HIV/AIDS associated malignancies of the head and neck

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BK Bunn[1], WFP van Heerden[2]

SUMMARY

Patients with HIV/AIDS are at increased risk for the development of malignancy. Kaposi's sarcoma, non-Hodgkin's lymphoma and cervical carcinoma in women are regarded as AIDS-defining malignancies. The spectrum of malignancy is, however, changing, particularly where patients receive highly active antiretroviral therapy (HAART). South Africa has the highest number of HIV-infected individuals globally. The possibility of the oral health care worker encountering HIV/AIDS-related pathology therefore seems inevitable. The aim of this article is to heighten the awareness of head and neck malignancies occurring in HIV/AIDS whilst highlighting some of the clinical features in order to facilitate early recognition and diagnosis. It is of clinical significance that in many instances, identification of these malignancies precedes HIV/AIDS diagnosis. Optimal patient management requires close co-operation between the oral health care practitioner and the extended health care team.

ACRONYM

EBV:	Epstein-Barr Virus
HAART:	Highly Active Antiretroviral Therapy
HPV:	Human Papilloma virus
KS:	Kaposi's Sarcoma
KSHV/HHV-8:	Kaposi's Sarcoma Herpes Virus
LEC:	Lymphoepithelial Carcinoma
NPC:	Nasopharyngeal Carcinoma
NHL:	Non-Hodgkin's Lymphoma
OKS:	Oral Kaposi Sarcoma
OPC:	Oropharyngeal Carcinoma
SCC:	Squamous Cell Carcinoma

INTRODUCTION

HIV-infected individuals are at far greater risk of developing malignancy compared with their uninfected counterparts. Kaposi's sarcoma (KS), high-grade B-cell non-Hodgkin's lymphoma (NHL) and cervical cancer in women are the most common neoplasms associated with HIV/AIDS and are regarded as AIDS-defining.[1-3] The incidence of non-AIDS defining neoplasms is also being seen with increased frequency in HIV-positive patients and more often in patients who live longer following the institution of highly active antiretroviral therapy (HAART). Non-AIDS defining malignancies of clinical significance in the head and neck include oropharyngeal carcinoma (OPC), nasopharyngeal carcinoma (NPC) as well as squamous cell carcinoma (SCC) and lymphoepithelial carcinoma (LEC) of salivary gland origin.[2] The immune suppression that accompanies HIV/AIDS is an essential co-condition which facilitates virally-induced carcinogenesis, most notably due to Kaposi's sarcoma Herpes virus (KSHV/HHV-8), Epstein-Barr virus (EBV) and Human Papilloma virus (HPV).[1,2] Failure of immune surveillance in HIV/AIDS allows for viral tumorigenesis which is potentiated by traditional risk factors such as tobacco and alcohol consumption.[4]

More than two-thirds of the global HIV infections are identified in sub-Saharan Africa, with an estimated number of 5.6 million infections in South Africa alone.[5] Seventy to eighty percent of HIV-positive patients will manifest a form of HIV/AIDS-related pathology at some stage of the disease.[5,6] The oral health care worker should therefore be adept at clinical recognition and disease management. Head and neck malignancies associated with HIV/AIDS occur at an earlier age than otherwise and are atypical in their clinical presentation. Tumour aggression and advancement signifies progressive immune deterioration, increased viral loads and low CD4 cell counts.[3,6] Malignancy is often the first clinical indication of underlying immune suppression and more so in populations such as ours which have high numbers of HAART-naïve patients.[7] Successful management of HIV/AIDS malignancies is severely hampered by the presence of disseminated, co-existent infectious pathology - which may be controlled by the implementation of HAART.[4,6] In developed countries, the successful initiation of HAART has greatly reduced the incidence of most HIV-related infectious and neoplastic pathology. Certain neoplasms, including Hodgkin's lymphoma, however, appear to be unaffected by HAART.[2]

KAPOSI'S SARCOMA

KS remains the most common HIV-associated neoplasm. It is an intermediate-grade vascular tumour of lymphatic endothelial cell origin composed of irregularly shaped blood vessels with an inflammatory component.[8,9] The clinical behaviour of KS depends on the epidemiological form of dis-

1. **BK Bunn:** *BDS, FC Path (SA)Oral Path.* Department of Oral Pathology and Oral Biology, School of Dentistry, Faculty of Health Sciences, University of Pretoria.
2. **WFP van Heerden:** *BChD, MChD, FC Path (SA)Oral Path, PhD, DSc.* Department of Oral Pathology and Oral Biology, School of Dentistry, Faculty of Health Sciences, University of Pretoria.

