A Real-world Study on a Large Retrospective Cohort of Castleman Disease from a Single Center

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Abstract

Castleman disease(CD) is a rare lymphoid tissue proliferative disease with an increasing focus on etiology and treatment in recent years. The consensus on CD diagnosis and treatment has been published by several organizations, playing an important role in promoting cooperation on CD managements and investigations among different teams. Based on the last 15-years retrospective real-world data from Peking University First Hospital (PKUFH), we re-classified and re-evaluated the clinical and pathological information of patients with pathologically suspected diagnosis of CD. A total of 203 patients were included in our study, in which the diagnosis of CD was confirmed in 189 cases, including 118 patients with unicentric CD (UCD, n = 118, 62.4%) and 71 patients with multicentric CD (MCD, n = 71, 37.6%). 44.1% (n = 52) of UCDs in our cohort were complicated with Paraneoplastic Pemphigus (PNP). The treatment of UCD is mostly surgical resection, with a 5-year overall survival(OS) 88.1%. Patients with PNP had a poorer prognosis than those without PNP [82.9% (95% CI 123–178) vs 92.8% (95% CI 168–196), log-rank P = 0.041). The rate of concurrent systemic symptoms was 74.6% (n = 53), and renal involvement occurred in 49.3% (n = 35) MCD patients. The MCD treatments were mainly chemotherapy regimens, with a 5-year OS of 77.6% (95% CI, 143–213). In conclusion, UCDs have a better overall prognosis than MCDs. But the prognosis of those complicated with PNP was poor. Differential diagnosis of MCD is difficult. MCD treatment in China is heterogeneous. The inaccessibility of anti-IL-6-targeted drugs in China may contribute to the poor prognosis of MCD.

Key Points

- A large cohort of CD from a single center were re-classified and re-evaluated according to the 2017 CDCN diagnostic criteria.
- In the real-world setting, UCD patients complicated with PNP and MCD have poor prognosis even after intensive therapeutic treatments.

Introduction

Castleman disease (CD), which was first reported in 1954 by Benjamin Castleman, is a highly heterogeneous lymphoproliferative disorder characterized by single or multiple lymph node enlargements with or without symptoms of multiple organ system involvements. In the United States, 6600–7700 people are diagnosed with CDs each year, of which 75% are Unicentric Castleman Disease (UCD) [1], but its incidence is often underestimated due to difficulties in diagnosis[2]. CD shares a spectrum of clinical and histopathological features with hematological disorders, autoimmune diseases, tumors and infectious diseases, making the differential diagnosis difficult. Recently, various diagnostic criteria and treatment consensus for CD have been released by several CD organizations. Castleman Desease Collaborative Network (CDCN) proposed a unified system of classification for CD in 2017, which divided CD into UCD and multicentric CD (MCD), and MCD encompasses three distinct clinicopathological subtypes: idiopathic MCD (iMCD), human herpes virus-8 (HHV-8) associated MCD (HHV8-MCD) and POEMS

(Polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes)-related MCD (POEMS-MCD). iMCD can be further classified into iMCD-TAFRO (Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis, and Organomegaly) and non-specific iMCD (iMCD- not otherwise specified, iMCD-NOS) [3–5]. From a histopathological perspective, CD can be divided into three groups: a) Hyaline-vascular (HV) subtype, b) plasma cell (PC) subtype, and c) mixed (Mix) subtype.

The treatment options, especially the therapy of MCD are generally highly heterogeneous before the treatment consensus. Now the anti-IL-6 therapy has been chosen as the front-line option in those regions where the drugs are available. But in mainland China, where the Siltuximab is still inaccessible, the treatment of MCD is mainly lymphoma-like chemotherapy, and the prognosis of this CD subtype was compromised. Herein, we review a series of pathologically suspected CD patients from Peking University First Hospital in the past fifteen years. These patients were reclassified according to the 2017 CDCN diagnostic criteria, their follow-up data were analyzed aiming to provide useful real-world information for the clinical and pathological experts who are working with CDs.

