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REVIEW

Epidemiology and clinical characteristics of classic Kaposi's sarcoma, seroprevalence, and variants of human herpesvirus 8 in South America: A critical review of an old disease

Salim Mohanna*, **Vicente Maco, Francisco Bravo, Eduardo Gotuzzo**

Instituto de Medicina Tropical "Alexander von Humboldt", Universidad Peruana Cayetano Heredia, Lima 27, Peru

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Summary

Objective: To review the current South American literature on classic Kaposi's sarcoma (KS) and human herpesvirus 8 (HHV-8), and point the way for studies that still need to be performed.
Materials and methods: The authors performed an exhaustive search in LILACS, SCIELO and PUBMED databases for classic KS and HHV-8 in South America. The relevant material was evaluated and reviewed.
Results: More than 250 cases have been reported with three big case series (Argentina, Colombia and Peru). The classic KS form seen in Colombia resembles the type of disease seen among African communities; the same unusual presentation with confluent exophytic nodules or eroded lesions has been noticed in Peru. Low rates of HHV-8 antibodies have been found in blood donors from Chile, Argentina and Brazil (3%, 4%, 2.8—7.4%, respectively); whereas high rates of HHV-8 antibodies have been found in Amerindians from Brazil and Ecuador. Five specimens from Argentina were subtyped: (three classic KS and two AIDS KS); the identified strains fell into subtypes A and C. AIDS-related KS specimens from Brazil and Venezuela were subtyped: (43 and nine respectively); analysis grouped them predominantly into subgroups A, B and C. A new HHV-8 subtype E was found endemic in Brazilian and Ecuadorian Amerindians. In French Guiana ten endemic KS and six AIDS-related KS specimens were subtyped; analysis grouped them predominantly into subgroups A, B and C.

* Corresponding author. Tel.: +511 475 0573; fax: +511 265 3646.
E-mail address: salim17@yahoo.com (S. Mohanna).

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Conclusion: Classic KS in South America has a very similar clinical presentation but not the same as the classic KS variety described in the Mediterranean. Initial seroprevalence studies performed in the general population and in blood donors showed low seroprevalence of HHV-8, whereas high seroprevalence rates were seen in Amerindian population. The existing serological assays, nonetheless, need to be further refined, and new assays need to be developed. Finally, the key to understanding the precise molecular epidemiology and phylogenetic distribution of HHV-8 in South America would be to perform more subtyping of classic KS cases.

Introduction

Kaposi's sarcoma (KS) was first described in 1872 by Moriz Kaposi.[1] Kaposi's sarcoma has been classified into four clinical-epidemiological variants. These variants include the original classic KS, African or endemic KS, iatrogenic or immunosuppression-related KS, and epidemic or AIDS-related KS. Classic KS occurs predominantly among elderly people, with a higher incidence in southern and eastern European countries, with a predominance among Jews, Italians and Greeks.[2]

In 1994, Chang et al.[3] identified by representational-difference analysis DNA sequences of a new herpesvirus, homologous to Epstein Bar virus and Herpes virus Saimiri, named Kaposi's sarcoma herpesvirus or human herpesvirus 8 (HHV-8). Since then, HHV-8 DNA sequences have been detected in almost all KS lesions analyzed, whether endemic, classic, iatrogenic or epidemic.[4]

HHV-8 is not found uniformly throughout the world's population as is the case for most other human herpesviruses.[5] The spread of the virus among the human population varies widely depending on the geographical region. Low HHV-8 seroprevalence rates (0—5%) were found in northern Europe, Asia and North America; intermediate HHV-8 seroprevalence rates (5—20%) were reported in the Mediterranean, Eastern European, and Caribbean countries; and high HHV-8 seroprevalence rates (>50%) were detected in central and southern Africa.[6] Molecular epidemiological studies have revealed that HHV-8 has a highly variable open reading frame (ORF) K1 gene at the left end of its genome, and that this variability makes the K1 gene a very good marker for HHV-8 genotyping and strain differentiation.[7] Six major molecular subtypes of the K1 gene have been described from specimens obtained around the world. The first subtypes to be identified were A, B, C, and D, followed by subtypes E and N.[8—12]

This article reviews the data that has been generated by investigators through South America and draws conclusions from the present body of knowledge, as well as shows where the data are still controversial, and leads the way for studies that still need to be performed.

Materials and methods

An exhaustive bibliographic search was performed on LILACS, SCIELO and PUBMED databases on records up until December 2004. The authors searched original articles, case series, case reports, and letters to editors concerning classic KS and HHV-8 in South America (Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Peru, Suriname, Uruguay, and Venezuela). Likewise, non-indexed journals and doctoral theses that contained information about these topics were also searched. All relevant material was evaluated and reviewed.

