RAPID COMMUNICATION

Kaposi's Sarcoma-Associated Herpesvirus-Like DNA Sequences in Multicentric Castleman's Disease

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Multicentric Castleman's disease (MCD) is an atypical lymphoproliferative disorder defined using clinical and pathologic criteria. A characteristic of the MCD is a close association with Kaposi's sarcoma (KS), which occurs during the clinical course of most human immunodeficiency virus (HIV)-associated MCD cases and also, but less frequently, in HIV-negative patients. Recently, sequences of a putative new Herpesvirus (KSHV) have been isolated and further detected in almost all the acquired immunodeficiency syndrome (AIDS) KS and in most of the non-AIDS KS samples. In this study, we searched for these Herpesvirus-like sequences in MCD samples of 31 patients. KSHV sequences were detected in 14 of 14 cases of HIV-associated MCD, including 5 cases without detectable KS. Moreover, KSHV was detected in 7 of 17 MCD cases in HIV-negative patients, including 1 case associated with a cutaneous KS. In 34 non-MCD reactive lymph nodes (follicular and/or interfollicular hyperplasia) in HIV-negative patients, KSHV was detected in only 1 case. In 1 HIV-negative case of MCD, KSHV was found in both the lymph node and peripheral blood samples. These data suggest that KSHV could play a role in the pathogenesis of MCD, especially in HIV-infected patients.

MULTICENTRIC Castleman's disease (MCD), also called multicentric angiofollicular lymphoid hyperplasia, is an atypical lymphoproliferative disorder (ALPD) defined using clinical and pathological characteristics.[1] This usually polyclonal lymphoid proliferation[2] with vascular hyperplasia involves multiple lymphoid organs. Severe systemic signs are frequently observed. Two types of recurrent malignancies, lymphoma and Kaposi's sarcoma (KS) have been described to occur during the course of MCD in 18% and 13% of cases, respectively.[1] Both the cutaneous and nodal forms of KS have been reported to be associated with this disease.[3-10] Similar clinical and pathologic features of MCD have been found in human immunodeficiency virus (HIV)-infected patients with lymph node hyperplasia.[11-13] Striking evidence is the close association between KS and MCD in these HIV-associated cases, with the presence at diagnosis or the subsequent development of KS being found in 75% of the patients with MCD (Oksenhendler et al, unpublished observations).

Sequences of a putative new Herpesvirus (descriptively named KSHV) have been isolated recently by the method of representational difference analysis (RDA).[14] KSHV sequences share homologies with Epstein-Barr virus (EBV) and Herpes virus saimiri sequences and were detected in almost all the acquired immunodeficiency syndrome (AIDS)-associated KS samples of both forms, cutaneous or nodular.[14-21] Moreover, KSHV sequences were also detected in the non-AIDS KS, classical or endemic (central Africa), whereas KSHV was rarely or not detected in panels of non-KS controls,[14-21] with the exception of a rare form of lymphomas occurring in HIV-infected patients (AIDS-related body-cavity–based lymphomas).[22] Infection with the putative new Herpesvirus-like appears to be a major factor in the development of KS.

The relevant association of MCD with KS and some common features of the two diseases led us to search for the presence of KSHV sequences in MCD samples. We report here that these sequences are frequently found in samples with HIV-associated and non-HIV–associated MCD.

MATERIALS AND METHODS

Patients. Thirty-one patients with MCD, who were mainly from two institutions (Hôpital Saint-Louis and Hôpital Pitié-Salpétrière, Paris, France), were analyzed in the study (Table 1). Patients are identified by the unique numbers used in a previously published report.[2] Seventeen patients were HIV negative, among whom 7 were associated with another pathologic process. Case C12 was associated with a cutaneous KS. In the C11 case, symptoms of the POEMS syndrome were present, including peripheral neuropathy.[23] Two cases (C8 and C9) were associated with a B-cell lymphoma, 3 cases (C5, C6, and C7) with Hodgkin's disease. In C10, a B-cell immunoblastic lymphoma was secondarily detected (no tissue of this subsequent lymphoma was conserved). Nine of the 14 HIV-positive patients presented an MCD associated with a KS.

Reactive lymph nodes (follicular and/or interfollicular hyperplasia) from 34 HIV-negative patients were also studied.

Tissues. Tissues were obtained by surgical biopsy for all patients except for case C35. For this last case, a lymph node aspirate and a peripheral blood sample were obtained. Tissue samples were fixed in buffered formalin and processed for histology. Samples were also immediately frozen and stored at −80°C. In each case, MCD was independently diagnosed by two investigators. MCD histologic characteristics[24] are summarized in Table 1. Four cases were found of

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This report is dedicated to the memory of Professor Marie-Françoise d'Agay, MD.