Methods

Participants of this study

This is a retrospective real-world cohort study on 203 consecutive adult patients (≥ 18 years) with pathologically suspected CD, who were hospitalized by Peking University First Hospital (PKUFH) between February 2007-January 2022. Patients with autoimmune diseases, neoplastic diseases, and infectious diseases were then excluded based on the 2017 CDCN diagnostic criteria[3] (Table 1). The main data information obtained included basic patient characteristics, histopathology, blood routine test, liver and kidney function, organ involvement, histopathology, clinical comorbidities, diagnosis, and treatment. The study was approved by the ethics committee of PKUFH (No.2022-174-002).

Table 1
The clinical and laboratory characteristics of UCD and MCD patients

Chracteristic	UCD(n, %)	MCD(n, %)	*P*
Number	118(62.4)	71(37.6)	-
Gender			0.182
Male	53(44.9)	39(54.9)	-
Female	65(55.1)	32(45.1)	-
Age(years)	31.5	47	0.041
Systemic symptoms	41(34.7)	53(74.6)	< 0.001
PNP	52(44.1)	3(4.2)	< 0.001
BO	15(12.7)	2(2.8)	0.043
Renal involvement	3(2.5)	35(49.3)	< 0.001
Serous cavity effusion	3(2.5)	26(36.6)	< 0.001
Hepatomegaly	0(0)	9(12.7)	< 0.001
Splenomegaly	0(0)	20(28.2)	< 0.001
Blood system involvement	7(5.9)	17(23.9)	< 0.001
Tumor transformation	1(0.8)	3(4.2)	0.150
Elevated CRP/hsCRP(mg/L)	28/51(54.9)	39/55(70.9)	0.015
Positive hematuria immunofixation electrophoresis	0	20/55(36.4)	0.085
Elevated LDH(IU/L)	5/59(8.5)	10/60(16.7)	0.178
Elevated ESR(mm/h)	21/41(51.2)	41/62(66.1)	0.130
Elevated IL-6(pg/ml)	5/9(55.6)	16/21(76.2)	0.389
Elevated VEGF(pg/ml)	0	8/11(72.7)	0.128
Positive ANA	11/19(9.3)	26/52(50)	0.556
Positive ANCA	1/10(0.8)	6/42(14.3)	1.00
Hb(g/L)	133.5 ± 5.358	106 ± 3.489	< 0.001

UCD: Unicentric Castleman disease; MCD: Multicentric Castleman disease; PNP: Paraneoplastic pemphigus; BO: Bronchiolitis obliterans; CRP: C-reactive protein; hsCRP: Hypersensitive C-reactive protein; LDH: Lactate dehydrogenase; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; VEGF: Vascular endothelial growth factor; ANA: Antinuclear antibody; ANCA: Anti-Neutrophil Cytoplasmic Antibodies; Hb: Hemoglobin; PLT:platelet; WBC: White blood cell; ALB: Albumin; Scr: Creatinine; Ig: Immunoglobulin.

Chracteristic	UCD(n, %)	MCD(n, %)	*P*
PLT(10^9/L)	251.5 ± 26.678	226 ± 17.843	0.079
WBC(10^9/L)	5.90 ± 0.827	6.60 ± 0.695	0.218
ALB(g/L)	38.55 ± 1.746	33.4 ± 0.854	< 0.001
Scr(umol/L)	64.4 ± 3.076	91.45 ± 18.806	< 0.001
IgG(g/L)	11.80 ± 2.212	15.25 ± 2.378	0.068

UCD: Unicentric Castleman disease; MCD: Multicentric Castleman disease; PNP: Paraneoplastic pemphigus; BO: Bronchiolitis obliterans; CRP: C-reactive protein; hsCRP: Hypersensitive C-reactive protein; LDH: Lactate dehydrogenase; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; VEGF: Vascular endothelial growth factor; ANA: Antinuclear antibody; ANCA: Anti-Neutrophil Cytoplasmic Antibodies; Hb: Hemoglobin; PLT:platelet; WBC: White blood cell; ALB: Albumin; Scr: Creatinine; Ig: Immunoglobulin.