Corresponding author
BK Bunn:
Department of Oral Pathology and Oral Biology, University of Pretoria, Pretoria, South Africa. Tel: +27 12 319 2630, Fax: +27 12 321 2225.
E-mail: belinda.bunn@up.ac.za

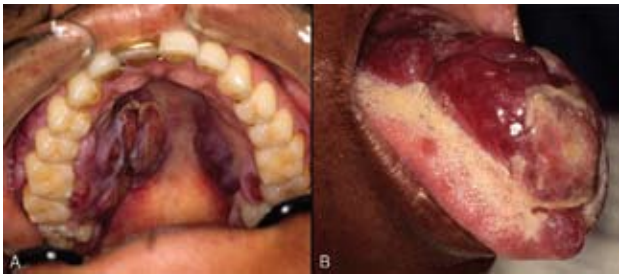

Figure 1. A: Multifocal purple-red lesions of nodular stage oral Kaposi's sarcoma. **B:** Ulcerated nodular stage Kaposi's sarcoma involving the dorsum of the tongue.

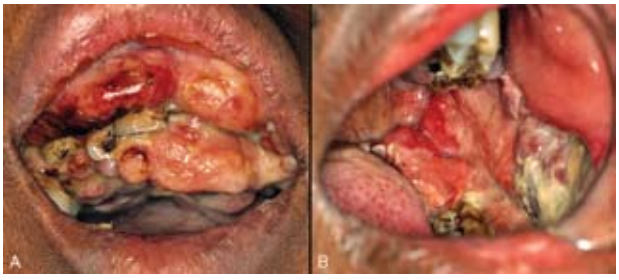

Figure 2. A: Plasmablastic lymphoma presenting clinically as an ulcerated mass on the labial and palatal mucosa with displacement of adjacent teeth. **B:** Extensive buccal and soft tissue ulceration with sulcular extension and involvement of the retromolar trigone area in an aggressive plasmablastic lymphoma.

ease.[10,11] Classic KS, the form first described in elderly males of Mediterranean descent, runs a protracted, indolent course. Patients present with purple patches and plaques which are usually restricted to the extremities. Iatrogenic (transplant associated) KS displays borderline to intermediate qualities. Endemic (African) KS is identified most often in young patients residing in central Africa and is frequently complicated by visceral and lymph node involvement. The most prevalent form of KS is seen in association with HIV/AIDS, referred to as epidemic KS. This is an aggressive form of disease with potentially fatal consequences.[12] HHV-8 is implicated as the aetiological agent in all forms of disease, yet, infection alone is inadequate for KS initiation and progression.[11,13,14] Widespread KS involvement in untreated HIV-positive patients is associated with a particularly poor prognosis and low overall survival rate.[12,15]

The oral cavity is the first site of KS in up to 22% cases. Oral lesions occur concomitantly with skin lesions in 71% of cases.[16] Widespread dermal lymphatic involvement leads to facial lymphoedema and cosmetic disfigurement.[17,18] KS lesions evolve clinically from small flat hyperpigmented patches to thicker, indurated raised plaques, ultimately forming red-purple, exophytic nodules which are frequently ulcerated within the oral cavity.[16,17,19] Intra-oral lesions are multifocal and often involve the hard and soft palate, gingiva, oropharynx and dorsum of tongue (Figure 1A and B). Soft tissue, bone and salivary gland involvement are also described.[16,17] Patients complain of mild pain and difficulty in eating and speaking. Secondary candidiasis and bacterial infection of ulcerated lesions is frequent.[16,17,20,21] Advanced, destructive disease may cause widespread bone loss and marked tooth mobility, the clinical and radiological appearance of which simulates a variety of high-grade malignancies.[20] The high incidence of oral Kaposi sarcoma (OKS) is thought to be due to salivary shedding of HHV-8 viral particles at distinctly higher levels compared with plasma. HHV-8 is most likely harboured within the oropharyngeal epithelium, allowing for replication and sustained salivary shedding.[22,23]

Management

The main objectives in the management of epidemic KS is to arrest lesional growth and the prevention of disease progression. Therapeutic intervention should be individualised according to the patient's state of immunity and stage of disease. Early clinical recognition and diagnosis coupled with vigilant follow-up is critical for therapeutic success. Large lesions which interfere with normal function may require surgical excision whilst radiotherapy and chemotherapy are useful adjuncts in cases with severe cosmetic disfigurement. The mainstay of disease control remains HAART which prevents viral replication, thereby decreasing viral loads and resulting in restoration of immune function. HAART alone results in regression in up to 80% of patients.[16,19,24,25]

