HIV-ASSOCIATED ORAL LESIONS: A REVIEW OF THEIR PROGNOSTIC SIGNIFICANCE AND THE IMPACT OF HAART ON THEIR PREVALENCE AND MANIFESTATION

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Summary

The oral manifestations of HIV infection have been considered to be a value in assessing disease progression in the developed world. However, the potential use of oral lesions as prognostic markers in resource-poor countries has yet to be fully investigated. There is reasonably compelling evidence in the developed world for an association between oral lesions and viral load. However, the true nature of this association is less clear and there are few data available from the developing world. With the introduction of HAART, a change in prevalence of the oral manifestations of HIV infection has been observed, including regression of oral candidiasis, Kaposi's sarcoma and oral hairy leukoplakia. However, oral condylomata and herpes simplex virus infection appear to persist with HAART therapy. Further research in developing countries is required to document disease progression and the associated oral lesions in both adults and children.

Keywords: HIV AIDS; prognosis; oral lesions

Introduction

Since the mid 1980s there has been an intensive search for clinical markers to assess and monitor disease progression from initial infection to the development of AIDS. Oral manifestations of HIV infection have been considered to be of particular value in assessing disease progression in the developed world. Oral candidiasis was recognized early on as having an association with a decrease in $CD4^+$ lymphocyte count and thereby with an increased risk for developing AIDS.[1] Oral hairy leukoplakia has also been considered to have prognostic value for the development of AIDS.[2-5]

Prognostic significance of oral lesions

In the developed world, the majority of HIV-infected individuals are closely monitored with $CD4^+$ lymphocyte counts and HIV RNA viral load. Although oral lesions may mirror this change and alert the clinician to immune deterioration, the need for clinical prognostic markers to assist management decisions in developed countries is questionable. HIV viral load and CD4+ counts are not only the best predictor of progression, but used together provide a method of staging without the problems associated with clinical sign detection and diagnosis.[6,7] Secondly, the presence of oral candidiasis in the individual may not be sufficiently prognostic unless interpreted in the context of the patient's medical history.[8] All studies reporting the prognostic value of oral lesions in children infected with HIV originate in the developed world.[9-13] The presence of oral candidiasis and cervical lymphadenopathy suggest disease progression.[12]

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However salivary enlargement is associated with a less rapid progression to death.[9] The majority of longitudinal studies from the USA[14-21] have demonstrated an association between the presence of oral candidiasis and oral hairy leukoplakia (OHL) and a decreased $CD4^+$ lymphocyte count in HIV-infected adult subjects. However, in a New York cohort, oral lesions were not predictive of progression in subject with $CD4^+$ lymphocyte counts $\geq$200 cells mm^{-3}.[4] Cross-sectional studies, in adults, confirm this association and have associated low $CD4^+$ lymphocyte counts with the presence of oral Kaposi's sarcoma[3], non-Hodgkin's lymphoma[22,23] and necrotizing ulcerative periodontitis.[3] It has been proposed that oral lesions may be utilized as surrogate markers of disease progression in the developing world, where their prognostic significance in the absence of laboratory markers would have the greatest value. As yet, few studies have addressed this issue in these populations. Only one longitudinal study from the developing world shows a more rapid progression to AIDS in patients with OHL and/or oral candidiasis.[24] A second longitudinal study from Rwanda showed that oral candidiasis is an independent predictor of early mortality in a female cohort.[25] No association between total lymphocyte count and oral candidiasis was reported from Thailand.[26] In Tanzania, there appeared to be no specific oral lesions of prognostic value[27] Erythematous candidiasis was the only lesion significantly associated with $CD4^+$ lymphocyte counts of less than 200 cells mm^{-3} in Zambia.[28] Unfortunately, the use of OHL, which has been reported most frequently to indicate progression in the developed world, is confounded by a decreased prevalence in many developing countries.[26,28] Further longitudinal studies are needed to confirm the potential use of oral lesions as prognostic markers in resource-poor countries. At the present time the presence of oral lesions strongly associated with HIV infection should alert the physician in the developing world to possible disease progression. Any suspicions should be confirmed by eliciting other signs and symptoms associated with a deteriorating immune system.

Is there an association between oral lesions and viral load? Are oral lesions markers of viral load?