Classification of CDs

Pathological and clinical classification of CDs were based on the 2017 CDCN diagnostic criteria[3]. Generally speaking, histopathological features of CD include abnormal degenerative or hyperplastic germinal centers, increased follicular dendritic cells, vascular hyperplasia, dilated set areas, and increased interfollicular plasma cells. CD was classified into hyaline vascular, plasma cell, and mixed types based on these pathological features. All cases were diagnosed independently by two or more pathologists after reviewing the slides. In addition, HHV-8 detection was performed by either immunohistochemical staining (LANA-1) or peripheral blood HHV8-DNA testing, and a positive result was diagnostic of HHV8-MCD. Based on the 2017 CDCN diagnostic criteria[3], CD was clinically divided into UCD and MCD, with the latter being subdivided into HHV8-MCD, POEMS-MCD and iMCD. Then iMCD includes two variants: iMCD-TAFRO and iMCD-NOS [3,6].

Statistical analysis

All enrolled patients were followed up by interviews, telephone interviews, or electronic medical records till February 28th, 2022. PFS was defined as the time from the onset of CD to progression of the disease, death, or last follow-up, whichever occurred first. Overall survival (OS) was defined as the time from the onset of CD to death from any cause or last follow-up. For continuous and categorical variables, medians (ranges), frequencies(n), and percentages where applicable were used. For the comparisons between UCD and MCD groups, we used descriptive statistics, two-sample tests, and Pearson's chi-square where appropriate. Log-rank test was employed to determine OS differences between treatment groups. Multivariable Cox regression analysis was performed to assess the associations between patient characteristics and OS. A p value of < 0.05 was considered statistically significant for all analyses. All statistics were carried out using IBM SPSS v26, R Studio, and Origin2021.

Results

Patient Characteristics

A total of 203 consecutive hospitalized patients with suspected CD in histopathology in our center in the past 15 years were enrolled in this study. According to the 2017 CDCN diagnostic criteria[3], finally, there were 189 patients diagnosed as CD after excluding 8 cases of Follicular dendritic cell sarcoma (FDCS) and 6 cases of IgG4-related disease (IgG4RD) (Fig. 1). The confirmed 189 CDs included 118 cases of UCD and 71 cases of MCD, the latter was subdivided into 16 patients with POEMS-MCD and 55 cases of iMCD. The iMCDs were composed of 15 cases of iMCD-TAFRO and 40 patients with iMCD-NOS. No HHV8-MCD patients were found in this cohort.

The clinical and laboratory characteristics of the 189 CD patients were summarized in Table 1. Briefly, the male to female ratio of UCD patients was 1:1.2 (53:65), and the median age of onset was 31.5 years. Compared to MCD patients, more patients with UCD in our cohort complicated with Paraneoplastic pemphigus (PNP) (44.1% vs 4.2%; $P < 0.001$) and Bronchiolitis obliterans (BO) (12.7% vs 2.8%; P = 0.042) Patients with MCD have more other systemic symptoms and signs than UCD (74.6% vs 34.7%; $P < 0.05$). Splenomegaly (28.2% vs 0; $P < 0.05$), hepatomegaly (12.7% vs 0; $P < 0.05$), pleural effusion and ascites (36.6% vs 2.5%; $P < 0.05$), and hematologic involvement (23.9% vs 5.9%; $P < 0.05$) were more frequent in MCD. There was no significant difference in tumor transformation rate between UCD and MCD patients (0.8% vs 4.2%). One UCD patient transformed to T-lymphoblastic leukemia/lymphoma. Three MCD patients developed other hematological malignancies, of which two were lymphomas and the rest one was myelodysplastic syndrome.

In terms of laboratory characteristics, MCD patients had lower hemoglobin ($P < 0$ .001) and albumin levels ($P < 0.001$) than UCD patients, C-reactive protein or hypersensitive C-reactive protein and creatinine were elevated compared to the UCD patients (P values 0.015 and < 0.001, respectively), positive hematuria immunofixation electrophoresis, polyclonal immunoglobulin level, white blood cell, lactate dehydrogenase, erythrocyte sedimentation rate, etc, did not differ between UCD and MCD groups (Table 1).

The majority of the pathological subtype in the 118 UCD patients were HV variants, accounting for 80.5% (n = 95) of all cases. The PC subtype accounted for 7.6% (n = 9), and the Mix subtype for the rest 11.9% (n = 14). About half of the MCD patients were PC subtype (n = 35, 49.3%), Mix and HV subtype splited the rest 50.8%, both of them accounting for 25.4% (n = 18) each (Fig. 2B).

