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Multicentric Castleman's Disease in HIV Infection: a Systematic Review of the Literature

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Abstract

The objective of this study is to systematically review the epidemiology and the clinical and virologic aspects of multicentric Castleman's disease in HIV-positive patients and to evaluate treatment strategies and outcome, especially in relation to HAART administration. The authors have conducted a systematic review of the English literature for all cases of newly diagnosed multicentric Castleman's disease in HIV-positive patients. The 25 studies which met the selection criteria included 84 HIV-positive patients with multicentric Castleman's disease (20 pre-HAART and 64 post-HAART era). Of them, the majority (90%) were men with 33 months median time from detection of HIV-positivity to multicentric Castleman's disease diagnosis in the HAART era. Fever and lymphadenopathy were the most common presenting symptoms and cytopenias, hypoalbuminemia, polyclonal hypergammaglobulinemia and raised C-reactive protein the most frequently revealed laboratory findings. Kaposi's sarcoma was present in 72% of the patients and respiratory system involvement in 34%. Although the majority of cases reported were positive for human herpesvirus-8, none of the reviewed patients was found to suffer from polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome. Of the 48 patients on HAART, 64% were already on HAART at multicentric Castleman's disease diagnosis, having a better immunologic profile and a lower incidence of Kaposi's sarcoma than the 35% of patients who initiated HAART after multicentric Castleman's disease diagnosis. Nevertheless, the two groups did not have significantly different mortality rates (30 vs. 38%). At multicentric Castleman's disease diagnosis, a wide range of CD4 counts was recorded, suggesting that disease presentation could occur at any CD4 count. With regard to treatment, the study confirmed the high rates of response with rituximab (anti-CD20 monoclonal). Monochemotherapy seems to give short-lived responses, which require maintenance to be sustained. Polychemotherapy with CHOP has given long-term remission in a subset of patients. Other regimens used in the treatment of HIV-related multicentric Castleman's disease were antiviral agents, immunomodulatory agents, and thalidomide. The fatality rate among HIV-related multicentric Castleman's disease cases reviewed was 44%, significantly lower than that of HIV-negative individuals (65%), while median survival of the latter was 29 months longer than that of HIV-infected individuals. The fatality rate among pre-HAART patients was 75 vs. 29% among HAART patients. Infection, multiorgan failure, Kaposi's sarcoma, non-Hodgkin lymphoma and progressive multicentric Castleman's disease were the most often reported causes of death. In conclusion, multicentric Castleman's disease is a lym-

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phoproliferative disorder with an increasing prevalence in HIV-infected individuals. Even though life expectancy in multicentric Castleman's disease seems to have significantly improved in the HAART era, it remains a disease with a poor prognosis and an increased incidence of non-Hodgkin lymphoma in the HIV-context. **(AIDS Rev. 2008;10:25-35)**

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Key words

HIV. Multicentric Castleman's disease. Highly active antiretroviral therapy.

Introduction

Castleman's disease, also known as angiofollicular lymph node hyperplasia, is a lymphoproliferative disorder with an increased prevalence in HIV infection, in which setting it has been associated with human herpesvirus 8 (HHV-8) and Kaposi's sarcoma (KS)[1]. Castleman's disease comprises two distinct entities[2]: the localized form (unicentric Castleman's disease) and the multicentric form. The multicentric form of Castleman's disease (MCD) in the HIV-negative population typically presents in the sixth decade with lymphadenopathy and multiorgan involvement, following a more aggressive natural history[1,2]. The histology of Castleman's disease is similarly divided in two subgroups. The hyaline vascular type is found in 90% of unicentric Castleman's disease but rarely in MCD, while plasma cell variant is found in only 10% of patients with unicentric Castleman's disease but in 80-90% of MCD. Moreover, mixed forms exist[2]. The pathogenesis of MCD is unclear. Infection of immunoblasts by HHV-8 and production of viral interleukin-6 (IL-6) seem to play a central pathogenetic role[3-5].

We reviewed the English-language literature for all cases of MCD in HIV-positive patients. The primary objectives of this investigation were to study the epidemiology and the clinical and virologic aspects of the disease, and to evaluate treatment strategies and outcome, especially in relation to HAART administration.

Methods

We collected the literature by searching the MEDLINE database from 1966 on. The MEDLINE search string was "giant lymph node hyperplasia" OR "angiofollicular lymph node hyperplasia" OR "Castleman's Disease" AND "HIV". The results were limited to human studies published in the English language. The literature search yielded 173 articles.

