International Journal Of

Recent Scientific Research

ISSN: 0976-3031

Volume: 7(2) February -2016

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THE OFFICIAL PUBLICATION OF
INTERNATIONAL JOURNAL OF RECENT SCIENTIFIC RESEARCH (IJRSR)
http://www.recentscientific.com/ recentscientific@gmail.com

ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 7, Issue, 2, pp. 8987-8994, February, 2016

International Journal of Recent Scientific Research

REVIEW ARTICLE

ORAL HEALTH AS A GATEWAY TO HIV DIAGNOSIS AND TREATMENT – A REVIEW

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ARTICLE INFO

Article History:

Received 16th November, 2015
Received in revised form 24th November, 2015
Accepted 23rd January, 2016
Published online 28th February, 2016

Keywords:

syndromes, gingival enlargement, gene mutation, gingivitis.

ABSTRACT

The course of HIV infection is associated with numerous oral and perioral lesions. These oral lesions can play a crucial role in diagnosis of HIV patients. It has been estimated that 20% to 80% patients infected with HIV will develop some oral lesion associated with the disease. They may be the first sign of infection or may be the prime indicator of progression of infection or declined immunity. Thus it can be concluded that along with dental expertise in diagnosis and management of the oral manifestations or complications of HIV, medical professionals should also be acquainted with recognisation and primary treatment of associated Oral manifestations related to HIV.

INTRODUCTION

HIV (Human Immunodeficiency Virus) is a virus that leads to Acquired Immunodeficiency Syndrome (AIDS) in humans.[1] It is characterised by profound immune-suppression that leads to opportunistic infections, secondary neoplasms and neurologic manifestations.[2] HIV infection compromises the immune system, and over a period of time, as the viral load overwhelms the body, the immunity is impaired, and the person becomes vulnerable to a host of infections and malignancies and eventually succumb to them.[3]

When a person becomes infected with HIV, there is an initial burst of viral replication and the individual may experience flu like symptoms for a few weeks. Antibodies to the virus are detectable from between 2 and 12 weeks after initial infection and there is a steady decline of CD4+ helper T cells. A reduction in these cells leads to a reduction in immune response to various pathogens. This results in a variety of opportunistic bacterial, viral and fungal infections.[4]

Dental Surgeons must be aware of the stages of HIV illness because they may see patients in early stages with signs and symptoms of HIV infection and may assist in making the diagnosis. Awareness on the manner of progression of disease is essential in properly treating patients at various stages of their disease.[5]

Historical Background

AIDS was first identified in 1981 following reports to Centre for Disease Control (CDC) in Atlanta, USA of two unusual diseases, Pneumocystis carinii pneumonia and Kaposi's sarcoma, affecting previously healthy homosexual men in New

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York, California and Los Angeles. More than 500 cases were reported over the next 15 months, and since then an escalating and continuing global pandemic has occurred.[6]

The term Acquired Immunodeficiency Syndrome (AIDS) was formally defined by the CDC in 1982 as: "a disease at least moderately predictive of a defect in cell mediated immunity, occurring in a person with no known case for diminished resistance for that disease." Credit for isolation of the etiological agent in 1983 is shared by Luc Montaigner & Barre Sinoussi *et al* Institut Pasteur in Paris, at which time it was called *Lymphadenopathy Associated Virus* (LAV). That same year, Dr. Robert Gallo of the National Cancer Institute in the United States cultivated LAV in immune system cells. In 1984, Gallo and colleagues reported the discovery of the cause of AIDS as *Human T-cell Lymphotrophic Virus –III* (HTLV-III). The International Committee on Virus Nomenclature (1986, Coffin *et al*) decided on the generic term Human Immunodeficiency virus (HIV) for these viruses. In 1987, subdivision of isolates into HIV – 1 and HIV – 2 was reported by Clavel *et al*. The introduction of the first antiretroviral drug, zidovudine (AZT) led the way in controlling the disease and for the development of subsequent HIV medications. In 1996, drug combination therapy introduced as Highly Active Anti Retroviral Therapy (HAART), revolutionised treatment and changed the natural progression of the disease for those on HAART therapy.[5] Nucleotide sequence analysis of a number of different isolates has revealed the organisation of genome and has led to cloning and expression of genes and gene fragments. This led to the preparation of putative vaccines and the availability of pure reagents for incorporation in diagnostic tests.[6]

Epidemiology

Of the total 34 million people infected with HIV, 2.08 million live in India alone (2014). Children less than 15 years of age account for 7% (1.45 lakh) of all infections; while 86% are in the age-group of 15-49 years. Of all HIV infections, 39% (8.16 lakh) are among women. The estimated number of People Living with HIV (PLHIV) in India maintains a steady declining trend from 23.2 lakh in 2006 to 20.9 lakh in 2011. The four high prevalence States of South India (Andhra Pradesh, Karnataka, Maharashtra and Tamil Nadu) account for 53% of all HIV infected population in the country. Declining trends are also observed in the overall incidence of new cases and in prevalence of HIV/AIDS in high prevalence states.[7]

