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

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Research

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Abstract

Background: Castleman disease (CD) is a rare lymphoproliferative disorder that has had limited clinical research. This study aims to detect the clinical manifestations, pathological features, and prognostic factors of this disease.

Methods: This study retrospectively analyzed the information of 54 patients with CD hospitalized in a single centre. A Cox regression model was employed to perform univariate analysis and multivariate analysis in order to identify independent prognostic factors for survival.

Results: Based on clinical classification, 30 patients (55.6%) had unicentric CD (UCD) and 24 patients (44.4%) had multicentric CD (MCD). Moreover, pathological classification identified 32 cases (59.3%) with hyaline vascular variant (HV), 3 (5.6%) with mixed cellular variant (Mix), and 19 (35.2%) with plasmacytic variant (PC). The MCD patients commonly exhibited clinical signs and symptoms, including fever, splenomegaly, and pleural effusion and/or ascites. Several clinical complications, such as liver injury, anemia, and polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes syndrome (POEMS) were more common in MCD patients. Univariate analysis showed that presence of paraneoplastic pemphigus (PNP) and elevated C-reactive protein (CRP) were unfavorable factors relating to CD patient survival. Multivariate analysis identified the presence of PNP as an independent prognostic factor in patients with CD.

Conclusions: This study provided a panoramic elaboration of CD cases and showed the presence of PNP was an independent unfavorable factor.

Introduction

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

CD is a highly heterogeneous disorder that presents 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, skin changes syndrome (POEMS)[8]. Clinically, CD is characterized as unicentric (UCD) and multicentric (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 disorder that comprises two subgroups: human herpesvirus 8 (HHV8)-related MCD[9, 10], and idiopathic multicentric Castleman disease (iMCD)[11, 12]. Systemic therapies are primarily applied to MCD. Based on pathology, CD can be classified into hyaline vascular variant (HV), plasmacytic

variant (PC) and mixed cellular variant (Mix). A systematic study on 416 CD patients established a novel classification system that provided a valuable model for the prediction of midterm outcome[13].

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

Methods

Patient characteristics

We retrospectively collected the clinical and pathological data for 54 Chinese patients diagnosed with CD from 2008 to 2018 in The First Affiliated Hospital of Nanjing Medical University. The pathological data of each patient was based on the tissue specimens obtained from 23 needle biopsies and 31 surgical excisions, and were reviewed by at least two experienced pathologists （Fig 1）. The pathological classification of CD was established according to Cronin and Kellers criteria[4, 5]. The clinical classification of all enrolled cases was based on physical and imageological examination. Other definitions in this study included: (1) anemia, defined as hemoglobin < 110 g/l for females and < 120 g/l for 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) elevation of Anti-Streptolysin O (ASO), defined as serum ASO > 200 IU/ml; and (6) elevation of erythrocyte sedimentation rate (ESR), defined as ESR > 20 mm/h for females and > 15 mm/h for males.

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 last interview. None of the enrolled patients were lost to follow-up.

Statistical analysis

Data were analyzed with SPSS 26.0 software for windows (SPSS, Inc., Chicago, IL, USA). The c^2-test was used to analyze the relationship between pathological/clinical subtypes and clinical features. The Kaplan-Meier method was applied to analyze the survival curve. The Log-Rank test was used to compare the differences in the survival curve. A Cox regression model was employed to perform univariate analysis and multivariate analysis in order to identify independent prognostic factors for survival. A P-value < 0.05 was considered to be statistically 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 from 12 to 40 years old, and 31 patients were between 41 and 82 years old (median, 43 years). A total of 24 patients were male and 30 were female. Based on the clinical subtype, 30 patients had UCD and 24 had MCD. According to the histopathological characteristics of all 54 specimens, 32 cases were HV, 19 cases were PC, and only 3 cases were Mix (Table 1).

