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Improving the detection of Human Herpes Virus -8 in AIDS Patients- A Narrative Review

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The AIDS Pandemic signified Kaposi's sarcoma as no longer prominent not only in African regions but also as the foremost AIDS Defining neoplasm. The Human Herpes virus-8 is the etiological agent of Kaposi's sarcoma and is similar to Epstein Barr Virus in that replication occurs in the epithelium of the oro pharynx, with tonsils possibly acting as the major reservoir of the infection. HHV-8 detection and prevalence varies greatly depending on geographic location, ethnicity, genetic co factors and the detection method used. Kaposi's sarcoma has been determined on histology utilizing immunohistochemistry and immunofluoresce nceassays designed to detect the latency associated molecular assays, including PCR, are highly specific for determining seropositivity. In India the clinical manifestations of HHV-8 in particular KS appears to be reduced or non-existent of serological assays- ELISA and IFA are highly dependent on assay design and antigen preparation. Serological assays to date are not highly specific or sensitive. Current advancements in serological methodologies, including immune-PCR flow conventional serological assays and permit multiplexing of antigenic targets. Research is going on determining the HHV-8 subtype and sero epidemiology in the Australian, Indian, And Kenyan HIV Positive populations to establish that will hopefully provide a much greater detection of HHV-8

Keywords: Herpes simplex virus-8, Immuno histochemistry, Kaopis's Sarcoma, Polymerase Chain reaction, Histological diagnosis

Introduction:

Human Herpes virus-HHV-8 is the most recently developed Human Herpes Virus. Detected in 1994, HHV-8, is the only virus of the family Herpes viridae, subfamily Gamma herpes virinae Genus Rhinovirus(Gammma-2 Herpes virus) known to infect humans(Chang et al., 1994). Similar to other members of the family Herpes viridae,HHV-8 displays the typical bulls eye morphology as the virion consists of an electron dense envelope and icosahedral capsid separated by an electron transparent tegument(Monini et al., 1999; Wu et al., 2000). The icosahedral capsid is 150nm in diameter and contains 162 capsomere with a double stranded DNA genome. The 170-270 kb linear double stranded DNA genome contains at least 95 open reading frames (ORF's) with 56 genes displaying 67% homologous at the nucleotide level with Epstein Barr virus (EBV) and Herpes virus saimiri(HVS) (Moore et al.;1996;Renne, Lagunoff, Zhong and Ganem, 1996.; Russo etal.,1996). HHV-8 is also known as Kaposi's Sarcoma associated herpes virus (KSHV) as it is the etiological agent of Kaposi's sarcoma (KS) ,Multicentric Cattleman's disease (MCD) and primary effusion lymphoma (PEL) which is also called body cavity based lymphoma (BCBL). Besides the clinical manifestations (KS, MCD and PEL) of HHV-8, it's transmission, seroepidemiology, and subtypes have shown co relation with a geographical location in patients with KS. The lack of a "gold standard" assay has confounded the diagnosis of HHV-8 in severe HIV- associated diseases. Although HHV-8 has been researched worldwide it has been overlooked in India, due to its low prevalence and also due to the introduction of Highly active antiretroviral therapy(HAART) in 1995-55 greatly reduced the incidence of KS as an AIDS defining condition.

Clinical Manifestations. HHV-8 is the confirmed etiological agent of KS, MCD and PEL (Caserman, Chang, Moore, Said and Knowles, 1995; Sarid , Kelpfish and Schatterner, 2002Soulier et al ., 1995). KS was first described as an "idiopathic multiple pigmented sarcoma of the skin" in five elderly men of Italian, Jewish and Mediterranean descent in 1872 by the Hungarian dermatologist ,Dr. Moritoz Kaposi and eponymously designated "Kaposi's Sarcoma"(Kaposi, 1872).KS is an angioproliferative disorder presenting in the oral mucosa, skin, lymph nodes and visceral organs which is characterized by the formation of pink to bluish patches, plaques or nodules depending on the stage of the manifestation (Sanders, Canninga-van Dijk and Borleffs, 2004).Appearance of intense angiogenesis, erythrocyte extravasation, spindled-shaped endothelial cell proliferation, inflammatory cell infiltration and nuclear polymorphism is diagnostic in haemotoxylin and eosin stained biopsies (Gessain and Duprez,2005;O' Connell, 1977).cutaneous KS Lesions appear on any part of the skin