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Table 1. Clinical and Laboratory Findings in 31 Patients With MCD

Case*	Age/Sex	Histology	Systemic Signs	γ-Globulins	KSHV Sequence		Associated Disease
					PCR	Southern	
HIV-negative cases							
C5	41/M	HV/PL	+	13	–	–	HD
C6	38/M	PL	–	22	–	–	HD
C7	39/M	PL	+	25	–	–	HD
C8	61/M	HV	+	8	–	–	B-NHL
C9	71/F	HV	–	12	+	–	B-NHL
C10	53/M	PL	+	64	+	+	†
C11	50/M	PL	+	14	+	–	POEMS
C12	62/M	PL	+	26	+	–	KS‡
C13	25/F	HV	–	16	+	–	
C14	21/M	PL	–	26	–	–	
C15	45/M	PL	+	70	–	–	
C16	46/F	PL	–	31	–	–	
C17	64/F	HV/PL	+	20	–	–	Bone lesions
C18	53/M	HV/PL	+	80	+	+	
C19	26/F	HV/PL	+	63	–	–	
C20	71/M	PL	+	40	–	ND	
C35	68/M	HV/PL	+	80	+	ND	
HIV-associated cases							
C21	32/F	PL	+	ND	+	ND	
C22	36/M	PL	+	22	+	ND	
C23	38/M	HV/PL	+	ND	+	+	KS
C24	24/M	HV/PL	+	24	+	+	KS
C25	41/M	HV/PL	+	42	+	+	KS
C26	52/M	HV/PL	+	23	+	+	KS
C27	47/M	PL	+	43	+	+	KS‡
C28	45/M	PL	+	27	+	+	KS
C29	67/M	PL	+	25	+	+	KS
C30	22/M	PL	+	33	+	+	KS
C31	32/M	HV	+	16	+	ND	KS‡
C32	36/M	HV/PL	+	13	+	+	
C33	28/M	HV/PL	+	25	+	+	
C34	26/M	HV/PL	+	20	+	+	

Abbreviations: PL, plasma cell type; HV, Hyaline vascular type; HV/PL, mixed type; HD, Hodgkin's disease; B NHL, B-cell non-Hodgkin's lymphoma; PCR, PCR amplification of the $KS330_{233}$ fragment; Southern blot, hybridization with both the KS631Bam and $KS330_{233}$ probes; ND, not done.

* Patients are identified by the unique numbers used in a previously published report.[2]

† An NHL was detected on a biopsy performed 2 months after.

‡ KS lesions on another site.

the hyaline-vascular type (1 HIV^+), 15 of the plasma cell type (6 HIV^+), and 12 cases of the mixed type (7 HIV^+).

Polymerase chain reaction (PCR) detection of KSHV sequences. PCR amplifications of KSHV sequences were performed on DNA from all samples using the primer set for $KS330_{233}$ as described in Chang et al.[14] After electrophoresis in agarose, PCR products were transferred to nylon membrane and were hybridized to a $^{32}\gamma$-kinased 25-base primer[14] or with the primer 5′-GGAACTTGATCTATA-TACCAC-3′ (KS-int/2).

Southern blot analysis of KSHV sequences. Two nonoverlapping probes, $KS330_{233}$ and KS631Bam, were produced by cloning the corresponding PCR-amplified products using the pCR-Script SK(+) cloning kit (Stratagene, La Jolla, CA). The KS631Bam fragment[14] was amplified from a KS tissue DNA with the primer set 5′-TAG-GATCCGCTGGCAGGTGGG-3′ and 5′-ATGGATCCACGGAGC-ATACACC-3′. The $KS330_{233}$ fragment was amplified as described.[14] Southern blots were performed on high molecular weight DNA accordingly to standard methods.[25] DNAs were digested by *Eco*RI, *Bgl* II, or *Xba* I restriction enzymes, transferred to nylon membrane, and hybridized to both probes. Final washes were performed at 60°C in 0.1× SSC, 0.1% sodium dodecyl sulfate (SDS).

Positive and negative controls for PCR and Southern blot. Four AIDS-KS lymph nodes without MCD were tested as positive controls for KSHV sequence PCR amplification. One of these samples was also tested by Southern blot and found to be positive with both KSHV probes. Peripheral blood mononuclear cells of a healthy blood donor, an EBV-immortalized cell line, and a B-cell lymphoma were used as negative controls and were found to be negative by PCR and Southern blot. Representative experiments are shown in Figs 1 and 2.

RESULTS

The results of KSHV sequence detection are summarized in Table 1.

