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RESEARCH ARTICLE

ORAL MANIFESTATIONS OF HUMAN IMMUNODEFICIENCY VIRUS DISEASE

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ABSTRACT

Oral lesions are among the earliest clinical manifestations of human immunodeficiency (HIV) infection and are important in early diagnosis and for monitoring the progression to acquired immunodeficiency syndrome (AIDS). Common or notable HIV-related oral conditions include candidiasis, oral hairy leukoplakia, periodontal diseases such as linear gingival erythema and necrotizing ulcerative periodontitis, Kaposi's sarcoma, Non Hodgkin's lymphoma, and ulcerative conditions including herpes simplex virus lesions, recurrent aphthous ulcers. Therefore, rapid oral HIV testing offers a promising innovation for early HIV diagnosis and for several reasons, dental offices provide a promising venue for such testing. The present paper discusses in detail the oral manifestations and diagnostic criteria of HIV infection.

INTRODUCTION

In December 1981, an article appeared in the New England Journal of Medicine describing a curious cluster of seven men who for no apparent reason, had severe infections with microorganisms that had previously infected only profoundly immunologically compromised individuals. Soon this disease became known as the Acquired Immunodeficiency Syndrome (AIDS). Since then the number of cases has increased at a startling rate. The United Nations (UN) estimates that globally 36.9 million people are now living with HIV. In 2014, over two million individuals became newly infected and 1.2 million people died from acquired immune deficiency syndrome (AIDS) related illnesses (UNAIDS, 2014). Among the estimated 1 million living with HIV and AIDS, roughly one fifth are unaware of their infected status. Only way to curb down high HIV incidence and reduce morbidity and mortality is early diagnosis, combined with other prevention services. To facilitate this, recent Centers for Disease Control and Prevention guidelines make it a priority to bring HIV screening into many medical and social service settings (Centers for disease control and prevention, 2012). Key professional associations have set similar priorities.

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Additionally, rapid oral HIV testing offers a promising innovation for early HIV diagnosis and for several reasons, dental offices provide a promising venue for such testing (Santella, 2016). Two different types of Human Immunodeficiency Virus (HIV), HIV-1 and HIV-2, cause infection and disease in humans. HIV-1 is thought to have arisen from cross-species transmission of a chimpanzee virus to humans and HIV-2 from cross-species transmission of a Sooty mangabey virus (Inciardi *et al.,* 2005). HIV is a retrovirus belonging to the sub-family of lenti viruses. It comprises of an outer envelope consisting of a lipid bilayer with spikes of glycoproteins (gp), gp120 and transmembrane protein gp41. Inside this envelope is a nucleocapsid (p 17), which surrounds a central core of protein, p24. Within this core, are two copies of single-stranded RNA (the virus genome) and enzymes named reverse transcriptase, integrase and polymerase. Pol gene codes for theses enzymes by formation of precurser protein which is further cleaved into proteins p31, p51 and p66 (Schochetman, 1994; McCutchan, 2000). Only certain body fluids blood, semen, pre-seminal fluid, rectal fluids, vaginal fluids, and breast milk from a person who has HIV can transmit HIV. These fluids must come in contact with a mucous membrane or damaged tissue or be directly injected into the bloodstream for transmission to occur. Known routes of HIV transmission include: sexual transmission (homosexual, bisexual or heterosexual), parentral

transmission (blood transfusions, blood products and organ/tissue transplants or through use of contaminated needles - used for intravenous drug injection, or for general medical purposes), vertical transmission from mother to child (in utero, during partum or perinatal). Sexual transmissions accounts for 75% of transmission, with anal sex being at the highest-risk sexual behavior (Levy, 1988). Second most common mode of transmission is through sharing needles or syringes, rinse water, or other equipment (works) used to prepare drugs for injection with HIV infected blood. Vertical transmission is less common. Chances of transmitting HIV through saliva remain extremely low because of the presence of effective anti-infective activity of human salivary secretions by a variety of salivary proteins such as defensins, lysozymes, lactoferrin secretory leukocyte protease inhibitor and DMBT1 (glycoprotein-340/salivary agglutinin), as well as lysis of HIV in the oral cavity owing to the hypotonicity of saliva (Galvin, 2004). The clinical consequences of HIV encompass a spectrum ranging from an acute syndrome associated with primary infection to a prolonged asymptomatic state to advanced disease. It is estimated that 50-70% of individuals with HIV infection experience an acute clinical syndrome ≈3-6 weeks after primary infection (Chan, 1999). During this phase the levels of HIV RNA (a marker of HIV infection) rise steeply. Typical clinical symptoms that may occur with the burst of viremia are listed in the table 1 (Fauci and Lane, 2005).