India is estimated to have around 1.16 lakh annual new HIV infections among adults and around 14,500 new HIV infections among children in 2011. Of the 1.16 lakh estimated new infections in 2011 among adults, the previously high HIV prevalence States of Andhra Pradesh, Karnataka, Maharashtra, Tamil Nadu, Manipur and Nagaland account for 31% of new infections, whereas, some low prevalence States (Odisha, Jharkhand, Bihar, Uttar Pradesh, West Bengal, Gujarat, Chhattisgarh, Rajasthan, Punjab & Uttarakhand) together account for around 57% of new infections.[8]

Oral Manifestations

Oral and perioral lesions often occur during the course of HIV infection.[9, 10] They have been important in the identification of patients harbouring the HIV virus.[11] It has been estimated that 20%[16] to 80%[12] patients infected with HIV will develop some oral lesion associated with disease. These lesions may be the first manifestation of infection in a previously undiagnosed patient, and are often important markers in disease progression[13] and predicting the decline in the immune system.[11] Factors that predispose to HIV related oral conditions include CD4+ count of less than 200/uL, plasma HIV RNA levels greater than 3000 copies /mL, xerostomia, poor oral hygiene and smoking.[12]

Oral health is an important component of overall health status in HIV infection.[14] Medical clinicians should be able to recognise HIV associated oral disease and provide appropriate primary care and referral. Dental expertise is necessary for proper management of oral complications in HIV infection and AIDS.[12] The manifestation of oral lesions during the course of HIV infection holds distinct connotations at different stages of the disease.[12]

- For individuals with unknown HIV status, oral manifestations may suggest possible HIV infection, although these are not diagnostic of infection.
- For persons living with HIV disease who are not yet on therapy, the presence of certain oral manifestations may signal the progression of HIV disease
- For patients on antiretroviral therapy, the presence of certain oral manifestations may signal an increase in the plasma HIV 1 RNA level.

Oral candidiasis and oral hairy leukoplakia appear to be the first and the second most common oral opportunistic infections associated with HIV. Other HIV associated infections and manifestations include linear gingival erythema, necrotizing ulcerative gingivitis, periodontitis or stomatitis, herpes simplex virus ulcers, cytomegalovirus ulcers, major aphthous ulcers, oral warts, Kaposi's sarcoma, non-Hodgkin's lymphoma, and HIV salivary gland disease.[11] Based on standard classification and diagnostic criteria, common HIV associated oral disorders can be broadly classified into four categories by pathophysiological processes into:[14]

Infection

Fungal: candidiasis, cryptococcus, hisptoplasmosis, aspergillosis
Viral: herpes simplex virus, oral hairy leukoplakia, human papilloma virus, cytomegalovirus
Bacterial: bacterial angiomatosis, syphilis, periodontal diseases - linear erythematous gingivitis, necrotising ulcerative periodontitis, necrotising stomatitis.

Neoplasms

Kaposi's sarcoma
Non-Hodgkin's Lymphoma

1. Immunological

Major Aphthous ulcers

2. Miscellaneous

Xerostomia

Salivary Gland Disease
Pain syndromes
Nutritional

Oropharyngeal candidiasis (OPC)

The most common HIV related oral lesion is candidiasis, predominantly due to infection by *Candida albicans.*[9-14] Non-*albicans* species such as C. glabrata, C. tropicalis, C. krusei and C. kefyr have been reported in 1% to 20% of HIV infected patients.[13] Other studies document cases of infection with C. paratropicalis and S. cerevisiae.[15] *C. albicans* forms a constituent of normal oral flora, being isolated from 30-50% of healthy oral cavities, rarely causing clinical infection. In contrast, oral candidiasis has been reported in 17-43% of patients with HIV infection,[10] and more than 90% of patients with AIDS at some point during the disease cours1e.[10,13,15] It is often the initial manifestation of symptomatic infection with HIV,[10] and may simply imply concurrent esophageal candidiasis, which is an AIDS indicator lesion,[15] or also be a predictor of the likelihood of other opportunistic infections.[10]
Oral candidiasis in HIV infected patients often portends a decline to AIDS, [13] and this lesion has commonly been used as a marker of disease severity in classifications of HIV infection.[10] The lesions are seen more commonly when CD4+ count falls below 200/mm^3.[13] In apparently healthy adults with risk factors for HIV infection, unexplained oral candidiasis has been shown to predict development of clinical AIDS within 3 months.[10]
Several forms of candidal infection have been recognised.[10, 12-14]

Pseudomembranous candidiasis: Acknowledged as the most common variant,[10] it presents as creamy, white, curd like plaques on the oral mucosa or tongue which can be wiped away, leaving a red erythmatous surface. Patients may complain of soreness or burning in the mouth.[12]

Erythmatous candidiasis: It presents as a red, flat, subtle lesion on the dorsum of tongue. A kissing lesion occurs when the lesion present on the tongue has a matching counterpart on the hard or soft palate where it comes in contact. The lesion is often symptomatic, with burning mouth sensations.[12]

