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Clinical and laboratory characterization of 114 cases of Castleman disease patients from a single centre: paraneoplastic pemphigus is an unfavourable prognostic factor

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Summary

This study retrospectively collected the clinical and laboratory data of 114 patients with Castleman disease (CD) from a single medical centre. Clinical classification identified 62 patients (54·4%) with unicentric Castleman disease and 52 (45·6%) with multi-centric Castleman disease. Pathological classification revealed 68 cases (59·6%) of hyaline vascular variant, 16 (14·1%) mixed cellular variant (Mix) and 30 (26·3%) plasmacytic variant. Clinical complications occurred in 69 CD patients, including 37 cases of paraneoplastic pemphigus (PNP) and 25 cases with renal complications. Haematological involvement, pleural effusion and/or ascites and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) were also found. Univariate analysis showed that presence of clinical complications and PNP were both risk factors relating to CD patient survival. Prognostic factors showing $P < 0{\cdot}15$ in univariate analysis and those with clinical significance were subjected to multivariate analysis using a Cox regression model. PNP presence and age over 40 years both significantly adversely affected survival. Thus, only presence of PNP was identified as an independent unfavourable survival risk factor in both univariate and multivariate analyses. Overall, the present data provide a panoramic description of CD cases and emphasize that the presence of PNP is an adverse prognostic factor.

Keywords: Castleman disease, clinical complications, paraneoplastic pemphigus, survival analysis, prognostic factors.

Castleman disease (CD) is a rare lymphoproliferative disorder that was first described in 1956 (Castleman *et al*, 1956). Due to its low incidence, research on CD has progressed much more slowly than in other haematological malignancies, such as lymphoma and myeloma. However, over the past 60 years, studies have gradually accumulated knowledge regarding CD aetiology, histopathology and treatment (Casper, 2005; Dong *et al*, 2009; Polizzotto *et al*, 2013; Fajgenbaum *et al*, 2014; Robinson *et al*, 2014).

Castleman disease is a highly heterogeneous disorder. The classical categorizations based on early clinical findings and characteristic histological alterations have required modifications to accommodate progress in diagnosis and treatments (Dong *et al*, 2009; Fajgenbaum *et al*, 2014). Clinically, CD is characterized as 'unicentric' (UCD) and 'multicentric' (MCD). Pathologically, CD can be classified into three variants: hyaline vascular variant (HV), plasmacytic variant (PC) and mixed cellular variant (Mix). Distinct clinical features and prognosis have been reported in some patients with paraneoplastic pemphigus (PNP) associated with CD, which is usually classified as UCD or HV (Jansen *et al*, 1995; Wang *et al*, 2004; Dong *et al*, 2009). MCD associated with human herpes virus type 8 (HHV8) – also called Kaposi sarcoma-associated herpes virus (KSHV) – seems to be a different entity compared to MCD without HHV8 (Polizzotto *et al*, 2013; Carbone *et al*, 2014; Fajgenbaum *et al*, 2014).

Several series have characterized CD clinical manifestations and histopathology (Dong *et al*, 2009; Liu *et al*, 2014; Robin-

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son *et al*, 2014). A meta-analysis of 416 CD patients from the literature found that centricity, pathology type, the presence of symptoms, gender and age all predict outcome in univariate analyses (Talat & Schulte, 2011). However, few case series studies have examined CD prognosis due to the rarity of this disease, the diversity of the clinical and pathological subtypes and the variations in therapeutic treatments. In the present study, a large group of 114 Chinese CD patients from a single centre was described and the prognostic factors were analysed. This panoramic description will contribute to the general information available regarding CD.

Methods

Patient information

This study was conducted at Peking University First Hospital (PUFH), and was approved by the PUFH Ethics Committee (number 2014–840). Data for the 114 included patients were obtained from the PUFH clinical database and confirmed in the PUFH pathology database. Of these 114 cases, 55 were previously reported by our group (Dong *et al*, 2009). The present paper describes and analyses the follow-up data for these 55 cases, along with 59 new cases from 2009 to 2014.

Clinical and laboratory data were available from diagnosis and during treatment for all 114 cases. Clinical diagnoses of CD and complications were established following generally accepted guidelines (Casper, 2005; Fajgenbaum *et al*, 2014). Of the 114 patients, 105 underwent computerized tomography (CT) examination of involved organs/regions or B-type ultrasonography (USG-B) examination of superficial lymph nodes (including cervical, axillary, inguinal regions and abdominal and pelvic cavities). The records for the remaining nine patients did not include radiographic imaging data because this technology was unavailable during their period of hospitalization. Their clinical classification was based on physical examination and surgical findings. MCD was defined by the involvement of ≥2 lymph nodes or regions. The remaining cases were classified as UCD. In all patients, pathological CD diagnosis was based on the histopathological characteristics of biopsy specimens from the involved lymph nodes, tissues, or organs with review by at least two experienced pathologists (Fig 1).

