ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

HUMAN HERPES VIRUS-8 IN ACQUIRED IMMUNODEFICIENCY SYNDROME-ASSOCIATED ORAL KAPOSI'S SARCOMA – A STRUCTURED REVIEW

This library dissertation is submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY

in partial fufillment of requirements for the award of the degree of

MASTER OF DENTAL SURGERY IN ORAL PATHOLOGY

BY

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BATCH: 2003 – 2006

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ACKNOWLEDGMENTS

I sincerely thank **Dr. T. R. Saraswathi**, **Professor and HOD**, Department of Oral Pathology, Ragas Dental College & Hospital, for her valuable guidance, support and encouragement throughout my postgraduate curriculum.

Words seem less to express my heartfelt gratitude to my guide **Dr. K. Ranganathan**, **Professor,** Department of Oral Pathology, Ragas Dental College & Hospital, for mentoring me throughout my study period.

I sincerely thank **Dr**. **S. Ramachandran**, **Principal**, Ragas Dental College & Hospital**,** for granting me permission to use the facilities of the institution during the course.

I wholeheartedly thank **Dr. M. Umadevi**, **Associate Professor**, Department of Oral Pathology, Ragas Dental College & Hospital for her invaluable support.

I am greatly indebted to **Dr. Elizabeth Joshua**, **Reader**, Department of Oral Pathology, Ragas Dental College & Hospital for her constant motivation.

I earnestly thank **Dr. T. Rooban, Dr. S. Nalinkumar** and **Dr. S. Balasundaram, SeniorLecturers**, Department of Oral Pathology, Ragas Dental College & Hospital, for the encouragement.

I am thankful to **Mrs. Hemalatha**, **Bio-statistician**, Ragas Dental College & Hospital, for all the help rendered for the study.

I specially thank my **Family & Friends** for their love and trust. Above all, I thank with all my gratitude to the **Almighty** for always being there for me!

INTRODUCTION

Viruses

History & Progress

Early concept of basic virology that defined the contagious nature of viruses (*contagium vivum fluidum*) has over the years evolved to modern virology through an elaborate characterization of viruses, host tissue selectivity, pathogenicity and immunologic effects. Several important advances that occurred in the mid-twentieth century laid the premise for the classic studies of immunization. These studies include the development of culture of cells, identification of deoxy ribose nucleic acid (DNA), development of growth medium, development of viral plaque assays and the development of vaccines. For example, growing of viruses in cell culture led to the development of the first oral vaccine. Introduction of vaccines remains to this day one of the greatest accomplishments of medical sciences for the benefit of mankind.

Infections of viruses analyzed using electrophoretic studies and biochemical assays provided greater knowledge of viral replication, their receptors and immunologic interactions. A better understanding of gene expression including transcription factors, ribose nucleic acid (RNA) polymerase, reverse transcriptase, as well as the discovery of proto-oncogenes and tumor suppressor proteins followed. Viruses were tagged to study viral protein accumulations, intracellular shuttling and neural circuitry. Genomic sequences of many viruses have been recorded and stored in databases. Use of positive and negative selection procedure has been extremely beneficial. Positive selection is a method wherein a gene or a genomic fragment is expressed in a suitable system and tested for pathogenicity. In contrast, negative selection aims to identify a change in phenotype when a viral mutant infects a particular cell. Use of these

selection techniques has led to the identification of virulence factors, cell surface receptors and signal transduction pathways. Genomics and proteomics allow for the functional analysis of protein sequences expressed during viral infection and provide newer insights to persistent viral infections and malignant transformation. The last decades have witnessed exponential growth in our understanding of viral reactivation and implementing gene therapy to target chronic viral infections especially cancer.[1]

Despite all the knowledge and practical applications thereof, mankind still suffers from transmission of viral diseases and the outcome is often severe when humans serve as hosts to infections such as that caused by Ebola virus, human immunodeficiency virus (HIV), sudden acute respiratory syndrome coronavirus etc. Of significant importance is the fact that the oral cavity continues to be an important source of transmission of viruses, the site of active replication and reactivation after latency.[1]

Structure

Viruses are obligate parasites that depend on the host cell for their replication. They consist of a nucleic acid genome surrounded by a protein coat **capsid** that is sometimes encased in a lipid membrane. The entire infectious unit is termed a **virion**. Viruses are classified by (i) their genome (DNA or RNA), (ii) the shape of capsid (icosahedral or helical), (iii) the presence or absence of a lipid envelope, (iv) their mode of replication, (v) the preferred cell type for replication (tropism) and (vi) the type of pathology. The viral nucleic acid contains information necessary for programming the infected cell to synthesize macromolecules specific for the production of their progeny. Viruses are best visualized with the electron microscope; however, some viral particles aggregate within the host cells and form characteristic inclusion bodies, which may be seen with the light microscope and are useful for diagnosis e.g. cytomegalovirus

(CMV); whereas some viruses do not give rise to inclusions e.g. Epstein-Barr virus (EBV). Viruses account for a large share of human infections e.g. acquired immunodeficiency syndrome (AIDS) caused by HIV. Many viruses cause transient illnesses (e.g. influenza), other viruses are not eliminated from the body and persist within the host for years, either continuing to multiply (e.g. chronic infection with hepatitis B virus) or surviving in some non-replicating form (e.g. latent infection with herpes zoster virus). Some viruses can transform a host cell into a tumor cell; e.g. human papilloma viruses (HPV) have been implicated in oral squamous cell carcinoma. Different species of viruses can produce the same clinical picture (e.g. upper respiratory infection); conversely, a single virus can cause different clinical manifestations depending on host age or immune status (e.g. CMV).[2]

