Oral Malignancies Associated with HIV

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ABSTRACT

Advances in the management of HIV infection have resulted in significant changes in survival and in the prevalence and incidence of oral diseases found in persons infected with HIV (as discussed in other articles in this series). HIV is associated with an increased risk of malignant disease that is related to immunosuppression and the activity of the HIV transactivator of transcription protein, coviral infection and exposure to carcinogens. The presence of oral malignancies varies with the route of the transmission of HIV and varies geographically, based on behaviour, viral cofactors, HIV therapy and genetic variation. Oral health care providers can identify these lesions early.

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People who are HIV-positive have more than a twofold increased risk of malignant disease, and an estimated 30% to 40% of them will develop a malignant disease.[1] AIDS-related cancers include Kaposi's sarcoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, basal cell carcinoma, cervical cancer, seminoma, leiomyoma and leiomyosarcoma.[2,3] A risk of Hodgkin's lymphoma, hepatocellular carcinoma and anogenital epithelial neoplasia has been associated with HIV, whereas data about the risk of testicular seminoma, multiple myeloma, melanoma and oral squamous cell carcinoma are limited.[4–6]

Oral Kaposi's sarcoma is highly associated with sexual transmission and is an AIDS-defining condition. This sarcoma is much less common in females than in males.[7] Oral signs of non-Hodgkin's lymphoma and oropharyngeal squamous cell carcinoma have been classified as malignancies and are non-AIDS-defining conditions. The route by which HIV is acquired carries a risk of transmission of additional viruses that may contribute to the development of malignant disease.[8] Smoking tobacco seems to play a major role in cancer in patients who are HIV-positive.[9]

Since the introduction of highly active antiretroviral therapy (HAART) in the mid 1990s, dramatic changes have occurred in the oral manifestations of HIV (see the article on the changes in the pattern of oral lesions associated with HIV infection on page 949), including a dramatic reduction in Kaposi's sarcoma. However, oral verrucous lesions caused by human papilloma virus (HPV) infection have increased. Lymphoma is the most rapidly increasing malignant disease in patients with HIV and its prevalence has not been affected by HAART. A number of non-AIDS-defining malignancies have been reported with increasing frequency, including melanoma, and cancers of the head and neck, anus, lung and testis.[9] Oral malignant disease may occur before a diagnosis of HIV, may arise during the progression of HIV disease or may be largely independent of the overall helper-cell counts, such as lymphoma. The purpose of this paper is to help dental practitioners identify the early signs of these diseases and maintain the oral health of their patients with HIV.

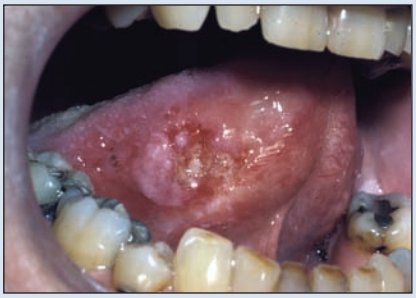

Figure 1: Ulcerated mass involving the right anterior ventrolateral surface of the tongue. The lesion was associated with mild sensitivity and occasional bleeding. Biopsy revealed squamous cell carcinoma.

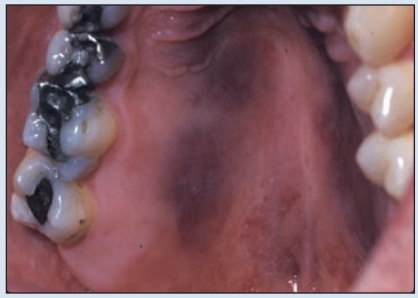

Figure 2: Purple-blue discolorations in the area of the greater palatine groove involving the hard palate on the right and left. Biopsy revealed Kaposi's sarcoma. The midline lesion in the posterior aspect of the hard palate represents candidiasis.

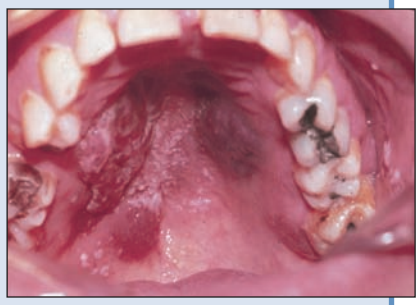

Figure 3: Bilateral elevated purple-blue masses of Kaposi's sarcoma. A more central lesion and pseudomembranous candidiasis is present.