Results

Peru

In 1968 Paredes-Pacheco and Albújar[13] reported the first case of classic KS. The patient was a 58-year-old indigenous male with purple nodules on his arms and legs. In 1985 Maita et al.[14], with the purpose of evaluating the immunoperoxidase method in the search for factor VIII antigen, reported 27 cases (21 male, six female) of classic KS found between 1968 and 1982. Patients ranged from 22 to 81-years-old. Most of them presented with multiple lesions (81.5%). The most common sites of presentation were the lower and upper limbs with ulcerated and hyperkeratotic lesions. There was one case on the trunk, one on the stomach, one on the breast and one with disseminated lesions. Seven cases presented with edema in the lower limbs. In 1998, Valverde and Albújar[15] reported two cases of classic KS with unusual characteristics in Trujillo. The first patient was a 51-year-old male with a nodule on his right index finger. The second patient

was a 74-year-old male with a nodule on his left thumb. Among the 4305 cases of malignant neoplasia registered between 1984 and 1990 in the Trujillo Metropolitan Cancer Registry, three were found to be classic KS cases.[8]

In 1996 Echegaray et al.[16] reviewed the clinical records from 81 patients with KS diagnosis (62 with classic KS and 19 with AIDS-related KS) between 1949 and 1994 at the National Cancer Center of Lima (INEN as per its Spanish abbreviation). The mean age of the patients was 64.1 years, with a male-female ratio of 3:1. Pain and edema were present in 34 (55%) patients. Forty-three patients (62%) had KS lesions localized on lower limbs and 16 patients (16%) had a diffuse presentation. Twenty-four patients (39%) had one lesion, whereas 38 (61%) had multiple lesions. Ten patients (16%) presented with eroded lesions. Five percent of patients had a past medical history of sexually transmitted diseases (STD). No reference was made to the place of origin and background of these patients. In 1997 Cano[17] reviewed 22,863 records for the period 1991—1995 from the pathology department of Hospital Nacional Cayetano Heredia. He found 29 cases of KS, making it the third most common malignant tumor (14.87%). There was no information regarding clinical presentation, ethnic origin or immune status of these patients. Finally, in 2004 Mohanna et al. (in press) reported the unusual presentation of a 53-year-old indigenous patient (Quechua) with purplish-brown nodular lesions in the lower extremities, miliary and central nervous system tuberculosis. ELISA-HIV tests were negative and immunohistochemistry (IHC) of the tumor tissue was positive for HHV-8. This was the first case in Peru where HHV-8 was found in KS lesions through immunohistochemical techniques.

Venezuela

In 1995 Essenfeld de Sekler et al.[18] reported one case of classic KS with pulmonary involvement in an immunocompetent patient. In 2003 Hernandez et al.[19] reported the molecular characterization of nine AIDS-related KS specimens. The results showed subtype B in five patients (56%), subtype C in three patients (33%), and subtype A in one patient (11%). Patients represented a mixed population that developed as a result of the intermixing of several generations of Spaniards, Indians, and blacks.

Ecuador

In 2004 Whitby et al.[20] reported that in Ecuadorian Amerindians, the Huaorani had a high prevalence of antibodies against HHV-8, with 38 of 38 subjects reacting in both the latent nuclear antigen (LNA) immunofluorescence assay (IFA) and LNA ELISA, while 24/38 (63%) were positive in the K8.1 assay. The Siona people had a lower prevalence of antibodies to LNA by IFA (10/41, 24%) and ELISA (8/41, 20%) and to K8.1 (10/41, 24%). Ecuadorians of African descent had the lowest prevalence, with 11/80 (14%) being positive for K8.1, 14/80 (17.5%) by LNA ELISA and 10/80 (12.5%) by LNA IFA. K1 sequence was obtained from three Huaorani and two Siona subjects. All sequences were characterized as subtype E, based on K1 analysis. Ecuadorian sequences formed a separate branch within the subtype E grouping and the Huaorani and Siona sequences clustered separately within this branch. All strains had the P allele of K15. They obtained a T0.7 sequence from an African Ecuadorian; this sequence was clearly characterized as subtype B.

Colombia

In 1989 Garcia et al.[21] reported 79 cases of classic KS seen at the National Institute of Cancer, Bogotá, from 1935 to 1985. Those cases represented 5% of all soft tissue sarcomas and approximately 1% of all malignant tumors. There were 70 men and nine women, with a male-female ratio of 8:1. The mean age of the patients was 65 years. Fifty-nine patients (74%) belonged to the 61 to 80 years-old age group. Most of them were white or mestizo patients of low socioeconomic status and the majority were farmers. The mean time of evolution of the disease before consultation was 1.7 years. Fifty-five patients (70%) had nodules, whereas 25 had patches and nodules (32%) and these were occasionally confluent and exophytic. Twenty-two patients (28%) had eroded lesions, most of which were bleeding ulcers. Leg, foot, or hand edema associated with the KS lesions was the main finding in 38 patients (48%). Satellite inguinal adenopathies were found in 18 patients (23%). No black patients were seen, but the classic KS form seen in their patients resembles the type of disease seen among African communities.

