Primary Hepatic Lymphoma: Dilemmas in Diagnostic Approach and Therapeutic Management

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Abstract Primary hepatic lymphoma (PHL) is a very rare malignancy and is characterized by liver involvement at presentation with no affectation of the spleen, lymph nodes, peripheral blood, bone marrow, or other tissues until at least 6 months after diagnosis. PHL should be considered in the differential diagnosis in a patient with space-occupying liver lesions and normal levels of alpha-fetoprotein and CEA. A computed tomography (CT) scan is the commonly used modality for staging lymphomas. The widespread use of positron emission tomography/CT results in the improvement in the accuracy of detecting the extent of disease, response evaluation, and prognostication. The liver biopsy, due to its pleomorphic appearances in the needle biopsy specimen, can be very challenging. Current literature favors the combination of chemotherapy as the frontline treatment for its least invasiveness and improved survival. Favorable prognosis of PHL can be obtained by early surgery combined with chemotherapy in strictly selected patients. However, the optimal therapy is still unclear and the outcomes are uncertain.

Keywords Primary hepatic lymphoma · Differential diagnosis · Therapeutic management

Introduction

Primary hepatic lymphoma (PHL) is a very rare malignancy, and constitutes about 0.0016 % of all cases of non-Hodgkin lymphoma (NHL) [1]. PHL usually affects patients in the seventh to eighth decade of life, but no consensus has been reached regarding the male to female ratio of incidence [2]. A lymphomatous infiltrate seen in a liver biopsy specimen has long been regarded as evidence of stage IV disease, the prognosis of which is poor [3]. Such an infiltrate may, however, represent a primary lymphoma of the liver itself in which case the outlook is similar to that of other organ based lymphomas [4]. Although the liver contains lymphoid tissue, host factors make it a poor environment for the development of malignant lymphoma. PHL is characterized by liver involvement at presentation with no affectation of the spleen, lymph nodes, peripheral blood, bone marrow, or other tissues until at least 6 months after diagnosis [5]. Experience over the past decade has indicated that the diagnosis should be born in mind in any case of an enlarged liver associated with an unusual cellular infiltrate, and that a tumor-like presentation is only one manifestation of the disease [6]. A computed tomography (CT) scan is the commonly used modality for staging lymphomas. The widespread use of positron emission tomography/computerized tomography (PET/CT) takes advantage of the anatomic resolution of the CT scan and the biological characterization provided by ¹⁸Fluoro-de-oxy Glucose (FDG)-PET [7]. Together, it results in the improvement in the accuracy of detecting the extent of disease, response evaluation, and prognostication. There is paucity of literature, addressing the best treatment course for PHL [8]. Most patients are treated with chemotherapy, with some physicians employing a multimodality approach. However, the optimal therapy is still unclear and the outcomes are uncertain

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[9]. The purpose of this report is to analyze the recent literature in order to provide an update on the current concepts of PHL, to evaluate the results of surgical treatment with special reference to the extent of its histological spread and define its correct management.

Histopathology and Immunohistochemistry

Non-Hodgkin lymphoma remains the major histological subtype of PHL. PHL with Hodgkin's histology is extremely rare, with very few case reports in the current literature. Based on liver infiltration, PHL can be subdivided into nodular or diffuse types. The pattern of liver infiltration though, has no prognostic value. Similarly, the disease may be of either T- or B-cell origin [10]. Most PHLs present with a larger cell type and demonstrate a B cell immunophenotype. The most commonly found are diffuse large B cell lymphomas (DLBCL). Other histologic subtypes of PHL include diffuse histiocytic lymphoma of the mucosa-associated lymphoid tissue (MALT), high-grade tumours (lymphoblastic and Burkitt lymphoma), follicular lymphoma, anaplastic large-cell lymphoma of the null type, mantle cell lymphoma and T cell-rich B cell lymphoma [11]. Mostly observed growth pattern of lymphoma cells is intrasinusoidal. The morphological patterns, although variable, present in many cases as diffuse portal tract infiltrates, with erosion of the limiting plate and "spillover" not only in the sinusoids, but also in the surrounding parenchyma [12]. The destructiveness of the infiltrate in the liver biopsy is a very helpful feature, to rule out benign inflammatory conditions; whereas immunocytochemistry is used to exclude an epithelial tumour—such as carcinoma—or inflammatory pseudotumour, which invariably contains polyclonal plasma cells in large numbers [13].