Oral Squamous Cell Carcinoma

Tobacco and alcohol use, HPV infection, immunodeficiency and possibly genetic changes represent risk factors for oral squamous cell carcinoma in patients with HIV infection (**Fig. 1**).[2] One study[1] reported a more than twofold increase in the incidence of oral and pharyngeal cancer, although the study did not control for the effects of tobacco and alcohol use. Oral squamous cell carcinoma in patients who were HIV-positive may affect younger people who have no other known risk factors commonly associated with squamous cell carcinoma. One study[10] showed that patients who were HIV-positive had a more advanced stage of oral squamous cell carcinoma and poorer survival (57% survival at 1 year and 32% at 2 years) than patients who were HIV negative (74% and 59%, respectively). The pathogenesis of oral squamous cell carcinoma in patients with HIV includes increased cell growth and proliferation caused by viral interference with tumour suppressor proteins (p53, Rb) and activity of the HIV transactivator of transcription protein and HPV. Squamous cell carcinoma of the tonsils has the highest prevalence of HPV-16 DNA[11] and may therefore be associated with some cases of oral squamous cell carcinoma in patients who are HIV-positive. The frequency of HPV-containing oral warts in adults who are HIV-positive and are on HAART is increasing. These warts are most often associated with oncogenic HPV-16 and HPV-18.[12] Regezi and others[13] reported that 20 of 22 dysplastic warts in patients with HIV showed high-proliferation protein levels, suggesting that these lesions may carry a risk of malignancy, although this was not demonstrated in the study cohort.

Epstein-Barr virus was identified in 17.59% of all oral tumours and in 63.1% of squamous cell carcinomas of the tongue in 12 patients, suggesting a potential relationship between Epstein-Barr virus and oral squamous cell carcinoma in some patients.[14]

Kaposi's Sarcoma

Kaposi's sarcoma (**Figs. 2** and **3**) is an angioproliferative disease that may arise from a mesenchymal progenitor cell infected by human herpes virus-8.[2] The risk of Kaposi's sarcoma in patients with HIV, which is closely associated with sexual transmission, is 5 to 10 times greater in male homosexuals than in other HIV-risk groups.[9] The HIV transactivator of transcription protein may promote the growth of Kaposi's sarcoma, the most prevalent AIDS-associated malignancy before the advent of HAART. The reduction in the incidence of Kaposi's sarcoma has been attributed to the protease inhibitors in HAART.

Kaposi's sarcoma may present with localized, regional or widespread involvement. Oral Kaposi's sarcoma frequently involves the palate, gingiva and tongue. Treatment is related to the distribution of lesions. If they are limited to the oral environment, local or regional therapy may be considered. If these lesions are widespread, systemic chemotherapy may be used.

Lymphoma

Non-Hodgkin's lymphoma in patients with HIV is an AIDS-defining condition. Oral signs of lymphoma may be soft-tissue masses with or without ulceration and tissue necrosis that frequently involves the gingival, palatal and alveolar mucosa, along with other oral tissues (**Figs. 4, 5** and **6**). Oral lymphoma may mimic periodontal disease, with thickening, mass, ulceration and radiographic changes, including widening of the periodontal ligament space, loss of lamina dura and bone destruction. The risk of non-Hodgkin's lymphoma for patients with AIDS is 15 times greater for those with low-grade and T-cell

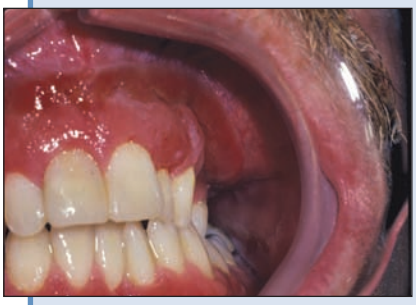

Figure 4: Abnormal elevated and thickened attached gingiva with a mass in the upper vestibule that was diagnosed as B-cell lymphoma.

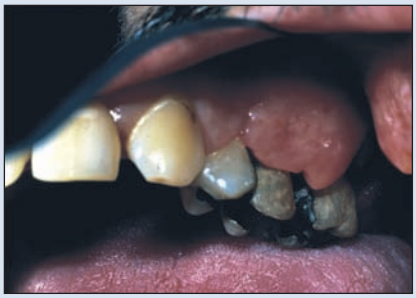

Figure 5: A pink, firm mass in the gingiva, found during oral examination in a patient being staged for lymphoma. This finding provided evidence of a more advanced stage of disease and led to a change in medical management.

