Am J Transl Res 2022;14(2):1051-1059
www.ajtr.org /ISSN:1943-8141/AJTR0139486

Original Article

Clinical characteristics and prognosis of patients with Castleman disease in a Chinese hospital: paraneoplastic pemphigus is an independent risk factor

Yibo Hua[1*], Chao Liang[1*], Jie Yang[1*], Luyang Wang[2], Aimin Xu[1], Lei Xi[2], Shangqian Wang[1], Zengjun Wang[1]

[1]Department of Urology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu Province, China; [2]Department of Pathology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu Province, China. [*]Equal contributors and co-first authors.

Received September 28, 2021; Accepted December 20, 2021; Epub February 15, 2022; Published February 28, 2022

Abstract: Objective: Castleman disease (CD) is a rare lymphoproliferative disorder with limited clinical research data. This study aimed to investigate the clinical manifestations, pathologic features, and prognostic factors of CD. Methods: The clinicopathological data of 54 patients with CD hospitalized in the First Affiliated Hospital of Nanjing Medical University were retrospectively analyzed. Univariate analysis and multivariate analysis were performed by Cox regression model to determine independent prognostic factors for patients' survival. Results: According to clinical classification, 30 cases (55.6%) had unicentric CD (UCD) and 24 cases (44.4%) had multicentric CD (MCD). Moreover, pathologic classification revealed 32 cases (59.3%) with hyaline vascular variant, 3 (5.6%) with mixed cellular variant, and 19 (35.2%) with plasmacytic variant. Patients with MCD commonly presented with clinical signs and symptoms, including fever, splenomegaly, and pleural effusion and/or ascites. Clinical complications, such as liver injury, anemia, and polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes (POEMS) syndrome were more common in patients with MCD. Univariate analysis showed that the presence of paraneoplastic pemphigus (PNP) and the elevation of C-reactive protein were unfavorable prognosticators of survival in patients with CD. By multivariate analysis PNP was an independent prognostic factor in patients with CD. Conclusions: This study provided a panoramic elaboration of CD cases and showed that the presence of PNP was an independent unfavorable factor.

Keywords: Castleman disease, paraneoplastic pemphigus, prognostic factors, survival

Introduction

Castleman disease (CD) is a rare lymphoproliferative disorder first described by Dr. Benjamin Castleman 60 years ago [1]. In recent decades, a large number of case reports and reviews have proposed the clinical manifestations [2, 3], pathologic features [4, 5], and clinical treatment [6] of this complicated disease, and have attempted to explain its pathogenesis [7]. However, the study of CD has still progressed slowly due to its low morbidity.

CD is a highly heterogeneous disorder with diverse clinical manifestations. The unique clinical signs and complications associated with CD include paraneoplastic pemphigus (PNP), thrombocytopenia, anasarca, fever, reticulin fibrosis, organomegaly, and polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes syndrome (POEMS) [8]. Clinically, CD is characterized as unicentric CD (UCD) or multicentric CD (MCD) based on the centricity. UCD is typically localized without systemic involvement, thus surgery is the main treatment. On the contrary, MCD is a systemic disease consisting of two subgroups: human herpesvirus 8 (HHV8)-related MCD [9, 10], and idiopathic multicentric Castleman disease (iMCD) [11, 12]. Systemic therapies are mainly used for MCD. According to pathology, CD can be classified into hyaline vascular variant (HV), plasmacytic variant (PC) and mixed cellular variant (Mix). A systematic study of 416 patients with CD established a novel classification system that provided a valu-

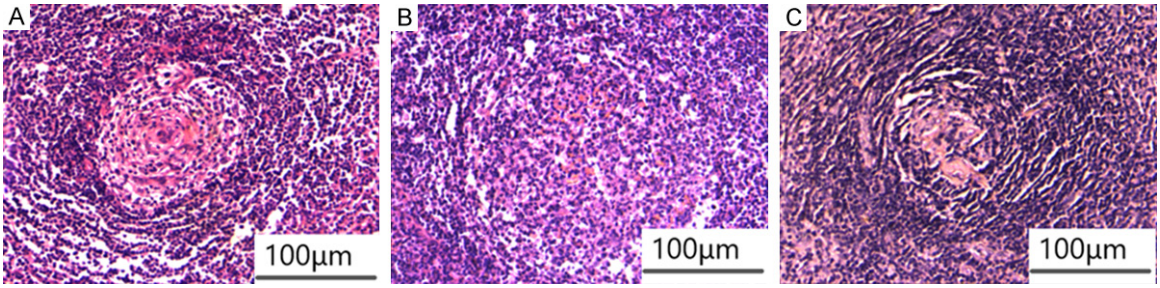

Figure 1. Histopathological features of different variants of Castleman disease. A. Hyaline-vascular variant. The germinal center of a follicle is penetrated by a hyalinized blood vessel, resembling a lollipop and surrounded by a mantle zone composed of lymphocytes in an "onion skin" pattern. B. Plasmacytic variant. The interfollicular region contains sheets of mature plasma cells. C. Mixed cellular variant. The histopathologic features were intermediate between Hyaline-vascular variant and Plasmacytic variant.

able model for predicting midterm outcome [13].