Viruses and Neoplasia

Viruses that can cause tumors are called oncogenic viruses and about 15% of human cancers have a viral etiology. The mechanism of virally induced oncogenesis is variable and complex. The tumorigenic potential of certain viruses is due to the ability to incorporate their genome into that of the host cell. Both DNA and RNA viruses have been implicated in the etiology of human cancers (Table 1). In vitro studies have demonstrated that these viruses are able to establish persistent infection and thereby transform or immortalize cells. The immortalized cells are more likely than normal cells to accumulate mutations, chromosomal rearrangements and more susceptible to tumor promoters. The characteristics of these transformed cells include an increased growth rate due to loss of inhibition and senescence as well as changes in their cellular morphology and metabolism. In contrast, demonstration of viral oncogenesis in-vivo is not as clear. Results of studies examining the effects of viruses in oncogenesis suggest modes of host cell interaction consistent with an infectious etiology.[3]

The relationship between viruses and neoplasia has intrigued researchers for decades, probably because their establishment in humans has been complex. Elucidating the pathogenic process of oncogenic viruses is important to both prevention and treatment of neoplasia. Also, it has not been possible to apply Koch's postulates and different criteria may be necessary for establishing the viral etiology of human neoplasms.

The proposed criteria are:[3]

- Regular presence of the viral genome in tumor biopsies.
- Demonstration of growth-promoting activity of viral genes or of virus-modified host cell genes in tissue cultures or in animal models.
- Epidemiological evidence linking the specific viral infection to development of neoplasm.
- Demonstration that the malignant phenotype depends on the continuous expression of viral oncogenes or on the modification of host cell genes containing viral sequences.

Herpesviruses

Most viruses that cause oral diseases are DNA viruses that are contracted in childhood or early adulthood through contact with tissue fluids, e.g. herpesviruses. Clinically, the herpesviruses exhibit a spectrum of diseases and the hallmark of herpesvirus infections is immune impairment. Active herpesvirus infections usually have severe consequences in HIV-infected and other immunocompromised patients.[4]

General Features

The characteristics of herpesviruses (Table 2) are enumerated:[5]

- Herpesviruses are large encapsulated viruses that contain four layers,
    1. **Genome**: inner core of DNA ranging in size 124 - 235 kbp
    2. **Protein**: icosahedral capsid made up of 162 capsomeres
    3. **Tegument**: an amorphous structure between the capsid and envelope
    4. **Lipid**: envelope derived from the nuclear membrane of the infected cell and containing viral glycoprotein spikes about 8 nm long.
- Herpesviruses cause primary infection (usually acute) followed by latent infection in which the viruses persist in a non-infectious form with periodic reactivation and shedding of infectious virus. Latency ensures survival of the viral genome throughout the lifetime of the infected individual. After reactivation, latent herpesviruses enter the productive phase and curiously, the reactivated infection may be clinically quite different from the disease caused by the primary infection.
- Herpesviruses exhibit tissue tropism; i.e. highly selective in regard to the surfaces or organs that they infect or invade.
- They are transmitted from host to host by direct contact with saliva or genital secretions. HHV-8 may also be transmitted by way of organ transplantation.
- They are shed in the saliva of asymptomatic hosts who act as constant reservoirs for new primary infections in previously uninfected individuals.

Classification

There are nine types of human herpesviruses, belonging to three subgroups defined by the type of cell most frequently infected and the site of latency (Table 3). They are:[6]

1. **α-group viruses**: herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), varicella zoster virus (VZV); infect epithelial cells and produce latent infection in neurons.
2. **β-group viruses**: CMV, human herpesvirus 6, human herpesvirus 7; infect and produce latent infection in a variety of cell types.
3. **γ-group viruses***:* EBV and HHV-8; produce latent infection mainly in lymphoid cells.

Herpesvirus Genome

Extensive DNA sequence information has been mapped for human herpesviruses which share homologous genes and blocks of conserved genes. These conserved genes called as the herpesvirus core define the herpesviruses as a distinct virus family. Several genes in the conserved core regions encode proteins characteristic of herpesviruses. In general, herpesvirus species of the same subfamily share the greatest number and exhibit the closest alignment of homologous genes. Herpesvirus species differ in their genomic sequence arrangement and base composition. Human herpesvirus genome sizes range from 125 kbp (VZV) to 230 kbp (CMV). A striking feature of herpesvirus DNA is their sequence arrangement. Herpesvirus genomes possess terminal and internal repeated sequences. Some members, such as the herpes simplex viruses, undergo genome rearrangements, giving rise to different genome 'isomers'. The nucleotide composition varies considerably too, for e.g. guanine-cytosine content in the α-herpesviruses and VZV is 68% and 46% respectively. There is little DNA homology among different herpesviruses

except for HSV-1 and HSV-2, which show 50% sequence homology; human herpesviruses 6 and 7, which show 30% sequence homology. Treatment with restricted endonucleases yields characteristically different cleavage patterns for herpesviruses. This 'fingerprinting' of strains allow epidemiologic tracing of a given strain. Thus, genes that are conserved among the various herpesvirus species, encode several of their basic biological characteristics, while genes that are not conserved, may be responsible for the biologic diversity of herpesviruses.[4,6]

Herpesvirus Proteins

The herpesvirus genome is large and encodes about 100 different proteins; of these, more than 35 polypeptides are involved in the structure of the virion and assembly of icosahedral capsule. Herpesviruses also encode many of the proteins which are necessary for viral DNA replication and repair and also nucleotide metabolism.

Herpesviruses express several genes in a cascade which are divided into: immediate-early, early and late phases. Immediate-early transcripts are regulatory proteins that activate early and late phases. Herpesvirus genes encode glycoproteins that are expressed on the surface of infected cell and viral envelope. These glycoproteins mediate entry into susceptible cells (gB), cell-to-cell viral spread (gH & gL) and serve as major determinants of tissue tropism.