There is reasonably compelling evidence in the developed world for an association between oral lesions and viral load. Firstly, disease progression, which is most accurately measured by increased viral load[29], is also characterized by increased prevalence of many oral lesions, including oral candidiasis, oral hairy leukoplakia, ulcerative periodontial diseases and xerostomia.[5,30] Furthermore, any reduction in viral load in patients taking highly active antiretroviral therapy (HAART) is associated with a reduction in the prevalence of oral lesions.[31-34] However, the true nature of this association is less clear. Is viral load

alone relevant and what is the associated role of the $CD4^+$ lymphocyte levels? Although viral load appears to be the best predictor of long-term clinical outcome, $CD4^+$ lymphocyte counts appear more relevant to short-term clinical outcome.[35] At present there are little or no data available from the developing world.

There is limited evidence-based support from a few controlled studies that show strong associations between oral lesions, particularly oral candidiasis and oral hairy leukoplakia, and viral load.[36] There is consensus-based support founded on two established concept. First, oral lesions predict disease progression.[1-5] and, secondly, that measured HIV-1 RNA is the best available surrogate marker of HIV-1 disease progression.[29] Therefore, it has been assumed that if disease progression is predicted by both an increase in the prevalence of oral lesions and an increase in viral load, then oral lesions will reflect viral load.

Much of the evidence for the association between viral load and oral candidiasis.[29,30,37], oral hairy leukoplakia[32], ulcerative periodontal disease[26] and Kaposi's sarcoma[32,33,38] has been based on this type of assumption. However, what are not known are the mechanisms by which viral load influences oral lesions or what oral lesions are seen at different viral loads. Is it a reduction in viral burden alone, the result of reconstitution of immune function, or perhaps in some instances the effect of therapy on the pathology of the lesion, or may be a combination of all of the above?

The impact of HAART on the prevalence and the clinical characteristics of oral lesions

The introduction of HIV-protease inhibitors (PI) in addition to new nucleoside agents and non-nucleoside reverse transcriptase inhibitors has had a marked effect on mortality and morbidity of patients with AIDS and HIV infection. In particular, a reduction in HIV-associated opportunistic infections was observed.[39] The potent combination therapies also called highly active antiretroviral therapies (HAART) have proven effective in suppressing plasma-HIV-viral load below detectable limits and elevating $CD4^+$ lymphocyte cell counts. Consequently, the immune status for compliant patients improves markedly. HAART has become the standard therapy for individuals with advancing HIV infection. However, PIs may have adverse side-effects, including hyperglycaemia, bleeding, lipodystrophy, abnormal liver function and abnormal lipid metabolism. There is also a wide range of drug interactions, that can occur between protease inhibitors and other medications, which may, in the case of astemizole and terfenadine, result in cardiac arrhythmias. A number of common and rare oral side-effects have been described[40].

With the introduction of PI therapy and HAART, a change in the prevalence of oral manifestations of HIV infection has been observed. Several studies have reported regression of oral candidiasis, Kaposi's sarcoma and oral hairy leukoplakia in conjunction with PI therapy or HAART.[41-43] studied the effects of HAART in preventing the occurrence of oral candidiasis. During a one year follow-up, oral candidiasis was diagnosed in 7% of PI-treated patients, compared to 36% in non-PI treated patients. The observed effect was not accounted for by reconstitution of anti-*Candida* cell-mediated immunity.[43] found oral candidiasis in 66% of patients examimed pre-HAART therapy, 10% after 4 weeks of HAART and no cases of oral candidiasis after 6 months of HAART therapy.[43,34] found a decrease in oral hairy leukoplakia from 26% to 11% after protease inhibitor therapy. This study also reported a fall in necrotizing periodontal diseases, from 4.8% to 1.7%, after initiation of PI treatment. Changes in the prevalence of candidiasis, aphthous ulcers, oral warts, herpes simplex viral infection and Kaposi's sarcoma were not statistically significant. Similar findings were reported[43], who also found that oral condylomata and herpes simplex virus infection seemed to persist after HAART therapy. As in other studies, findings indicate that in some patients the immunological effects of HAART therapy may not provide sufficient protection against some lesions such as HPV-induced warts. In this context it was interesting[34] observed a significant increase in the prevalence of HIV-associated salivary gland disease from 1.8% to 5% in their study.

Little is known about changes in clinical characteristics of HIV-associated oral lesions during HAART therapy. There are anecdotal reports suggesting that oral warts (condylomata and verrucae) and oral herpes virus-associated infections persists HAART treatment. As most researchers in this field have only observed a few cases, no final conclusions as to the persistence and clinical picture of oral and facial infections associated with HIV can be drawn at this time. An interesting phenomenon, which has been termed 'immune reconstitution', has been described in some patients undergoing HAART therapy. This reaction is characterized by a paradoxical clinical deterioration of HIV-infected patients. Inflammatory reactions have been described as a sarcoid-like pulmonary disorder[44] or intraoccular inflammatory changes.[45] Similar changes related to oral lesions have not, so far, been reported.