Analysis of MCD samples in HIV-infected patients. In all 14 cases with histologic evidence of MCD (16 samples), KSHV sequences were detected by PCR analysis (Table 1

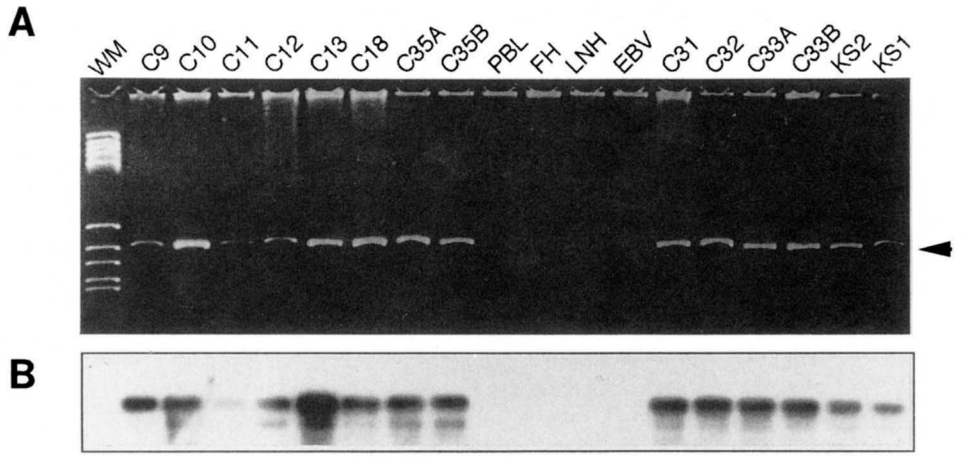

Fig 1. PCR amplification of Herpesvirus-like sequences in MCD cases. (A) Electrophoresis in polyacrylamide of the $KS330_{233}$ PCR products stained by ethidium bromide. (B) Hybridization with KS-int/2 primer of the same PCR products after electrophoresis in agarose and transfert. The 233-bp PCR products hybridized at high stringency to the 25-mer primer designed by Chang et al[14] in all cases except C18 and KS2 (an AIDS-KS positive control; data not shown), probably because of a sequence variability (polymorphisms of the $KS330_{233}$ sequences have been shown).[16] MCD case numbers are indicated according to Table 1. C35A, HIV-negative MCD lymph node; C35B, peripheral mononuclear blood cells. C33A, HIV-associated MCD lymph node; C33B, spleen. PBL, peripheral mononuclear blood cells of a healthy blood donor; NHL, a B-cell non-Hodgkin lymphoma; FH, an HIV-negative follicular hyperplasia; EBV, an EBV-immortalized cell line of another healthy blood donor. KS1 and KS2, AIDS-associated KS. WM, weight marker.

and Fig 1). These sequences were detected in the MCD lesions not associated with KS (5 cases), associated with KS in separate sites (2 cases), or as expected when both processes were present in the same lymph node (7 cases; Table 1). Southern blot hybridization detected KSHV with both probes in 11 tested cases (Table 1). In cases C27 and C33, KSHV were present in both the MCD-involved lymph node and spleen.

Analysis of MCD samples in HIV-negative patients. Seven of 17 MCD lymph nodes DNAs from HIV-negative patients were PCR positive for KSHV (Table 1 and Fig 1). Of them, 6 were tested by Southern blot, which detected KSHV with both probes in 2 cases (C10 and C18), whereas in 4 other cases (C9, C11, C12, and C13) no signal was detected (Fig 2). In 1 case (C35), peripheral mononuclear blood cells were studied and were found to contain KSHV sequences at a level detectable by PCR but not by Southern blot (Figs 1 and 2). Among the 7 MCD cases showing evidence of KSHV, case C9 was associated with a B-cell lymphoma, C11 was associated with a POEMS syndrome, and only case C12 was associated with a cutaneous KS. New samples of 5 available MCD tissues that had been found to be positive (C10, C12, C13, C18, and C35) were prepared and analyzed by PCR with consistent results (data not shown).

Analysis of reactive lymph nodes samples from HIV-negative patients. Thirty-four non-KS non-MCD lymph nodes from different patients with reactive follicular and/or interfollicular hyperplasia were tested by PCR. One sample contained KSHV sequences. This sample was an isolated axillar lymph node with pathologic evidence of follicular hyperplasia from a 29-year-old HIV-negative woman without associated clinical signs. The 33 other lymph nodes were negative for KSHV detection (data not shown).