Herpesvirus Diseases

A wide variety of diseases in humans are associated with infection by herpesviruses. HSV-1 is classically associated with oropharyngeal lesions and causes recurrent attacks of "fever blisters". HSV-2 primarily infects the genital mucosa and is responsible for genital herpes. Both can cause neonatal infections which are often severe. Both the types also cause neurologic disease. VZV causes chickenpox (varicella) on primary infection and zoster (shingles) upon reactivation from

latency. CMV replicates in epithelial cells of the respiratory tract, salivary glands, and kidneys and persists in lymphocytes. In newborns, CMV is an important cause of congenital defects and mental retardation. Human herpesvirus 6 infects T-lymphocytes and causes exanthem subitum (roseola infantum). Human herpesvirus 7, also a T-lymphotropic virus, has not yet been linked to any specific disease. EBV replicates in epithelial cells of the oropharynx and parotid gland and establishes latent infections in lymphocytes; it causes infectious mononucleosis, lymphoma and nasopharyngeal carcinoma. HHV-8 is associated with the development of KS, a vascular tumor that is common in patients with AIDS. Primary infection and reactivated disease by a given virus may involve different cell types and present different clinical picture. Human herpesviruses are frequently, also reactivated in immunocompromised patients and may cause severe disease such as pneumonia or lymphomas.[6]

AIM

- To determine the prevalence percentage of HHV-8 in AIDS-associated oral Kaposi's sarcoma.

OBJECTIVES

- To determine whether there is sufficient evidence in the medical literature for a causal role of HHV-8 in the pathogenesis of AIDS-associated Kaposi's sarcoma.
- To determine whether there is sufficient evidence in the medical literature to conclude that HHV- 8 infection is a definite risk for the development of Kaposi's sarcoma in AIDS patients.

REVIEW OF LITERATURE

Kaposi's Sarcoma

Epidemiology and Clinical Features

Helmut Kobner, a German physician, appears to have been the first to describe cases of metastatic cutaneous sarcoma. In 1872, the Hungarian physician, Moricz Kaposi, described an idiopathic, multi-pigmented tumor-like lesion of the skin that eventually was named Kaposi's Sarcoma (KS).[7] During the late nineteenth century, KS was a rare disease and by the early twentieth century, an increased incidence was observed.[8,9] KS is now a common tumor arising in HIV-infected patients and is considered an AIDS-defining illness.[8,10] KS occurs in approximately 10% of all HIV-infected patients and in about 20% of patients in the homosexual/bisexual risk group.[11] The oral cavity is involved in 50% to 80% of these cases, with the mucosa of the hard and soft palate, gingiva and tongue being the most common locations.[12,13] The prevalence of oral KS is variable and has been reported from 0 to 12% in Africa, and from 0 to 38% in United States and Europe.[14,15] Also, differences in the frequency of both oral and non-oral KS in HIV disease between the various countries do occur. In US and Europe, the incidence of AIDS-associated KS declined after highly active antiretroviral therapy (HAART) became available, while the prevalence of KS had risen alarmingly in Africa. And since the advent of AIDS, KS has become more frequent in both the genders, the male to female ratio changing from 19:1 to7:1, particularly in East Africa. Also, high prevalence of oral KS was demonstrated by the observation that 18.6% of a group of HIV-infected patients from Zimbabwe had oral KS.[16]

Based on epidemiological studies, there are four variants of KS: 1) **Classic KS** that is relatively less aggressive and predominantly occurs in elderly men of Middle Eastern, Mediterranean and

Eastern European origin with a median age of > 70 years; 2) an **Endemic/African form of KS** that occurs predominantly in men with a median age of 35 to 39 years; 3) **Iatrogenic or post-transplant KS** that occur in HIV-seronegative immune-compromised individuals, long term users of steroids and cytotoxic drugs, and individuals with autoimmune disorders; and 4) **AIDS-associated KS**. Although the four variants of KS are distinctive, they share similar clinical and histologic features, suggestive of common pathogenesis.[17] Classical KS is often limited to the extremities, on the contrary AIDS-associated KS is rarely limited to a single anatomic site and frequently involves the head and neck as primary sites and visceral involvement is also present.[18] On the basis of clinical appearance, lesions of KS have been classified into six major overlapping types: patch, plaque, nodular, lymphadenopathic, infiltrative, florid and telangiectatic.[19,20] Oral lesions appear red to purple macules, papules or nodules that may ulcerate and cause localized destruction.[21] Palate and gingiva are the most commonly affected intra-oral sites.[19-22] The clinical outcome of AIDS-associated oral KS is often unpredictable, but the majority of cases represent aggressive disease and have associated disseminated cutaneous and visceral lesions. Slow growing oral tumors are usually associated with patients who have no additional opportunistic infections.[23]

Differential Diagnosis

Early lesions are difficult to distinguish from ecchymosis, nevi and erosive lichen planus.[24] Nodular and plaque-like lesions should be biopsied to rule out bacillary angiomatosis, hemangioma, pyogenic granuloma, angiosarcoma or lymphangiosarcoma.[24,25]

Histopathology

The cellular origin of KS is difficult to determine as lesions typically exhibit multiple cell types.

AIDS-associated KS consists predominantly undifferentiated mesenchymal cells and spindle shaped cells.[26-29] The spindle cell component, considered the tumor element, are of mesenchymal origin and have features that resemble both endothelial and smooth muscle cells.[28,29] The tumor cells are derived from cells of either lymphatic or venous differentiation.[23,28] And, biopsies of KS feature numerous vascular channels with extravasation of erythrocytes, hemosiderophages, eosinophilic hyaline inclusions and inflammatory infiltrate.[26,27] The histogenesis of the spindle cell component remains controversial and many studies favor an endothelial cell origin.[28-30] Another pertinent issue is whether KS is a clonal "neoplastic" lesion or polyclonal "reactive" lesion and evidence suggests that KS lesions are mostly hyperplastic and polyclonal in nature. The debate is either these lesions contain a small proportion of clonal, neoplastic tumor cells that are difficult to identify or some of these polyclonal lesions undergo full transformation during disease progression.[30]