Treatment and prognosis

All of the 118 UCD patients underwent lymph node biopsy or surgical resection. Patients with PNP were generally treated with hormone-based therapy after the surgery (Supplement Table 1). In UCD patients without PNP, 90.9% (n = 60) of patients experienced surgical resection only. The 5-year OS was 88.1% (Fig. 3A, 95% CI, 153–184) in the UCD group, and UCD patients complicated with PNP had a poor prognosis. Statistically significant unfavorable OS was seen in the survival curves of UCD patients with

PNP compared to those without PNP, with 5-year OS 82.9% (95% CI, 123–178) and 92.8% (95% CI, 168–196) respectively (Fig. 3B, log-rank $P = 0.041$). The differences were not statistically significant when a multifactorial analysis was performed using the Cox regression analysis, incorporating P value of < 0.15 in the univariate analysis as well as clinically significant elements (Table 2), including the presence of comorbidities, systemic symptoms, combined PNP, hypoalbuminemia, and hyperimmunoglobulinemia.

Table 2
Univariable analysis of UCD and MCD

Candidate factor	Univariable analysis			
	OS			
	UCD		MCD	
	HR(95% CI)	P	HR(95% CI)	P
Gender	0.86(0.69–1.077)	0.738	1.29(0.89–1.86)	0.656
Complications	1.61(1.30–1.98)	0.004	0.37(0.22–0.63)	0.013
Systemic symptoms	0.53(0.42–0.68)	< 0.001	3.12(1.96–4.97)	0.196
PNP	0.51(0.42–0.61)	0.041	13.80(3.51–54.31)	0.542
BO	0.72(0.57–0.92)	0.752	2.39(0.84–6.81)	0.691
Renal involvement	0.10(0.04–0.31)	0.624	3.86(2.86–5.21)	0.999
Elevated CRP/hsCRP	1.32(0.89–1.98)	0.993	0.77(0.52–1.15)	0.173
Elevated LDH	1.56(0.74–3.26)	0.476	0.72(0.48–1.09)	0.795
Elevated ESR	1.44(0.90–2.30)	0.974	0.78(0.55–1.10)	0.635
Elevated IL-6	1.87(0.65–5.38)	0.666	0.73(0.39–1.37)	0.861
Hypoalbuminemia	0.70(0.55–0.90)	0.105	1.74(1.20–2.53)	0.561
Anemia	0.46(0.33–0.64)	0.128	2.89(1.98–4.24)	0.945
Hyperimmunoglobulinemia	2.78(0.89–8.68)	0.546	0.78(0.62–0.97)	0.818

UCD: Unicentric Castleman disease; MCD: Multicentric Castleman disease; OS: Overall Survival; HR:Hazard Ratio; CI: Confidence Interval; PNP: Paraneoplastic pemphigus; BO: Bronchiolitis obliterans; CRP: C-reactive protein; hsCRP: Hypersensitive C-reactive protein; LDH: Lactate dehydrogenase; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6.

63% (n = 44) of patients with MCD received chemotherapy, with front-line regimens consisting of main glucocorticoids or lymphoma-like chemotherapy regimens, while the refractory and relapsed MCD patients received immunomodulators, rituximab, or bortezomib-based regimens (Supplement Table 2). Although the difference was not statistically significant between MCD and UCD groups [Figure 3C, 5-year OS 77.6% (95% CI, 143–213) vs 88.1% (95%CI, 153–184); log-rank $P = 0.13$], the overall survival curve had

a downward trend in the MCD group. However, when MCD compared with UCD patients without PNP, the difference was statistically significant [Figure 3D, 5-year OS 77.6% (95% CI, 140–211) vs 92.6% (95%CI, 168–196); log-rank $P = 0.018$]. A univariate analysis of data from MCD patients revealed that only patients with complications affected prognosis (Table 2, log-rank $P = 0.013$). There was no statistical difference in survival between patients in MCD patients with or without renal involvement (Fig. 3E, log-rank $P = 1.00$). In this cohort, CDs with complications were shown to have a poor prognosis compared to those without complications, with 5-year OS 90.6% (95% CI, 166–194) and 79.0% (95%CI, 142–207) respectively (Fig. 3F, log-rank $P = 0.007$).

