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The full spectrum of Castleman disease: 273 patients studied over 20 years

Eric Oksenhendler,[1,2,3] **David Boutboul,**[1,3] **David Fajgenbaum,**[4] **Adrien Mirouse,**[1] **Claire Fieschi,**[1,3,5,6] **Marion Malphettes,**[1,3,5] **Laetitia Vercellino,**[7] **Véronique Meignin,**[3,8] **Laurence Gérard**[1,2,3] **and Lionel Galicier**[1,2,3]

[1]*Department of Clinical Immunology, Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris (APHP),* [2]*EA3518, Université Paris Diderot Paris 7,* [3]*National Reference Centre for Castleman Disease (CRMdC), Paris,France,* [4]*Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA,* [5]*Inserm U1126, Centre Hayem, Hôpital Saint-Louis,* [6]*Université Paris Diderot Paris 7,* [7]*Department of Nuclear Medicine, Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris (APHP), and* [8]*Department of Pathology, Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris (APHP), Paris, France*

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Correspondence: Professor Eric Oksenhendler, Département d'Immunologie Clinique, Hôpital Saint-Louis, 1 avenue Claude Vellefaux, 75010 Paris, France.
E-mail: eric.oksenhendler@aphp.fr

Summary

The spectrum of Castleman disease (CD) has considerably extended since its first description in 1956. Recently, an international collaborative working group has reached consensus on the diagnostic criteria and classification of CD. We herein report 273 patients with lymph node histopathology consistent with CD and investigate the newly established diagnostic criteria. Twenty of these patients with Castleman-like histopathology were removed from analyses, because they were diagnosed with an exclusionary disorder (18 with haematological malignancy). Among the 253 remaining patients, 57 were considered unicentric CD (UCD), 169 were multicentric CD associated with Human Herpesvirus 8 (HHV-8+MCD), including 140 patients with human immunodeficiency virus (HIV) infection and 29 patients without HIV infection, and 27 were HHV-8 negative/idiopathic multicentric CD (iMCD). 2-(^{18}F)fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography was useful in 62 patients for staging/classification of the disease and for excluding associated lymphoma. UCD was mainly associated with hyaline-vascular histopathological features, and most patients were asymptomatic. Of the 27 patients that we had originally diagnosed with iMCD, 26 met the newly established diagnostic criteria. Patients with iMCD and HHV-8+ MCD demonstrated similar characteristics, including fever, splenomegaly, cytopenia and inflammatory symptoms. However, the disease was more aggressive in HHV-8+ MCD, particularly in HIV-infected patients.

Keywords: Castleman disease, HHV-8, HIV, PET-CT.

Since the first description by Benjamin Castleman, 60 years ago, of a peculiar histological pattern observed in a series of lymph node lesions of the mediastinum, the spectrum of the diseases considered under his eponym has considerably extended (Castleman *et al*, 1956; Weisenburger *et al*, 1985; Waterston & Bower, 2004; Wang *et al*, 2016). Castleman disease (CD) now encompasses several distinct clinicopathological disorders at the intersection of haematology, immunology, oncology, rheumatology and virology that share a spectrum of histopathological features. The initial description of the disease referred to a usually idiopathic and asymptomatic solitary lesion showing characteristic hyaline vascular histopathological changes. In the following decades « variants » have been described according to several dichotomies: unicentric *versus* multicentric, hyaline-vascular *versus* plasmacytic, asymptomatic *versus* symptomatic, and the possible associations with haematological malignancies (Larroche *et al*, 2002), autoimmune disorders (Carrington *et al*, 1990; Miltenyi *et al*, 2009; Muskardin *et al*, 2012), human immunodeficiency virus (HIV) (Oksenhendler *et al*, 1996) or herpesvirus-8 (HHV-8) infections (Soulier *et al*, 1995; Bower, 2010). Recently, an international collaborative working group has reached consensus definitions and classification, defining diagnostic criteria for CD for the first time (Fajgenbaum *et al*, 2016).

Three distinct entities can now be considered at diagnosis (Fajgenbaum *et al*, 2017): (i) Unicentric CD (UCD), usually exhibiting hyaline vascular morphological changes, often asymptomatic, and surgical excision is often curative; (ii) Idiopathic multicentric CD (iMCD), usually associated

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with plasmacytic morphological changes and involving inflammatory symptoms, polyclonal lymphoproliferation, cytopenias and, in some cases, life-threatening multiple organ dysfunction; (iii) HHV-8 associated MCD (HHV-8+ MCD), in which large plasmablastic cells infected with HHV-8 – often in the context of HIV infection – drive a cytokine storm, presents with similar features to iMCD. In parallel, and before considering the diagnosis of CD, a number of associated diseases that can exhibit Castleman-like features on lymph node biopsy, should be ruled out, while some autoimmune diseases may actually be considered as true complications of CD. In most cases of MCD, interleukin-6 (IL6), either human IL6 in iMCD or viral IL6 in HHV-8+ MCD, plays a major role in the pathophysiology of the clinical and biological symptoms of the disease (Yoshizaki *et al*, 1989; Brandt *et al*, 1990; Oksenhendler *et al*, 2000; Uldrick *et al*, 2012). Therefore the IL6 pathway has been considered as a major target for therapy in iMCD (Nishimoto *et al*, 2000; van Rhee *et al*, 2014), whereas targeting B cells with rituximab has been shown to be very effective in HHV-8+ MCD (Bower *et al*, 2007; Gérard *et al*, 2007).