Paraneoplastic pemphigus was diagnosed based on the minimal criteria proposed by Anhalt (2004). These criteria included progressive stomatitis; acantholysis, lichenoid, or interface dermatitis in cutaneous or oral histology; serum anti-plakin autoantibodies detected by immunoblotting or immunoprecipitation; and underlying lymphoproliferative neoplasm.

Follow-up

Patient follow-ups were conducted by interviews in the outpatient department, telephone interviews, letters and by analysing documented information in the PUFH databases. Survival time was defined as the period from diagnosis to death or last interview. Patients were followed to the end of June 2014. The longest follow-up duration was 366 months, and the median follow-up duration (the median of the survival times only from patients alive at last follow-up) was 37 months. Thirteen patients were lost to follow-up.

Statistical analysis

The Kaplan–Meier method was applied to calculate overall survival (OS) and 1- and 3-year survival rates and to

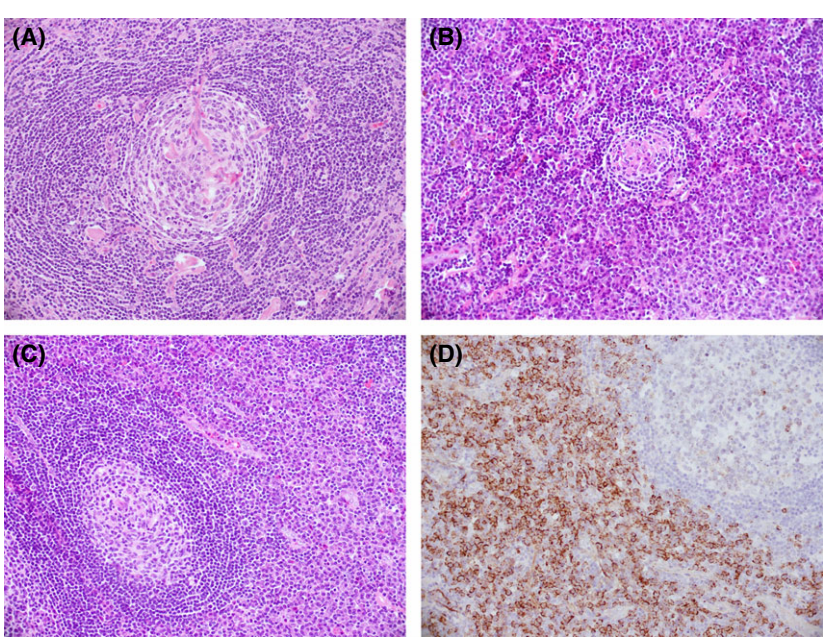

Fig 1. Histopathological features of different variants of Castleman disease. (A) Hyaline-vascular variant. The germinal centre of a follicle is penetrated by a sclerotic blood vessel (so-called 'lollipop') and surrounded by a broad mantle zone composed of concentric rings of small lymphocytes (so-called 'onion skin') (original magnification ×100). (B) Mixed cellular variant. A burned-out germinal centre is surrounded by numerous mature plasma cells (original magnification ×100). (C) Plasmacytic variant (original magnification ×100). Sheets of mature plasma cell are present within the interfollicular region and are highlighted by positive immunostaining of CD138 (original magnification ×200) (D). A, B and D: haematoxylin and eosin stain; C: immunohistochemistry.

perform univariate analysis of possible prognostic factors. Survival curve differences were compared with Log-Rank tests. A multivariate Cox proportional hazards model was employed to identify independent prognostic factors for survival, using the SPSS 14.0 software for windows (SPSS, Inc., Chicago, IL, USA). A P value of $<0{\cdot}05$ was considered to indicate statistically significant differences.

Results

Patient characteristics

All 114 patients were hospitalized between November 1977 and June 2014. Within this cohort, 61 patients were male and 53 female. The median age was 35 years old, with 62 patients between 12–40 years old and 52 patients between 41–72 years old (Table I).

Table I. Patient characteristics of 114 cases of Castleman disease.

	N	(%)
Age (11–74 years)		
≤40 years	67	54·4
>40 years	45	45·6
Sex		
Male	61	53·5
Female	53	46·5
Main complaints*		
Skin or mucosal ulcers, blisters, or anabrosis	37	32·5
Lymph node enlargement or tumour mass	46	40·4
Oedema, haematuria, proteinuria or elevated serum creatinine	21	18·4
Others	12	10·5
Clinical subtype		
UCD	62	54·4
MCD	52	45·6
Pathological subtype		
HV	68	59·6
Mix	16	14·1
PC	30	26·3
Therapy		
Biopsy only	48	42·2
Surgery + IVIG + glucocorticoids	37	32·4
CHOP-like chemotherapy	18	15·8
Rituximab + CHOP-like chemotherapy	11	9·6
Siltuximab†	3	2·6

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

*Two patients complained of both lymph node enlargement and elevated serum creatinine.