Role of HHV-8

Viruses such as CMV, hepatitis B virus, human herpes virus 6 and HIV have been suspected in the past as causing KS, but none of these have been proven to have a causal association with KS.[30] It was only in the year 1994 that HHV-8 was first detected in KS specimen.[31] HHV-8, a member of γ herpesvirus subfamily, is unequivocally considered the causative agent of AIDS-associated, classic, endemic and iatrogenic KS and hence also known as Kaposi's sarcoma-associated herpesvirus (KSHV).[32] In addition, HHV-8 is believed to be the causative agent of primary effusion lymphomas / body cavity-based lymphomas), multicentric Castleman's disease and oral plasmablastic lymphomas.[32-34] Serological studies have indicated that the prevalence of HHV-8 is low in the United States and parts of Europe (0 - 20%), rising in Mediterranean countries and reaching level greater than 50% in parts of Africa.[16] In North America and Europe,

primary infection with HHV-8 mainly occurs among homosexual men, transmitted principally via sexual contact.[32] Transmission of HHV-8 via saliva has also been documented. In African populations, HHV-8 infection seems to occur largely before puberty through casual family and community contacts, oral secretions being a potential vehicle of non-sexual horizontal spread; vertical transmission of HHV-8 being insignificant.[35] A study conducted in Malawi, Africa has also shown that, apparently healthy people in regions where HHV-8 is hyper-endemic can be infected by multiple strains.[36] However, it remains to be confirmed if this reflects a simultaneous co-infection by several HHV-8 strains, reactivation of latent strains or a super-infection.[36]

Pathogenesis

HHV-8 is a lymphotropic γ herpesvirus, closely related to EBV.[17,33] The HHV-8 genome contains several genes related to cell proliferation and host responses that may contribute to the pathogenesis of KS (Table 4). The pathogenesis of AIDS-associated KS is multi-factorial and involves HHV-8, altered expression to cytokines and stimulation of KS growth by HIV type-1 Tat protein.[37-40] HHV-8 encodes protein homologues of interleukin-6, cytokines, cyclins and bcl-2.[37,38] The HIV type-1 Tat protein can promote growth of spindle cells of endothelial origin, but in the presence of inflammatory cytokines.[38,39] The synergistic relation between the inflammatory cytokines and HIV type-1 Tat protein combined with the AIDS-associated immune suppression, provides for a plausible explanation for the aggressive nature of AIDS-associated KS.[39] The sequence of events creating the inflammatory angiogenic environment has best been described by Dezube: (i) circulating KS progenitor cells and cells latently infected with HHV-8 seek sites of pre-existing inflammation, (ii) exposure to inflammatory cytokines results in differentiation of latently infected cells into KS-like spindle cells and induces HHV-8 reactivation, (iii) reactivation of HHV-8 leads to expression of potentially pathogenic genes such

as viral interleukin-6 which activates vascular endothelial growth factor to induce angiogenesis, (iv) viral lytic replication in the cells activates inflammation and promotes angiogenesis, (v) the creation of inflammatory and angiogenic environment increases the chances of infection of endothelial / KS spindle cells, (vi) these cells also become reactive to HIV type-1 Tat protein, (vii) the HIV type-1 Tat protein further augments the inflammation and angiogenicity through matrix metalloproteinases and the infected cells eventually lead to the development of KS.[39]

Prognosis and Management

The prognosis of patients with AIDS-associated KS is more often related to other factors rather than the tumor itself. The AIDS Trial Council Group has devised the TIS staging system based upon: the extent of the tumor (T), the status of immune system (I), the presence of systemic illnesses (S).[16] Treatment for AIDS-associated KS is directed towards reduction of pain and edema, relief from symptoms caused by visceral involvement and elimination of cosmetically unacceptable lesions.[39] HAART is useful in the management of AIDS-associated KS since it reduces the HIV viral load and increases the CD4+ T-cell count and in fact, studies have shown a reduced incidence or regression of KS in HIV-infected individuals treated with at least one protease inhibitor. Both in vivo and in vitro studies have demonstrated that protease inhibitors have a direct anti-angiogenic, anti-KS and anti-tumorigenic activity. HAART causes fall in HHV-8 levels in the blood presumably because of reduction in (a) HIV proliferation, (b) HIV/HHV-8 mediated oncogenesis and (c) HIV-induced immune suppression.[16]

Local therapy may be effective for mild disease forms but systemic therapy is required for disseminated KS. Earlier approaches of managing KS have included surgical excision, local irradiation, intralesional injections of vinblastine, cytotoxic therapy and laser therapy. The pronounced angiogenic component of KS makes it particularly suitable for treatment with anti-

angiogenic agents such as thalidomide. Several retinoid compounds have also been tested in clinical trials with variable response rates.[16] However, only few agents are of use for the treatment of KS: alitretinoin gel for topical therapy and liposomal daunorubicin / oloxorubicin and interferon-α for systemic therapy. Single agent therapy with interferon-α may be associated with significant toxicity, but in combination with anti-retroviral agents find suitable application for treatment of disseminated KS.[16]

MATERIALS & METHODS

A MEDLINE search was done using the keywords HHV-8, KSHV, oral Kaposi's sarcoma, HIV, AIDS to obtain literature pertaining to the study. A total of eight scientific articles could be included in the study; case reports being excluded. The details of the articles included in the study are provided in Table 5.[41-48] Based on the literature collected, the study sample could be categorized into three groups i.e. samples from

1. HIV-positive patients [HIV (+)] with oral KS
2. HIV-positive patients with other oral lesions
3. HIV-negative patients [HIV (-)] with other oral lesions

Data entry and statistical analysis were done using SPSS version 10.0.5®. Analysis of variance (ANOVA) was done to compare the prevalence percentage in each group.

RESULTS

The prevalence percentage of HHV-8 was 82% in HIV (+) oral KS samples, 23% in HIV (+) other oral lesions and 0% in HIV (-) other oral lesion samples. (Table 6, Graph 1). The difference in prevalence percentage between the three sample groups was statistically significant (p=.001).

