

Looking into the mouth - oral manifestations of HIV infection

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Very early on in the AIDS epidemic publications indicated that HIV infection is associated with a variety of oral lesions that often occur early in the course of the disease, and tend to increase in prevalence with the decline of infected individual's immune function. In order to carry out proper epidemiologic studies on the occurrence of these lesions a sound classification had to be constructed. In September 1992 members of the EC Clearinghouse on Oral Problems Related to HIV Infection met in London, together with members of the US Workshop on Oral Manifestations of HIV Infection, to review the previously published classification of the oral manifestations of HIV infection and their diagnostic criteria. A consensus was reached; the classification incorporated a group of oral lesions based on their frequency of occurrence. (SA Fam Pract 2003;45(5):44-50)

The resultant classification of oral lesions associated with HIV infection is as follows:

- Group I. Lesions strongly associated with HIV infection.
 - Candidosis
 - Erythematous
 - Pseudomembranous
 - Hyperplastic
 - Angular cheilitis
 - Hairy leukoplakia
 - Kaposi's sarcoma
 - Non-Hodgkin's lymphoma
 - Periodontal disease
 - Linear gingival erythema
 - Necrotising (ulcerative) gingivitis
 - Necrotising (ulcerative) periodontitis
- Group II. Lesions less commonly associated with HIV infection.
- Group III. Lesions seen in HIV infection.

Oral Candidosis / Candidiasis

Debate continues over use of the term 'candidiasis' versus 'candidosis'. Either term is acceptable, although for many candidosis is the preferred term. It has been suggested that the difference in terminology is geopolitical, with candidiasis a distinctly American term and candidosis essentially European. The suffix 'osis' is consistent with use for most fungal infections, eg, aspergillosis, and the suffix 'iasis' should be used mainly for parasitic diseases, eg,

amoebiasis.

It is well known that there is a strong association between oral candidosis and AIDS; the first documented patient with AIDS had oral candidosis. A substantial amount of data now emphasise its high prevalence in HIV-infected individuals. The manifestations of candidal infection in HIV-infected persons are restricted to superficial mucosal lesions of varying degrees of severity that are persistent and debilitating but not life-threatening. *Candida* species are frequently isolated and the clinical signs of oral candidosis increase with progression of HIV infection. *Candida albicans* is the primary causative agent, and is associated with almost all initial episodes and approximately 75-90% of recurrent infections. Oral candidosis has been shown to be a reliable marker for immune deterioration and disease progression and may also predict the future development of full-blown AIDS. Early in the AIDS epidemic Klein et al focused the attention of clinicians world-wide on this disease entity by demonstrating its predictor of full-blown AIDS in adults.

The traditional classification of oral candidosis was acute pseudomembranous (thrush), acute atrophic, chronic atrophic and chronic hyperplastic; with the subsequent addition of candida-associated angular cheilitis. The rapid spread of HIV-related diseases and the great susceptibility of these patients to oral candidosis has necessitated a modified classification for this particular group, namely inclusion of the clinical variants chronic erythematous, chronic pseudomembranous, angular cheilitis, and lastly mucocutaneous candidosis seen mainly in children with perinatal HIV infection (the first three being most commonly encountered).

Pseudomembranous candidosis (thrush) usually presents as creamy whitish-yellow, soft, semi-adherent plaques (cottage-cheese-like). These plaques may be as small as 3 mm in size, or often extensive confluent plaques covering large areas of the tongue, buccal mucosa and hard and soft palate, extending past the uvula into the pharynx and beyond. It is possible to remove these plaques using a wooden spatula or gauze leaving a red and sometimes slightly bleeding surface underneath. Very often the oral mucosa is extensively and intensely erythematous.

Erythematous candidosis appears as red maculas or patches on any mucosal surface of the mouth, the most common sites being the dorsum of the tongue and the hard palate. It is usually asymptomatic and is therefore quite easily overlooked unless specifically looked for. It is more difficult to recognise than the pseudomembranous type and hence is often missed. The palatal lesions may mirror those on the tongue because of intimate contact between the tongue and the palate, especially during swallowing. The combination of these two lesions has been termed CITNIP (pronounced kitnip) by Touyz and Peters. Before the AIDS era, erythematous candidosis was known as atrophic candidosis.

Hyperplastic candidosis has been rather infrequently reported in the developed world, and therefore has been removed from the classification of 'diseases strongly associated with HIV infection'. In South Africa this form is seen regularly enough to be retained in our classification. Characteristically it presents as adherent whitish-yellow patches, most commonly noted bilaterally on the buccal mucosa. When present on the lateral margins of the tongue it may clinically mimic

hairy leukoplakia and be misdiagnosed as such.

Angular cheilitis (angular stomatitis) usually appears bilaterally at the labial commissures with deep horizontal fissures, often with superficial exudative crusts. It usually causes burning pain or discomfort, or both, when opening the mouth, and it does not involve the oral mucosa. Angular cheilitis is prevalent among older denture-wearing individuals with a decreased bite (vertical dimensions); however a lesion like the one illustrated, occurring in younger patients, should immediately raise suspicion of HIV infection if iron and vitamin B₁₂ deficiencies are excluded. Mucocutaneous candidosis is seen mainly in children with perinatal HIV infection in the first year of life. In young HIV-infected infants it may act as a warning sign for early and severe morbidity.

