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Original Article

An analysis on clinicopathological features and prognostic factors of patient with primary hepatic lymphoma

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Abstract: Objective: To explore the clinicopathological features and prognostic factors of primary hepatic lymphoma. Methods: A retrospective analysis was performed on the clinicopathological features and follow-up data of 105 patients with PHL in our hospital from January 1980 to October 2012. Survival rates were estimated by Kaplan Meier analysis and prognostic factors were analyzed with Cox regression model. Results: The mean age of patients with PHL was (54.3 ± 14.7) years old and the tumor was 4 to 15 cm in long diameter. In the mode of invasion, nodular invasion accounted for 63.8% (67/105) and diffuse invasion accounted for 36.2% (38/105). In pathological type, diffuse large B-cell lymphoma accounted for 57.1% (60/105), peripheral T-cell lymphoma accounted for 34.3% (36/105) and extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue accounted for 8.6% (9/105). The median survival time of the 105 patients with PHL was 28 months (8~120 months), and the survival rates in 1, 3 and 5 years were 69.5%, 42.9% and 26.7% respectively. Univariate analysis showed that the survival rate was statistically significant among patients with differences in age, number and size of tumor, mode of invasion and pathological type ($P < 0.05$). Cox proportional hazards regression analysis showed that age above 60 years old (*HR* = 1.92, 95% *CI*: 1.28~2.89), tumor size ≥ 10 cm (*HR* = 2.17, 95% *CI*: 1.32~3.56), diffuse invasion (*HR* = 1.79, 95% *CI*: 1.21~2.65) and peripheral T-cell lymphoma (*HR* = 2.76, 95% *CI*: 1.65~4.63) were independent risk factors of prognosis for the patients. Conclusion: The main pathological type of PHL is diffuse large B-cell lymphoma. Old age, tumor size ≥ 10 cm, peripheral T-cell lymphoma and diffuse infiltrative tumor cells are the risk factors of prognosis for patients with PHL.

Keywords: Liver neoplasm, lymphoma, pathology, prognosis, survival analysis

Introduction

Primary hepatic lymphoma (PHL) is an extranodal lymphoma localized in the liver, without spreading to the lymph nodes or outside the liver at the early stage [1]. Although liver is the commonly affected extranodal site in advanced lymphoma, PHL is a relatively rare disease, and as reported in previous studies [2], the incidence of PHL is 0.1% in malignant liver tumors, taking up 0.4% of extranodal lymphomas. Currently, definite diagnosis of PHL relies mainly on pathological examination since clinical findings and laboratory and imaging tests are not specific [3]. So far, there have been few studies on the factors influencing prognosis of patients with PHL, particularly those on the impact of clinicopathological features on prognosis of these patients, and there has been no systematic study. The present study is to discuss the clinicopathological features and their influence on survival of patients with PHL by analyzing the clinicopathological features and survival of the 105 patients with PHL treated in our hospital from January 1980 to October 2012.

Materials and method

Clinical data

Subjects in the study were the 105 patients with PHL confirmed with surgery and pathology in our hospital from January 1980 to October 2012. There were 76 males and 29 females, aged 27 to 78 years old, with a mean age of 54.3 ± 14.7 and a median age of 56. All patients

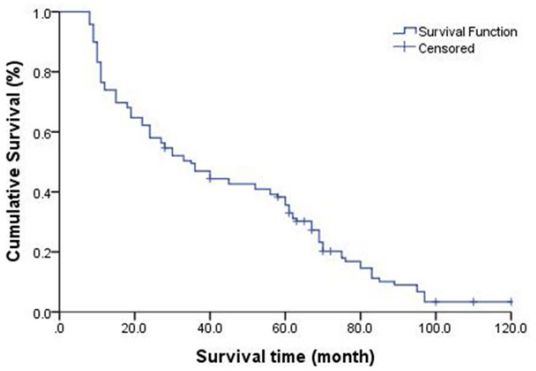

Figure 1. Survival plot of patients with PHL.

met the diagnostic criteria for extranodal lymphomas in *World Health Organization (WHO) classification of tumors of haematopoietic and lymphoid tissues* [4]: (1) clinical symptoms mainly due to liver involvement; (2) no invasion to other tissues or organs and no swelling of distal lymph nodes; (3) no leukemia involvement as shown by peripheral blood smear; (4) normal bone marrow picture; and (5) complete follow-up data. Clinical data of the 105 patients with PHL were collected, including clinical manifestations, examination results of blood routine, liver and kidney functions and tumor markers, and imaging test results of ultrasonography and CT.

