



## CASE STUDY

### IMAGING OF PRIMARY HEPATIC LYMPHOMA

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#### ABSTRACT

Primary hepatic lymphoma (PHL) is a rare malignancy, and constitutes about 0.016% of all cases of non-Hodgkin's lymphoma. Primary hepatic lymphoma most commonly affected middle-aged males. Presenting symptoms and physical findings were non-specific. Ultrasonography and computed Tomography (CT) can help in the diagnosis, which can be confirmed only by histological examination of a liver biopsy specimen. In this article, we retrospectively reviewed the imaging features of 19 pathologically proven cases of primary hepatic lymphoma.

## INTRODUCTION

Primary hepatic lymphoma (PHL) is a rare malignancy, making up 0.4% of extranodal non-Hodgkin's lymphomas, and 0.016% of all non-Hodgkin's lymphomas (Steller *et al.*, 2012; Tanaka *et al.*, 2013). Presenting symptoms and physical findings were non-specific. Major presenting symptoms include abdominal pain, fever, weight loss, fatigue, anorexia, nausea and vomiting. There is a male to female preponderance, and presentation is largely in middle age (Lei, 1998). The pathologic diagnosis is usually diffuse large cell lymphoma or large B-cell lymphoma, or immunoblastic lymphoma in immunosuppressed patients, in whom the incidence is increased (Cazejust *et al.*, 2013; Agmon-Levin *et al.*, 2004). The case report is approved by the patient. Informed consent has been obtained from the patients for publication of this case.

## MATERIALS AND METHODS

We retrospectively reviewed the imaging findings of patients with a histological diagnosis of PHL between 2006 and 2016. The study population consisted of 19 patients (twelve men and seven women), with a mean age of 61 years. Presenting symptoms included right upper quadrant pain (eleven), laboratory abnormalities (ten), constitutional symptoms (five)

and gastrointestinal symptoms (three). Five patients had hepatitis B e-antibody positivity, whereas the serum HBV DNA levels were low in three patients and fairly elevated in two patients. Twelve patients had CT examinations and 19 patients underwent B-mode ultrasonography for screening. Imaging characteristics, clinico-pathologic features and differential diagnostic considerations of PHL are presented.

## RESULTS

During the 5-year period, 19 patients who satisfied the criteria for PHL, as described by Lei *et al.* (1998) underwent either ultrasound or CT examinations. Seven of the 19 patients presented with a single focal lesion (Fig. 1). Eleven of 19 patients presented with multiple well-defined lesions (Fig. 2). One patient presented with a diffuse hepatic involvement (Fig. 3). All twelve patients who underwent ultrasound evaluation demonstrated hypoattenuating solid lesions. Most of these were well-defined lesions (Fig. 4). Four patients demonstrated target lesions on ultrasound, with a hypoattenuating halo and central necrosis (Fig. 5). All 19 patients who underwent ultrasound evaluation demonstrated solid appearing lesions, which were hypoechoic when compared with the adjacent liver (Fig. 6). In nine patients, some or all of the lesions demonstrated a 'target' appearance on ultrasound imaging (Fig. 7). Treatment consisted of an en bloc resection of tumor, and hepatoduodenal lymphadenectomy (Fig. 8). Histopathology revealed a diffuse, large B-cell, non-Hodgkin lymphoma (NHL) with negative surgical margins (Fig. 9). Postoperative recovery was uncomplicated.

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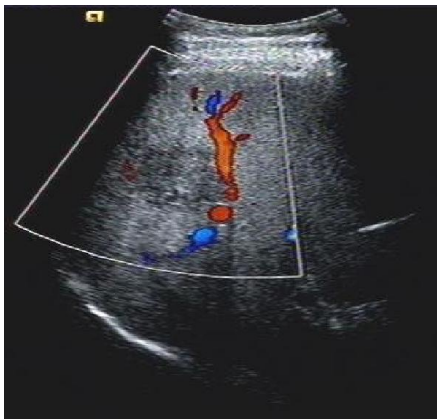


Figure 1. Ultrasound shows a single 3×3 cm<sup>2</sup> heterogeneous hypoattenuating lesion with areas of central necrosis

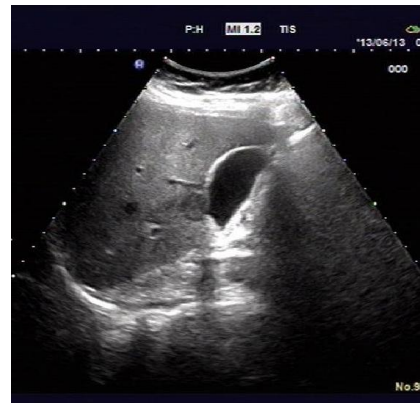


Figure 4. Ultrasound shows a well defined hypoattenuating lesion in a 62-year-old man



Figure 2. Ultrasound images in a 62-year old man show multiple well-defined hypoattenuating and hypoechoic lesions

