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Plasmablastic lymphoma

Review of 60 Chinese cases and prognosis analysis

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Abstract

Background: Plasmablastic lymphoma (PBL) is a B-cell malignancy associated with human immunodeficiency virus (HIV). PBL could also influence the HIV-negative patients. The study aimed to identify prognostic factors for survival among Chinese PBL patients.

Materials and methods: Eligible patients from literature and Peking Union Medical College Hospital (PUMCH) were included in this study. Clinical characteristics and immunophenotypic data were extracted. Kaplan–Meier curve was used to describe the survival status. Cox regression was used for multivariate analysis.

Results: A total of 60 Chinese PBL patients were included, including 54 patients from 36 published articles and 6 new patients that have not been reported. The median overall survival was 7 months (95% confidence interval 3.853–10.147 months). An overwhelming majority (79.31%) of the included cases were Ann Arbor stage IV patients. All the Chinese PBL patients were HIV-negative; 46.81% were Epstein-Barr virus-positive. CD38, CD138, or MUM1 was positively expressed in more than 80% of patients; CD20 expression was also found in 22.03% of cases. Kaplan–Meier curve revealed obvious differences in patient survival between patients in primary stages and advanced stages, as well as between patients with kidney involvement and those without kidney involvement. Cox regression analysis indicated that stage and age were 2 prognostic factors for patient survival.

Conclusions: Advanced stage might be associated with poor prognosis among PBL HIV-negative patients in Chinese.

Abbreviations: CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone, CHOPE = etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone, EBV = Epstein-Barr virus, HHV-8 = herpesvirus-8, HIV = human immunodeficiency virus, NHL = non-Hodgkin lymphoma, PBL = plasmablastic lymphoma, PUMCH = Peking Union Medical College Hospital.

Keywords: Cox regression, Kaplan–Meier analysis, plasmablastic lymphoma, prognostic factor

1. Introduction

Plasmablastic lymphoma (PBL) is an aggressive B-cell malignancy that highly correlated with human immunodeficiency virus (HIV).[1] Recently, PBL is also identified as a subtype of non-Hodgkin lymphoma (NHL), and it is estimated incidence of PBL accounts for approximately 5% of all HIV-positive NHL cases.[2] Despite the strong relationship with HIV infection, PBL could also influence the HIV-negative patients.[3] Previously, a case report has recorded the characteristics of the first PBL case in an HIV-negative individual.[4] It is speculated the HIV-negative PBL cases might derive from previous lymphoproliferative or autoimmune disorders.[5] However, incidence of HIV-negative PBL is still unclear.

With regard to the management of PBL, the common treatments are chemotherapy, radiotherapy with or without surgical excision, or the combination of chemotherapy and radiotherapy. Despite these advances, PBL has a poor prognosis, with a relapse rate of approximately 60% in the first year.[6] Therefore, many studies have been conducted to identify prognostic factors in PBL patients, mostly in HIV-positive patients.[7,8] Several factors such as $CD4^+$ count, HIV infection, Epstein-Barr virus (EBV) status, clinical stage, and the response to chemotherapy have been suggested to be associated with survival in PBL patient[7,9–11]; however, effects of the above factors on the prognosis are not consistent in different individual reports. Thus, further investigation on patient survival is imperatively required.

Currently, most of the data available on PBL are from case reports and case series owing to the low incidence.[8] Furthermore, different populations might generate different outcomes.[8,12] In the present study, we systematically analyzed the demographic, clinicopathological, etiological, and immunophenotypic characteristics of Chinese PBL patients by reviewing the published cases and using several new cases that have never been reported. In addition, we also tried to identify prognostic

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MD and LH are co-first authors.

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factors for patient's survival. This study aimed to provide a more comprehensive understanding of this rare disease in China.

2. Patients and methods

2.1. Literature retrieval and patient collection

Electronic databases including PubMed and Web of Science online database were retrieved from 1997 to March 2015, using the key search terms: "plasmablastic lymphomaor" AND "Chinese"; meanwhile, Chinese CNKI, Wanfang, and Vip databases were also retrieved using the key search term: "jiang mu xi bao lin ba liu" to search studies published in Chinese.

