5-5-2017

Hairy Leukoplakia

James E. Cade
Meharry Medical College School of Dentistry

Richard P. Vinson
Paul L Foster School of Medicine

Jeff Burgess
University of Washington School of Dental Medicine

Sanjiv S. Agarwala
Temple University Shool of Medicine

Denis P. Lynch
Marquette University, denis.lynch@marquette.edu

See next page for additional authors

Published version. *Medscape Drugs & Diseases* (May 5, 2017). Publisher link.

Overview

Background

Oral hairy leukoplakia (OHL) is a disease of the mucosa first described in 1984. This pathology is associated with Epstein-Barr virus (EBV) and occurs mostly in people with HIV infection, both immunocompromised and immunocompetent, and can affect patients who are HIV negative.{ref1}{ref2} The first case in an HIV-negative patient was reported in 1999 in a 56-year-old patient with acute lymphocytic leukemia. Later, many cases were reported in heart, kidney, and bone marrow transplant recipients and patients with hematological malignancies.{ref3}{ref4}

Pathophysiology

The Epstein-Barr virus (EBV), a ubiquitous herpesvirus estimated to infect 90% of the world's population, is linked to a growing number of diseases, especially in immunocompromised hosts. Like all herpesviruses, EBV establishes a life-long, persistent infection of its host. The pathogenesis of hairy leukoplakia is clearly complex, potentially requiring a convergence of factors including EBV co-infection, productive EBV replication, EBV genetic evolution, expression of specific EBV "latent" genes, and immune escape. All of these factors are likely facilitated by local and systemic host immunodeficiency.{ref5}

EBV initially infects basal epithelial cells in the pharynx, where it enters a replicative state leading to the release of infectious virus into the saliva throughout the life of the infected person. In the pharynx, the virus also enters B cells, where it persists indefinitely in a latent state. Cytotoxic T lymphocytes cannot eliminate EBV from the body, but they are essential in maintaining the latent state of the infection. In states of immune dysfunction in which the number of EBV-specific cytotoxic T lymphocytes is decreased, there is an increase in the number of circulating EBV-infected B cells.

In addition, a marked decrease or an absence of Langerhans cells occurs in hairy leukoplakia biopsy tissues.{ref6}{ref7} Langerhans cells are the antigen-presenting immune cells that are required for an immune system response to the viral infection and their deficiency may permit EBV to persistently replicate and escape immune recognition.

Epidemiology

Frequency

United States

Hairy leukoplakia is one of the most common virally induced, oral diseases of HIV-infected individuals, with a point prevalence as high as 25-53%.{ref8} The 6-year incidence of oral hairy leukoplakia (OHL) in this patient population was reported to be around 32%. A significant trend to a lower prevalence of oral hairy leukoplakia was observed in the group of patients who were already taking antiretroviral therapy, non–highly active antiretroviral therapy (HAART) and HAART (P <.001 and P = .004, respectively).{ref9}

Fewer cases of oral hairy leukoplakia were reported in non-HIV–infected patients. This is probably due to underdiagnosis and underreporting of this disease in patients with hematological malignancies or solid organ transplantation. Some studies showed the prevalence of oral hairy leukoplakia in renal transplant recipients to be more than 11%.{ref10}

International

The incidence of oral hairy leukoplakia is similar to that in the United States and thereby reflects the prevalence of HIV. In populations where the prevalence of HIV is low, oral mucosal lesions alone are poor prognostic predictors of HIV infection.{ref11}

A cross-sectional study from Brazil reported on data collected from clinical examinations, interviews, and medical records for adult patients treated an HIV/AIDS clinic at the University Hospital of the Federal University in Rio Grande. Three hundred persons were observed (April 2006 to January 2007). Of these patients, 51% were male and the mean age was 40 years. Thirty-nine percent presented with oral lesions. The most common was candidiasis (59.1%), followed by hairy leukoplakia (19.5%).{ref12}

A study from Saudi Arabia reported that compared with age and sex-matched healthy control subjects (N = 52), 8.6% of stable renal transplantation patients (N = 58) had oral leukoplakia. Other oral lesions reported were gingival hyperplasia (74.1%) and erythematous candidiasis (15.5%).{ref13} However, a study from Spain reported only one case of hairy leukoplakia in 500 renal transplant recipients studied.{ref14}

Race

No racial predilection has been established for oral hairy leukoplakia.

Sex

Oral hairy leukoplakia is most commonly observed in homosexual men who are HIV positive, especially in those who smoke.

Age

No age predilection has been established for oral hairy leukoplakia.