Discussion

In this study, we retrospectively collected the information of 203 hospitalized patients with CD-like pathologically features in the past 15 years and re-analyzed these patients according to the 2017 CDCN criteria. 93.1% (n = 189) of these patients were confirmed to be CDs, of which 37.6% (n = 71) were HHV8-negative MCD and finally only 47 cases (29%) met the CDCN diagnostic criteria of iMCD.The ratio of iMCD was comparable to those reported previously. This suggested that the differential diagnosis of iMCD was still a challenge for pathologists and clinicians. In this cohort, eight patients with CD-like pathological features were subsequently diagnosed as FDCSs. Due to the variety of the pathological manifestations of CD, sometimes it is difficult to distinguish CD from thymoma, FDCS, and Hodgkin's lymphoma[9–11]. The diagnosis of iMCD requires the exclusion of infections, autoimmune diseases, primary or acquired immunodeficiency syndromes, and malignancies, of which the differentiation of PC-MCD and IgG4RD had always been a challenge in clinical practice[12–15]. Both of them have an appearance of generalized lymph node enlargement and extra-nodal involvement, and iMCD patients may have high serum IgG4 levels, whilst some IgG4RD patients may have CD-like pathological changes [16]. According to the most recent diagnosis and exclusion criteria for IgG4RD [7, 8], six patients with IgG4RD were excluded, and two patients previously diagnosed with IgG4RD were re-diagnosed as iMCD. The 2021 IgG4RD guidelines[7] state that even if the diagnostic criteria for IgG4RD are met, the presence of elevated CRP, IgA, or IgM in clinical indicators or pathology with any of the manifestations of lamellar-like mature plasma cell proliferation, high iron-containing heme deposition, and neutrophil infiltration cannot directly diagnose IgG4RD, the diagnosis of MCD takes precedence over IgG4RD. To summarize, diagnosing IgG4RD solely based on lymph node pathology without evidence of organ involvement should be interpreted cautiously. Clinical response to glucocorticoid therapy will favor the diagnosis of IgG4RD, and the IgG4/IgG ratio of serum and tissues will be also informative[17], while the most recent IgG4RD diagnostic and exclusion criteria can help distinguish IgG4RD from MCD effectively.

Controversy remains regarding the transformation of CD into other tumors. Generally, iMCD patients are at increased risk of the second tumorigenesis. One PC variant UCD patient in this study transformed to T-lymphoblastic leukemia/lymphoma, with the onset of transformation occurring 2 years after the CD diagnosis. It is reported in the literature that iMCD patients have an increased risk of lymphoma, which is usually regarded as typical Hodgkin's lymphoma (usually mixed cell type), diffuse large B-cell lymphoma,

mantle cell lymphoma, and peripheral T-cell lymphoma[18]. Three other patients with iMCD in this cohort transformed to marginal zone B-cell with large B-cell lymphoma transformation, and myelodysplastic syndrome, with transformation times of 2, 10, and 1.2 years, respectively. In the four cases of CD in which tumor transformation occurred in this study, the diagnosis of the second tumor was more than 1 year after the initial diagnosis of CD, and retrospective analysis of pathological biopsy specimens of the initial CD diagnosis revealed no evidence of the presence of subsequent tumors. The specific mechanism by which tumor transformation occurs in CD patients is unclear and may be related to the production of IL-6 and other important cytokines. Further clonality analysis of both tumor cells was needed to clarify the possible mechanisms of CD transformation.