Brazil

In 1986 Fagundes et al.[22] reported one case of classic KS associated with mycosis fungoides in a 65-year-old male. In 1998 Alonso et al.[23] reported seven cases of classic KS on which they reviewed histopathology and immunohistochemical aspects. In 2001 Costa et al.[24] reported one case of classic KS. In 2002, Arnone et al.[25] reported one case of disseminated classic KS in a 68-year-old male. In 1998 Caterino-de-Araujo[26] reported the molecular char-

acterization of seven tissue samples obtained from AIDS-related KS patients from Sao Paulo. Three patients were of Italian origin, three of Portuguese origin, and one of Arabian origin. Analysis of HHV-8 Brazilian isolates grouped them predominantly into groups B and C. In 1998 Zhang et al.[27] reported a study where nine of 14 homosexual men HIV-positive/KS-positive (64%) were seropositive by IFA for LNA of HHV-8. In 1999 Caterino-de-Araujo[28] reported the seroprevalence of HHV-8 in a small group of blood donors. They used IFA for LNA, and found that six of 81 blood donors (7.4%) were seropositive.

In 2000, Zago et al.[29] reported that HHV-8 antibodies were detected in a low frequency in blood donors (4.6%) and in patients attending casualty departments (9.6%). In the HIV-negative group from the STD/AIDS clinics, HHV-8 antibodies were present in only 3.7% of patients. In contrast, a higher frequency of antibodies was observed in the HIV-positive/KS-positive group (80%) and in the HIV-positive/KS-negative group (14.6%). All serum samples were analyzed by an IFA method to the LNA of HHV-8. In the same year, Biggar et al.[30] using an IFA test for LNA demonstrated that the prevalence of HHV-8 in 781 Amerindians of diverse tribes (overall 53% prevalence) was not related to language group or sex, but rather increased gradually from 41% in children $<$10 years of age to 65% in adults $\geq$30 years of age. In IFA positive subjects, HHV-8 DNA was detected in three (16%) of 19 mononuclear cell samples from peripheral blood. K1 was amplified from blood samples from two of the three PCR positive subjects, using nested PCR, and samples were sequenced. The Amerindian K1 sequences were 95% identical to each other, but they differed from previously reported A, B, C and D subtype HHV-8 K1 sequences by 25–30%. Thus, a new HHV-8 subtype, E, is hyper-endemic in Brazilian Amerindians, although KS has not been reported.

In 2001 Keller et al.[31] reported the seroprevalence of HHV-8 on HIV-positive patients. Using PCR, 74.4% (29/39) of the KS-positive patients and 3.7% (1/27) of the KS-negative patients were positive for the KS330 sequence. LNA and lytic assays detected the same number of HHV-8 positive patients in each group, 31 (79.5%) in the KS-positive group and five (18.5%) in the KS-negative group; of these, 24 (77.4%) and three (60%), respectively, were detected by both antigens. Thirty-eight (97.4%) of the KS patients were found to be HHV-8 seropositive by both serological tests. In 2002 Freitas et al.[32] reported a seroprevalence study in normal populations inhabiting two neighboring, crowded districts of northern Brazil. Detection of IgG antibodies to HHV-8 was done using a commercial ELISA. Overall, 16.3% (81/497) of tested persons had HHV-8 antibody, with prevalence rates increasing from 12–33.3% across age groups. Similar prevalence rates were found for women and men (18.4% and 14%, respectively). In 2002 Zong et al.[33] reported the molecular characterization of three AIDS-related KS cases from Brazil. The results showed A1, A8, and C3 subtypes.

In 2003 Caterino-de-Araujo[34] reported a seroprevalence study performed in women from Sao Paulo. The first group was comprised of 163 HIV-positive women; they presented an overall HHV-8 antibody frequency of 8.6%, a 1.2% frequency of anti-latent antibodies and an 8% frequency of anti-lytic antibodies. The second group was comprised of 108 children born to HIV-positive mothers; they presented an overall frequency of 7.4% HHV-8 antibodies, ranging from 10.9–0%. A 10.9% frequency of HHV-8 antibody was detected among HIV-positive children, and an 8.3% frequency was observed in children with undefined HIV status. The third group was comprised of 630 HIV-negative healthy women; they presented an overall HHV-8 antibody frequency of 1.3%, a 1.1% frequency of anti-latent antibodies and a 0.3% frequency of anti-lytic antibodies. In the same year, Caterino-de-Araujo and Lopes Cibella[35] reported a study that searched for HHV-8 antibodies in plasma samples from children born to HIV-infected mothers from Sao Paulo. All plasma samples were tested by an IFA LNA and IFA to lytic antigens. No cases of anti-latent antibodies were detected, contrasting with the 7.4% of anti-lytic antibodies detected among children born to HIV-infected mothers. High frequencies of HHV-8 antibodies were detected in confirmed HIV-infected children (6/55; 10.9%) and in children with undefined HIV status (2/24; 8.3%). In contrast, no cases of HHV-8 positive antibodies were detected among HIV-negative children (0/29).

