

Primary Hepatic B-Cell Lymphoma with Obstructive Jaundice: A Rare Case Presentation and Literature Review

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Abstract: Primary hepatic lymphoma (PHL) is a rare form of non-Hodgkin's lymphoma, which usually presents with hepatomegaly, constitutional symptoms and signs of cholestatic jaundice without involvement of the bone marrow, spleen and lymph nodes at the early stage of the disease. PHL is often misdiagnosed as hepatitis, primary liver cancer or metastatic disease due to its non-specific clinical symptoms and perplexing laboratory results. This case is presenting a 66 year old female, who was primarily diagnosed with obstructive jaundice, which was a case of PHL based on full range of examinations. The patient presented with yellowish discoloration of the sclera, right upper quadrant pain, nausea, vomiting and fever. Physical examination revealed an enlarged liver with no evidence of generalized lymphadenopathy. Initial investigation with biochemical tests demonstrated a picture of obstructive jaundice, imaging studies revealed a large liver mass, which was confirmed by histopathology as PHL. The patient underwent chemotherapy by oncology service. Liver lymphomas might clinically present with obstructive jaundice masking other liver and biliary tree pathologies. Treatment of this pathology should be planned after thorough clinical and radiological examinations with the histological confirmation.

Keywords: Primary hepatic lymphoma, obstructive jaundice, liver biopsy, liver tumors.

CASE REPORT

This case describing of a 66 year old female with a history of hypertension and insulin dependent diabetes, who was admitted to the surgical department with symptoms of yellow discoloration of the sclera, right upper abdominal pain, generalized itching, dark urine, nausea and vomiting for a period of two weeks. She also had occasional episodes of fever, but no history of weight loss, night sweats and changes of bowel habits. General physical examination revealed icteric sclera and itch marks, tenderness in the right upper quadrant of abdomen examination and palpable firm, smooth surface non-pulsatile liver lesion with approximate 7x6cm dimensions with no detectable lymphadenopathy. A primary diagnosis of obstructive jaundice was made based on the clinical findings and the patient admitted for the further evaluation. Initial laboratory biochemistry results showed elevation of total bilirubin of 46 mmol/L, serum transaminases (AST 160 U/L, ALT 80 U/L) and ALP 300 U/L. The patient was also tested positive for hepatitis B, but negative for hepatitis C. The levels of tumor markers alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) were normal. The imaging studies by ultrasonography of the abdomen showed a 10.5x9.5x8.5 cm hypoechoic mass, arising from segment IV and extending into the porta hepatis compressing the common bile duct, causing intra-hepatic biliary ducts

dilatation. A computerized tomography (CT) showed a liver lesion in segment IV, which had heterogeneous enhancement with contrast, measuring 11x10x10 cm and suggesting necrosis within the lesion. The lesion was associated with dilated intra-hepatic biliary tree and peri-portal lymph nodes enlargement as demonstrated in Fig-1 A. CT guided biopsy was performed in the same setting for histological diagnosis

Endoscopic studies were performed in search for suspected primaries either in the upper gastrointestinal tract or the colon. Upper gastroenteroscopy revealed mild chronic gastritis with no evidence of dysplasia or malignancy in the stomach and duodenum. The colonoscopy was also normal.

Histopathology of the liver lesion was reported as a diffuse large B-cell lymphoma with immunohistochemistry stains being positive for CD45 and CD20 and negative for CD3 and CK (AE1/AE3) (Fig-2).

The patient was referred to the medical oncology department and started on systemic chemotherapy with (R-CHOP) chemotherapy regime including Rituximab, Cyclophosphamide, Doxorubicin, Oncovin, Prednisolone and was followed up after she underwent six cycles of chemotherapy in five months.

After treatment the improved symptomatically with a marked fall of icterus and reduction of all liver function test parameters. A repeat CT of the abdomen showed

regression of the liver lesion to the size of 5x4x3cm (Fig-3).