Although a large number of studies have focused on the clinical and pathologic features of CD during its occurrence and progression, few studies have explored the risk factors that influence the prognosis of CD. In this study, we reviewed a cohort of 54 patients with CD from a single center in China to describe the outcome of this disease with complex clinical manifestations and determine prognostic factors.

Materials and methods

Patient characteristics

Clinical and pathological data of 54 Chinese patients diagnosed with CD in the First Affiliated Hospital of Nanjing Medical University from 2008 to 2018 were retrospectively collected. The pathologic data for each patient were based on tissue specimens obtained from 23 needle biopsies and 31 surgical excisions which were reviewed by at least two experienced pathologists (**Figure 1**). This study was carried out under the approval of Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (Approval No. 2019-SRFA-003). An informed consent was signed by the patients.

Inclusion and exclusion criteria

Inclusion criteria: Patients with the pathological examination of lymph node biopsy according to CD manifestations; Patients with the pathological classification of CD established according to Cronin and Kellers criteria [4, 5]; Patients with the clinical classification based on physical and imaging examination. Other definitions in this study included: (1) anemia, defined as hemoglobin <110 g/L in females and <120 g/L in males; (2) hypoalbuminemia, defined as serum albumin <35 g/L; (3) elevated lactate dehydrogenase (LDH), defined as serum LDH >270 U/L; (4) elevated C-reactive protein (CRP), defined as serum CRP >8 mg/L; (5) elevated anti-streptolysin O (ASO), defined as serum ASO >200 IU/mL; and (6) elevated erythrocyte sedimentation rate (ESR), defined as ESR >20 mm/h in females and >15 mm/h in males.

Exclusion criteria: (1) Patients with other lymph node biopsy pathologic diseases similar to Castleman's disease, such as Ig G4-related diseases, lymphoma, or autoimmune diseases. These diseases must be confirmed by clinicians and meet the corresponding diagnostic criteria; (2) Patients with incomplete clinical data.

Follow-up

Enrolled patients were followed until January 2020. Data were collected through telephone, letters, and case records. Survival time was defined as the period from diagnosis to death or the last interview. None of the enrolled patients were lost to follow-up.

Statistical analysis

Data were analyzed with Statistic Package for Social Science (SPSS) 26.0 software (SPSS, Inc., Chicago, IL, USA). The χ^2-test was used to

Table 1. Characteristics of the 54 Castleman disease patients

Characteristic	Number	Percentage
Age		
Mean ± SD (years old)	42.9±14.4	
≤40	23	42.6%
>40	31	57.4%
Gender		
Male	24	44.4%
Female	30	55.6%
Clinical subtype		
UCD	30	55.6%
MCD	24	44.4%
Pathological subtype		
HV	32	59.3%
Mix	3	5.6%
PC	19	35.2%
Main complaints		
Tumor mass or lymph node enlargement	31	57.4%
Fever, hypodynamia or myalgia	12	22.2%
Skin/mucosal ulcers, blisters or stomatitis	9	16.7%
Others	10	18.5%
Therapy		
Biopsy only	2	3.7%
Surgery	23	42.6%
Surgery + CHOP chemotherapy	8	14.8%
CHOP-like chemotherapy	11	20.4%
Rituximab + CHOP chemotherapy	6	11.1%
IVIG + glucocorticoids	11	20.4%
Symptomatic treatment	2	3.7%
Tocilizumab	1	1.9%

SD, standard deviation; UCD, unicentric Castleman disease; MCD, multicentric Castleman disease; HV, hyaline-vascular variant; Mix, mixed cellular variant; PC, plasmacytic variant; IVIG, intravenous immunoglobulin; CHOP, cyclophosphamide, vincristine and prednisone.

analyze the relationship between pathological/clinical subtypes and clinical features. The Kaplan-Meier method was applied to analyze the survival of patients. The Log-Rank test was applied to compare the differences in survival curves. Cox regression univariate and multivariate analyses were performed to determine the independent prognostic factors of survival. A *P*-value <0.05 was considered significant.

