Oral Hairy Leukoplakia as Prediction Oral Lesion for HIV Disease: A Review Article

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Introduction
Oral Hairy Leukoplakia (OHL) is a hyperplastic mucocutaneous epithelial cell disease, induced by Epstein Barr virus (EBV). The clinical appearance of OHL is as white, corrugated, painless, and asymptomatic lesion, as a patch that cannot be removed by scraping, located often bilaterally on lateral borders of the tongue. The prevalence of OHL was reported to be 20% in asymptomatic HIV infection in the United States to 36% with Acquired Immunodeficiency Syndrome (AIDS). Worldwide 2006, the prevalence of OHL in Brazil was 28.8%, also reported a prevalence of 38.8% and 21.8% in northern and southern USA.

Discussion:
Oral hairy leukoplakia is a specific lesion in HIV infection caused by Epstein Barr virus, and has been reported in over more than 28% patients and is a sign of disease progression. OHL appear clinically as an asymptomatic, white, or grayish white, well demarcated plaque with corrugated texture [1]. The “hairy” surface varies in size from a few millimeters to extensive lingual and oral mucosal involvement. These lesion typically occurs on the lateral tongue but may also appear on the ventral and dorsal surface of the tongue, and more rarely, on the buccal mucosa.

Conclusion:
The establishment of Oral Hairy Leukoplakia as a diagnosis have a diagnostic value for HIV infection. Oral manifestations are the earliest and most important indicators of HIV infection. OHL is often wrongly diagnosed and thus proper treatment is delayed. The present of OHL in the absence of known cause of immunosuppression strongly suggest HIV infection. In the early diagnosis of OHL health care provider must be cautious and seek further examination to establish HIV infection.

Keywords: OHL; infection; HIV; oral lesion

Abbreviations:
OHL: Oral Hairy Leukoplakia; EBV: Epstein Barr Virus; AIDS: Acquired Immunodeficiency Syndrome

Abstract

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worldwide, the serologic prevalence of EBV estimated around 95%. Latently infected, circulating B-lymphocytes are believed to be a site of lifelong EBV persistence. The productive replications of EBV occur in the surfaces of the oral mucosa and sheds infectious, transmissible virus into the saliva [6]. HIV infections represent a spectrum disease that can begin with a brief acute retroviral syndrome that typically transitions to a multiyear chronic and clinically latent illness. Without treatment, this illness eventually progresses to a symptomatic, life threatening immunodeficiency disease known as AIDS. OHL has been associated with more rapid progression to AIDS among HIV viral-infected individuals, and with HIV viral loads exceeding 20,000 copies/ml, and with CD4+ counts below 200/mm³ [7,8]. OHL is a disease of minimal morbidity that does not always require intervention. This is due to the fact that OHL is a benign, asymptomatic, and potentially self-limiting lesion. Therapy is indicated when symptoms become troubling or when there is a need for cosmetic reasons [9].

Discussion
Oral hairy leukoplakia

Oral hairy leukoplakia is a specific lesion in HIV infection caused by Epstein Barr virus, and has been reported in over more than 28% patients and is a sign of disease progression [10]. OHL appear clinically as an asymptomatic, white, or grayish white, well demarcated plaque with corrugated texture [11]. The "hairy" surface varies in size from a few millimeters to extensive lingual and oral mucosal involvement [12]. These lesion typically occurs on the lateral tongue but may also appear on the ventral and dorsal surface of the tongue, and more rarely, on the buccal mucosa [13]. The characteristic appearance of OHL is caused by hypertrophy of the involved lingual papillae. In general, the lesion is painless and irremovable by blunt manipulation [13]. When the lesion became symptomatic, it may represent superimposed or coinfection with candidiasis [14]. OHL is a benign lesion characterized by abundant EBV productive replication. EBV (or also called human herpesvirus 4) is from the gamma subfamily of Herpesviridae [14-16]. The virus remains in lifelong latency by residing in circulatory memory B lymphocytes of the peripheral blood, which serve as the cellular reservoir of persistent latent EBV infection [17,18]. The virus is transmitted by means of mucosal excretions, for example, saliva, through shedding of EBV-infected oropharyngeal cells during viral reactivation [19]. It remains unclear whether EBV derives from reactivation of latent strains in the tongue epithelium or is acquired through contact with EBV-infected saliva or through EBV-positive circulating B lymphocytes [18]. Recent studies have shown that infected monocytes, macrophages, or Langerhans cells of the peripheral blood migrate through lamina propria into oral epithelium and infect terminally differentiated cells of the upper portion of the spinous layer, initiating productive viral replication and EBV dissemination [20,21]. These cells could be the source of reactivation for EBV productive replication [8,20,22].