Prognosis

The majority of patients with oral hairy leukoplakia (OHL) tend to have significant immunosuppression at the time of diagnosis. Oral hairy leukoplakia occurs relatively soon after HIV seroconversion, typically before AIDS. Median CD4 count when oral hairy leukoplakia is first detected is 235-468/µL. Another study showed oral hairy leukoplakia occurred mostly in patients with CD4 counts of 200-500/µL.{ref15}

In patients with HIV, the median CD4 count when oral hairy leukoplakia is first detected is 468/µL. If these patients do not have AIDS-defining disease at the time oral hairy leukoplakia is diagnosed, the probability of developing AIDS if not receiving highly active antiretroviral therapy (HAART) is 48% by 16 months and 83% at 31 months. In addition, studies have shown that patients with AIDS with oral hairy leukoplakia have a shorter lifespan than those who do not present this lesion. Furthermore, if these patients are concomitantly co-infected with hepatitis B virus, the risk of early progression to AIDS increases 4-fold. Further studies in HIV-seropositive patients show that the median survival after the diagnosis of oral hairy leukoplakia is around 20 months. In patients with CD4 count greater than or equal to 300/µL, oral hairy leukoplakia is associated with median survival time of 25 months, compared with 52 months in patients with normal counts.{ref16}

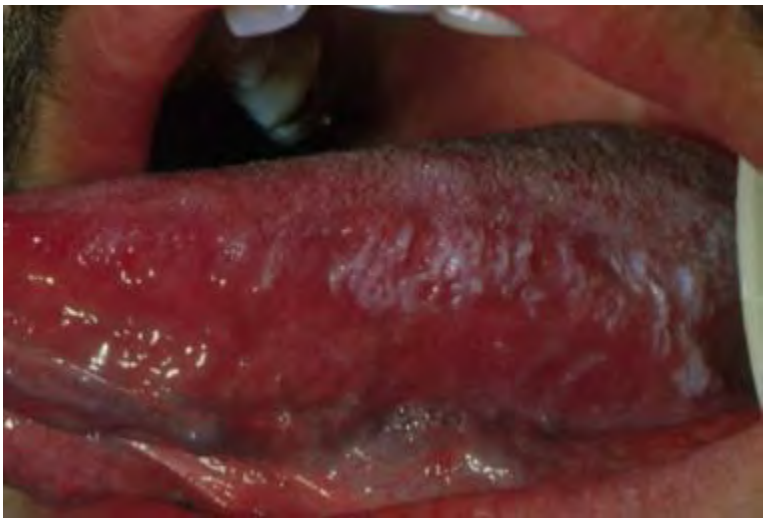
Presentation

History

Patients with oral hairy leukoplakia (OHL) may report a nonpainful white plaque along the lateral tongue borders. The appearance may change daily. The natural history of hairy leukoplakia is variable. Lesions may frequently appear and disappear spontaneously. Hairy leukoplakia is often asymptomatic, and many patients are unaware of its presence. Some patients with hairy leukoplakia do experience symptoms including mild pain, dysesthesia, alteration of taste, and the psychological impact of its unsightly cosmetic appearance.

Physical Examination

Unilateral or bilateral nonpainful white lesions can be seen on the margins, dorsal or ventral surfaces of the tongue, or on buccal mucosa, as shown in the image below. Oral hairy leukoplakia (OHL) lesions may vary in appearance from smooth, flat, small lesions to irregular "hairy" or "feathery" lesions with prominent folds or projections.

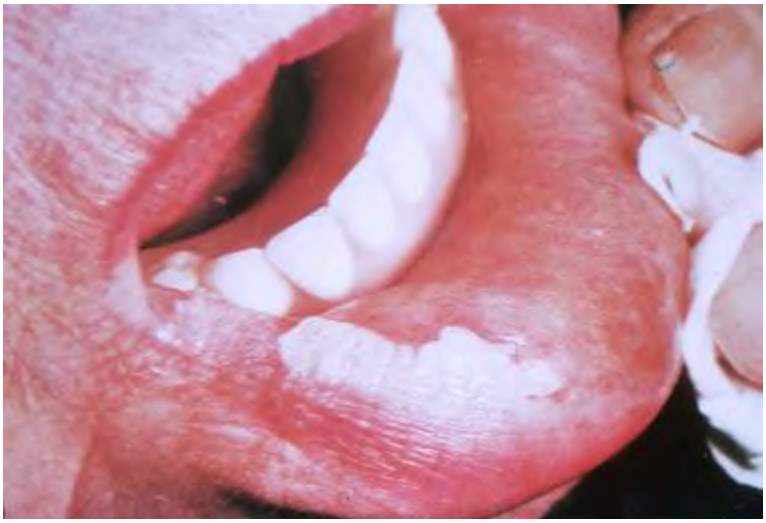


Lateral tongue in oral hairy leukoplakia.

