

Critical review of topical management of oral hairy leukoplakia

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Abstract

Oral hairy leukoplakia (OHL) is a disease associated with Epstein-Barr virus and human immunodeficiency virus infections. OHL is usually an asymptomatic lesion, but in some cases treatment is recommended to reestablish the normal characteristics of the tongue, to eliminate pathogenic microorganisms, to improve patient comfort and for cosmetic reasons. Proposed treatments for this condition include surgery, systemic antiviral treatment and topical management. Topical treatment is an inexpensive and safe therapy that is easy to apply, noninvasive, free of systemic adverse effects and effective over a long period of time. The aim of this study was to present a review of the literature for topical therapy for OHL. Gentian violet, retinoids, podophyllin, acyclovir and podophyllin associated with topical antiviral drugs were used to treat OHL. Reports with this focus are limited, and since 2010, no new studies have been published that discuss the efficacy of topical treatments for OHL. Podophyllin with acyclovir

cream was found to be effective, causing regression of lesions with no recurrences. Additional searches are necessary to provide clinical evidence of topical management effectiveness.

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Key words: Oral hairy leukoplakia; Human immunodeficiency virus infection; Topical treatment; Topical agents; Recurrence rate

Core tip: This literature review was performed to assess the evidence for topical treatments for oral hairy leukoplakia (OHL). Although highly active antiretroviral therapy has reduced oral lesions associated with human immunodeficiency virus, prevalence studies revealed that OHL is still observed in patients with HIV infections. Knowledge about appropriate management of this condition is relevant, specifically regarding topical treatments that are less invasive, low-cost, easy to apply and free of systemic adverse effects.

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INTRODUCTION

Oral hairy leukoplakia (OHL) was first described in 1984 by Greenspan *et al*^[1] and is described as a white plaque generally on the lateral borders of the tongue in patients with human immunodeficiency virus (HIV) that later developed acquired immunodeficiency syndrome (AIDS). Later, other studies confirmed OHL as an early indicator of HIV infection and revealed that this disease may be related to the progression to AIDS. However, OHL

Table 1 Topical agents used in the treatment of oral hairy leukoplakia and study types

	Case reports	Case series	Randomized clinical trial
Gentian violet	Bhandarkar <i>et al</i> ^[3]		
Retinoids		Schöfer <i>et al</i> ^[11] Alessi <i>et al</i> ^[12]	
Podophyllin		Lozada-Nur <i>et al</i> ^[13] Sanchez <i>et al</i> ^[15] Gowdey <i>et al</i> ^[14] Ficarra <i>et al</i> ^[16]	
Acyclovir			Moura <i>et al</i> ^[2]
Combined topical therapy (Topical antiviral agents and podophyllin)			Moura <i>et al</i> ^[4]

is not exclusive to HIV infection and may be associated with other cases of immunosuppressed patients^[1-3]. OHL appears clinically as an asymptomatic white lesion on the lateral border of the tongue, unilaterally or bilaterally, with imprecise boundaries, a flat, corrugated or hairy surface, that is not removed by scraping^[4]. Some patients may present with symptoms including mild pain and alteration of taste^[5].

The pathogenesis of OHL is related to the infection of oral squamous epithelial cells with the Epstein-Barr virus (EBV)^[3,4]. The absence of or high reduction of Langerhans cells in OHL has been demonstrated^[6]. Langerhans cells are the antigen-presenting immune cells that are required for an immune system response to a viral infection. This deficiency of Langerhans cells may permit EBV to replicate^[5-7].

