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Multicentric Castleman's Disease Experience in an HIV Treatment Network

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Introduction

We present the experience with treatment of multicentric Castleman's disease in a network of 12 practices dedicated to the treatment of HIV disease and other infectious diseases. A total of 4 cases were found. Three out of 4 patients received chemotherapy treatment, which included rituximab. All treated patients responded and have experienced a remission lasting from 5 to 89 months.

Keywords: SARS-COV-2; COVID-19; Multi-drug resistant HIV; Micro-embolic disease; Ischemia

Background

Dr. Benjamin Castleman first described a unicentric lymphoproliferative disease in 1954, later referred to as Castleman's disease [1,2]. Several authors later noted multicentric lymphadenopathies with similar histological features [3-6]. The unicentric form of Castleman's disease presents as a solitary adenopathy, typically affecting a thoracic lymph node [7]. The multicentric form causes a syndrome of diffuse adenopathy, thrombocytopenia, hemolytic anemia, and fever often resulting in death with a 3-year disease-free survival rate of 40% [7,8]. Since these descriptions, a subset of multicentric Castleman's disease (MCD) has been shown to be a result of Human Herpes-8 (HHV-8) infection [9]. HHV-8 can be found in variable prevalence in different geographic locales and different risk groups [10]. Infection rates of HHV-8 are highly associated with both homosexual activity among men and HIV positive status [11]. The HHV-8 negative cases of MCD remain idiopathic (iMCD) [12].

Another variant of HHV-8 related disease is primary effusion lymphoma [13]. Finally, HHV-8 has also been shown to cause Kaposi sarcoma in HIV positive patients, Africans in the central Africa region, and individuals from the Mediterranean basin [14]. Our network (Midway Specialty Care) consists of 12 practices dedicated to the treatment of HIV positive individuals as well as patients with conditions such as Hepatitis B and C and other infections. We are located throughout Florida. We currently manage approximately 5,400 HIV positive individuals from all strata of society.

Methods

We aimed to identify patients who fit the clinical and pathological criteria for multicentric Castleman's disease [15]. A retrospective chart review was performed in a sample size of 5,400 people living with HIV, consented for treatment. Demographics (ex. age, sex, race, ethnicity, and MSM status), lab data (ex. HIV and HHV-8 viral status), treatment regimen (ex. antiretroviral, chemotherapy) and clinical course were extracted from electronic medical records and clinical charts. Pathology reports were consistent with diagnosis of Castleman's disease including the hyaline-vascular variant (small hyaline-vascular follicles and capillary proliferation) and plasma-cell variant (large lymphoid follicles separated by sheets of plasma cells). Basic descriptive analysis was used to describe this data.

Results

We found 4 HIV positive patients who fit the pathologic criteria for multicentric Castleman's disease [15]. Their characteristics are described in Table 1. All were male with a history of sex with other men (MSM) and all showed evidence of HHV-8 viremia at the time of diagnosis. Three of the four patients received chemotherapy, which included rituximab. Rituximab has been shown to be very effective in treating HIV/HHV-8+ MCD [16,17]. Of the three treated patients, remission duration has been 5 to 89 months (Table 2). One patient declined chemotherapy treatment. No developments of lymphoma or deaths occurred during follow up. Lymphoma development has previously been described in multicentric Castleman's disease.7 All treated patients have regained normal function to date. All patients who received chemotherapy continued HIV treatment during the period of MCD treatment.

Table 1: Demographics and medical history of patients diagnosed with MCD

Patient #:	1	2	3	4
Current Age	50	54	48	38
Sex	M	M	M	M
Race	White	White	White	White
Ethnicity	Hispanic	Hispanic	Non-Hispanic	Hispanic
MSM Status	Yes	Yes	Yes	Yes
Years with HIV	0.5	7.5	1.8	7.9
Age at Dx of MCD	50	47	46	35
HHV-8 Status at Time of MCD Dx	Positive	Positive	Positive	Positive

Comorbidities	1. Kaposi Sarcoma 2. Hx of Salmonella Sepsis	1. Hepatitis C Virus 2. Primary Effusion Lymphoma 3. Squamous Intraepithelial Rectal lesion (p16+) 4. Herpes Zoster Virus 5. Hx of Secondary Sphilis 6. HPV Rectal Condyloma 7. Hx of Gonorrhea 8. Hx of Chlamydia	1. IRIS 2. Hx of H. pylori Gastritis 3. Hx of CMV Colitis 4. Hx of Chlamydial Lymphogranuloma 5. Hx of Syphilis 6. Hx of Chlamydia	1. Anal Papilloma 2. Thrombocytopenia 3. Hyperlipidemia 4. HPV 5. Oral Candidiasis 6. HHV-6
HIV Treatment(s)	1. bictegravir, emtricitabine, & tenofovir (current)	1. Hx of atazanavir, ritonavir, emtricitabine, & tenofovir 2. Hx of atazanavir, cobicistat, emtricitabine, & tenofovir 3. Hx of elvitegravir, cobicistat, emtricitabine, & tenofovir 4. bictegravir, emtricitabine, & tenofovir (current)	1. Hx of emtricitabine, tenofovir, & dolutegravir 2. Hx of bictegravir, emtricitabine, & tenofovir 3. Currently untreated	1. Hx of raltegravir, emtricitabine, & tenofovir 2. Hx of dolutegravir, abacavir, & lamivudine 3. Hx of darunavir, ritonavir, dolutegravir, & rilpivirine 4. Hx of darunavir, ritonavir, dolutegrarvir, emtricitabine, & tenofovir 5. dolutegrair, emtricitabine, & tenofovir (current)
Last CD4+ count before MCD Dx (cells/mm3)	49	85	451	102

Table 2: Treatments and length of remission of patients diagnosed with MCD

Patient	MCD Treatment	Length of Remission
1	rituximab & doxorubicin	5 months
2	R-EPOCH x6 (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)	7 years & 5 months (89 months)
3	Chemo declined	N/A
4	rituximab x10, gamma globulin x2	2 years & 10 months (34 months)

Conclusions

Our experience with multicentric Castleman's disease in HIV/HHV-8+ patients is consistent with the experience reported by others. Our experience also confirms the likely superiority of a regimen containing rituximab in achieving a longer remission in multicentric Castleman's disease (Table 3) [17-22]. We plan to continue our study of Castleman's disease in our population to try to understand better its pathophysiology. Limitations of our study include the retrospective review nature of our investigation and a small sample size with potential for selection bias, as well as a short follow up duration.

Table 3: Studies of HIV/HHV-8 patients with MCD treated with rituximab chemotherapy

Studies of HIV/HHV-8+ patients with MCD treated with rituximab			
Study	**n of patients**	**Associated treatment**	**Survival (mos)**
Corbellino, *et al.* [18]	1	None	14+
Marcelin, et al. [20]	5	None	4+, 6+, 14+, 1, 1
Newsom-Davis, et al. [22]	1	None	4+
Neuville, et al. [21]	2	etoposide	22+, 32+
Gérard, et al. [17]	24	None	12+ (n = 22) 1 (n = 1) 4 (n = 1)

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