{file63311}

Lesions may be either continuous or discontinuous along both tongue borders, and they are often not bilaterally symmetric. Lesions are adherent, and only the most superficial layers can be removed by scraping. There is no associated erythema or edema of the surrounding tissue. Hairy leukoplakia may also involve dorsal and ventral tongue surfaces, the buccal mucosa, or the gingiva. On the ventral tongue, buccal mucosa, or gingiva, the lesion may be flat and smooth, lacking the characteristic "hairy" appearance.{ref2}

See the image below.



Oral leukoplakia.

{file28244}

Causes

Oral hairy leukoplakia (OHL) has been associated with HIV infection and/or immunosuppression.{ref17} The risk of developing oral hairy leukoplakia doubles with each 300-unit decrease in CD4 count. A high viral load was strongly associated to the oral lesions occurrence independently of $CD4^+$ cell count.{ref8} More recently, it has been described in patients with other forms of severe immunodeficiency including those associated with chemotherapy, organ transplant, and leukemia. Rarely, it may occur in patients who are immunocompetent.

Oral hairy leukoplakia also has been described in association with Behçet syndrome and ulcerative colitis.

Smoking more than a pack of cigarettes a day is positively correlated with the development of oral hairy leukoplakia in HIV-positive men.

No increase in oral hairy leukoplakia was observed when controlled for number of oral sex partners.

Complications

The complication associated with oral hairy leukoplakia (OHL) is an occasional candidal superinfection, which often results in an uncomfortable glossopyrosis (burning tongue).

Altered taste sensation is a rare complication.

The presence of oral lesions has a significant impact on health-related quality of life, because oral health is associated with physical and mental health.{ref18}

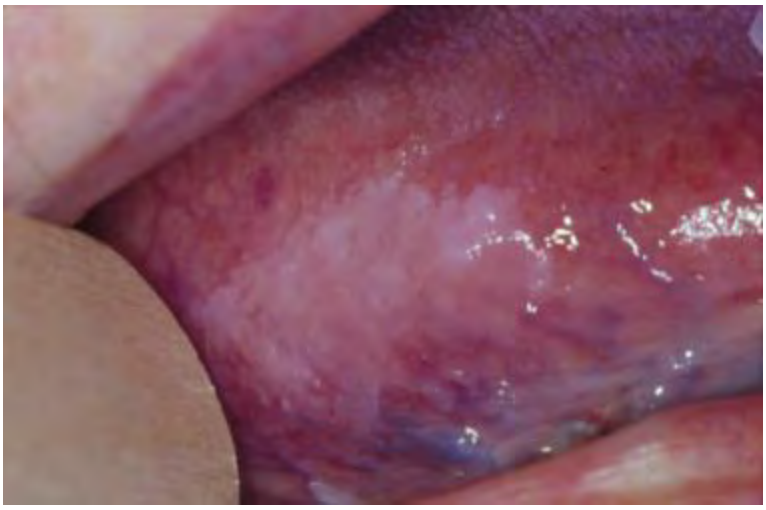
DDx

Diagnostic Considerations

Also consider the following:

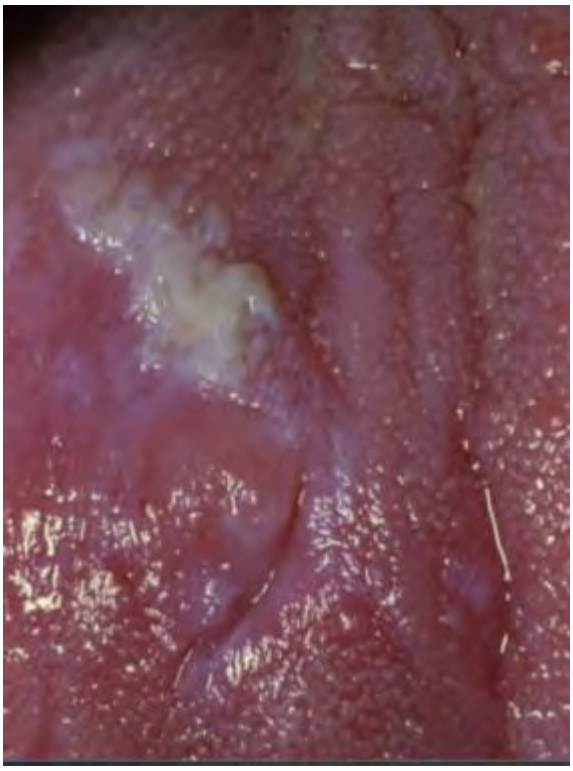
- Geographic tongue
- Frictional keratosis
- Squamous cell carcinoma
- Lichen planus
- Tobacco-associated leukoplakia
- Pseudo–hairy leukoplakia
- Human papillomavirus (HPV)–induced neoplasia
- Syphilitic mucous patch
- Idiopathic leukoplakia
- White sponge nevus
- Hyperplastic candidiasis