In addition, we also collected the eligible patients in Peking Union Medical College Hospital (PUMCH).

2.2. Informed consent and ethical approval

The enrolled patient information was approved by the Ethics Committee of PUMCH, and all the patients signed the informed consent.

2.3. Data extraction

From each included study, the following information in each PBL patient was extracted and recorded: demographic data (such as age, sex), clinicopathological data (clinical stage, organ involvement), expression profiles of immunophenotypic markers (CD38, CD138, MUM1, CD20, CD79α, CD56, Ki-67, Bcl-6, CD3, PAX-5, and ALK), etiological factors (EBV infection, hepatitis B virus infection, herpesvirus-8 (HHV-8) infection, immunosuppression), treatment strategy (chemotherapy, radiotherapy, and surgery), and overall survival (defined as the period from diagnosis to death or latest follow-up).

2.4. Statistical analysis

Kaplan–Meier curve was used to describe the survival status.[13] Cox regression was used for multivariate analysis.[14] The software Stata 12.0 (Stata Corp, College Station, TX) was used for data analysis. P value <0.05 was considered as the cut-off for statistical significance.

Table 1

Demographic, clincipathological, etiological, and genetic characteristics, as well as treatments of the included plasmablastic lymphoma cases in this study.

Characteristics	n (%)
Age, y (n = 60)	
Mean at diagnosis	56.73 ± 14.02
<30	3 (5.00)
30–60	36 (60.00)
>60	21 (35.00)
Sex (n = 59)	
Male	38 (64.41)
Female	21 (35.59)
Ann Arbor stage (n = 58)	
I	5 (8.62)
II	3 (5.17)
III	4 (6.90)
IV	46 (79.31)
Prognosis (n = 60)	
Censored	32 (53.33)
Dead	28 (46.67)
Bone marrow involvement (n = 54)	
With involvement	25 (49.06)
Without involvement	29 (50.94)
HIV infection (n = 60)	
Without HIV infection	60 (100.00)
With HIV infection	0 (0)
EBV infection (n = 47)	
With EBV infection	22 (46.81)
Without EBV infection	25 (53.19)
Immunosuppression (n = 57)	
No immunosuppression	37 (64.91)
With immunosuppression	20 (35.09)
Surgery (n = 50)	
Received surgery	8 (16.00)
No surgery	42 (84.00)
Radiotherapy (n = 50)	
Received radiotherapy	7 (14.00)
No radiotherapy	43 (86.00)
Chemotherapy (n = 50)	
Received chemotherapy	49 (98.00)
No chemotherapy	1 (2.00)

EBV = Epstein–Barr virus.

3. Results

3.1. Study selection and case inclusion

A total of 54 PBL eligible patients in 36 studies were included in this study, including 45 cases in 27 Chinese studies, and 9 cases in 9 English studies (Supplemental Table 1, http://links.lww.com/MD/B544). Moreover, 6 additional PBL cases from PUMCH that have not yet been published were also included (Supplement Table 2, http://links.lww.com/MD/B544). Thus, there included a total of 60 cases in this study.

3.2. Clinical characteristics of the patients

The demographic data and clinicopathological characteristics of the 60 Chinese PBL patients are presented in Table 1. Sex information is provided in 59 PBL patients, and the ratio of male (38) to female (21) was 1.8:1. Patients younger than 30 years had a very low proportion (5.00%), whereas middle-age patients (30–60 years' old) accounted for a high percentage (60%). Majority (79.31%) of the included patients were in stage IV based on Ann Arbor classification.

Notably, all the included PBL patients were HIV-negative. Meanwhile, 22 of 47 cases (46.81%) were infected by EBV (Table 1). All the patients included were HHV-8-negative.