HIV/AIDS-RELATED LYMPHOMAS

Non-Hodgkin's lymphoma is the second most prevalent HIV-related neoplasm.[26] Lymphomas seen in HIV/AIDS are high-grade neoplasms typically of B-cell phenotype. These include diffuse large B-cell lymphoma, plasmablastic lymphoma (PBL) and non-endemic Burkitt's lymphoma.[27] Anaplastic large cell lymphoma and certain subtypes of Hodgkin's lymphoma have shown similar increases in incidence.[7] A significant number of these malignancies are associated with EBV co-infection. EBV-driven lymphomas are rapidly fatal with most patients failing to survive beyond a year after diagnosis.[28] The pathogenesis of HIV/AIDS-related lymphomas is complex; however, some of the more aggressive subtypes have shown similar genetic features.[27]

HIV/AIDS-related lymphomas are diagnosed at an advanced stage in patients with low CD4 cell counts and often in those who are HAART-naïve.[1] Tumours are predominantly extranodal and are identified at unusual sites such as the oral cavity, gastrointestinal tract and central nervous system.[3] The risk of developing an HIV/AIDS-related lymphoma may be up to 200 times greater than in HIV-negative patients. The prevalence of HIV/AIDS-related lymphomas continues to increase, even in areas where HAART has been implemented successfully.[3] Nodal based lymphomas may be difficult to identify in patients with the persistent generalised lymphadenopathy of HIV/AIDS. PBL is a recently recognised, distinct tumour entity occurring predominantly within the oral cavity of immunocompromised patients.[27] Constitutional signs and symptoms including fever, night sweats and significant weight loss are frequently noted.[3,29] Lesions have a predisposition for involving the attached gingiva and often present as non-specific oral ulceration. Occasionally they present as rapidly enlarging, exophytic, and haemorrhagic masses often resembling KS or other soft tissue sarcomas (Figure 2A and B). Tumours presenting as small buccal mucosal or gingival ulcers may be associated with tissue necrosis and clinically resemble necrotising ulcerative gingivitis and other infectious causes.[4] EBV reservoirs have been identified within the lymphoid-rich areas of Waldeyer's ring as well as within epithelial cells of the oropharynx and nasopharynx which possibly accounts for the high incidence of intraoral tumours.[30]

Management

Response to treatment in the HIV-infected patient is poor compared with the immunocompetent patient. The advanced stage at diagnosis in these patients is associated with low survival times with many patients dying within weeks to months. The small percentages of patients who

show complete treatment response tend to suffer frequent relapses. Therapy is directed at restoration of immune function through the use of antiretroviral therapy and a combination of chemotherapy and radiation therapy. Improvement in prognosis depends largely on successful HAART and early therapeutic intervention. It is recommended that, for best results, patients be referred for appropriate treatment within two weeks of diagnosis.[3,29]

NON-AIDS DEFINING MALIGNANCIES

HPV-related oropharyngeal carcinoma

There has been a dramatic increase in the number of oropharyngeal cancers in the setting of HIV/AIDS. Tumours are strongly associated with high-risk subtypes of HPV and occur in a younger subset of patients as compared with conventional smoking and alcohol-associated head and neck SCC. The mode of HPV transmission is through high-risk oral sex practices. It is predominantly a disease of young males and often presents with early nodal involvement.[31] Tumours arise deep within tonsillar crypts or within the base of tongue where they may easily escape clinical detection. Recent studies have also shown a link between HPV and laryngeal and conjunctival SCC.[2]

Tumours seen in patients on HAART

The longer life span afforded to those patients who receive HAART has seen a rise in the incidence of several 'infectious neoplasms'. These include EBV-related SCC and LEC of salivary gland origin, NPC and occasional smooth muscle tumours as well as Merkel cell carcinoma due to Merkel cell Polyoma virus. The acquisition of such neoplasms is closely related to male gender, smoking, older age and a slightly higher CD4 cell count as compared with the AIDS-defining tumours. These malignancies have been attributed to the direct oncogenic effect of HIV in an aging HIV-positive population.[2]

CONCLUSION

Heightened awareness of the malignancies associated with HIV/AIDS will allow for greater recognition and appropriate management. Malignancies are increased in both HAART-naïve patients as well as those who receive antiretroviral therapy. The clinical significance in the dental setting lies in the fact that many such neoplasms are the first indication of underlying immune suppression. A multidisciplinary approach will allow for optimal patient management.

Declaration: No conflict of interest declared

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