Study selection criteria

Two investigators independently screened the abstracts of these articles and we retrieved the full text of the ones we considered as important. After a detailed review, 38 items were identified as potentially relevant, but only 25 of them had HIV-positive patients newly diagnosed with MCD. Moreover, when there were studies of the same working group which some of their participants had published again, detailing different clinical characteristics of the disease, we included the more detailed study regarding the clinical presentation and outcome.

Data extraction

Two reviewers extracted the data independently and any disagreement was resolved by consensus. The reviewers extracted the following data from each study: number of subjects, age, sex, race, HAART (received or not, and if reported, which), CD4 cell count, HIV viral load, the presence of fever, lymphadenopathy, hepatomegaly and/or splenomegaly, involvement of the respiratory system, edema, KS coexistence, hemoglobin, white blood cell and platelet count, C-reactive protein (CRP) and albumin levels, Coombs test, tissue used for histopathologic diagnosis (lymph node, spleen, bone marrow), histopathologic type of MCD, coexistence of other pathologic entities in the biopsy material (KS, non-Hodgkin's lymphoma, other), presence of HHV-8, treatment received, follow-up duration, outcome and causes of death. For the categorical variables, we calculated their incidence taking into account the number of subjects involved. For the con-

Table 1. Demographic characteristics, clinical presentation, histopathology and HHV-8 detection in the reviewed studies

Characteristic	Patients (n)
Age (years)	
– Mean	40.70
– Median (range)	40 (21-67)
Sex	
– Male	76/84 (90.47%)
– Female	8/84 (9.52%)
Race	
– Caucasian	42/51 (82.35%)
– Black	9/51 (17.64%)
Clinical presentation	
– Fever	72/72 (100%)
– Lymphadenopathy	69/72 (95.83%)
– Hepatomegaly	45/72 (62.5%)
– Splenomegaly	62/72 (86.11%)
– Pulmonary symptoms	25/72 (34.72%)
– Edema	21/72 (29.16%)
– Ascites	4/72 (5.55%)
Biopsy	
– Lymph node	80/82 (97.56%)
– Spleen	16/82 (19.5%)
– Bone marrow	8/82 (9.75%)
Histopathology	
– Plasma cell	22/49 (44.89%)
– Hyaline type	2/49 (4.08%)
– Mixed type	25/49 (51%)
Coexistent pathology	
– Kaposi's sarcoma	18/44 (40.90%)
– Non-Hodgkin's Lymphoma	3/44 (6.80%)
HHV-8 detection	56/57 (98.24%)

tinuous variables, we calculated means, medians and range.

Results

The total database consisted of 84 patients found in 25 published reports[6-30].

Demographic characteristics

The median age of the patients was 40 years (range 21-67 years). A total of 90% of all MCD occurred in males and 82% of the affected patients were Caucasians (Table 1).

HIV-positivity status

Information on the duration of HIV seropositivity was reported only for 26 out of the 84 reviewed patients. The median time from detection of HIV-positivity to MCD diagnosis was 33 months in the HAART era. Regarding the pre-HAART patients (n = 24), the authors of the largest series found (20 patients) had just categorized the patients in three groups according to duration of HIV-positivity before Castleman's diagnosis (> 5, 2-5, and < 2 years), which did not allow comparisons between pre-HAART and HAART patients. The median CD4 lymphocyte value for the whole group was 160 cells/mm^3, while for the pre-HAART and HAART groups the values were 170 and 156 cells/mm^3, respectively. The median HIV viral load was 2,200 copies/ml, relating exclusively to the HAART-era patients since studies before 1996 do not report values of viral load. Kaposi's sarcoma was present in 72% of the patients (Table 2).

Clinical presentation

Fever and lymphadenopathy were by far the most common presenting symptoms, followed by splenomegaly, hepatomegaly, and fluid retention, either in the form of peripheral edema or effusions such as ascites (Table 1). Hepatomegaly was only rarely described in the absence of splenomegaly (2/84). Involvement of the respiratory system was reported in 34% of cases. Means, medians, and range of laboratory values in the total, pre-HAART, and HAART populations are summarized in table 2. As shown, white blood cell values seemed to be lower in the pre-HAART era, while CRP was significantly higher. Coombs test was reported to be positive in four out of 10 cases (40%; data not shown).