Fig-1: CT of the liver showing a 11x10x10 cm heterogeneous hypoechoic lesion in the liver (arrow points to lesion (a b c d

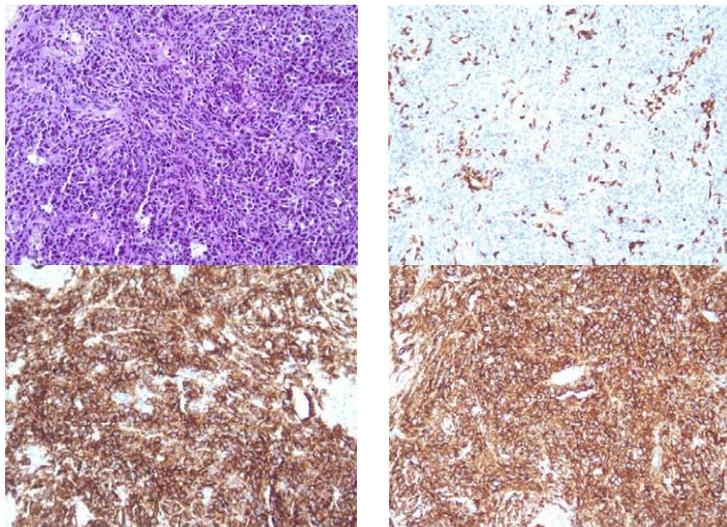


Fig-2: Immunohistochemistry staining of the liver lesion. a) CK stain, b) CD3 stain, c) CD20 stain, d) CD45 stain



Fig-3: CT of the liver post chemotherapy showing regression of the original lesion size in the liver (arrow points to lesion)

LITERATURE REVIEW

Primary hepatic lymphoma was first described in 1965 by Ata et al, as a rare liver tumor and represents less than 1% of all extra-nodal lymphomas. Since then only about 100 cases have been reported worldwide in medical literature [1]. Caccamo *et al.*, defined (PHL) as a lymphoma localized and limited to the liver without extra-hepatic involvement. Hepatic involvement in non-Hodgkin's lymphoma occurs in one out of ten cases and represents advanced disease. The constellation of symptoms and signs seen in (PHL) are explained by the liver involvement, although after the initial six months of appearance as the liver lesion, the patients generally present with superficial lymphadenopathy, splenomegaly, abnormal hematological parameters, spleen or bone marrow localization [2].

The liver is the most frequently, after lymph nodes, to be affected by metastasis from intra and extra abdominal primary tumors. The nature of these hepatic lesions is best diagnosed and staged by histopathology and imaging studies. Primary hepatic lymphoma (PHL) has been defined as an extra-nodal lymphoma of the liver without involvement of lymph nodes, spleen and bone marrow. Liver involvement occurs in one out of ten of non-Hodgkin's lymphoma cases and constitutes as stage 4 of the disease [1, 2]. PHL usually affects middle-aged men, who present clinically with abdominal pain, nausea and constitutional symptoms. Four percent of the patients present with jaundice and hepatomegaly, which occur in up to 75% of the patients. In affected by PHL patients, %86-37 have B symptoms (fever, sweating and weight loss). PHL presents as a liver mass in 42-50% of patients with elevated liver function tests, mostly lactate dehydrogenase (LDH) and alkaline phosphatase (ALP). Unlike in most hepatic neoplasms the level of tumor markers in PHL patients, like alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) are normal.

The pathogenesis of (PHL) is still unclear and associations have been made to (HIV), (HBV), (HCV), (EBV), liver cirrhosis, and auto immune etiology [3]. Our patient was tested positive for Hepatitis B and was not known to have any complications as a consequence of this infection. From the previously published in literature case reports it is understood, that the clinical presentation of (PHL) is nonspecific with mostly B symptoms (fever, loss of weight and night sweats), while some patients have presented with right upper abdominal pain, epigastric pain, abdominal distension, nausea, vomiting and itching caused either due to the lesion itself or due to compression of adjacent viscera. The physical findings described are abdominal tenderness and hepatomegaly as initial presentation, near 30% of the patients present with a solitary liver nodule, while another 30% may have multiple lesions, and the remaining of cases have diffuse infiltration of the liver [3]. Our patient had both hepatomegaly and abdominal tenderness in addition to icterus, which

influenced the diagnosis making towards obstructive jaundice due to a probable malignant cause in the peri-ampullary area. In most cases, laboratory investigations usually reveal elevation of transaminases and bilirubin with normal (LDH) and (ALP) values [3]. This may cause a confusion to clinicians, while following the initial laboratory investigations to think in terms of cholestatic jaundice, but the physical findings demand further investigations in terms of imaging and histopathology.