OHL as prediction lesion in HIV disease

Severe immunosuppression can lead into reactivation of EBV replication in the oropharynx of EBV-seropositive patients. EBV replication has also been found in normal oral epithelium, this suggest that replication alone is insufficient for the pathogenesis of OHL and that cofactors are required [23]. The lateral border of the tongue is the most common location of OHL. The development of OHL on the tongue may be related to the accumulation of saliva in the floor of the mouth and the resting position of the tongue in a pool of EBV-shedding saliva [4]. Other explanation is the decreased number of Langerhans cells in OHL lesions when compared with nonregional oral mucosa. A comparative study of normal mucosa revealed that the lowest density of Langerhans cells was found on the lateral border of the tongue and the sublingual region. Thus, normal epithelium of the lateral and ventral sides of the tongue is more susceptible to EBV infection [23]. The importance of OHL as an indicator of immunosuppression was recognized soon after it was first described, when the authors observed that a proportion of the patients developed AIDS-defining illness within a relatively short time following the diagnosis of OHL [3,24,25]. In 1992 the European Economic Community published a revised classification of oral lesion associated with HIV infection in adults [26], where OHL is one of the lesions strongly associated with HIV infection as can be seen in Table 1 [27]. The findings of OHL in patients who are tested positive for HIV infection can give some predictive immune system condition of how progressive the infection is, as it is believed to have correlation with CD4 T cell counts. The rare occurrence of OHL in healthy individuals and the association of OHL in HIV-positive patients with low CD4+ T Cells Count and high viral load suggests a role of stimulation of EBV by HIV or a distinct role of CD4 T cells in protection against disease (Table 2).
Table 1: WHO Clinical Staging of HIV/AIDS for Adults and Adolescents [27].

| Primary HIV Infection | Clinical Stage 1 | Clinical Stage 2 |
|-----------------------|-----------------|-----------------|
| a) Asymptomatic       | a. Asymptomatic | i. Moderate unexplained weight loss (<10% of presumed or measured body weight) |
| b) Acute retroviral syndrome | b. Persistent generalized lymphadenopathy | ii. Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) |
|                       |                 | iii. Herpes zoster |
|                       |                 | iv. Angular cheilitis |
|                       |                 | v. Recurrent oral ulceration |
|                       |                 | vi. Papular pruritic eruptions |
|                       |                 | vii. Seborrheic dermatitis |
|                       |                 | viii. Fungal nail infections |
|                       |                 | ix. Fungal nail infections |
| a)  Asymptomatic      |                 | A. Unexplained severe weight loss (>10% of presumed or measured body weight) |
| b)  Acute retroviral syndrome |                 | B. Unexplained chronic diarrhea for >1 month |
|                       |                 | C. Unexplained persistent fever for >1 month (>37.6°C intermittent or constant) |
|                       |                 | D. Persistent oral candidiasis (thrush) |
|                       |                 | E. Oral hairy leukoplasia |
|                       |                 | F. Pulmonary tuberculosis (current) |
|                       |                 | G. Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) |
|                       |                 | H. Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis Unexplained anemia (hemoglobin <8 g/dL) |
|                       |                 | I. Neutropenia (neutrophils <500 cells/µL) |
|                       |                 | J. Chronic thrombocytopenia (platelets <50,000 cells/µL) |
| a) HIV wasting syndrome, as defined by the CDC. | a) Asymptomatic | i. Moderate unexplained weight loss (<10% of presumed or measured body weight) |
| b) Pneumocystis pneumonia |                    | ii. Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) |
| c) Recurrent severe bacterial pneumonia |                    | iii. Herpes zoster |
| d) Chronic herpes simplex infection (oralabial, genital, or anorectal site for >1 month or visceral herpes at any site) |                    | iv. Angular cheilitis |
| e) Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) |                    | v. Recurrent oral ulceration |
| f) Extrapulmonary tuberculosis |                    | vi. Papular pruritic eruptions |
| g) Kaposi sarcoma |                    | vii. Seborrheic dermatitis |
| h) Cytomegalovirus infection (retinitis or infection of other organs) |                    | viii. Fungal nail infections |
| i) Central nervous system toxoplasmosis |                    | ix. Fungal nail infections |
| j) HIV encephalopathy |                    | A. Unexplained severe weight loss (>10% of presumed or measured body weight) |
| k) Cryptococcosis, extrapulmonary (including meningitis) |                    | B. Unexplained chronic diarrhea for >1 month |
| l) Disseminated nontuberculosis mycobacteria infection. |                    | C. Unexplained persistent fever for >1 month (>37.6°C intermittent or constant) |
| m) Progressive multifocal leukoencephalopathy |                    | D. Persistent oral candidiasis (thrush) |
| n) Candida of the trachea, bronchi, or lungs |                    | E. Oral hairy leukoplasia |
| o) Chronic cryptosporidiosis (with diarrhea) |                    | F. Pulmonary tuberculosis (current) |
| p) Chronic isosporiasis |                    | G. Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) |
| q) Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis) |                    | H. Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis Unexplained anemia (hemoglobin <8 g/dL) |
| r) Lymphoma (cerebral or B-cell non-Hodgkin) |                    | I. Neutropenia (neutrophils <500 cells/µL) |
| s) Invasive cervical carcinoma |                    | J. Chronic thrombocytopenia (platelets <50,000 cells/µL) |
| t) Atypical disseminated leishmaniasis |                    | a) HIV wasting syndrome, as defined by the CDC. |
| u) Symptomatic HIV-associated nephropathy |                    | b) Pneumocystis pneumonia |
| v) Symptomatic HIV-associated cardiomyopathy |                    | c) Recurrent severe bacterial pneumonia |
| w) Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis) |                    | d) Chronic herpes simplex infection (oralabial, genital, or anorectal site for >1 month or visceral herpes at any site) |

