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## Personal Opinion

# Pathogenesis of Oral Kaposi's Sarcoma in HIV-infection: Relevance of Endogenous Glucocorticoid Excess in Blood and Saliva

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**Endogenous glucocorticoid excess with concomitant hypercortisolaemia and increased saliva level of the free active hormone, is a common feature of HIV-infected/AIDS patients. Exposure of the oral tissues to virtually uninterrupted high burden of glucocorticoids through saliva may contribute to the high frequency of oral Kaposi's sacoma (KS) in these patients. AIDS-KS cells contain unusually high levels of glucocorticoid receptor protein and recent studies indicate that growth of these cells in culture is significantly stimulated by glucocorticoids, particularly in the presence of growth factors, such as oncostatin-M. The suggestion that glucocorticoid excess may be important in the pathogenesis of KS in AIDS is not in conflict with the suspected aetiological role of newly reported KS-associated herpesviruses (KSHV), since steroid hormones may upregulate the expression of the viral gene. The latter is consistent with the observation that infection by specific oncogenic viruses does not necessarily result in cancers in the human, and does require the presence of other cellular factors or events.** 

**Keywords: oral Kaposi's sarcoma, steroids, AIDS**

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## INTRODUCTION

Kaposi's sarcoma (KS) is a multicentric, multiorgan neoplasm, with individual lesions characterised by the proliferation of "spindle-shaped" cells (KS cells), mixed with fibroblasts, endothelial cells and inflammatory cells [1, 2]. The malignant potential of KS is conferred by the KS cells which are generally believed to be of mesenchymal origin, although it is not clear whether they are derived from endothelial or smooth muscle cells [1, 3, 4]. Cytomegalovirus (CMV), an oncogenic herpes virus, may be associated with the pathogenesis of KS in view of findings of positive CMV serology, CMV-DNA, CMV-RNA, and CMV-antigens in biopsy specimens [4, 5]. Several recent studies have described KS-associated herpesviruses (KSHV) with DNA sequence homology to gamma-herpesviruses [6, 7]. Because of the widely variable rates and extent of progression of the lesions among patients, there are suggestions that KS is not a true malignancy but rather a reactive tumour [8, 9].

Four epidemiological types of KS are known, namely, the classic type, endemic African KS, KS found in organ-transplant patients receiving immunosuppressive therapy, and HIV-infection/AIDS-associated KS [9]. Kaposi's sarcoma is the most common neoplasm found in HIV-infected individuals, at a frequency of 20–50%, particularly but not exclusively in homosexual and bisexual men [10, 11]. This brief report examines the possibility that basal endogenous hypercortisolism plays an important role in the pathogenesis of AIDS-associated KS. In effect, it is suggested that at least from the pathogenetic point of view, the AIDS-related KS shares much in common with KS associated with immunosuppressive therapy in organ-transplant recipients.

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## ORAL INVOLVEMENT OF KAPOSI'S SARCOMA

It is difficult to obtain reliable published information on the frequency of involvement of different organs in patients with KS. About 40% of individuals with KS are believed to have oral lesions [12, 13]. These lesions may appear as red or purplish macules, papules or nodules anywhere on the oral mucosa, but most frequently on the hard palate [12, 14]. They do not blanch on pressure, and are usually symptomless unless

infected or ulcerated [12]. The oral lesions of KS contain a greater proportion of spindle cells (KS cells) than do the cutaneous lesions [13].

In Western Europe and North America, oral KS has been reported mainly in homosexual males but other risk groups are not exempt [5]. The co-factors causing KS in the presence of HIV-infection/AIDS are still poorly defined. The suspected factors include viral infection, reticuloendothelial disorder and systemic (hormonal, neural) factors [6, 7, 15, 16]. Prior or current heavy psychotropic drug usage is a very common habit in patients with oral KS [14]. Important pharmacological interactions occur between many of such drugs and the hypothalamic–pituitary–adrenal axis (HPA) [17]. For example, both acute and chronic cocaine abuse alters endocrine and neurochemical functions [18, 19], resulting quite often in significant hypercortisolaemia [17, 20].

## BLOOD AND SALIVA LEVELS OF GLUCOCORTICOIDS IN HIV-INFECTION

Individuals suffering from HIV-infection/AIDS present with complex endocrine changes [21]. In many patients, particularly in the early and late stages of HIV-infection, basal and stimulated blood concentrations of non-protein bound endogenous cortisol are significantly higher than those in controls, and the hypercortisolaemia may not be associated with any evidence of clinical hyperadrenalism [21–25]. In a group of HIV-infected children, mean basal plasma cortisol concentration (μg/dl) was $16.4 \pm 8.7$ (range 6.7–38.0) and was significantly higher ($P < 0.001$) than the mean of $9.3 \pm 3.8$ (range 3.5–15.0) observed in age-matched controls [26]. Similar findings are reported in adult victims of the viral infection [21, 22, 27]. In 17% of adult HIV-infected patients studied by Norbiato and colleagues [23], there was evidence of acquired glucocorticoid resistance, resulting in elevated blood and urinary levels of cortisol among other findings. In these patients, the normal circadian pattern is therefore maintained at higher blood levels of cortisol. Associated with increased glucocorticoid production in some patients with HIV infection is a reduction in adrenal production of dehydroepiandrotestosterone sulphate (DHEAS) and its derivative dehydroepiandrosterone (DHEA), resulting in significant reductions in the ratios of DHEAS and DHEA to cortisol [22–24]. Both DHEAS and DHEA are physiological antagonists of the immunoregulatory activities of glucocorticoids [21, 25]. Some of the hormonal disturbances in HIV-infected individuals, particularly the increased glucocorticoid production, may result from drug therapy [17, 21, 28] or may reflect a normal adaptive response to stress [21, 22]. Studies have shown that in severely ill, HIV-seronegative patients, basal serum cortisol concentration is significantly increased compared to findings in a control group [29].