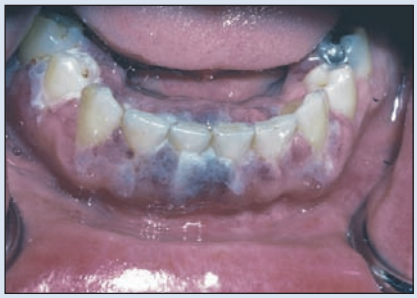

Figure 6: Infiltration and enlargement of the mandibular gingiva with ulceration and ecchymoses. Diagnosed as lymphoma, this condition responded rapidly to therapy for lymphoma.

non-Hodgkin's lymphoma, and up to 400 times greater for those with high-grade non-Hodgkin's lymphoma than for patients without HIV.[15] Non-Hodgkin's lymphoma is evenly distributed for different HIV transmission groups and is often diagnosed at an advanced stage with bone marrow involvement in about half of patients. The risk of developing non-Hodgkin's lymphoma is 1.6% per year of HIV infection; the risk for patients on HAART for 3 years is 19%.[16] Unlike Kaposi's sarcoma, the incidence of non-Hodgkin's lymphoma has not changed since the introduction of HAART.

The majority of cases of AIDS-related non-Hodgkin's lymphoma are aggressive large-cell lymphomas or immunoblastic lymphomas that are associated with the Epstein-Barr virus. Most non-Hodgkin's lymphomas are high-grade B-cell lymphomas. B-cell mucosa-associated-lymphoid-tissue lymphoma may involve mucosal sites or the salivary glands. Patients with HIV who have enlargement of the salivary glands may have benign lymphoepithelial lesions involving the gland that are associated with a 44-fold increased risk of developing lymphoma, most often mucosa-associated lymphoid tissue lymphoma.[17] While the lesions are generally benign, the potential for the development of malignant lymphoma requires further study. AIDS-related non-Hodgkin's lymphomas are commonly aggressive B-cell lymphomas, mucosa-associated-lymphoid-tissue large-cell lymphomas, or immunoblastic lymphomas. T-cell lymphomas are less common. Survival rates for patients with non-Hodgkin's lymphoma are lower for those who are HIV-positive.

Treatment includes systemic chemotherapy given in conjunction with HAART, and supportive care with hematopoietic growth factors and prophylaxis for HIV-associated infections.[9] High-dose chemotherapy combined with autologous hematopoietic transplantation may be considered. Patients with advanced Hodgkin's lymphoma are usually treated with a combination chemotherapy regimen, such as MOPP (mechlorethamine, vincristine sulfate, procarbazine and prednisone), or ABVD (doxorubicin hydrochloride, bleomycin, vinblastine and dacarbazine), or EBVP (epirubicin, bleomycin, vinblastine and prednisone). Autologous stem-cell transplantation may also be considered.[9]

Conclusion

The pattern of cancer in patients with HIV may continue to change as HAART and new therapies prolong the life of patients. Chronic immunosuppression because of HIV, other viral risk factors and tobacco play a significant role in a number of malignancies in patients who are HIV-positive. Oral Kaposi's sarcoma is rarely seen, but may be identified in untreated people or be a sign of the progression of HIV. Tobacco use and HPV may play an increasing role in oral squamous cell carcinoma in the future. Lymphoma is now the most common malignant disease in patients with HIV. Hodgkin's lymphoma may be more common with injection drug users than other HIV-risk groups. Patients who are HIV-positive and have Hodgkin's lymphoma have a higher frequency of infection with the Epstein-Barr virus than those who are HIV negative. Challenges in the management of malignancies include marrow suppression and opportunistic infections, as well as potential drug–drug interactions between chemotherapy and HAART. In most cases, HAART is continued unless excessive toxicity develops. Active prophylaxis of infections, new regimens of systemic chemotherapy and increased use of hematopoietic stem-cell transplantation are part of modern anticancer therapy when patients have HIV. The dentist's role is to identify early changes in the mucosa that lead to a diagnosis of cancer and to maintain the patient's oral and dental health.

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