The main complaints of the 54 CD patients were categorized into four groups, and each patient may have had one or more complaints. The first group included 31 patients with enlarged superficial lymph nodes or serendipitous tumor masses, which were confirmed to be CD after biopsies or surgeries. The second group included 12 patients with 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 to be CD after biopsies or surgeries. The third group included 9 patients with skin ulcers, blisters, or stomatitis, which were considered to be PNP and were diagnosed as CD after biopsies or surgeries. The remaining 10 cases complained of non-typical symptoms, such as abdominal distension, pain, or body edema (Table 1).

Clinical symptoms and complications

At the time of hospitalization, several obvious signs and symptoms occurred in CD patients, including fever, splenomegaly, and pleural effusion and/or ascites. Fever was observed in 11 patients and splenomegaly was observed in 12 patients. Pleural effusion and/or ascites were determined in 16 patients by CT scans (Table 2).

Pulmonary infection was diagnosed in 16 patients whose main complaints were fever and cough, and X-ray film or CT assisted with the definite diagnosis. A total of 18 cases were diagnosed with kidney 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 glutamic oxalacetic transaminase (AST). In total, 18 patents were diagnosed with anemia, according to obviously decreased hemoglobin, and 3 patients were diagnosed with autoimmune hemolytic anemia (AIHA) by positive Coombs' test results. Nine patients with skin involvement were diagnosed with PNP, with chief complaints of skin or mucosal ulcers, blisters, or pigmentation. Six MCD cases were diagnosed with POEMS syndrome, with presence of 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). MCD patients commonly exhibited clinical signs and symptoms, including in 9 of the 11 patients with fever ($P < 0.01$), 9 of the 12 patients with splenomegaly ($P < 0.05$), and 11 of the 16 patients with pleural effusion and/or ascites ($P < 0.05$) (Table 2).

In all CD patients with clinical complications, liver injury, anemia, and POEMS syndrome were more likely to be found in MCD patients. Of the 9 patients with liver injury, 6 had MCD, and of the 19 patients with anemia, 11 had MCD; 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 were no significant differences in the remaining clinical complications between patients with UCD and MCD. Furthermore, the MCD subtype was found in 7 of the 16 patients with pulmonary infection, in 10 of the 18 patients with kidney injury, in 1 of the 3 patients with AIHA, and in 5 of the 9 patients with PNP (Table 2).

Relationship between pathological subtypes and clinical symptoms and complications

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

Patients with MCD may show abnormal laboratory parameters

Of the 54 included patients, 17 showed a pretreatment albumin level of < 35 g/l. Patients with PC were more likely to have lower serum albumin than those with HV (P < 0.05). Prior to treatment, 6 patients showed elevated lactate dehydrogenase (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 showed elevated CRP and ESR levels; of the 10 patients with elevated CRP, 9 were diagnosed with MCD (P < 0.01), and of the 13 patients with elevated ESR, 11 were diagnosed with MCD (P < 0.01). Eight patients had an ASO level > 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 took a “watch and wait” 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 received standard treatment with intravenous infusion of immunoglobulin (IVIG) and glucocorticoid (prednisone, methylprednisolone, or dexamethasone). Two patients in critical condition received supportive treatment only, including anti-infection, blood pressure control, and hemodialysis, which led 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. Univariate analysis of prognostic factors using the Cox univariate analysis identified two risk factors: 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 for patients with PNP (P < 0.001) or elevated CRP (P = 0.021) (Fig 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 statistically significant (0.05 < P < 0.1) (Table 3).

Multivariate analysis identified PNP as the only risk factor

A Cox proportional hazards model was used for multivariate analysis, in which characteristics with P-values < 0.15 in univariate analysis and those with clinical significance, were included. These characteristics included fever, pleural effusion and/or ascites, PNP, low serum albumin, and elevated CRP. Multivariate analysis showed that the presence of PNP was as 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, its P-value was 0.639 in multivariate analysis (Table 3).