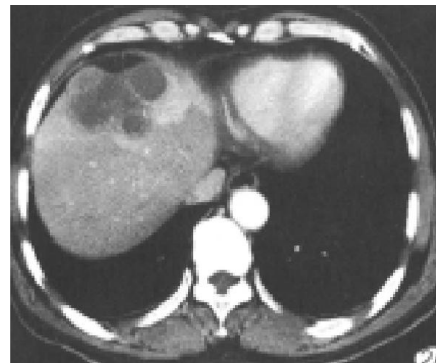
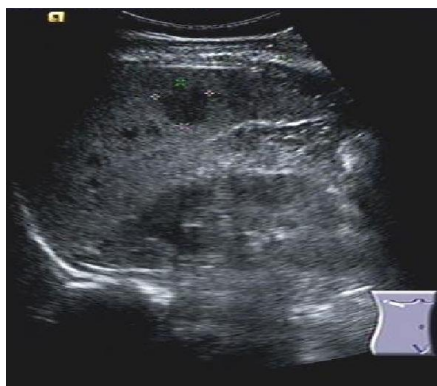


Figure 5. Contrast enhanced CT in a 65-year-old male patient shows lesions with hypoattenuating halos surrounding enhancing intermediate zones. There is central hypoattenuating necrosis. The overall effect is of a target sign



A



Figure 6. Ultrasound image shows well-defined hypoechoic lesions



B

Figure 3. (A) Ultrasound and (B) contrast enhanced axial CT images in two different patients show diffuse heterogeneous ill-defined coalescent lesions

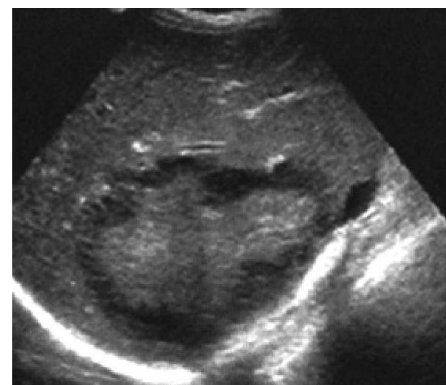
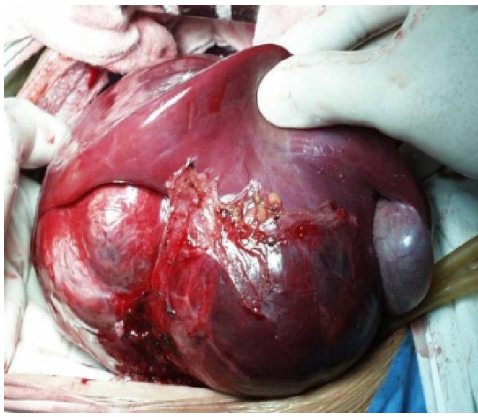
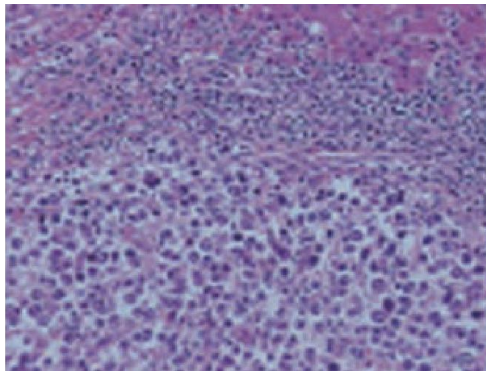


Figure 7. Ultrasound image shows lesion with hyperechoic centers and hypoechoic rims, creating a target appearance



**Figure 8. Intraoperative aspect of hepatic lesion in a 63-year-old male patient**



**Figure 9. Histopathological results. Hematoxylin eosin staining (200X) shows a large cell malignancy with mostly loose tumor cells with nuclear polymorphism**

## DISCUSSION

Primary hepatic lymphoma (PHL) is a rare malignancy, making up 0.4% of 12447 extranodal non-Hodgkin's lymphomas, and 0.016% of all non-Hodgkin's lymphomas. Lei *et al.* (1995) defined PHL using the following criteria: (1) symptoms mainly caused by liver involvement at presentation; (2) absence of distant lymphadenopathies palpable clinically at presentation or detected during staging radiologic studies; and (3) absence of a leukemic blood profile. Presentation is common during middle age, largely in the male population. The most common symptom is abdominal pain and other symptoms include weight loss, fever, anorexia, nausea, night sweats, and vomiting. Laboratory data showed the elevation of liver-associated enzymes in about 80% of the patients, such as Lactate dehydrogenase (LDH) and alkaline phosphatase (AKP) are sometimes elevated but  $\alpha$ -fetoprotein (AFP) and carcinoembryonic antigen (CEA) were within the normal range in all patients (Tan and Xiao, 2013; Kingston *et al.*, 1985). HBV surface antigen and/or antibody were positive in 22% of patients, antihuman immunodeficiency virus (HIV) antibody was evident in 6% of patients (Lee *et al.*, 2008; Foschi *et al.*, 2010; Lanjewar *et al.*, 2004). Primary hepatic lymphoma (PHL) is a rare form of extranodal non-Hodgkin's disease that commonly presents with non-specific hepatobiliary signs and symptoms. Diffuse large cell lymphoma is the most commonly encountered histological subtype (Memeo *et al.*, 1999). Almost invariably, primary hepatic lymphoma is composed of lymphocytes reacting with B-cell markers (Shetty *et al.*, 2012; Zafar *et al.*, 2012). Most cases are intermediate or high grade

according to the classification of the working formulation for clinical usage.