†Three MCD patients received siltuximab therapy in the MCD328 clinical trial (van Rhee *et al*, 2014), followed by administration of rituximab when they withdrew from the clinical trial due to disease progression.

Main complaints at hospitalization

The 114 patients were categorized into four groups based on their main complaints at the time of hospitalization. The first group included 37 cases with mucosal erosions and/or cutaneous lesions, which were suspected to be PNP and were diagnosed as such after finding enlarged lymph nodes or tumour masses. Pathologists then further diagnosed these cases as CD after examining specimens obtained from biopsies or surgeries. The second group included 46 patients with enlarged lymph nodes or tumour masses, which were confirmed to be CD after biopsy. The third group comprised 21 patients with kidney injuries, facial or lower limb oedema, haematuria, proteinuria and/or elevated serum creatinine. Physical examination, USG-B or CT of these patients revealed two or more enlarged superficial lymph nodes, which were then biopsied. These patients were finally diagnosed with CD of the PC or Mix variants. The remaining 12 patients complained of non-specific symptoms, such as abdominal distension or hypodynamia (Table I).

Clinical complications

Clinical complications occurred in 69 cases. PNP was diagnosed in 37 CD patients whose main complaints were mucosal erosions and/or cutaneous lesions. Among 37 patients with respiratory system involvement, 10 cases were confirmed to be bronchiolitis obliterans (BO), which was characterized by progressive dyspnoea, severe hypoxaemia, obstructive pulmonary ventilatory dysfunction, bilateral pulmonary hyperinflation on X-ray films and diffuse bronchiectasis on CT. One patient with PNP was found to have deep venous thrombosis following surgical removal of a retroperitoneal mass, and was later diagnosed with pulmonary thrombosis. Patients with lung involvement were poorly responsive to glucocorticoid treatment.

Twenty-five of the examined cases involved the kidneys, including clinical diagnoses of nephrotic syndrome, nephritis syndrome, acute progressive nephritis syndrome, acute renal failure and chronic kidney disease. We identified six cases of autoimmune haemolytic anaemia (AIHA) and six cases of idiopathic thrombocytopenic purpura (ITP). Twelve patients with MCD showed pleural effusion and/or ascites. Seven cases fulfilled the diagnostic criteria of POEMS syndrome, which is characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes.

Relationship between clinical subtypes and complications

Of all included patients, 62 (54·4%) were clinically classified as having UCD and 52 (45·6%) were diagnosed with MCD (Table I). We observed a strong relationship between clinical subtypes and complications. Of the 37 patients with PNP, 32 had UCD – including 9 of the 10 PNP patients with BO and all 6 of the PNP patients with myasthenia gravis. UCD is

characterized by single lymph node or regional lymph node enlargement and, among patients with PNP and UCD, the majority of enlarged lymph nodes were localized to the retroperitoneum or pelvic cavity. In contrast, the MCD subtype was most commonly found in patients with other complications – including in 24 of the 25 patients with kidney involvement, 11 of the 12 patients with ITP or AIHA, all 12 patients with pleural effusion and/or ascites and 7 patients with POEMS syndrome (Table II).

Relationship between pathological subtypes and complications

Regarding the pathological subtypes, 68 cases (59·6%) were HV, 16 cases (14·1%) were Mix, and 30 cases were PC (Fig 1) (Table I). Of the 37 patients with PNP, 32 (86·5%) had the HV subtype and 5 had Mix subtype. Ten PNP patients were concurrently diagnosed with BO, of whom eight had CD of the HV variant and two had Mix (Table II). Six PNP patients were identified as having myasthenia gravis, of whom five were HV and one was Mix (Table II).

The HV subtype was relatively uncommon among patients with other organ or system involvements. Of the 25 patients with kidney involvement, only four had HV, with the rest being the PC or Mix type. The HV subtype of CD was found in one of the six patients with ITP and in one of the six patients with AIHA, while the remaining patients with complications involving the haemotological system were PC or Mix variants. Among the 12 patients with pleural effusion and/or ascites, 50% were PC variant, the other 50% were Mix. Regarding the seven patients with POEMS syndrome, four were PC, two were Mix and only one case was HV.