Herein, we review the largest series of CD patients from a single centre reported to date, investigate concordance with newly-established diagnostic criteria, and discuss possible « grey zones » in the current classification.

Patients and methods

Patients

All patients with biopsy-proven histopathological features consistent with a CD diagnosed at Hôpital Saint Louis (Paris, France) over a 20-year period were reviewed for analysis. Patients with HIV infection had been included in a prospective registry on HIV-associated lymphoproliferative disorders and HIV negative patients had been included in a national registry on CD.

Pathology

Eligibility was based on the pathological diagnosis. The biopsy specimens have not been specifically reviewed for the present study but were discussed with the pathologist at entry in both registries.

The histopathological features consistent with a CD diagnosis included abnormal regressed or hyperplastic germinal centres, follicular dendritic cells prominence, hypervascularization, expanded mantle zones and interfollicular plasmacytosis. According to the grading of these pathological features, two ends of a pathological spectrum could be defined: a hyaline-vascular subtype and a plasmacytic subtype, with some lesions exhibiting mixed characteristics. In addition, HHV-8 specific staining (LANA-1) allowed detection of HHV-8 infected plasmablasts found in HHV-8+ MCD.

Classification

Classification and diagnostic criteria were based on the criteria recently established by an international collaborative group, the Castleman Disease Collaborative Network (www.cdcn.org). Classification was based on 4 steps: (i) exclusion of diseases that can present with Castleman-like histopathology on lymph node biopsy but that are considered to mimic CD; (ii) staging of the disease: Unicentric (one single lymph node station) *versus* Multicentric (disseminated disease); (iii) Testing for HHV-8 using specific immunohistochemistry; (iv) context of HIV infection (Fajgenbaum *et al*, 2017). The newly-established diagnostic criteria for iMCD were tested in this group for validation (Appendix S1).

Positron emission tomography/computed tomography (PET/CT) scans

A large number of patients were examined with a dual modality PET/computed tomography (PET/CT). PET using the glucose analogue 2-(^{18}F)fluoro-2-deoxy-D-glucose (FDG) was performed from the base of the skull to the upper thighs after a 6 h fast. The CT images were evaluated for the presence and distribution of enlarged lymph nodes (greater than 1 cm in short diameter) and splenomegaly. Nodes were designated positive if FDG activity was increased relative to that of adjacent normal soft-tissue. The SUV_{max} corresponds to the maximum standardized uptake value in a voxel within a circular region of interest drawn for each nodal group with FDG uptake.

Analysis

All patients with complete datasets were included in the analysis. Descriptive statistics were reported as medians (interquartile range) or numbers (%). Overall survival (OS) was calculated from CD diagnosis until June 2017 or death from any cause. Survival was estimated using the Kaplan–Meier product-limit method and compared using log-rank test. Statistical analysis was conducted using STATA Statistical Software version 14.2 (Stata Corp., College Station, TX, USA).

Results

Patients

A total of 273 patients with biopsy-proven histopathological features consistent with a diagnosis of CD and complete datasets were included in the study over a 20-year period. Among these patients, 20 were not considered as CD as they presented with another primary disease known to mimic CD histopathology. Most of them were lymphoid malignancies: Hodgkin lymphoma ($n = 7$), non-Hodgkin lymphoma ($n = 2$), POEMS (Polyneuropathy, Organomegaly,

Endocrinopathy, Monoclonal plasma cell disorder, Skin changes) Syndrome, $n = 5$), primary lymph node plasmacytoma ($n = 3$), follicular dendritic cell sarcoma ($n = 1$) or systemic diseases: systemic lupus erythematosus, Sjögren syndrome and IgG4-related disease (one each). Fifty-seven patients were considered to have localized disease or UCD. Among the 196 patients with multicentric lymphadenopathy or MCD, 169 were diagnosed with HHV-8+ MCD, including 140 patients with HIV infection and 29 patients without HIV infection. The remaining 27 patients were diagnosed with iMCD (Fig 1).

Unicentric Castleman disease

Fifty-seven patients presented with UCD. Most patients (72%) were Caucasians. Regarding possible related diseases, one patient had associated thymoma, one patient was an organ transplant recipient, one patient developed UCD in a lymph node station associated with recent vaccination and another in the pelvis after intrauterine device insertion. One patient was infected with HIV, but presented with classical HHV-8 negative hyaline-vascular UCD. The sex ratio was 1:1 and median age at diagnosis was 35 years, including 8 patients with a diagnosis before the age of 15 years (Table I). Most patients were asymptomatic or mildly symptomatic. The lymph node was detected after autopalpation of an enlarged lymph node or by chance on a radiographic examination (Fig 2A). Most lesions were located in the thoracic or cervical lymph node stations. When analysed by CT scan, the lymph node showed some features suggestive of Castleman lesion with calcifications or an intense homogeneous enhancement following contrast (Fig 2B). A few patients presented with severe complications, such as paraneoplastic pemphigus (PNP, $n = 4$), polyneuropathy ($n = 3$), failure to thrive ($n = 2$ children), bronchiolitis obliterans organizing pneumonia (BOOP, $n = 1$) and autoimmune haemolytic anaemia ($n = 1$). Blood counts were usually within normal limits and inflammatory symptoms were present in only 10 (18%) patients.