Hypertrophic Candidiasis: Thick white plaques that cannot be readily removed may indicate the presence of hyperplastic candidiasis. This may occur concurrently with oral hairy leukoplakia.[13]

Angular Cheilitis: It presents as cracking, fissuring, ulceration or erythema of the corners of the mouth, and may occur with or without the presence of erythmatous or pseudomembranous candidiasis. It tends to persist for long periods of time if left untreated.[12, 13]

Pathophysisology: Clinically significant OPC is related to decreased CD4+ count, anti-retroviral combination therapy, and cigarette smoking. The impact of reduced numbers of CD4+ cells results in compromise in mucosal immune surveillance and function thus directly contributing to increased risk for opportunistic infections, including OPC. It is theorised that before the use of protease inhibitors, there may have been less than optimal suppression of viraemia, contributing to continued decrease in CD4+ number and resultant persistent OPC. Protease inhibitors have an anticandidial effect that is independent of immune reconstitution. The potential pathogenic basis for smoking, though established, is unclear, and further study is warranted.[9]

Treatment: Early treatment of oral candidiasis is warranted not only because of the discomfort caused by the lesions, but also because the foci may act as reservoirs of organisms for local spread of disease.[10] It takes longer to eradicate candidiasis in HIV infected population, and relapse rates are high.[13] High fungal counts and smoking appear to increase the tendency for poor response.[15] Use of topical agents for treatment of OPC is recommended as initial therapy, more so owing to concerns of drug interactions between systemic antifungals and antiretroviral therapy.[9] Topical antifungal agents include nystatin, clotrimazole, amphoterecin B which can be delivered as oral suspensions, troches or tablets. Systemic therapy with ketoconazole, fluconazole, or itraconazole is indicated in recurrent cases.[13] Silverman *et al* recommend 200mg once daily oral dose of Nizoral (ketoconazole) for resolution of oral signs and symptoms. Although fluconazole is an effective mucosal antifungal drug, candidal recurrence and resistance to fluconazole appear to be an emerging problem.[15]

Both fluconazole and amphoterecin resistant OPC are associated with a median survival rate of 184 and 83 days respectively, indicating that such OPC is a marker for end stage immune system breakdown.[13] New antifungals in the pneumocandin class show promise against resistant strains with in vitro studies. Oral solutions of *melaleuca*, an Austrailian tea leaf showed clinical responses in two thirds of patients who had fluconazole resistant candidiasis.[13]

Histoplasmosis

Histoplasmosis is a fungal infection caused by inhalation of micronidia of *Histoplasma capsulatum,*[16] an organism found in greatest abundance in bird droppings. The disease is characteristically endemic, although cases of histoplasmosis from centres in non-endemic areas have also been reported in patients with AIDS.[17] The endemicity of histoplasmosis in India is not clearly known with pockets of distribution in Eastern India and Vellore. Since the emergence of AIDS in India, the number of cases presenting as chronic disseminated disease with oropharyngeal ulcers has steadily increased.[16]

Histoplasmosis may present clinically as a pulmonary infection, mediastinal fibrosis, or granulomas. Disseminated histoplasmosis is seen in patients with impaired cell mediated immunity with signs and symptoms of fever, weight loss, oropharyngeal ulcers, hepatosplenomegaly. lymphadenopathy, and adrenal enlargement.[16]

Intraoral histoplasmosis is a rare condition presenting as painful indurated ulcers, usually on the palate gingiva, tongue, or any oral site(s).[13] These lesions may present as solely intraoral entities or as part of a disseminated disease process. Biopsy and culture of the lesion for H. capsulatum is imperative for diagnosis.[9] In AIDS patients, these lesions can be the primary or only manifestation of this disease and may occasionally even herald HIV seropositive status.[16] Treatment includes single or multiple agent systemic antifungal therapy with fluconazole, itraconazole, ketoconazole and amphoterecin B.[9]

Herpes simplex infection

Even in immunocompetent hosts, herpes simplex (HSV1) infection is quite widespread and oral lesions are common.[12] Oral and peri-oral infections with herpes simplex virus is fairly common in HIV infection.[10] The majority of opportunistic viral infections are a result of reactivation of latent herpes viruses due to decreased immune surveillance.[13] Antibodies indicating prior exposure to HSV-1 are estimated to be present in greater than 80% of the population. Amongst PLHIV, 8% have oral ulcers that culture for either HSV 1 or 2. [13]

The mechanistic basis for development of recurrent oral herpes infection in HIV patients is linked to reduced CD4+ cell count. Patients with CD4+ counts <200 cells/mm^3 (particularly between 50 and 200 cells) are significantly more likely to develop HSV ulcers (odds ratio 6.5). Frequent mucosal herpes simplex reactivation, including oral HSV infection may lead to higher levels of plasma HIV 1 RNA. Reactivation of herpes infection may contribute to the pathobiologic expression of HIV disease itself and increase the risk of HIV transmission.[9]