In 2004 Nascimento et al.[36] reported the molecular characterization of 33 AIDS-related KS specimens from Sao Paulo. Nineteen patients reported their ethnicity to be Caucasian, nine reported African descent, four reported mixed origin, and one patient was of Amazonian descent. Only three of the major HHV-8 subtypes were detected, with 48%, 21%, and 30% of patients harboring subtypes A, B, and C. In the same year, Souza et al.[37] reported a seroprevalence study performed in 643 healthy children and young adults from the general population in ten different areas in Sao Paulo, all in high risk groups for HHV-8 infection. They found an overall seroprevalence of 2.5% among healthy children and adults from the general population using lytic IFA. No cases were found positive using the LNA IFA. For high risk groups they found 32.6% seroprevalence of HHV-8 in HIV negative homosexuals; 39.2% in HIV-positive/KS-negative patients; and, 98.7% in HIV-positive/KS-positive patients, using lytic or LNA IFA.

Finally, Perez et al.[38] reported a seroprevalence study performed in 319 blood samples obtained from Campinas, Sao Paulo. They found an overall seroprevalence of 2.8% (3.8% in males and 0% in females) using IFA for lytic antibodies.

Argentina

In 1983 Eigelman et al.[39] reported four cases of KS. In 1985 Paterno et al.[40] reported ten cases of KS in which factor VIII was demonstrated by immunohistochemical techniques. In 1989 Nudenberg[41] reported a 73-year-old male with classic KS characterized by lesions on the trunk, lower and upper limbs. Partial remission was obtained after radiotherapy. In 1994, Freuler et al.[42] reported KS in two middle-aged males without evidence of HIV infection. The first patient presented with nephrotic syndrome; after treatment he developed fever and diffuse lymphadenopathies. Biopsies revealed KS and Castleman's disease. Serology for HIV proved negative several times. The second patient was admitted with sepsis caused by *Proteus mirabilis* and died 48 hours later. Serology for HIV proved negative. Necropsy revealed KS on his knee and liver.

In 1998 Bacchiocchi and Brusco[43] reviewed the clinical records of 42 patients with classic KS observed during the previous 25 years at the Hospital Privado de la Comunidad de Mar del Plata. Those 42 cases comprised 0.01% of dermatological consultations and 0.0005% of general consultations. Patients ranged from 51 to 86-years-old, with a male-female ratio of 1:1. The background was obtained for 34 patients: 24 were Italian, seven were Spanish, two Polish, one Jewish and eight Argentines. Multiple lesions were presented in 42.9% of patients. Most of them presented with nodular lesions (85.7%). Lower limbs were affected in 83.3% of patients. Ulceration was presented in 31%, edema in 23.8% and pain in 2.4%. A second primary malignancy was noted in 11.9%. During the 6.5 years of follow up, no deaths were associated with classic KS.

In 2001 Feinsilber et al.[44] reported six patients with classic KS treated with intralesional interferon with no complications. In the same year, Meng et al.[45] reported the molecular characterization of five specimens of KS (three classic KS and two AIDS-related KS). Two of the identified strains fell into subtype I/A and three in subtype II/C. The two subtype I/A strains were more divergent within the subtype, with one falling into each of the two main subtypes I/A clades. The three subtype II/C strains clustered relatively closely within one of the two main II/C clades. Two of the classic KS patients had European origins.

In the same year Sosa et al.[46] reported seroprevalence of HHV-8 among HIV-positive IVDUs, and HIV-negative IVDUs and non-IVDUs by an in-house IFA. Among the HIV-positive IVDUs, 25/144 (17.36%) were HHV-8 positive. In the HIV-negative IVDUs, 11.1% were HHV-8 positive. In contrast, HHV-8 seroprevalence in HIV-negative non-IVDUs was 5.71%.

In 2004, Perez et al.[38] reported an overall seroprevalence of 4% (3.6% in males, and 4.9% in females) performed in 1859 blood samples obtained from blood banks from three different geographic regions: Buenos Aires (4.3%), Bahia Blanca (2.4%), and Cordoba (3.4%). They used IFA for lytic antibodies.