The pathological examination of the biopsy specimen revealed classical hyaline-vascular (HV) features in 39 (68%) cases and plasmacytic (PC) or mixed features in 18 (32%) cases. Age at diagnosis was slightly higher in the PC cases (42·5 years) than in HV cases (32 years). PNP was usually associated with the HV variant (3 out of 4) while inflammatory symptoms were more often present in association with the PC variant (6 out of 10).

In 19 cases, multiple lymph nodes were enlarged in a single station (Fig 2C). These patients were still considered to have a diagnosis of UCD. The clinical and biological characteristics of these patients were very similar to that of patients with single lymph node involvement.

Twenty-five patients underwent therapeutic surgical resection and only 3 of them relapsed (all with PC features); 5 patients were treated with radiotherapy and all responded; 9 patients received steroids with 4 partial responses and 5 failures; 5 patients were treated with tocilizumab with a complete response in the inflammatory symptoms in all of them; 2 patients received rituximab with a partial response in one and failure in the other patient; 9 patients did not receive any treatment and only one of them worsened during follow-up.

No patient developed lymphoma during follow-up, but 2 died, due to PNP in one and BOOP in the setting of acute myeloid leukaemia in the other one. After a median follow-up of 39 months, the estimated 2-year OS was 98·1% [95% confidence interval (CI): 87·1–99·7] (Fig 3).

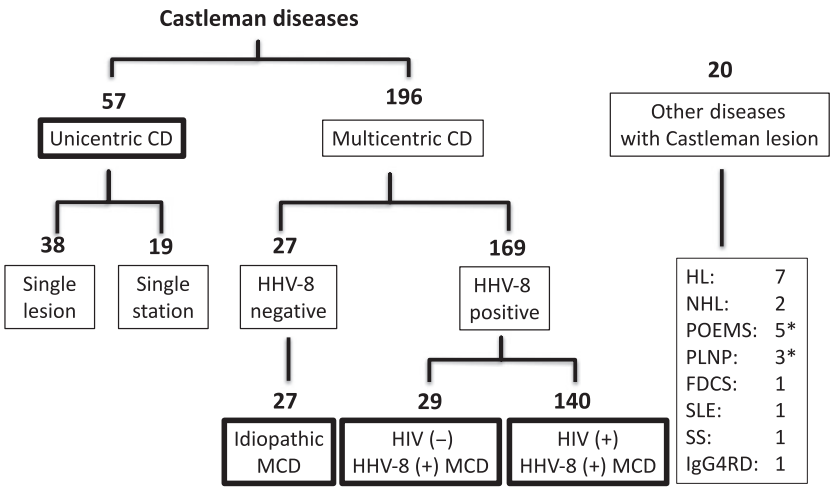

Fig 1. Classification of 273 patients with a Castleman lesion. After exclusion of 20 patients with Castleman-like lesions in the context of another disease, 253 patients were classified with Unicentric Castleman disease, Idiopathic Castleman disease and HHV-8 associated Castleman disease (either in the context of HIV infection or not). CD, Castleman disease; FDCS, follicular dendritic cell sarcoma; HHV-8, human herpes virus 8; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma;IgG4RD, IgG4 related disorder; MCD, multicentric Castleman disease; NHL, non-Hodgkin lymphoma; PLNP, primary lymph node plasmocytoma; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes, syndrome; SLE, systemic lupus erythematosus; SS, Sjögren syndrome. * one patient with both disorders.

Table I. Unicentric Castleman disease. Patient characteristics.

	Total	Single lesion	Single station	HV	PC or mixed
N	57	38	19	39	18
Sex male/female	29/28	19/19	10/9	18/21	11/7
Age (median), years	35	33·5	39	32	42·5
Ethnicity					
Caucasian	41 (72%)	27	14	29	12
Northern Africa	9 (16%)	5	4	5	4
Sub Saharan Africa	6 (11%)	5	1	4	2
Asian	1 (2%)	1	0	1	0
HIV positive	1	1	0	1	0
Localisation					
Mediastinum	19	10	9	15	4
Abdominal	13	9	4	6	7
Cervical	15	11	4	11	4
Axillary	3	1	2	2	1
Inguinal	3	3	0	2	1
Extranodal	4	4	0	3	1
Delay to diagnosis (median, months)	5·6	7·2	4·2	5·6	11·6
Fever	5	0	5	2	3
Complications					
Splenomegaly	1	1	0	1	0
Oedema/effusion	1	0	1	1	0
Lung	6	4	2	4	2
Skin	4	3	1	2	2
Kidney	1	1	0	1	0
PNP	4	3	1	3	1
Polyneuropathy	3	0	3	1	2
AIHA	1	1	1	0	1
AITP	3	2	1	2	1
Leucocyte count, $\times 10^9$/l	5·9	5·9	5·88	5·955	5·7
Lymphocyte count, $\times 10^9$/l	1·515	1·51	1·545	1·52	1·49
Haemoglobin, g/l	138	139	130	138	134
Platelet count, $\times 10^9$/l	254	244	288	255	244
CRP, mg/l	2	2	8	2	6
Serum albumin, g/l	43·6	44·1	41·6	44·1	43
Gammaglobulin, g/l	12·5	12·5	13·7	12·1	12·9
Monoclonal gammopathy	5 (10%)	3 (8%)	2 (13%)	3 (8%)	2 (12·5%)
LDH > normal	3 (5%)	1 (3%)	2 (11%)	3 (8%)	0
Ferritin > 5 times normal	0	0	0	0	0
DAT +	4 (12·5%)	1 (5%)	3 (25%)	2 (9%)	2 (20%)
$CD4^+$ T-cell count, $\times 10^9$/l	0·658	0·643	0·698	0·645	0·665
$CD19^+$ B-cell count, $\times 10^9$/l	0·186	0·186	0·2	0·187	0·14
Follow-up (median, months)	39	24	57	36	46
Lymphoma during follow-up	0	0	0	0	0
Deaths	2	0	2	1	1
			PNP	PNP	BOOP, AML
			BOOP, AML		