White sponge nevus, candidiasis, or thrush typically occurs as a flat lesion, removable by scraping, which reveals an erythematous base. However, hyperplastic candidiasis lesions are adherent and do not wipe off, making this disease especially difficult to distinguish from oral hairy leukoplakia (OHL). Resolution of the lesion with antifungal therapy suggests candidiasis over hairy leukoplakia. However, hairy leukoplakia lesions are commonly also infected with *Candida*, further confusing the clinical diagnosis. See the images below.



White sponge nevus.

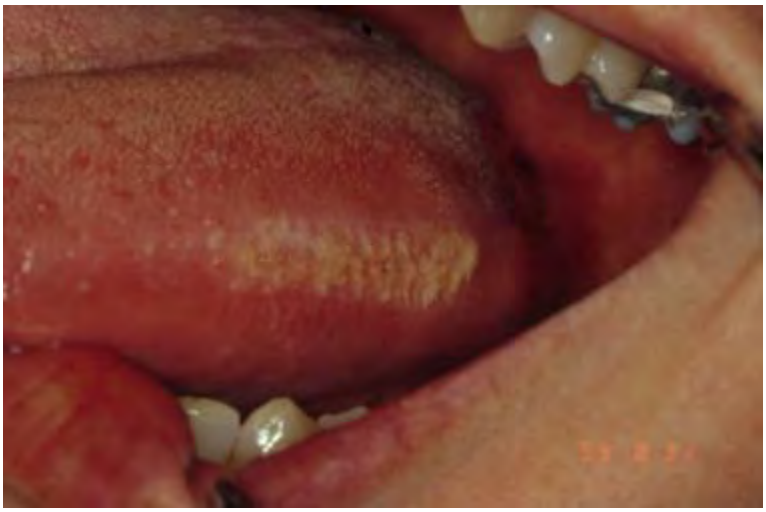
{file63339}



Hyperplastic candidiasis.

{file63341}

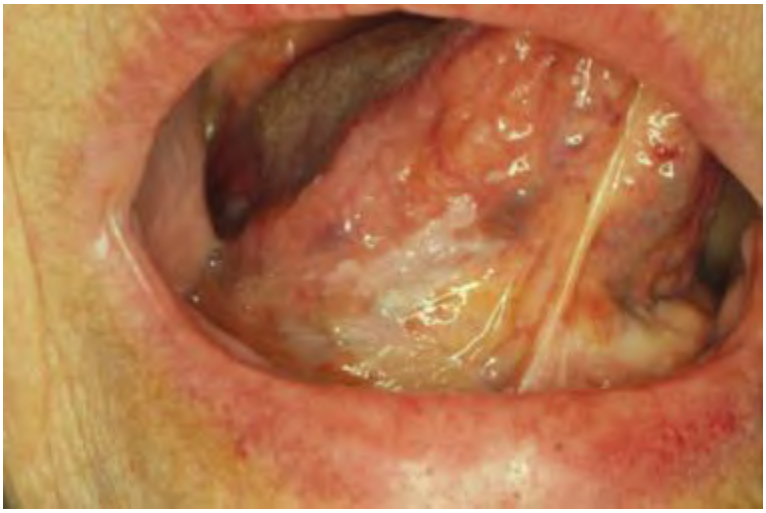
Frictional keratosis typically occurs on the lateral borders of the tongue as a consequence of tongue biting by the molar teeth or some other abrasive irritant (eg, from rubbing upon poorly fitting dental work), as shown in the image below. This lesion should quickly resolve after removal of the provoking stimulus.



Morsicatio linguarum, or tongue biting.