Chile

In 1992 Fich and Moraga[47] reported one case of classic KS in a 33-year-old male with nodules and plaques on lower limbs. Moncayo et al.[48] reported four cases of classic KS between 1979 and 1994. In 2004 Perez et al.[38] reported a seroprevalence study performed in 300 blood samples obtained from the blood bank of the Hospital Clinico J.J. Aguirre, Santiago de Chile. They found an overall seroprevalence of 3% (2.5% in males, and 3.8% in females) using IFA for lytic antibodies.

French Guiana

In 2000 Fouchard et al.[4] reported the molecular characterization of seven specimens of KS (five endemic KS and two epidemic KS). They performed sequence analysis for fragments of gene coding for the capsid protein (ORF26) and the tegument protein (ORF75). By subtyping the fragment of ORF26, they found that two strains belonged to subtype B and the remainder to subtype C. Surprisingly, sequence analysis of the ORF75 fragment only revealed the A or the C subtype, with several minor variants (A″, A‴ and C). They mentioned that the low level of genomic diversity is similar (1—2%) in subtypes A, B and C when considering ORF26 and ORF75.

In 2000 Plancoulaine et al.[49] reported a seroprevalence study to evaluate HHV-8 transmission from mother to child and between siblings. They included 1337 individuals that belonged to Noir-Marron, descendants from slaves of African origin. The overall HHV-8 seroprevalence was 13.2%, with no significant difference between sexes. All plasma samples were tested by IFA. In the same year Lacoste et al.[50] reported the molecular characterization of ten specimens of KS (four AIDS-related KS, five endemic KS, and one iatrogenic KS). Analysis revealed three of the major subtypes (A, B and

C). In 2002 Plancoulaine et al.[51] reported a seroprevalence study to evaluate the influence of age and gender on anti-HHV-8 antibody titers among HHV-8 seropositive subjects in an endemic population. The study included 1819 subjects with an overall HHV-8 seroprevalence of antibodies against lytic antigens of 11.8%. Among the 214 HHV-8 seropositive subjects, anti-HHV-8 antibody titers were found to strongly increase with age and were statistically significantly higher in males than in females.

No information was obtained for classic KS or HHV-8 in Bolivia, Uruguay, Paraguay, Guyana or Suriname.

Discussion

Classic KS has been described in the literature as occurring predominantly in elderly men of Jewish, eastern European, or Mediterranean descent. In countries where seroprevalence of HHV-8 has been studied, data show that HHV-8 is not ubiquitous in general healthy human populations as is the case with other human herpesviruses.[5] Due to this particular distribution of HHV-8 in the world, a strong direct correlation between HHV-8 prevalence and classic KS occurrence has been shown by numerous studies. There are some exceptions, for example in Africa, where endemic juvenile KS is found in Uganda and Zambia, but not in Gambia or Ivory Coast even though all four countries have similar seroprevalence of antibodies to HHV-8. Likewise, in Alexandria (Egypt), Papua New Guinea, and in areas of China, the prevalence of HHV-8 is high, but KS prevalence is low.[52–54] Something similar has been described in Brazilian Amerindians, who had a high prevalence (53%), although KS has not been reported. This finding could suggest that some cofactors might be necessary for the development of KS, or it could be caused by some genetic predisposition.

This review shows that more than 250 cases have been reported, with three big case series (Argentina, Colombia and Peru) demonstrating that classic KS is a prevalent pathology in South America (Figure 1). The oldest series in South America was reported in Colombia in 1935, followed by the Peruvian series in 1949. An interesting clinical observation from Colombia is that the classic KS seen in their patients resembles the type of disease seen among African communities. The same unusual