Detailed treatments were reported among 50 patients: 8 of them underwent surgery (16%), 7 of them received radiotherapy (14%), and 49 (98%) received chemotherapy (Table 1). For those receiving chemotherapy, most of them underwent regimens like CHOPE (etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Other regimens were also applied in some patients, such as HyperCVAD (high-dose cyclophosphamide + vincristine + doxorubicin + dexamethasone or methotrexate + cytosine arabinoside), R-CHOP (rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone), and ESHAP (etoposide + cis-platinum + methylprednisolone + cytosine arabinoside). Based on description of PBL cases in the original article, immunosuppression was empirically speculated in 20 of 57 (35.09%) PBL patients, including 7 hepatitis B-infected patients, 7 elder patients (older than 70 years) and 6 patients receiving radiotherapy or

Table 2

Immunophenotyping of the included plasmablastic lymphoma cases.

Immunophenotypic marker	Number of cases with positive expression	Percentage (%)
CD38	38/43	88.37
CD138	43/51	84.31
MUM1	39/46	84.78
CD20	14/58	22.33
CD795	29/46	63.04
CD56	12/38	31.58
Ki-67	73.84	
Bcl-6	2/13	15.38
CD3	7/40	17.50
PAX-5	5/32	12.50
ALK	0/16	0.00

Note: Ki-67 has mean expression level of 73.84, with a range of 50–99.

chemotherapy because of other tumors (e.g., breast cancer, cervical cancer).

3.3. Immunohistochemical examination

Immunohistochemistry revealed that CD38, CD138, and MUM1 proteins were positively expressed in >80% of the enrolled patients; CD20, CD79α, CD56, BCL-6, CD3, and PAX-5 were positively expressed in >10% patients. No patient had positive expression with ALK among the 16 cases undergoing examination. The mean expression level of Ki-67 was 73.84, with a range of 50 to 99 (Table 2).

3.4. Cytogenetic examination

Among the 60 Chinese cases, 18 underwent cytogenetic examination. There were a total of 14 types of cytogenetic variations, and the type of IgH rearrangement was predominant, accounting for 33.3% for all the cases (Table 3).

Table 3

Types of cytogenetic variations and percentage of cases with each variation type among all the 18 cases undergoing cytogenetic examination.

Type of cytogenetic variation	Number of cases	Percentage, %
PML/RARα-	1	5.6
IgH rearrangement	6	33.3
IgH monoclonal rearrangement	2	11.1
Ig light chain rearrangement	4	22.2
IgH deletion	1	5.6
C-myc rearrangement	4	22.2
MYC translocation	1	5.6
amplification of (CKS) 1B/1q21, del (TP53), and D13S319/13q14	1	5.6
51,XY,+7,+7,der (8)t (7;8)(p14;p21),+12,+15,+19[5]/51,XY,+7,+7,der (8)t (7;8)(p14;p21),+12,+15,+der (19)t (1;19)(q23;p13) [5]	1	5.6
amplification of (CKS) 1B/1q21	1	5.6
47, XY, 11p+, 22q−, +MRK	1	5.6
TCR7 rearrangement Jv (−)	1	5.6
1q21 (−)13q14 (RB1)(−), 13q14.3 (D13s319)(−), 17p13.1 (p53)(−), IgH rearrangement	1	5.6
1q21 amplification	1	

3.5. Prognostic analysis

Overall, 28 of the 60 PBL patients were found dead (Table 1). The median overall survival was 7 months (95% confidence interval 3.853–10.147). Kaplan–Meier curves showed that the survival between PBL patients in primary stages (I and II) and those in advanced stages (III and IV) (Fig. 1A), and between patients with and without kidney involvement were obviously different (Fig. 1B). Cox regression analysis indicated that stage and age were 2 significant prognostic factors for patient survival ($P < 0.05$, Table 4).

4. Discussion

As far as we know, this is the first systematical review to summarize the PBL characteristics and identify the prognostic factors among Chinese population. In this study, we collected 60 Chinese PBL cases from literature retrieval or hospital, and analyzed the demographic and clinicopathological characteristics. Furthermore, we also performed survival analysis with some of the demographic and clincipathological characteristics, and found that the overall survival of PBL patients in stages I and II dramatically differed with those in stages III and IV, indicating that disease stage was a prognostic factor of PBL.

