Geographically Distinct HHV-8 DNA Sequences in Saudi Arabian Iatrogenic Kaposi's Sarcoma Lesions

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A new member of the γ -herpesvirus family, HHV-8 (also known as Kaposi's sarcoma (KS)-associated herpesvirus), has been linked to KS and body cavity-based lymphoma. Other members of this family, eg, Epstein-Barr virus, were originally thought to have only one strain, but subsequent analysis revealed different strains correlating to cellular patterns of infectivity and geographical location. To determine whether multiple strains of HHV-8 exist, we compared DNA sequences among KS and body cavity-based lymphoma-derived HHV-8 and examined differences in HHV-8 subgroups between American and Saudi Arabian iatrogenic KS patients. Samples were analyzed by polymerase chain reaction using multiple primer sets to five different open reading frames from HHV-8, and DNA sequencing was performed. HHV-8 DNA was present in all of our KS and body cavity-based lymphoma samples by polymerase chain reaction. HHV-8 DNA was detected in each body cavity-based lymphoma sample using a majority of the primers, whereas only two primer sets consistently amplified HHV-8 DNA derived from KS lesions. DNA sequencing within open reading frames 26 and 27 indicate the existence of at least three variants of HHV-8, with the majority of iatrogenic KS patients in Saudi Arabia containing unique nucleotide changes that may define a distinct, previously unidentified subgroup we term SA, whereas those from America were of Group A or B. Thus, although the sequencing data within open reading frames 26 and 27 did not permit discrimination between patients with lymphoma *versus* KS disease processes, HHV-8 derived from Saudi Arabian KS lesions were shown to have a distinct nucleotide sequence not seen in any of the other clinical samples examined. (*Am J Pathol* 1998, 153:1001-1004)

Kaposi's sarcoma (KS) was first described in 1872 as a rare tumor primarily seen in elderly men of eastern European or Mediterranean descent.¹ Since the original description of classical (or Mediterranean) KS, three addi-

tional forms of KS have been described, including acquired immune deficiency syndrome (AIDS)-related, iatrogenic (posttransplantation), and African (endemic). Although histologically indistinguishable, each form of KS affects a distinct population of patients, which indicates that, besides immunosuppression, genetic and environmental factors may be important risk factors.² Recent studies identified a novel γ -herpesvirus (human herpesvirus 8 (HHV-8), also known as KS-associated herpesvirus), in all four types of KS.^{3,4} HHV-8 has also been identified in human immunodeficiency virus-1-positive patients with body cavity-based B-cell lymphoma (BCBL, also referred to as primary effusion lymphoma).^{5,6} Sequence analysis demonstrated HHV-8 is closely related to other members of the γ -herpesvirus family, Epstein-Barr virus (EBV) and *Herpesvirus saimiri*. In human patients, it was initially believed that there was only a single strain of EBV, but it subsequently became apparent that there were two different strains.⁷ We noted two important characteristics of EBV that we pursued with our investigation of HHV-8. First, different strains of EBV have different cellular patterns of infectivity and susceptibility to transformation, and second, the two different EBV genomes and serological reactivities are present at different frequencies in patients depending on geographical location (American, European, or African).⁸ Based on sequence homology between HHV-8 and EBV, we explored the possibility that more than one strain of HHV-8 exists and examined differences in HHV-8 isolates from different geographical locations. Although sequence analysis within open reading frames (ORFs) 26 and 27 did not permit clear-cut distinctions between the KS and BCBL DNA, the KS lesions from Saudi Arabia did contain consistent nucleotide variations that were reproducibly different in comparison with either American KS or lymphoma samples.

Patient Samples and Methods

Archival formalin-fixed paraffin-embedded KS tissue samples from 18 KS patients were tested for HHV-8 DNA.