Diagnosis

Diagnosis of MCD was established histologically by lymph-node biopsy in 97% of cases (Table 1). Overall, splenectomy was performed in 16% (14/84). Of those cases, splenectomy was essential for diagnosis in only two (2.24%). With regard to histology, mixed type was recognized in 51%, plasma cell variant in 44% and hyaline type in 4%. In addition to MCD histopathology, KS and non-Hodgkin's lymphoma (NHL) were also recognized in 18/47 (38%) and 3/47 (6%) of the examined tissue samples. Presence of HHV-8 either by immunohistochemistry or as DNA sequences identified by polymerase chain reaction (PCR) in biopsy tissue or peripheral blood mononuclear cells (PBMC), was reported in 98% of cases (Table 1).

Table 2. Significant data pertinent to HIV infection and other laboratory data at multicentric Castleman's disease presentation in the reviewed cases

HIV-positivity status	All patients (n = 84)	Pre-HAART era (n = 24)	HAART era (n = 60)
Duration of seropositivity (months)			
– Mean	42.28	NR	42.28
– Median (range)	33 (0-168)		33 (0-168)
CD4 cells/µl			
– Mean	204.49	157.57	229.68
– Median (range)	160 (1-1,050)	170 (1-363)	156 (19-1,050)
HIV viral load copies/ml			
– Mean	90,503	NR	90,503
– Median (range)	2,200 (50-600,400)		2,200 (50-600,400)
Kaposi's sarcoma	52/72 (72.22%)	19/24 (79.16%)	32/47 (68.08%)
Laboratory investigation			
Hb (g/dl)			
– Mean	8.36	8.13	8.63
– Median (range)	8 (5.0-12.7)	8 (5.4-11.0)	8 (5.0-12.7)
WBC (10/ul)			
– Mean	5	4.23	6.5
– Median (range)	4.95 (1.5-11.1)	4 (1.5-8.6)	6.15 (4.13-9.6)
PLT (10/ul)			
– Mean	123.19	128.5	107.75
– Median (range)	99 (9-389)	99 (9-389)	102 (23-205)
CRP (mg/l)			
– Mean	165.8	212.5	125.3
– Median (range)	152 (10-368)	190 (10-368)	131 (45-250)
Albumin (g/l)			
– Mean	28.9	29.76	26.66
– Median (range)	29 (12-48)	29 (17-48)	26 (12-36.2)
Gamma-globulin (g/l)			
– Mean	26.28	27	24.33
– Median (range)	25 (14-43)	25 (14-43)	25 (15.1-33)

NR: not reported; Hb: hemoglobin; WBC: white blood cells; PLT: platelets; CRP: C-reactive protein.

Treatment and follow-up

Information concerning each patient's treatment (both HAART and chemotherapy) is shown in table 3. As far as HAART is concerned, there was information for 49 of 60 patients from the HAART era, of which 91% were reported to be on HAART while 8% were not. Of the 48 patients on HAART, 64% were already on HAART at MCD diagnosis while 35% were not. Detailed information on HIV-seropositivity status and outcome is shown in table 4. What is obvious is that patients already on HAART at MCD diagnosis had a better immunologic profile (higher CD4 count, lower viral load) and a lower incidence of KS than the patients who initiated HAART after MCD diagnosis. Nevertheless, the two groups did not have significantly different mortality rates (30 vs. 38%). In the majority of reports of patients developing MCD while on HAART, the authors have not provided adequate data about baseline CD4 and viral load counts at HIV-diagnosis or duration of HAART before MCD diagnosis, so no pertinent comments could be attempted. The same holds true about the specific HAART regimens used in the MCD patients reviewed; details were available only for 13 out of 48 cases.