Table 2: Staging of HIV Infection Based on CD4 Cells Count and Percentage [26].

| CD4 Cells/µL, Absolute Count | CD4% | Staging for Adults |
|------------------------------|------|--------------------|
| >600                         | 32-50| Normal             |
| <500                         | <29  | Initial immune suppression |
| <400                         | <29  | Oral lesions may appear |
| 200-400                      | 14-28| Increased severity and number of opportunistic infections and oral lesions |
| <200                         | <14  | AIDS, severe immune suppression |
Clinical manifestation of OHL

Clinical findings are usually enough to be a presumptive diagnose in patients with HIV infection. A further definitive criterion when necessary must be demonstrated by the presence of EBV in the lesions to be determined by histopathology, exfoliative cytology, in situ hybridization, or PCR [28]. Histopathologically, epithelial hyperplasia, hyper and parakeratosis, and ballooning, vacuolated, koliocytic epithelial cells with minimal or no surrounding inflammation [29], and also nuclei that have a ground-glass appearance and nuclear beading can be found in OHL. Exfoliative cytopathology of OHL revealed features of Cowdry type A inclusion bodies, ground glass nuclei, and nuclear beading. If the facilities to demonstrate the presence of EBV are not available, a lack of response to antifungal treatment or a demonstration of an immunodeficient status can reinforce the presumptive diagnose [30] (Figure 1).

![Figure 1: (A) Cowdry type A inclusion bodies along with perinuclear halo (B) Glass appearance of the nucleus and a peripheral nuclear beading, both (A) and (B) are PAP-stained, 100x magnification [30].](image)

Treatment of OHL

Treatments for OHL when required consist of varying options. Usually, the institution of HAART with reduced viral load and increased CD4 count help a significant reduction in the prevalence of OHL patients. Systemic antiviral therapy produces rapid resolution, although sometimes the recurrence can be expected when therapy is discontinued. Systemic antiviral therapies known to be used are acyclovir and valacyclovir, with several reports the use of desiclovir and famciclovir. Acyclovir is a nucleoside analog available in the form of oral, intravenous, and topical. The triphosphate form of the drug is the active form, which has a potent inhibitory effect on herpesvirus-induced DNA polymerases but relatively little effect on host cell DNA polymerase [31]. In OHL, acyclovir effectively resolves the permissive infection, although cessation of treatment often results in a recurrence of lesions within 1-4 months [14,31].

Conclusion

The establishment of Oral Hairy Leukoplakia as a diagnosis have a diagnostic value for HIV infection. Oral manifestations are the earliest and most important indicators of HIV infection. OHL is often wrongly diagnosed and thus proper treatment is delayed. The present of OHL in the absence of known cause of immunosuppression strongly suggest HIV infection. In the early diagnosis of OHL, health care provider must be cautious and seek further examination to establish HIV infection. Institution of HAART after the diagnosis of HIV infection could induce the resolution of OHL. Other treatments such as systemic antiviral accelerate the resolution process. The ability to recognize early OHL manifestation in patient with HIV is key to providing optimal and appropriate care, give early medical intervention and thus prolonging patient’s life and revise its quality.
Conflict of Interest

None

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