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Three patients had AIDS-related KS, 3 patients had classical KS, and 12 patients had iatrogenic KS after organ transplantation. Tissue samples from 7 of 12 iatrogenic KS patients were obtained from King Faisal Hospital in Riyadh, Saudi Arabia, with clinical information previously reported.^{2,4,9} Tissue samples from the other organ transplant patients as well as AIDS-related and classical KS patients were obtained from either the University of Michigan (Ann Arbor, MI) or Loyola University Medical Center (Maywood, IL). Other HHV-8-positive samples included the BC-1 cell line (American Type Culture Collection, Manassas, VA); BCBL-1 cell line (National Institutes of Health AIDS Research and Reference Reagent Program, Rockville, MD); and formalin-fixed paraffin-embedded tissues, including kidney, liver, lymph node, spleen, and lung from a patient with AIDS-related BCBL and KS.^{10,11}

DNA was isolated from tissues and amplified by polymerase chain reaction (PCR) as previously described.^{4,12} Each sample was shown to contain amplifiable DNA using standard PCR conditions and primers for β -actin. For initial PCR studies, a series of nine primers to various portions of the HHV-8 genome including ORFs 17, 22, 26, 27, and 34, were used. In addition to the 233-bp primers (primer set 1) originally described by Chang et al,³ other primers were designed based on a GenBank sequence (accession number U40377), including two sets of primers used for sequencing that amplified a larger portion of ORF 26 (722 bp), a small portion of ORF 27 (143 bp), and the noncoding region (approximately 20 bp) between these regions. Successful PCR amplification with these primers resulted in a single band at 461 bp (primer set 2) and 524 bp (primer set 3). Primer sequences used for amplification of HHV-8 were as follows: 5'-AGC CGA AAG GAT TCC ACC ATT GTG CTC-3' and 5'-TCC GTG TTG TCT ACG TCC AGA CGA TAT-3' (primer set 1, 233 bp), 5'-CTA TCC AAG TGC ACA CTC GCT GTC C-3' and 5'-GGA ACC AAG GCT GAT AGG ATA CAA AGG-3' (primer set 2, 461 bp), 5'-TTT GAT GGC GTC GGT CTC TAC C-3' and 5'-CGC ACA TAT CGT CTG GAC GTA G-3' (primer set 3, 524 bp), 5'-CAA GTT CCG CCA TAT TTA C-3' and 5'-CAT CTC CGG ACT ACA TCC-3' (primer set 4, 360 bp), 5'-GTG ATG TCA TCT GGG ACG CTC AAC-3' and 5'-GTG AGA CAT CTC CGG ACT ACA TCC-3' (primer set 5, 634 bp), 5'-CGG ATC AGG TGA CGG ATT ATC TC-3' and GAT TTT TCA CGG GGG CTC TG-3' (primer set 6, 210 bp), 5'-AGG CAG GTG TGG GAA ATG TAA G-3' and 5'-GTT GCT ATG GCT GCT GTT CAA C-3' (primer set 7, 300 bp), 5'-GAT GTC ATC TGG GAC GCT CAA C-3' and 5'-CGC ACA TAT CGT CTG GAC GTA G-3' (primer set 8, 234 bp), and 5'-TCT GTG CAT GCC CAC GTT CAC C-3' and 5'-TGC AGC GCG TGG AGC AAT TC-3' (primer set 9, 576 bp). DNA sequencing of HHV-8 PCR products was performed without cloning using the Promega fmol DNA sequencing system (Promega, Madison, WI) and the Thermosequenase radiolabeled terminator cycle sequencing kit (Amersham, Cleveland, OH). To ensure that the observed mutations were not the result of Taq-generated errors in PCR, sequencing was performed on at least two distinct PCR products generated from each DNA sample, and both strands of each product were independently sequenced.

Results

PCR Analysis for HHV-8 in KS and BCBL

PCR analysis was performed using nine different primer sets specific for HHV-8 with a series of samples as summarized in Table 1. Of interest, the BC-1 and BCBL-1 cell lines were positive for HHV-8 using all nine sets of primers, and the paraffin-embedded tissue samples from a case of BCBL were positive with all but two sets of primers. AIDS-related KS samples were also positive with all tested primers; however, not all primers could be examined due to a lack of DNA. In contrast, HHV-8 could only be consistently demonstrated in classic and iatrogenic KS with two of the primer pairs—the 233-bp fragment from HHV-8 ORF 26 and a 210-bp fragment specific for HHV-8 ORF 17. We were unable to amplify the HHV-8 DNA in the KS-derived samples with several of the other primer sets despite the presence of amplifiable DNA.