Table 3. Treatment received and outcome in the reviewed patients

Author	Patient	HAART	First-line regimen	Second-line regimen	Follow-up (mo)	Outcome	Cause of death
Lachant, et al.	1	No	CRT, Vcr	No	2	Dead	Infection
	2	No	Vcr, Vlb	No	7	Dead	Infection
Lowenthal, et al.	3	No	CRT	Vlb	20	Dead	KS
Wynia, et al.	4	No	Spl, Cycl, CRT	No	8	Dead	KS
Oksenhendler, et al.	5	No	Spl, Cycl	Eto	7	Dead	KS
	6	No	Spl, ABV	No	39	Dead	KS
	7	No	ABV	No	1	Dead	Infection
	8	No	ABV	No	9	Dead	NHL
	9	No	Spl	No	7	Dead	MOF
	10	No	ABV	No	4	Dead	Infection
	11	No	No	No	1	Dead	MOF
	12	No	No	No	2	Dead	Infection
	13	No	Spl, Cycl	No	25	Dead	KS
	14	No	Vlb, Spl	No	33	Alive	
	15	No	Vlb	ABV	17	Dead	KS
	16	No	Vlb, Spl	Eto, IFNa	27	Alive	
	17	No	Cycl	Vcr	1	Dead	MOF
	18	No	No	No	10	Alive	
	19	No	Vlb	ABV	25	Dead	NHL
	20	No	Vlb	No	14	Dead	MOF
	21	No	Vlb, Spl	ABV	10	Alive	
	22	No	Vlb, Spl	IFNa	15	Alive	
	23	No	Vlb, Spl	IFNa	5	Alive	
	24	No	Vlb	ABV	9	Dead	MOF
Lanzafame, et al.	25	ZDV, DDC, RTV	No	No	12	Alive	
	26	ZDV, 3TC, RTV	No	No	12	Alive	
Corbellino, et al.	27	D4T, 3TC, EFV	cidofovir, anti-IL6	Doxo, Vcr, Bleo-antiCD20 Ab	40	Alive	
Scott, et al.	28	NR	doxil	Eto, Vpd	12	Alive	
	29	NR	Eto	Vpd		Alive	
Marache, et al.	30	D4T, 3TC, EFV	anti-CD20 Ab	No	8	Alive	
Aaron, et al.	31	Yes	No	No	4	Alive	
	32	Yes	Vlb	No	15	Alive	
	33	Yes	Vlb	No	39	Alive	
	34	Yes	Eto	Vbn	6	Alive	
	35	Yes	Eto	No	43	Alive	
	36	Yes	Vlb	No	38	Dead	NR
	37	Yes	Vlb	No	108	Alive	
Aoki, et al.	38	D4T, 3TC, NFV	CRT	foscarnet	15	Alive	
Liberopoulos, et al.	39	ZDV, 3TC, IDV	CHOP	0	12	Alive	
Hiller, et al.	40	NR	NR	NR	NR	NR	NR
	41	NR	NR	NR	NR	NR	NR
	42	NR	NR	NR	NR	NR	NR
	43	NR	NR	NR	NR	NR	NR
	44	NR	NR	NR	NR	NR	NR
	45	NR	NR	NR	NR	NR	NR
	46	NR	NR	NR	NR	NR	NR
	47	NR	NR	NR	NR	NR	NR
	48	NR	NR	NR	NR	NR	NR

(Continue)

Table 3. Treatment received and outcome in the reviewed patients *(continued)*

Author	Patient	HAART	First-line regimen	Second-line regimen	Follow-up (mo)	Outcome	Cause of death
Jung, et al.	49	Yes	Vpd	thalidomide	34	Alive	
Casper, et al.	50	No	ganciclovir		1	Dead	Infection
	51	No	ganciclovir	valganciclovir	18	Alive	
	52	Yes	valacyclovir	cycl, valganciclovir	36	Alive	
Loi, et al.	53	Yes	foscarnet	lipo doxo	10	Dead	IHF
	54	Yes	cycl, CRT	CVP, adriamycin	32	Dead	IP
	55	Yes	no	No	52	Alive	
	56	Yes	chlorambucil	No	9	Dead	HPS
	57	Yes	Vcr, bleo,vbl	CRT, lipo Doxo	43	Alive	
	58	No	no	No	3	Dead	NHL
	59	Yes	chlorambucil	No	1	Dead	MCD
	60	Yes	Vcr, bleo,vbl	No	48	Alive	
	61	Yes	lipo doxo	No	11	Dead	MCD
	62	Yes	chlorambucil	IFN-α, foscarnet	25	Dead	MCD
	63	Yes	No	No	7	Dead	Infection
Bacon, et al.	64	Yes	spl, CHOP	No	20	Alive	
	65	Yes	CRT	No	1	Dead	NR
	66	Yes	spl	No	40	Alive	
	67	Yes	CHOP	No	34	Alive	
	68	Yes	Vcr, Bleo	No	3	Dead	NR
	69	Yes	CRT	No	36	Alive	
	70	Yes	CRT, Spl	No	NR	NR	
	71	No	CHOP	No	12	Alive	
	72	Yes	Vcr, bleo,CRT	No	1	Dead	NHL
	73	Yes	No	No	1	Dead	NHL
	74	Yes	CHOP	No	1	Alive	
Neuville, et al.	75	Yes	Eto	Anti-CD20 Ab, Eto	NR	NR	
	76	Yes	Eto	Anti-CD20 Ab, Eto	NR	NR	
Kotb, et al.	77	ZDV, 3TC, ABC, LPV, NVP	Vlb	No	4	Alive	
Fowler, et al.	78	Yes	Vcr, lipo Doxo	CHOP, Vcr, CRT, Vpd	48	Dead	Infection
Nord, et al.	79	D4T, 3TC, NFV	foscarnet, CRT, Spl	Cycl, Vcr, CRT, Doxo-IFN-α	NR	NR	
Casquero, et al.	80	DDI, 3TC, EFV	doxo, CRT	Anti-CD20 Ab	60	Alive	
Bouvresse, et al.	81	TDF, FTC, RTV, LPV	Vlb	Anti-CD20 Ab	NR	NR	
Kumari, et al.	82	D4T, 3TC, IDV	IFNα	No	24	Alive	
Izuchukwu, et al.	83	D4T,3TC,EFV	CHOP	No	18	Alive	
Newsom-Davis, et al.	84	D4T, 3TC, EFV	Anti-CD20 Ab	No	4	Alive	