HSV infection in healthy individuals characteristically presents with cold sores on the vermillion border of the lips, or small shallow ulcers with irregular white borders or vesicles on keratinised oral tissues. Lesions in HIV infected population however, often occur as ulcers on the non-keratinised tissues such as labial mucosa, buccal mucosa, ventral tongue, and soft palate. Such ulcers are extremely painful, may be clustered or coalescent, or present as a discrete large ulcer mimicking and aphthous ulcer. Flaitz *et al* noted a 28% incidence of co-infection with cytomegalovirus (CMV).[13]

Herpetic ulcerations are often self limiting, however the use of antiviral medications is sometimes necessary.[12] Systemic acyclovir is generally used to manage the lesions, [9, 10, 12-14] with dosages varying from 1g to 4 g per day in divided doses. However, the incidence of acyclovir resistant HSV infection has increased among patients with HIV infection. Oral famicyclovir and valacyclovir and intravenous foscarn*et al*one or in combination are effective.[14] Famciclovir has been shown to reduce both viral shedding and symptoms associated with recurrent HSV 1 infection in HIV patients. The drug also has greater bioavailability and can be dosed on a twice daily basis. Valacyclovir is also useful at a dose of 1g tds, however there have been reports of possible toxicity.[13] Intravenous foscarnet at 200mg/ kg has been found to be useful in acyclovir resistant strains,[13] however it itself has been implicated in causing oral ulcerations as a side effect.[10] Cimetidine has also been reported as beneficial in treating oral HSV lesions in HIV infected people.[10]

Oral hairy leukoplakia (OHL)

Oral hairy leukoplakia is caused by the Epstein-Barr virus[11] which is a member of the herpes virus family.[13] It has been demonstrated in infectious mononucleosis, Burkitts Lymphoma, nasopharyngeal carcinoma, post transplant lymphomas, HIV associated lymphomas and in oral ulcers in HIV infected patients. Although these lesions have been documented in healthy, immunocompetant, seronegative patients, these are usually noted when CD4+ counts are less than 300/mm^3 and thus their presence may portend a progression to full blown AIDS within 2 years.[13]

HIV is not found within the genome of epithelial cells in OHL, thus suggesting that hyperparakeratosis and other features are a consequence of an opportunistic infection. Human herpes virus (HHV)-8 may induce production of EBV receptor facilitating infection with multiple or new strains of EBV. Co-infection on the surface by candida and human papilloma virus is not unsusal.[13]

It is diagnosed by the clinical appearance as asymptomatic, adherent, flat or vertically correlated whitish grey lesions on dorsum of tongue, usually on lateral borders. They often have a shaggy, corrugated or “hairy” appearance. These have been associated with immune suppression, as evidenced by reduced CD4+ cell counts and viremia measured by high HIV RNA level in plasma. These lesions have been shown to predict progression to AIDS even independent of CD4+ count.[11]

Oral hairy leukoplakia is nearly always asymptomatic and self limiting and generally requires no treatment. Antifungal therapy may be used to resolve the symptoms of superimposed candidiasis, methods of treatment for OHL include high dose topical acyclovir, zidovudine, podophyllin and surgical exision.[13]

Human papilloma virus

Human Papilloma Virus (HPV) is the agent responsible for condyloma acuminata, veruca vulgaris, focal epithelial hyperplasia and a variety of other warty lesions. HPV infection is one of the most common and widespread viral infections transmitted by close and repeated sexual contact. It has been found in normal mucosa of adults with a prevalence of upto 25%. In HIV infected individuals it is more common.[18] The incidence of HPV infection has increased dramatically in the potent antiretroviral therapy era.[12]

They present in the oral cavity as single or multiple soft pink pedunculated or sessile masses that have a cauliflower like surface. The lip, gingiva, palate, and tongue are preferred sites.[13] More than 50 strains of HPV exist. The most common genotypes found in the mouth of patients with HIV infection are HPV 2,6,11,13,16, and 32.[10]

Several treatments for HIV associated warts have been reported. Most treatments target extraoral warts and are not

applicable for intraoral warts. These treatments have included caustic or acidic agents, cantharidin, podophyllin resin, tretinoin, intralesional bleomycin, topical 5-fluorouracil, surgical treatment – cryosurgery, CO_2 slush, electrosurgery, and curettage, blunt dissection, CO_2 laser, imiquimod, vitamin A, oral etretinate, cimetidine, zinc sulphate, x-ray, heat ant tape occlusion, excision, or a combination of the above.[9]

PERIODONTAL DISEASE

Linear Erythematous Gingivitis

This entity appears as a 1-3mm band of marginal gingival erythema, often with petechiae. It is typically associated with no symptoms or only mild gingival bleeding and mild pain. Histological examination reveals and incomplete or aborted inflammatory response with principally hyperaemia present. Oral rinsing with chlorhexidine gluconate 0.12% often reduces or eliminates the erythema and typically requires prophylactic use to avoid recurrence.[14]