Results

Patient characteristics

All 54 patients diagnosed with CD were hospitalized between February 2008 and August 2018. Within this cohort, 23 patients were aged 12-40 years old, and 31 patients aged 41-82 years old (median, 43 years old). The 54 patients included 24 males and 30 females. According to the clinical subtypes, 30 cases had UCD and 24 cases had MCD. According to the histopathological features of all 54 specimens, 32 cases were HV, 19 cases were PC, and 3 cases were Mix (**Table 1**).

The main complaints of the 54 patients with CD were categorized into four groups, and each patient may have had one or more complaints. In the first group, 31 patients with enlarged superficial lymph nodes or serendipitous tumor masses were diagnosed as CD after biopsy or surgery. In the second group, 12 patients had recurring symptoms such as fever, hypodynamia, or myalgia. After physical examination, ultrasonography, or CT, enlarged lymph nodes or tumor masses were found and then confirmed as CD after biopsy or surgery. In the third group, patients with skin ulcers, blisters, or stomatitis were considered to have PNP and were diagnosed as CD after biopsies or surgeries. In the fourth group, the remaining 10 cases complained of non-typical symptoms, such as abdominal distension, pain, or body edema (**Table 1**).

Clinical symptoms and complications

At hospitalization, patients with CD presented with several obvious signs and symptoms, including fever, splenomegaly, and pleural effusion and/or ascites. There were 11 cases of fever and 12 cases of splenomegaly. Pleural effusion and/or ascites were determined in 16 patients by CT scans (**Table 2**).

Pulmonary infection was diagnosed in 16 patients, with fever and cough as the main complaints, and X-ray film or CT assisted with

Table 2. Distribution of clinical characteristics according to clinical and pathologic subtype

Clinical characteristic	Total	Clinical subtype		*P*	Pathologic subtype			*P*
		UCD (n=30)	MCD (n=24)		PC (n=19)	Mix (n=3)	HV (n=32)	
Signs and symptoms								
Fever	11	2	9	**0.007**	7	1	3	**0.028**
Splenomegaly	12	3	9	**0.011**	5	0	7	0.743
Pleural effusion and/or ascites	16	5	11	**0.020**	8	0	8	0.203
Clinical complications								
Pulmonary infection	16	9	7	0.947	6	0	10	0.980
Renal injury	18	8	10	0.245	8	0	10	0.433
Liver injury	9	3	6	0.165	4	1	4	0.450
Anemia	19	8	11	0.143	8	1	10	0.433
AIHA	3	2	1	1.000	3	0	0	**0.047**
PNP	9	4	5	0.489	5	1	3	0.131
POEMS syndrome	6	0	6	**0.005**	3	0	3	0.659
Other abnormal laboratory data								
Lower serum albumin	17	8	9	0.394	10	1	6	**0.012**
Elevated LDH	6	1	5	0.078	4	1	1	0.058
Elevated CRP	10	1	9	**0.003**	6	1	3	0.062
Elevated ESR	13	2	11	**0.001**	6	1	6	0.325
Elevated ASO	8	3	5	0.443	7	0	1	**0.003**

UCD, unicentric Castleman disease; MCD, multicentric Castleman disease; HV, hyaline-vascular variant; Mix, mixed cellular variant; PC, plasmacytic variant; PNP, paraneoplastic pemphigus; AIHA, autoimmune haemolytic anaemia; POEMS syndrome, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes; LDH, lactate dehydrogenase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ASO, Anti-Streptolysin O. Bold: $P<0.05$. *P* values were two-tailed and based on the Pearson chi-square test.

the definite diagnosis. A total of 18 cases were diagnosed as renal injury based on proteinuria and significantly elevated serum creatinine. Liver injury was observed in 9 patients with abnormal elevation of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST). In total, 18 patents were diagnosed with anemia based on obviously decreased hemoglobin, and 3 patients were diagnosed with autoimmune hemolytic anemia (AIHA) based on positive Coombs' test results. Nine patients with skin involvement were diagnosed with PNP, with main complaints of skin or mucosal ulcers, blisters, or pigmentation. Six cases with MCD were diagnosed as POEMS syndrome, presenting with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (**Table 2**).

Patients with MCD may exhibit more symptoms and complications

In this retrospective study, 30 (55.6%) patients were diagnosed with UCD and 24 (44.4%) patients were diagnosed with MCD (**Table 1**). Patients with MCD commonly exhibited clinical signs and symptoms, with fever in 9 of 11 patients ($P<0.01$), splenomegaly in 9 of 12 patients ($P<0.05$), and pleural effusion and/or ascites in 11 of 16 patients ($P<0.05$) (**Table 2**).