NR: not reported; D4T: stavudine; DDC: zalcitabine; 3TC: lamivudine; ZDV: zidovudine; DDI: didanosine; ABC: abacavir; TDF: tenofovir; IDV: indinavir; RTV: ritonavir; LPV: lopinavir; EFV: efavirenz; NVP: nevirapine; NFV: nelfinavir; FTC: emtricitabine; CRT: corticosteroids; Cycl: cyclophosphamide; Vlb: vinblastine; Spl: splenectomy; Eto: etoposide; Doxo: doxorubicin; Vcr: vincristine; Bleo: bleomycin; ABV: adriamycin-bleomycin-vinblastine; CHOP: cyclophosphamide-doxorubicin-vincristine-prednisone; Vpd: oral etoposide; IL-6: interleukin-6; CVP: cyclophosphamide-vincristine-dexamethazone; IFNα: interferon alpha; KS: Kaposi sarcoma; MOF: multiorgan failure; MCD: multicentric Castleman's disease; NHL: non-Hodgkin's lymphoma; AMI: acute myocardial infarction; IHF: idiopathic hepatic fibrosis; IP: interstitial pneumonitis; HPS: hemophagocytic syndrome.

Table 4. HIV-positivity status and outcome according to HAART initiation (prior to or after multicentric Castleman's disease diagnosis)

	HAART initiation	
	Prior to MCD diagnosis n = 26	**After MCD diagnosis n = 15**
Duration of HIV-seropositivity (months)		
– Mean	72.66	26
– Median (range)	72 (18-168)	2 (0-120)
CD4 cells/μl at MCD diagnosis		
– Mean	275.95	167.2
– Median (range)	195 (40-1,050)	138 (19-490)
– > 200 cells/ml	11/24 (45.83%)	3/15 (20%)
HIV VL (copies/ml) at MCD diagnosis		
– Mean	37,054	211,934
– Median (range)	500 (50-600,400)	93,100 (48,000-500,000)
< 500 copies/ml	13/21 (61.9%)	0/15 (0%)
Kaposi's sarcoma	15/24 (62.5%)	12/14 (85.71%)
Follow-up (months)		
– Mean	23.33	16.69
– Median (range)	18 (1-60)	12 (1-48)
Outcome		
– Alive	15/23 (65.21%)	8/13 (61.53%)
– Dead	8/23 (34.78%)*	5/13 (38.46%)

*Attributable deaths 7/23 (30.43%)
MCD: multicentric Castleman's disease; VL: viral load.

Data on chemotherapy treatment was available for 75 out of the 84 patients reviewed (Table 3). Symptomatic recurrences of MCD were often treated with monochemotherapy (32/75), including vinblastine (15/32), cyclophosphamide, doxorubicin, chlorambucil, etoposide, and vincristine. Combined chemotherapy, such as Adriamycin/bleomycin/vinblastine in the pre-HAART era and cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) in the HAART era, was used either as first-line regimen (10/75) or second-line regimen (6/75) after failure of the monochemotherapy to control disease relapses. Anti-CD20 antibody (rituximab) was used in 7/75[5,12,21,25,26,29] patients, either as a first-line (2/7)[12,29] or as a second-line (5/7) regimen[5,21,25,26]. In all but two cases[21], rituximab was reported to have led to complete response. Other regimens used in the treatment of HIV-related MCD were antiviral agents such as cidofovir, foscarnet and ganciclovir, and immunomodulatory agents such as interferon-α (IFNα), either as a salvage or first-line regimen, and thalidomide. Finally, oral etoposide has been used as low-dose suppressive therapy (4/75)[11,17,23]. Additionally, there were 11 patients who received no chemotherapy, three in the pre-HAART era[9] and eight in the HAART era[10,13,19,20]. Of the former group, two died, while one was reported to be still alive 10 months after MCD diagnosis. Of the latter group, three patients died, while the remaining five were alive after a follow-up period ranging from 4-52 months; all of them were receiving HAART. Regarding morbidity, 14 out of 75 patients, as already mentioned, were subjected to splenectomy.