Table 1.

General:	Fever, pharyngitis, lymphadenopathy, headache, retro-orbital pain, arthralgias, myalgia, malaise,lethargy, anorexia, weight loss, diarrhea, nausea, vomiting
Neurologic:	Meningitis,encephalitis,peripheral neuropathy,myelopathy
Dermatologic:	Erythematous maculo-papular rash, mucocutaneous ulceration

Symptoms of HIV disease can appear at anytime during the course of HIV infection. A diagnosis of AIDS is made in any one with HIV infection and a with CD4+ T cell < 200/µl and in anyone with HIV infection who develops one of the HIV associated diseases considered to be indicative of a severe defect in cell mediated immunity. Oral complications are increasingly recognised as an important cause of morbidity in patients with HIV infection. The mouth is one of the most common target organs for both opportunistic infections and neoplasms. About 80% to 90% of patients with HIV infection develop oral symptoms at some point in their course of disease (Rajiv saini, 2011). The most commonly encountered oral manifestations today are:

Candidiasis

The most common fungal infection seen in association with HIV infection is oropharyngeal candidiasis. Klein and coworkers showed that unexplained oral candidiasis in healthy adults at risk for HIV infection was a predictor for the development of clinical signs of AIDS in 59% of these patients within 3 months.among the individuals with more severe immunosuppression in this cohort, AIDS developed in 80% within 3 months (Magaldi *et al.,* 2001). In another study of individuals with HIV, the presence of candidiasis was strongly associated with both xerostomia and HIV disease progression. There are four frequently observed forms of oral candidiasis in HIV patient: erythematous candidiasis, angular cheilitis, pseudomembranous candidiasis and chronic hyperplastic candidiasis. Erythematous candidiasis is found to be associated with early stages of HIV disease, pseudomembranous candidiasis is usually associated with initial and progressive immune deterioration and HIV disease progression, hyperplastic candidiasis is associated with severe immune deterioration where as angular cheilitis can be detected during all stages of HIV disease. However there is a decline in the occurrence of pseudo membranous candidiasis in patients who are on successful highly active retroviral regimens containing protease inhibitors. This may be due to immune reconstruction and more importantly because of the added effect of protease inhibitors on candidal virulence factors such as aspartyl protease (Cartledge *et al.,* 1994).

Management

Additionally, many differences in response to conventional antifungal therapy among HIV seropositive patients and HIV seronegative individuals exist. Exposure to azoles (most notably fluconazole), has led to increased emergence of azole resistent candida albicans and non- albican species such as candida glabrata, C tropicalis, C krusei. Also as ketoconazole requires gastric acid for absorption, therefore patients with gastric hypochlorydria may be associated with decreased absorption of ketoconazole. In such cases, this medication can be dissolved in a carbonated soft drink prior to ingestion. Chronic candidiasis does not respond to oral therapy and intravenous delivery of antifungal medications should be considered. Oral troches should be avoided in patients with xerostomia, since troches will not dissolve efficiently and may even cause mucosal abrasions. In such cases, oral suspensions are more comfortable for the patients. Topical antifungal medications containing carbohydrate should be avoided as HIV patients are at greater risk of caries due to xerostomia (Cauda *et al.,* 1999). In resistant cases, oral rinse with amphotericin B solution may be useful before systemic medications are used. This oral rinse consists of 50 mg of amphotericin B injection diluted in 500 ml of sterile water, resulting in a concentration of a 0.1 mg/ml. Patients are instructed to use 15 ml and to swish and expectorate four time per day (Maenza *et al.,* 1996; Lauren, 2013).

Oral Hairy Leukoplakia

Since oral hairy leukoplakia is associated with a localized Epstein- Barr virus (EBV) infection, the appearance of this lesion is an early marker of immune suppression and disease progression when CD4+ cell counts drop below 300 cells/$mm^{3.}$ It is more common among homosexual/bisexual men.