The immunohistological characteristics most commonly present in DLBCL suggest that the tumour cells are tested positive for the following antigens: CD10, Bcl2, Bcl6, MUM1 and CD25. On the contrary neoplastic cells of the MALT lymphomas seem to be negative for CD5, CD23, CD10, Bcl6, MUM1 and CD25 and positive for Bcl12. Recent immunochemical investigations support that both tumour infiltrates from patients with BLBCL and MALT PHL are also commonly positive for leukocyte common antigen [14].

Clinical Features and Correlations

The exact cause of PHL is unknown, although viruses such as HCV, HBV and Epstein-Barr have been implicated [15, 16]. There appears to be a strong association between PHL

and HCV. Hepatitis C is found in 40–60 % of patients with PHL, with significantly higher prevalence to the diffuse B cell non-Hodgkin's subtype [17]. Persistent inflammatory processes associated with HCV infection or also autoimmune diseases seem to play independent roles in the lymphogenesis of hepatic B cells. Case reports of PHL combined with rheumatoid arthritis, ataxia—telangiectasia and Sjogren syndrome have also been published [18]. Finally, there have been reported patients with AIDS in whom PHL developed and the suggestion has been made that it be regarded as a tumour associated with human immunodeficiency virus infection. The increasing incidence of PHL cases in immunocompromised patients requires further investigation in the comorbidities and pathogenesis of PHL [19].

Although its clinical manifestations vary, from asymptomatic presentation to rapidly progressing acute liver failure, encephalopathy, coma or death, the patients with PHL usually present with right upper quadrant or epigastric discomfort. The liver is upon clinical examination often enlarged, with a discrete palpable mass [20]. B symptoms including fever, night sweats and weight loss are common among patients, whereas case reports also indicate that PHL can present with other nonspecific symptoms such as anaemia, anorexia, nausea or fatigue. Jaundice is also an occasional finding at physical examination. Therefore, a definite diagnosis of PHL is difficult to establish on clinical grounds. Furthermore, an incidental identification of the entity has been supported in 10 % of affected patients. Hepatoma and metastasis from gastrointestinal (mostly colon) carcinoma present in a similar manner and are much more common [18].

Diagnostic Approach

Laboratory abnormalities associated with PHL include anaemia, neutropenia, hypercalcaemia and variably raised LDH, one serum alkaline phosphatase, β -microglobulin and aminotransferase activities. The tumour markers AFP and CEA are found within normal range, in almost all cases of PHL. The presentation of PHL is usually a solitary lesion, as revealed by imaging studies. Ultrasound (U/S), performed on patients with PHL, demonstrates a hypoechoic lesion to the surrounding normal liver parenchyma, usually with irregular margins [21]. Contrast enhanced CT depicts slight hyperenhancement of the lesion in the arterial phase and hypoenhancement in the remaining phases. Therefore recent surveys support that U/S and CT offer no characteristic findings to differentiate PHL from HCC [22]. On the other hand, MRI can be more helpful to support the diagnosis of a PHL instead of HCC, when no morphological changes of cirrhosis are evident in the surrounding

Table 1 Case series or isolated case reports published in the field of PHL the last decades

	Number of cases	Age	Sex M/F	Tumour lesions diffuse/multinodular	Treatment surgery/ chemotherapy/combination	Cumulative survival
Anthony et al. [12]	10	31–85	7/3	8/2	1/6/3	1 week–6 years
Masood et al. [8]	1	65	M	Multinodular	Multiagent chemotherapy (R-CHOP)	Disease remission
Miyashita et al. [35]	1	65	M	T cell lymphoma	Low dose corticosteroid	>50 months
Cecinati et al. [18]	1	8	No data	B cell NHL	R-CHOP and rituximab	3 years
Mattar et al. [19]	1	No data	No data	Burkitt lymphoma	Chemotherapy	Disease remission
Ma et al. [27]	1	67	M	Multinodular	R-CHOP without surgical resection	6 months
Cerban et al. [28]	1	62	M	Diffuse anaplastic T cell lymphoma	Chemotherapy (CHOP + etoposide)	Disease remission
Zafar et al. [29]	1	68	F	Diffuse	R-CHOP	Disease remission
Lee et al. [30]	1	19	M	Burkitt's lymphoma	CHOP + methotrexate	Disease remission
Mantadakis et al. [32]	1	8.5	M	Burkitt lymphoma	Intensive multiagent chemotherapy	Disease remission