Relationship between clinical and pathological subtypes

Among patients with UCD, 92% were HV variants (Fig 2), with only 5% classified as Mix and 3% as PC variants. Pathological analysis showed that more than half of the MCD patients (54%) were PC variants, 25% were Mix variants and 21% were HV variants. Among the CD patients with the HV variant, 84% were clinically classified as UCD. On the other hand, 81% and 93% of the CD patients classified as Mix and PC variants, respectively, were diagnosed as MCD (Fig 2).

Other laboratory findings

Indirect immunofluorescence assay on rat bladder tissue showed that PNP patients usually had >1:160 positivity. Of the 13 tested patients, anti-desmoglein (Dsg)3 antibody was positive in eight, and one patient with PNP was Dsg1 positive. Nine patients with kidney involvement underwent renal biopsy, which revealed crescentic glomerular nephritis, renal capillary endotheliopathy, thrombotic microangiopathic renal injury and minor glomerulopathy (Table I). Of the nine tested patients, four were positive for platelet-associated immunoglobulin G. All six AIHA patients had positive Coombs' test results. Of 26 examined patients, 18 showed an elevated erythrocyte sedimentation rate (ESR). Seven patients had a pretreatment albumin level of <30 g/l. Prior to treatment, three of the eight tested patients showed elevated lactate dehydrogenase (LDH) levels. Serum immunofixation electrophoresis (IFE) assays in 37 patients showed that 11 had monoclonal gammaglobulinemia, all of whom had MCD. Of these 11 patients, 8 were PC variants and 3 were Mix variants. Sixty-seven patients were screened for human immunodeficiency virus (HIV) infection (32 of whom were MCD patients), and all were negative. Of the 18 patients tested for HHV8 infection, 1 was positive, and this patient had MCD.

Treatments

In 48 patients without clinical complication, a 'watch and wait' strategy was applied. These patients were regularly followed-up by ultrasound scan, ESR, and serum LDH level at

Table II. Distribution of clinical complications according to clinical and pathological subtypes.

Clinical complications	Total number	Clinical subtype		Pathological variants		
		UCD	MCD	HV	Mix	PC
PNP	37	32	5	32	5	0
PNP with BO	10	9	1	8	2	0
PNP with myasthenia gravis	6	6	0	5	1	0
Kidney injury	25	1	24	4	7	14
AIHA	6	1	5	1	0	5
ITP	6	0	6	1	2	3
POEMS syndrome	7	0	7	1	2	4
Pleural effusion and/or ascites	12	0	12	0	6	6

UCD, unicentric Castleman disease; MCD, multicentric Castleman disease; HV, hyaline-vascular variant; Mix, mixed cellular variant; PC, plasmacytic variant; PNP, paraneoplastic pemphigus; BO, bronchiolitis obliterans; AIHA, autoimmune haemolytic anaemia; ITP, idiopathic thrombocytopenic purpura; POEMS syndrome, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes.

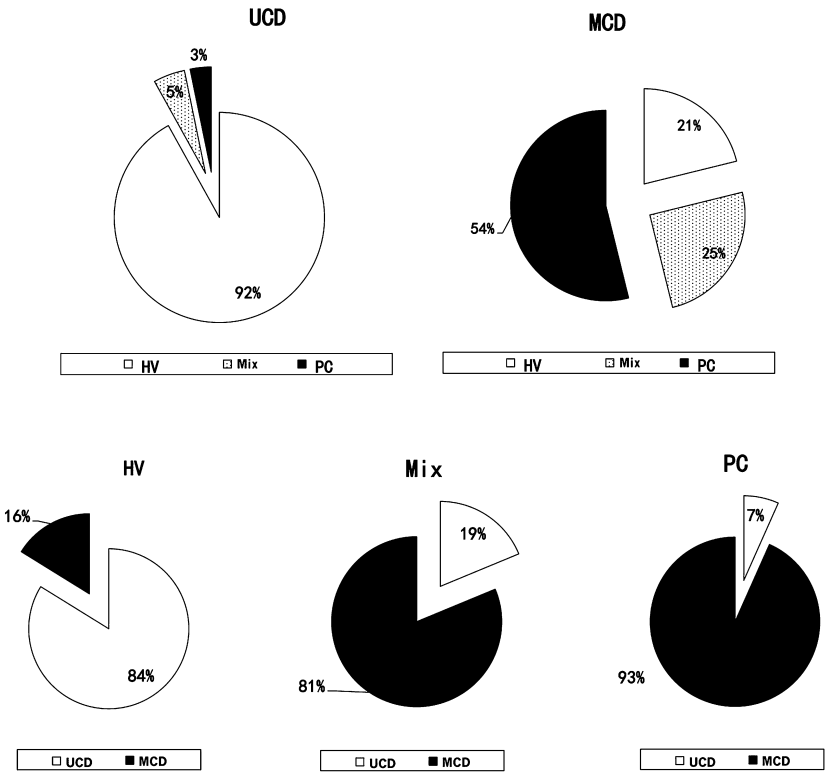

Fig 2. Relationship between clinical subtypes and pathological variants. Circles show the constitutional ratio of each subtype. UCD, unicentric Castleman disease; MCD, Multicentric Castleman disease; HV, hyaline vascular variant; PC, plasmacytic variant; Mix, mixed cellular variant.