TABLES & GRAPH

Table 1: Viruses linked to human cancers

Virus	Cancer
DNA viruses	
• Human Papilloma Virus	➢ Anogenital cancers ➢ Cancers of the skin ➢ Oral verrucous carcinoma ➢ Oral squamous cell carcinoma
• Epstein-Barr Virus	➢ Burkitt's lymphoma ➢ Nasopharyngeal carcinoma ➢ Hodgkin's lymphoma ➢ Thymic lymphoepithelial carcinoma ➢ Immunosuppression-related lymphomas ➢ Squamous cell carcinoma
• Human Herpes Virus-8	➢ Kaposi's Sarcoma
• Hepatitis B Virus	➢ Hepatocellular carcinoma
• Hepatitis C Virus	➢ B-cell non-Hodgkin's lymphoma
RNA viruses (retroviruses)	
• Human T-lymphotropic Virus 1	➢ Endemic T-cell leukemia / lymphoma

Table 2: Important properties of herpesviruses

Virion	Spherical, 150-200 nm in diameter (icosahedral)
Genome	Double-stranded DNA, linear, 124-235 kbp
Protein	More than 35 proteins in virion
Envelope	Contains viral glycoproteins, Fc receptors
Replication	Nucleus, bud from nuclear membrane
Characteristics	Establish latent infections Persist indefinitely in infected hosts Frequently reactivated in immunosuppressed hosts Some are oncogenic

Table 3: Classification of human herpesviruses

Subfamily	Biologic Properties		Genus	Examples	
	Growth cycle /	Latent infection		Official Name	Common Name
Alpha (α)	Short, cytolytic	Neurons	Simplex	1	Human Simplex Virus-1
				2	Human Simplex Virus-2
			Varicello	3	Varicella Zoster Virus
Beta (β)	Long, cytomegalic	Glands, kidneys	Cytomegalo	5	Cytomegalo Virus
	Long, lympho-proliferative	Lymphoid tissue	Roseolo	6	Human Herpes Virus-6
				7	Human Herpes Virus-7
Gamma (γ)	Variable, lympho-proliferative	Lymphoid tissue	Lymphocrypto	4	Epstein-Barr Virus
			Rhadino	8	Human Herpes Virus-8

Table 4: HHV-8 genes implicated in tumorigenesis

Host cell homologue	HHV-8 encoded protein	Possible function
D-type cyclin	v-Cyc	Inactivation of pRb Promotes G_1 to S phase transition
IL-8 GPCR	v-GPCR	Cellular growth signal
Interferon regulatory factor	v-IRF	Inhibits p21 and MHC class I expression
CC chemokines	v-MIP-I, v-MIP-II, v-MIP-1a	Chemoattraction, angiogenesis
Interleukin 6	v-IL-6	Growth factor for KS cells
Bcl-2 family protein	v-bcl-2	Inhibition of apoptosis
FLICE inhibitory protein	v-FLIP	Inhibition of CD95L and TNF-induced apoptosis
N-CAM family protein	v-Ox-2	Cellular adhesion molecule
CD21/CR2 complement binding protein	ORF 4	Escape from host immune response

Table 5: Scientific articles included in this structured review

S. No.	Title	Author	Year	Study Type	Sample Type	Sample Group	Sample Size	HHV-8 (+)	HHV-8 (-)	HHV-8 Prevalence %
1	Kaposi's sarcoma herpesvirus in oral Kaposi's sarcoma[41]	DiAlberti L et al	1996	PCR	Tissue	HIV (+) oral KS	11	5	6	45.5
2	Presence of human herpesvirus-like DNA sequence in oral Kaposi's sarcoma[42]	Jin YT et al	1996	PCR	Tissue	HIV (+) oral KS	3	3	0	100
						HIV (-) other oral lesions	74	0	74	0
3	Presence of human herpes 8 variants in the oral tissues of human immunodeficiency virus-infected persons[43]	DiAlberti L et al	1997	PCR	Tissue	HIV (+) oral KS	11	5	6	45.5
						HIV (+) other oral lesions	14	11	3	78.8
						HIV (-) other oral lesions	20	0	20	0

4	Epstein-Barr virus and human herpes virus 8 prevalence in human immunodeficiency virus-associated oral mucosal lesions[44]	Webster-CyriaqueJ et al	1997	PCR	Tissue	HIV (+) oral KS	3	3	0	100
						HIV (+) other oral lesions	26	0	26	0
5	Frequent detection of Kaposi's sarcoma associated herpes virus (HHV-8) DNA in saliva of HIV-infected men[45]	Koelle DM et al	1997	PCR	Saliva	HIV (+) oral KS	10	7	3	70
6	Kaposi's sarcoma-associated herpesvirus-like DNA sequences (KSHV/HHV-8) in oral Kaposi's sarcoma[46]	Flaitz CM et al	1997	PCR	Tissue	HIV (+) oral KS	54	53	1	98.2
						HIV (+) other oral lesions	5	0	5	0
						HIV (-) other oral lesions	3	0	3	0

7	Transmissible Kaposi's sarcoma-associated herpesvirus (HHV-8) in saliva of men with a history of Kaposi's sarcoma[47]	Vieira Jet al	1997	PCR	Saliva	HIV (+) oral KS	3	3	0	100
8	Oral Kaposi's sarcoma: A clinicopathologic study from South Africa[48]	Lager I et al	2003	PCR	Tissue	HIV (+) oral KS	45	44	1	97.8
						HIV (+) other oral lesions	7	1	6	14.3