Discussion

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

Our study retrospectively analyzed 54 patients with CD in a single center from 2008 to 2018. We found that MCD may present with more systemic manifestations such as fever, splenomegaly, and pleural effusion and/or ascites. Furthermore, POEMS syndrome, as a complication, also occurred more 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 applied to MCD. In terms of pathology, PC cases were more likely to have fever, and decreased albumin and elevated ASO were often detected in the serum of PC patients.

Univariate analysis identified the presence of PNP and elevated CRP in serum as risk factors influencing the survival of CD patients. 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. This result was consistent with the research of Dr. Dong[3].

PNP is a rare mucocutaneous autoimmune disease associated with neoplasm that was first described in 1990[15]. The clinical features of PNP include stomatitis, mucositis, and skin lesions. Furthermore, PNP is frequently 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 pathological classification showed that 5 were PC, 1 was Mix, and 3 were HV. Although several previous studies have reported that PNP usually occurs in UCD or HV[3, 15], our study found no correlation between PNP and clinical or pathological subtype. 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 infection due to immunosuppressive therapy, associated malignancy, and bronchiolitis obliterans[18]. Thus, with poor prognosis and high mortality, the treatment of PNP is challenging. Patients with PNP should receive systemic corticosteroids combined with other immunosuppressive agents, including cyclosporine, cyclophosphamide, azathioprine, and mycophenolate mofetil[19]. In our 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 pathology type are important clinical factors that could help to predict prognosis and guide treatment at early diagnosis. Several recent studies have reported that MCD patients have significantly worse survival rates than UCD patients[20, 21]. Furthermore, based on pathological classification, PC patients were also reported to have a worse prognosis than both HV and Mix patients[13]. Unfortunately univariate analysis in our study could not identify centricity (UCD or MCD) and histopathology types (HV or PC) as prognostic factors in this series of patients. It will be important to collect more cases of CD for further analysis in order to investigate the correlations between the centricity/pathology type and the prognosis.

Complete resection of the tumor mass was reported to be the standard treatment for UCD[22]. Among 30 UCD patients, 20 cases only received surgical resection, 7 cases received the CHOP regimen after surgery, 1 case was too sick to tolerate surgery and only received symptomatic and supportive treatment. For MCD, the optimal treatment for has not been well established. The MCD patients in our study received a variety of agents, including corticosteroids, cytotoxic chemotherapy, immunoglobulin, rituximab, and anti-IL-6 (tocilizumab). MCD patients could benefit from cytotoxic chemotherapy based on that used in lymphoma therapy[23]. In our study, most of MCD the patients 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, a humanized anti-IL-6 monoclonal antibody was approved for treatment of CD in Japan in 2005[26], and has been shown to induce remission in MCD patients in a series of case reports[27, 28]. These target therapy regimens have the potential to be alternative treatments for CD after replacement of chemotherapy. Due to the high heterogeneity of CD, precision and individual therapy should be urgently applied in the clinic.

The present study 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 requires to be expanded for further

analysis.

Conclusions

CD was an unusual lymphoproliferative disorder that continues to present clinical challenges. Our study helped to identify the clinical characteristics and prognosis of CD patients. The results indicated that the presence of PNP was an independent risk factor, and should be paid more attention during diagnosis and treatment.

Abbreviations

CD: Castleman disease; UCD: Unicentric castleman disease; MCD : Multicentric castleman disease; iMCD: Idiopathic multicentric Castleman disease; HV: hyaline vascular variant; PC: Plasmacytic variant; POEMS: polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes syndrome; PNP: Paraneoplastic pemphigus; CRP: C-reactive protein; HHV8: Human herpesvirus 8; LDH: lactate dehydrogenase; ASO: Anti-Streptolysin O; ESR: erythrocyte sedimentation rate; ALT: Alanine aminotransferase; AST: Glutamic oxalacetic transaminase; AIHA: Autoimmune hemolytic anemia; IVIG: Intravenous infusion of immunoglobulin.

Declarations

Acknowledgments

Not applicable.