Necrotizing ulcerative periodontitis and linear gingival erythema

In 1987, Winkler and Murray described the clinical characteristics of HIV- related periodontal diseases. The most common intraoral bacterial manifestations in individual with HIV are associated with the periodontium. In general, it has been suggested that patients with HIV and pre- existing periodontal disease show a more rapid periodontal attachment loss than individuals without HIV. These patients exhibit an increased periodontal disease complex, but they do not have an

increased plaque retention or gingival inflammation. It is possible that the increased periodontal attachment loss is directly associated with T-lymphocyte dysfunction rather than with a specific pathogen. Two distinct clinical entities that differ from regular periodontal disease have been described among patients with HIV- Necrotising ulcerative periodontitis (formerly known as HIV associated periodontitis or HIV-P and linear gingival erythema (formerly known as HIV associated periodontitis or HIV-G) (Lamster *et al.,* 1998). NUP is associated with decreased number of CD4+T cells below 100 cells/mm^3 in HIV patient and also these patients are at a greater risk of progressing to noma if not treated. Also NUP is more common in men having sex with men. LGE is also associated with decreased number of CD4+T cells. Additionally, there may be a relationship between sub-gingival colonization of Candida species and HIV-related periodontal conditions including linear gingival erythema. This is supported by the fact that the most recent classification of periodontal diseases by the America Academy of Periodontology grouped LGE under "gingival disease of fungal origin" (Yeung, 2000). Both these lesions are less responsive to conventional treatment.

Kaposi's sarcoma

In 1981, first case of Kaposi's sarcoma(KS) associated with AIDS was reported in homosexual men and since then it has been the most common intraoral neoplasm found in HIV-infected individuals. At one point KS was the second most common AIDS defining illness, second only to pneumocystis carinii pneumonia but over the years its incidence has declined. There is evidence that HIV encoded Tat protein might stimulate spindle cells. In addition it has been reported that transgenic mice bearing the tat gene develop KS like lesions. Thus, Tat, or some other infectious cofactor, in presence of immune- activation cytokines, may induce a change in normal cells to the spindle cell morphology. These spindle cells may then secrete cytokines that induce autocrine and paracrine proliferation, neovascularisation, and recruitment of the various cells normally found in KS lesions in vivo. Findings of intraoral KS are important since the first manifestation of the disease may occur in the oral cavity in 20% to 70% of cases, making this lesion a diagnostic criterion for AIDS. Over 90% of intraoral AIDS associated KS lesions appear on the hard or soft palate. The gingiva is the second most common location but usually in conjunction with palatal lesions. Extrapalatal manifestations of intraoral KS may be associated with a more rapid progression and a more aggressive course of the lesion. Symptomatic ulcerations may be seen in advanced cases. One study of individuals with HIV indicated that oral manifestations of AIDS associated KS were significantly more common in patients with lower CD4+T cells count. A mean CD4+T cell count of less than 70 cells/mm^3 and a predictive value over 93%of finding this lesion in patients with CD4+T cell counts below 200cells/mm^3 have also been reported (Baillargeon *et al.,* 2001). Apart from conventional treatment therapy, in HIV infected patients interferons have been used to treat . Interferon alpha has been shown to be active against HIV associated KS when administered at doses greater than 20 million units, the overall response rate is 30% to 40%. Systemic chemotherapy with cytotoxic agents is generally reserved for patients with widespread symptomatic or life threatening disease who have not responded, or are unlikely to respond, to interferon therapy.

Non Hodgkin's lymphoma

Non Hodgkins lymphoma (NHL) is the most common lymphoma found in oral cavity among HIV infected individuals. Intraoral NHL has been reported to be associated with an incidence of between 1.1% and 4.4 %. It is found in a much younger bracket in individual with HIV than among individuals without HIV. Although rare, but symptomatic ulcerations may also be seen in NHL.

Oral ulcerations

As with other immunocompromised patients, opportunistic infections are one of the most common causes of symptomatic oral ulcers in HIV infected patients.Viral infections, bacterial infections, fungal infections, tumors and various drugs are frequently identified causes of ulcers in these patients.