such as the lower extremities, torso, and genitalia while oral lesions occur mainly on the palate but also the gingival and dorsum of the tongue(Lager, Altini, Coleman and Ali,2003;Reznik, 2005;Rohrmus et al.; 2000). While cutaneous lesions are more , oral lesions are present in upto 60% of KS Cases and are associated with higher mortality rate with mortality occurring 24 months after diagnosis compared to 72 months seen in cutaneous lesions.

The four KS Epidemiological variants are classical, iatrogenic or immunosuppressant and AIDS-KS. Classical KS also called traditional or sporadic KS, is a rare cutaneous lesion traditional of elderly men of Mediterranean (Eg. Greece and Italy). Jewish and eastern European decent before the onset of the HIV/AIDS epidemic. (Dal Maso et al.; 2005; Guttmann –Yassky et al.;2006; Hjalgrim et al.; 2001). Endemic KS was highly prevalent in sub saharan Africa before the HIV/AIDS pandemic(Cook-Mozaffari, Newton, Beral and Burkett, 1998). Iatrogenic KS develops following a renal or other solid organ allograft or blood transfusion transplanting HHV-8 from an HHV-8 positive donor to an HHV-8 negative recipient on immunosuppressant Drugs (Montagnino, Bencini, Tarantino, Caputo and Ponticelli, 1994; Penn, 1979). AIDS-KS was identified in 1981 when a fulminant and disseminated form of KS was first reported in the USA Heralding the HIV/AIDS Epidemic (Friedman- Kien, 1983). This unusual and more aggressive form of KS was named AIDS-KS or epidemic KS, due to the co relation between both prevalence and presence of HIV and HHV-8 manifestations at epidemic numbers in a population where KS was previously a rare event. The aggressiveness and progressively enlarging lesions is due to severe immunosuppression caused by the reduction of CD4+ cells and host virus interactions between HIV-1 tat, IL-6, FGF and HHV-8, resulting in enhanced HHV -8 replication in KS –derived spindles shaped cells (Ensoli, Barillari, Salah Uddin, Gallo and Wong-staal , 1990;Ensoli et al; 1994;Ensoli, Salah Uddin and Gallo, 1989) The introduction of highly active anti retroviral Therapy (HAART) in 1995-96 greatly reduced the incidence of KS as an AIDS- defining condition as 90% of AIDS-KS cases displayed complete remission of cutaneous lesions within six months as well as an 81% reduction in mortality (Ziegler et al.; 1997). But today KS is still the most frequent AIDS associated neoplasm worldwide due to poor access to HAART and the health delivery infrastructure in developing nations.

The other two confirmed HHV-8 manifestations , MCD and PEL also occur predominately in AIDS patients. MCD is a severe lymph node enlargement related to immune dysregulation (Soulier et al.; 1995). Due to the presence of HHV-8, KS manifests in 75% of HIV positive patients with MCD

(Dupin et al.; 1999).PEL is a cancer of the lymphocytes making up a distinct subgroup of AIDS- associated non- Hodgkin Lymphomas (NHL) localized in the body cavity and presenting as pleural, peritoneal and pericardial lymphomatous effusions (Soulier et al.;1995). It is rare, but constitutes 3% of AIDS associated lymphomas. HHV-8 is present in every cell with high viremia of 40-80 copies of HHV-8 DNA/cell (Cesar man et al., 1995). The role of HHV-8 in as been suggested in a variety of cutaneous and visceral diseases including sarcoidosis, multiple myeloma, pemphigus vulgaris, pemphigus foliaceous, angiosarcoma, AK, SCC, basal cell carcinoma, atypical squamous proliferations, sebarrhoeic keratosis and verruca vulgaris, primary pulmonary hypertension and post transplant skin cancers but these findings remain controversial.(Cathomas et al.; 1998;Hsue et al., 2008; Laney et al., 2005; Parravicini et al., 1997 Rady et al., 1995;Rettig et al., 1997). The extent of clinical manifestations where HHV-8 is either the etiological agent, a co factor or simply a passenger virus remains to be defined.

