Primary Focal T-cell Lymphoma of the Liver: a Case Report and Review of the Literature

Razvan Cerban, Liana Gheorghe, Gabriel Becheanu, Valentin Serban, Cristian Gheorghe

Center for Digestive Disease and Liver Transplantation, Fundeni Clinical Institute, Bucharest, Romania

Abstract

We present the case of a previously healthy 62 year old man who developed primary non-Hodgkin lymphoma of the liver. Biopsy confirmed that it was a diffuse large anaplastic T-cell lymphoma of an extremely rare type. The diagnosis of this type of lesions is suggested by the presence of a hepatic mass without lymphadenopathy, splenomegaly or bone marrow involvement associated with normal tumor markers (carcinoembryonic antigen, alpha-fetoprotein and CA 19-9 levels). Histological examination of tissue is essential to confirm the diagnosis. Treatment options are surgical resection and/or chemotherapy but the rate of response to treatment varies widely. Some patients can achieve prolonged remission.

Key words


Introduction

Primary hepatic lymphoma (PHL) is a very rare malignancy representing approximately 0.016% of all cases of non-Hodgkin’s lymphoma (NHL) [1] and 0.4% of extranodal NHL [2]. The majority of cases reported are of B-cell origin. Primary T-cell lymphoma of the liver is extremely rare with only few cases reported in the literature [3] and accounts for only 5-10% of all primary hepatic lymphomas [4]. Although the liver contains lymphoid tissue, host factors seem to make the liver a poor environment for the development of malignant lymphomas. We present an interesting case of primary focal T-cell non-Hodgkin lymphoma originating in the liver, treated with multi-agent chemotherapy, alive for 12 months after the diagnosis, despite the poor prognosis. A literature review of clinical features, diagnosis, and management is also provided.

Case presentation

A 62-year-old man presented to our clinic with a two-month history of right upper abdominal pain, fatigue, and mild weight loss (less than 5%). He did not drink alcohol, and had no significant medical history. Patient denied any fever, night sweats, vomiting, chest pain, diarrhea or stool blood loss. He was not on any current or chronic medication.

Physical examination was unremarkable, except a slightly enlarged liver, 2 cm below the costal arch with no peripheral lymphadenopathy. Laboratory results included hemoglobin 13.3 g/dl and a white cell count of 4.8×10⁹/L, with a normal differential. Alanine and aspartate aminotransferase, alkaline phosphatase (ALP), and gamma glutamyl transpeptidase (GGT) were within normal limits. Levels of serum alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) were not elevated. Serology was negative for human immunodeficiency (HIV), human T-lymphotropic-1 (HTLV-1), Epstein-Barr (EBV), cytomegalic (CMV), hepatitis C (HCV) and hepatitis B (HBV) viruses. Serum calcium was within normal limits. He had a serum lactate dehydrogenase (LDH) of 630 UI/ml (normal range 135-225 UI/ml) and a slightly elevated serum fibrinogen 480 mg/dl (normal range 200-400mg/dl). Imaging revealed a normal chest X-ray. Abdominal ultrasound (US) examination showed three solid lesions, of 4 to 6 cm, in the liver, suggestive of secondary lesions, without intra-abdominal lymphadenopathy. A contrast-enhanced ultrasound (CEUS) was performed showing hypocaptant lesions throughout arterial, portal and delayed phase (Fig. 1). A computed tomography (CT) scan of the abdomen confirmed the US findings. Upper endoscopy and colonoscopy were normal.

A US-guided biopsy of the liver mass was performed.
The histological examination of the liver specimen showed a diffuse infiltrate with medium-to-large-sized lymphoid cells suggestive for lymphoma but a poorly differentiated carcinoma could not be excluded. Immunohistochemistry of the tumor cells showed reactivity for CD3, CD30, CD4, and EMA and was negative for Ck7, ALK, CEA and CD8 (Fig. 2). Bone marrow biopsy examination showed normal cellularity with maturing tri-lineage hematopoiesis in normal proportion and no evidence of T-cell lymphoma was present.

Due to the good performance status (PS1) the patient was treated with the multi-agent combination regimen of anticancer cytotoxics (CHOP + Etoposide) consisting of cyclophosphamide (1,200 mg/m² day1), doxorubicin (40 mg/m² day1), vincristine (1.4 mg/m² day1), prednisone (40 mg/m² PO day1-5) and etoposide (200 mg/m² days 1, 3 and 5). The chemotherapy was well tolerated, no serious complications occurred during the treatment, and LDH level decreased progressively during therapy. Chemotherapy was administered every three weeks with six cycles, after which a follow up CT was performed. CT scan six months after the initial diagnosis, revealed the fusion of the two large lesions situated in segments VIII and V in one large hypodense lesion with central necrosis, while the lesion situated in segment VI decreased by 50% (Fig. 3). There was no sign of lymphadenopathy or splenic involvement. He was subsequently followed up for another six months until the time of writing this paper with no tumor progression or extrahepatic involvement.