Necrotising Ulcerative Periodontitis/ Necrotising Stomatitis

Characterised by deep osseous pain, significant erythema associated with spontaneous bleeding and rapidly progressive destruction of periodontal attachment and bone. The destruction is not self limiting and causes the loss of the entire alveolar process in the involved area. The lesion results from altered immune response in HIV infection. More than 95% of patients with NUP have CD4+ cell counts of <200 cells/ mm^3. Treatment consists of twice daily rinsing with chlorhexidine gluconate 0.12%, metronidazole 250mg orally four times a day for ten days, periodontal debridement. Relief of pain is generally afforded with 36-48 hours of start of antibiotic therapy.[12]

Bacterial Epitheloid Angiomatosis

Unique to individuals with HIV infection, it is often clinically indistinguishable from oral Kaposi's Sarcoma. It presents as an erythematous soft mass which may bleed upon gentle manipulation, and biopsy and histological examination are required to distinguish it from the latter. The presumed etiological pathogen, *Rochalimea henselae,* can be identified using Warthin-Starry staining. It is histologically characterised by atypical vascular channels, extravasated red blood cells, and inflammatory cells. Erythromycin 500 mg q.i.d. for ten days is the treatment of choice.[14]

Syphilis

It is an uncommon cause of oral ulceration, even in HIV infected patients. Presenting as a chronic, non-healing, deep and solitary ulceration, its clinical presentation is the same as that in healthy individuals. It is often confused with tuberculosis, deep fungal infections, or malignancy. Dark field microscopy may demonstrate treponema. Positive reactive plasma regain (RPR) and histologic demonstration of Treponema is diagnostic. Combination treatment with penicillin erythromycin and tetracycline is the treatment of choice.[14]

NEOPLASTIC DISEASES

Kaposi's sarcoma

Kaposi's sarcoma has been associated with AIDS since the disease was first described by the CDC.[25] It is the single most common neoplasm occurring in patients with AIDS, but there has been a dramatic decrease in its incidence since the advent of HAART. [12, 13] There is a strong association with HHV-8. This virus is found in all forms of KS, and has also been termed Kaposi's sarcoma associated Herpesvirus (KSHV).[13]

It is a macular or nodular lesion can be raised or ulcerated with colour ranging from red to purple, diagnosis is frequently missed in African American patients due to the coloration.[12] Orally, it initially presents as blue red or purple macules on the palate, gingival and tongue that may not blanch on pressure. With progression of the disease, the nodules may become ulcerative, extensive and painful. A biopsy provides definitive diagnosis with histopathology being characterised by proliferation of spindled cells that form vascular channels. Treatment is focussed on palliation and local control. There is no curative therapy and modalities such as chemotherapy which further suppress the immune system favour the growth of KS. Local measures include excision, laser ablation, radiation or intralesional injections.[13]

Non-Hodgkin's Lymphoma

Lymphomas are tumors of the lymphoreticular tissue where there is clonal expansion of neoplastic cells derived from immune system.[20] Non-Hodgkin's lymphoma is the second most prevalent intraoral neoplasm in patients with AIDS. HIV positive patients are at 60 to 70 times greater risk of developing NHL than are healthy individuals. Unlike KS, the incidence of NHL has not decreased with the advent of HAART.[13]

An increased occurrence of malignant lymphomas has been reported in male homosexuals, in haemophiliacs, and i.v. drug users with HIV infection. Higher risk in HIV positive patients has been established as 10-15 times greater as compared with healthy individuals of the same age.[21]

AIDS associated NHL often reveals unusual clinical features which include presentation at advanced stages, poor prognosis and high frequency of primary brain and intranodal involvement including rectal, and intraoral sites.[21] Intra-orally, the lesions present as ulcerations or soft-tissue masses that are painful and enlarge rapidly, with the most common sites being the palate, retromolar pads, tonsillar pillars, and tongue, however, most HIV-positive individuals presenting with oral NHL will already have nodal and quite likely extra-nodal involvement.[13]

Patients are treated with radiation therapy (for localised disease) and combination chemotherapy. Unfortunately, chemotherapy exacerbates immunosuppression by inducing profound neutropenia, placing these patients at further risk for opportunistic infections. Complete remission occurs in approximately 65% of patients, and the median survival time for individuals with AIDS-related lymphomas is between 4 and

11 months. Low CD4 counts and involvement of bone and extra-nodal sites are associated with poorer prognosis.[13]

Plasmablastic Lymphoma: First reported in 1997 by Delecluse, this entity is strongly associated with HIV infection, and accounts for 3% of all HIV related non-Hodgkin's lymphomas. It is characterised by diffuse large painless gingival growth sometimes associated with trauma or spontaneous bleeding. It may be poorly recognised due to rarity of the lesion and its unusual immunophenotype.