Viruses

Infections caused by herpes viruses are common in HIV-seropositive patients. Herpes simplex virus(HSV) is commonly involved in both primary and recurrent infections of the oral cavity. Herpetic gingivostomatitis in these patients is rare, but it can be severe and clinically atypical. Multiple ulcerations of the gingiva, tongue, and hard palate accompanied by fever and malaise, are usually characteristic of this disease, but in HIV seropositive patients systemic symptoms may be absent, making the diagnosis more difficult. Recurrent HSV generally occurs in keratinising oral mucosa as multiple ulcerations, but in HIV seropositive patients, recurrent HSV lesions may have an unusual clinical appearance and persists for several weeks. Smith et al recently supported that herpes simplex as well as molluscum contagiosum, may take the form of unusual havefactor 13a- positive dendritic cells. These cells belong to the dermal dendrocytes and may function as accessory antigen-presenting cells and may mediate the production of lymphokines that lead to proliferation of keratinocytes. In most cases herpetic gingivostomatitis and recurrent herpes simplex are caused by HSV-1, but in HIV- seropositive patients there are reports of HSV-2 associated lesions. Bagdades et al demonstrated that patients whose CD4+ cell count has fallen below 50×10^6 per liter have a significantly higher risk of developing HSV infection of the oral, anal, and genital mucosa (Arduino *et al.,* 2008). Varicella zoster, cytomegalovirus, Epstein Barr virus also cause oral and esophageal ulcers in HIV- positive patients. Electron microscopy and immunohistochemistry of endoscopic mucosal biopsy specimens from esophageal ulcerations identified mature retroviral virions and the gp41 protein of HIV, indicating HIV as possible direct cause. Kotler et al, using in situ hybridization, demonstrated HIV-1 RNA in lymphocytes and mononuclear cells from esophageal ulcers in two AIDS patients.

Management

Oral labial lesions: Valacyclovir 1g orally twice daily/Famciclovir 500mg twice daily / Acyclovir 400mg orally 3 times daily

Severe mucocutaneous infection: initial therapy acyclovir, 5mg/kg IV every 8h. After lesions begin to regress, change to oral therapy as above.

Acyclovir resistant cases: Foscarnet 90-120mg/kg/d IV in 2-3 divided doses until clinical response (Lauren, 2013).

Bacteria

Oral and esophageal ulcerations caused by mycobacterium tuberculosis and mycobacterium avium-intracellulare have been documented in HIV positive patients. Cases of ulcerative lesions of the dorsum of the tongue containing klebseilla pneumonia, enterobactor cloaca, and escherichia coli have been described, but whether these bacteria are pathogens or just passengers remains unknown. Neisseria gonorrhoeae and treponema pallidum can be another source of ulcerations in HIV positive patients.

Atypical or apthous like oral ulcers

Apthous ulcers that develop in HIV- seropositive patients may be more severe and persistent than those developing in immunocompetent persons. They may involve other areas of the gastrointestinal tract and seriously interfere with patient's quality of life. Both minor and major apthous like ulcers have been reported among HIV seropositive persons; the reported prevalence ranges between 1.1% and 12% (Kutcher *et al.,* 2001). Because apthae are very common in the immunocompetent population, there presence in HIV patients may be coincidental . Recent studies have suggested that HIV-seropositive patients with major apthae are significantly more immunosuppressed than those with minor or herpetiform apthae, as measured by counts of both peripheral blood CD4+ T lymphocyte subsets and neutrophils. These findings may also reflect a local imbalance in the immune cells that form the infiltrate of the ulcers (Birnbaum *et al.,* 2002).

Management

For isolated and accessible lesions, potent (Fluticasone proprionate, Dexamethasone, fluocinonide) or ultrapotent (Clobetasol proprionate, Halobetasol proprionate) topical steroids can be used. For multiple ulcers, dexamethasone elixir as a swish and spit can be effective. If lesions are severe, systemic steroids such as ingested dexamethasone or prednisone tablets, may be needed. Systemic thalidomide (200mg daily) is effective in treatment of major apthae in HIV infected patients in cases in which benefit outweighs the risk and limitations of drug side effects (Lauren, 2013)

Laboratory parameters of HIV infection

Medical and dental health care rely on laboratory markers to determine the status and progression of diseases. Because the risk of infections and bleeding tendencies are major concerns for dental care providers, knowledge of pertinent laboratory parameters associated with HIV disease helps practitioners anticipate and prevent potential complications that may result from dental therapy. Various parameters includes CD4+ T cell count or % age, CD8+ T cell count , CD4+/ CD8+ ratio, p24 antigen/ antibody , HIV RNA, β-2 microglobulin, Erythrocyte sedimentation rate, Neopterin, platelet count, bleeding time, total WBC count and differential WBC count, hemoglobin, prothrombin time and partial thromboplastin time (Centers for Disease Control and Prevention, 2001).