R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, *PHL* primary hepatic lymphoma, *NHL* non-Hodgkin lymphoma

liver parenchyma, when the tumour markers mentioned above are negative, and when the hepatic lesion shows iso-intensity with spleen parenchyma in both T1 and T2 weighted images. Some mild perilesional enhancement in delayed images, after administration of intravenous contrast, can also be observed. These MRI findings can be helpful for the radiologists to suspect a PHL [23]. Relevant studies also mention that 18FDG PET/CT can further assist to a PHL's diagnosis by demonstrating the absence of pathologically hypermetabolic foci in any other nodes or organs, when CT scan alone is inadequate to differentiate PHL and secondary liver lymphoma [24]. Final diagnosis of PHL requires, in any case, a liver biopsy compatible with the histological findings of PHL. The appearances, especially in a needle biopsy specimen, may be difficult to interpret, but recognition is very important as the prognosis is favourable [5]. Last but not least, the PET/CT scan can also be used to assess the early treatment response [7]. In each case differential diagnosis from biliary cystadenoma or cystic adenocarcinoma is implemented [25].

Therapeutic Management

Despite recent research on the therapeutic strategies against PHL, surgical resection appears the only potentially curative approach. Unfortunately, a mere minority of patients is eligible to undergo surgical intervention. Alternative treatment options include chemotherapy, radiation or varying combinations of these modalities [26]. Most patients are treated with chemotherapy, with some physicians employing a multimodality approach. A recent meticulous analysis of 72 patients has shown the median survival to be 15.3 months (range 0–123.6 months). It has

been suggested that for low-volume localized PHL, surgical resection, alone or in combination with chemotherapy, might be a treatment option [9]. Nevertheless, as relapse after surgery is not unusual and PHL is chemosensitive, combination chemotherapy should be always employed. Solitary lesions should be considered as the best candidates for radical hepatectomy even diagnosed preoperatively. In a review of 84 cases of PHL, the longest survivor underwent surgical resection followed by adjuvant chemotherapy and radiotherapy (61 months), while median survival of 27.5 months was experienced with chemotherapy and radiotherapy alone, 22 months with isolated hepatectomy, 6 months with chemotherapy and 3 months with radiotherapy [20]. In a previous study, one patient treated with surgery followed by chemotherapy and radiation was reported to be alive at 5 years following initial diagnosis.

The standard treatment for patients with DLBCL is CHOP [27–30]. The addition of rituximab, a chimeric mouse-human monoclonal antibody targeting the pan-B cell antigenic marker CD20 (the first monoclonal antibody licensed for use in the treatment of cancer), to the CHOP regimen, when given in eight cycles, augments the complete response rate and prolongs the overall survival, without a clinically significant increase in toxicity [31, 32]. For patients with diffuse large B cell NHL (including follicular NHL), several large-scale prospective randomized trials have established prolongation of remission when rituximab is incorporated into first-line treatment [33]. Primary hepatic DLBCL cases are characterised by a good prognosis after cytotoxic with or without rituximab. Anti-viral treatment after cytotoxic therapy also contributed to a significantly longer disease-free survival period in HCV-seropositive B cell lymphoma cases. These data strongly suggest that rituximab administered in combination with

cytotoxic treatment followed by antiviral therapy may result in an improved clinical outcome in primary hepatic and systemic HCV-seropositive DLBCL cases [34]. Cases of primary hepatic peripheral T cell lymphoma successfully treated with corticosteroids have also been described [35] (Table 1).

