation index was approximately 70% by labeling for ki67/mib1. Labeling for CD68 was seen in Kupffer cells, and in a few scattered histiocytes only. There were rare, scattered, unremarkable small B-lymphocytes (CD20+, CD79a+). Stains for CD138, kappa, lambda, were noncontributory. The above histological profile was consistent with hepatic peripheral T-cell lymphoma. The patient was subsequently transferred to a tertiary care center for further management where he had a bone marrow biopsy which was negative for malignancy, further supporting hepatic origin.

DISCUSSION

H-PTCL is mainly diagnosed by the presence of a hepatic mass in the absence of lymphadenopathy, splenomegaly, bone marrow involvement, and associated with normal tumor markers6. After six months following diagnosis, other tissues may become involved including the spleen, lymph nodes, peripheral blood, and/or bone marrow7. According to literature, H-PTCL commonly occurs around the fifth decade of life8.

While the etiology of H-PTCL remains unclear, certain risk factors have been described such as Hepatitis C virus (HCV), Hepatitis B virus (HBV), and Epstein-Barr virus (EBV)9-12. In patients diagnosed with H-PTCL, HCV was identified in 20%-60% of cases9. This finding hints that viruses such as HCV may play a role in the pathogenesis of H-PTCL. Furthermore, H-PTCL has been diagnosed in immunocompromised patients with Human Immunodeficiency Virus (HIV), Human T-Lymphotropic Virus (HTLV), systemic erythematous lupus (SLE), and immunosuppressive therapy13. Our patient was negative for HCV and HBV infections, but his medical history indicated a prior EBV infection. While the tumor was CD30+, we did not pursue in-situ hybridization for Epstein-Barr virus.
virus-encoded RNA in lymphoma cells. Peng et al\cite{14} reported the first case of EBV-associated CD30-positive peripheral T-cell lymphoma of cytotoxic phenotype. Our case provides further confirmation of an association of EBV infection and PTCL.

The clinical presentation of H-PTCL is non-specific, with the most reported symptom being abdominal pain in 40%-70% of patients, similar to our patient\cite{3}. About 35% of PTCL patients experience systemic B symptoms including fever, night sweats, and weight loss\cite{15}. Tumor markers alpha fetoprotein (AFP) and carcinoembryonic antigen (CEA) are typically normal in these patients\cite{16}. Abnormal laboratory findings include elevated liver function aminotransferases, bilirubin, γ-glutamyl transferase, ALP and LDH. Approximately 70% of cases present with abnormal liver function enzymes, 30 to 80% with elevated LDH, 90% with elevated β2-microglobulin, and 80% with elevated ALP\cite{17-20}. Mitarnun et al\cite{20} reported that out of 100 patients with EBV associated H-PTCL, ALP was found elevated in 80%, while LDH was elevated in 65% of cases. Our patient presented with significantly notable ALP, LDH, total bilirubin, and liver function enzymes.

The proliferation index measured by Ki-67 has traditionally been used in assessing patient prognosis and response to therapy. Went et al\cite{21} proposed a prognostic model which incorporated age (> 60 years), high lactate dehydrogenase, poor performance status, and Ki-67 greater or equal to 80%. Their model was significantly associated with patient outcome (P < 0.0001). Weisenburger et al\cite{15} reported a Ki-67 > 25% was an adverse predictor of survival.

Our case was classified as PTCL-NOS according to guidelines outlined by the World Health Organization\cite{4}. The running differential diagnosis included extranodal NK/T-cell lymphoma, nasal type and adult T-cell leukemia/lymphoma. Extranodal NK/T-cell lymphoma, nasal type, was considered due to a prior EBV
infection, however, it was ruled out after being CD56 negative. CD56 is a diagnostic requisite for extranodal NK/T-cell lymphoma, nasal type[22]. Adult T-cell leukemia/lymphoma was ruled out given that the patient’s calcium levels and WBC were within normal limits[23].