Among all CD patients with clinical complications, liver injury, anemia, and POEMS syndrome were more likely to be found in patients with MCD. MCD was found in 6 of 9 patients with liver injury and 11 of 19 patients with anemia; however, these differences were not statistically significant ($P=0.165$ and $P=0.143$, respectively). All 6 patients with POEMS syndrome were diagnosed with MCD ($P<0.01$). There was no significant difference in the remaining clinical complications between UCD and MCD patients. Furthermore, the MCD subtype was found in 7 of 16 patients with pulmonary infection, 10 of 18 patients with renal injury, 1 of 3 patients with AIHA, and 5 of 9 patients with PNP (**Table 2**).

Relationship between pathologic subtypes and clinical symptoms and complications

Among all the included patients, 32 (59.3%) cases were HV, 19 (35.2%) cases were PC, and 3 (5.6%) cases were Mix (**Table 1**). Since the sample size of Mix cases was too small for statistical analysis, only PC and HV cases were included for analysis. In terms of the signs and symptoms, patients with PC were more likely to develop fever than those with HV (P<0.05). In terms of clinical complications, all 3 patients with AIHA were diagnosed with PC (P<0.05), and of the 9 patients with PNP, 5 were classified as PC and 3 were classified as HV; however, the difference was not significant (P=0.131) (**Table 2**).

Patients with MCD may experience abnormal laboratory values

Of the 54 included patients, 17 had a pretreatment albumin level of <35 g/L. Patients with PC were more likely to have a lower serum albumin than those with HV (P<0.05). Prior to treatment, 6 patients had elevated LDH levels, which tended to be more common in patients with MCD or PC, although no significant difference was found (P=0.078, P=0.058). Prior to treatment, patients with MCD also had elevated CRP and ESR levels; MCD was diagnosed in 9 of 10 patients with elevated CRP (P<0.01) and 11 of the 13 patients with elevated ESR (P<0.01). ASO level of 8 patients was >200 IU/mL, and patients with PC were more likely to have elevated ASO (P<0.01) (**Table 2**).

Treatment

Two patients who complained of enlarged superficial lymph nodes only received lymph node biopsy, and both refused further treatment. A total of 23 patients without serious complications received surgery, and then followed a "watchful waiting" strategy. Eight patients were treated with the CHOP regimen (cyclophosphamide 600 mg/m^2, vincristine 1 mg/m^2, and prednisone 1 mg/kg) after surgery, and 7 were classified as UCD. In MCD cases, 9 received CHOP, 6 received R-CHOP (at least two doses of rituximab 375 mg/m^2). Patients with PNP underwent standard treatment with intravenous infusion of immunoglobulin (IVIG) and glucocorticoid (prednisone, methylprednisolone, or dexamethasone). Two patients in critical condition received only supportive treatments, including anti-infection, blood pressure control, and hemodialysis, leading to symptomatic improvement (**Table 1**).

Univariate analysis identified PNP and elevated CRP as unfavorable risk factors

Among the 54 evaluated cases, the longest follow-up duration was 143 months, and the median follow-up duration was 57.5 months. Cox univariate analysis was used to analyze the prognostic factors, and two risk factors were identified: presence of PNP (HR=31.895, P< 0.01) and elevated CRP (HR=5.363, P<0.05) (**Table 3**). Kaplan-Meier analysis and log-rank test also indicated a significantly shorter survival in patients with PNP (P<0.001) or elevated CRP (P=0.021) (**Figure 2**). In addition, univariate analysis showed that fever, pleural effusion and/or ascites, and low serum albumin level may be unfavorable risk factors, but these results were not significant (0.05<P<0.1) (**Table 3**).

Multivariate analysis identified PNP as the only risk factor

The Cox proportional hazards model was used for multivariate analysis, and characteristics with P-values <0.15 in univariate analysis and those with clinical significance were included. The characteristics included fever, pleural effusion and/or ascites, PNP, low serum albumin, and elevated CRP. Multivariate analysis showed that the presence of PNP was an independent risk factor associated with the prognosis of CD (HR=22.834, P<0.01). Although elevated CRP was identified as an unfavorable risk factor in univariate analysis, it had a P-value of 0.639 by multivariate analysis (**Table 3**).