Treatment may consist of chemotherapy, using prednisolone, cyclophosphamide, adriamycin and/or vincristine, or local excision followed by radiation. The prognosis for plasmablastic lymphoma is poor and death usually occurs 1-24 months after diagnosis, the average survival period being 6 months.[22]

Squammous Cell Carcinoma: In face of HIV infection, Squammous Cell Carcinoma (SCC) is the third most common head and neck cancer, after Kaposi's sarcoma and non-Hodgkin's lymphoma. These tumors present in younger individuals in HIV infected population, have a unique course, and may be associated with poorer overall survival. The presentation of SCC usually precedes the development of AIDS and is often the initial presentation (in about 33% of cases.) The hastened development to AIDS and the drop in CD4+ cell count has been attributed to the stress of undergoing treatment and HIV associated factors.

Treatment via operative therapy is not without risk of transmission to health care providers, although this can be minimised with the use of appropriate precautions. Wound healing problems are common in HIV infected population and are worsened by a poor nutritional status. Alterations in the presentation of infectious complications may be seen, making it especially important to meticulously monitor the wounds in all patients.[23]

Immunological

While HIV infection and progression is characterised by progressive immune deterioration, it is equally well characterised by an abnormally activated immune system. The immune system activation itself leads to tissue injury and worsening health of the patient.[14]

Major Aphthous Ulceration

It is the most common immune-mediated HIV related oral disorder[14] with a prevalence ranging from 1-47%. Major aphthae are associated with advanced HIV infection, with patients generally having a CD4+ cell count of less than 100 cells/mm^3, and less than 50 cells/mm^3 in 875% patients, thus these ulcers may be an indicative marker for progression of AIDS.[13] Their cause is unknown,[12] but are often associated with fungal, bacterial and viral infections, neoplasia and medications in HIV infected population.[24, 25]

The ulcers resemble those seen in major aphthous stomatitis.[13,14] Appearing on non-keratinised or non-fixed tissues such as labial or buccal mucosa, floor of mouth, ventral surface of tongue, posterior oropharynx,[12] they are painful with clearly defined borders and a diameter of 10mm or more.[13] These lesions are characterised by a halo of inflammation and a yellow grey pseudomembranous covering.[12] In immunocompromised patients, these lesions persist for longer than 7-14 days as in immunocompetent patients, usually for three weeks or more.[12,13]

Neutropenic ulcers are very painful and appear on both keratinised and non-keratinised mucosa, and are associated with absolute granulocyte counts of less than 800/µl. These lesions are found with increasing frequency in HIV infected population although the cause of this increase in frequency remains unknown.[12]

The diagnosis must include the possibility of a primarily infectious entity which can be determined by histological examination of biopsy material. Atypical ulcers, called Ulcers, Not Otherwise Specified (NOS), are non-tumefactive, do not correspond to any recognised patterns of aphthous stomatitis, histological features are non-specific, and cultures fail to identify a specific etiological agent. The prevalence of these ulcers among HIV infected population ranges from 1.1- 12%.[24] Treatment requires the use of a potent topical steroid such as clobetesol (0.5% ointment applied for 45 seconds 3 times daily) when the lesion is accessible or dexamethasone oral rinse (0.5mg/5ml dexamethasone elixir 3 times daily) when inaccessible. When multiple ulcers are present or response to topical treatment is incomplete, systemic gluco-corticosteroid therapy is required (prednisolone 1mg/kg). Prophylactic medications are recommended since lesions often return after discontinuing medication. Long term use of systemic prednisolone may lead to complications such as oral candidiasis, reactivation of tuberculosis, and worsening of Kaposi's sarcoma. Alternative therapies such as dapsone 50-100 mg daily and thalidomide 200mg daily for 4 weeks may be considered. When immune modulating drugs are used, concurrent antifungal and antibacterial medications may be required to prevent super-infection and opportunistic growth.[14] Pain management is a crucial component of treating ulcerative oral diseases. Pain is usually treated with topical anaesthetics or systemic analgesics. The relief afforded is short lived and tends to numb the mouth and taste buds.[12]

Miscellaneous

Xerostomia

Xerostomia is common in HIV disease,[14] approximately 30-40% of HIV infected individuals experience moderate to severe xerostomia.[12] The medications implicated thus include antivirals, antihypertensives, antidepressants, anxiolytics, or analgesics all of which may routinely be prescribed for patients with HIV infection.[14] Stimulated parotid saliva flow rates have been shown to be diminished in patients with AIDS.[13] Other studies show clinical reduction in the salivary flow rates of all the major salivary glands. Furthermore, HIV infected individuals are known to have saliva containing increased sodium, chloride, lysozyme, peroxidise, lactoferrin and immunoglobulin A levels.[26]

The resultant oral dryness presents a significant risk factor for caries and can lead to rapid dental decay and periodontal deterioration.[12,14] Xerostomia also contributes to oral candidiasis, mucosal injury, dysphagia and is often associated with pain and reduced oral intake of food.[14] In patients with residual salivary gland function, determined by gustatory challenge, oral pilocarpine (5mg up to 3 times daily) often provides improved salivary flow and consistency. Oral hygiene instructions, regular maintenance and use of fluoridated dentifrices is essential.[14]