Median follow-up time was 12 months. Outcome was available for 70 patients. All-cause mortality was 47%, while the MCD fatality rate was 44%. The prevalence of the causes of death in the pre-HAART group, HAART group, and overall is shown in table 5.

Discussion

We performed a systematic review of HIV-related MCD studies and case reports and we identified 84 HIV-positive patients with MCD at its first presentation. Based on information of these patients, we tried to clarify demographic, clinical, laboratory, and virologic characteristics of the disease, with particular attention to the received treatment and outcome. When possible,

Table 5. Outcome and causes of death in pre-HAART, HAART patients and overall

HAART administration	All patients	Pre-HAART	HAART era
Yes		0	46/49 (93.87%)
No		0	3/49 (6.12%)
Follow-up (months)			
– Mean	18.67	12.4	22.1
– Median (range)	12 (1-108)	9 (1-39)	13 (1-108)
Outcome			
– Alive	37/70 (52.85%)	6/24 (25%)	31/44 (70.45%)
– Dead	33/70 (47.14%)	18/24 (75%)	15/44 (34.09%)*
Cause of death			
– Infection	8/33 (24.24%)	5/18 (27.77%)	3/15 (20%)
– MOF	5/33 (15.15%)	5/18 (27.77%)	0
– KS	6/33 (18.18%)	6/18 (33.33%)	0
– NHL	5/33 (15.15%)	2/18 (11.11%)	3/15 (20%)
– MCD	3/33 (9.09%)	0	3/15 (20%)
– Various†	2/33 (6.06%)	0	2/15 (13.33%)
– Unrelated‡	2/33 (6.06%)	0	2/15 (13.33%)

*Attributable deaths 13/44 (29.54%).
†Interstitial pneumonitis, hemophagocytic syndrome.
‡Acute myocardial infarction, idiopathic hepatic fibrosis.
MOF: multiorgan failure; KS: Kaposi sarcoma; MCD: multicentric Castleman's disease; NHL: non-Hodgkin's lymphoma.

comparison of patients' characteristics between the pre-HAART and HAART era was performed.

Epidemiology

The HIV-related MCD was found to affect mainly men with a median age of 40 years. On the contrary, in HIV-negative individuals the median age at the onset of the disease has been reported to be 56 years[3]. Interestingly, in two studies including HIV-negative individuals with MCD, median patient ages were 35 and 38 years, similarly to the younger age distribution of HIV-positive patients[30,31]. A predilection for male gender had initially been reported in the literature for HIV-negative individuals[3], but subsequent studies have not confirmed this observation[30,32].

Clinical presentation

The clinical presentation of HIV-related MCD seemed to be rather nonspecific and similar to that of HIV-negative MCD, characterized by fever, lymphadenopathy, hepatomegaly/splenomegaly, edema and effusions. Ascites was present in 5% of cases. Given the etiological association between MCD and primary effusion lymphoma (HHV-8-related disorders) and their reported coexistence in HIV-infected individuals[33], one wonders about the immunophenotyping and molecular features of the abovementioned peritoneal effusions and the possibility of them representing manifestations of unsuspected primary effusion lymphomas. Moreover, from our database of HIV-related MCD, respiratory system involvement was documented in one-third of the patients, a rate of involvement higher than that reported previously in HIV-negative MCD[1]. This is an element of information largely anecdotal so far[34]. However, in the study by Nishimoto, et al., which included 28 HIV-negative patients, in 18 of them (64%) the course was complicated by lymphocytic interstitial pneumonitis[31], which may indicate that pulmonary involvement may be higher in HIV-negative MCD than previously thought. Whether this represents an unrelated phenomenon, an HHV-8-driven proliferation, or an overlooked involvement of the pulmonary parenchyma by MCD is unknown. The main CT findings include poorly defined centrilobular nodules, thin-walled cysts, thickening of bronchovascular bundles, and interlobular septal thickening[35]. Clinically, an acute interstitial pneumonitis was predominant in MCD patients, as opposed to a more chronic course in HIV-positive patients without MCD[36]. Specific dysfunction of the immune system could account for an increased susceptibility for MCD and for a different tempo of lymphocytic interstitial pneumonitis. Alternatively, the high

levels of circulating cytokines including IL-6 could contribute for this clinical difference.