Transmission:

Transmission of HHV-8 and Ks depends upon geographical location and the patient cohort examined. In developed nations like the USA and Australia where prevalence of both HHV-8 and KS is low, the high risk sexual practices of homosexual males and their multiple partners permit easy HHV-8 transmission (Grulich et al.; 2005; Grulich et al.; 1999). In developing nations, like Kenya, where KS is endemic, HHV-8 is transmitted via non sexual routes either vertically from mother to child, horizontally between siblings and child hood playmates, or perinatally between mother and baby before during and /or after birth (Mbulaiteye and Goedert, 2008; Plancoulaine et al.;, 2000). In both vertical and horizontal transmission HHV- 8 is passed via saliva from mother to child at a rate as high as 30% (Casper et al., 2006). Similar to EBV, the oral mucosa plays a dominant role in both sexual and non sexual HHV-8 transmission as viral loads are highest in the saliva and barely detectable in genital fluid or blood as well as HHV-8 replication occurring predominately in the epithelium of the oropharynx with the tonsils being a reservoir of infection (Pak et al., 2007Taylor et al.; 2004).

Sero epidemiology and subtypes

Epidemiology and phylogenetic studies have shown strong correlations between HHV-8 seroprevalence and strains with the geographical origin of specimens, patient cohorts examined and prevalence of KS. HHV-8 and KS is endemic in sub Saharan African countries (Eg; Uganda, Botswana and the Gambia) with seroprevalence reaching as high as 80 % in some areas (Engels, Sinclair et al.; 2000; Olweny, 1984;Schatz et al.;

2001).Geographical regions where both HHV-8 and seroprevalence and KS is uncommon include North and South America, Northern and Western Europe where HHV-8 seroprevalence levels are only between 5-2-% and incidence of KS is 5 %Based on phylogenetic analysis to ORFK1 HHV-8 can be divided into three genotypes and six subtypes(A,B,C,D, E and Z) that are strongly co related with geographical origin of the isolates(Hayward, 1999).HHV-8 subtypes A and C occur in Europe, North America, Northern Asia and the middle east, subtypes A5 and B are found in Africa and subtypes C2 and C6 occur n the North African Sephardic Jews (Cook et al., 1999; Hayward, 1999). The rare subtype E is only found in the Brazil Amerindians and subtype Z detected in only Zambian children (Ishak Mde et al.,2007; Kasolo et al.,1998). The pacific islands and Australia are the only places where the rare subtype D is found (Cassar et al., 2007; Meng et al., 1999). To date there has only been one phylogenetic study in Australia.

Detection methods

HHV-8 and its three clinical manifestations have been extensively characterized in many parts of the world. However, 14 years since the discovery of HHV-8 there is a considerable knowledge gap regarding the prevalence of infection, variation in geographically distinct populations as well as the route and risk factors associated with its transmission. Bridging these gaps through a gold standard diagnostic test is still beyond universal acceptance. Molecular assays such as PCR, and immunohistochemistry (IHC) are useful diagnostically for detecting HHV-8 latent replication in KS lesion biopsies. Although PCR ORF26 assays was used to discover and detect HHV-8 , due to laboratory contamination, sampling error and lack of co relation with serological assays it is difficult to accept the validity of many of the early epidemiological studies(LaDuca et al., 1998;Pellett et al., 1999).Today, q PCR ORF73 assays are used for detecting HHV-8 in biopsies as over 90% of HHV-8 latently infected cells express LANA-1 the ORF26 assays are still useful for monitoring treatment regimens because ORF26 is a lytic gene that is expressed in actively replicating in infected cell with HHV-8 viremia detectable in PBMC (Asahi- Ozaki, Sato, Kanno, Sata and Katano, 2006
;Chang et al., 1994; Senanayake et al., 2003).PCR will detect HHV-8 in most KS lesions but is unreliable in peripheral blood as HHV-8 viremia is low and periodic and in asymptomatic patients the sensitivity of PCR tests is still found wanting. Serology is currently the only method useful for epidemiological studies in which HHV-8 antibodies can be detected before the appearance of clinical manifestations.