The treatment of UCD in our patients was divided into two categories: those UCD patients without complications are usually followed up after surgery or biopsy. Patients complicated with PNP/BO still require vigorous treatment before and after surgical resection. But these patients still have a poorer prognosis than those without complications, mostly dying due to pulmonary infection and respiratory failure, consistent with previous studies[19]. In a former study conducted in our center, PNP was shown to be an independent risk factor for poor prognosis in UCD[19,20]. The proportion of PNP and BO in our group of CD patients was high than in other centers, which may be due to a fact that the dermatology department of our hospital is a PNP referral center in China. This bias in single-center studies should be rectified by multicenter data. The treatment of MCD varies significantly in different regions, siltuximab has become the first-line treatment in Europe and the United States[3]. A study that included[7,8] patients with iMCD showed that siltuximab significantly improved patients' anemia, the inflammatory marker levels, and systemic symptoms compared to placebo[21]. In China, owing to a lack of anti-IL-6-targeted drug accessibility, front-line treatment for MCD patients is rarely based on drugs targeting IL-6 or its receptors. In our cohort, the lymphoma-like regimen was the main treatment option, with rituximab- or bortezomib-based regimen for refractory and relapsed patients. A nationally reported phase II clinical trial on 25 patients with primary iMCD treated with oral thalidomide, cyclophosphamide, and prednisone showed that 48% of patients achieved oncologic and clinical symptomatology remission for more than 24 weeks[22]. Another prospective study of 24 patients with relapsed refractory iMCD demonstrated the safety and efficacy of the bortezomib-cyclophosphamide-dexamethasone (BCD) regimen, with an estimated 1-year PFS and OS of 79% and 92%, respectively[23]. Previous four large studies of iMCD cases reported 5-year OS of 55%, 55%, 65%, and 77%, respectively[24–27], whereas the 5-year OS of the iMCD population in this study was over 80%, possibly related to the higher rate of loss of follow-up rates, geographical differences, changes in diagnostic criteria, and small sample size. In short, Patients with MCD have a relatively poor prognosis. We did not find differences on survival between patients with MCD and UCD in this study, which may be attributed to a higher proportion of UCD patients combined with PNP.

There are some limitations in our study. First, as a retrospective study, the data were quite heterogeneous. Second, the available data were somewhat biased as a single-center study, for example, the percentage of UCD patients complicated with PNP was higher than reported in the literature. Future multicenter and

larger sample data will be more informative and accurate in illustrating the real-world status of CD diagnosis and treatment.

Conclusions

The clinicopathological data of 203 hospitalized patients from our center were re-analyzed according to the 2017 CDCN diagnostic criteria of CD. The results revealed that there are some difficulties in the diagnosis and treatment of CD in the real world. The differential diagnosis of iMCD is still a great challenge for pathologists and clinicians. Recently, the diagnostic and exclusion criteria of IgG4RD can be helpful to distinguish IgG4RD from iMCD. The prognosis of UCD patients complicated with PNP/BO was unfavorable albeit intensive therapeutic approach. There is greater heterogeneity in the treatment of MCD in China due to the inaccessibility of anti-IL-6-targeted drugs, being one of the reasons for the poor prognosis of MCD.

Declarations

Conflict of interest statement

All authors disclosed no relevant relationships.