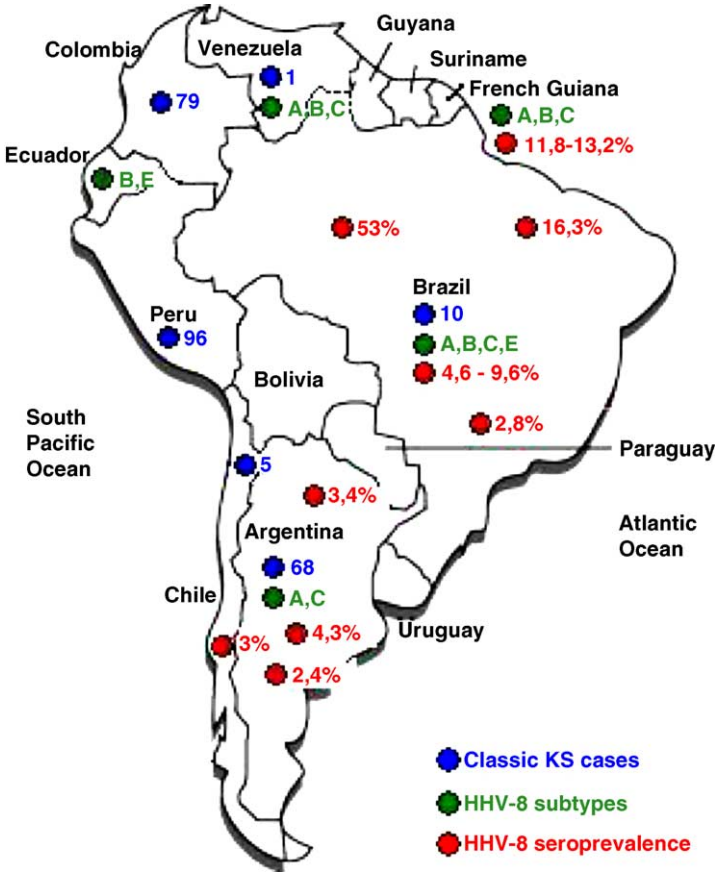

Figure 1 Distribution of classic KS cases, HHV-8 subtypes and seroprevalence in South America.

Table 1 HHV-8 seroprevalence studies in South America.

Country	Reference	Group	No. tested (positive %)	Test method
Ecuador	20	Huaorani Amerindians	38 (100%)	BCP-1 LNA IFA
			38 (100%)	LNA ELISA
			38 (63%)	K 8.1
		Siona Amerindians	41 (24%)	BCP-1 LNA IFA
			41 (20%)	LNA ELISA
			41 (24%)	K 8.1
		Ecuadorians of African descent	80 (12.5%)	BCP-1 LNA IFA
			80 (17.5%)	LNA ELISA
			80 (14%)	K 8.1
Chile	38	Blood donors	300 (3%)	Lytic BCBL-1 IFA
Argentina	38	Blood donors	1851 (4%)	Lytic BCBL-1 IFA
	46	HIV pos/IVDU	144 (17.36%)	BCBL-1 IFA
		HIV neg/IVDU	9 (11.1%)	BCBL-1 IFA
		HIV neg/non-IVDU	70 (5.71%)	BCBL-1 IFA
French Guiana	49	General population	1337 (13.2%)	IFA
	51	General population	1819 (11.8%)	Lytic IFA
Brazil	27	Homosexuals HIV pos/KS pos	14 (64%)	LNA IFA
	28	Blood donors	81 (7.4%)	BCP-1 LNA IFA
	29	Blood donors	747 (4.6%)	BCP-1 LNA IFA
		Casualty department patients	73 (9.6%)	BCP-1 LNA IFA
		HIV neg from STD clinic	136 (3.7%)	BCP-1 LNA IFA
		HIV pos/KS pos	40 (80%)	BCP-1 LNA IFA
		HIV pos/KS neg	48 (14.6%)	BCP-1 LNA IFA
	30	Amerindians	781 (53%)	BCP-1 LNA IFA
	31	HIV pos/KS pos	39 (74.4%)	PCR
		HIV pos/KS neg	27 (3.7%)	PCR
		HIV pos/KS pos	39 (79.5%)	LNA IFA & Lytic IFA
		HIV pos/KS neg	27 (18.5%)	LNA IFA & Lytic IFA
	32	General population	497 (16.3%)	ELISA
	34	HIV pos women	163 (1.2%)	IFA and WB LNA
		HIV pos women	163 (8%)	Lytic IFA
		Children born to HIV pos mother	108 (7.4%)	Lytic IFA
		HIV neg healthy women	630 (1.3%)	IFA & WB LNA
		HIV neg healthy women	630 (0.3%)	Lytic IFA
	35	Children born to HIV pos mother	108 (7.4%)	BCBL-1 Lytic IFA
		Children born to HIV pos mother	108 (0%)	BCBL-1 LNA IFA
	37	Healthy children and young adults	643 (2.5%)	Lytic IFA
		Healthy children and young adults	0	LNA IFA
		Homosexuals HIV neg	95 (21.1%)	Lytic IFA
		Homosexuals HIV neg	95 (20%)	LNA IFA
		HIV pos/KS neg	130 (34.6%)	Lytic IFA
		HIV pos/KS neg	130 (24.6%)	LNA IFA
		HIV pos/KS pos	78 (97.4%)	Lytic IFA
		HIV pos/KS pos	78 (75.6%)	LNA IFA
	38	Blood donors	319 (2.8%)	BCBL-1 Lytic IFA

IVDU: intra venous drug users; LNA: latent nuclear antigen; IFA: immunofluorescence assay; WB: western blot; Lytic: lytic antigen; BCP-1: cell line used as source of HHV-8; BCBL-1: cell line used as source of HHV-8; K8.1: lytic phase glycoprotein.

Table 2 Molecular characterization of Kaposi's sarcoma in South America.