On ultra-sonography (U/S), the PHL lesions are usually seen as hypo-attenuating or iso-attenuating, whereas on CT they present themselves as a heterogenous, hypodense lesions. On triphasic CT the lesions appear as local areas of rim enhancement or calcifications. On the magnetic resonance imaging (MRI) the lesions tend to be hypo-intense compared to the healthy liver parenchyma on T1, and have slight enhanced signal intensity on T2 weighed images. Hepato-biliary specific contrast does not show any enhancement of PHL either in the early dynamic or late hepato-biliary phase. The findings are similar when contrasts such as Gadobenate and Gadopentate dimeglumine are employed [4, 5]. Our patient was investigated with U/S and CT, both of which showed a liver lesion, but since the endoscopies did not demonstrate any primary lesion of the gastrointestinal tract, it was decided that a liver biopsy would be the next best option to reach the diagnosis.

Previous studies have reported that grossly the tumor has a nodular or diffuse growth pattern, in which the lymphoma cells expand into the liver parenchyma. One case has been reported of PHL presenting as a hepatic cyst [6].

On microscopic study, the tumor tissue consists of atypical cells with little basophilic cytoplasm, large vesicular nucleus, irregular nuclear membrane and often multiple prominent nucleoli [7]. The predominant histology of PHL showed diffuse large B-cell lymphoma (DLCL) in 63% cases and T-cell lymphoma in 25% cases [8]. In some cases, the liver biopsy is reported as poorly differentiated carcinoma and immunohistochemistry helps to differentiate the diagnosis. Although the information on (PHL) is scanty, it is associated with a poor prognosis due to its aggressive nature and frequent severe co-morbidity. Further, the lack of controlled trials, due to the low incidence of PHL, make well supported treatment recommendations based on available literature difficult. Chemotherapy is the recommended therapeutic treatment for all extra-nodal diffuse large B-cell lymphoma and T-cell lymphoma, making it the treatment of choice when PHL is diagnosed. Indication for surgical treatment is localized disease, which can be resected completely, or surgical debulking in an effort to palliate the symptoms [7-11]. Our patient was considered as a good candidate for CHOP

chemotherapy since short history of symptoms would mean that hepatic lesion developed about six months prior to her presentation to the hospital and the response to chemotherapy would be rapid .

Surgical treatment, radiotherapy and chemotherapy were all reported as treatment modalities alone or in combination. The prognosis of (PHL) was considered very poor with median survival as low as six months for patients treated with chemotherapy alone, and longer for patients treated with a combination of modalities. Chemotherapy protocols for the treatment of lymphomas have changed in the last decade to multi-drug regimens such as (CHOP), alternating triple combination therapy, IMVP-16 (ifosfamide, methotrexate, etoposide, (OAP) vincristine, etoposide, cytosine arabinoside) [7, 12-17]. Multi regimen protocols significantly improve the survival for patients with (PHL), thus it is recommended that the new aggressive multi-agent chemotherapy without the addition of surgery or radiation is probably the recommended optimal therapy [15-17]. Rituximab, a monoclonal chimeric antibody directed against CD20 B cell antigen, is now recommended as first line therapy together with CHOP for diffuse large cell lymphoma in the elderly. The addition of Rituximab to the CHOP regimen increased the complete-response rate and prolonged survival without an increase in toxicity [17].

Although the best treatment for (PHL) is not defined, multi-agent chemotherapy seems to be an appropriate single therapy in many cases.

CONCLUSION

A differential diagnosis of PHL must always be considered in an elderly patient presenting with a liver mass with history of B symptoms and normal levels of (CEA) and (AFP). (Histopathology and immunohistochemistry studies help to confirm the diagnosis of PHL and are valuable to decide the treatment plan with multidrug chemotherapy. Although the prognosis of PHL was considered to be poor, there are reports of some patients with an improved five year survival and thus the treatment should be planned after discussing these aspects with the patient and multi-disciplinary meeting with oncology specialties.

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