Discussion

Compared to other common hemopathies such as leukemia and lymphoma, the research on CD is limited by its rarity. Although CD is not a malignant disease, it is associated with an increased risk of multiple complications. Although studies have focused on establishing the diagnostic criteria of CD [13, 14], more cohort studies are required to better understand its prognostic factors.

Our study retrospectively analyzed 54 patients with CD in a single center from 2008 to 2018. It was found that MCD may present with more

Table 3. Univariate and multivariate analyses of the 54 patients with Castleman disease

Clinical characteristic	N	Univariate analysis			Multivariate analysis		
		P	HR	95% CI HR	P	HR	95% CI HR
Gender							
Male	24	0.164	0.312	0.060-1.609			
Female	30						
Age							
≤40	23	0.197	0.018	0.000-8.118			
>40	31						
Clinical subtype							
UCD	30	0.984	1.016	0.226-4.562			
MCD	24						
Pathological subtype							
HV	32	0.252	0.409	0.089-1.887			
PC + Mix	22						
Fever	11	0.078	3.898	0.859-17.697	0.805	0.544	0.004-68.873
Splenomegaly	12	0.686	1.404	0.271-7.258			
Pleural effusion and/or ascites	16	0.087	3.735	0.826-16.882	0.962	1.075	0.057-20.417
Pulmonary infection	16	0.256	2.529	0.510-12.534			
Renal injury	18	0.499	1.678	0.374-7.524			
Liver injury	9	0.954	0.939	0.112-7.850			
Anemia	19	0.721	0.741	0.143-3.840			
AIHA	3	0.686	0.045				
PNP	9	**0.002**	31.895	3.711-274.135	**0.007**	22.834	2.309-225.817
POEMS	6	0.630	1.696	0.198-14.527			
Presence of complications	37	0.249	3.534	0.413-30.232			
Lower serum albumin	17	0.060	5.135	0.936-28.169	0.468	3.086	0.147-64.580
Elevated LDH	6	0.674	1.585	0.185-13.570			
Elevated CRP	10	**0.040**	5.363	1.080-26.638	0.639	3.190	0.025-407.041
Elevated ESR	13	0.566	0.538	0.065-4.482			
Elevated ASO	8	0.217	2.820	0.544-14.613			

UCD, unicentric Castleman disease; MCD, multicentric Castleman disease; HV, hyaline-vascular variant; Mix, mixed cellular variant; PC, plasmacytic variant; PNP, paraneoplastic pemphigus; AIHA, autoimmune haemolytic anaemia; POEMS syndrome, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes; LDH, lactate dehydrogenase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ASO, Anti-Streptolysin O; HR, hazard ratio; 95% CI, 95% confidence interval. Bold: $P<0.05$. *P* values were based on Cox proportional-hazards model. Factors with $P<0.15$ in univariate analysis went into the Cox multivariate analysis.

systemic manifestations such as fever, splenomegaly, and pleural effusion and/or ascites. Furthermore, POEMS syndrome, as a complication, also occurredmore frequently in patients with MCD. MCD commonly presented with serological abnormalities corresponding to inflammatory markers, including elevated CRP and ESR levels. These results indicated that MCD may induce systemic inflammation; thus, systemic therapies were primarily used for MCD. In terms of pathology, PC patients are more prone to fever, and decreased albumin and elevated ASO were often found in the serum of patients with PC.

Univariate analysis identified that the presence of PNP and elevated CRP in serum were risk factors influencing the survival of patients with CD. However, when all candidate risk factors, including fever, pleural effusion and/or ascites, PNP, low serum albumin, and elevated CRP were included in multivariate analysis, the presence of PNP was the only independent unfavorable risk factor for the prognosis of CD, which was consistent with the research of Dong *et al.* [3].

PNP is a rare mucocutaneous autoimmune disease associated with neoplasms that first