A weak male predominance (male/female ratio of 1.8) was noticed upon the PBL cases included here, which was inconsistent with a previous finding in HIV-associated PBL that reports a male/female ratio of 4:1.[7] More strikingly, all the Chinese PBL cases included here were HIV-negative, suggesting HIV might be more easily affected in male patients with PBL. Actually, most PBL cases are HIV-positive. Furthermore, Castillo et al[10] have compared the clinicopathological characteristics between 157 HIV-positive and 71 HIV-negative PBL cases, and found that HIV-positive patients had a better response to chemotherapy, as well as longer survival. This finding suggests that HIV might influence the survival rate of PBL. However, as all the Chinese PBL cases included here were HIV-negative, we needed more evidence to confirm the role of HIV among Chinese population. In addition to HIV, both of EBV and HHV-8 may also play key roles in the pathogenesis of PBL. Infection with these 2 viruses has been reported in many PBL patients, especially EBV.[15] Therefore, it could be understandable that the EBV infection rate in this study was as high as 47.92%. However, HHV-8 infection was not investigated in our study. Meanwhile, hepatitis B virus infection was observed in 11.7% (7 cases) of the total PBL cases, accounting for more than one-third of the patients with immunosuppression (20 cases). Previously, 2 HIV-negative PBL patients have been reported with a history of hepatitis B.[16,17] Another study also supposes that hepatitis B or C may also have a more important role than HIV-induced immunosuppression in the development of non-AIDS-defining cancers.[18] Thus, our finding might validate their speculation that the hepatitis B-induced immunosuppression has an important role in the development of HIV-negative PBL in Chinese.

PBL cells are known to be positive to plasma cell markers, such as CD138 (syn-1, a member of the transmembrane heparin sulphate proteoglycan family),[19–21] MUM1/IRF4 (multiple myeloma oncogene 1/interferon regulatory factor 4),[19,22] and CD38 (cyclic adenosine diphosphate ribose hydrolase),[19,22] whereas they are negative or weakly negative to B-cell markers as CD20 or CD45.[8,23] Many patients included in the present study have shown the immunophenotype. In accordance with these previous findings, the immunophenotypic markers as CD38, CD138, or MUM1 were positively expressed in >80% of PLB

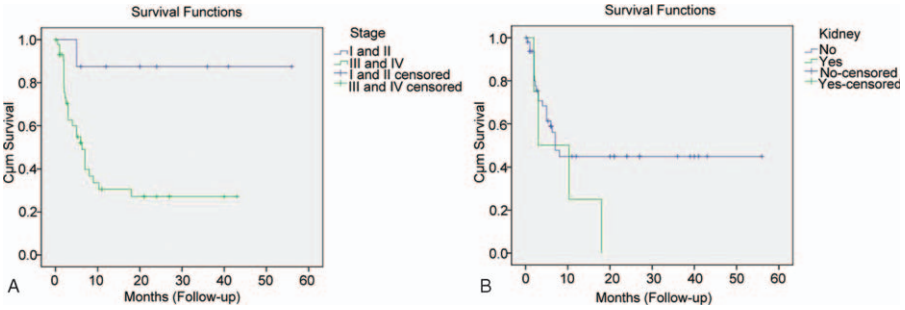

Figure 1. Kaplan–Meier analysis of patient survival with plasmablastic lymphoma stage (A) and kidney involvement (B).

cases, whereas CD20 expression was only found in 22.03% of cases.

Based on Cox regression analysis, the radiotherapy and surgery had no different effect on patient survival. Therefore, an overwhelming majority of patients underwent chemotherapy and most of them received CHOPE or CHOP, which is the most commonly used regimen at present.[24] Additionally, other regimens were also employed in some cases.