AIHA, autoimmune haemolytic anaemia; AITP, autoimmune thrombocytopenia; AML, acute myeloid leukaemia; BOOP, bronchiolitis obliterans organizing pneumonia; CRP, C reactive protein; DAT, direct agglutination test; HIV, human immunodeficiency virus; HV, hyalin-vascular; LDH, lactate dehydrogenase; PC, plasmacytic; PNP, paraneoplasic pemphigus.

Idiopathic HHV-8 negative multicentric Castleman disease

Twenty-seven patients were classified as iMCD. Twenty-six (96%) met the recently proposed criteria for iMCD, which requires both major criteria and at least two minor criteria (Appendix S1). The only patient who did not fulfill the criteria presented with multiple supra- and infra-diaphragmatic lymphadenopathy with HV features on pathological

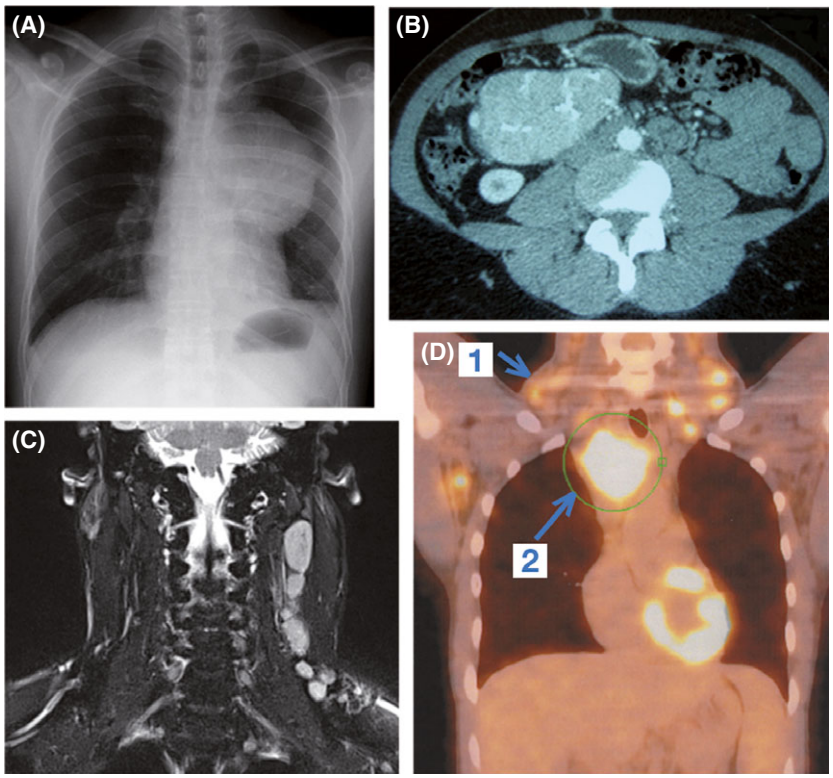

Fig 2. Imaging in Castleman disease. (A) Chest X-ray revealing an asymptomatic unique mediastinal mass; (B) Abdominal computed tomography (CT) scan showing a unique hypervascular mesenteric mass with an intense homogeneous enhancement following contrast; (C) Cervical magnetic resonance imaging (MRI) revealing several pathological lymph nodes in a single station, compatible with a diagnosis of unicentric Castleman disease; (D) Positron emission tomography/CT revealing a large tumoural mass of the upper mediastinum associated with multiple cervical and axillary lymphadenopathy; the first biopsy (i) performed on a cervical lymph node with moderate avidity [maximum standardized uptake value (SUV_{max}): 5·8] showed Castleman disease features while a second biopsy; (ii) performed on the mediastinal mass with a higher avidity (SUV_{max}: 11) was diagnostic for Hodgkin lymphoma.

examination and no inflammatory symptoms. Twenty-five patients met four or more of the minor criteria.

Three patients were born from consanguineous parents, two had Hepatitis C viral (HCV) infection, and one presented with inflammatory bowel disease. The median age at diagnosis was 47 years with a male predominance (74%).