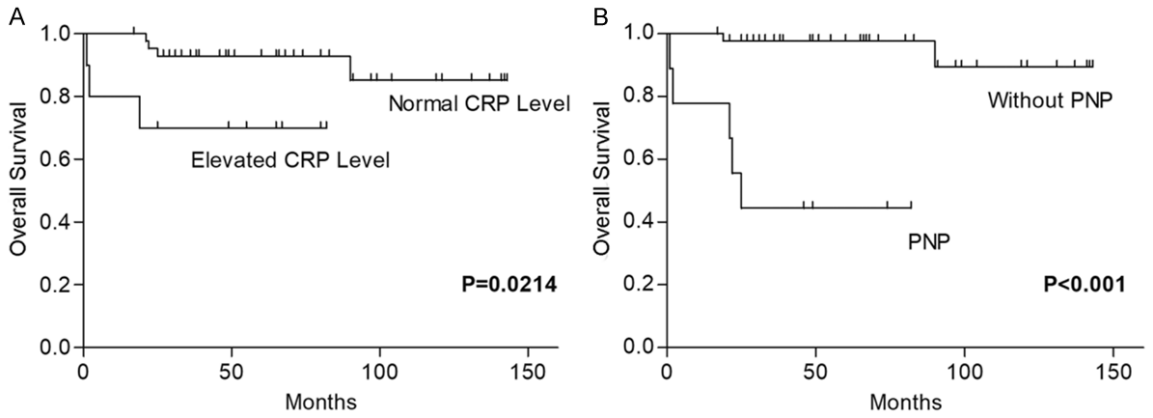

Figure 2. Kaplan-Meier survival analysis of 54 patients with Castleman disease. Log-rank regression was used to test the significance between the two groups. A. The survival rate of CD patients with elevated CRP was significantly lower than that of patients with normal CRP level. B. Prognosis of Castleman disease patients with PNP was worse than that of patients without PNP. CRP, C-reaction protein; PNP, paraneoplastic pemphigus.

described in 1990 [15]. The clinical features of PNP include stomatitis, mucositis, and skin lesions. Furthermore, PNP is often associated with hematologic neoplasms, including non-Hodgkin lymphoma, chronic lymphocytic leukemia, and CD [16, 17]. In this series of CD cases, 9 were considered to have PNP. Clinical classification showed that 4 were UCD and 5 were MCD, while pathologic classification showed that 5 were PC, 1 was Mix, and 3 were HV. Although several previous studies have reported that PNP often occurs in UCD or HV [3, 15], no correlation was found between PNP and clinical or pathological subtype in this study. The main complaints of these patients were polymorphic skin lesions, including skin blisters, ulcers, and lichenoid eruptions, while stomatitis and mucositis were also observed. Some studies revealed that patients with PNP tended to die from severe infections caused by immunosuppressive therapy, associated malignancy, and bronchiolitis obliterans [18]. Therefore, the treatment of PNP is challenging, with poor prognosis and high mortality. Patients with PNP should receive systemic corticosteroids combined with other immunosuppressive agents, including cyclosporine, cyclophosphamide, azathioprine, and mycophenolate mofetil [19]. In this retrospective study, all 9 CD patients with PNP received IVIG and steroids, but 5 died by the date of the last follow-up.

The centricity and pathologic type are important clinical factors to predict prognosis and guide treatment in early diagnosis. Several recent studies have reported that patients with MCD have significantly lower survival rates than those with UCD [20, 21]. Furthermore, according to pathological classification, patients with PC were also reported to have worse prognosis than patients with HV and Mix [13]. Unfortunately, univariate analysis in our study failed to identify centricity (UCD or MCD) and histopathologic types (HV or PC) as prognostic factors for this series of patients. It is important to collect more cases of CD for further analysis to investigate the correlation between the centricity/pathologic type and the prognosis.

Complete resection of the tumor mass was reported to be the standard treatment for UCD [22]. Among 30 patients with UCD, 20 cases only received surgical resection, 7 cases received the CHOP regimen after surgery, 1 case was too severe to tolerate surgery and only received symptomatic and supportive treatment. The optimal treatment for MCD has not been well established. Patients with MCD in our study received a variety of agents, including corticosteroids, cytotoxic chemotherapy, immunoglobulin, rituximab, and anti-IL-6 (tocilizumab). Patients with MCD could benefit from cytotoxic chemotherapy based on that used for lymphoma therapy [23]. In this study, most of the patients with MCD received cytotoxic chemotherapy as a first line therapy. Rituximab, a monoclonal anti-CD20 antibody, was used in HIV- and/or HHV8-positive MCD patients [24, 25]. Tocilizumab is a humanized anti-IL-6 mo-

noclonal antibody that was approved for treatment of CD in Japan in 2005 [26], and has been shown to induce remission in patients with MCD in a series of case reports [27, 28]. These target therapy regimens have the potential to be alternative treatments for CD after chemotherapy. Due to the high heterogeneity of CD, precision and individual therapy should be urgently applied in theclinic.

The current study also had some limitations. First, it was a retrospective study and there might be a bias for patient selection and data collection. Second, the sample size was small and must be expanded for further analysis.

Conclusions

CD is a rare lymphoproliferative disorder that still presents clinical challenges. Our study helped to identify the clinical characteristics and prognosis of patients with CD. The results indicated that the presence of PNP was an independent risk factor, and this deserves attention in diagnosis and treatment.