Here, various types of cytogenetic variations were also detected in PBL cases. Among them, IgH gene rearrangement occurred in the most cases, and c-Myc gene rearrangement also had a relatively high incidence. Actually, IG/MYC rearrangements are the main cytogenetic alteration in plasmablastic lymphomas.[25] In addition, gene fusion (PML-RARα), robertsonian translocation (der (8)t(7;8)(p14;p21), der(19)t(1;19)(q23;p13) were also found in the PBL cases in this study. *MYC* translocation has been reported in plasmablastic lymphoma.[25,26] *PML/RARα* fusion gene has an essential role in the leukemogenesis,[27,28] and here it was reported in PBL for the first time.

On the contrary, the Kaplan–Meier curve revealed an obvious difference on overall survival between PBL patients in the primary stages (I and II) and those in the advanced stages (III and IV), as well as between PBL patients with kidney involvement and those without kidney involvement. Further Cox regression analysis showed that disease stage was a significant prognostic factor of survival in HIV-negative PBL patients, suggesting different stages might have different survival outcomes. Previously, Castillo et al[7] reported that the early clinical stage was associated with a longer survival in a study of 248 PBL cases (including 157 HIV-positive cases) by literature search, and they further confirmed this finding in a recent study involving 47 HIV-positive cases diagnosed in Europe, United States, and South America.[29] Recently, Liu et al[11] investigate multiple factors that may affect the overall survival in 114 HIV-negative PBL cases, and also find that Ann Arbor stage IV is a poor prognostic factor of overall survival in addition to immunosuppression status, EBV negativity, and refractory to treatment in HIV-negative PBL. However, in an earlier study including 112 HIV-positive PBL cases, Castillo et al[8] reported no association between neither sex, $CD4^+$ count, viral load, clinical stage, EBV status, primary site of involvement, nor use of CHOP chemotherapy regimen with survival. In addition, we should note that in our study, a majority of the patients were in stage IV, which might influence the statistical analysis of this factor and overstress its relationship with the survival. Moreover, the large proportion of censored data may contribute to a few prognostic factors in the present study, and substantial heterogeneity might exist among the included cases, which could probably lead to a bias in the result. Thus, it remains confusing whether clinical stage is associated with survival, and human race, HIV infection status, and number of included cases may contribute to the discrepancies among different studies.

Table 4

Prognostic factors by multivariate Cox regression analysis.

	B	SE	Wald	*P*
Stage (III + IV vs. I + II)	25.639	12.048	4.529	0.033
Kidney involvement	−1.141	178.202	0.000	0.995
Age	−19.923	9.989	3.978	0.046
Sex	45.314	28.259	2.571	0.109
EBV	20.345	16.362	1.546	0.214
Bone marrow involvement	−39.650	21.438	3.421	0.064
Breast involvement	−8.922	10.908	0.669	0.413
Adrenal gland involvement	39.094	180.107	0.047	0.828
Involvement of dropsy of serous cavity	−10.623	10.115	1.103	0.294
Oral cavity involvement	13.976	11.356	1.515	0.218
Stomach involvement	42.305	26.134	2.621	0.105
Spleen involvement	9.262	175.943	0.003	0.958
Liver involvement	—	—	—	—
Involvement of nose or nasopharynx	−50.127	38.678	1.680	0.195
Lymph node involvement	−11.034	10.610	1.082	0.298
Involvement of skin or subcutaneous tissue	−1.697	5.271	0.104	0.747
Surgery	−63.971	40.539	2.490	0.115
Radiotherapy	—	—	—	—
CD138	−2.230	4.891	0.208	0.648
CD20	32.840	18.255	3.236	0.072

EBV = Epstein–Barr virus, SE = standard deviation.

5. Conclusions

Here, we systematically described the demographic characteristics, clinicopathological features, expression profiles of immunophenotypic markers, etiological factors, and treatment strategy of the PBL cases among Chinese population for the first time, and one of our most striking findings was that all the Chinese PBL cases were HIV-negative. Moreover, the advanced clinical stage was associated with the poor survival and identified as a prognostic factor for HIV-negative PBL patients in Chinese.

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