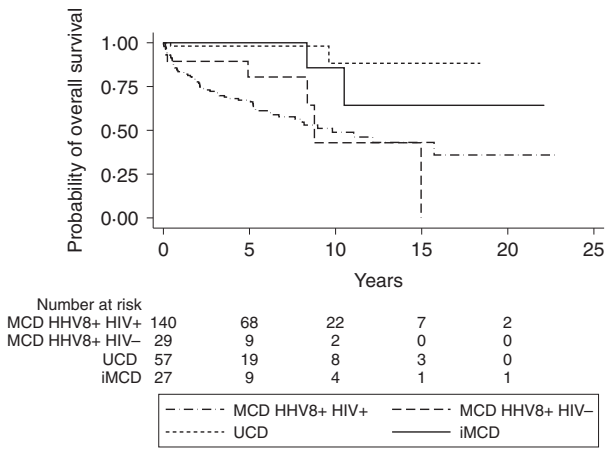

Fig 3. Overall survival in 253 patients with Castleman disease (CD). Overall survival plots according to CD classification. iMCD, idiopathic Castleman disease; MCD HHV8+ HIV-, multicentric Castleman Disease associated with human herpes virus 8 (HHV-8) but not with human immunodeficiency virus (HIV); MCD HHV8+ HIV+, Multicentric CD associated with HHV-8 in HIV-infected patients. UCD, unicentric Castleman disease.

Most patients were symptomatic at diagnosis with fever, splenomegaly, oedema, effusion, or respiratory symptoms (Table II). In addition, 11 (41%) presented with renal involvement and 2 cases demonstrated features consistent with TAFRO (Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis/Renal failure and Organomegaly) syndrome, also called Castleman-Kojima disease, according to the recent definition (Kawabata *et al*, 2013; Iwaki *et al*, 2016). The major biological abnormalities among the iMCD cases were anaemia, thrombocytopenia or thrombocytosis, high serum C-reactive protein (CRP), low serum albumin and hypergammaglobulinaemia. Five out of 21 patients had a positive direct agglutination test, usually without overt haemolysis.

Lymph node examination revealed PC or mixed features in 21 (78%) cases and HV features in 6 (22%) cases. The patients with PC features were more symptomatic than the patients with HV features, and specifically presented with more inflammatory symptoms. The median haemoglobin level was significantly lower, 97 vs. 123 g/l ($P = 0·03$) while the median serum CRP level was much higher, 115 vs. 24 mg/l ($P = 0·02$).

Seventeen patients received steroids with 9 responses and 8 failures. Ten patients were treated with tocilizumab with a complete response in all of them; 8 maintained the response on therapy, one relapsed on therapy and one achieved a persistent response after discontinuation of therapy. Seven patients received rituximab with a response in 4 and failure in 3. Five patients were treated with etoposide with a partial response in 4 and failure in one. Three patients did not

Table II. HHV-8 negative idiopathic multicentric Castleman disease. Patient characteristics.

	Total	HV	PC or Mixed
N	27	6	21
Sex male/female	20/7	6/0	14/7
Age (median), years	47	38·5	47
Ethnicity			
Caucasian	18 (67%)	4	14
Northern Africa	5 (18%)	2	3
Sub Saharan Africa	3 (11%)	0	3
Asian	1 (4%)	0	1
Delay to diagnosis (median, months)	3·0	2·6	3·1
Fever	19 (73%)	1	18
Complications			
Splenomegaly	10 (37%)	3	7
Oedema/effusion	10 (37%)	2	8
Lung	13 (48%)	1	12
Skin	6 (22%)	1	5
Kidney	11 (41%)	3	8
Neuropathy	3 (11%)	0	3
Haemophagocytic syndrome	1 (4%)	0	1
AIHA	1 (4%)	0	1
TAFRO syndrome	2 (7%)	1	1
Leucocyte count, $\times 10^9$/l	8·6	7·75	9·1
Lymphocyte count, $\times 10^9$/l	1·48	1·45	1·48
Haemoglobin, g/l	104	123	97
Platelet count, $\times 10^9$/l	222	198	225
CRP, mg/l	112	24	115
Serum albumin, g/l	33	40·8	32
Gammaglobulin, g/l	20	16·8	20
Monoclonal gammopathy	6 (22%)	2	3
LDH > normal	6 (22%)	0	6
Ferritin > 5 times normal	2 (7%)	0	2
DAT +	5 (24%)	1	4
$CD4^+$ T-cell count, $\times 10^9$/l	0·524	0·768	0·486
$CD19^+$ B-cell count, $\times 10^9$/l	0·086	0·099	0·068
Follow-up (median, months)	27	23	28
Lymphoma during follow-up	1	0	1
Deaths	2	0	2

AIHA, autoimmune haemolytic anaemia; CRP, C reactive protein; DAT, direct agglutination test; HV, hyalin-vascular; LDH, lactate dehydrogenase; PC, plasmacytic; TAFRO, thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure and organomegaly.

receive any treatment, two of whom progressed during follow-up.

After 26 months of median follow-up, one patient had developed lymphoma and died. Another patient died with cancer. The estimated 2-year OS was 100% (Fig 3).

HHV-8 associated multicentric Castleman disease in HIV negative patients

Twenty-nine HIV negative patients were diagnosed with HHV-8+ MCD. Seventeen patients (60%) originated from an African country and only 11 (39%) were European Caucasians. Two patients were born from consanguineous parents, 2 had thymoma, 2 had chronic viral hepatitis (Hepatitis B virus and HCV infection in one each), one was an organ transplant recipient on immunosuppressive therapy, and 4 were men who had sex with men. The median age at diagnosis was 65 years with a male predominance (72%). Most patients were symptomatic at diagnosis with fever, splenomegaly, oedema, effusion, respiratory symptoms or haemophagocytic syndrome (Table III). In addition, 12 patients (41%) presented with Kaposi sarcoma lesions. Infrequent complications were also noted: thrombotic thrombocytopenic purpura, insulin resistance, retinal vasculitis and facial atrophy (one each). The major biological abnormalities were anaemia, thrombocytopenia, high serum CRP, low serum albumin and hypergammaglobulinaemia. Nineteen out of 26 patients (73%) had a positive direct agglutination test and 12 (41%) presented with a monoclonal gammapathy without malignant lymphoproliferative disease. All patients had detectable HHV-8 DNA in plasma with a median value of 5·15 logs copies/ml. Lymph node examination revealed a plasmacytic variant in all cases with a positive nuclear staining in plasmablastic cells when using the HHV-8 associated LANA IHC.

