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Hairy Leukoplakia

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Updated: Jul 18, 2007

Introduction

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, both immunocompromised and immunocompetent, albeit it can affect patients who are HIV negative. 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 have been reported in heart, kidney, and bone marrow transplant recipients and patients with hematological malignancies.

Pathophysiology

The Epstein-Barr virus (EBV), a ubiquitous herpesvirus estimated to infect 90% of the world's population, has been 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.

The virus 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, there is a marked decrease or an absence of Langerhans cells in hairy leukoplakia biopsy tissues. 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.

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%.[1] The 6-year incidence of OHL in this patient population was reported to be around 32%. A significant trend to a lower prevalence was observed in the group of patients who were already taking antiretroviral therapy, non-HAART and HAART ($p < 0.001$ and $p = 0.004$, respectively).[2]

Fewer cases of OHL have been reported in non-HIV patients. This is probably due to underdiagnosis and underreporting of this disease in patients with hematological malignancies or solid organ transplantation. Some studies have shown the prevalence of OHL in renal transplant recipients to be more than 11%.

International

The incidence of OHL 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 predictors of HIV infection.[3]

Mortality/Morbidity

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Mortality/Morbidity

In patients with HIV, the median CD4 count when OHL is first detected is 468/µL. If these patients do not have AIDS-defining disease at the time OHL 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 OHL have a shorter lifespan than those that 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.

Race

No racial predilection has been established.

Sex

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

Age

No age predilection has been established.

Clinical

History

Patients 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

Unilateral or bilateral nonpainful white lesions can be seen on the margins, dorsal or ventral surfaces of the tongue, or on buccal mucosa. The lesions may vary in appearance from smooth, flat, small lesions to irregular "hairy" or "feathery" lesions with prominent folds or projections.

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.

Causes

OHL has been associated with HIV infection and/or immunosuppression.[4] The risk of developing OHL 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.[1] 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.

OHL 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 OHL in HIV positive men.

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

Differential Diagnoses

Candidiasis
Condyloma Acuminatum

Other Problems to Be Considered

Geographic tongue
Frictional keratosis
Squamous cell carcinoma
Lichen planus
Tobacco-associated leukoplakia
Pseudo–hairy leukoplakia

Human papillomavirus (HPV)–induced neoplasia
Syphilitic mucous patch

White sponge nevus candidiasis or thrush typically occurs as a flat lesion, removable by scraping that reveals an erythematous base. However, hyperplastic candidiasis lesions are adherent and do not wipe off, making this disease especially difficult to distinguish from hairy leukoplakia. 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.

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). This lesion should quickly resolve after removal of the provoking stimulus.

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.

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.

Lesions that clinically and histologically mimicked OHL but were not associated with EBV were recently characterized as pseudo-hairy leukoplakia.

Workup

Laboratory Studies

- In most cases the diagnosis is established on clinical basis, while a definitive diagnosis requires both an appropriate histopathological appearance and the demonstration of EBV DNA, RNA, or protein within the epithelial cells of the lesion.
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- Several immunohistochemical and in situ hybridization kits are commercially available for this purpose. Whilst 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 hairy leukoplakia is characterized by 5 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.
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- 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.
-
- The basal epithelial layer is histologically normal.

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

Treatment

Medical Care

As a benign lesion with low morbidity, hairy leukoplakia 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. Oral therapy with acyclovir requires high doses (800 mg 5 times per day) to achieve therapeutic levels. 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 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.
-
- 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.

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

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 OHL.

Diet

Diet may be as tolerated.

Medication

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

Antiviral agents

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

Acyclovir (Zovirax)

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 h from onset of outbreak. May prevent recurrent outbreaks. Early initiation of therapy is imperative.

Dosing

Adult

400 mg PO bid/qid

Pediatric

20-40 mg/kg PO bid

Interactions

Probenecid or zidovudine prolongs half-life and increases CNS toxicity

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Usually safe but benefits must outweigh the risks.

Precautions

Caution in renal failure or when using nephrotoxic drugs

Valacyclovir (Valtrex)

Prodrug rapidly converted to active drug acyclovir. More expensive but has more convenient dosing regimen than acyclovir.

Dosing

Adult

1 g/d PO tid

Pediatric

Not established

Interactions

Probenecid, zidovudine, or cimetidine prolongs half-life and increases CNS toxicity

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Usually safe but benefits must outweigh the risks.

Precautions

Caution in renal failure and coadministration of nephrotoxic drugs; associated with onset of hemolytic uremic syndrome

Famciclovir (Famvir)

Prodrug that when biotransformed into active metabolite, penciclovir, may inhibit viral DNA synthesis/replication.

Dosing

Adult

500 mg/d PO bid

Pediatric

Not established

Interactions

Probenecid or cimetidine may increase toxicity; increases bioavailability of digoxin

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Usually safe but benefits must outweigh the risks.

Precautions

Caution in renal failure or coadministration of nephrotoxic drugs

Ganciclovir (Cytovene, Vitrasert)

Indication is for CMV retinitis and prevention of CMV infection in individuals who are HIV positive.

