

Primary lymphoma of the liver: clinical features and outcome of 9 patients

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Summary

Purpose: Primary liver lymphoma (PLL) is a rare lymphoproliferative disorder of unknown etiology. The prognosis in affected patients is poor; consisting of brief remissions, rapidly developing resistance to chemotherapy, early recurrence, and short survival. Most studies related to PLL are based on case reports. The aim of this retrospective study was to review our experience with PLL.

Patients and methods: From 1985 to 2000, 9 patients who fulfilled the diagnostic criteria for PLL were treated at our hospital. All patients underwent a thorough work-up and were staged accordingly.

Results: The disease occurred in middle and higher-aged patients (median age 63 years). Primary presenting complaints were abdominal pain, mainly in the right upper quadrant, and hepatomegaly. Liver function tests and

lactate dehydrogenase (LDH) levels were elevated. Liver imaging (computed tomography-CT) and isotopic methods (gallium scan) demonstrated liver involvement either as solitary or multiple space-occupying lesions. Pathologic examination demonstrated diffuse, large cell (DLCL), B-type lymphoma in 7/9 (78%) patients. Doxorubicin-based chemotherapy was the mainstay of treatment. Good partial or complete remission rates were achieved in 7 patients, albeit for a brief period of time.

Conclusion: Most patients with PLL succumb to their illness, despite its being relatively chemotherapy-sensitive. The introduction of intensive chemotherapy, plus/minus radiotherapy, and/or surgery has been considered in some studies.

Key words: lymphoma, outcome, primary liver lymphoma, review, treatment

Introduction

PLL is an uncommon disease, representing less than 1% of all extranodal lymphomas with an unknown etiology [1]. Generally, the liver is secondarily involved in the late stages of lymphoma. Some suggest

chronic hepatitis B and/or C infection, with or without liver cirrhosis, systemic lupus erythematosus, acquired immunodeficiency syndrome, post-transplant Epstein-Barr virus infection, and primary biliary cirrhosis as a cause [2-4]. In his review, Lei [2] noted that most PLL patients had diffuse, large, B-cell type lymphoma, occurring in middle-aged men, with presenting complaints of abdominal pain, fatigue and constitutional "B" symptoms. Hepatomegaly was frequent, as was pathologic elevation of liver function tests and LDH levels. Imaging, such as CT of the liver and gallium scans, are helpful in the diagnosis and follow-up. There is little consistency in the literature regarding the appropriate treatment of PLL, whether surgery alone, aggressive chemotherapy alone, or combined chemo-radiotherapy is the most useful mode of treatment [1,2,5]. In general, the prognosis for PLL patients is dismal. Patients with early-stage, localized PLL

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generally do better than those with advanced stages. Lymph node and bone marrow involvement are considered to be poor prognostic factors.

In an attempt to gather additional information on the subject, a retrospective study of 9 PLL patients diagnosed and treated from 1985 to 2000 in the Department of Oncology at Rambam Medical Center in Haifa, Israel, was conducted.

Patients and methods

The true incidence of PLL is difficult to determine because of the lack of uniform criteria for diagnosis. In our review, cases of PLL were selected by the following criteria: 1) symptoms caused mainly by liver involvement at presentation; 2) absence of other visceral involvement; 3) absence of a leukemic picture in the peripheral blood film [2,5,6]. Generalized lymphadenopathy does not exclude the diagnosis of PLL. The 9 patients who fulfilled the criteria were staged through hematologic and biochemistry profiles, CT of the liver and gallium scans, and bone marrow study. Diffuse liver involvement was regarded as stage IV disease.

Results

The clinical presentation, histology, treatment and outcome are summarized in Table 1. Five patients were males and 4 females, with age range of 45-81 years (mean 63). No known or presumed etiology for PLL was known. The main presenting symptoms were abdominal pain, either localized to the right upper quadrant with/without a radiating character or spread over the entire abdomen. Mild to moderate weakness, loss of appetite and weight were present in all patients. No patient presented with jaundice, and only 3 (No. 1, 7 and 8) presented with clear "B" symptoms.

In all patients, serum laboratory data revealed some type of derangement of liver function (transaminases, gamma-glutamyl-transpeptidase, alkaline phosphatase). Another important prognostic pretreatment finding, LDH, was elevated in 2 patients (No. 7 and 8). Imaging, such as CT and gallium scans, revealed typical, unspecific findings, such as solitary or multiple lesions, filling defects, signs of hepatocellular damage and pathological uptake. A definitive diagnosis was established on the basis of histologic findings in liver tissue obtained by needle biopsy. The most common histopathologic diagnosis was DLCL, B-type lymphoma (Table 1).