{file63312}

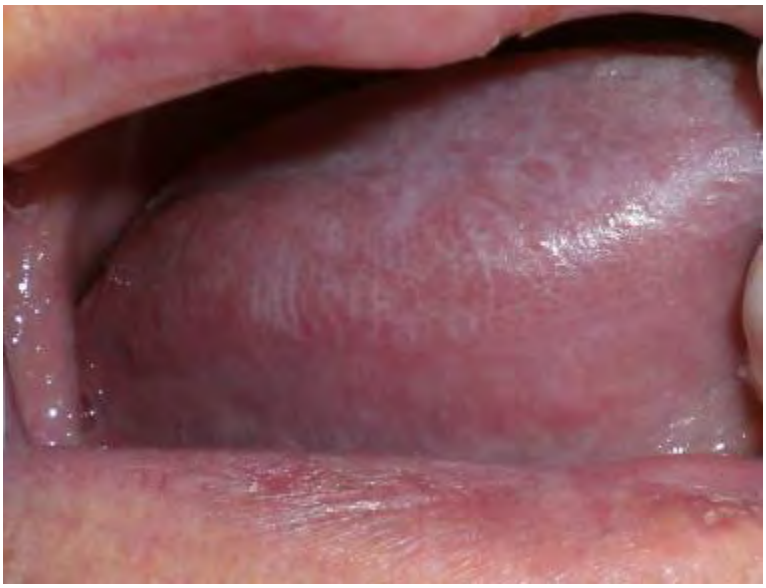
Tobacco-induced leukoplakia occurs in smokers and individuals who chew tobacco. These lesions are typically not shaggy like hairy leukoplakia, and they may occur anywhere in the oral cavity. They are often premalignant and should be evaluated by biopsy and histologic examination. See the image below.



Ventral tongue in oral leukoplakia.

{file63313}

Lichen planus or lichenoid eruptions occur as autoimmune or allergic reactions to an unknown stimulus. In HIV-infected patients, lichen planus often occurs on the buccal mucosa, typically with a reticulated pattern. Oral lichen planus may also be associated with cutaneous lesions. See the image below.

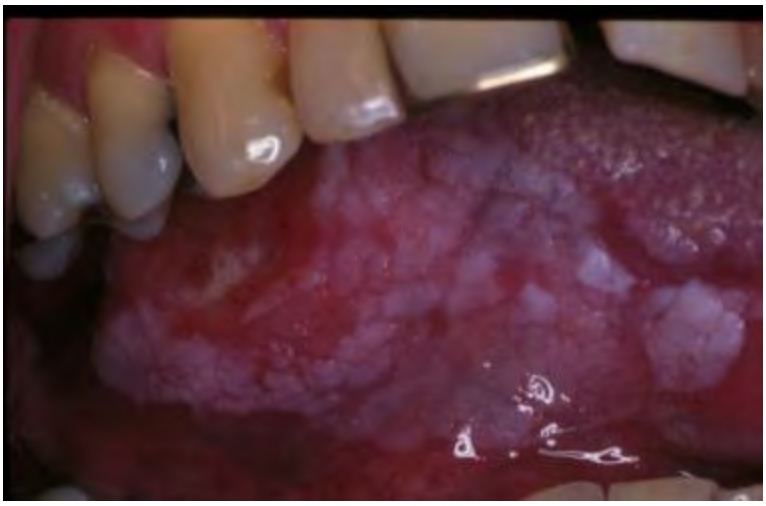


Lateral tongue in lichen planus.

{file63314}

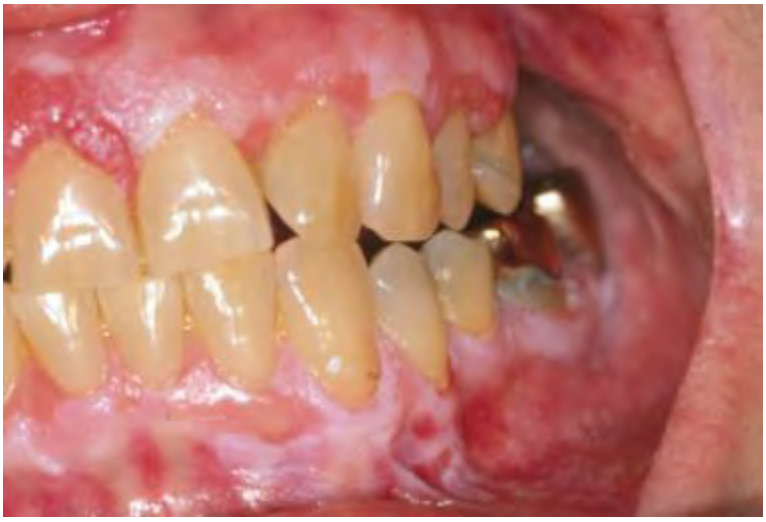
Lesions that clinically and histologically mimicked oral hairy leukoplakia but were not associated with EBV infection have been characterized as pseudo–hairy leukoplakia.