3- to 6-month intervals. Patients with PNP received standard treatment with intravenous infusion of immunoglobulin (IVIG) and glucocorticoid (prednisone, methylprednisolone or dexamethasone) prior to, during and after surgical removal of the tumour mass. BO patients were treated with bronchodilators and glucocorticoid, which led to symptomatic improvement but no change in prognosis. Patients with renal complications received oral prednisone or pulsed methylprednisolone.

Eighteen MCD patients were treated with a CHOP-like regimen (cyclophosphamide 600 mg/m^2, vincristine 1 mg/m^2 and prednisone 1 mg/kg). In patients with renal failure, haemodialysis was employed as supportive treatment. Plasma exchange was performed in one patient positive for anti-glomerular basement membrane antibodies. Eleven MCD patients received a R-CHOP-like regimen (at least two doses of rituximab 375 mg/m^2). After two cycles of chemotherapy, patients were evaluated with USG-B or CT.

Univariate analysis identified PNP and complications as unfavourable risk factors

Among the 114 evaluated cases, the longest follow-up duration was 365 months, and the median follow-up duration was 37 months. Univariate analysis of prognostic factors using the Kaplan–Meier method identified two risk factors among the CD patients: presence of PNP (HR = **4·351**) and presence of complications (HR = 11·595) (Table III). The 1- and 3-year survival rates, respectively, were 76·9% and 57·6% among patients with PNP patients and 98·6% and 88·3% among patients without PNP ($P < 0·001$ by the log-rank test) (Fig 3B). A statistically significant survival difference ($P = 0·002$) was observed between patients without clinical complications and those with complications, including PNP (Fig 3A) (Table III). CD patients over 40 years of age had 1- and 3-year survival rates of 83·3% and 69·8%, respectively. These rates were lower than the corresponding survival rates for CD patients less than 40 years of age (93·1% and 85·7%, respectively); however, this difference was not statistically significant ($P = 0·110$). Univariate analysis did not identify statistically significant differences related to any other investigated factors, including sex, clinical subtype, pathology subtype, LDH, C-reactive protein (CRP) level, etc. (Table III).

Kaplan–Meier analysis of the 75 patients without PNP according to clinical subtype revealed that UCD patients had better survival than MCD, but the difference was not statistically significant ($P = 0·142$) (Fig 3C). Analysis according to pathological subtype showed the highest survival rate for the Mix variant and the lowest for PC ($P = 0·106$ in overall comparisons by the log-rank test) (Fig 3D).

Multivariate analysis identified PNP and age >40 years as risk factors

Factors with P values of <0·15 in univariate analysis and those with clinical significance were subjected to multivariate analysis using a Cox proportional hazards model. These

Table III. Univariate and multivariate analyses of overall survival of the 114 patients with Castleman disease.

		Univariate analysis						Multivariate analysis†			
		Survival rate (%)			Median					95% CI for HR	
Clinical factor	*N*	1 year	3 year	*P* value*	survival (months)	HR	95% CI HR	*P*	HR	Lower	Upper
Gender											
Male	60	94·9	76·7	0·277	263·5	0·589	0·224–1·551	–	–	–	–
Female	52	89·0	86·3		153·2						
Age											
≤40 years	67	93·1	85·7	0·110	304·5	2·172	0·854–5·527				
>40 years	45	83·3	69·8		147·9			0·013	3·855	1·331	11·164
Date of diagnosis											
Before 01-01-2005	37	89·7	71·8	0·693	269·6	0·830	0·326–2·108				
After 01-01-2005	75	91·6	82·1		101·3						
Clinical subtype											
UCD	62	94·8	82·4	0·883	290·7	0·935	0·379–2·303	0·564	1·550	0·349	6·876
MCD	50	93·8	73·5		158·1						
Pathological subtype											
HV	68	92·1	81·0	0·652	287·1	0·886	0·521–1·506	0·423	0·710	0·306	1·643
Mix	14	76·9	–		77·5						
PC	30	79·5	71·6		124·0						
Presence of PNP											
Yes	36	76·9	57·6	<0·001	317·0	4·351	1·699–11·143	0·038	4·760	1·087	20·838
No	76	98·6	88·3		91·0						
Presence of complications											
Yes	68	94·7	–	0·002	113·3	11·595	1·546–86·984	0·378	0·354	0·035	3·560
No	44	88·0	75·5		348·3						
Lower serum albumin											
Yes	38	80·8	66·5	0·094	101·3	2·124	0·859–5·253	0·257	0·566	0·211	1·515
No	65	96·6	85·7		145·0						
Elevated LDH											
Yes	4	–	–	0·564		1·825	0·229–14·518	–	–	–	–
No	46	87·6	69·5		121·0						
Elevated CRP											
Yes	22	77·7	–	0·844		1·155	0·275–4·852	–	–	–	–
No	15	76·2	–								
Elevated SCr											
Yes	16	95·2	85·6	0·851	83·3	0·872	0·254–2·998	–	–	–	–
No	88	77·3	–		136·0						
Elevated ESR											
Yes	56	88·7	72·4	0·726	117·1	1·251	0·356–4·394	–	–	–	–
No	19	88·1	–		79·3						
Monoclonal bands by IFE											
Yes	10	63·0	–	0·255	88·8	2·476	0·493–12·430	–	–	–	–
No	25	91·8	–		138·8						