Interestingly, despite the high percentage of HHV-8 detection, none of the 84 reviewed HIV-positive patients was found to suffer from polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome, which is seen in approximately 15% of HIV-negative individuals with MCD, especially those infected by HHV-8[3,37].

Laboratory findings

The laboratory investigation of the reviewed patients revealed cytopenias, hypoalbuminemia, polyclonal hypergammaglobulinemia and raised CRP (all of which can be explained by the high IL-6 levels). Pre-HAART patients tended to have lower white blood cell counts and higher CRP than HAART patients, which may reflect differences in disease severity at presentation. At MCD diagnosis, a wide range of CD4 counts was recorded, especially among the HAART patients (range 19 up to 1,050 cells/μl; 19/46 patients with CD4 count > 200). Additionally, 27 of 43 patients from the HAART era had an HIV viral load < 500 copies/ml at MCD presentation. In other words, according to the present review, MCD seems to be developed in any CD4 and HIV viral load count, this being consistent with the previous observation that symptomatic flares of MCD also may occur at any CD4 count[13,18,19].

Pathology

Histopathologically, and although MCD is believed to typically present as plasma cell variant, at least in HIV-negative individuals[3], our review revealed an almost equal prevalence of plasma cell and mixed types, with hyaline type representing only 4% of the cases, as expected. The majority of HIV-related MCD cases were associated with KS (72%). On the contrary, in HIV-negative MCD, KS prevalence has been reported to range from 0-13%[3]. The association between HHV-8 and MCD is widely accepted nowadays; however, HHV-8 is found less in HIV-negative MCD patients[19,38]. Furthermore, among HIV-infected individuals, the quantity of HHV-8 DNA in PBMC or plasma has been found to be correlated with symptoms during flares of MCD[5,18]. The present review is in agreement with the association of HHV-8 with HIV-related MCD, since HHV-8 immunologic expression or DNA sequences were detected in all but one case of HIV-related MCD. In that case, both PCR and immunohistochemistry failed to detect HHV-8[28], a finding which needs further confirmation and raises questions about alternative etiopathogenesis mechanisms of MCD.

Lymph nodes of patients with HHV-8-related MCD harbor the virus in immunoblasts localized to the mantle zone of B-cell follicles[39]. Molecular studies have shown that although the infected cell population is usually polyclonal, microscopic foci of *in situ* neoplastic clones may exist, which could give rise to plasmablastic, HHV-8-related, NHL[40]. Indeed, in a prospective study of 60 HIV-infected patients with MCD not eligible to be included in our review according to the predefined inclusion criteria, 14 patients developed HHV-8-associated NHL, which is a 15-fold increase in lymphoma risk over that observed in the general HIV-positive population[41]. In the present review, development of NHL was reported in only five cases. Interestingly, the coexistence of MCD and KS or NHL histopathology in the same biopsy samples was reported in some cases[7,9,10,20], supporting the existence of common pathogenetic events. The prevalence of NHL in the HIV-negative population with MCD has been reported to be 18%[3], comparable to that reported by the aforementioned prospective study of HIV-infected individuals[40].

Treatment

This study confirmed the high rates and quality of responses with rituximab (anti-CD20 monoclonal) which targets the abnormal immunoblasts in the mantle cell area. However, there are three cases of anti-CD20 responders who developed worsening of their KS[24,41], so the use of rituximab in patients with KS should be applied with extreme caution, if at all. Even though monochemotherapy can give temporary responses, these are short-lived and require maintenance (e.g. low-dose oral etoposide) to be sustained[11,23]. On the other hand, polychemotherapy with CHOP has given long-term remissions and may be curative in a subset of patients[15,20,23,28]. Many experts nowadays treat MCD patients with good performance status with CHOP in combination with rituximab; like aggressive diffuse large B-cell lymphomas. The long-term outcomes of this approach are unknown. The treatment of relapses is controversial and high-dose chemotherapy in second remission, followed by autologous stem cell transplantation, has been successfully employed. Monoclonal antibody against IL-6 has given responses in HIV-negative patients, but the experience in HIV-positive patients is limited[5,43].