Proliferative verrucous leukoplakia can have a papillary and roughened surface, which may simulate the corrugated surface of oral hairy leukoplakia. Proliferative verrucous leukoplakia is known for malignant transformation. The two examples on the tongue and gingiva in the images below showed squamous cell carcinoma with biopsy.



Proliferative verrucous leukoplakia of the lateral tongue; biopsy showed squamous cell carcinoma.

{file63336}



Proliferative verrucous leukoplakia of the gingiva; biopsy showed squamous cell carcinoma.

{file63337}

Differentials

Candidiasis

Condyloma Acuminatum

Morsicatio buccarum, labiorum, and linguarum

Cheek, lip, and tongue biting

Oral Frictional Hyperkeratosis

Oral Leukoplakia

Proliferative Verrucous Leukoplakia

White sponge nevus

Workup

Laboratory Studies

In most cases of oral hairy leukoplakia (OHL), the diagnosis is established on clinical basis, while a definitive diagnosis requires both an appropriate histopathological appearance and the demonstration of Epstein-Barr virus (EBV) DNA, RNA, or protein within the epithelial cells of the lesion.

Several immunohistochemical and in situ hybridization kits are commercially available for this purpose.{ref19} Tissue biopsy is indicated only if the lesions are unusual in appearance or ulcerated and suggest cancer.

Procedures

It is important to differentiate hairy leukoplakia from other, more serious, oral lesions that may have a similar clinical appearance. In some cases, biopsy and histologic examination are required to exclude cancer.

Histologic Findings

The histopathology of oral hairy leukoplakia (OHL) is characterized by the following five major features:

- Hyperkeratosis of the upper epithelial layer that represents an altered pattern of keratin expression in the squamous epithelial cells: This hyperkeratosis is largely responsible for the characteristic shaggy or "hairy" gross appearance of the lesion. Superficial infections of the hyperkeratinized epithelium with bacteria or *Candida* may also be seen.

- Parakeratosis of the superficial epithelial layer: This abnormal persistence of cell nuclei in the superficial epithelial layers may represent incomplete squamous differentiation.

- Acanthosis of the stratum spinosum in the epithelial mid layer: This abnormal expansion of cells occurs with foci or layers of ballooning koilocyte-like cells. The nuclei have a homogenous ground-glass appearance and may contain Cowdry type A intranuclear inclusions.

- Minimal or no inflammation in the epithelial and subepithelial tissues

- Histologically normal basal epithelial layer

Although these characteristic histologic features of hairy leukoplakia are highly suggestive of the diagnosis, none is unique to the lesion. Thus, a definitive diagnosis of hairy leukoplakia requires both an appropriate histologic/cytologic appearance and demonstration of Epstein-Barr virus (EBV) DNA, RNA, or protein within the epithelial cells of the lesion.

Treatment

Medical Care

As a benign lesion with low morbidity, oral hairy leukoplakia (OHL) does not require specific treatment in every case. Indications for treatment include symptoms attributable to the lesion, or a patient's desire to eliminate the lesion for cosmetic reasons. The variable natural history of the lesion and its tendency toward spontaneous resolution should be considered in any management decision. Several treatment options are available.

Systemic antiviral therapy usually achieves resolution of the lesion within 1-2 weeks of therapy.{ref20} Oral therapy with acyclovir requires high doses (800 mg 5 times per day) to achieve therapeutic levels.{ref21} Valacyclovir (1000 mg 3 times a day) and famciclovir (500 mg 3 times a day) are newer antiviral drugs with higher oral bioavailability than acyclovir and can be dosed less often. Antiviral drugs inhibit productive Epstein-Barr virus (EBV) replication but do not eliminate the latent state of infection. Hairy leukoplakia often recurs several weeks after the cessation of antiviral therapy.

Topical therapy with podophyllin resin 25% solution usually achieves resolution after 1-2 treatment applications. The treatments may temporarily cause local pain, discomfort, and alteration of taste. Podophyllin has cellular cytotoxic effects, but the mechanism of action in resolving hairy leukoplakia is not known. Again, hairy leukoplakia often recurs several weeks after successful podophyllin therapy.{ref22}

Topical therapy with retinoic acid (tretinoin) has been reported to resolve hairy leukoplakia. Retinoic acids are known to inhibit EBV replication in vitro and induce epithelial cell differentiation. As with the antiviral agents and podophyllin, hairy leukoplakia often recurs several weeks after successful retinoic acid therapy.

Ablative therapy can also be considered for small hairy leukoplakia lesions. Cryotherapy has been reported as successful but is not widely used.{ref23}

Institution of HAART, considered to be the standard care in the United States, is useful in eliminating the lesions of oral hairy leukoplakia.