Nine patients received steroids with 5 achieving partial responses and 4 failing this therapy. Fifteen patients were treated with etoposide with a transient complete response in 10 and a partial response in 5. Eleven patients received rituximab with a complete response in 9 and a partial response in 2. Two patients were treated with tocilizumab and both failed to respond.

After a median follow-up of 30 months, 5 patients developed lymphoma and 7 had died (3 with active CD, 2 with lymphoma, one with cancer and one with infection), providing an estimated 2-year OS of 89·4% (95% CI: 70·5–96·4), significantly lower than that observed in patients with iMCD ($P = 0·03$) (Fig 3).

HHV-8 associated multicentric Castleman disease in HIV positive patients

One hundred and forty HIV positive patients were diagnosed with HHV-8+ MCD. All patients but one were infected with HIV through sexual contacts, including 87 men who have sex with men. Most patients (60%) were Caucasians. The median age at diagnosis was 41·4 years with a male predominance (86%). Almost all patients were symptomatic at diagnosis with fever, splenomegaly, oedema, effusion, respiratory symptoms or haemophagocytic syndrome (Table III). In addition, 79 (56%) presented with Kaposi sarcoma. The major biological abnormalities were anaemia, thrombocytopenia, high serum CRP, low serum albumin and hypergammaglobulinaemia. Fifty out of 110 patients (46%) had a positive direct agglutination test and 29 out of 102 (28%) presented with a monoclonal gammapathy. HIV replication was controlled, with a plasma HIV-RNA level below the limit

Table III. HHV-8 positive multicentric Castleman disease. Patient characteristics.

	Total	HIV positive	HIV negative
N	169	140	29
Sex male/female	142/27	121/19	21/8
Age (median) years	44·6	41·4	65
Ethnicity			
Caucasian	95 (57%)	84 (60%)	11 (39%)
Northern Africa	19 (11%)	10 (7%)	9 (31%)
Sub Saharan Africa	52 (31%)	44 (31%)	8 (29%)
Asian	3 (2%)	2 (1·5%)	1 (3%)
Delay for diagnosis (median, months)	4·7	4·8	4·3
Fever	148 (88%)	126(90%)	22 (79%)
Complications			
Splenomegaly	131 (78%)	113 (81%)	18 (62%)
Oedema/effusion	67 (40%)	49(35%)	18 (62%)
Lung	44 (26%)	35 (25%)	9 (31%)
Skin	22 (13%)	17 (12%)	5 (17%)
Kidney	11 (6·5%)	6 (4%)	5 (17%)
Haemophagocytic syndrome	64 (38%)	56 (40%)	8 (28%)
AIHA	23 (14%)	8 (13%)	6 (21%)
TAFRO syndrome	0	0	0
Kaposi sarcoma	91 (54%)	79 (56%)	12 (41%)
Leucocyte count, $\times 10^9$/l	4700	4315	5900
Lymphocyte count, $\times 10^9$/l	1200	1040	1920
Haemoglobin, g/l	8·4	8·1	9·7
Platelet count, $\times 10^9$/l	98000	96000	156000
CRP, mg/l	154	159	112
Serum albumin, g/l	28	27·5	30·2
Gammaglobulin, g/l	24·4	24	27·2
Monoclonal gammopathy	41 (31%)	29 (28%))	12 (41%)
LDH > normal	67 (40%)	57 (41%)	10 (36%)
Ferritin >5 times normal	67 (54%)	56 (55%)	11 (50%)
DAT +	69 (51%)	50 (46%)	19 (73%)
HHV-8 DNA (median, log copies)	4·63	4·57	5·15
$CD4^+$ T-cell count (median, $\times 10^9$/l)	227	184	625
$CD19^+$ B-cell count (median, $\times 10^9$/l)	na	na	312
Plasma HIV RNA copies <2 logs	na	37 (26%)	na
Follow-up (median, months)	54	58	30
Lymphoma during follow-up	28	23	5
Deaths	68 (40%)	61 (44%)	7 (24%)

CRP, C reactive protein; DAT, direct agglutination test; HHV-8, human herpes virus 8; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; TAFRO, thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure and organomegaly.

of detection, under combined antiretroviral therapy, in only 37 (26%) of the patients. All tested patients had detectable HHV-8 DNA in plasma with a median value of 4·57 logs copies/ml. Lymph node examination revealed the presence of HHV-8 positive plasmablastic cells in all cases.

Sixty-one patients received short term steroids, but prolonged utilization was avoided because of the risk of Kaposi flare. One hundred and ten patients were treated with etoposide with a transient response in 87. Fifty-three patients received combination chemotherapy and 39 experienced a good response. Sixty-one patients received rituximab with a complete response in 44. Three patients were treated with tocilizumab and one had a partial response.