As far as antiviral therapy is concerned, cidofovir has been used with no response[5] and foscarnet with controversial findings[13,19,24]. Ganciclovir was the only antiviral for which complete response was reported when used in three patients along with HAART[18]. Interferon-α was administered either alone, as a starting treatment[27], or in combination with chemotherapy as a salvage therapy[9], being associated with long-term remissions. Interferon-α is thought to exert an antiproliferative effect through its direct binding on cell surface receptors, an antiviral effect via inhibition of viral replication, enhanced natural killer cell activity, and an increase in major histocompatibility complex class I expression on cells infected by HHV-8[27]. Its role as a maintenance treatment in second complete remission is worth assessing.

Bortezomib is a proteasome inhibitor of nuclear factor kappa-B (NFκB) degradation which subsequently downregulates NFκB (overactive in HHV-8 lymphoma genesis). Additionally, it inhibits autocrine IL-6 production. It has been used with success in an HIV-negative individual with MCD[44]. There is no reference in the literature for the use of bortezomib in HIV-infected individuals.

Outcome and the role of HAART

The fatality rate among HIV-related MCD cases reviewed was 44%, which is significantly lower than that reported for HIV-negative individuals (65%). On the contrary, median survival of HIV-negative MCD patients has been reported to be 29 months, longer than that of the HIV-infected individuals reviewed in the present study (median 12 months). The fatality rate among pre-HAART patients was 75%, while among HAART patients it was significantly lower (29%). Within the latter group, patients already on HAART at MCD diagnosis had a better immunologic profile (higher CD4 count, lower viral load) and a lower incidence of KS than those who initiated HAART after MCD diagnosis. Nevertheless, among HAART patients with detailed data we found no difference in mortality rates between patients already on HAART at MCD diagnosis and those who initiated HAART after MCD diagnosis (30 and 38%, respectively). Moreover, there was no significant difference in the mortality rate between the subgroup of patients on documented "successful" HAART (defined as documented CD4 > 200 cells/ml and/or HIV viral load < 500 copies/ml) and the rest of HAART patients (33 vs. 40%; data not shown). These observations could be viewed as a two-sided coin; while patients not on HAART at MCD diagnosis seem to have the same chance of survival as that of patients already on HAART, who are considered immunologically superior, both groups, despite the help of HAART, have at least 30% chance of dying.

The introduction of HAART has been associated with a reduction in the incidence of many HIV-related malignancies, including KS[45]. Moreover, HAART has been shown to prevent the development of KS and to prolong the time to treatment failure in KS[46]. Among the reviewed MCD patients of the HAART era, no death was related to progressive KS or multiorgan failure, while 3/15 (20%) deaths were attributed to progressive MCD, being consistent with the suggestion that, in contrast to KS that often resolves after immune reconstitution, MCD seems to escape that[15]. In a small case series (seven MCD patients, four with KS), where all patients received HAART and chemotherapy, even though the KS resolved in three of four patients when the CD4 count rose on HAART, their MCD relapsed when chemotherapy was stopped, despite the immune reconstitution[15]. On the other hand, there are five cases of successful treatment of clinical symptoms of MCD on HAART alone, with a follow-up of 4-52 months[9,12,18,19]. Finally, Zietz, et al. have previously reported an unusual "cluster" of MCD cases in three patients after starting HAART, suggesting that at least in the short term, HAART may aggravate MCD (possibly representing an immune reconstitution syndrome)[47].

Overall, five MCD patients developed NHL. Of them, two belonged to the pre-HAART and three to the HAART era. Interestingly, all three NHL patients of the HAART era had a very short follow-up period of 1-3 months before dying, suggesting that MCD and NHL were almost simultaneously diagnosed. However, of the latter group, two of the three had refused to receive antiretroviral therapy, which means that only one patient developed plasmablastic lymphoma while being on HAART. Moreover, HHV-8-related NHL is usually associated with extremely poor outcomes[45]. This is consistent with our finding of five patients developing NHL and surviving 1-25 months from diagnosis. Overall, KS, multiorgan failure and bacterial infection were less often met in the HAART era, which is probably associated with HAART-related immune reconstitution.

Conclusion

Multicentric Castleman's disease is a lymphoproliferative disorder with an increasing prevalence in HIV-infected individuals. Although its pathogenesis is still unclear, it is believed to be associated with HHV-8-mediated IL-6 production. Even though life expectancy in

MCD seems to have significantly improved in the HAART era, MCD remains a disease with a poor prognosis and an increased incidence of NHL in the HIV-context. Moreover, due to the low incidence of the disease it is difficult to draw conclusions as to whether HAART has exerted any impact on the relative risk of MCD in HIV-infected individuals. Further investigation is required to understand better the pathogenesis of the MCD and to define optimum therapeutic interventions.

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