Pathological examination

The location, size, number, texture, color, invasion range and capsule status of tumor were recorded, and all tumor tissues were fixed with 10% neutral formalin, conventionally dehydrated, paraffin embedded and sectioned. The slices were 4 μm in thickness and were observed under the light microscope after HE staining. The Envision two-step method was applied to perform LCA, CD20, CD3, CD45RO and CD79a immunohistochemical staining on all tissue slices (kit purchased from Dako, USA), and classification was done according to the *WHO classification of tumors of haematopoietic and lymphoid tissues* [5].

Follow-up method

Follow-up data were collected by telephone or by reviewing inpatient medical records for all patients. Follow-up was performed once every 6 months to find out complete medical history and carry out tumor marker detection and imaging tests such as liver ultrasonography and CT. The follow-up lasted till May 2014, with duration up to 25-97 months. Survival time was calculated from the day of definite diagnosis to the day of death due to PHL or the day of occurrence of related complications, and data were censored for the patients still alive at the end of follow-up.

Statistical analysis

Statistical analysis was performed with the software SPSS 19.0. Statistically, enumeration data was described by relative numbers like rate and constituent ratio and analyzed with the χ^2 test. The survival rate of patients with PHL with different characteristics was estimated by the Kaplan-Meier analysis and the relationship between each factor and prognosis was analyzed with the log-rank test. Statistically significant factors in the univariate analysis were introduced into the Cox proportional hazards regression model to determine the independent factors influencing prognosis of the patients with PHL, and statistical significance was indicated with a p value less than 0.05.

Results

Clinical features

The initial symptoms of PHL were mostly distending pain in the right upper abdomen or discomfort in the upper abdomen, occurring in 75 patients (71.4%); 41 patients (39.0%) experienced symptoms of B-cell lymphoma such as fever, night sweat and emaciation. Intrahepatic space-occupying lesions were confirmed with CT or ultrasonography in the 105 patients, including 66 patients (62.9%) with isolated space-occupying lesions and 39 patients (37.1%) with multiple space-occupying lesions.

There were 10 patients (9.5%) with increase in the level of serum alpha-fetoprotein (AFP), 7 patients (6.7%) with increase in the level of serum glycoprotein antigen 199 (CA199), and 63 patients (60.0%) with positive serum hepatitis B surface antigen (HBsAg).

Ninety-four patients (89.5%) had partial hepatectomy to remove the tumor tissues, and received 4 to 6 cycles of post-operative chemotherapy with the CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone); 11 patients (10.5%) had only isolated partial hepatectomy.

Table 1. Comparison of survival rates in patients with PHL by clinical features (n = 105)

Clinical features	Number of patients	Survival rate (%)★			χ^2 value&	*P* value&
		1 year	3 years	5 years		
Total	105	69.5	42.9	26.7		
Age (year)						
≤ 60	65	76.9	47.7	32.3	4.504	0.034*
> 60	40	57.5	35.0	17.5		
Sex						
M	76	67.1	42.1	28.9	0.164	0.686
F	29	75.9	44.8	20.6		
Symptoms of B-cell lymphoma						
Yes	41	60.9	36.6	21.9	1.348	0.246
No	64	75.0	46.9	29.7		
Number of tumor						
Isolated space-occupying lesions	66	75.8	48.5	31.8	4.680	0.031*
Multiple space-occupying lesions	39	58.9	33.3	17.9		
Size of tumor (cm)						
< 10	73	75.3	47.9	30.1	8.239	0.004*
≥ 10	32	56.3	31.2	18.8		
Mode of invasion						
Nodular invasion	67	79.1	49.3	31.3	7.049	0.008*
Diffuse invasion	38	52.6	31.6	18.4		
Pathological type▼,Δ						
DLBCL	60	68.3	50.0	30.0	5.235	0.022*
PTCL	36	61.1	33.3	19.4		
HBsAg						
Positive	63	71.4	41.2	25.4	1.939	0.164
Negative	42	66.7	45.2	28.6		

Note: ★Survival rate as determined by Kaplan-Meier analysis. &χ^2 and *p* value as calculated by the log-rank test. ▼DLBCL = diffuse large B cell lymphoma, PTCL = peripheral T-cell lymphoma. ΔPatients with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue were not included since there were only 9. The survival time was 22 to 69 months with median survival time of 40 months. *Statistically significant.