Salivary Gland Disease

The most common presentation is salivary gland swelling which can be attributed to acute sialadenitis or HIV-associated Salivary Gland Disease (HIV-SGD). It is observed in all age groups although it is more common in children and might present with an altered disease progression.[26]

Parotid Gland Enlargement: reported to occur in 1-10% of HIV infected patients it is usually secondary to the development of benign lymphoepithelial cysts.[13,14,26] It is usually painless, without signs of infection by CMV or EBV and unassociated with meal symptoms.[13] The enlargement typically involves the tail of the parotid gland, or less commonly the submandibular gland, and it may present uni- or bilaterally with periods of increased or decreased size. While the appearance is suggestive of malignancy or infection, aspiration of a yellow mucinous secretion supports the diagnosis of HIV-SGD.[14] These lesions are best diagnosed with ultrasonography, or computerised tomography.[13] Occasional swelling can be managed simply by repeated aspiration.[14] Treatment if desired is by surgical excision.[13]

Benign Lymphoepithelial Cysts: A rare manifestation of HIV disease characterised by bilateral parotid swelling, diffuse visceral CD8 lymphocytic infiltration, persistent CD8 lymphocytosis, and cervical lymphadenopathy. It has been reported to occur in salivary glands or their lymph nodes, oral cavity (usually floor of mouth), tonsils, thyroid gland, pancreas, and juxta-bronchial.

With the emergence of HIV epidemic, the incidence of parotid gland BLEC has increased dramatically, the incidence being 3-6% in HIV-positive adults and 1-10% in HIV-positive children. However, its incidence appears to be on the decline with the advent of HAART.

The pathogenesis of BLEC is unclear but it is seen to develop with increase viral loads. It is postulated that parotid enlargement results from lymphoid proliferation causing ductal obstruction resulting in ductal dilatation that mimics a true cyst. The diagnostic evaluation consists mainly of ultrasound scan, CT and or MRI. Multiple thin walled cysts with diffuse cervical lymphadenopathy are evident. The management is not well established. The treatment options range from close observation, repeat aspiration, antiretroviral therapy, sclerosing therapy, radiation, surgery, or a combination of the above. [26]

Pain Syndromes

Pain is a common symptom experienced by patients with HIV infection. It may result from a wide variety of diseases including direct effects of HIV on central or peripheral nervous system, infection, malignancy or ART. Headache is a common symptom, occurring in approximately 46% patients with HIV infection. Neuropathic pain is common in patients with HIV infection, the most common diagnosis being painful peripheral sensory neuropathy.[14]

Pigmentation

In HIV infected patients, progressive hyperpigmentation of skin, fingernails, and toenails has been reported to be linked with primary adrenocortical deficiency or in some cases, to zidovudine therapy. Acquired oral hyperpigmentation has been described as a result of inflammatory reactions, drug exposure, or due to unknown cause. It is hypothesised that oral hyperpigmentation is the expression of a local inflammatory or post inflammatory reaction. When immune surveillance of the mucosa associated lymphoid tissues (MALT) fails, these hyperpigmentations may lead to the development of malignant lesions.[27]

CONCLUSION

The pattern of oral opportunistic infections in this HIV infected cohort is changing in the era of HAART. Hairy leukoplakia is undergoing a significant reduction in clinical prevalence. Destructive immune-mediated periodontal diseases, oral candidiasis and Kaposi's sarcoma appear to be on the decline whereas prevalence of salivary gland disease and oral warts has increased significantly.[28] Combination ART has been documented to play a critical role in the prevention of oral manifestations of HIV because of its role in the reconstitution of the immune system.[29]

The escalating number of patients infected with HIV and the resulting cases of AIDS has produced an increased observation of oral manifestations associated with this syndrome.[19] Thus, in addition to comprehensive general health care, oral health care is integral in the management of patients with HIV infection. The need of the hour is comprehensive quality dental care in a multidisciplinary setting with medical and social support providers as poor oral health care in these patients can complicate the management of systemic conditions, lead to nutritional deficiencies, affect antiretroviral treatment compliance and adversely affect quality of life.[3]

In these patients, good oral health care is especially important because:

1. Oral manifestations are common in people with HIV infection. More than 90% of HIV infected patients are seen to have atleast one HIV related oral manifestation.
2. Oral lesions may be an early indicator of decline in immune function and may warrant further investigations
3. Control of focal infection within the oral cavity may retard adverse consequences such as progression to systemic diseases.

4. Poorly functioning dentition can adversely affect quality of life, and exacerbate weight loss in HIV infected patients, who may already be malnourished.