Dosing

Adult

1000 mg PO tid

Pediatric

Not established

Interactions

Cytotoxic drugs such as dapsone, vinblastine, doxorubicin, pentamidine, flucytosine, vincristine, amphotericin B, trimethoprim/sulfamethoxazole combinations, or other nucleoside analogs may result in additive toxicity in bone marrow, spermatogonia, and germinal layers of skin and GI mucosa (coadminister only if potential benefits outweigh risks); imipenem-cilastatin may cause generalized seizures (use only if potential benefits outweigh risks); cyclosporine or amphotericin B may increase serum creatinine; probenecid reduces renal clearance; administration of didanosine either 2 h prior to or simultaneously may increase bioavailability; zidovudine may decrease bioavailability, while ganciclovir increases bioavailability of zidovudine

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Safety for use during pregnancy has not been established.

Precautions

Clinical toxicity includes granulocytopenia, anemia, and thrombocytopenia; since oral ganciclovir associated with higher rate of CMV retinitis progression than IV formulation, use only when benefits outweigh risks (advanced HIV disease); half-life and plasma/serum concentrations may be increased as result of reduced renal clearance; dosages >6 mg/kg IV may result in increased toxicity; rapid infusions may result in increased toxicity; initially, reconstituted solutions of IV ganciclovir have a high pH (11); phlebitis or pain may occur at site of IV infusion despite further dilution in IV fluids; administration should be accompanied by adequate hydration; photosensitization (photoallergy or phototoxicity) may occur

Foscarnet (Foscavir)

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

Dosing

Adult

40 mg/kg IV tid

Pediatric

Not established

Interactions

Potentially nephrotoxic drugs (eg, aminoglycosides, amphotericin B, IV pentamidine) may increase nephrotoxicity (do not administer unless potential benefits outweigh risks); IV pentamidine may cause hypocalcemia

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Safety for use during pregnancy has not been established.

Precautions

May cause decline in renal function; for correct dosing, obtain 24-h serum creatinine at baseline and continue to monitor (discontinue if serum creatinine <0.4 mL/min/kg); hydration may reduce nephrotoxicity
Carefully monitor electrolytes (eg, calcium, magnesium); assess for electrolyte and mineral level abnormalities if mild perioral numbness, paresthesia symptoms, or seizures; granulocytopenia and anemia may occur (regularly monitor CBC)
Infuse foscarnet solutions into veins with adequate blood flow to avoid local irritation; to avoid toxicity do not administer by rapid or bolus IV injection

Keratolytic agents

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

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

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.
Arrests mitosis in metaphase; active agent is podophyllotoxin; type of podophyllum resin used determines strength. American podophyllum contains one fourth the amount of Indian source. Used in symptomatic OHL.

Dosing

Adult

Apply 25% liquid for 20 min

Pediatric

Not established

Interactions

None reported

Contraindications

Documented hypersensitivity; diabetes; impaired peripheral circulation; avoid use on mucous membranes, eyes, bleeding warts, moles, birthmarks, or unusual warts with hair

Precautions

Pregnancy

X - Contraindicated in pregnancy

Precautions

Powerful caustic and severe irritant; do not use if surrounding tissue swollen or irritated; 25% solution should not be applied near mucous membranes; do not use large amounts; avoid contact with cornea; avoid use on mucous membranes, eyes, bleeding warts, moles, birthmarks, or unusual warts with hair

Antifungals

These agents reduce *Candida* superinfection.

Nystatin (Nilstat, Mycostatin, Nystex)

Fungicidal and fungistatic antibiotic obtained from *Streptomyces noursei*; effective against various yeasts and yeastlike fungi. Changes permeability of fungal cell membrane after binding to cell membrane sterols, causing cellular contents to leak. Treatment should continue until 48 h after disappearance of symptoms. Drug is not absorbed significantly from GI tract.

Dosing

Adult

200,000 U lozenges; 1-2 lozenges, 4-5 times daily

Pediatric

Administer as in adults

Interactions

None reported

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Safety for use during pregnancy has not been established.

Precautions

Do not use to treat systemic mycoses

Follow-up

Complications

- The complication associated with oral hairy leukoplakia 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.[5]

Prognosis

- The majority of patients with OHL tend to have significant immunosuppression at the time of diagnosis. OHL occurs relatively soon after HIV seroconversion, typically before AIDS. Median CD4 count when OHL is first detected is between 235 and 468 per microliter.
-

- Some studies of oral hairy leukoplakia in HIV-seropositive patients have shown that the median survival after the diagnosis of OHL is around 20 months. In patients with CD4 count greater than or equal to 300 per microliter, OHL is associated with median survival time of 25 months, compared to 52 months in patients with normal counts.

Miscellaneous

Medicolegal Pitfalls

- Failure to inform patient with OHL who does not carry a diagnosis of HIV infection that they should have a thorough workup to evaluate for HIV infection or immunosuppression
-
- Failure to tell patients that immunosuppression is a risk factor for oral cancer
-
- Failure to remain alert to signs and symptoms of oral cancer and premalignancy in persons who are immunocompromised
-
- Failure to counsel OHL patients to discontinue the use of all forms of tobacco and to limit consumption of alcohol
-
- Always instruct patient to comply with regular dental and medical care regimens.
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