A noteworthy feature of oral candidosis in HIV infection is presentation of the lesions in multiple oral sites. Among the four types, two or all four types may appear together in the oral cavity. Oropharyngeal candidosis occurs in approximately 56% of all HIV-infected patients. The infection is recurrent and becomes progressively more severe as immunodeficiency continues. It is seen predominantly in patients with advanced disease and severe depletion of CD4+ cells. Oesophageal involvement has been reported in 20-40% of all AIDS patients; these individuals typically experience dysphagia because they develop pseudomembranes, erosions and ulcers on the oesophageal lining mucosa.

Diagnosis

Diagnosis is initially made from the clinical appearance of these lesions and from smears or scrapings of the lesions. Fungal cultures are rarely required for diagnosis, and may even cause confusion since yeasts are commonly found orally in about a third of healthy subjects examined and nearly 50% of individuals seen for one or more medical conditions. When antifungal resistance is encountered, then culture is useful to determine the species of infecting candida. Culture may also be useful in predicting likely drug resistance. In sub-Saharan African where finances are inadequate and very few laboratory technicians are available to carry out tests for thousands of new cases that occur daily, diagnosis has to be clinically based, hence charts with coloured clinical photographs of the various HIV-associated lesions are used to instruct all types of health personnel, mainly the senior nurses, especially at rural clinics.

Treatment

Early treatment of oral candidosis is necessary not only to alleviate the discomfort caused by the lesions, but also to eradicate the foci which may act as reservoirs of organisms for local spread of the disease. Symptoms may include a burning sensation, pain, dysgeusia, and occasionally difficulty in eating and dysphagia. A number of options are available for the treatment of oral candidosis, both topically and systemic.

Management of the HIV-infected person is a team approach and there must always be close collaboration with appropriate colleagues, especially when the oral lesions are not present

in isolation.

Topical treatment

Topical treatment of candidosis is often successful within about 14 days. It controls the infection initially, but relapses are common, mainly because of the underlying immunodeficiency, which may necessitate the use of systemic agents. However, before opting for systemic treatment the reason for failure must be sought. It may be found to be due to other factors such as use of broad-spectrum antibiotics or steroids, diabetes, decreased salivary gland saliva flow, or denture wear; and poor patient compliance may be due to gastrointestinal upsets, unpalatable taste, drug intolerance and most likely the incorrect drug regimen for use of the topical agents.

Standard antifungal drug regimens consist of topical administration of either polyenes (nystatin or amphotericin) or imidazoles. Sucrose or dextrose may be a constituent in certain topical agents; they are cariogenic, and if used frequently and for a long time, daily fluoride rinses must be included to assist in reducing the risk of caries. To be successful, topical treatment depends on adequate contact time between the drug and the oral mucosa, and sufficient saliva for the drug to dissolve if lozenges are used. While the dosage must be adequate, the success of treatment is frequency-dependent rather than dose-dependent.

Fungizone lozenges (amphotericin B) should be broken into quarters, with one-quarter sucked 10 times a day, ie, 2.5 lozenges per day, which will be more effective than the one lozenge 4 times per day, as suggested by the manufacturers.

Daktarin gel (miconazole) should be applied by the patient in very small amounts onto the dorsum of the tongue, and worked around the mouth; this should be done 10 times a day. Often the clinician is tempted to prescribe a polyene together with an azole, but this may not be as effective as expected, because azoles reduce membrane ergosterol, thereby interfering with nystatin binding.

Chlorhexidine 0.2% gluconate is used as a mouth rinse and is an effective antibacterial agent. Its primary side-effects are staining of the teeth and the oral mucosa, particularly the dorsal surface of the tongue. However, this is transient. It has been shown to be effective as a prophylactic agent in preventing oral candidosis in a group of patients undergoing bone marrow transplantation.

For good results the patient should use the mouth rinse last thing at night, after clearing his/her mouth of all toothpaste, and just before retiring; chlorhexidine gluconate and sodium monofluorophosphate, contained in many toothpastes, are not compatible. The patient must be instructed not to drink anything after the mouth rinse. A 0.2% chlorhexidine mouth rinse has been shown to be active in the mouth for up to 24 hours, provided that the subject does not drink or eat anything during that period. Thus, if the patient sleeps for up to 7 hours per night there is about 50 hours per week of antimicrobial activity.

Gentian violet causes purple staining of the mouth, and there are reports of an association with oral ulcers occurring in neonates. However, in a study in Zaire of persons with oropharyngeal candidosis and AIDS, gentian violet eliminated clinical oral candidosis in 42% of patients compared with 43% of those on ketoconazole and 95% of those using a nystatin mouth rinse. The mechanism of gentian violet is unknown, and its usefulness has not been studied in detail.

In patients wearing partial or full dentures, the prostheses should be soaked in a chlorhexidine solution; thereafter a very small amount of amphotericin B gel should be placed on the acrylic portion of the appliance before re-inserting it into the mouth. This will prevent re-infection of the appliance; patients who cannot sleep without their dentures must follow this regimen.

Whenever a drug is chosen for topical use in the treatment of mucosal candidosis, several important points should be observed, namely:

- Administer the antifungal drug in adequate doses.
- With proper instructions for correct use.
- Sufficiently frequent (8-10 times daily).
- Just after meals, tea, snacks, brushing teeth (for adequate contact time to work effectively).
- For a long enough period of time (1-2 weeks initially, then 5 or 6 weeks with most agents).
- Check progress and outcome using smears/swabs or even cultures, especially when anti-fungal resistance is suspected.

The vast majority of oral candidosis are endogenous in origin and total eradication of the organism from the host using antifungal therapy is difficult.

Often in the treatment of fungal infections attention to the underlying cause will avoid the need for prolonged or repeated courses of treatment.