Most patients (5/9) were found with stage IV dis-

ease. Only 2 patients (No. 2 and 6) presented with stage I disease (solitary liver lesion). Seven patients were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) combination chemotherapy. Complete and good partial remissions were achieved in 8 patients, albeit for a brief period of time (range 3-35 months).

Outcome was poor in all patients. Patient No. 3, who achieved complete remission of all disease sites, developed symptomatic hypertrophic cardiomyopathy following 4 cycles of CHOP. After relapse, treatment was changed to cyclophosphamide, etoposide, vincristine, steroids (6 cycles) and a second good partial remission was achieved for another 3 months. This patient died due to massive hepatic and retroperitoneal masses. Patient No. 9 relapsed 33 months after complete remission (bilateral cervical and abdominal lymphadenopathy). He was treated with 3 cycles of salvage DVIP (cisplatin, VP-16, ifosfamide, dexamethasone) regimen with partial remission and subsequent massive progression (generalized lymphadenopathy). One patient (No. 7) died of a massive stroke apparently unrelated to his disease or treatment, without any evidence of recurrent lymphoma. Patient No. 8 died of neutropenic sepsis, complicated by acute renal failure 6 months following termination of chemotherapy but with no evidence of disease.

Discussion

Worldwide PLL is a very rare disease and represents less than 1% of extranodal lymphomas, but the true incidence of this type of lymphoma is difficult to determine, partly because of lack of uniform criteria for diagnosis [2,7]. Most reports published to date have described either single patients or small numbers of patients [1,5,7,8]. The largest series reported are those of Osborne et al. [5] and Anthony et al. [6], each consisting of 10 patients. Using a comprehensive MEDLINE search of the literature up to 1993, Lei [2] found 69 reported cases of PLL. Thus, it is easy to understand why the clinical and pathologic features of patients with PLL, including etiologic factors, natural history and optimal treatment, remain uncertain. The incidence of PLL, presenting symptoms, clinical and laboratory features observed in our patients agree for the most part with those described elsewhere. Patients typically were male and middle-aged. Characteristic presenting complaints were right upper quadrant pain, nausea, and significant weight loss, with some patients also presenting with "B" symptoms. Levels of LDH, alkaline phosphatase and, to some degree, transaminases were elevated, but alpha-

Table 1. Clinical characteristics of patients with primary liver lymphomas

Patient No.	Age/ Gender	Symptoms/Abnormal lab findings	Imaging	Pathology (liver biopsy)	Stage
1.	73/F	General malaise, "B" symptoms, abdominal pain, hepatomegaly, positive bone marrow, PLFT	<i>CT scan</i> Filling defects <i>Liver scan</i> Hepatocellular damage, filling defects	Diffuse, mixed (large + small), B-type lymphoma	IV(B)
2.	54/M	Abdominal pain, weight loss, PLFT	<i>Liver scan</i> SOL of right lobe	Diffuse, large cell, B-type lymphoma	IE(A)
3.	69/M	Abdominal pain, PLFT	<i>CT scan</i> Liver and mediastinal masses <i>Gallium scan</i> Pathological uptake (liver, mediastinum)	Diffuse, large cell, B-type lymphoma	IV(A)
4.	81/M	Abdominal pain, weight loss, PLFT	<i>CT scan</i> Retroperitoneal lymphadenopathy, Liver SOL	Diffuse, large cell, B-type lymphoma	IE(A)
5.	62/F	Abdominal pain, weakness, PLFT	<i>CT scan</i> Mediastinal mass, diffuse liver involvement	Diffuse, large cell, non-cleaved, with sclerosis, B-type lymphoma	IV(A)
6.	48/M	Abdominal pain, PLFT	<i>CT/Gallium scan</i> Liver SOL	Anaplastic [high grade], large cell, B-type lymphoma	IE
7.	60/F	Abdominal pain, general deterioration, weight loss, fever, anemia, PLFT	<i>CT/Gallium scan</i> Mediastinal and retroperitoneal masses, liver lesions	Large, B-cell type lymphoma	IV(B)
8.	78/M	Abdominal pain, weakness, fever, positive bone marrow, PLFT	<i>CT scan</i> Liver lesions	Large, B-cell type lymphoma	IV(B)
9.	45/F	Abdominal pain, weakness, PLFT	<i>CT/Gallium scan</i> Liver SOL, cervical / abdominal masses	Diffuse, large (immunoblastic), B-type lymphoma	II(A)

M: male; F: female; PLFT: pathologic liver function tests; SOL: space-occupying lesion

fetoprotein (AFP) and carcinoembryonic antigen (CEA) levels were normal in all our patients [2]. All imaging studies were positive, demonstrating either an enlarged liver containing solitary or multiple masses. Generally, PLL is homogeneous with decreased attenuation on CT and hypointense on T1 weighted imaging on magnetic resonance imaging (MRI) [9].