Topical therapy is the most highly recommended treatment for OHL because it has a low cost, is easy to use, has few side effects and is effective for a long period of time^[4]. However, there are few studies that evaluate the effects of topical treatment in patients with OHL. This can be explained by the significant reduction in the prevalence of the oral lesions in HIV patients after the introduction of highly active antiretroviral therapy^[4,8]. The purpose of this article is to present a review of topical therapies for OHL. The methodology was a search of the literature, from 1966 through December 2013, related to the topical treatment of OHL and listed on PubMed. The search was conducted in both English and Portuguese, and the keywords used were “oral hairy leukoplakia”, “oral hairy leukoplakia and topical management” and “oral hairy leukoplakia and topical treatment”. Additional studies were found in the reference lists of the selected articles. Randomized clinical trials, case reports and review articles were included in the current paper (Table 1).

REVIEW

Usually, OHL does not require specific therapy, and when indicated, therapy is intended to restore the patient's comfort, eliminate the hairiness, reestablish the normal appearance of the tongue for aesthetic reasons and remove

niches for bacteria, viruses (EBV) and fungi to prevent the establishment of other oral diseases^[2]. Proposed treatments include surgery, systemic antiviral therapy and topical management. A search of the literature found 16 articles related to topical treatments for OHL. All forms of topical management of OHL identified in published studies will be presented herein.

Gentian violet

Gentian violet is a triphenylmethane dye that was synthesized by Charles Lauth, in 1861, under the name of “Violet de Paris”. Churchman, in 1912, demonstrated the bacteriostatic action of gentian violet against Gram-positive microorganisms *in vitro* and in animal models, as well as the antimycotic effects of this agent against multiple species of *Candida*^[9]. Since then, several studies have evaluated the antibacterial and antifungal actions of gentian violet.

The antiviral properties of gentian violet were investigated based on evidence that EBV viral products induce the generation of reactive oxygen, and gentian violet is a potent inhibitor of reactive oxygen species^[10]. Given that gentian violet is well-tolerated, approved for human use and is an inexpensive agent, Bhandarkar *et al*^[3] performed a study using gentian violet (2%) as a topical treatment for OHL in one HIV-infected man. Gentian violet was applied topically to the lesion three times in a one-month period. Complete regression of OHL was observed at a one-month follow-up, and there was no recurrence of the OHL one year after treatment.

Retinoids

Retin-A is a dekeratinizing agent responsible for the modulation of the presence of Langerhans cells in OHL. Local application of 0.1% vitamin A twice daily was performed in twelve cases of OHL and regression of the lesions was observed after 10 d^[11]. Daily application of a tretinoin solution (Retin-A) for 15 to 20 d was performed in 22 patients, and 37 patients received no treatment. Lesion healing was observed in 69% of treated patients and spontaneous regression was detected in 10.8% of untreated patients^[12]. Retin-A is a costly drug and causes a burning sensation after prolonged use^[13,14].

Podophyllin

Podophyllin is a dry, alcoholic extract of rhizomes and roots of *Podophyllum peltatum*. It is a lipid-soluble substance that crosses cell membranes and interferes with cell replication; this substance is commonly used as a topical chemotherapy agent^[14]. It is inexpensive, simple to apply, and effective over a long period of time. Although podophyllin has a very bitter and unpleasant taste, the palate returns to normal two hours after of application^[2].

The results of a 25% alcoholic solution of podophyllin as topical therapy for OHL are significant, especially in the first week after application. In a case series, nine patients were treated with podophyllin resin 25% sol in a benzoin compound tincture. The results showed complete regression of all lesions: five patients within one

week and four after a second application a week later. Those four patients had presented with more extensive lesions^[13]. In another study, six men with OHL were treated with a once-daily application of podophyllin 25%, and healing of all lesions was verified in three to 5 d^[15]. Gowdey *et al.*^[14] assessed ten HIV-infected patients with OHL on the tongue and treated one side with a single application of topical podophyllin resin 25% solution. The other side was used as a control. The patients were evaluated at days two, seven, and thirty of the study. They described a slight change of taste, burning sensation and pain with a short duration. There was regression of lesions, especially on the second day after application.

The dose usually applied in topical therapy for OHL varied from 10 mg to 20 mg of podophyllin^[2,14]. This dose has not been associated with adverse or systemic effects; these effects are observed after ingestion or when more than 100 mg of podophyllin is topically applied and not removed within 4 to 6 h^[14].