In conclusion, the occurrence of PHL is extremely rare, presents with great morphological and phenotypic variability and needs a high index of suspicion for its diagnosis. PHL should be considered in the differential diagnosis in a patient with space-occupying liver lesions and normal levels of alpha-fetoprotein and CEA. The liver biopsy, due to its pleomorphic appearances in the needle biopsy specimen, can be very challenging. Recognition, though, of PHL is essential, for it is a treatable malignancy if detected early. Current literature favors the combination of chemotherapy as the frontline treatment for its least invasiveness and improved survival. Favorable prognosis of PHL can be obtained by early surgery combined with chemotherapy in strictly selected patients.

References

1. Yang XW, Tan WF, Yu WL, Shi S, Wang Y, Zhang YL, Zhang YJ, Wu MC (2010) Diagnosis and surgical treatment of primary hepatic lymphoma. *World J Gastroenterol* 16:6016–6019
2. Kikuma K, Watanabe J, Oshiro Y, Shimogama T, Honda Y, Okamura S, Higaki K, Uike N, Soda T, Momosaki S, Yokota T, Toyoshima S, Takeshita M (2012) Etiological factors in primary hepatic B-cell lymphoma. *Virchows Arch* 460:379–387
3. Li ZM, Zhu YJ, Xia Y, Huang JJ, Jiang WQ (2012) Clinical characteristics of the patients with Hodgkin's lymphoma involving extranodal sites. *Chin J Cancer* 31:342–347
4. Saikia UN, Sharma N, Duseja A, Bhalla A, Joshi K (2010) Anaplastic large cell lymphoma presenting as acute liver failure: a report of two cases with review of literature. *Ann Hepatol* 9:457–461
5. El-Sharkawi D, Ramsay A, Cwynarski K, Hughes D, Prentice A, Davies N, Goode A, Wylie P, Malhotra A, Warbey V, Dooley J, McNamara C (2011) Clinico-pathologic characteristics of patients with hepatic lymphoma diagnosed using image-guided liver biopsy techniques. *Leuk Lymphoma* 52:2130–2134
6. Noronha V, Shafi NQ, Obando JA, Kummur S (2005) Primary non-Hodgkin's lymphoma of the liver. *Crit Rev Oncol Hematol* 53:199–207
7. Seshadri N, Ananthasivan R, Kavindran R, Srikanth G, Chandra S (2010) Primary hepatic (extranodal) lymphoma: utility of [(18)F]fluorodeoxyglucose-PET/CT. *Cancer Imaging* 10:194–197
8. Masood A, Kairouz S, Hudhud KH (2009) Primary non-Hodgkin lymphoma of liver. *Curr Oncol* 16:74–77
9. Romaguera JE, Osborne B, Medeiros LJ, Rodriguez J, North L, Sanz-Rodriguez C, Cabanillas F (2001) Primary hepatic lymphoma: favourable outcome after combination chemotherapy. *Cancer* 92:2023–2029
10. Kaneko K, Nishie A, Arima F, Yoshida T, Ono K, Omagari J, Honda H (2011) A case of diffuse-type primary hepatic lymphoma mimicking diffuse hepatocellular carcinoma. *Ann Nucl Med* 25:303–307
11. Agmon-Levin N, Berger I, Shtalrid M, Schlanger H, Sthoeger ZM (2004) Primary hepatic lymphoma: a case report and review of the literature. *Age Ageing* 33:637–640
12. Anthony PP, Sarsfield P, Clarke T (1990) Primary lymphoma of the liver: clinical and pathological features of 10 patients. *J Clin Pathol* 43:1007–1013
13. Salmon JS, Thompson MA, Arildsen RC, Greer JP (2006) Non-Hodgkin's lymphoma involving the liver: clinical and therapeutic considerations. *Clin Lymphoma Myeloma* 6:273–280
14. Zucca E, Gregorini A, Cavalli F (2010) Management of non-Hodgkin lymphomas arising at extranodal sites. *Ther Umsch* 67:517–525