UCD, unicentric Castleman disease; MCD, multicentric Castleman disease; HV, hyaline-vascular variant; Mix, mixed cellular variant; PC, plasmacytic variant; PNP, paraneoplastic pemphigus; LDH, lactate dehydrogenase; CRP, C-reactive protein; SCr, serum creatinine; ESR, erythrocyte sedimentation rate; IFE, Sera immunofixation electrophoresis; HR, hazard ratio; 95% CI, 95% confidence interval.

*P value of log-rank test.

†Factors with $P < 0{\cdot}15$ in univariate analysis and those with clinical significance went into the Cox regression model.

factors included presence of complications, PNP, age, low albumin level, clinical subtype and pathological subtype. Multivariate analysis showed that PNP remained independently associated with OS [Hazard ratio (HR) = 4·760, $P = 0{\cdot}038$] (Table III). Although presence of complications was identified as an unfavourable risk factor in univariate analysis, its P value was 0·378 in multivariate analysis. The Cox regression model showed that age of more than 40 years was a risk factor for survival, with an HR of 3·855 and P of 0·013 (Table III).

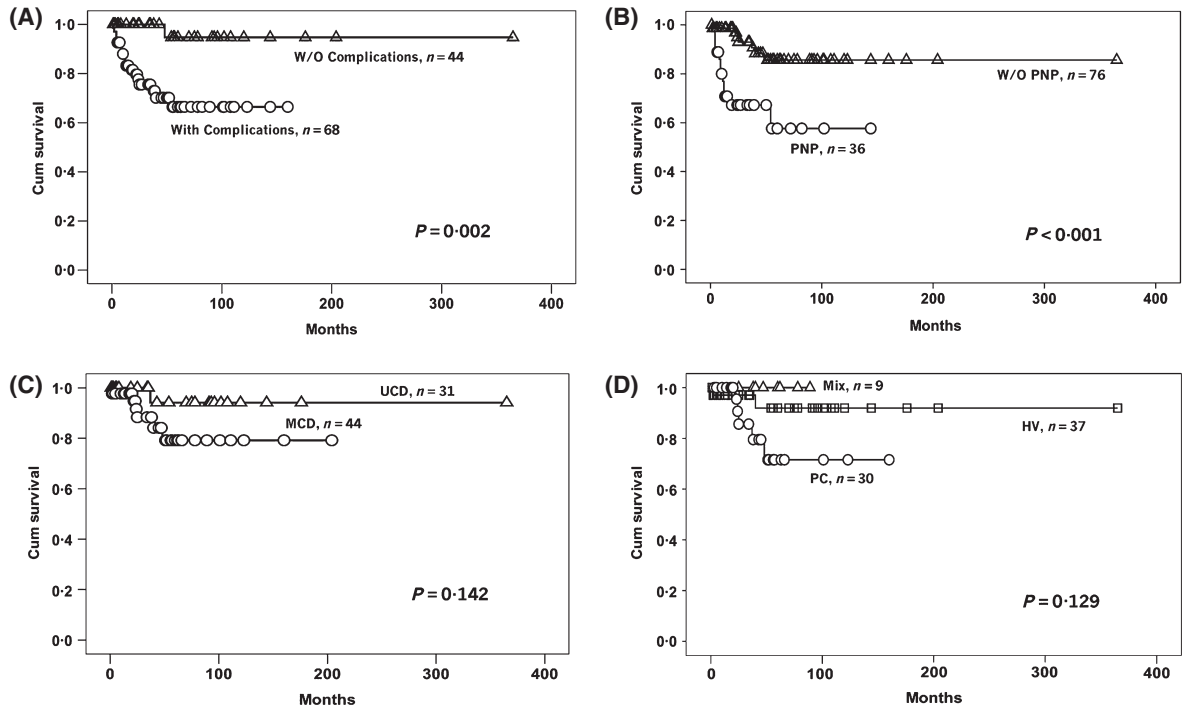

Fig 3. Kaplan–Meier survival analysis of 114 patients with Castleman disease according to the presence of clinical complications. *P* values indicate the significance of the overall comparisons between the two groups by log-rank (Mantel-Cox) test. (A) Prognosis of Castleman disease patients without complications was superior to that of patients with complications ($P = 0{\cdot}002$). (B) Survival analysis according to the presence of PNP showed that patients with PNP had an unfavourable prognosis ($P < 0{\cdot}001$). (C and D) Kaplan–Meier survival analysis of patients without PNP, according to clinical subtypes (C) and pathological variants (D). PNP, paraneoplastic pemphigus; HV, hyaline-vascular variant; Mix, mixed cellular variant; PC, plasmacytic variant.

Discussion

To date, few series studies have focused on the prognosis of CD patients, largely due to the rarity of this disease. However, prognostic factors are important for making clinical decisions. The present study investigated factors affecting the survival of CD patients. The results will be helpful in determining treatment of this rare lympho-proliferative disorder.

Univariate analysis identified the presence of clinical complications and PNP as risk factors with regard to CD patient survival. However, multivariate analysis showed that PNP and older age significantly impacted survival. Thus, only the presence of PNP was identified as an independent unfavourable risk factor for survival in both analyses. Compared to CD patients without PNP, CD patients with PNP show distinct clinical, laboratory and histopathological features. Their unfavourable prognosis emphasized the importance of earlier diagnosis and more effective treatment. This group of patients should be considered an independent disease entity or an isolated clinical subtype of CD.