Superinfection with *Candida* can be addressed with medical therapy.

Consultations

Consultations with dentists, dermatologists, or infectious disease specialists may be in order depending upon the underlying disease process resulting in oral hairy leukoplakia (OHL).

Diet

Diet may be as tolerated.

Medication

Medication Summary

The goals of pharmacotherapy are to reduce morbidity and prevent complications.

Medications

Antiviral agents

Nucleoside analogs initially are phosphorylated by viral thymidine kinase to eventually form a nucleoside triphosphate.

Acyclovir (Zovirax)

Acyclovir has affinity for viral thymidine kinase and, once phosphorylated, causes DNA chain termination when acted on by DNA polymerase. Patients experience less pain and faster resolution of lesions when used within 48 hours from onset of an outbreak. Acyclovir may prevent recurrent outbreaks. Early initiation of therapy is imperative.

Valacyclovir (Valtrex)

Valacyclovir is a prodrug that is rapidly converted to the active drug acyclovir. It is more expensive but has a more convenient dosing regimen than acyclovir.

Famciclovir (Famvir)

Famciclovir is a prodrug that when biotransformed into the active metabolite, penciclovir, may inhibit viral DNA synthesis/replication.

Ganciclovir (Cytovene, Vitrasert)

Ganciclovir is indicated for CMV retinitis and the prevention of CMV infection in individuals who are HIV positive.

Foscarnet (Foscavir)

Foscarnet is indicated only for acyclovir-resistant mucocutaneous herpes simplex virus, which occurs almost exclusively in individuals who are HIV positive.

Keratolytic agents

These agents cause cornified epithelium to swell, soften, macerate, and then desquamate.

Podophyllum resin (Pod-Ben-25, Podofin, Podocon-25)

The major active constituent, podophyllotoxin, is a lipid-soluble compound that easily crosses cell membranes. Podophyllotoxin and its derivatives are potent cytotoxic agents that inhibit cell mitosis and deoxyribonucleic acid (DNA). Cell division is arrested, and other cellular processes are impaired, gradually resulting in the disruption of cells.

Podophyllum resin arrests mitosis in the metaphase; the active agent is podophyllotoxin; the type of podophyllum resin used determines strength. American podophyllum contains one fourth the amount of Indian sources. It is used in symptomatic OHL.

Antifungals

These agents reduce *Candida* superinfection.

Nystatin (Nilstat, Mycostatin, Nystex)

Nystatin is a fungicidal and fungistatic antibiotic obtained from *Streptomyces noursei*; it is effective against various yeasts and yeastlike fungi. Nystatin changes the permeability of the fungal cell membrane after binding to cell membrane sterols, causing cellular contents to leak. Treatment should continue until 48 hours after the disappearance of symptoms. Nystatin is not absorbed significantly from the GI tract.

References

1. Khammissa RA, Fourie J, Chandran R, Lemmer J, Feller L. Epstein-Barr Virus and Its Association with Oral Hairy Leukoplakia: A Short Review. *Int J Dent*. 2016. 2016:4941783. [Medline].

2. Mangold AR, Torgerson RR, Rogers RS 3rd. Diseases of the tongue. *Clin Dermatol*. 2016 Jul-Aug. 34 (4):458-69. [Medline].

3. Schmidt-Westhausen A, Gelderblom HR, Reichart PA. Oral hairy leukoplakia in an HIV-seronegative heart transplant patient. *J Oral Pathol Med*. 1990 Apr. 19(4):192-4. [Medline].

4. Greenspan JS, Greenspan D, Webster-Cyriaque J. Hairy leukoplakia; lessons learned: 30-plus years. *Oral Dis*. 2016 Apr. 22 Suppl 1:120-7. [Medline].

5. Sachithanandham J, Kannangai R, Pulimood SA, Desai A, Abraham AM, Abraham OC, et al. Significance of Epstein-Barr virus (HHV-4) and CMV (HHV-5) infection among subtype-C human immunodeficiency virus-infected individuals. *Indian J Med Microbiol*. 2014 Jul-Sep. 32(3):261-9. [Medline].

6. Daniels TE, Greenspan D, Greenspan JS, et al. Absence of Langerhans cells in oral hairy leukoplakia, an AIDS-associated lesion. *J Invest Dermatol*. 1987 Aug. 89(2):178-82. [Medline].

7. Gondak RO, Alves DB, Silva LF, Mauad T, Vargas PA. Depletion of Langerhans cells in the tongue from patients with advanced-stage acquired immune deficiency syndrome: relation to opportunistic infections. *Histopathology*. 2011 Dec 14. [Medline].