Sequence Analysis of ORF 26

To further study the possibility of sequence variation and/or existence of multiple strains, sequence analysis of PCR-amplified products of an 886-bp DNA segment (bases 828-1715) within and surrounding ORFs 26 and 27 (primers for 233-bp, 524-bp, and 461-bp fragments) were generated from 15 of the 19 HHV-8-positive samples. Three of the remaining samples could not be sequenced, as the 461-bp and/or 524-bp fragment could not be amplified from the sample, and there was insufficient DNA to perform the analysis on one AIDS-KS specimen. Comparison with the original HHV-8 sequence published by Chang et al³ demonstrated as many as eight nucleotide changes within the coding region of ORF 26 (bases 828-1550, Table 2). The nucleotide changes at bases 1055, 1086, 1139, and 1490 (numbered as in Chang et al³) did not encode for amino acid substitutions. However, other nucleotide changes did result in amino acid substitutions including at base 981 phenylalanine (F) to leucine (L), and at base 1132 aspartate (D) to glycine (G). In the case of iatrogenic KS from the United States, changes at both bases 1032 and 1033 results in substitution of isoleucine (I) for proline (P), whereas the change of only base 1033 in the other cases of KS codes for a proline (P) to leucine (L) substitution. Several nucleotide changes were also noted in the 143 bases (base variability, 3/143 or 2.1%) sequenced in the coding region for ORF 27 (bases 1573-1715). Substitution of G→T at base 1594 occurred in four of the five iatrogenic KS cases from Saudi Arabia, but not in the other patient samples. This nucleotide change did not encode for an amino acid substitution. In addition, all sequences demonstrated a C→T change at 1616 and a T→C change at 1617, which has been noted by other investigators in HHV-8 samples from various sources. Within the noncoding region between the two ORFs (approximately 20 bp), each sequence also showed insertion of either one or two guanine residues at base 1569. It should be noted that the sequence data presented in Table 2 may explain some of the negative PCR results in Table 1. The change

Table 1. PCR-Based Results to Detect HHV-8 DNA Sequences

Diagnosis		Sample number	Control primer actin	Primer 1 (233 bp) ORF 26	Primer 2 (461 bp) ORF 26	Primer 3 (524 bp) ORF 26	Primer 4 (360 bp) ORF 26	Primer 5 (634 bp) ORF 26	Primer 6 (210 bp) ORF 17	Primer 7 (300 bp) ORF 34	Primer 8 (234 bp) ORF 27	Primer 9 (576 bp) ORF 22
Lymphoma	BC-1	Cell line	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
	BCBL-1	Cell line	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
KS lesions	BCBL, lymph node	Patient 1	Positive	Positive	Positive	Positive	Negative	ND	Positive	Positive	Positive	Positive
	BCBL, lung	Patient 1	Positive	Positive	Positive	Positive	ND	ND	Positive	Positive	ND	Negative
	BCBL, Liver	Patient 1	Positive	Positive	Positive	Positive	ND	ND	Positive	Positive	ND	Negative
	Classic	Patient 2	Positive	Positive	Positive	Positive	ND	ND	Positive	Negative	ND	Negative
	Classic	Patient 3	Positive	Positive	Negative	ND	Positive	Negative	Positive	Positive	Positive	Negative
	Classic	Patient 4	Positive	Positive	Positive	Positive	Positive	ND	Positive	Negative	ND	ND
	Iatrogenic, Saudi Arabian	Patient 5	Positive	Positive	Positive	Positive	Positive	ND	Positive	Positive	ND	Positive
	Iatrogenic, Saudi Arabian	Patient 6	Positive	Positive	Positive	Positive	Negative	Positive	Positive	Positive	Negative	Positive
	Iatrogenic, Saudi Arabian	Patient 7	Positive	Positive	Positive	Positive	Negative	Negative	Positive	Negative	Negative	Negative
	Iatrogenic, Saudi Arabian	Patient 8	Positive	Positive	Negative	ND	Negative	Negative	Positive	Negative	Negative	Negative
	Iatrogenic, Saudi Arabian	Patient 9	Positive	Positive	Negative	Negative	Negative	ND	Positive	Negative	Negative	Negative
	Iatrogenic, Saudi Arabian	Patient 10	Positive	Positive	Positive	Positive	ND	ND	Positive	Positive	ND	Positive
	Iatrogenic, Saudi Arabian	Patient 11	Positive	Positive	Positive	Positive	ND	ND	Positive	Positive	ND	Positive
	Iatrogenic, USA	Patient 12	Positive	Positive	Positive	Positive	Positive	ND	Positive	Positive	ND	ND
	Iatrogenic, USA	Patient 16	Positive	Positive	Positive	Positive	Negative	ND	Positive	Positive	ND	ND
	Iatrogenic, USA	Patient 17	Positive	Positive	Positive	Positive	Negative	ND	Positive	Positive	ND	ND
	Iatrogenic, USA	Patient 18	Positive	Positive	Positive	Positive	ND	ND	ND	ND	ND	ND
	Iatrogenic, USA	Patient 19	Positive	Positive	Positive	Positive	Positive	ND	Positive	Positive	ND	ND
	AIDS	Patient 13	Positive	Positive	Positive	Positive	ND	ND	Positive	ND	ND	Positive
	AIDS	Patient 14	Positive	Positive	Positive	Positive	ND	ND	Positive	Positive	ND	Positive
	AIDS	Patient 15	Positive	Positive	Positive	Positive	ND	ND	Positive	Positive	ND	Positive