Multivariate analysis showed that CD patients more than 40 years of age had an unfavourable prognosis compared to those less than 40 years of age, with a *P* value of 0·019 (Table III). Although univariate analysis showed a *P* value of 0·11 (log-rank test), patients over 40 years of age had lower 1-year and 3-year survival rates (83·3% and 69·8%, respectively) compared with those aged less than 40 years (93·1% and 85·7%, respectively). Thus, age should be considered as a prognostic factor for the survival of CD patients.

Lactate dehydrogenase and CRP levels were not associated with CD survival. However, these results should be interpreted with caution. These data were retrospectively collected, and thus no complete records were available for some CD patients – for example, only 37/114 patients had CRP data available. Therefore, the statistical results are not as meaningful as those from a well-designed perspective study.

A meta-analysis of 416 CD patients from the published literature identified centricity, pathology type, presence of symptoms, gender and age as prognostic factors by univariate analysis (Talat & Schulte, 2011). In our series studies, we also found that the 1- and 3-year survival rates of UCD patients were higher than those for MCD. The survivals of CD patients with HV variants were also better than those of PC variant (Table III) (1-year survival: 92·1% vs. 79·5%; 3-year survival: 81·0% vs. 71·6%). But the difference was not statistically significant. Another reason for this difference between the results reported by Talat and Schulte (2011) and ours maybe due to the different constitution of CD patients. The present series of patients included more

patients with PNP than Talat's (33·3% vs. 1·3%) (Talat & Schulte, 2011). The majority of PNP patients belonged to the UCD subtypes and HV variants. The poor prognosis of PNP patients compromised the better survival of UCD subtype and HV variant group. Analysis of the 75 patients without PNP according to clinical subtype revealed that UCD patients had better survival than MCD, but the difference was still not statistically significant ($P = 0{\cdot}142$) (Fig 3C). Thus statistically, we could not find centricity (UCD or MCD) and histopathology types (HV or PC) as important outcome factors in this series of patients. But the centricity and pathology type are important clinical factors, and further analysis should be undertaken when more CD patients are collected in the future.

In this series of CD patients, 33·3% (38/114) were diagnosed as PNP. Clinical classification showed that 32 of these cases were UCD and pathological classification showed that 32 were HV and 5 were Mix. These patients' main complaints were ulcers and erosions of mucosa, and polymorphic cutaneous eruptions that could mimic pemphigus vulgaris (erosions and blisters), erythema multiforme and/or lichen planus. Serum analysis revealed auto-antibodies against Dsg3 (in 8/13 tested cases) as well as a series of plakin family proteins (including envoplakin, periplakin, desmoplakin, and bullous pemphigoid antigen 1) and the alpha2-macroglobulin-like-1 protein (Poot *et al*, 2013). These patients also showed solitary tumour masses in the internal regions – usually in the mediastinum, retroperitoneal or pelvic cavities. Skin and mucosal lesions often achieved remission after surgical removal of the tumours.

