Increased prevalence of Kaposi′s sarcoma-associated herpesvirus in the Kaposi′s sarcoma-endemic area of Western Kenya in 1981–2000

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Summary. – Kaposi′s sarcoma (KS) had been endemic in Africa before the appearance of human immuno-deficiency viruses (HIV) in 1985. Incidence of African KS has increased over the time and the risk of contracting KS become greater in HIV-positive as opposed to HIV-negative individuals. KS specimens were collected in 1981–2000 from 228 surgical cases originating from a KS-endemic area of Western Kenya and examined for Kaposi′s sarcoma-associated herpesvirus (KSHV) by an immunoperoxidase assay. The results showed that the specimens from 1981–1985 (before the HIV epidemic) were KSHV-positive in 10.3% in contrast to the KSHV positivity of 50.1–63.5% in 1986–2000. The linear increase of KSHV positivity in 1981–2000 was statistically significant. The most plausible explanation for the increased prevalence of KSHV in KS cases is that the endemic KS has changed to the epidemic one.

Introduction

Kaposi′s sarcoma (KS) is a vascular lesion of low-grade malignant potential that presents most frequently in the cutaneous area (Sanders *et al.*, 2004). KS lesions contain numerous infiltrating inflammatory cells as well as a profusion of neo-vascular elements. In the affected populations, KS is usually classified by clinical and epidemiological characteristics into four distinct types such as classic (sporadic), endemic (African), post transplantation (immunosuppression therapy), and epidemic (AIDS-associated). At present, KS is the most common neoplasm in patients with AIDS (Antman and Chang, 2000). Despite clinical and epidemiological differences, the four KS forms have a very similar histological appearance. KS manifests most frequently in cutaneous sites like the skin at the lower limb, face, trunk, genitalia, and oropharyngeal mucosa followed by the lymph nodes and visceral organs most notably the respiratory and gastrointestinal tracts. It is also observed in unusual locations, such as the musculoskeletal system, central and peripheral nervous system, larynx, eye, salivary glands, endocrine organs, heart, thoracic duct, urinary system, and breast (Pantananowitz and Dezube, 2008).

KSHV was identified by Chang *et al.*, 1994 and since then, it has been classified as a human herpesvirus type 8. These viruses are specifically associated with the neoplasm induction during immunosuppression. KSHV is linked to the KS, multicentric Castleman′s disease, and primary effusion lymphoma (Chang *et al.*, 1994; Boshoff and Weiss, 2002; Dourmishev *et al.*, 2003). KSHV is present in spindle cells from all four types of KS (Boshoff, *et al.*, 1995; Zhong, *et al.*, 1996) and the experimental infection with KSHV produces KS-like lesions in animals (Foreman, *et al.*, 2001).

The highest viral loads were detected in saliva (Koelle *et al.*, 1997; Mancuso *et al.*, 2008). Safe sex practices do not protect against the KSHV infection probably due to the virus presence in saliva. KS was endemic in equatorial Africa before AIDS was known to be present in the area.

In this study, we assessed the prevalence of KSHV in endemic area of Kenya before and after the spread of HIV.

Materials and Methods

Patient specimens. The biopsy materials comprised 228 cases of African KS obtained from Rift Valley Provincial General Hospital in Nakuru, Kenya and Nyanza Provincial General Hospital in Kisumu, Kenya from 1981–2000. Children were 1.5–10-year-old.

Immunoperoxidase assay. Detection of KSHV was done by the mouse monoclonal antibody against latency-associated nuclear antigen 1 (LANA-1). In brief, the tissue specimens were fixed in 10% formalin and embedded in paraffin for histochemical and immunohistochemical studies. The tissue sections were examined with monoclonal antibody against LANA-1 diluted 1:50 (Novacastra Laboratories). Immunohistochemical procedure was performed as described in our previous study (Senba *et al.*, 2009). Results were evaluated using a light microscope. The statistical method used in analysis of this study was the Cochran-Armitage trend test.

Results

KS patients in 1981–1985, 1986–1990, 1991–1995, and 1996–2000 showed presence of KSHV in 10.3, 50.1, 56.8, and 63.5%, respectively (Table 1). Cochran-Armitage trend test for a linear trend in the percentage of KSHV positives from all African KS cases during these periods was highly significant ($x^2 = 25.04$, $p = 0.000$). On the other hand, a similar trend was not observed in childhood KS ($x^2 = 0.0003$, $p = 0.986$).