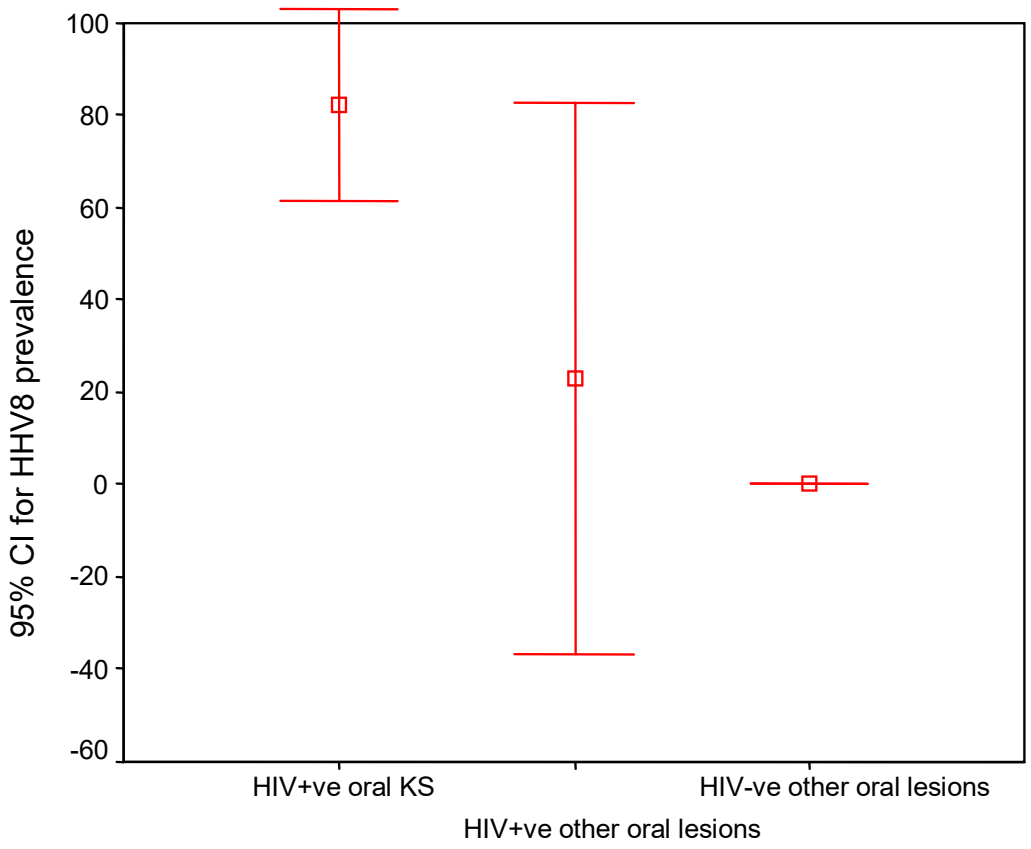
Table 6: Mean prevalence percentage of HHV-8 in the sample groups

Virus	Sample Group	*n*	Mean Prevelance (%)	SD	*p* value
HHV-8	HIV (+) oral KS	8	82.1	24.8	0.001
	HIV (+) other oral lesions *	4	23.2	37.5	
	HIV (-) other oral lesions #	3	0.00	0.00	

* CMV/HSV/apthous ulcers, hairy leukoplakia, condyloma acuminatum, pyogenic granuloma, lymphoma.

Pyogenic granuloma, hemangioma, lymphangioma, papilloma, fibroma, pleomorphic adenoma, squamous cell carcinoma, verrucous carcinoma, dentigerous cyst.

Graph 1: Prevalence percentage of HHV-8 in the sample groups



DISCUSSION

Since the identification of HHV-8 DNA sequences, many investigators have confirmed the association of these sequences and AIDS-associated KS. Table 5 shows a compilation of studies published, aimed at assessing the presence of HHV-8 in oral KS and other oral lesions. It is evident that HHV-8 is present in a high proportion of tissues from HIV (+)/AIDS-associated oral KS as compared to other lesions (Table 6, Graph 1).

Studies documenting the presence of HHV-8 in AIDS-associated KS have been extended to include the other types of lesions in HIV (+)/AIDS patients and HIV (-) patients.[42-44,46,48] All the oral KS lesions obtained from all clinical stages have been found to contain HHV-8 DNA sequences and the HHV-8 copy number is higher in the KS lesions than in other groups.[42-44,47,48] These studies suggest that HHV-8 may not be an opportunistic infectious agent related to AIDS. Although some non-KS tissues (other oral lesions) have been found to contain HHV-8 sequences, most of these are from patients who either have cutaneous/systemic KS or are obtained from HIV (+) patients likely to represent disseminated HHV-8 infection.[43,48] Furthermore, most studies have reported a lack of these sequences in other oral lesions, including a wide variety of vascular tumors and inflammatory conditions that resemble KS in their cellular composition.[42,44,46] Therefore, it appears that HHV-8 sequences are present specifically in oral KS tissues, as well as in some other oral lesional tissues from patients with KS or at high risk of developing KS. Support for a causal association between HHV-8 and KS also comes from the analysis of peripheral blood from patients with KS or at high risk of developing KS, compared with other AIDS risk groups and HIV (-) individuals.[35,49,50] In these studies, the presence of HHV-8 DNA sequences in the peripheral blood of many patients has preceded the development of KS, and the presence of HHV-8 DNA sequences in the peripheral blood of KS (-) patients has

predicted the subsequent appearance of KS lesions in some patients. Serological assays have been developed and used to analyze many serum samples from various patients with or without KS.[36,51,52] These studies have shown that the rate of HHV-8 seropositivity is high in HIV (+) patients with KS and in HIV (+) patients without KS, but is much lower in HIV (-) individuals. An exception although is finding of a high percentage HHV-8 seropositive individuals without KS regardless of HIV status, suggesting that HHV-8 infection rates are higher in populations in whom KS is endemic.[51] HHV-8 seropositivity has been found to occur before the clinical appearance of KS in a significant proportion of patients with AIDS-associated KS.[53] Thus, the distribution of HHV-8 seropositivity indicates that its presence varies among different populations and is not always ubiquitous.[50] Regardless of the incidence of HHV-8 infection in the general population, it is possible that the mechanisms in the pathogenesis of HHV-8 associated diseases could be explained by viral reactivation rather than primary infection.[17] As in the case of other human herpesviruses, many conditions including immune suppression, viral dose at the time of infection, multiple genetic, environmental, and behavioral factors may cooperate in variable combinations in the pathogenesis of KS.