Notably, PNP can occur in association with several neoplasms – mainly lymphoproliferative disorders, including non-Hodgkin lymphoma (NHL), chronic lymphocytic leukaemia, CD and thymoma (Anhalt *et al*, 1990). In China, CD is the neoplasm most frequently associated with PNP (Wang *et al*, 2005a). In CD, thymoma, and follicullar dendritic cell sarcoma (FDCS), the auto-antibodies detected in PNP patients may be at least partly secreted by tumour cells (Wang *et al*, 2004, 2005b) and tumour mass removal can lead to temporary or permanent remission of the skin lesions. This further suggests that CD with PNP is a unique subtype of CD, possibly with a predisposing genetic background (Liu *et al*, 2008). However, to date, there is no direct evidence supporting this 'auto-secreting' hypothesis, and the source of antibodies in kidney disease and AIHA or ITP remains unclear. Further studies in this field are needed.

Castleman disease is generally considered a lympho-proliferative disorder, rather than a malignant disease. Thus, CD may originate from multi-clonal sources, as has been confirmed in previous studies in HIV-positive CD patients (Soulier *et al*, 1995). However, this concept has been challenged by growing evidence. Wang *et al* (2004) showed that that seven PNP patients were positive for immunoglobulin heavy chain recombination, indicating monoclonal proliferation of B lymphocytes or plasma cells. Recently, methylation-specific human androgen receptor α gene analyses were performed and a monoclonal pattern in 74% of cases of HV variant CD (17/23) was found (Chang *et al*, 2014). In our present series, IFE assay revealed monoclonal immunoglobulin in 11 of 37 cases of MCD. So, at least, some CD patients are monoclonal.

In the present patient series, within 1–4 years after the diagnosis of CD, patients were additionally diagnosed with Hodgkin lymphoma ($n = 1$), NHL ($n = 1$), multiple myeloma ($n = 1$), myelodysplastic syndrome, refractory anaemia with excess of blasts (MDS-RAEB II, $n = 1$). Two patients were diagnosed with FDCS synchronously with CD. MDS was considered to be secondary to chemotherapy. In other patients, tumours were assumed to have transformed from pre-existing CD. However, no direct evidence supports this 'transformation' hypothesis, and we cannot rule out the possibility that two tumours arise synchronously.

Currently, there are no generally accepted treatment regimens available for CD (Castleman *et al*, 1956; Dong *et al*, 2009; Fajgenbaum *et al*, 2014). In cases of UCD without PNP, surgical excision was usually followed by a 'watch and wait' strategy. CD patients with PNP often received IVIG and steroids in combination with tumour mass removal. Skin injury remission was achieved in many cases, but some patients would still progress to BO, either before or after surgery. The available treatment options did not alter the adverse prognosis of PNP patients. Rituximab and autologous peripheral blood stem cell transplantation should been tested in these patients.

The past decade has seen progress regarding the treatment of MCD. Thalidomide (Lee & Merchant, 2003; Starkey *et al*, 2006), lenalidomide (Szturz *et al*, 2012), and Bortezomib (Hess *et al*, 2006) were proven effective in several MCD patients. Rituximab has been used in HIV- and/or HHV8-positive MCD patients (Gérard *et al*, 2007, 2012). Anti-interleukin 6 (IL6) receptor antibodies have long been used for MCD treatment (Galeotti *et al*, 2012; Nagao *et al*, 2014). The humanized anti-IL6 monoclonal antibody, siltuximab, was recently proven to be effective against MCD in a randomized multi-centre clinical trial (van Rhee *et al*, 2014) and has now been approved for use in MCD patients in US and Europe (Markham & Patel, 2014). Among these new therapeutic options, none has yet been generally accepted as first-line treatment. As shown in the present study, due to the high heterogeneity of CDs, the most important issue in CD treatment may be to determine who needs therapy. Future studies should investigate the possibility of stratified or individualized therapy.

The present study has several obvious limitations. First, it was a retrospective study and some laboratory data were not available. Second, the CD patient population was from one single centre, which creates a bias. The proportion of PNP patients in this CD population was higher than in other published papers, possibly due to this bias. Despite

these limitations, this study provides a useful panoramic view of CD, a highly complicated and heterogeneous disease. A major conclusion of this study is that the presence of PNP should be paid great attention in clinical practice.

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Author contributions

Y.D. and H.R. designed the research; Y.D. wrote the paper; M.W., W.L., X.C., Y.S., Z.L., Y.L., J.O. and Z.Q. contribute to patient follow-up and data collection; L.W. and S.Z. analysed the data; L.N. reviewed the pathological data.

Competing interests

The authors have no competing interests.

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