Disclosure of conflict of interest

None.

Address correspondence to: Shangqian Wang and Zengjun Wang, Department of Urology, The First Affiliated Hospital of Nanjing Medical University, No. 300, Guangzhou Road, Gulou District, Nanjing 210029, Jiangsu Province, China. Tel: +86-025-83780079; E-mail: wangshangqian@njmu.edu.cn (SQW); Tel: +86-025-83780075; E-mail: zengjunwang@njmu.edu.cn (ZJW)

References

[1] Castleman B, Iverson L and Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. Cancer 1956; 9: 822-830.

[2] Herrada J, Cabanillas F, Rice L, Manning J and Pugh W. The clinical behavior of localized and multicentric Castleman disease. Ann Intern Med 1998; 128: 657-662.

[3] Dong Y, Wang M, Nong L, Wang L, Cen X, Liu W, Zhu S, Sun Y, Liang Z, Li Y, Ou J, Qiu Z and Ren H. Clinical and laboratory characterization of 114 cases of Castleman disease patients from a single centre: paraneoplastic pemphigus is an unfavourable prognostic factor. Br J Haematol 2015; 169: 834-842.

[4] Cronin DM and Warnke RA. Castleman disease: an update on classification and the spectrum of associated lesions. Adv Anat Pathol 2009; 16: 236-246.

[5] Keller AR, Hochholzer L and Castleman B. Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer 1972; 29: 670-683.

[6] van Rhee F, Voorhees P, Dispenzieri A, Fosså A, Srkalovic G, Ide M, Munshi N, Schey S, Streetly M, Pierson SK, Partridge HL, Mukherjee S, Shilling D, Stone K, Greenway A, Ruth J, Lechowicz MJ, Chandrakasan S, Jayanthan R, Jaffe ES, Leitch H, Pemmaraju N, Chadburn A, Lim MS, Elenitoba-Johnson KS, Krymskaya V, Goodman A, Hoffmann C, Zinzani PL, Ferrero S, Terriou L, Sato Y, Simpson D, Wong R, Rossi JF, Nasta S, Yoshizaki K, Kurzrock R, Uldrick TS, Casper C, Oksenhendler E and Fajgenbaum DC. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood 2018; 132: 2115-2124.

[7] Hengge UR, Ruzicka T, Tyring SK, Stuschke M, Roggendorf M, Schwartz RA and Seeber S. Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 2: pathogenesis, Castleman's disease, and pleural effusion lymphoma. Lancet Infect Dis 2002; 2: 344-352.

[8] Szalat R and Munshi NC. Diagnosis of Castleman disease. Hematol Oncol Clin North Am 2018; 32: 53-64.

[9] Dupin N, Diss TL, Kellam P, Tulliez M, Du MQ, Sicard D, Weiss RA, Isaacson PG and Boshoff C. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. Blood 2000; 95: 1406-1412.

[10] Powles T, Stebbing J, Bazeos A, Hatzimichael E, Mandalia S, Nelson M, Gazzard B and Bower M. The role of immune suppression and HHV-8 in the increasing incidence of HIV-associated multicentric Castleman's disease. Ann Oncol 2009; 20: 775-779.

[11] Liu AY, Nabel CS, Finkelman BS, Ruth JR, Kurzrock R, van Rhee F, Krymskaya VP, Kelleher D, Rubenstein AH and Fajgenbaum DC. Idiopathic multicentric Castleman's disease: a systematic literature review. Lancet Haematol 2016; 3: e163-175.

[12] Yu L, Tu M, Cortes J, Xu-Monette ZY, Miranda RN, Zhang J, Orlowski RZ, Neelapu S, Boddu PC, Akosile MA, Uldrick TS, Yarchoan R, Medeiros LJ, Li Y, Fajgenbaum DC and Young KH. Clinical and pathological characteristics of HIV- and HHV-8-negative Castleman disease. Blood 2017; 129: 1658-1668.

[13] Talat N and Schulte KM. Castleman's disease: systematic analysis of 416 patients from the literature. Oncologist 2011; 16: 1316-1324.

[14] Fajgenbaum DC, Uldrick TS, Bagg A, Frank D, Wu D, Srkalovic G, Simpson D, Liu AY, Menke D, Chandrakasan S, Lechowicz MJ, Wong RS, Pierson S, Paessler M, Rossi JF, Ide M, Ruth J, Croglio M, Suarez A, Krymskaya V, Chadburn A, Colleoni G, Nasta S, Jayanthan R, Nabel CS, Casper C, Dispenzieri A, Fosså A, Kelleher D, Kurzrock R, Voorhees P, Dogan A, Yoshizaki K, van Rhee F, Oksenhendler E, Jaffe ES, Elenitoba-Johnson KS and Lim MS. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 2017; 129: 1646-1657.