Table 1. Prevalence of KSHV in Kaposi´s sarcoma in Western Kenya in 1981–2000

	1981–1985	1986–1990	1991–1995	1996–2000	Linear trend of increase
KSHV in total	4/39 (10.3%)	29/57 (50.1%)	42/74 (56.8%)	38/58 (63.5%)	Present
KSHV in children	2/4 (50.0%)	5/9 (50.6%)	4/7 (57.1%)	2/4 (50.0%)	Absent

Linear trend of increase was evaluated by the Cochran-Armitage test.

Discussion

A few cases of AIDS in Kenya were reported in the years 1985–1986 (Bayley, *et al.*, 1985; Wendler, *et al.*, 1986; Kreiss, *et al.*, 1986). In our data, an increasing linear trend in the presence of KSHV in KS tissues over time was highly significant. Specifically, the incidence of KSHV has increased rapidly since 1986. Therefore, these findings suggested that the number of epidemic cases of KS increased in an endemic area of Kenya. KS had been endemic in Africa before the HIV epidemic became apparent. Endemic KS is divided into two types. The first type of KS affects the middle-aged adult population residing in several sub-Saharan countries such as Uganda, Sudan, Congo, Rwanda, Burundi, as well as Malawi, eastern Zaire and the coast of Cameroon. The second subtype affects mainly young children under 10 years of age (Wabinga, *et al.*, 1993; Ziegler and Katongole-Mbidde, 1996). In children, KS was predominantly originated in the lymph node and was diagnosed by generalized lymphadenopathy that was especially pronounced in the cervical region. The clinical course of childhood KS is quite different from the adult KS, which exhibits a very slow progression. Childhood endemic KS is an aggressive disease and is associated with the involvement of lymph nodes and visceral organs. The conditions of childhood endemic KS is not clear. However, a possible explanation may be that there is a different immunological response in adults and children. Unlike adults, KSHV incidence in children did not have the linear increase. The reason is not clear, but it is suggested that there are different behavior patterns between adults and children such as the sexual behavior.

The incidence of African KS has increased over time representing greater risk for the HIV-seropositive individuals (Wabinga, *et al.*, 2000; Szajerka and Jablecki, 2007). High prevalence of KSHV was observed in Uganda (14–86%), Congo (25–82%), Nigeria (6–56%), South Africa (16–75%), Ivory Coast (43–100%), Vietnam (11.3–15.5%), Colombia (13%), and Costa Rica (11.1%) (Sitas and Newton, 2001; Dedicoat and Newton, 2003; Sanjose, *et al.*, 2009; Butler, *et al.*, 2009). Therefore, it is conceivable that endemic KS may be caused by KSHV infection.

KSHV DNA was first identified in a tumor biopsy of a KS patient suffering from AIDS. KSHV is the most recently discovered human oncogenic herpesvirus, which is found in tissues from all four types of KS (Chang, *et al.*, 1994; Boshoff and Weiss, 2002; Dourmishev, *et al.*, 2003). KSHV latent genes play an important role in the pathogenesis of KS, since the virus usually infects endothelial cells. In the latent form, viral genes induce the cell regulation allowing cell to replicate, prevent cell death, and shut off the immune response (Miller, *et al.*, 1997). The expression of LANA-1 is currently used to confirm the presence of KSHV in KS patients (Renne *et al.*, 2001; Dupin *et al.*, 1999). The majority

of LANA-1 is found in spindle cells in late nodular stage. In early patch stage lesions, LANA-1 expression is also found in the walls of lymphatic endothelium and in the infiltrating spindle cells. However, the mature endothelial cells surrounding normal vascular blood vessels are negative for LANA-1 (Dupin, *et al.*, 1999).

KS development is now considered as a multi-step process involving both viral and cellular factors that include the infection of spindle cells by KSHV and production of several inflammatory cytokines, chemokines, and angiogenic factors (Dourmishev, *et al.*, 2003; Senba and Mori, 2010).

With regard to the clinical and epidemiological characteristics, KS is usually divided into four distinct types, e.g. classic, endemic, post-transplantation, and epidemic. The incidence of Kenyan KS increased significantly and the risk of contracting KSHV is greater in HIV-positive than in HIV-negative individuals. According to our data, KS had been endemic in Kenya before the appearance of HIV in 1985. Therefore, it is suggested that the increase of KSHV incidence is associated with HIV infection. Moreover, in Kenya, the incidence of epidemic KS increases more than that of the endemic KS.

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