Unfortunately, all these clinical, laboratory and radiologic features are not specific for PLL and cannot distinguish between primary liver cancer and metastatic tumors. In our patients, a confident diagnosis could only be established after histologic examination of the liver tissue, obtained by needle or surgical biopsy and the use of appropriate immunohistochemical studies.

In our series, as in others, the most frequent histologic diagnosis was DLCL, B-cell type (7/9). The majority of patients with PLL reported in the literature had DLCL [2,8]. Other histologic subtypes of PLL described included high-grade lymphoblastic and Burkitt's lymphoma, follicular lymphoma, and true

diffuse histiocytic lymphoma. Of interest are several unusual histologic subtypes of liver lymphoma, such as lymphoma of mucosa-associated lymphoid tissue (MALT)-type, anaplastic large cell lymphoma, Mantle cell lymphoma, T-cell-rich B-cell lymphoma, and hepatosplenic T-cell lymphoma [2,10-12].

PLL has traditionally been considered as an aggressive disease associated with poor prognosis. Patients usually have some risk factors at the time of diagnosis, including advanced age, aggressive histologic subtype, "B" symptoms and bulky or advanced disease. Concomitant diseases [5], such as chronic active hepatitis, primary biliary cirrhosis, immunodeficiency states such as acquired immune deficiency syndrome (AIDS), or immunocompromised states such as post-transplantation or Sjögren's syndrome, can also contribute to the aggressive and therapy-resistant pattern of PLL [2-4,10-13].

The treatment of PLL patients reported in the literature has not been consistent, with some patients

Table 2. Treatment and outcome

<i>Patient No.</i>	<i>Treatment (cycles, no.)</i>	<i>Response</i>	<i>Follow-up¹ (months)</i>	<i>Outcome</i>
1.	COP ² (×2)	Deterioration, gastric bleeding (steroid-induced)	4	DOD ³
2.	CHOP ⁴ (×6)	Partial remission	4	DOD
3.	CHOP (×4)	Complete remission	3	DOD
4.	CHOP (×6)	Good partial remission	6	DOD
5.	CHOP (×6)	Good partial remission	6	DOD
6.	High-dose CHOP (×5)	Complete remission	5	Dead of unknown cause
7.	CHOP (×6)	Complete remission	8	DOC ⁵ , no evidence of disease
8.	CHOP (×5)	Good partial remission ⁶	6	Died of neutropenic sepsis, hemolytic syndrome and acute renal failure ⁷
9.	PROMACE/MOPP ⁸ (×8)	Complete remission	35	Dead of massive recurrent disease

¹From termination of first-line chemotherapy until relapse or death; ²cyclophosphamide, vincristine, prednisone; ³dead of disease; ⁴cyclophosphamide, doxorubicin, vincristine, prednisone; ⁵dead of other causes; ⁶disappearance of "B" symptoms, bone marrow became negative, normalization of LDH level, marked regression of lymphadenopathy and liver lesions; ⁷six months following termination of chemotherapy, there was no evidence of disease clinically or biochemically; ⁸prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide/nitrogen mustard, vincristine, procarbazine, prednisone

undergoing surgery alone and others receiving chemotherapy alone or in combination with other modalities, such as surgery and/or radiotherapy [2,5,8,11,14]. According to some autopsy series and radiological follow-up studies, it appears that PLL in adults may remain confined to the liver without visceral and bone marrow involvement. This is also supported by successful and long-term survival of patients who underwent complete excision of their PLL [5,14]. The use of curative radiation therapy in PLL is less described, mainly in sporadic clinical cases. Page et al. [1] reported an excellent response rate associated with various combinations of chemotherapy (doxorubicin-based, some with involved field radiation therapy), with a complete response rate of 83.3% and a 5-year relapse-free survival rate of 83.1%. Generally, oncologists were reluctant to apply high-dose radiation therapy to the liver because of the extensive hepatocellular damage caused by the lymphoma and co-existing liver diseases, such as active hepatitis [1,2]. Contrary to these results, Lei [2,11] observed an inferior outcome in PLL patients treated with chemotherapy alone as compared with patients who were treated with additional surgery or radiation therapy. Generally, the inferior outcome described in many studies may be attributed to the use of suboptimal chemotherapeutic regimens, such as steroids, single-agent chemotherapy or non-doxorubicin-based chemotherapy, as well as to patient selection with poor prognostic factors (extrahe-

patic involvement, high-grade histologic subtype).

In conclusion, PLL is an extremely rare tumor of unknown etiology. It may be difficult to diagnose and should be considered in the differential diagnosis of any patient with solitary or multiple liver lesions, particularly when the AFP and CEA levels are normal. The best treatment modality remains uncertain. Controlled studies with anthracycline-based regimens, with or without surgery and/or involved field radiation therapy might reveal the most appropriate treatment.

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