CD4+ T cell count/ percentage

CD4+ T cell count is the best indicator of the immediate state of immunologic competence of the patient with HIV infection. A normal CD4+ T cell count is estimated to be 544 to 1663 cells/mm^3 with a median cell count of 935 cells/mm^3. In HIV patients, CD4+ T cell count is suppressed. According to most guidelines, a CD4 T cell count <350 cells/mm^3 is an indication for consideration of initiating anti - retroviral therapy (ARV) therapy, and a decline in a CD4+ T cell count of >25% is an indication for considering a change in therapy. Once CD4 T cell count <200 cells/mm^3, patients should be placed on a regimen for P. Carinii prophylaxis, and once the count is <50 cells/mm^3, primary prophylaxis for MAC infection is indicated. CD4+ T cell percent is more reliable than CD4+ T cell count.

CD8+ T cell count

A normal CD8+ T cell count is 272 to 932 cells/mm^3 with a median count of 519 cells/mm^3. Activation and an increased number of CD8+ T cell count have been noted during the early course of HIV disease. But the number of CD8+ T cells eventually decrease during the more advanced stages of HIV disease.

CD4+/ CD8+ ratio

This measurement passes some of the biologic factors associated with CD4+ cell variations. A normal ratio is 0.93 to 4.50, with a median of 1.72. Low ratios are associated with increased immune suppression.

P24 antigen/ antibody

The p24 antigen represents the core protein of HIV, and detectable serum levels are associated with increased HIV replication and more rapid disease progression. Antibodies to this protein are formed shortly after seroconversion and detectable during the quiescent stages of HIV disease. Approximately 7% of asymptomatic patients with high CD4+ T cell counts show very low levels of measurable antigens, while 75% of individuals below 200 cells/mm^3 show signs of p24 antigenemia.

β-2 microglobulin

It is a short chain of class 1 major histocompatiblity complex. A non specific marker for cell destruction, increased levels of this protein can be found during seroconversion and during progression of disease. The normal serum concentration, as measured in homosexual men, is equal or less than 254 nmol/L.

Erythrocyte sedimentation rate

An elevated erythrocyte sedimentation rate (ESR) is present in disease causing an inflammatory response. This marker is not disease specific and is elevated in many autoimmune disorder. In patients with HIV and CD4+ T cell counts below 500

cells/mm^3 , an elevated ESR, in combination with a decreased CD4+ T cell count and an elevated β-2 microglobulin level is a good predictor for disease progression . Some studies have indicated that an ESR level >35 mm in 1 hour is a significant and relatively early marker for progression to AIDS.

Neopterin

Neopterin is produced by macrophages in response to T cell activation. This protein is a marker for immune stimulation and is therefore associated with HIV disease progression. Neopterin can be measured in serum and in urine of individuals with HIV. A normal serum concentration is less than 10nmol/L. This marker is also mostly used for research purposes. Both β-2 microglobulin and neopterin are non-specific markers for HIV infection since they can be elevated in other immune disorders, malignancies, and other viral infections such as that with cytomegalovirus (Zhang *et al.,* 2002).

HIV and Health care worker

Health care workers especially those who deal with large numbers of HIV infected patients, have a small but definite risk of becoming infected with HIV as a result of professional activities. Most cases of health care worker seroconversion occur as a result of needle- stick injuries. Several factors have been associated with an increased risk for transmission which includes deep injury, the presence of visible blood on the instrument causing the exposure, injury with a device that had been placed in the vein or artery of the source patient, terminal illness in the source patient, and lack of postexposure ARV therapy in the exposed health care worker. Other important considerations when considering post exposure prophylaxis (PEP) in the health care worker include known or suspected pregnancy or breast feeding, the possibility of exposure to drug resistant virus, and toxicities of PEP regimens. Regardless of the decision to use PEP, the wound should be cleansed immediately and antiseptic applied. If a decision is made to offer PEP, U.S public health service guidelines recommend 1) a combination of two nucleoside analogue reverse transcriptase inhibitors given for 4 weeks for more severe exposures, or 2) a combination of two nucleoside analogue reverse transcriptase inhibitors plus a third drug given for 4 weeks for more severe exposures (Petersen, 2006). Health care workers can minimize their risk of occupational HIV infection by following the CDC guidelines of July 1991, which include adherence to universal precautions, refraining form direct patient care if one has exudative lesions and sterilizing reusable devices employed in invasive procedures.

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