Several issues regarding the incidence of HHV-8 infection and its relationship with the KS cells await further studies. However, the almost invariable presence of HHV-8 in all types of KS (virtually 100% of cases in most studies), its absence from other conditions that histologically resemble KS, its presence in the peripheral blood and tissues of patients with KS or at high risk for developing KS, and the patterns of immunoreactivity to HHV-8 antigens suggest an important, and most likely causal role for HHV-8 in the pathogenesis of KS.

CONCLUSIONS

This structured review is suggestive of

- ✓ HHV-8 prevalence percentage of 82% in AIDS-associated oral KS.
- ✓ A causal role of HHV-8 in the multi-factorial pathogenesis of AIDS-associated KS involving a complex interplay of HHV-8 infection, altered response to cytokines and HIV type-1 Tat protein.
- ✓ HHV-8 infection is a high-risk factor for the development of KS in AIDS patients.

REFERENCES

1. Miller CS. Pleotropic mechanisms of virus survival and persistence. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;100: 27-36.
2. McAdam AJ, Sharpe AH. Infectious diseases. In: Kumar V, Abbas AK, Fausto N ed. Pathologic Basis of Disease. Pennsylvania, Saunders. 2004; p. 343-414.
3. Phelan JA. Viruses and neoplastic growth. Dent Clin N Am. 2003; 47: 533-43.
4. Contreras A, Slots J. Herpesviruses in human periodontal disease. J Periodont Res. 2000; 35: 3-16.
5. Stoopler ET, Greenberg MS. Update on herpesvirus infections. Dent Clin N Am. 2003; 47: 517-32.
6. Brooks GF, Butel JS, Morse SA, ed. Medical Microbiology. USA, McGraw-Hill. 2001; p. 370-4.
7. Goldberg AN. Kaposi's sarcoma of the head and neck in acquired immunodeficiency syndrome. Am J Otolaryngol. 1993; 14: 5-14.
8. Schiff NF, Annino DJ, Woo P, Shapshay SM. Kaposi's sarcoma of the larynx. Ann Otol Rhinol Laryngol. 1997; 106: 563-7.
9. Barrett AP, Bilous AM, Buckley DJ, Kefford RF, Packham DR. Clinicopathological presentation of oral Kaposi's sarcoma in AIDS. Aust Dent J. 1988; 33: 395-9.
10. Dodd CL, Greenspan D, Greenspan JS. Oral Kaposi's sarcoma in a woman as a first indication of HIV infection. J Am Dent Assoc. 1991; 122: 61-3.
11. Flaitz CM, Nichols CM, Hicks MJ. Role of intralesional vinblastine administration in treatment of intraoral Kaposi's sarcoma in AIDS. Eur J Cancer B Oral Oncol. 1995; 31B: 280-5.

12. Porter SR, Scully C. HIV: the surgeon's perspective. Diagnosis and management of malignant neoplasms. Br J Oral Maxillofac Surg. 1994; 32: 241-7.

13. Reichart PA, Schiodt M. Non-pigmented oral Kaposi's sarcoma (AIDS). Intl J Oral Maxillofac Surg. 1989; 18: 197-9.

14. Holmes HK, Stephen LX. Oral lesions of HIV infection in developing countries. Oral Dis. 2002; 8(Suppl.2): 40-3.

15. Patton LL, Phelan JA, Ramos-Gomez FJ, Nittayananta W, Shiboski CH, Mbuguye TL. Prevalence and classification of HIV-associated oral lesions. Oral Dis. 2002; 8(Suppl. 2): 98-109.

16. Frezzini C, Leao JC, Porter S. Current trends of HIV disease of the mouth. J Oral Pathol Med. 2005;34: 513-31.

17. Porter SR, Di Alberti L, Kumar N. Human herpesvirus 8 (Kaposi's sarcoma herpesvirus): Review. Oral Oncol. 1998; 34: 5-14.

18. Cremer KJ, Spring SB, Gruber J. Role of human immunodeficiency virus type-1 and other viruses in malignancies associated with acquired immunodeficiency disease syndrome. J Natl Cancer Inst. 1990; 82: 1016-24.

19. Epstein JB, Silverman S Jr. Head and neck malignancies associated with HIV infection. Oral Surg Oral Med Oral Pathol. 1992; 73: 193-200.

20. Gorsky M, Epstein JB. A case series of acquired immunodeficiency syndrome patients with initial neoplastic diagnoses of intraoral Kaposi's sarcoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000; 90: 612-7.

21. Langford A, Pohle HD, Reichart P. Primary intraosseous AIDS-associated Kaposi's sarcoma. Intl J Oral Maxillofac Surg. 1991; 20: 366-8.

22. Nichols CM, Flaitz CM, Hicks MJ. Primary intraosseous Kaposi's sarcoma of the maxilla in human immunodeficiency virus infection. J Oral Maxillofac Surg. 1995; 53: 325-9.

23. Lausten LL, Ferguson BL, Barker BF, Cobb CM. Oral Kaposi sarcoma associated with severe alveolar bone loss: Case report and review of the literature. J Periodontol. 2003; 74: 1668-75.

24. Blumenfeld W, Egbert BM, Sagebiel RW. Differential diagnosis of Kaposi's sarcoma. Arch Pathol Lab Med. 1985; 109: 123-7.

25. Beckstead JH. Oral presentation of Kaposi's sarcoma in a patient without severe immunodeficiency. Arch Pathol Lab Med. 1992; 116: 543-45.

26. Green TL, Beckstead JH, Lozada-Nur F, Silverman SJ, Hansen LS. Histopathologic spectrum of oral Kaposi's sarcoma. Oral Surg. 1984; 58: 306-14.

27. Regezi JA, MacPhail LA, Daniels TE, Greenspan JS, Greenspan D, Dodd CL et al. Oral Kaposi's sarcoma: A 10 year retrospective histopathologic study. J Oral Pathol Med. 1993; 22: 292-7.