ND, not determined. In most cases, this was due to insufficient DNA for analysis.

at base 1139 (A→C) occurs in the DNA target sequence for one of the primers for the 360-bp fragment of ORF 26 (primer set 4). Lack of binding of the primer to the target DNA sequence due to this mutation may explain the negative result seen with the majority of iatrogenic KS patients studied (ie, patients 6 to 9).

Evaluation of all sequences revealed that they could be segregated into 3 major groups: A, B, and SA (Table 2). Of interest, tissues from 80% of patients (four of five) studied from Saudi Arabia contained unique nucleotide changes (group SA) compared with tissues from patients from the United States, which were of group A or B.

Table 2. Sequence Analysis for ORF 26 of HHV-8

DNA samples			ORF 26 (722 bp)*															Sub-group	Base variability [†]
Case	Diagnosis	Geographical region	926	981	989	1032	1033	1055	1086	1132	1139	1199	1315	1326	1478	1490			
AIDS-KS [¶]	AIDS-KS	USA	A	T	C	C	C	G	C	A	A	T	C	C	T	G	A		
BC-1 [¶]	BCBL		T	T	C	C	T	G	C	A	A	C	C	C	T	G	A	3/722 (0.42%)	
BC-2 [¶]	BCBL		T	C	G	A	T	T	C	G	C	T	T	A	C	G	B [‡]	11/722 (1.5 %)	
BC-1 cell line	BCBL		A	T	C	C	T	G	C	A	A	T	C	C	T	G	A	1/722 (0.14%)	
Patient 1	BCBL	USA	A	T	C	C	T	G	C	A	A	T	C	C	T	G	A	1/722 (0.14%)	
Patient 13	AIDS-KS	USA	A	T	C	C	T	G	C	A	A	T	C	C	T	G	A	1/722 (0.14%)	
Patient 14	AIDS-KS	USA	A	T	C	C	T	G	C	A	A	T	C	C	T	G	A	1/722 (0.14%)	
Patient 2	Classical KS	USA	A	T	C	C	T	G	C	A	A	T	C	C	T	G	A	1/722 (0.14%)	
Patient 4	Classical KS	USA	A	T	C	C	T	G	C	A	A	T	C	C	T	G	A	1/722 (0.14%)	
Patient 12	Iatrogenic KS	USA	A	C	C	A	T	T	C	G	C	T	C	C	T	G	B [‡]	6/722 (0.83%)	
Patient 16	Iatrogenic KS	USA	A	C	C	A	T	T	C	G	C	T	C	C	T	G	B [‡]	6/722 (0.83%)	
Patient 17	Iatrogenic KS	USA	A	C	C	A	T	T	C	G	C	T	C	C	T	G	B [‡]	6/722 (0.83%)	
Patient 18	Iatrogenic KS	USA	A	T	C	C	T	G	C	A	A	T	C	C	T	G	A	1/722 (0.14%)	
Patient 19	Iatrogenic KS	USA	A	T	C	C	T	G	C	A	A	T	C	C	T	G	A	1/722 (0.14%)	
Patient 10	Iatrogenic KS	Saudi Arabia	A	C	C	C	T	G	T	A	A	C	T	C	C	T	T	SA [§]	
Patient 11	Iatrogenic KS	Saudi Arabia	A	C	C	C	T	G	T	A	A	C	T	C	C	T	T	SA [§]	
Patient 6	Iatrogenic KS	Saudi Arabia	A	C	C	C	T	G	T	A	C	T	C	C	C	T	T	SA [§]	
Patient 7	Iatrogenic KS	Saudi Arabia	A	C	C	C	T	G	T	A	C	T	C	C	C	T	T	SA [§]	
Patient 5	Iatrogenic KS	Saudi Arabia	A	T	C	C	T	G	C	A	A	T	C	C	C	T	G	A	