Can the presence of oral lesions assist in monitoring the clinical status of patients with HIV infection? Can oral lesions be used as clinical markers for opportunistic systemic diseases?

If oral lesions can be used as surrogate markers of immune deterioration, it has been suggested that their presence may predict the development of unrelated systemic illness. [46] noted that 59% of patients at risk for HIV disease presenting with an episode or oral candidiasis acquired a major opportunistic infection or Kaposi's sarcoma at a median of 3 months.[47] showed, in patients enrolled in a Multicenter AIDS cohort study, that oral candidiasis of at least 2 weeks' duration was significantly associated with an increased risk of *Pneumocystis carinii* pneumonia among those whose $CD4^+$ lymphocyte count was <200 cell mm^{-3}, counts consistent with an AIDS diagnosis. The authors concluded that prophylaxis should be reserved for subjects whose count is less than 200 cells mm^{-3}.

In a San Fransisco cohort, oral Kaposi's sarcoma was significantly associated with *Molluscum contagiosum*, and seborrhoeic dermatitis with oral hairy leukoplakia and candidiasis.[48] Neither cutaneous disease is preventable by prophylaxis and therefore these associations are of negligible clinical value.

An association between oral candidiasis and the presence of tuberculosis in Thailand most probably documents an immune deterioration predisposing to opportunistic infections.[49] This is likely, as the association is strongest in advanced disease. There is at present insufficient evidence for a physician to commence prophylaxia for opportunistic infections solely on the presence of an HIV-associated oral lesion.

Many systemic diseases present initially in the oral cavity. The presence of an oral lesion may alert the physician to the presence of the same disease process at different sites. The oral lesions of bacillary angiomatosis presenting in HIV-infected subjects characteristically heralds diffuse systemic involvement.[50,51]

Relationship between viral load and oral health and disease

Baqui *et al*[130] indicated a correlation between the presence of oral lesions and HIV viral load, most notably oral candidiasis and oral hairy leukoplakia. There have been few publications investigating the relationship between viral load and oral diseases, other than mucosal pathology. In the above cross-sectional study, a high viral load in excess of 10,000 copies ml^{-1} was significantly associated with advanced periodontal lesions when compared to patients with a low viral load of less than 400 copies ml^{-1}. DMFT and oral fungal colonisation had the highest prevalence with high viral load, but there was no significant difference when compared with low viral loads. It was concluded there was insufficient evidence to confirm a relationship between viral load and oral disease, although there was an association suggested by this small study. Discussion by the participants also included the report of a possible association with periodontal disease. The need to evaluate specific confounding variables including smoking and recreational drug use often failed to be addressed by the authors.

The presence of oral candidiasis and cervical lymphadenopathy suggest disease progression.[12] However

Do the different subtypes of HIV influence the development of oral lesions?

An exhaustive search of the literature found no published papers on the influence of different subtypes of HIV on the development of oral lesions. There, is thus, no information, observations or data on HIV subtypes and oral lesions.

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Conclusions

1. Knowledge of the natural course of HIV infection is predominantly derived from studies undertaken in the developed world, especially regarding oral disease.
2. Knowledge of the natural course of HIV infection and its effect on the oral cavity in children in the developing world is particularly sparse.

In response to these conclusions future areas of research can be targeted.

1. More oral studies need to be undertaken in developing countries to evaluate the prognostic significance of HIV-associated oral lesions and their relation to therapy.
2. Such studies should be large multi-centre longitudinal study, using validated diagnostic criteria. The sites chosen should reflect possible differences in the oral manifestations of HIV disease. This would require resources to monitor disease progression (CD4 counts and viral loads).
3. A similar study to that proposed in adults needs to target children. The children of HIV-infected mother should be followed from birth.
4. The effects of HAART on the oral cavity need to be investigated. It is often difficult to distinguish drug-related adverse effects from disease manifestations.
5. There is need to find the influence of the different subtypes of HIV on the development of oral lesions.
6. Finally, there is also a need to investigate the influence of malnutrition, co-infectious agents and confonders such as smoking and hygiene on the occurrence HIV-associated oral lesions

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