28. Green TL, Meyer JR, Daniels TE, Greenspan JS, DeSouza YG, Kramer RH. Kaposi's sarcoma in AIDS: Basement membrane and endothelial cell markers in late-stage lesions. J Oral Pathol. 1988; 17: 266-72.

29. Regezi JA, MacPhail LA, Daniels TE, DeSouza YG, Greenspan JS, Greenspan D. Human immunodeficiency virus-associated oral Kaposi's sarcoma: A heterogeneous cell population dominated by spindle-shaped endothelial cells. Am J Pathol. 1993;143: 240-9.

30. Cesarman E, Knowles D M. Kaposi's sarcoma-associated herpesvirus: A lymphotropic human herpesvirus associated with Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease. Sem Diagnostic Pathol. 1997; 14: 54-66.

31. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 1994; 266: 1865-9.

32. Leao JC, Porter S, Scully C. Human herpesvirus 8 and oral health care: An update. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000; 90: 694-704.

33. Moore PS. The emergence of Kaposi's sarcoma –associated herpesvirus (HHV-8). N Eng J Med. 2000; 343: 1411-3.

34. Cioc AM, Allen C, Kalmar JR, Suster S, Baiocchi R, Nuovo GJ. Oral plasmablastic lymphomas in AIDS patients are associated with human herpesvirus 8. Am J Surg Pathol. 2004; 28: 41-6.

35. Pauk J, Huang ML, Brodie SJ, Wald A, Koelle DM, Schacker T, Celum C, Selke S, Corey L. Mucosal shedding of human herpesvirus 8 in men. N Eng J Med. 2003; 343: 1369-77.

36. Beyari MM, Hodgson TA, Cook RD, Kondowe W, Molyneux M, Scully CM et al. Multiple human herpesvirus 8 infection. J Infect Dis. 2003; 188: 678-89.

37. Brooks LA, Wilson AJ, Crook T. Kaposi's sarcoma- associated herpesvirus (KSHV) / human herpesvirus 8 (HHV-8): A new human tumor virus. J Pathol. 1997; 182: 262-5.

38. Barillari G, Ensoli B. Angiogenic effects of extracellular human immunodeficiency virus type-1 Tat protein and its role in the pathogenesis of AIDS-associated Kaposi's sarcoma. Clin Microbiol Rev. 2002; 15: 310-26.

39. Dezube BJ. New therapies for the treatment of AIDS-related Kaposi sarcoma. Curr Opin Oncol 2000; 12: 445-9.

40. Hille JJ, Webster-Cyriaque J, Palefski JM, Raab-Traub N. Mechanisms of expression of HHV-8, EBV and HPV in selected HIV-associated oral lesions. Oral Dis 2002; 8(Suppl. 2): 161-8.

41. DiAlberti L, Teo CG, Porter S, Zakrewska J, Scully C. Kaposi's sarcoma herpesvirus in oral Kaposi's sarcoma. Oral Oncol Eur J Cancer 1996; 32B:68-9.

42. Jin YT, Tsai ST, Yan JJ, Chen FF, Lee WY, Li WY et al. Presence of human herpesvirus-like DNA sequence in Oral Kaposi's Sarcoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996; 81: 442-4.

43. DiAlberti L, Ngui SL, Porter SR, Speight PM, Scully CM, Zakrewska JM et al. Presence of human herpesvirus 8 variants in the oral tissues of human immunodeficiency virus-infected persons. J Infect Dis. 1997; 175:703-7.

44. Webster-Cyriaque J, Edwards RH, Quinlivan EB, Patton L, Wohl D, Raab-Traub N. Epstein-Barr virus and human herpesvirus 8 prevalence in human immunodeficiency virus-associated oral mucosal lesions. J. Infect. Dis. 1997; 175: 1324-32.

45. Koelle DM, Huang ML, Bala Chandran, Vieira J, Piepkorn M, Corey L. Frequent detection of Kaposi's sarcoma-associated herpesvirus (HHV-8) DNA in saliva of human immumodeficiency virus- infected men: Clinical and immunologic correlates. J Infect Dis. 1997; 176: 94-102.

46. Flaitz CM, Jin YT, Hicks MJ, Nichols M, Wang YW, Su IJ. Kaposi's sarcoma-associated herpesvirus-like DNA sequences (KSHV/HHV-8) in oral AIDS-Kaposi's sarcoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997; 83: 259-64.

47. Vieira J, Huang ML, Koelle DM, Corey L. Transmissible Kaposi's sarcoma-associated herpesvirus (HHV-8) in saliva of men with a history of Kaposi's sarcoma. J Virol. 1997; 71: 7083-87.

48. Lager I, Altini M, Coleman H, Ali H. Oral Kaposi's sarcoma: A clinicopathologic study from South Africa. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96: 701-10.

49. Marcelin AG, Gorin I, Morand P, Ait-Arkoub Z, Deleuze J, Morini JP et al. Quantification of Kaposi's sarcoma-associated herpesvirus in blood, oral mucosa, and saliva in patients with Kaposi's sarcoma. AIDS Res Hum Retroviruses 2004; 20: 704-8.

50. Cannon MJ, Dollard SC, Black JB, Edlin BR, Hannah C, Hogan SE et al. Risk factors for Kaposi's sarcoma in men seropositive for both human herpesvirus 8 and human immunodeficiency virus. AIDS 2003; 17: 215-22.

51. Ablashi D, Chatlynne L, Cooper H, Thomas D, Yadav M, Norhanom AW et al. Seroprevalence of human herpesvirus 8 (HHV-8) in countries of Southeast Asia compared to the USA, the Caribbean and Africa. Br J Cancer 1999; 81: 893-7.

52. Lampinen TM, Kulasingam S, Min J, Borok M, Gwanzura L, Lamb J et al. Detection of Kaposi's sarcoma-associated herpesvirus in oral and genital secretions of Zimbabwean women. J Infect Dis. 2000; 181: 1785-90.

53. Gao SJ, Kingsley L, Hoover DR. Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related nuclear antigens before the development of Kaposi's sarcoma. N Eng J Med. 1996; 335: 233-41.