Country	Reference	Specimen	Sex	Age	Origin	Biopsy	K1
Venezuela	19	AIDS KS	M	NS	Mixed[a]	Skin	B
		AIDS KS	M	NS	Mixed[a]	Skin	B
		AIDS KS	M	NS	Mixed[a]	Skin	B
		AIDS KS	M	NS	Mixed[a]	Skin	B
		AIDS KS	M	NS	Mixed[a]	Skin and Mucosa	B
		AIDS KS	M	NS	Mixed[a]	Skin	C
		AIDS KS	M	NS	Mixed[a]	Skin	C
		AIDS KS	M	NS	Mixed[a]	Skin and Mucosa	C
		AIDS KS	M	NS	Mixed[a]	Skin	A
Argentina	45	AIDS KS	M	40	Argentine	Skin	I/A
		AIDS KS	M	42	Argentine	Skin	II/C
		Classic KS	M	82	Caucasian	Skin	II/C
		Classic KS	M	75	Caucasian	Skin	II/C
		Classic KS	F	71	Argentine	Skin	I/A
Ecuador	20	Blood	NS	NS	Huaorani	—	E
		Blood	NS	NS	Huaorani	—	E
		Blood	NS	NS	Huaorani	—	E
		Blood	NS	NS	Siona	—	E
		Blood	NS	NS	Siona	—	E
		Blood	NS	NS	African Ecuadorian	—	B[b]
French Guiana	4	Endemic KS	M	78	African	Skin	C
		Endemic KS	M	59	African	Skin	C
		Endemic KS	M	75	African	Skin	C/A″[c]
		Endemic KS	F	37	African	Skin	B′/A‴[c]
		AIDS KS	M	33	African	Skin	C′/C[c]
		AIDS KS	M	78	African	Skin	B′/A‴[c]
		Endemic KS	M	52	African	Skin	C
	50	AIDS KS	M	33	African	Skin	B2
		AIDS KS	M	53	African	Skin	B1
		AIDS KS	F	37	African	Skin	A
		AIDS KS	F	53	African	Skin	B1
		Endemic KS	M	78	African	Skin	C
		Endemic KS	M	75	African	Skin	A5
		Endemic KS	M	78	African	Skin	B3
		Iatrogenic KS	M	62	African	Skin	A5
		Endemic KS	M	61	African	Skin	B1
		Endemic KS	M	70	African	Skin	B1
Brazil	26	AIDS KS	F	67	Italian	Lung	C/B[d]
		AIDS KS	M	43	Portuguese	Lymph node	C/B[d]
		AIDS KS	M	NS	Italian	Skin	C/B[d]
		AIDS KS	M	32	Arabian	Skin	B/C[d]
		AIDS KS	M	NS	Portuguese	Skin	B/A[d]
		AIDS KS	M	NS	Portuguese	Skin	B/C[d]
		AIDS KS	M	29	Portuguese	Skin	Other/Other[d]
	30	Blood	M	64	Arawete	—	E
		Blood	F	66	Asurini	—	E
	33	AIDS KS	NS	NS	Caucasian	NS	A1
		AIDS KS	NS	NS	Caucasian	NS	A8
		AIDS KS	NS	NS	Caucasian	NS	C3
	36	AIDS KS	M		African	Skin	B′
		AIDS KS	M		Mulatto	Skin	A‴
		AIDS KS	M		Amerindian	Skin	A5
		AIDS KS	M		Mulatto	Skin/Lung	A′
		AIDS KS	M		Caucasian	Lung	B1

Table 2 (*Continued*)

Country	Reference	Specimen	Sex	Age	Origin	Biopsy	K1
		AIDS KS	M		Caucasian	Lung	C′
		AIDS KS	M		Caucasian	Lung	C2
		AIDS KS	M		African	Skin	A″
		AIDS KS	F		Mulatto	Skin	C3
		AIDS KS	M		African	Skin	A1
		AIDS KS	M		Caucasian	Skin	C2
		AIDS KS	F		Caucasian	Skin/GI	C3
		AIDS KS	M		Caucasian	GI	A′
		AIDS KS	M		Mulatto	Lung	B′
		AIDS KS	M		Caucasian	Skin	A′
		AIDS KS	M		Caucasian	Skin	C3
		AIDS KS	M		Caucasian	Skin	B1
		AIDS KS	M		Caucasian	Lung	C′
		AIDS KS	M		African	Skin	C′
		AIDS KS	M		Caucasian	GI	B1
		AIDS KS	M		Caucasian	GI	A′
		AIDS KS	M		Caucasian	Skin	A″
		AIDS KS	M		Caucasian	Skin	C3
		AIDS KS	M		Caucasian	GI	C3
		AIDS KS	M		African	Skin	B′
		AIDS KS	M		Caucasian	Skin	B′
		AIDS KS	M		African	Skin	A′
		AIDS KS	M		Caucasian	Skin	Á
		AIDS KS	M		African	Skin	A′
		AIDS KS	M		Caucasian	Skin/GI	A5
		AIDS KS	M		African	Skin	A′
		AIDS KS	M		Caucasian	Skin	A1
		AIDS KS	M		African	Skin	A6

M: male; F: female; NS: not specified; GI: gastro-intestinal. Caucasian: white European descendant; African: black African descendant; Mulatto: mixed African/Caucasian descendant.