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Figures

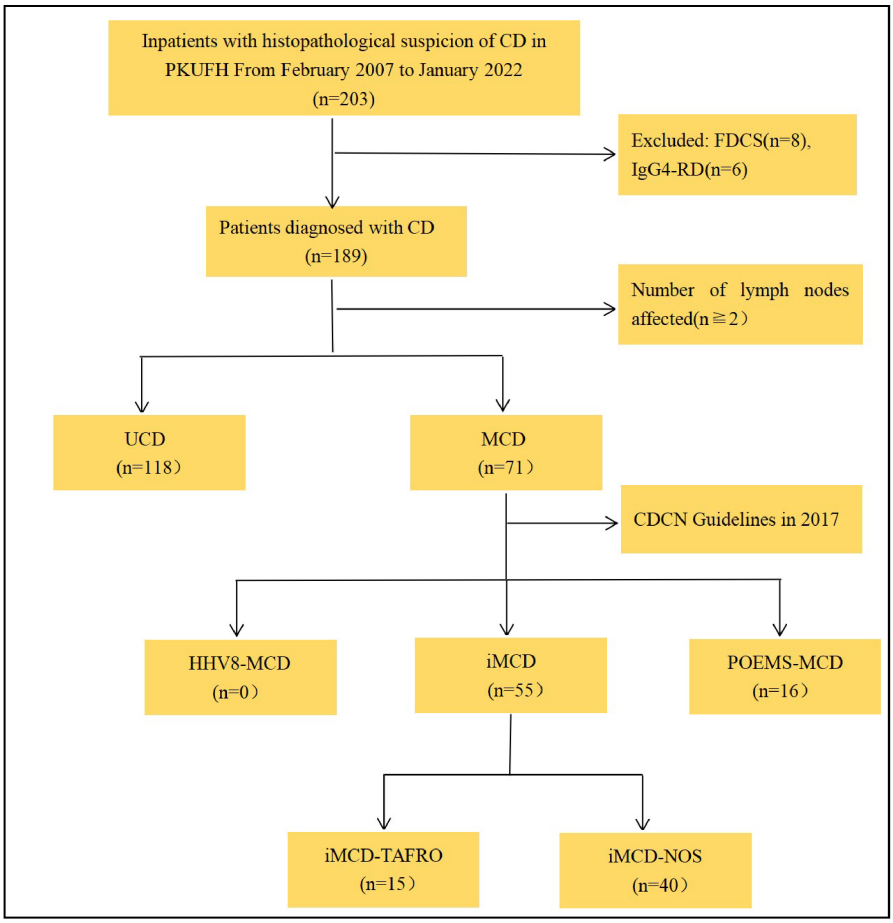

Figure 1

Patient selection and classification flowchart.

CD: Castleman disease,

FDCS: Follicular Dendritic Cell Sarcoma,

IgG4-RD: IgG4-related disease,

UCD: Unicentric Castleman disease,

MCD: Multicentric Castleman disease,

iMCD: idiopathic Multicentric Castleman disease,

POEMS: Polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes,

TAFRO: Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis and Organomegaly,

iMCD-NOS: iMCD-not otherwise specified.

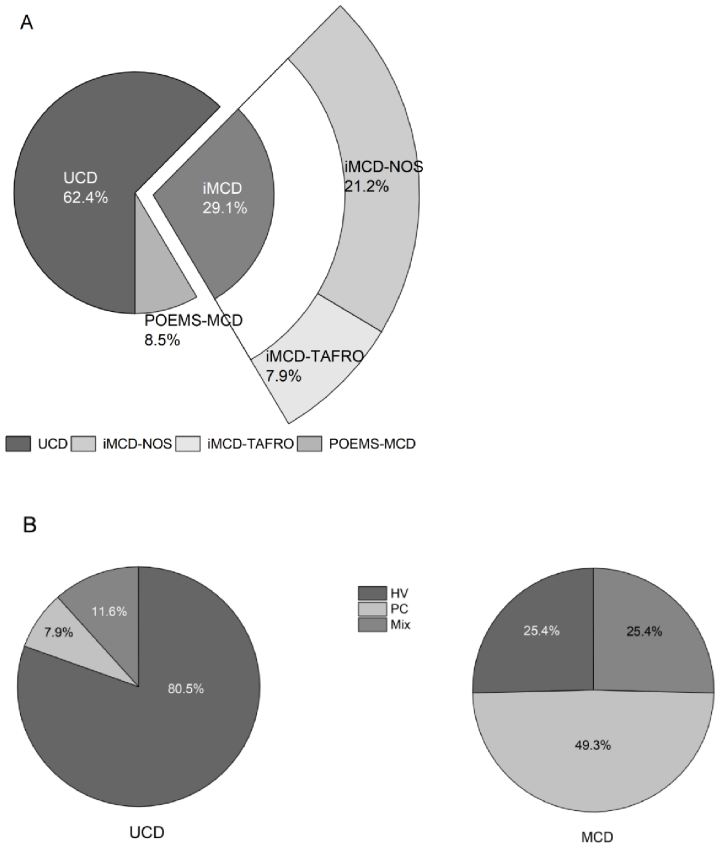

Figure 2

The constitution of CDs in our cohort. A. the clinical subtypes of CDs; B. the percentage of pathological subtypes of UCD and MCD.

CD: Castleman disease,

UCD: Unicentric Castleman disease,

MCD: Multicentric Castleman disease,

iMCD: idiopathic Multicentric Castleman disease,

TAFRO: Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis and Organomegaly,

iMCD-NOS: iMCD-not otherwise specified,

HV: Hyaline-vascula subtype,

PC: Plasma cell subtype,

Mix: Mixed subtype.