8. Bravo IM, Correnti M, Escalona L, et al. Prevalence of oral lesions in HIV patients related to CD4 cell count and viral load in a Venezuelan population. *Med Oral Patol Oral Cir Bucal*. 2006 Jan 1. 11(1):E33-9. [Medline].

9. Ramirez-Amador V, Esquivel-Pedraza L, Sierra-Madero J, Anaya-Saavedra G, Gonzalez-Ramirez I, Ponce-de-Leon S. The Changing Clinical Spectrum of Human Immunodeficiency Virus (HIV)-Related Oral Lesions in 1,000 Consecutive Patients: A 12-Year Study in a Referral Center in Mexico. *Medicine (Baltimore)*. 2003 Jan. 82(1):39-50. [Medline].

10. King GN, Healy CM, Glover MT, Kwan JT, Williams DM, Leigh IM, et al. Prevalence and risk factors associated with leukoplakia, hairy leukoplakia, erythematous candidiasis, and gingival hyperplasia in renal transplant recipients. *Oral Surg Oral Med Oral Pathol*. 1994 Dec. 78 (6):718-26. [Medline].

11. Coogan MM, Greenspan J, Challacombe SJ. Oral lesions in infection with human immunodeficiency virus. *Bull World Health Organ*. 2005 Sep. 83(9):700-6. [Medline]. [Full Text].

12. Gasparin AB, Ferreira FV, Danesi CC, et al. [Prevalence of oral lesions in persons with HIV and associated factors in a southern Brazilian city]. *Cad Saude Publica*. 2009 Jun. 25(6):1307-15. [Medline].

13. Guteta S, Feleke Y, Fekade D, Neway M, Diro E. Prevalence of oral and perioral manifestations in HIV positive adults at Tikur Anbessa Teaching Hospital Addis Ababa, Ethiopia. *Ethiop Med J*. 2008 Oct. 46(4):349-57. [Medline].

14. Lopez-Pintor R, Hernandez G, de Arriba L, de Andres A. Comparison of oral lesion prevalence in renal transplant patients under immunosuppressive therapy and healthy controls. *Oral Dis*. 2009 Jul 27. [Medline].

15. Vale DA, Martins FM, Silva PH, Ortega KL. Retrospective analysis of the clinical behavior of oral hairy leukoplakia in 215 HIV-seropositive patients. *Braz Oral Res*. 2016 Nov 28. 30 (1):e118. [Medline].

16. Coogan MM, Greenspan J, Challacombe SJ. Oral lesions in infection with human immunodeficiency virus. *Bull World Health Organ*. 2005 Sept. 83:700-6. [Full Text].

17. Miziara ID, Weber R. Oral candidosis and oral hairy leukoplakia as predictors of HAART failure in Brazilian HIV-infected patients. *Oral Dis*. 2006 Jul. 12(4):402-7. [Medline].

18. Coulter ID, Heslin KC, Marcus M, et al. Associations of self-reported oral health with physical and mental health in a nationally representative sample of HIV persons receiving medical care. *Qual Life Res*. 2002 Feb. 11(1):57-70. [Medline].

19. De Souza YG, Freese UK, Greenspan D, Greenspan JS. Diagnosis of Epstein-Barr virus infection in hairy leukoplakia by using nucleic acid hybridization and noninvasive techniques. *J Clin Microbiol*. 1990 Dec. 28(12):2775-8. [Medline]. [Full Text].

20. Schofer H, Ochsendorf FR, Helm EB, Milbradt R. Treatment of oral 'hairy' leukoplakia in AIDS patients with vitamin A acid (topically) or acyclovir (systemically). *Dermatologica*. 1987. 174(3):150-1. [Medline].

21. Resnick L, Herbst JS, Ablashi DV, eet al. Regression of oral hairy leukoplakia after orally administered acyclovir therapy. *JAMA*. 1988 Jan 15. 259(3):384-8. [Medline].

22. Brasileiro CB, Abreu MH, Mesquita RA. Critical review of topical management of oral hairy leukoplakia. *World J Clin Cases*. 2014 Jul 16. 2(7):253-6. [Medline]. [Full Text].

23. Goh BT, Lau RK. Treatment of AIDS-associated oral hairy leukoplakia with cryotherapy. *Int J STD AIDS*. 1994 Jan-Feb. 5(1):60-2. [Medline].

Citation: Cade JE. Hairy Leukoplakia. *Medscape Drugs & Diseases*. Updated May 5, 2017. Available at: https://emedicine.medscape.com/article/279269-overview.