After a median follow-up of 58 months, 23 patients had developed lymphoma and 61 had died providing an estimated 2-year OS at 77·7% (95% CI: 69·8–83·7), significantly lower than that observed in patients with iMCD ($P = 0·01$) but not statistically different to that observed in HHV8+ MCD in patients not infected with HIV ($P = 0·43$) (Fig 3).

PET/CT scans

A total of 62 patient underwent PET/CT scans at time of diagnosis: 21 with UCD, 17 with iMCD, 12 with HHV8+ MCD (HIV-) and 12 with diseases that mimic CD. Increased FDG activity was noted in all patients with a median SUV_{max}

of 5·1 (range, 2·2–10) in UCD, 4·5 (range, 2·2–15) in iMCD and 5·15 (range, 2·8–17·6) in HHV8+ MCD. In these patients, PET/CT was helpful to determine the unicentric or multicentric nature of the disease. In patients with diseases that mimic CD, the median SUV_{max} in the most active lymph node was 8·4 (range, 2·2–13·8). The higher values were observed in the 4 patients with Hodgkin lymphoma (9·5–13·8). In two of these patients with lymphoma, the SUV_{max} observed in the cervical lymph nodes with Castleman-like histopathology were 4·2 and 6·1. In each case, the presence of a more active lesion with SUV_{max} of 11·7 on a mediastinal mass and 11·4 on an axillary lymph node led to a second biopsy and a final diagnosis of Hodgkin lymphoma (Fig 2D).

Discussion

Sixty years after the initial description by Benjamin Castleman of a new clinico-pathological entity, the spectrum of CD is considerably wider and now includes several distinct diseases. An important effort has been made by an international collaborative group (www.cdcn.org) to better define the criteria for diagnosis and provide a useful classification (Fajgenbaum *et al*, 2014, 2017). In a single centre, we had the opportunity to take care of patients with all forms of CD and to describe the full spectrum.

The unicentric form of CD appeared quite homogeneous. Most patients presented with a single asymptomatic mass and pathological examination usually revealed HV histopathological features. However, there were two remaining « grey zones ». The first one concerns patients with more than one lymph node but still in a single station, and the second concerns patients with UCD of the plasmacytic variant. Fifty-seven patients were considered to have UCD as a single lymph node or lymph node station was involved. In addition to traditional imaging, such as CT and magnetic resonance imaging, PET/CT scan was used in 21 patients to investigate the possibility of multicentric involvement (Barker *et al*, 2009; Lee *et al*, 2013; Polizzotto *et al*, 2015). One third of the patients had multiple lymph nodes involved in a single station (Fig 2C). These patients did not clinically differ from patients with a single involved lymph node and most of them were asymptomatic. However, the 3 UCD patients with inflammatory symptoms fell into the group with multiple lymph nodes in a single lymph node station. In addition, curative surgery was not possible for 12 cases. Eighteen patients (31%) with UCD presented with plasmacytic or mixed pathological features, a proportion similar to that observed in a recent series of 43 patients (Yu *et al*, 2017). The lymph node stations with PC features were less frequently thoracic than nodes with HV features. As in the HV group, most of the patients were asymptomatic and only one had inflammatory symptoms. One patient had a typical, asymptomatic, HV, HHV-8 negative UCD in the context of HIV infection. The most severe complications observed in this group were paraneoplastic pemphigus (PNP) (Miltenyi *et al*, 2009), polyneuropathy (Dispenzieri *et al*, 2012), autoimmune cytopenia (Carrington *et al*, 1990) and failure to thrive in children. In the present series, the prevalence of PNP was lower than that observed in a recent Chinese series, suggesting a possible role for genetic background for this complication (Dong *et al*, 2015). PNP remains devastating and one patient died because of this complication. Polyneuropathy was also a severe complication in 3 patients while autoimmune cytopenia was easy to control in all 4 patients.

Twenty-seven patients were diagnosed with iMCD. All of them met both major diagnostic criteria (pathology and involvement of multiple lymph node stations) and all but one met at least 3 minor criteria (range: 3–9). Both major and at least two minor criteria are required. Most patients were symptomatic and 19 (73%) had fever. Lung and kidney involvement were the most frequent complications and were often associated with oedema or effusions. Anaemia, high serum CRP levels and hypergammaglobulinaemia were the major biological markers of iMCD. Most patients exhibited PC or mixed histopathological features, but, interestingly, out of the 27 iMCD patients, the 6 who exhibited HV features had a different presentation with rare complications, and fever in only 1 of them. In this small group of patients, the median values for haemoglobin, serum CRP, and gammaglobulins were close to normal values. Compared to a recent series of 31 patients with iMCD published by Yu *et al* (2017), iMCD was less severe than in the present series with less frequent fever (13% vs. 73%) splenomegaly (19% vs. 37%) and oedema/effusion (13% vs. 37%). The CRP value was not available but only 9 out of 17 patients had an elevated serum erythrocyte sedimentation rate (ESR). Of note, 52% of the patients exhibited HV histopathology in the series reported by Yu *et al* (2017). Nevertheless, these patients experienced a worse OS than the present series (Yu *et al*, 2017). Furthermore, four large iMCD case series reported 5-year OS of 55% (Shin *et al*, 2011), 55% (Melikyan *et al*, 2015), 65% (Dispenzieri *et al*, 2012) and 77% (Seo *et al*, 2014). This variability in outcomes may reflect too short follow-up in the present series, geographic differences, a « grey zone » in staging UCD *versus* iMCD, or pathophysiological misclassification.