[a] Population that developed as a result of the intermixing of several generations of Spaniards, Indians, and blacks.

[b] This subtype was characterized from a T0.7 sequence.

[c] They performed sequence analysis of fragments of genes ORF26 and ORF75.

[d] HHV-8 subgroups according to Di Alberti et al.[60] and Zong et al.[8].

presentation with confluent exophytic nodules or eroded lesions has been noticed in Peru. Likewise, reports from Colombia and Peru characteristically mention that KS cases presented in indigenous or mestizo populations, whereas cases from Argentina more generally presented in European descendents. It is important to note that classic KS distribution is probably underdiagnosed and underreported because it occurs in areas of the continent with extremely low socioeconomic conditions.

This classic KS incidence must correlate with HHV-8 presence in the continent. Most seroprevalence studies carried out to date in South America have focused on groups with an increased risk of acquiring HHV-8 infection, instead of the general population or localized populations where classic KS has been described (Table 1). An important contribution has been made by studies performed on Brazilian and Ecuadorian Amerindians, where results have demonstrated high frequency rates of HHV-8. Studies performed on blood donors from Chile, Brazil, and Argentina have demonstrated similar low frequency rates of HHV-8.

As can be seen in this study, one of the most important problems with seroprevalence studies is the difference in reported HHV-8 seroprevalence rates. This may be the result of different laboratory algorithms, sera dilutions (1:10 to 1:160) and the assays used. Serological tests measure antibodies to latent or lytic antigens by IFA; against recombinant structural proteins, synthetic peptides, or whole virus by enzyme immunoassays or Western blots.[7] There is no gold standard for HHV-8 because the virus cannot be reliably cultured. As immunofluorescence assays that detect lytic antigens are generally more sensitive than other assays, their use results in higher estimates of prevalence.[55] The existing serological assays, nonetheless, need to be further refined and new assays need to be developed.

Another important step in the acknowledgement of the global spread of HHV-8 is the molecular characterization of its variants. Six major molecular subtypes of HHV-8 have been reported based on the highly variable K1 gene. Interestingly, these subtypes have been found to correlate very strongly with geographic and ethnic backgrounds. Subtypes A and C are found in Europe, the USA and Australia, whilst subtype C alone predominates across Asia. Subtypes B and A5 are found mainly in Africa and French Guiana. Subtype D has been reported in Aboriginals of the Pacific rim, including Taiwan, Australia and Japan. Subtype E has been found among Amerindian populations of the Brazilian and Ecuadorian Amazon regions. Subtype N, has been identified only in South Africa.[4,8,9,11,20,30,45,50,56–59]

Some of these subtypes may have co-evolved with certain human populations. The most plausible explanation for this pattern is the theory that modern humans migrated out of Africa in three major waves producing the separation of the main branches. The first migration spread across sub-Saharan Africa beginning 100,000 years ago (subtype B). The second went to south Asia and ultimately Australia, Taiwan and the Pacific Islands, beginning 60,000–70,000 years ago (subtype D). The third migration with separate branches to Europe and north Asia initially occurred 35,000 years ago (subtypes A and C), with later expansion into the Americas (subtype E) approximately 15,000 years ago and northern Europe 10,000 years ago at the end of the last Ice Age.[33]

This raises interesting questions as to the origin of the virus in different populations of South America. The few specimens reported and the fact that almost all of them were AIDS-related KS cases does not give precise information about the origin of the virus in the continent, except for the E Amerindians subtype (Table 2). More genotyping of the virus present in patients with classic KS, especially in Amerindians, could be extremely helpful in answering this question and should be the next step.

With all this information it can be concluded that classic KS in South America has a very distinct clinical presentation, but differs from the classic KS variety described in the Mediterranean. This should be analyzed with more retrospective studies on areas where classic KS has been described, and used to perform a comparative analysis of KS within the region to determine whether South America has its own endemic type of KS.

Countries like Colombia and Peru must perform HHV-8 seroepidemiological studies to corroborate pocket zones of HHV-8 as they have reported several cases of classic KS in the indigenous population. Initial seroprevalence studies performed on the general population and on blood donors showed low seroprevalences of HHV-8, whereas high seroprevalence rates were seen in the Amerindian population.

Finally, the key to understanding the precise molecular epidemiology and phylogenetic distribution of HHV-8 in South America would be to perform more subtyping of these classic KS cases.

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