Acyclovir

Acyclovir is a chemotherapeutic antiviral agent that is highly effective against herpes simplex virus types I and II, EBV, Varicella zoster virus, and cytomegalovirus^[2]. The only previous study performed using acyclovir cream for topical treatment was performed by Ficarra *et al.*^[16]. The authors observed OHL in 23 out of 120 HIV-positive patients (19%), and found a complete resolution of OHL in two patients and partial regression in one patient after topical application of acyclovir cream.

Combined topical therapy

Topical antiviral drugs may be used in combination with podophyllin, increasing the efficiency of OHL treatment. After the dekeratinization of superficial epithelial cells by podophyllin, the topical antiviral drug acts on exposed and infected cells located below the surface^[4]. A clinical trial study, performed randomly, proposed a combined topical therapy of 25% podophyllin and 5% acyclovir cream and compared the results with 25% podophyllin^[2]. In both protocols, applications were performed weekly. All lesions treated with podophyllin and acyclovir showed total clinical regression, and in the podophyllin group, four lesions did not display total clinical resolution after 25 applications. Furthermore, in the 25% podophyllin group, smaller lesions showed clinical regression with fewer applications than larger lesions. In the 25% podophyllin and 5% acyclovir cream group, there was no significant difference in the number of applications.

Based on their previous study, a new topical treatment for OHL employing 25% podophyllin resin with 1% penciclovir cream was tested and the results were compared to 25% podophyllin resin and 25% podophyllin resin with 5% acyclovir cream applied topically^[14]. Fourteen patients were treated in each protocol. The authors concluded that about half of the patients (55%) had clinical healing of OHL within 7-8 wk of each topical treatment, but the 25% podophyllin resin with 5% acyclovir cream resulted in a faster clinical healing rate of OHL after the

sixth week; moreover, no recurrent lesions were observed in this treatment group twelve months after clinical healing of OHL.

Recurrence rate

Some studies evaluated the recurrence rate of OHL after topical treatment. Bhandarkar *et al.*^[3] and Ficarra *et al.*^[16] showed no recurrence of the lesion one year after 2% gentian violet treatment and six months after acyclovir cream topical therapy, respectively, in patients with total clinical regression. For topical retinoid, recurrence is observed a few days following discontinuation of treatment^[11]. Sanchez *et al.*^[15] observed a recurrence rate of 33.3% of OHL treated with 25% podophyllin. Two of the six cases evaluated presented with regression of the lesion four and nine months after treatment. Moura *et al.*^[2] showed a recurrence of 11.2% twelve months post-therapy with 25% podophyllin. No recurrence was observed in the 25% podophyllin resin with 5% acyclovir cream group. These data suggest that synergism of podophyllin and acyclovir decreases recurrence of OHL after topical therapy.

Systemic antiviral drugs such as desciclovir, valacyclovir, acyclovir and ganciclovir have been used for OHL treatment with recurrence observed after discontinuation^[17,18]. The possibility of the occurrence of side effects and drug resistance must be carefully evaluated so that the potential harm of treatment does not exceed the expected benefits^[18]. Surgical excision as a treatment for OHL has been performed, and no recurrence was observed within three months. However, most patients presented with new foci of OHL after this time^[19]. Considering this, and comparing it to systemic therapy and surgery, topical treatment is recommended because it does not produce systemic adverse effects, is less invasive and is effective over a long period of time^[4].

CONCLUSION

A combined topical therapy of 25% podophyllin and 5% acyclovir cream is effective, demonstrating fast healing without recurrence. In this case, additional multicenter studies are necessary. As for other agents, gentian violet (2%) was also used successfully in the treatment of OHL, with no recurrences in a year, although only one previous study has evaluated the effectiveness of this therapy. Future double-blind and placebo-controlled trials are needed to provide clinical evidence for the efficacy of topical management of OHL.

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