15. Wu SJ, Hung CC, Chen CH, Tien HF (2009) Primary effusion lymphoma in three patients with chronic hepatitis B infection. *J Clin Virol* 44:81–83
16. Ohsawa M, Tomita Y, Hashimoto M, Kanno H, Aozasa K (1998) Hepatitis C viral genome in a subset of primary hepatic lymphoma. *Mod Pathol* 11:471–478
17. Kim JH, Kim HY, Kang I, Kim YB, Park CK, Yoo JY, Kim ST (2000) A case of primary hepatic lymphoma with hepatitis C liver cirrhosis. *Am J Gastroenterol* 95:2377–2380
18. Cecinati V, Arcamone G, Mattia DD, Santoro N, Mantire B (2012) Hepatic non-Hodgkin lymphoma and hepatoblastoma complicating ataxia-telangiectasia. *Immunopharmacol Immunotoxicol* 34:1–3
19. Mattar WE, Alex BK, Sherker AH (2010) Primary hepatic burkitt lymphoma presenting with acute liver failure. *J Gastrointest Cancer* 41:261–263
20. Lei KI (1998) Primary non-Hodgkin's lymphoma of the liver. *Leuk Lymphoma* 29:293–299
21. Beaty SD, Silva AC, DePetrasi G (2008) Incidental hepatic mass. *Am J Roentgenol* 190:62–64
22. Foschi FG, Dall'Aglia AC, Marano G, Lanzi A, Savini P, Pisaglia F, Serra C, Cursaro C, Bernardi M, Andreone P, Stefanini GF (2010) Role of contrast-enhanced ultrasonography in primary hepatic lymphoma. *J Ultrasound Med* 29:1353–1356
23. Elsayes KM, Menias CO, Willatt JM, Pandya A, Wiggins M, Platt J (2009) Primary hepatic lymphoma: imaging findings. *J Med Imaging Radiat Oncol* 53:373–379
24. Gota VS, Purandare NC, Gujral S, Shah S, Nair R, Rangarajan V (2009) Positron emission tomography/computerized tomography evaluation of primary Hodgkin's disease of liver. *Indian J Cancer* 46:237–239
25. Valladolid G, Adams LL, Weisenberg E, Maker VK, Maker AV (2013) Primary hepatic lymphoma presenting as an isolated solitary hepatic cyst. *J Clin Oncol* 31:e21–e23
26. Gatselis NK, Dalekos GN (2011) Education and imaging. Hepatobiliary and pancreatic: primary hepatic lymphoma. *J Gastroenterol Hepatol* 26:210
27. Ma YJ, Chen EQ, Chen XB, Wang J, Tang H (2011) Primary hepatic diffuse large B cell lymphoma: a case report: primary hepatic diffuse large B cell lymphoma. *Hepat Mon* 11:203–205
28. Cerban R, Gheorghe L, Becheanu G, Serban V, Gheorghe C (2012) Primary focal T-cell lymphoma of the liver: a case report and review of the literature. *J Gastrointest Liver Dis* 21:213–216
29. Zafar MS, Aggarwal S, Bhalla S (2012) Complete response to chemotherapy in primary hepatic lymphoma. *J Cancer Res Ther* 8:114–116
30. Lee SH, Kim HJ, Mun JS, Oh HC, Lee HW, Choi CH, Kim JW, Do JH, Kim JG, Chang SK, Kim MK (2008) A case of primary hepatic Burkitt's lymphoma. *Korean J Gastroenterol* 51:259–264
31. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 346:235–342

32. Mantadakis E, Raissaki M, Tzardi M, Katzilakis N, Chatzimichael A, Kalmanti M (2008) Primary hepatic Burkitt lymphoma. *Pediatr Hematol Oncol* 25:331–338
33. Marcus R, Hagenbeek A (2007) The therapeutic use of rituximab in non-Hodgkin's lymphoma. *Eur J Haematol Suppl* 67:5–14
34. Winter MC, Hancock BW (2009) Ten years of rituximab in NHL. *Expert Opin Drug Saf* 8:223–235
35. Miyashita K, Tomita N, Oshiro H, Matsumoto C, Nakajima Y, Ito S, Matsumoto K, Fujita H, Ishigatsubo Y (2011) Primary hepatic peripheral T-cell lymphoma treated with corticosteroid. *Intern Med* 50:617–620