Histopathological features

Gross pathology: In the 105 patients with PHL, it could be seen that the tumor was sticking out of the liver, with hard texture and rough and uneven surface. The long diameter of tumor was 4~15 cm, with it < 10 cm in 73 patients (69.5%) and ≥ 10 cm in 32 patients (30.5%). The cross section of tumor was grey-white or grey-red, solid with a fine texture, and hemorrhagic necrosis and liquefaction area could be seen. The tumor in 70 patients (66.7%) had no obvious capsule and showed infiltrative growth against the liver, and incomplete capsule was seen in 35 patients (33.3%).

Histological examination: All of the 105 patients had non-Hodgkin lymphoma (NHL), and the tumor cells were relatively large with a volume about 2 times of the normal lymphocytes, with a round or quasi-circular shape, abundant cytoplasm, karyomegaly and anachromasis, thick karyolemma, non-homogeneous nuclear chromatin and obvious pathologic nuclear division.

Under the light microscope, the lymphoma cells in 67 patients (63.8%) showed nodular invasion and destructive growth, and no portal structure was seen in the tumor tissues; in 38 patients (36.2%), the lymphocytoma cells showed diffuse invasion, the liver structure in the tumor tissues was basically complete, and the tumor cells were seen infiltrating the portal structure or spreading and growing along the hepatic sinusoid.

Immunohistochemistry: PHL in 69 patients (65.7%) were from the B lymphocytes (positive expression for LCA, CD20 and CD79a), including 60 patients with diffuse large B-cell lympho-

Table 2. Results of Cox proportional hazards regression on the factors influencing prognosis of patients with PHL (n = 105)

Factors	B	SE	Wald χ^2	*P value*	*HR*	95% *CI*
Age > 60 (< 60 in the reference group)	0.656	0.426	4.546	0.035*	1.92	1.28~2.89
Tumor ≥ 10 cm (< 10 in the reference group)	0.774	0.522	5.616	0.019*	2.17	1.32~3.56
Diffuse invasion (reference group = nodular invasion)	0.583	0.412	6.282	0.013*	1.79	1.21~2.65
PTCL (reference group = DLBCL)▼	1.018	0.543	7.561	0.023*	2.76	1.65~4.63

Note: ▼DLBCL = diffuse large B cell lymphoma, PTCL = peripheral T-cell lymphoma. *Statistically significant.

ma (DLBCL) and 9 patients with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-MZL); PHL in 36 patients (34.3%) were from the T lymphocytes (positive expression for LCA, CD3 and CD45RO), all being peripheral T-cell lymphoma (PTCL).

Overall survival

Follow-up data showed that the survival time was 8 to 120 months for the 105 patients with PHL, with median survival time of 28 months and the 1-, 3- and 5-year survival rates were 69.5% (73/105), 42.9% (45/105) and 26.7% (28/105) respectively (**Figure 1**).

Univariate analysis on prognosis

According to univariate analysis using the log-rank test, the difference of survival was statistically significant in the patients with differences in age, number and size of tumor, mode of invasion and pathological type ($P < 0.05$), while it was not statistically significant in the patients with differences in sex, symptoms of B-cell lymphoma and hepatitis B surface antigen ($P > 0.05$) (**Table 1**).

Multivariate analysis on prognosis

Statistically significant factors influencing prognosis of the patient with PHL in the univariate analysis were introduced into the Cox proportional hazards regression model and results indicated that age > 60 years old, tumor size ≥ 10 cm, diffuse infiltrative tumor cells and the pathological type of peripheral T-cell lymphoma are independent risk factors of prognosis for the patients ($P < 0.05$) (**Table 2**).

Discussions

Primary hepatic lymphoma is relatively rare in clinical practice, first reported by Ata et al. in 1965 [6]. Between January 1980 and October 2012, a total of 25,685 patients were diagnosed with malignant liver tumor in our hospital, including only 105 patients with PHL, taking up 0.4% of the total. At present, there is no uniform therapeutic regimen for the treatment of PHL in clinical practice. In the past, most scholars believed that surgical resection was the primary and the most effective treatment [7], but in recent years, it has been found out that PHL is a disease sensitive to chemotherapy, which localizes the lesions and provides some patients with a chance for radical surgical resection [8]. In the present study, 94 patients with PHL had surgical resection in combination with post-operative chemotherapy using the CHOP regimen. The overall survival rates in 1, 3 and 5 years after treatment were up to 69.1%, 44.7% and 28.7% respectively, and results indicated that surgical resection in combination with chemotherapy was a relatively effective method in treating PHL at present.