Discussion

Malignant lesions found in the liver due to widespread availability of imaging methods are not uncommon since the liver is, after lymph nodes, the most common tissue affected by metastatic lesions and HCV/HBV-related hepatocellular carcinoma is rising continuously due to the aging of infected population. In the present case, US, CEUS and US-guided liver biopsy were used for an accurate diagnosis of focal liver lesions in a patient with nonspecific symptoms and no risk factors for primary liver neoplasm.

Whereas secondary liver involvement is relatively common in advanced stages (stage 4) of NHL, being encountered in as many as 20% of patients, PHL is extremely rare [5]. Primary hepatic lymphoma is defined according to
Fig 3. Follow-up contrast-enhanced CT of the abdomen. A solid, hypodense hepatic lesion (segments V, and VIII), 115/66 mm in diameter with central necrosis.

Caccamo’s criteria as lymphoma with only liver involvement at presentation and no spleen, lymph nodes, peripheral blood, bone marrow, or other tissues involvement until at least six months after diagnosis [6]. Primary hepatic lymphoma is notably rare, representing less than 1% of all extranodal lymphomas, with less than 300 cases published until date. Although PHL can occur at any age, it is more frequently seen in the fifth or sixth decade of life, with a male/female ratio of 2-3/1 [7]. The pathogenesis of PHL has not yet been well established, despite being found to be associated with several disorders, including EBV, HCV, HIV or HTLV infections, liver cirrhosis, systemic erythematous lupus and immunosuppressive therapy [8]. Our patient had none of the above conditions or risk factors for PHL.

The most common symptoms of PHL at presentation are abdominal pain (39-70%) and general malaise. Hepatomegaly is the most frequent finding (75–100%). Low-grade fever, night sweats, and weight loss are also common, or exceptionally, the disease can present as fulminant hepatic failure. Liver function tests are abnormal in up to 70% of cases, LDH is increased in 30-80%, and β2-microglobulin, a well-described prognostic marker, in 90% of cases. Our patient had an initial β2 microglobulin value of 3.4 mg/L (normal range 0.9-2 mg/L) with subsequent values of 3.1 mg/L and to 2.9mg/L after 2 and 4 month of therapy but failed to decrease any further during the 12 months follow up. There are no specific tumor markers for PHL, but normal levels of AFP and CEA are found in almost 100% of patients, facilitating the differential diagnosis. Hepatocellular carcinoma and metastases from gastrointestinal tract have a very similar clinical pattern, are much more common and should be excluded first. Primary hepatic lymphoma may present as solitary liver mass (42%) or multiple focal lesions (50%); diffuse infiltration of the liver is rare in Caucasian (8%) and more common in Asian patients. Diagnosis of PHL requires a liver biopsy compatible with lymphoma and the absence of lymphoproliferative disease outside the liver. Because liver biopsy may not distinguish between PHL and poorly differentiated carcinoma, immunohistochemical typing and flow studies are almost always required. In some cases a surgical biopsy might be required. Our patient presented with no clinical or laboratory features suggestive for PHL (only increased LDH and β2 microglobulin and normal AFP, CEA and CA 19-9).

The prognosis of PHL is considered to be very poor, with a median survival time of 15 months; however it varies widely, ranging from 3 to 124 months [3], with median survival as low as 6 months for patients treated with chemotherapy alone, and longer for patients treated with a combination [9]. The following factors have been associated with worse prognosis: massive liver infiltration/replacement, high index of proliferation, advanced age, elevated LDH levels, the presence of underlying liver cirrhosis and elevated levels of β2-microglobulin [10]. Stancu et al reviewed 14 cases of primary hepatic T-cell lymphoma, with 3 cases representing their own series and 11 previously reported cases. They reported that primary hepatic T-cell lymphoma has a poor prognosis and an aggressive clinical course [11]. In the series reviewed by Miyashita in 2011 [1], 17 of 19 cases showed diffuse liver infiltration, while only the 2 remaining cases showed nodular involvement, similarly to our patient.

The optimal treatment of PHL is not yet defined. Surgical treatment, radiotherapy and chemotherapy were all reported as treatment modalities alone or in combination. In the present case, multi-agent chemotherapy was applied and well tolerated due to the good clinical condition (PS1). Chemotherapy protocols for the treatment of lymphomas have changed in the last decade to multi-drug regimens such as CHOP, alternating triple combination therapy (ATT), IMVP-16, OAP (that include etoposide, cytosine arabinoside and others) [12]. Multidrug protocols improve survival significantly for patients with PHL, and at least in one report almost 100% of patients reached complete remission and 83% reached 5 years survival with ATT chemotherapy [3]. The new aggressive multi-agent chemotherapy with or without the addition of surgery or radiation is probably the recommended optimal therapy but, unfortunately, hepatectomy is rarely possible [13-15].

Conclusion

We presented a rare case of primary hepatic T-cell lymphoma of focal multinodular type. Due to the good clinical condition, multi-agent chemotherapy was possible, well tolerated and with partial response. Though a rare disease, primary hepatic lymphoma should be considered in any patient at any age who presents with liver mass or diffuse liver infiltration. The exclusion of HBV and HCV infections, absence of liver cirrhosis, normal levels of CEA and AFP and no primary detected malignancy should rise the index of suspicion for primary hepatic lymphoma.

Conflicts of interest

No conflict to declare.
References