[15] Anhalt GJ, Kim SC, Stanley JR, Korman NJ, Jabs DA, Kory M, Izumi H, Ratrie H 3rd, Mutasim D, Ariss-Abdo L, et al. Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia. N Engl J Med 1990; 323: 1729-1735.

[16] Kaplan I, Hodak E, Ackerman L, Mimouni D, Anhalt GJ and Calderon S. Neoplasms associated with paraneoplastic pemphigus: a review with emphasis on non-hematologic malignancy and oral mucosal manifestations. Oral Oncol 2004; 40: 553-562.

[17] Lehman VT, Barrick BJ, Pittelkow MR, Peller PJ, Camilleri MJ and Lehman JS. Diagnostic imaging in paraneoplastic autoimmune multiorgan syndrome: retrospective single site study and literature review of 225 patients. Int J Dermatol 2015; 54: 424-437.

[18] Leger S, Picard D, Ingen-Housz-Oro S, Arnault JP, Aubin F, Carsuzaa F, Chaumentin G, Chevrant-Breton J, Chosidow O, Crickx B, D'Incan M, Dandurand M, Debarbieux S, Delaporte E, Dereure O, Doutre MS, Guillet G, Julien D, Kupfer I, Lacour JP, Leonard F, Lok C, Machet L, Martin L, Paul C, Pignon JM, Robert C, Thomas L, Weiller PJ, Ferranti V, Gilbert D, Courville P, Houivet E, Benichou J and Joly P. Prognostic factors of paraneoplastic pemphigus. Arch Dermatol 2012; 148: 1165-1172.

[19] Frew JW and Murrell DF. Current management strategies in paraneoplastic pemphigus (paraneoplastic autoimmune multiorgan syndrome). Dermatol Clin 2011; 29: 607-612.

[20] Shin DY, Jeon YK, Hong YS, Kim TM, Lee SH, Kim DW, Kim I, Yoon SS, Heo DS, Park S and Kim BK. Clinical dissection of multicentric Castleman disease. Leuk Lymphoma 2011; 52: 1517-1522.

[21] Zhang X, Rao H, Xu X, Li Z, Liao B, Wu H, Li M, Tong X, Li J and Cai Q. Clinical characteristics and outcomes of Castleman disease: a multicenter study of 185 Chinese patients. Cancer Sci 2018; 109: 199-206.

[22] Talat N, Belgaumkar AP and Schulte KM. Surgery in Castleman's disease: a systematic review of 404 published cases. Ann Surg 2012; 255: 677-684.

[23] Lee JH, Kwon KA, Lee S, Oh SY, Kwon HC, Han JY, Hong SH and Kim SH. Multicentric Castleman disease complicated by tumor lysis syndrome after systemic chemotherapy. Leuk Res 2010; 34: e42-45.

[24] Gérard L, Bérezné A, Galicier L, Meignin V, Obadia M, De Castro N, Jacomet C, Verdon R, Madelaine-Chambrin I, Boulanger E, Chevret S, Agbalika F and Oksenhendler E. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 CastlemaB Trial. J Clin Oncol 2007; 25: 3350-3356.

[25] Bower M, Powles T, Williams S, Davis TN, Atkins M, Montoto S, Orkin C, Webb A, Fisher M, Nelson M, Gazzard B, Stebbing J and Kelleher P. Brief communication: rituximab in HIV-associated multicentric Castleman disease. Ann Intern Med 2007; 147: 836-839.

[26] Nishimoto N, Kanakura Y, Aozasa K, Johkoh T, Nakamura M, Nakano S, Nakano N, Ikeda Y, Sasaki T, Nishioka K, Hara M, Taguchi H, Kimura Y, Kato Y, Asaoku H, Kumagai S, Kodama F, Nakahara H, Hagihara K, Yoshizaki K and Kishimoto T. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood 2005; 106: 2627-2632.

[27] Turcotte LM, Correll CK, Reed RC and Moertel CL. Sustained remission of severe multicentric Castleman disease following multiagent chemotherapy and tocilizumab maintenance. Pediatr Blood Cancer 2014; 61: 737-739.

[28] Cai S, Zhong Z, Li X, Wang HX, Wang L and Zhang M. Treatment of multicentric Castleman disease through combination of tocilizumab, lenalidomide and glucocorticoids: case report. Medicine (Baltimore) 2019; 98: e17681.