Treatment for PTCL requires an aggressive course of chemotherapy, typically cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP). A recent study by Kim et al.[22] reported that patients with whole blood EBV-DNA were more likely to have aggressive clinical characteristics and inferior survival. Overall, H-PTCL has a poor prognosis due to life threatening complications and tumor progression. Clinical studies report that CHOP therapy can provide up to 60% complete remission, and a 30%-50% five-year survival rate[24-26].

More recently, a prospective study of 499 patients showed that patients who received doxorubicin had a significantly longer survival than those who did not (P = 0.03)[27]. Furthermore, in a study involving 775 patients, better survival outcomes were seen in one third of patients who remained in remission 2 years after diagnosis, especially in younger patients less than 60-years of age[28]. However, Abramson et al.[29] reported that the most dominant prognostic factor was response to initial therapy, with no overall survival difference based on the choice of upfront regimen. These studies further reemphasizes the need for early detection and treatment.

In conclusion, we report a rare case of H-PTCL in a 37-year old male with a medical history of EBV infection who presented with worsening jaundice, abdominal pain, and vomiting. H-PTCL is an aggressive form of NHL which requires early diagnosis and a robust treatment regimen. However, the diagnosis of H-PTCL remains challenging due to the presence of multiple granulomas, histiocytosis, and focal neoplastic infiltrates. In the setting of worsening symptoms and abnormal liver enzymes of unknown etiology, clinicians should consider performing a differential liver biopsy.

**ARTICLE HIGHLIGHTS**

**Case characteristics**
A 37-year-old male with a past medical history of Epstein-Barr Virus infection reported having jaundice, right upper quadrant pain, and decreased appetite and weight loss of 10 lbs over the past two months.

**Clinical diagnosis**
Abdominal magnetic resonance imaging showed mild intrahepatic ductal dilatation, peripheral areas of arterial enhancement in the liver felt to be related to vascular shunting, periportal edema, a cut off in the course of biliary tree at the bifurcation, simple liver cyst, and enlarged left retroperitoneal nodes.

**Differential diagnosis**
Cirrhosis, hepatocellular carcinoma, cholangiocarcinoma.

**Laboratory diagnosis**
Laboratory was significant for total bilirubin of 5.7 mg/dL, alkaline phosphatase of 1005 U/L, albumin of 3.2 g/dL, and AST/ALT of 257/239 U/L.

**Imaging diagnosis**
Upper endoscopy showed gastropathy in the gastric fundus and body. Endoscopic ultrasound was unremarkable.

**Pathological diagnosis**
A liver biopsy showed several large dense clusters of atypical T-lymphocytes, which appeared to be centered in portal areas. The atypical lymphocytes were medium to large in size and were CD2+, CD3+, CD7+, CD8+, CD56+, CD57+, CD30+, by immunohistochemistry. The proliferation index was approximately 70% by labeling for ki67/mib1. Labeling for CD68 was seen in Kupffer cells, and in a few scattered histiocytes only. There were rare, scattered, unremarkable small B-lymphocytes (CD20+, CD79a+). Stains for CD138, kappa, lambda, were noncontributory. The above histological profile was consistent with hepatic peripheral T-cell lymphoma (H-PTCL).

**Treatment**
The patient was transferred to a tertiary center for chemotherapy (CHOP) treatment.

**Related reports**
H-PTCL has a poor prognosis due to life threatening complications and tumor progression. Clinical studies reports that CHOP therapy can provide up to 60% complete remission, and a 30%-50% five-year survival rate.

**Term explanation**
H-PTCL is one of the rarest forms of non-Hodgkin lymphoma. It constitutes approximately 0.0016% of all extranodal lymphomas.

**Experiences and lessons**
In the setting of worsening symptoms and abnormal liver enzymes of unknown etiology, clinicians should consider performing a differential liver biopsy. Clinicians should also be aware of the risk factors for H-PTCL.

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