Serology is the method of choice for large scale epidemiological studies. Both EIA and IFA are commercially available for screening patients for HHV-8 antibodies. The IFA is comparatively the most sensitive assay (Schatz et al., 2001.) The highly antigenic proteins of HHV -8 include ORFK8.1, ORF73 and ORF65 (de Souza et al., 2007). The IFA -LANA-1 assay was considered to be a reference serological test as it has 98% specificity but only 54% Sensitivity (Nascimento et al., 2007). Comparison of serological assays have found that ELISA towards the capsid antigen are best for large scale epidemiological studies as they are more sensitive than IFS, which are only useful for lytic antigens and require cell lines as positive and negative controls (Dedicoat et al.,2004; Placoulaine al., 2000) Although ELISA are more sensitive easier and faster assays to use, the IFA are much more specific with lytic antigen based assays but require significant expertise and a great deal of time to do large sample sizes (Corchero, Mar, Spira , Pellett and Inoue, 2001).

Despite the problems with HHV-8 serological assays ELISA has been useful to detect HHV- 8 antibodies in oral specimens (Pica and Volpi, 2007) and assays using lytic antigens have been useful to evaluate viral transmission (Engels, Whitby et al., 2000 et al., 2000; Plancoulaine et al., 2000). The development of improved molecular and serological assays that are sensitive , specific and standardized are essential to further understand HHV-8, its route of transmission and provide improved diagnosis of this potentially fatal neoplasm-KS.

Research in India

Although HHV-8 has been the focus of research worldwide it has been largely overlooked in India as the introduction of highly active antiretroviral therapy (HAART) in 1995-96 greatly reduced the incidence of KS as an AIDS defining condition. Australian researchers have briefly looked at the risk factors associated with the sexual transmission of HHV-8 and the genotyping of a few HHV-8 isolates. The phylogenetic study sequenced four isolates and found each isolate to be different clades, which were genotypes 1 (subtype A, clades g and K), 11 (clade c) and 111 (clade b) thus providing little insight into the distribution and prevalence of the HHV-8 subtypes in Australia (Meng et al., 1999).

Research is required to compare the serotypes and seroprevalence of HHV-8 in India. While HHV-8 has been overlooked because KS and MCD rarely occur in developed nations, further research is required to understand the nature of HHV-8 in both the developed and the developing countries Large scale epidemiological studies to expand the understanding of HHV-8 in India phylogenetic analysis will hopefully provide an insight into seroprevalence of HHV-8 in a selected cohort of HIV-infected patients in India.

In order to further define HHV-8 in India, a q PCR assay for both orf73(latent associated nuclear antigen or LANA-1) and ORF26 (major capsid protein) will be designed and used to detect HHV-8, it's replicative state and viral load in both tissue and blood. It can also be used to further understand the transmission of HHV-8 in oral mucosa. The circulating HHV strain will be performed on ORFK1, ORF75, and RFK14.1/15 with information useful to design improved molecular assays for the detection of HHV8 in saliva and sera. The Indian HHV-8 subtype is unknown, but it is possible that the Indian HHV-8 subtype will either be subtype C (clad C2 or C3 as it is part of Southern Asia) or a previously undetected subtype and /or clade.

THIS INFORMATION COULB BE USED TO:

- Design improved diagnostic methods, like the Immuno-PCR, that can be used to screen individuals at risk of developing KS.
- Confirm a clinical or histological diagnosis of KS.
- To monitor treatment regimes for HHV-8 in diseased or at risk individuals.
- To screen new anti viral drugs and perhaps vaccines

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