Of more potential relevance to the pathogenesis of oral lesions of KS in HIV-infected subjects is the well-documented, strong, linear correlation ($r \geqslant 0.82$–$0.90$) between saliva concentrations of cortisol plus cortisone, and serum levels of the active, nonprotein bound hormones [30–36]. This relationship is observed in both children [36] and adults [30, 32]. The circadian change in saliva cortisol concentrations is similar to that of plasma patterns [32]. Recent studies in our laboratory have demonstrated a mean 2-fold significant increase in unstimulated whole saliva concentration of free cortisol in HIV-infected adults, most of whom were asymptomatic compared with age- and gender-matched healthy subjects sampled at the same time of the day [37].

The mean ($\pm$S.D.) cortisol production rate in normal children and adolescents of both sexes irrespective of pubertal stage, as measured by stable isotope-dilution technique employing high-performance liquid chromatography/mass spectrometry, is $9.5 \pm 2.5$ mg/day ($6.8 \pm 1.9$ mg/m$^2$/day) [38]. Treatment of children with hydrocortisone at a dose of 12 mg/m$^2$/day (about 76% higher than the estimated normal cortisol production rate) for adrenal insufficiency, elicits clinical evidence of glucocorticoid excess [38]. The latter is within the range of increase in plasma free cortisol in HIV-infected children compared with healthy controls [26, 39].

## CORTICOSTEROIDS AND PATHOGENESIS OF KARPOSI'S SARCOMA

A recent report by Scully and Porter [40] underscores the well-documented but often forgotten observation that therapy with immunosuppressive drugs, such as the corticosteroids, makes the oral mucosa and other tissues more susceptible to infections (e.g. CMV, EBV) and neoplasia (oral KS, oral carcinoma). Historically, glucocorticoid therapy has been linked to increased risk of KS in non-HIV related conditions, with complete or partial remission occurring following steroid withdrawal [9, 16, 41]. In one study on non-AIDS patients, the interval between initiation of steroid therapy and appearance of KS ranged from 3 to 36 months (mean 13.7 months) [9]. A similar relation between steroid therapy and incidence of KS is reported in HIV-infected/AIDS patients [8, 42]. HIV-patients, treated with glucocorticoids continuously for 2 weeks or intermittently for 30 days, developed new KS lesions as well as accelerated clinical progression of the lesions, and these lesions showed spontaneous resolution within 8 weeks of discontinuation of steroid therapy [42].

The exact mechanisms of development of KS in AIDS still remain poorly understood. Studies both *in vivo* and *in vitro* suggest that some cytokines and growth factors may play an important role in the pathogenesis of KS [2, 43]. Compared to other well-studied cell lines, AIDS-KS cells contain an unusually high level of glucocorticoid receptor protein [2]. A very recent study has shown that growth of cultured KS cells derived from AIDS patients is significantly stimulated by dexamethasone, and the stimulatory effect becomes even more pronounced if the KS cells are exposed simultaneously to the steroid and oncostatin-M (OSM) [2]. OSM is an autocrine growth factor (a 28–30-kDa protein) for KS [43]. RU-486 (a glucocorticoid receptor antagonist) reduces the synergistic effect of OSM and dexamethasone on proliferation of the KS cells, but completely abolishes the effect of the steroid when used alone [2].

The newly described Kaposi's sarcoma-associated herpesviruses (KSHV), which occur in both AIDS-related and unrelated forms of KS, have been assigned an aetiological role in this tumour [6, 7, 44, 45]. KSHV was detectable in peripheral blood mononuclear cells of 52% (24 out of 46) of KS patients, but in none of 134 blood donors or 26 HIV-uninfected hospital controls, and there was evidence of inverse correlation between KSHV detection and degree of immunosuppression as assessed by the number of CD4 positive T-cells [44]. It is possible that viral infection alone does not result in cancer [46]. In a very recent review of the potential role of specific viruses in the pathogenesis of some human cancers,

Morris and colleagues [46] emphasize the disproportionately lower incidence of such cancers relative to the frequencies of the relevant viral infections. The latter observation suggests the importance of additional cellular events/factors which may be genetic, hormonal, immunological or the expression of viral proteins in an inappropriate cell type [46, 47]. There is, for example, evidence of increased incidence of CMV disease in HIV-seropositive patients given corticosteroids [47]. The state of relative glucocorticoid excess induced by HIV infection may promote enhancement of the viral gene expression [48]. Steroids have also been shown to potentiate transformation of cervical cells by the human papillomaviruses (HPVs) through interaction with hormone-response elements in the viral long control region [49].

## CONCLUSION

Glucocorticoid excess, particularly from exogenous sources, has been associated with increased incidence of Kaposi's sarcoma. It is now increasingly evident that some HIV-infected/AIDS patients are victims of endogenously mediated hypercortisolism. In these individuals, there is virtually uninterrupted, prolonged exposure of the oral mucosa to elevated levels of corticosteroids in whole saliva. The enhanced supply of corticosteroids to the oral cavity may not only promote increased susceptibility of the mucosa to infections by oncogenic herpes viruses, but also interact with some growth factors, as well as the viruses (KSHV), in stimulating the proliferation of KS cells. This report suggests an urgent need for studies of endogenous hypercortisolism, particularly increased saliva concentration of corticosteroids, on the frequency and rate of clinical progression of oral KS lesions in HIV-infected/AIDS patients.


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