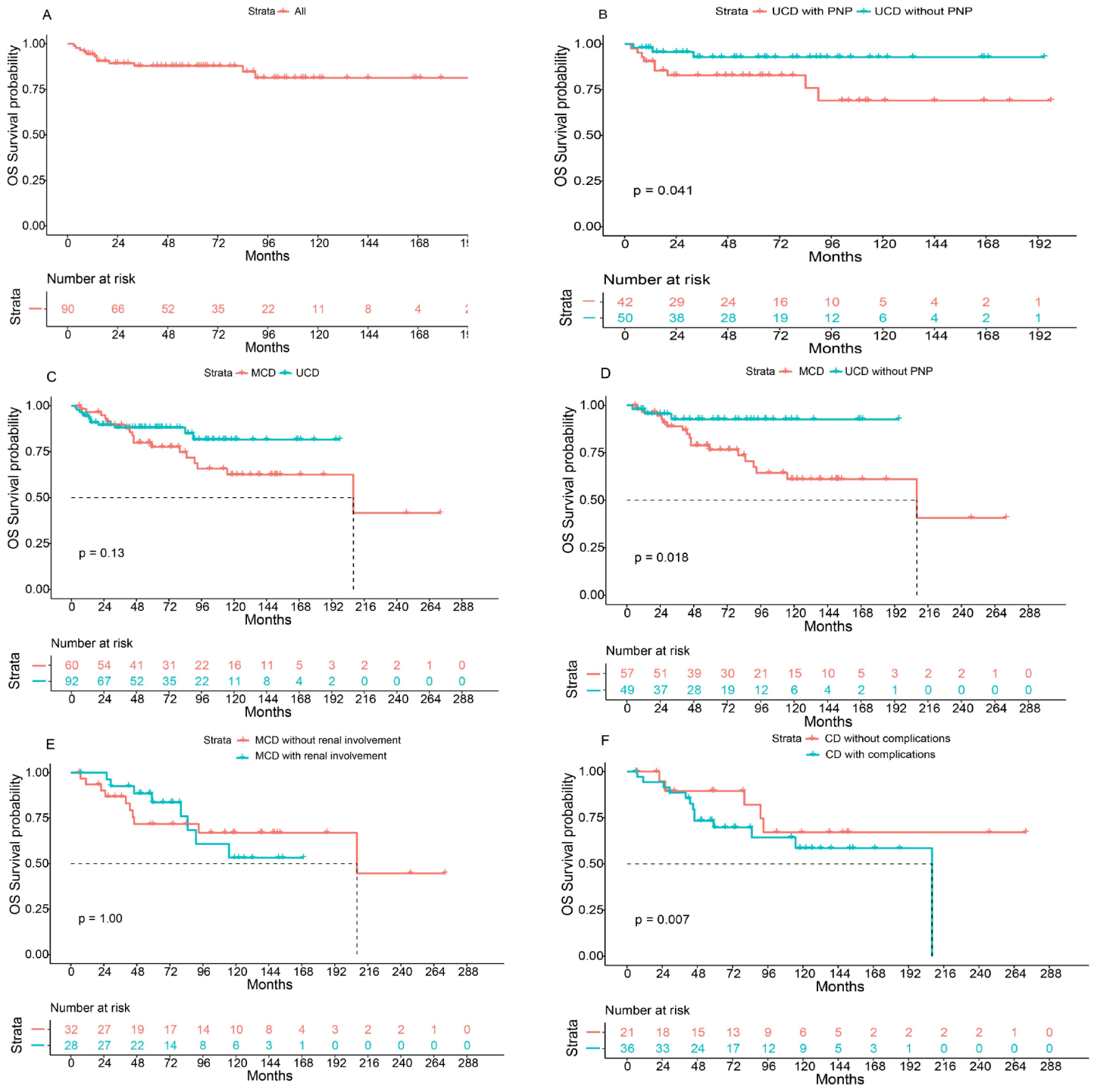

Figure 3

The survival analysis of CD patients.

A. Analysis of UCD survival curve;

B. Overall survival analysis of UCD patients based on with/without PNP;

C. Subgroup overall survival analysis based on UCD and MCD;

D. Subgroup overall survival analysis based on UCD without PNP and MCD;

E. Effect of renal involvement on MCD survival;

F. Difference of iMCD-NOS and iMCD-TAFRO on survival.

UCD: Unicentric Castleman disease,

MCD: Multicentric Castleman disease,

PNP: Paraneoplastic pemphigus,

iMCD: idiopathic Multicentric Castleman disease,

TAFRO: Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis and Organomegaly,

iMCD-NOS: iMCD-not otherwise specified

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementmaterial.docx
- Supplementmaterial2.docx