Our results confirm previous reports that primary hepatic lymphoma can present as a solitary mass or as multiple discrete masses (Noronha *et al.*, 2005; Maher *et al.*, 2001). Seven patients demonstrated a single hepatic mass, and eleven demonstrated multiple masses. Rarely, the disease presents as diffuse involvement of the liver. From our series of 19 patients, there was one case of diffuse disease. Our findings are concordant with previous papers describing the ultrasound appearances as of well-defined hypoechoic or anechoic areas (Gazelle *et al.*, 1994; Appelbaum *et al.*, 2005). Our findings are also consistent with previous descriptions of hepatic lymphoma as of hypodense lesions or multilobular on Computed tomography or ultrasound. Some lesions contained low density areas because of necrosis (Diehl *et al.*, 2013; Balduzzi *et al.*, 2010). There was no calcification in our series. Calcification has been previously described (Sanders *et al.*, 1989). However, intravenous contrast was used in all of our cases, possibly resulting in obscuration of small foci of calcification. There are rarely previous reports, to our knowledge, describing the target appearances we identified in four of our 12 patients at CT and in 9 of our 19 patients at ultrasound. Ultrasonography is the first examination performed for screening of a focal liver lesion in patients with chronic liver disease (Bonder and Afdhal, 2012). The detection of a focal liver lesion requires further diagnostic techniques to reach a definite diagnosis. The criteria for establishing the diagnosis of PHL include both clinical and histopathological factors. Macroscopic findings at laparotomy or autopsy showed a solitary mass in 61%, multiple masses in 35%, or a diffuse lesion without nodule formation in 4%. However three quarters of the patients with immune deficiency or chronic liver diseases had multiple liver lesions (Cecinati *et al.*, 2012; Aozasa *et al.*, 1993). The imaging appearance of hepatic lymphoma is nonspecific and mainly includes hypovascular metastatic deposits. The common picture of PHL consists of a solitary well-defined tumor, but multiple nodules and a diffuse infiltrative form may also be found as the presentation of secondary lymphoma. On ultrasonography, hepatic lymphoma usually appears as a hypoechoic lesion. Colon, lung, prostate, gastric and transitional cell carcinomas are the most common primary tumours with hypovascular metastases to the liver (Elsayes *et al.*, 2005). Infectious and inflammatory pathologies can sometimes result in similar imaging appearances with multiple focal hepatic lesions, but clinical and laboratory values can often help in their differentiation. Primary tumors of the liver are difficult to characterize and are frequently associated with a poor prognosis. Primary hepatic lymphoma (PHL) is a rare primary liver tumor. Due to its clinical and radiological resemblance to liver metastases of adenocarcinoma, PHL is frequently diagnosed intra- or post-operatively. The prognosis of PHL is generally perceived as dismal, with early disease recurrence at extra-hepatic locations and an overall short survival. Treatment options for primary liver lymphoma are surgery, radiation, chemotherapy, or a combination. Many reports have suggested that resection alone or in combination with chemotherapy can offer a good outcome for these patients (Nasr Ben Ammar *et al.*, 2006). Since primary hepatic lymphomas are usually multiple and of high grade histology, combination chemotherapy is a rational option. However reported median survival is as low as 6 months for patients treated with chemotherapy alone. While there is little consistency in recommendations for management, recent studies indicate



improved remission rates with combination chemotherapy (Gatselis and Dalekos, 2011). High risk factors at the time of diagnosis include patient age, bulky disease and comorbidities, such as active hepatitis or cirrhosis. Given these factors, early detection is vital for patient management.

## Conclusion

Primary hepatic lymphoma (PHL) is confined to the liver with no evidence of lymphomatous involvement in other lymphoid structures. It is a very rare malignancy representing less than 1 % of all extra nodal lymphomas that commonly presents with non-specific haepatobiliary signs and symptoms. There is a wide spectrum of imaging findings on CT and ultrasound. Like many other hepatic malignancies, PHL generally presents as hypoattenuating or hypoechoic lesions. Lesions may be single, multiple or diffuse. Rim enhancement is occasionally seen. A target appearance to the lesions on both ultrasound and CT is also seen. In conclusion, our experience with these 19 cases suggests that PHL, although rare, should be considered in the differential diagnosis of focal liver lesions, especially in patients with chronic HBV infection or other risk factors for lymphoproliferative disorders.

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