References

1. Centre for Disease Control and Prevention [Internet]. Atlanta Georgia. Centre for Disease Control and Prevention, 2015 [Updated 2015, January 16, cited 2015 March 7]. Available from http://www.cdc.gov/
2. Kumar V, Abbas AK, Fausto N, editors. Robbins and Cotran pathological basis of disease. 7th ed. Philadephia (PA): Reed Elsevier India Private Limited 2010.
3. Prabhu SR, Kohli A, Rao CB, editors. HIV/AIDS in dental practice: handbook for dental practioners in India- a publication of the dental council of India. India: Thomson Press 2007.
4. Norris S. HIV/AIDS past present future. Ottawa (Canada): Library of Parliament Publication 2011.
5. Smith JA. HIV and AIDS in the adolescent and adult: an update for the oral and maxillofacial surgeon. Oral Maxillofacial Surg Clin N Am 2008;20:535-65
6. Sim AJW, Jeffries DJ, editors. AIDS and surgery. London(England): Blackwell Scientific Publications; 1990.
7. National AIDS Control Organisation [Internet]. State HIV epidemic fact sheets. [Updated 2014, August 22, cited 2015 March 7]. Available from http://naco.gov.in/NACO/Quick_Links/Publication/State_Fact_Sheets/Fact_Sheets/State_HIV_Epidemic_Fact_Sheet_July_2014/
8. National AIDS Control Organisation [Internet]. Annual Report 2012-13. [Updated 2013, cited 2015, March 7]. Available from http://naco.gov.in/
9. Baccaglini L, Atkinson JC, Patton LL, Glick M, Ficarra G, Perterson DE. Management of oral lesions in HIV positive patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103(suppl1):s50.e1-s50.e23
10. Scully C, Laskaris G, Pindbord J, Porter SR, Reichart P. Oral manifestations of HIV infection and their management. I. More common lesions. Oral Surg Oral Med Oral Pathol 1991;71:158-66
11. Patton LL. HIV disease. Dent Clin N Am 2003;47:467-92
12. Oral manifestations of HIV disease. Perspective 2005; 13:143-8
13. Casiglia JW, Woo SK. Oral manifestations of HIV infection. Clinics in Dermatology 2000;18:541-51
14. Sirosis DA. Oral manifestations of HIV disease. The Mount Sinai Journal of Medicine 1998;65(5&6):322-32
15. Silverman S, Gallo JW, McKnight ML, Mayer P, de Sanz S, Tan MM. Clinical Characteristics and management responses in 85 HIV infected patients with oral candidiasis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;82:402-7
16. Mohammed S, Sinha M, Chavan P, Premlata CS, Shivaprakash MR, Chakrabarti A, *et al*. Oral histoplasmosis masquerading as oral cancer in HIV infected patient: a case report. Medical Mycology Case Reports 2012;1:85-7
17. Economopoulou P, Laskaris G, Kittas C. Oral histoplasmosis as an indicator of HIV infection. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;86:203-6
18. Infante-Cossio P, Gonzalo DH, Hernandez-Gutierrez J, Borrero-Martin JJ. Oral inverted ductal papilloma associated with condyloma acuminata and HPV in an HIV+ patient. Int J Oral Maxillofac Surg 2008;37:1159-61
19. Brahim JS, Katz RW, Roberts MW. Non-Hodgkin's lymphoma of the hard palate mucosa and buccal gingiva associated with AIDs. J Oral Maxillofac Surg 1988;46:328-30
20. Singla A, Vats RS, Vohra R, Gupta P, Vats A, Rai P. Oral non-Hodgkin's lymphoma in HIV +ve patient- a report on two cases. Journal of Dentistry Defence Section 2011;6(1):57-60
21. Langford A, Dienemann D, Schurman D, Pohle HD, Pauli G, Stein H, Reichart P. Oral manifestations of AIDS associated non-Hodgkin's lymphomas. Int J Oral Maxillofac Surg 1991;20:136-41
22. Sarode SC, Zarkar GA, Desai RS, Sabane VS, Kulkarni MA. Plasmablastic lymphoma of the oral cavity in an HIV-positive patient: a case report and review of literature. Int J Oral Maxillofac Surg 2009;38:993-9
23. Singh B, Sabin S, Rofim O, Shaha A, Har-El G, Lucente FE. Alterations in head and neck cancer occurring in HIV infected patients. Acta Oncologica 1999;38(8):1047-50
24. Piluso S, Ficarra G, Lucatorto FM, Orsi A, Dionisio D, Stendardi L, *et al*. Cause of oral ulcers in HIV infected patients a study of 19 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;82:166-72
25. Reichart PA. Oral ulceration and iatrogenic disease in HIV infection. Oral Surg Oral Med Oral Pathol 1992;73:212-4
26. Shanti RM, Aziz SR. HIV associated salivary gland disease. Oral Maxillofac Surg Clin N Am 2009;21:339-43
27. Langford A, Pohle HD, Gelderblom H, Zhang X, Reichart PA. Oral hyperpigmentation in HIV infected patients. Oral Surg Oral Med Oral Pathol 1989;67:301-7
28. Patton LL, McKaig R, Strauss R, Rogers D, Eron JJ Jr. Changing prevalence of oral manifestations of human immunodeficiency virus in the era of protease inhibitor therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:623-8
29. Tappuni AR, Fleming GJP. The effect of antiretroviral therapy on the prevalence of oral manifestations of HIV infected patients: a UK study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:623-8

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TSSN 0976-3031