Authors' contributions

Conception and design: SQW, ZJW. Acquisition of data: YBH, CL, JY, LYW, AMX. Pathological diagnosis: LX. Analysis and interpretation of data: YBH, CL, JY. Drafting the manuscript: YBH, SQW. All authors approved the final version. YBH, CL and JY contributed equally to this work.

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Availability of data and materials

All methods were carried out in accordance with relevant guidelines and regulations. The data and materials are available.

Ethics Declarations

Ethics approval and consent to participate

Written Informed consent was obtained from all the adult patients and parents or guardians for participants under 18 years old. Dead patients' kin or legally authorized representative provided written informed consent. This study was approved by ethical committee of The First Affiliated Hospital of Nanjing Medical University.

Consent for publication

Written informed consent for publication was obtained from all participants.

Competing Interests

The authors declare no conflict of interests in association with the present study.

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Tables

Table 1 Characteristics of the 54 Castleman disease patients.

Age		
Mean±SD(year)	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.

Table 2 Distribution of Clinical characteristics according to clinical and pathological subtypes.

	Total	Clinical subtype		P	Pathological 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
Kidney 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-reactionprotein; 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

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

Clinical characteristics	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			
Kidney 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-reactionprotein; 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

Figures

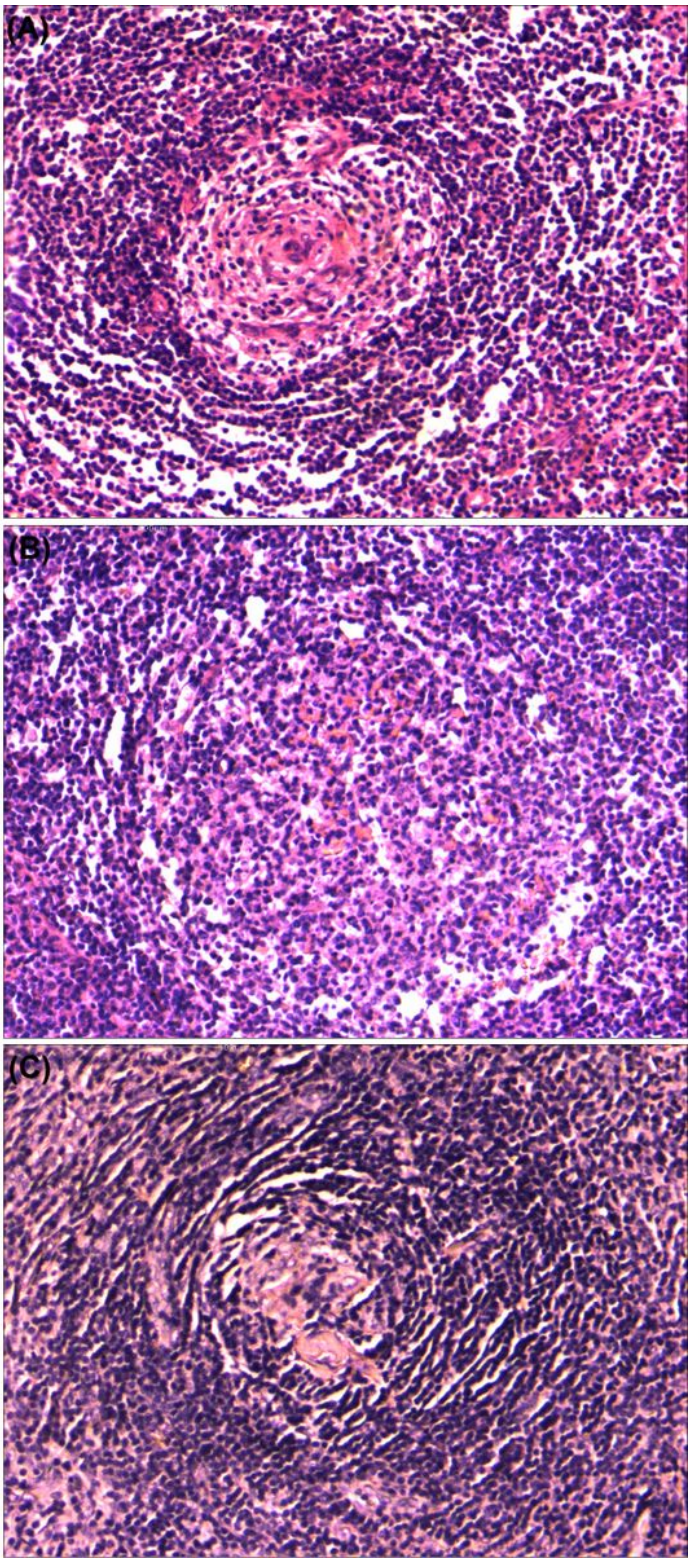

Figure 1

Histopathological features of different variants of Castleman disease . (A) Hyaline-vascular variant. The germinal centre 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

histopathological characteristics were intermediate between Hyaline-vascular variant and Plasmacytic variant.

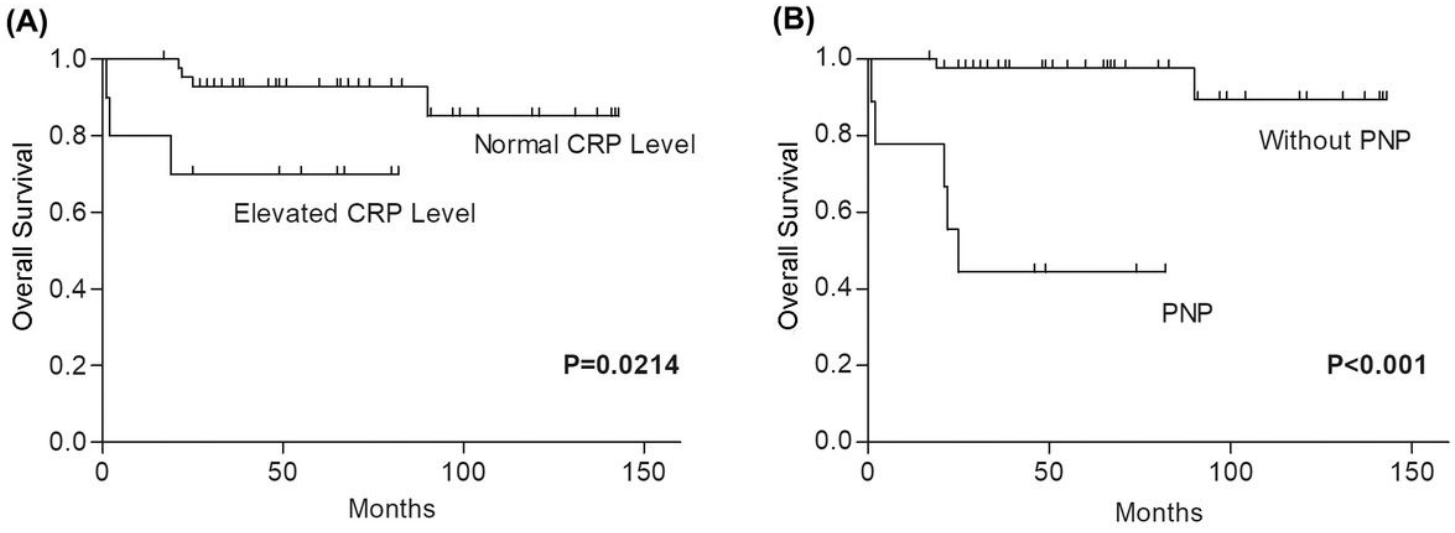

Figure 2

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 the survival of patients with normal CRP level. (B) Prognosis of Castleman disease patients with PNP was worse than that of patients without PNP. CRP, C-reactionprotein; PNP, paraneoplastic pemphigus.