*Start, 828; end, 1550.

†Base variation was calculated as the number of base changes compared to the original sequence published by Chang et al³ within the 722-bp coding region of ORF 26. Nucleotide changes in the noncoding region (approximately 20 bp) and ORF 27 (143 bp) were not included in the analysis.

‡HHV-8 found in the BC-2 cell line was originally described as a "B subgroup" by Zong et al,¹² but has recently been changed to C-3 based on sequence analysis of additional ORFs (G.S. Hayward, personal communication).

§Unique HHV-8 subgroup found in these Saudi Arabian patients.

¶Sequence analysis published by Chang et al³ (AIDS ICS) or Cesarman et al⁶ (BC-1, BC-2).

Discussion

The results of the current study support and extend the findings of Zong et al,¹³ Nicholas et al,¹⁴ and DiAlberti et al,¹⁵ indicating the existence of variants of HHV-8. Zong et al¹³ sequenced portions of ORF 26, ORF 75, and upstream UPS 75, concluding there were at least three strains of HHV-8 designated as A, B, and C. The data supported a geographical correlation with strain variation in HHV-8, as samples originating from Africa were of strain B or C, whereas BCBL samples and AIDS-related KS originating from the United States were generally of strain A. DiAlberti et al¹⁵ sequenced a portion of ORF 26 from human immunodeficiency virus-infected individuals and found evidence for four variants. Group A and D strains were found exclusively in patients from the United States and Africa, whereas groups B and C were also identified in American- and African-derived tissues.

In the current report, we studied tissues from a total of 19 patients, including several samples from a patient with BCBL, and 18 patients with KS. PCR studies demonstrated differences in our ability to amplify portions of the HHV-8 genome despite the presence of amplifiable DNA.¹⁶ Specifically, we documented that in comparison to the BCBL *in vitro* B-cell lines or *in vivo* paraffin-embedded tissue samples that were positive with seven of nine primer sets, HHV-8 DNA isolated from classic and iatrogenic KS samples was consistently positive with only two of nine primers used. Although the results may be due to poor quality of DNA or to the lower copy number of HHV-8 in KS lesions compared to lymphoma, an alternative interpretation could be the existence of mutations that did not permit primer binding and amplification. Indeed, sequence analysis of an 886-bp region within and surrounding ORFs 26 and 27 identified a mutation in the target DNA sequence in primer set 4 that may explain the negative PCR results with this primer.

Although a majority of the mutations found did not encode for amino acid substitutions, it is of interest that the changes were consistent within a patient population. It is highly unlikely that random errors of Taq polymerase incorporation resulted in these reproducible patterns. At least two independently amplified PCR products were sequenced to confirm all data, and the consistency of mutation patterns in a specific patient population would make random mutations unlikely. Since publication of their data,¹³ Hayward and colleagues have reclassified the pattern for HHV-8 in the BC-2 cell line as group C-3 based on sequence analysis of other ORFs (G. S. Hayward, personal communication). As the ORF 26 sequences from several of our HHV-8 samples from American iatrogenic KS patients are similar to the BC-2 sequence, it is possible that these samples also represent group C-3. Of interest, the HHV-8 sequences from Saudi Arabian iatrogenic KS patients contained unique and consistent nucleotide changes within the ORF 26 coding region that may represent a new HHV-8 subgroup different from the previously recognized A, B, and C groups. Analysis of these samples at additional ORFs, particularly those encoding genes expressed during the viral latency, is necessary to establish whether these

changes represent a new strain variant and to determine the relationship of this subgroup with those already described.

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