The only patient of Asian ancestry presented with symptoms that appear to be more frequent in this population (Nishimoto *et al*, 2000): lymphoid interstitial pneumonia, skin lesions and severe hypergammaglobulinaemia (80·4 g/l) responsible for hyperviscosity syndrome.

TAFRO syndrome, also called Castleman-Kojima disease, is a clinical subtype of iMCD, which was diagnosed in two patients. It involves thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure and organomegaly. The histological pattern is typically consistent with HV or "hyper-vascular" and mixed histopathology (Kawabata *et al*, 2013; Iwaki *et al*, 2016). The two patients considered to have TAFRO syndrome had a quite severe clinical and biological presentation; one of them indeed had hyper-vascularized lesions while the second exhibited PC features. Therefore, given the absence of

specific pathological features, it may be difficult, at least in some patients, to make a clear distinction between TAFRO syndrome associated with iMCD and severe cases of iMCD. Regardless of whether the iMCD patient has TAFRO syndrome, anti-IL6 is considered to be first line treatment and it outperformed other treatment options in this series. However, siltuximab was effective at inducing a response in only 34% of patients in the phase II study compared to 0% on placebo (van Rhee *et al*, 2014). Thus, identification of additional therapeutic targets is necessary. However, the limited understanding of iMCD aetiology (which has been hypothesized to be autoimmune, autoinflammatory, paraneoplastic or viral) and pathogenesis has impeded new treatment discoveries.

Patients with HHV-8+ MCD exhibited several distinct features. Most patients had a risk factor for HHV-8 infection: born in a country with a high prevalence of this infection and/or men who had sex with men. All these patients had detectable HHV-8 DNA in their blood. In this series, a large number of patients were co-infected with HIV and this may reflect the orientation of our department that has been involved in the care of patients with HIV-associated haematological disorders since the 1980s.

HHV-8+ MCD exhibited a more aggressive clinical and biological presentation than iMCD in this series. Splenomegaly and haemophagocytic syndrome were more frequent, cytopenias and inflammation were more severe (Tables II and III). In the absence of HIV infection, we noted a higher prevalence of oedema/effusion and nephropathy. Besides this high activity, some differences could be demonstrated between HIV-infected and non-infected HHV-8+ MCD patients. In the context of HIV infection, we observed a higher prevalence of splenomegaly, severe cytopenias and haemophagocytic syndrome. We also observed a higher incidence of lymphoma and deaths, although the median follow-up was longer in these patients. Recent studies of HHV-8+ MCD have found improved short- and long-term survival with rituximab (Bower *et al*, 2007; Gérard *et al*, 2007, 2012). Thus, we expect outcomes to improve as more patients are treated with rituximab.

The classical imaging modality for evaluating patients with CD is CT (Hillier *et al*, 2004). PET/CT may provide additional value in the initial staging and follow-up of these patients (Murphy *et al*, 1997; Enomoto *et al*, 2007; Barker *et al*, 2009; Polizzotto *et al*, 2015). In the present series, the SUV_{max} values observed in UCD and iMCD were very similar to that reported in a recent series (Yu *et al*, 2017). A major issue regarding the diagnosis of CD remains the exclusion of other diseases including lymphomas that can present with Castleman-like lesions in a lymph node biopsy. PET/CT can help to assess the unicentric or multicentric nature of the disease and also help to look for a distinct and more active lesion that could be considered for a second biopsy (Fig 2D).

The estimated survival was significantly different in the four groups of patients, with an almost normal life expectancy in patients with UCD while patients with HHV8+ MCD in the context of HIV infection had the worse prognosis ($P = 0{\cdot}0001$; Fig 3). However, a significant limitation is the length of follow-up for the various groups.

Conclusion

Our review of the largest single institution case series to date found that CD is a diagnosis encompassing very distinct clinico-pathological situations. UCD is often cured with surgical excision or may even be considered for a watch-and-wait approach. An important step before diagnosing CD, either unicentric or multicentric, remains the exclusion of diseases, such as lymphomas, that can demonstrate CD-like features. PET/CT is an important modality for evaluating centricity and excluding disorders that mimic iMCD. MCD, either idiopathic or associated with HHV-8, is usually an aggressive disease requiring specific care and therapy. Monoclonal antibodies targeting B cells for HHV-8+ MCD and the IL6 pathway for iMCD are cornerstones of treatment. Additional treatment options for the significant proportion of iMCD patients who do not respond to IL6 blockade are needed.

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Authors' contributions

EO, LGé and LGa designed the study, EO and LGé performed the data gathering, EO, DB, CF, MM and LGa took care of the patients, AM and LV analysed the PET-CT data, LGé performed the statistical analysis, VM performed the pathological analysis, EO and DF prepared the initial draft. The final manuscript was read and approved by all the authors.

Disclosures

DF has received research funding from Janssen Pharmaceuticals. EO and DF have served on advisory boards for Janssen Pharmaceuticals. EO has performed consultancy for CSL Behring and Shire. The remaining authors declare no competing financial interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Diagnostic criteria for iMCD.

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