Results of the present study showed that patients with PHL were aged between 27 and 78 years old, with a mean age of 54.3 ± 14.7 and a median age of 56, which was consistent with the conclusion that PHL often occurred in middle-aged people about 55 years old in the previous literature reports [9]. Multivariate analysis revealed that age > 60 was an independent risk factor influencing prognosis in PHL (*HR* = 1.92, 95% *CI*: 1.28~2.89), probably because of the fact that elderly patients with PHL were usually accompanied by various chronic diseases including liver and kidney dysfunction and diabetes, and their poor physical conditions making them intolerant to surgery and post-surgery chemotherapy and prone to complications like infection, gastrointestinal bleeding and liver and kidney failure [10]. Results indicated that PHL could occur in patients of any age group, and monitoring on patients' condition and prevention and treatment of compli-

cations should be intensified in patients with PHL because of poor prognosis in the elderly.

It was also found out in the study that the tumor cells showed nodular invasion in 67 patients (63.8%) and diffuse invasion in 38 patients (36.2%), which was similar to the study report of El-Sharkawi et al. [11]. Furthermore, the Cox proportional hazards regression analysis indicated that the tumor cells showing diffuse invasion was an independent risk factor of prognosis in PHL (*HR* = 1.79, 95% *CI*: 1.21~2.65), consistent with the reports of relevant foreign studies [12]. The reason was possibly that differentiation of the tumor cells showing nodular invasion was at a relatively higher level, and poorly differentiated lymphoma was usually related with the tumor cells showing diffuse invasion, making patients prone to acute hepatic failure and a relatively poorer prognosis [13].

Results of immunohistochemistry in this study indicated that the pathological types included diffuse large B-cell lymphoma (57.1%), peripheral T-cell lymphoma (34.3%) and MALT-MZL (8.6%). PHL reported in the previous literatures was non-Hodgkin lymphoma, mostly B-cell lymphoma (62.0%~87.0%) in histological typing, mainly diffuse large B-cell lymphoma followed by MALT-MZL and Burkitt's lymphoma; T-cell lymphoma accounted for 13.0%~30.0%, mainly peripheral T-cell lymphoma and anaplastic large T-cell lymphoma [11]. In addition, the study also revealed that the survival rate of patients with diffuse large B-cell lymphoma was significantly higher than those with peripheral T-cell lymphoma, with the latter as an independent risk factor of prognosis in PHL (*HR* = 2.76, 95% *CI*: 1.65~4.63). This result was consistent with that of the previous study that prognosis of patients with B-cell-derived non-Hodgkin lymphoma was superior to those with T-cell-derived non-Hodgkin lymphoma [14].

In this study, the gross pathology of PHL was mainly isolated space-occupying lesions (62.9 %), 4~15 cm in long diameter; univariate analysis showed that the survival rate of patients with PHL ≥ 10 cm in long diameter and multiple space-occupying lesions was significantly lower than those with PHL < 10 cm in long diameter and isolated space-occupying lesions; in the Cox regression analysis with the two factors included, it was indicated that tumor ≥ 10 cm in long diameter was an independent risk factor affecting prognosis in PHL (*HR* = 2.17, 95% *CI:* 1.32~3.56). This was probably because most of the patients with a relatively large tumor had T-cell-derived multiple space-occupying lesions. Multivariate analysis indicated that the number of tumors was not statistically significant, which was possibly related to the interaction with other factors and further verification was needed.

In conclusion, the main clinicopathological feature of PHL is diffuse large B-cell lymphoma, with mostly nodular invasion of liver tissues by the tumor cells. Prognosis is poor in these patients at old age and with large tumors in terms of long diameter, diffuse large B cell lymphoma in pathology and diffuse invasion. Therefore, in clinical diagnosis and treatment of PHL, attention should be paid to the above pathological features influencing prognosis and measures be taken for intervention in order to improve the quality and rate of survival in patients with PHL.

Disclosure of conflict of interest

None.

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