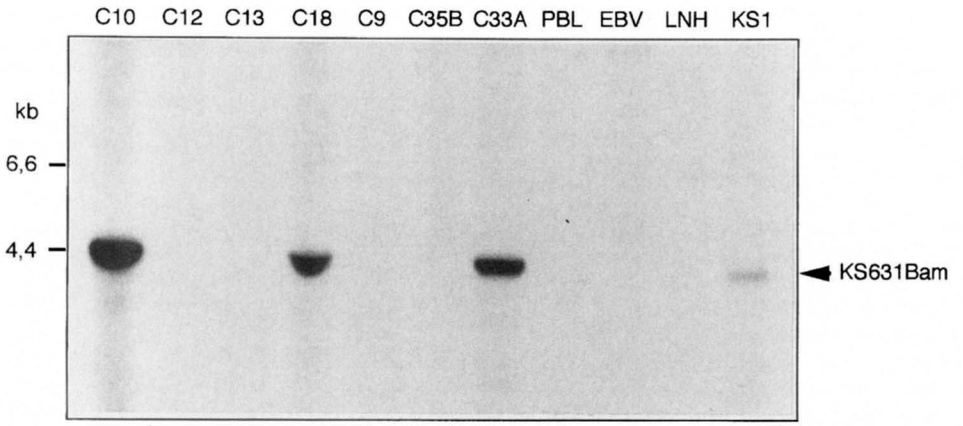

Fig 2. Southern blot analysis of Herpesvirus-like sequences in MCD cases. The *Eco*RI-digested DNAs were hybridized with the KS631Bam probe. MCD case numbers are indicated. Abbreviations are as in the legend for Fig 1.

Table 2. KSHV Sequences in KS, MCD, and Reactive Lymph Nodes

Tissue	HIV⁻	HIV⁺	References
KS	67/73	88/91*	14-21, this study†
MCD	7/17‡	14/14§	This study
Reactive lymph nodes	1/51	3/17	14, 15, this study

* Includes 2 samples negative for probable technical reasons.[14]

† Includes the 4 AIDS-KS cases (positive controls) of this study.

‡ One case with an associated cutaneous KS.

§ Five cases without detectable KS, 2 cases with KS in another site, and 7 cases with both MCD and KS lesions associated on the same sample.

DISCUSSION

We have searched for KSHV sequences recently isolated from KS[14] in MCD tissues. We detected KSHV sequences in all HIV-associated MCD tissues, including 7 cases with both KS and MCD in the same sample and 7 cases in which no KS lesions were detectable in MCD tissue (5 cases without KS and 2 cases associated with KS in another site). In non-KS AIDS lymph nodes, KSHV has been reported to be detected in 3 of 12 and 0 of 5 cases (Table 2).[14,15] In HIV-negative MCD, we detected KSHV in 7 of 17 cases, including 1 case associated with a cutaneous KS. In 7 and 10 reported cases of non-KS non-AIDS lymph nodes, KSHV has not been detected (Table 2).[14,15] To evalue the significance of this positivity rate in the HIV-negative MCD cases, reactive lymph nodes (follicular and/or interfollicular hyperplasia) of 34 HIV-seronegative patients were analyzed, with only 1 positive case found. Statistical analysis showed that KSHV was detected in the HIV-negative MCD cases in a significantly higher rate than in the reactive lymph nodes of the control group ($\chi^2 = 12.5$; $P < 10^{-3}$).

KS has been significantly reported in the course of MCD in 13% of HIV-negative patients[1] and in 75% of HIV-infected cases (Oksenhendler et al, unpublished observations). Vascular hyperplasia are observed in both pathologic lesions. Both processes are associated with immune dysregulation, including HIV infection.[1,11-13,26] Cytokines, including interleukin-6, are major growth factors for both cellular proliferations and are detected at high levels in involved tissues.[26-30] Whereas the presence of KSHV sequences in near all KS samples strongly suggests a key role for this putative new virus in the pathogenesis of KS, the presence of KSHV in most cases of MCD in our series needs to be elucidated. As suggested by Chang et al,[14] undetected microscopic KS foci may have been present in some AIDS lymph nodes referred as non-KS, given the high life-time occurence (>50%) in some high-risk groups of AIDS patients. This could also be suggested for HIV-negative MCD because the affected patients are also at risk for developing KS (13%). Alternatively, MCD lymph nodes may have been asymptomatically infected by this putative virus. Third, it could be hypothetized that the cellular proliferation seen in MCD may have been related to the presence of this putative new virus acting as a cofactor (perhaps as a stimulus for cytokines) in a context of immune dysregulation. Other Herpesviruses, such as EBV, should play a role in some cases of MCD.[31] As in AIDS-KS, HIV infection may enhance the MCD proliferation by inducing immunodeficiency and synergy of HIV proteins with cytokines.[32]

Epidemiologic analysis of KS in AIDS patients has suggested a transmission by sexual contact of putative KS-associated infectious agents.[33] The presence of KSHV in mononuclear blood cells of an MCD patient (other cases not tested) raises the possibility of a blood transmission of this putative virus, as also suggested in patients with KS by two recent reports.[19,34] KSHV sequences were not detected in mononuclear blood cells of the wife and son of this patient (unpublished data).

In conclusion, sequences of the new putative Herpesvirus associated with KS were detected in a significant number of MCD cases. Infection with this putative Herpesvirus could play a role, associated with abnormal cytokines regulation, in the pathogenesis of this lymphoproliferative disorder, especially in HIV-infected patients.

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Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease [see comments]

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